ABSTRACTS

This publication contains the abstracts submitted and accepted for the EUROGIN 2015 Congress, held in Sevila, February 4 - 7, 2015.
For uniformity, all abstracts have been formatted electronically. Occasionally, symbols in electronically submitted abstracts may have been lost or changed in the re-formatting process. Please advise the congress staff of errors that distort the data or change the meaning.

The abstracts have been organized to reflect the scientific program.
This section contains summaries provided by the speakers presenting in the Training Courses and the Main Scientific Sessions, followed by those of the Scientific Sessions, Clinical Sessions and Satellite Sessions, ending with Oral Communications abstracts.

Abstracts of Poster presentations are listed in a separate section.
Poster codes correspond to the numbers of the poster boards.

Please refer to the Final Program for a detailed explanation of the coding system.

The codes are also used as a reference in the Index of Authors.

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MTC 1-1

HPV-RELATED CANCERS: THE COMPARATIVE FIGURES

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Objective: Estimates of HPV-attributable cancer cases worldwide with focus on the still uncertain fraction in HPV-attributable oropharyngeal cancer (OPC) in men and women.

Methods and Results: Worldwide, approximately 610,000 new cancer cases are estimated to be caused annually by HPV infection.[1] The HPV-attributable fraction of all cancers is larger in women (9.4%) than in men (0.6%). The current estimate of HPV-attributable OPC is much larger in men (17,000) than women (4,400), assuming the same proportion of HPV-attributable OPC in the two sexes. To validate this assumption, we systematically retrieved HPV prevalence data from 63 studies reporting separately on OPC by gender.[2] As an example, the Table shows the male/female (M/F) ratios of HPV prevalence in OPC and the age (world)-standardized OPC incidence rates in 1998-2002 that would correspond to our HPV prevalence findings in four well-studied countries. Of note, these countries widely differ in respect to smoking habits in the two sexes (see lung cancer cumulative risk up to age 69). The M/F ratio for incidence rates of HPV-positive OPC was rather stable across countries (around 4). In contrast, the M/F ratio for incidence rates of HPV-negative OPC reached 10.2 in France versus <3 elsewhere.

Table. Prevalence of HPV, incidence rates of oropharyngeal cancer (OPC) by HPV attribution, and lung cancer cumulative risk in males and females by country.

	Prevalence of HPV in OPC (%)	**OPC incidence rate** / 100,000			**Lung cancer cumulative risk** (%)
		HPV-pos	HPV-neg	All	
United Kingdom					
Males/Females	60.3/57.0	2.8/0.9	1.9/0.6	4.7/1.5	2.6/2.1
M/F ratio	1.1	3.3	2.9	3.1	1.2
Australia					
Males/Females	49.3/39.5	2.8/0.6	2.8/1.0	5.6/1.6	2.4/1.8
M/F ratio	1.3	4.4	2.9	3.5	1.4
United States					
Males/Females	66.3/45.2	4.8/1.0	2.5/1.2	7.3/2.2	3.4/2.8
M/F ratio	1.5	4.9	2.0	3.3	1.2
France					
Males/Females	40.6/61.5	7.2/1.7	10.6/1.0	17.8/2.7	4.6/1.8
M/F ratio	0.7	4.3	10.2	6.6	2.5

Conclusions: HPV prevalence in OPC differs by gender and country probably as a consequence of the vast international variation in smoking habits by sex. Nevertheless, HPV-positive OPC may consistently affect men more heavily than women for reasons that require further study.

[1]de Martel C, et al. Lancet Oncol 2012;13:607-15. [2]Combes JD, et al. Cancer Epidemiol Biomarkers Prev. (In press) 2014

MTC 1-4

HPV IMMUNOLOGY: AN UPDATE

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Human papillomavirus (HPV) has been shown to be the etiological agent that causes several important cancers, including anogenital cancer, and a subset of head and neck cancers. The life cycle of HPV is unique in that it coordinates closely with the differentiation of basal keratinocytes of the squamous epithelium in the cervix, which serve as the primary infectious site. Upon successful infection, the early genes are first expressed in the early stages of keratinocyte differentiation. Initial immune responses against these HPV early genes are weak due to lack of systemic viraemia, non-lytic infection, low expression level of viral genes and immune escape mechanisms. Immune cells in the circulation have difficulties reaching the virus in the basal cells. Furthermore, HPV infection does not trigger major inflammation that would lead to an immunostimulatory environment. Innate immune responses against HPV are compromised. It has been reported that in the transformation zone in the cervix, the site most susceptible to HPV infection, there's a decrease in the number of Langerhan's cells and costimulatory agents for effective antigen presentation to activate adaptive immune response. Moreover, HPV disrupts the Toll-like receptor signaling pathways and recruits immunosuppressive cells like tumor-associated macrophages to cervix. Upon integration of the HPV genome into the host such as in the case of cervical cancer, the expression of the oncogenes E6 and E7 are significantly upregulated. resulting in activation of E6 and E7 specific immune responses. It has been reported that E6-specific cellular immune responses correlate with regression of CIN lesions. However, in the site of HPV-associated tumor lesions, a Th2 cytokine profile and humoral response appear to be dominant. Although antibody responses are effective in preventing HPV infection, they are ineffective in clearing infected and transformed cells. The presence of regulatory T cells in the HPV-associated lesions further suppresses the HPV-specific cellular immune response that potentially could eliminate infected cells. As a result, therapeutic strategies against HPV-associated cancers should aim to manipulate the site of HPV lesion into an environment more attractive to, and favorable for the activation of an antigen-specific CD8+ T cell response to clear HPV viral infection and HPV-associated cancers.

MTC 2-1

NEW STANDARDS FOR HPV-BASED CERVICAL CANCER SCREENING

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Although the value of HPV testing in primary screening is now widely accepted much remains to be understood before policymakers can gain full confidence in its implementation in cervical cancer prevention. Many questions remain unanswered. Is HPV testing followed by cytologic triage a better approach than HPV plus Pap cytology cotesting? If HPV testing is adopted for women ages 30 and older what screening options should be recommended for younger women? What are the best triage options for HPV-positive women? What is the role of genotyping in cervical cancer screening? Is self-sampling a solution to expand the coverage and bring equity to screening? Algorithm management versus risk stratification: what is most suitable for guidelines? What is the role of HPV viral load as clinical tool? What is the role of cytology-based staining for prognostic markers of lesion progression? How should we educate healthcare providers and patients concerning HPV testing results? What will be the impact of HPV vaccination on screening performance? These questions remain promising avenues for new research on cervical cancer prevention.

As HPV testing makes inroads in cervical cancer screening, physicians and healthcare providers cannot confidently decide among a bewildering array of options for molecular tests, the majority of which have not been validated for clinical use. Benchmarks of performance are urgently needed and realistic standards for regulatory approval must also be adopted to permit innovation and rapid deployment of validated molecular technologies.

MTC 2-2

HPV PROPHYLACTIC VACCINES: LESSONS LEARNED FROM 10 YEARS EXPERIENCE

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Objective: To summarise some of the key lessons learned since the registration of HPV vaccines.

Methods: HPV vaccination experts across the fields of implementation and delivery, immunology and vaccine development, epidemiology, vaccine safety and cervical screening were invited by email in September 2014 to nominate the three most important lessons they had learned about HPV vaccines that had influenced their practice.

Results: Key lessons highlighted strategies for effective delivery which included: school based programs and young age of routine vaccination being most effective; need for providers across all relevant disciplines to endorse HPV vaccination using simple, clear communication strategies centred on cancer prevention; need for high level visible government and 'champion' support (eg celebrity, patron); and a need for proactive preparation for handling negative media reports, internet based rumours and anti-vaccination activity and for an ongoing active presence of public health on social media/the web. The cost of vaccines, and the difficulty gaining political support when cancers to be prevented occur far into the future, were identified as ongoing challenges to countries supporting the use of the vaccine. Whilst the data to date indicate that the vaccines are very safe, and even more effective than initially anticipated due to efficacy at non-cervical sites, confirmed herd immunity effects and cross protection, establishing the long term and relative efficacy of less than three doses will guide future vaccine strategies.

Conclusions: Education, planning, implementation of robust systematic approaches to vaccination and coordinated communication strategies are the key to successful HPV vaccine implementation.

MTC 2-3

INTEGRATING PRIMARY AND SECONDARY PREVENTION: NEW STRATEGIES FOR CERVICAL CANCER CONTROL IN LOW- VERSUS HIGH-INCOME COUNTRIES

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The tools available to facilitate the reduction in the global burden of cervical cancer continue to evolve. Two prophylactic vaccines, Gardasil and Cervarix, have shown both efficacy and population-level effectiveness in the prevention of infection and precancer from the two most oncogenic HPV genotypes – HPV16 and HPV18. Merck has presented data to suggest that a nonavalent HPV vaccine offers similar protection against infection and precancer caused by an additional five oncogenic HPV types (HPV31, 33, 45, 52, and 58). HPV testing is already widely used as an adjunct to morphology-based Pap cytology in many organized screening programs in high-income countries (HICs), and is likely to replace cytology as the first line screen in the coming years. In low-income countries (LICs), many of which are lacking functional cytology-based screening programs, screening tests such as visual inspection with acetic acid (VIA) or low-cost HPV testing offers alternative strategies for secondary cervical cancer prevention. This presentation will discuss several programmatic considerations for optimal implementation of the various strategies for LICs vs. HICs in regionally-appropriate cervical cancer control programs, including (1) affordability and access to each technology, (2) patient acceptance relevant to vaccine/screening coverage, and (3) infrastructural requirements and alternative implementation strategies such as fewer vaccine doses and self-sampling for screening. In addition, the impact of anticipated changes in the epidemiology of HPV type-specific infections in vaccinated populations on fully integrated solutions to cervical cancer prevention will be discussed.

MTC 2-4

CHALLENGES FACING NOVEL MULTIVALENT HPV VACCINE

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Objective: To address the perspectives of a novel multivalent HPV vaccine.
After the finalization of the pivotal clinical trials the ninevalent HPV vaccine is under review by FDA and EMA. The US approval is expected by the end of 2014. This is the basis for many health authorities globally and hence for the global distribution. The vaccine has been demonstrated to be highly effective against the new HPV types (HPV 31/33/45/52/58) and HPV 6/11/16/18. A key point is if the approval will be similar to the currently available vaccines with respect of sex and age. The second point is the price, which has to be affordable in various regions. The key issue remains: In most countries with just a few exceptions the coverage with the currently available vaccines is anything but perfect. Programs for long term surveillance are in place, people have to be reassured about safety.

Conclusion: The new vaccine has the potential to substantially reduce the burden of HPV related disease.It also has the potential to equalize the regional differences in type distribution. However the coverage achieved remains key.

MTC 3-1

MANAGEMENT OF HPV-DRIVEN CERVICAL DISEASE: THE STATE OF THE ART IS BASED ON CIN3+ RISK.

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Objectives: Cervical neoplasia screening and treatment guidelines have been crafted to reduce patient risk for developing cancer by optimizing triage to and detection of treatable precancer. The principle of equal management for equal risk permeates US guidelines. The readily available datapoints for screening are the age of the patient, HPV status and the interpretation of the Pap smear. Hence, current US cervical cancer screening guidelines are age stratified and recommend a combination of clinically valid HPV testing and cytology. Triage of HPV positive women with genotyping is also recommended, if such testing is available, as a method for focusing attention on the subset of screen positive women that need colposcopic referral as opposed to noninvasive follow-up. Data from recent clinical trials clearly reinforces the concept that there is differential risk of pre-cancer and cancer associated with different HPV types. Here we will present data on the interplay between cytology and HPV status at stratifying risk for colposcopic referral

Methods and results: What is the risk of CIN3+ in women that are HR HPV positive stratified by genotype? Furthermore, once the genotype is known, does cytology status add further useful discriminating information? Epidemiologic surveillance studies demonstrate a 4-10 fold variation in risk of CIN3+ at 12 years depending on whether a women is persistently HPV16 positive as opposed to screen HPV 16 positive, screen HPV18 positive or other HPV type positive (JNCI 2010 102; 1478-1488). Likewise, in ATHENA, the cross-sectional risk of CIN 3 varies in NILM patients who are 14 type HPV positive almost 5 fold from ~2% for 12 hr-HPV+ to 10% for HPV 16+ women (*Am J Clin Pathol* 2011; 136: 578–586). Similarly, in women with ASC-US, cross-sectional risk of CIN3 varies in patients who are 14 type HPV positive 5 fold from ~4% for 12 hr-HPV+ to 20% for HPV 16+ women (*Am J Clin Patho*l 2011; 135:468–475). The consistency of these relative risks stands in contradistinction to the variability in diagnoses used by cytology laboratories on comparable population of patients.

Conclusions: High Risk HPV status defines the majority of a patient's risk for CIN3+. Genotyping helps stratify that risk, perhaps more reliably than cytology. Whether, more detailed genotyping will provide further useful patient stratification based on the genoptype specific risk vs. prevalence is debatable and will potentially incur algorithmic complexity as a tradeoff with clinical utility.

MTC 3-3

RATIONALE, METHODS, RESULTS AND OPPORTUNITIES FOR IMPROVEMENT OF THE CURRENT U.S. TRIAGE OF WOMEN WITH ABNORMAL CYTOLOGY

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Objective: To review the current U.S. recommendations.

Methods: Description of the statistical methods, data, results and opportunities for improvement.

Results: Assessment of outcomes in 1.4 million cotested women followed up to 9 years provided information concerning risk. The risk associated with cytology at 3 year intervals was chosen as the "benchmark" risk. The principle of equal management for equal risk was employed. We learned that:

1) Endpoints matter! Results may differ when cancer is used in place of CIN3+
2) There were not sufficient cancers to use cancer as the endpoint for many judgments
3) Cytology contributes significantly more to assessment of risk in the setting of abnormal followup than in screening (data to be shown)
4) There is no path back to 5 year screening supported by data in women other than those with low grade abnormalities (ASC-US, LSIL, Pap neg HPV pos times 2) and a negative or CIN1 colpo

Opportunities for improvement include:

1) Incorporation of new tests as data becomes available
2) Reconsideration of the 3 year cytology benchmark for risk
3) Improvement of accuracy of 5 year risk assessment
4) Acquisition of data to permit use of cancer as the predominant endpoint

Conclusions: This first set of recommendations based on risk of high grade dysplasia or cancer over time is a large step forward from previous recommendations which were defined based on immediate risk only. Additional outcomes data and the inclusion of different screening and triage tests will provide opportunities for improvement.

MTC 4-1

COMPARATIVE EPIDEMIOLOGY OF HPV NATURAL HISTORY BY GENDER

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Objective: Human papillomaviruses (HPVs) cause cancer at multiple anatomic sites in men and women including cervical, oropharyngeal, anal, vulvar, and vaginal cancers in women, and oropharyngeal, anal, and penile cancers in men. Differences in HPV-related cancer and infection burden by gender and anatomic site are reviewed.

Methods: Systematic review of the literature.

Results: The proportion of cancers attributable to HPV varies by anatomic site with nearly 100% of cervical, 88% of anal, and less than 50% of lower genital tract and oropharyngeal cancers attributable to HPV, depending on world region and prevalence of tobacco use. Often mirroring cancer incidence rates, HPV prevalence and infection natural history varies by gender and anatomic site of infection. Oral HPV infection is rare and significantly differs by gender; yet HPV-related cancer incidence at this site is several fold higher than at either the anal canal or penile epithelium. HPV seroprevalence is significantly higher among women compared to men and likely explains the differences in age-specific HPV prevalence and incidence patterns observed by gender.

Conclusion: More research is needed to characterize HPV natural history at each anatomic site where HPV causes cancer in men and women, information that is critical to inform the basic science of HPV natural history and to the development of future infection and cancer prevention efforts.

MTC 4-3

CLINICAL ISSUES RELATED TO ANAL HPV INFECTION AND CANCERS

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This presentation will discuss anal HPV infection and cancer from a clinician's perspective.
Anal HPV infection is almost universal in men who have sex with men (MSM), and clinical anal warts are common. Despite this, the incidence of invasive anal cancer in MSM without HIV is relatively low (5 per 100,000 per year) although the available data is limited. However in MSM with HIV, the incidence is thought to be about 100 per 100,000 or 1 in 1,000 per year. This means most large clinical services will be diagnosing at least one case every year. Unfortunately recent clinical series show that many cases are diagnosed late when morbidity and mortality are high.
How should a clinician working HIV manage their patients who are at greatly increased risk of anal cancer?
What is the role of screening?
What is the role of routine clinical examinations?
What lesions are suspicious and how should they be managed?
What is the current clinical competence of HIV clinicians to deal with these issues are do they differ by areas of expertise (Sexual Health Physicians, Infectious Disease Physicians or Immunologists and Primary Care Clinicians).
The presentation will answer these questions from the perspective of a clinician managing people living with HIV.

MTC 4-4

HPV-ASSOCIATED OROPHARYNGEAL CANCER, THE STATE OF THE ART

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Head and neck squamous cell carcinomas (HNSCC) arise in the mucosal linings of the upper aerodigestive tract. Risk factors are smoking and excessive consumption of alcohol, but also infection with the human papillomavirus (HPV). The proportion of HPV-infected tumors is highest in oropharyngeal cancers (OPC) but varies regionally over the world. OPC caused by HPV is a distinct class of tumors, both at the clinical level as well as at the molecular level, and HPV+ve and HPV-ve OPC should be considered as separate disease entities. In this review, the state of the art will be discussed with respect to the testing for HPV, increasing prevalence, the molecular differences between HPV+ve and HPV-ve tumors, the clinical differences between HPV+ve and HPV-ve tumors and prognostic risk modeling of OPC, the natural history of infection, and the missing information to date. Also innovative options for changing treatment protocols will be outlined.

MTC 4-5

THE POTENTIAL IMPACT OF HPV VACCINATION ON NON-CERVICAL HPV-RELATED CANCERS

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Objectives: To estimate and compare the potential population-level effectiveness of HPV vaccination on HPV-associated cancers in non-cervical sites for the bivalent, quadrivalent and nonavalent HPV vaccines.

Methods: We used HPV-ADVISE, an individual-based transmission-dynamic model of multi-type HPV infection and diseases (anogenital warts, and cancers of the cervix, vulva, vagina, anus, penile and oropharynx). For model predictions, we used two versions of the model, HPV-ADVISE-US and HPV-ADVISE-Can, which were calibrated to highly stratified sexual behavior and HPV-type specific epidemiology from the US and Canada, respectively. For the bivalent, quadrivalent and nonavalent HPV vaccines, we used vaccine-type and cross-protective vaccine efficacy values based on a comprehensive review of the literature.

Results: Under base-case assumptions (coverage=80%, vaccine duration=20 years), vaccinating with the bivalent/quadrivalent/nonavalent HPV vaccine in Canada is predicted to reduce the incidence of vulvar-vaginal, anal, penile and oropharyngeal cancers by 50/48/51%, 51/51/53%, 29/28/29%, and 34/34/34%, respectively (70 year post-vaccination). The US population-level reductions in HPV-related cancer incidence are predicted to be smaller than in Canada given lower vaccination coverage.

Conclusions: HPV vaccination is expected to substantially reduce the burden of non-cervical HPV-related cancers. However, given that HPV16/18 are present in more than 90% of HPV+ non-cervical cancers, there is little difference between the 3 vaccines when assuming similar durations of protection and using the cross-protective efficacy found in the literature.

MSS 1-1

DO THE CURRENT CRITERIA FOR THE RECOMMENDATION OF NEW HPV TESTS FOR CERVICAL CANCER SCREENING NEED TO BE REFINED?

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Emerging results of a number of randomized controlled trials (RCT) indicate that HPV testing is more sensitive than cytology and could be used effectively in primary screening of women aged over 30 years. HPV testing has a lower specificity for the detection of CIN 3+ lesions than cervical cytology, but is much better reproducible. To be introduced into primary screening for cervical cancer HPV tests have to fulfill certain criteria, some of which have been generally accepted. According to those, the HPV test must be able to identify all 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 81, 52, 56, 58, 59, and 68) that have been classified as class I or class II carcinogens by the IARC. The clinical sensitivity and specificity of an HPV test for the detection of CIN 2+ needs to be at least 90% and 98%, respectively, of already established and validated HPV tests (e.g.HC2) measured in samples from a routine screening population of women aged 30 years and older. In addition, the intra- and inter-reproducibility agreement of the test in question must be high compared to an established and validated HPV test. Recent publications have demonstrated however, that tests which fulfill those criteria show an unacceptably high positivity rate in women with normal cytology, which would lead to an unnecessarily high referral rate. Therefore the additional criterion should be included that the positivity rate of an HPV test in women of a routine screening population with normal cytology shall not be higher than that of an established and validated HPV test. HPV tests which do not comply with these criteria including those approved by the FDA, should not be applied in primary screening for cervical cancer. HPV testing is made far more feasible by liquid based cytology and testing for HPV has become possible on a mass scale with the availability of quality-assured kit tests, while the usage of homebrew HPV tests with insufficient quality controls should be discouraged. It is necessary that all HPV tests applied in primary screening need to be performed according to the manufacturer instructions and according to validated standard operating procedures. Lastly HPV tests implemented in primary screening need to be automated to a certain amount to avoid the risk of contamination or mistakes introduced by manual handling of the samples. Due to the particular importance of HPV16, genotyping will add specificity to the result as women with a positive test result for HPV16 have a higher likelihood for prevalent CIN3 than women with e.g. HPV51. Therefore genotyping should be part of primary screening with HPV testing. Data from randomized controlled trials indicate that a negative HPV test provides the same degree of protection over two screening rounds than negative cytology for one screening round. This suggests that with primary HPV screening, screening rounds can be extended. HPV-based primary screening requires adequate triage options for the management of HPV-positive women and should be implemented and monitored within the program based on controlled demonstration projects. As this creates increasingly complex screening algorithms than those currently practiced, HPV testing should ideally be implemented in the context of organized screening to ensure adequate follow-up strategies of positive test results

MSS 1-2

INTRODUCING HPV TESTING INTO PRIMARY SCREENING: COTESTING VS PRIMARY STAND ALONE HPV TESTING

Lawson H

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Objectives: Describe background and rationale for changing methods and timing of cervical cancer screening based on better risk assessment, improved technology and advances in molecular science.

Methods: In 2011, we evaluated randomized clinical trial and population based observational data to facilitate estimation of risk, set benchmarks and develop algorithms for cervical cancer screening and management of abnormal cytology and diagnosed precursor disease. Evaluation of using primary HPV testing for screening was considered, but evidence for its use was lacking at the time. In 2013, an interim guidance panel sponsored by US professional societies was convened to review a growing body of published evidence about primary HPV screening and the application for FDA approval of a HPV assay for this indication. The panel's challenge was to evaluate evidence; address specific questions and concerns about using a HPV test for primary screening, develop interim recommendations for using primary HPV testing and consider how to integrate this method with recently published screening and management guidelines.

Results/Conclusions: While strong evidence exists to recommend cytology screening only for women ages 21-64 on a triennial basis if the test is negative, and cytology and HPV cotesting for women 30-64 every 5 years if both results are negative, clinical trial data from Europe and now the US show that primary HPV testing on a triennial basis, beginning at age 25, is both safe and effective and offers high sensitivity for early identification of women at greatest risk for progressive precursor disease and invasive cervical cancer. Nevertheless, test specificity is still lacking and so the risk of potential harms to many women with false positive testing, who require follow up, exists. Yet to be answered are many questions of triage and appropriate management of women with positive HPV results, age to begin screening, frequency of screening if results are negative, and how to integrate primary HPV screening with existing evidence based guidelines for cytology alone and cytology/HPV cotesting.

MSS 1-3

THE ROLE OF TYPING IN HPV TESTING

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HPV testing is more sensitive than cytology and has the advantage of being fully objective. However it is less specific, esp for younger women, so that if HPV testing is used as the primary screening modality, some sort of triage test is necessary to avoid excessive referral to colposcopy. At the moment reflex cytology is the most studied approach and when LSIL or higher results are obtained this can identify women at sufficiently high risk to warrant colposcopy. However there is still an appreciable amount of CIN2+ in women with normal or ASCUS cytology and additional triage is needed for these women. It has become clear form recent studies that the positive predictive value (PPV) for CIN2+ of different HPV types is very different,and this suggests typing may be a useful triage tool. Several tests now provide results for HPV type 16 and 18 separately and HPV 16 positivity indicates substantially greater risk than consensus high risk positivity, and esp for women over age 30-35y, it provides a basis for immediate colposcopic referral.

HPV 18 positivity is more problematic, as most studies indicate the cross-sectional PPV is similar to that for other high risk types, and it may not justify immediate colposcopy. It is suggestive of disease higher in the endocervical canal, and when found to be present on two consecutive tests more than 6 months apart is grounds for colposcopy and full evaluation of the endocervical canal by curettage, and careful surveillance. Similar management for HPV 45 may also be appropriate, but it is much less common and its significance is less well characterized.

It has recently become apparent that HPV 33, although much less prevalent than HPV16, carries a similar PPV when present, and it may be appropriate to manage women carrying it similarly, although it is not routinely assayed by any of the well-studied HPV screening tests. Additionally, of the remaining high risk types there is a clear difference in PPV and they should probably be separated into 'high risk' and 'intermediate risk'. Based on a recently study in women referred for colposcopy we have proposed a three level classification – very high risk (types 16 and 33) , high risk (types 18,31,35,51,52,58) and intermediate risk (39,45,56,59, 66,68). Some upgrading of types 18 and 45 may be useful in view of their predilection for endocervical lesions, but this probably should require evidence for persistence.

Further work is necessary, esp in a screening context, to confirm the validity of this classification and to determine how it should influence management

MSS 1-4

AGES FOR HPV SCREENING: WHEN TO START, WHEN TO STOP

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There is broad consensus to the notion that molecular HPV testing should not be used to screen for cervical cancer in women younger than 25 years of age. In fact, implementation of HPV testing in screening, whether as primary test or concomitantly (cotest) with cytology tend to apply to women aged 30 years and older. The reason, broadly accepted, is the fact that cervical HPV infection is very common soon after the onset of sexual activity. The vast majority of these infections will be transient with little to no consequence in terms of cervical carcinogenesis. Testing at younger ages will inevitably have unacceptably low positive predictive value and the attendant costs of referring large numbers of women for triage or diagnostic tests will be more than what most jurisdictions will be willing to pay. Moreover, aggressive lesion management among young women carries reproductive health risks that must be taken into account.

The 2012 professional guidelines adopted by multiple professional societies reached a consensus that for average (or low) risk women HPV testing should begin at age 30, be done not more frequently than every 5 years, and end at age 65. The decision concerning the age when screening must stop is based on comparable considerations of the balance of benefits to harm and cost to patients, providers, and society.

Age-related decisions in designing screening recommendations are not based on level-1 evidence from randomized controlled trials. They will likely remain based on observational data in the future when guidelines will have to be revisited because of the reduction on the prevalence of HPV infection and cervical lesions caused by broad coverage of HPV vaccination. If new generations of HPV vaccines continue to exceed in efficacy the ones that are currently available and vaccination uptake continues to be high, the day will come in a few decades from now when as a society we may have to decide to stop screening for cervical cancer altogether.

MSS 1-5

WHAT TO DO IF HPV NEGATIVE? INTERVAL OF SCREENING

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The interval of screening is determined by the duration of low risk for test-negative women ("duration of the protective effect"). Different countries have made different decisions regarding what constitutes an acceptable cancer risk in relation to the resources available and the screening intervals used for cytology-based screening therefore vary. In the European Union, screening intervals of 3-5 years are recommended. Studies investigating the CIN3 risk among test-negative women have found that a negative HPV test provides an approximately twice as long protection as a negative cytology. During the last year, 2 additional important pieces of evidence have become available. Long-term follow-up of the Swedish randomized primary HPV screening trial Swedescreen have found that this rule holds true also on very long-term follow-up, even up to 14 years. For example the 5-year risk after a negative cytology is about the same as the 10-year risk after a negative HPV test. Also, results from a pooled joint follow-up of randomized clinical trials in Italy, Sweden, UK and the Netherlands have found a similarly increased duration of the protective effect also when considering invasive cervical cancer. However, it should be emphasized that it is by no means a given that the aim of the program should be to keep the cancer risks at the same low level as with a cytology-based screening program. An alternative strategy could be to screen with HPV at about the same or marginally increased intervals in order to obtain an even better protection against cervical cancer. The optimal choice of the interval will thus depend on a balance of the available resources and the weight given to maximal cancer protection and avoidance of side effects of screening.

MSS 2-1

HPV VACCINE UPTAKE IN THE WORLD

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Objectives
Present an overview of the uptake of HPV vaccines in the world

Methods
Based on the data obtained through the global WHO/UNICEF Joint Report Form monitoring system and empirical data from the GAVI HPV vaccine demonstration programme review trends in the uptake of HPV vaccines in the world

Results
Since 2009, WHO has recommended that HPV vaccination be introduced into national immunization programmes where prevention of cervical cancer is a public health priority, and it is programmatically feasible and financially sustainable. Targeting 9-13 year old girls with a currently recommended 2-dose schedule, HPV vaccination should be part of a comprehensive approach to cancer control (education, vaccination, screening, treatment, palliative care). Globally more than 50 countries have introduced HPV vaccine into their national immunization schedule. In addition, more than 20 low income countries have started to implement GAVI supported HPV vaccination demonstration programmes at sub national level. In developing countries HPV vaccination poses particular challenges in terms of strategies to reach the target group, cost, sustainability, and communication. At the same time HPV vaccination provides promising opportunities to integrate with other adolescent health services.

Conclusions
In spite of several barriers that make HPV vaccination challenging to implement (price, target audience and strategies, communication) the HPV vaccine is one of the new vaccines being introduced most rapidly beyond industrialized rich countries.

MSS 2-2

MONITORING IMPACT IN POPULATION

K. Soldan, D. Mesher, S. Beddows, K. Panwar, N.Gill

Objectives: Anonymised collection and testing of residual genital specimens from females undergoing chlamydia screening allows us to monitor the early impact of the high-coverage of HPV immunisation achieved in England on type-specific HPV infection prevalence in the young, sexually-active female population.

Methods: Residual vulva-vaginal swab (VVS) specimens have been collected from laboratories around England in 2008 (pre-vaccination) and since 2010 (post-vaccination) and linked to reported demographic and sexual behaviour data. Specimens are tested for type-specific HPV DNA. Analyses have been conducted on 2,369 pre-immunisation and 4,178 post-immunisation specimens.

Results: The post-immunisation prevalence of HPV16 and/or HPV18 infection was lowest in 16–18 year olds and increased with increasing age. This increase with age was a reversal of the pattern seen pre-immunisation and was inversely associated with estimates of age-specific immunisation coverage (65% for 16–18 year olds). The prevalence of HPV16/18 infection post-immunisation was 6.5% amongst 16–18year olds, compared to 19.1% pre-immunisation.

Conclusions: The reductions in HPV16/18 seen in England suggest, for the estimated coverage, high vaccine effectiveness and some herd-protection benefits. Continued surveillance is needed to determine the effects of immunisation on non-vaccine HPV types. The impact of immunisation on cervical abnormalities and cancers in young females will be the next key population-level outcome to monitor.

MSS 2-4

CHANGES IN DISEASE PREVALENCE IN VACCINATED WOMEN – GENITAL WARTS

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Genital warts are the first clinical endpoint to study when investigating HPV vaccine effectiveness of the quadrivalent vaccine. Several countries, such as Australia, Sweden, Denmark, USA and Germany, have been able to demonstrate a substantial decline in genital warts incidence or prevalence already five years after introduction of the quadrivalent HPV vaccine. Genital warts prevalence in e.g. Australia fell with 93% in women below 21 years after introduction of the HPV vaccine.

A few countries were also been able to study HPV vaccine effectiveness against genital warts utilizing individual data, linking HPV vaccination status to disease outcome, and also assessed dose effectiveness of the HPV vaccine. Vaccine effectiveness of 76% has been demonstrated in Sweden among girls vaccinated before age 20 and even higher (93%) if vaccinated before the age of 14 years.
Continuous monitoring of long-term protection is needed for protection against genital warts in addition to other endpoints such as CIN and cervical cancer. Further, most of the available data so far are based on a 3-dose schedule with the quadrivalent HPV vaccine. Therefore, changes in disease prevalence in girls and women vaccinated with 2 doses need to be studied as well. Of special importance is to monitor timing between doses for women with only 2 doses of the HPV vaccine in 3-dose vaccination programs.

This presentation will display the most recent data available on genital wart prevalence and incidence following HPV vaccination.

MSS 2-5

CHANGES IN DISEASE PREVALENCE IN VACCINATED WOMEN: CERVICAL DISEASES

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National HPV Vaccination Program Register, VCS, East Melbourne, Australia

Objective: To review the changes in rates of high-grade cervical disease in Australia since implementation of quadrivalent HPV vaccination for women aged 12- 26 years in 2007.

Methods: Rates of cervical abnormalities per 1,000 women screened, by age group and over time, can be estimated by Australia's population based cervical screening registers.

Results: By the end of 2009, data from the Victorian Cervical Cytology Registry demonstrated declining rates of histologically confirmed high grade cervical lesions amongst very young women (<18 years of age) (from 8.5 per 1,000 in 2006 to 2.2 in 2009; p=0.003). Since that time declines have continued, with pronounced declines in high grade abnormality rates occurring in women <20 years of age (from 10.9 per 1000 in 2006 to 5.0 in 2013 (p<0.0001) and in those aged 20-24 years (from their peak rate in 2008 at 21.5 per 1,000 to 13.5 per 1,000 in 2013 (p<0.0001). Similar declines in the same age groups have been seen in national cervical screening data. Whilst registry data is ecological in nature, two data linkage projects have linked vaccination registry data with screening registry data and demonstrated that vaccinated women have lower rates of high grade and low grade abnormalities than unvaccinated women.

Conclusions: HPV vaccination has changed the epidemiology of high-grade cervical disease in Australia. Rates of high grade abnormalities are no longer highest in 20-24 year olds, but now peak in the 25-29 year old age group.

MSS 2-7

IMPACT OF VACCINATION ON JUVENILE ONSET RECURRENT RESPIRATORY PAPILLOMATOSIS – SURVEILLANCE IN CANADA

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Objectives: To monitor the incidence and prevalence of juvenile onset recurrent respiratory papillomatosis (JoRRP) in Canada following the introduction of provincial HPV vaccination programs in 2007.

Methods: This is a retrospective, multicenter study. Cases were reported to the national database from 11 pediatric academic health centers across Canada. Trends in incidence and prevalence of JoRRP from 2008 to 2012 were calculated at a national and regional level using the national database and Canadian census data.

Results: The mean incidence of JoRRP in children 14 years of age and younger between 2008 and 2012 was 0.168 per 100,000 children. The prevalence was 0.778 per 100,000 children. These values have decreased from the mean reported incidence and prevalence rates from 1994-2007.

Conclusions: An earlier than expected decrease in the incidence and prevalence of JoRRP has been detected at the national level. Further surveillance is required to determine if the observed trend is the result of HPV vaccination programs or a short-term temporal variation in disease burden.

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MSS 2-8

LONG-TERM EFFICACY OF HPV VACCINATION AGAINST HARD ENDPOINTS

J Paavonen[1], **M Rana**[2], **D Apter**[3], **T Eriksson**[2], **K Natunen**[2], **J Palmroth**[2], **T Petäjä**[2], **E Pukkala**[2], **J Dillner**[4], **M Lehtinen**[2,4]
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Vaccination against oncogenic HPV types has been implemented in many countries. Due to long lag time between HPV infection and cancer development, efficacy data from the vaccination programmes will emerge slowly. We now report on 85,000 follow-up years of cancer registry-based passive surveillance of unvaccinated and HPV vaccinated women cohorts. In May-July 2003 and 2005, 6,486 and 9,258 young women from Finland formed a cohort of unvaccinated women. In August 2002-April 2005, 874 and 875 young women from Finland were enrolled in a phase III (FUTURE) trial and vaccinated with the quadrivalent vaccine or placebo. In May 2004-April 2005, 2,408 and 2,399 young women from Finland were enrolled in another phase III (PATRICIA) trial and vaccinated with the bivalent vaccine or hepatitis A-virus (HAV) vaccine. 4-year cancer registry follow-up was established in November 2007 and 2009, respectively, 6 months after the active follow-up had been closed. Follow-up of the unvaccinated cohort was also 4 years. We identified 63 cases of CIN grade 3 (CIN3) and 3 cases of invasive cervical cancer (ICC) in the unvaccinated cohort, and 3 CIN3 cases in the placebo-vaccinated cohort and 4 CIN3 cases in the HAV-vaccinated cohort. The corresponding CIN3 incidence rates were 105, 88 and 42 per 100 000 women years with overlapping 95% confidence intervals. However, long-term follow-up by cancer registry continues. This will soon deliver real-life vaccine efficacy estimates against ICC.

MSS 3-1

BEING VICTIMS OF OUR OWN SUCCESS: FUNDING DECREASES FOR CERVICAL CANCER CONTROL

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Cervical cancer prevention and control has been a unique example of accelerated knowledge translation from the scientific discoveries concerning the cause of cervical cancer (HPV infection) and interventions based on that cause (vaccination and molecular technologies in screening). No other paradigm of cancer control and prevention has advanced to measurable benefit in so little time. Much of the research that led to these advances happened during the last three decades, at a time when governmental funding agencies and cancer charities saw their budgets being reduced because of the threat of AIDS, which emerged in the early 80's requiring substantial investments in research. Although anecdotal, there is general perception that funding for HPV and cervical cancer research, whether basic or applied, has gradually declined in the last decade. Although agencies do not specifically prescribe disease-specific budget compartments for investigator-initiated grants, requests for proposals tend to reflect political decisions and the general perception by donors that research on some cancers should be considered priority. Funding mechanisms for breast and prostate cancer research tend to be more prominent in agencies' portfolios. Is funding decreasing for HPV and cervical cancer research? Are agencies and review panels favoring a more comprehensive view of HPV-related diseases when making funding decisions? Should our research community develop an activist's role in lobbying for more research funds for basic and applied HPV prevention research?

MSS 3-2

THE NIH PEER REVIEW PROCESS

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The purpose of the presentation will be to provide an overview of the peer review process at the National Institutes of Health (NIH). NIH is the largest supporter of biomedical and behavioral research in the world. In a typical year researchers submit about 80,000 grant applications of various kinds seeking support for fellowships, program projects, research resources centers, training programs, small businesses, and individual investigator research. The talk will aim to help investigators understand what happens to their research grant application after it has been submitted.

The NIH is a plural organization composed of 27 distinct institutes and centers, or ICs. Twenty-four of these fund research in their respective health related fields. The Center for Scientific Review (CSR) is a non-funding center at NIH and is the point of intake for NIH grant applications. It is also where 70% of the applications are reviewed initially. The 24 funding ICs of the NIH are essentially clients of CSR and use the results of its merit evaluations of applications as part of their deliberations on funding.

The objective of the presentation will be to provide an overview of the process by which a grant first comes into the NIH, through to the point of the final decisions of the funding Institutes on allocation of support.

MSS 3-3

THE AGENDA OF AGENCIES AND CHARITY ORGANIZATIONS

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The World Health Organization recognizes and recommends that a comprehensive approach to cervical cancer prevention is required in order for significant reductions in morbidity and mortality to be realized. High income developed countries have been successful in reducing cervical cancer deaths through intensive screening programs, early treatment, and quality care. However, these programs were costly to establish and require significant resources to maintain. In developing countries, where more than 85% of all cervical cancer occurs, the establishment of similar screening programs has been challenged by lack of financial and human resources, constrained health systems, weak or absent cytopathology capacity, inadequate treatment, and fragmented political will. However, HPV vaccine has catalyzed a new conversation with donors and foreign governments to provide cervical cancer prevention to adult women as the vaccine is providing to young adolescent girls. This presentation will summarize country experience in leveraging HPV vaccine for expanded options and new investments in cervical cancer screening. It will provide illustrations of how NGOs and advocacy groups have worked with country stakeholders and government leaders to foster this new dialogue and reposition the importance of cervical cancer prevention in country health priorities. The talk will conclude with a brief summary of newly funded cervical cancer prevention initiatives that have resulted from these global advocacy efforts.

MSS 4-1

METHODS OF TRIAGE OF HPV-POSITIVE WOMEN: CYTOLOGY

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The large number of HPV-positive women implies that HPV-based screening is preferably complemented with a triage method in order to avoid unnecessary treatments and side effects. Cytology has the obvious advantage that the method is validated by many studies all over the world for half a century and that the clinical management algorithms on how to deal with different types of cytological abnormalities is already well worked out. The classical criteria for evaluating new screening programs do postulate that the management of the test positive should be known – this is the case if cytology is used for the triaging.

The question on how to manage HPV+/Cyt- women is more uncertain, but as different randomized trials of primary HPV screening that have used somewhat different management algoritms have not found significantly different results, it appears that the different effects of the different managements are small and that the most conservative management should be chosen in order to save resources and avoid side effects of screening. The joint follow-up of the HPV screening trials in Italy, Sweden, UK and the Netherlands have found that the risk for invasive cervical cancer is similarly low for 3 years both for all HPV-negative women and for all cytology-negative women. Provided that the HPV+/Cyt- women are not lost to follow-up, there is no evidence (using invasive cancer as endpoint) to suggest that they would benefit from a repeat screen at a shorter interval than 3 years.

MSS 4-3

METHODS OF TRIAGE OF HPV+ WOMEN BY DNA METHYLATION AND p16 RNA

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Objectives: An active search continues for accurate molecular tests to triage high risk HPV (hrHPV) positive women so that those who need colposcopy can be correctly identified. Two new molecular triage methods are based on 1) quantitative measurement of DNA methylation in human and or hrHPV genes, and 2) testing for mRNA expression of the CDKN2A gene (codes for the p16 protein). These two assays may be combined to produce a potentially superior classifier. An evaluation of the new methods is needed to better inform future triage algorithms.

Methods: A literature review and laboratory experimentation employing quantitative DNA methylation assay and RT-PCR assays for p16 RNA were done on a large number of specimens from several major clinical studies. The current status and prospects for DNA methylation and p16 RNA assays as clinically useful triage tests for hrHPV+ women were explored.

Conclusions: Methylation was substantially and significantly higher in cancers than in CIN2/3, which were in turn consistently more methylated than CIN1 or normal women in six studies from Costa Rica, Mexico, Canada, Wales and England combined, with a total of more than 2500 women tested ($p<0.0001$). A new triage classifier named S5 (based on EPB41L3, HPV16, HPV18, HPV31 and HPV33) was developed and applied to 1493 hrHPV+ women attending colposcopy in London England. S5 produced an area under the curve (AUC) of 0.82 (95%CI 0.80–0.84), with a specificity of 50% (47–53%) and a PPV of 52% (49–54%) at 90% sensitivity. S5 was also validated using a sample of 693 hrHPV+ women from a UK screening study ($n=6000$) with an AUC of 0.80 (0.71–0.88). Preliminary evaluation of a p16 RNA test in 100 specimens from a London colposcopy clinic showed modest triage results with an AUC of 0.75 (0.65–0.84) for classifying normal/CIN1 versus CIN2+. The p16 RNA test added significantly to S5 ($p=0.01$) with a combined AUC of 0.88 (0.80–0.95). In summary our new S5 molecular triage test for hrHPV+ women appears to meet initial reasonable requirements for clinical utility and may be improvable by methylation measurement of other hrHPV types. S5 could perhaps be further improved by addition of a test for p16 RNA.

MSS 4-4

P16/KI-67 FOR TRIAGE OF HPV-POSITIVE WOMEN

Nicolas Wentzensen

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HPV-based cervical cancer screening requires triage markers to decide who should be referred to colposcopy. One candidate triage marker is detection of p16/Ki-67-stained cells in cytology (dual stain). The dual stain has been evaluated for triage of ASC-US and LSIL cytology, for primary screening, and more recently for triage of HPV-positive and HPV-positive/cytology-negative women. The dual stain assay is very reproducible after limited training and can be evaluated automatically. In an evaluation of the dual stain among women undergoing HPV-cytology co-testing at Kaiser Permanente Northern California, dual stain-positive women had a risk of precancer higher than the colposcopy referral threshold in this population while the risk among dual stain-negatives was below the threshold for a 1-year repeat test. Similar results were observed for HPV-positive/cytology-negative women in the same population. In an evaluation of the dual stain assay in the Costa Rica Vaccine Trial, the assay performed well among vaccinated women, with equal sensitivity but higher specificity compared to unvaccinated women. These findings suggest that the dual stain may be an effective triage strategy for HPV-positive and HPV-positive/cytology-negative women.

MSS 4-5

TRIAGE OF HPV+ WOMEN: COMBINATION STRATEGIES TO OPTIMIZE COLOPSCOPIC YIELD

Stoler M

University of Virginia Health System

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Objectives: Cervical neoplasia screening guidelines have been crafted to reduce patient risk for developing cancer by optimizing triage to and detection of treatable precancer. The principle of equal management for equal risk permeates US guidelines. In contemporary studies it is clear that High Risk HPV status defines the majority of a patient's risk for CIN3+. But given that risk and the impracticality of referring all HPV + women, how can one triage these patient to maximize yield at coloposcopy? The readily available datapoints for triage are the age of the patient, HPV genotype, Pap cytology or potentially another biomarker like p16/ki-67 dual stain cytology. Triage of HPV positive women with cytology and / or genotyping are the currently recommended methods for focusing attention on the subset of screen positive women that need colposcopic referral as opposed to noninvasive follow-up. But what is the optimal combination and sequence of testing. Can we achieve equivalent triage efficiency with different combinations of tests and if so how does one choose? Here we will present data on the interplay between age, cytology, HPV genotype status and dual stain status at stratifying risk for colposcopic referral of HPV positive women.

Methods and results: When HPV testing is used for primary screening, what is the risk of CIN3+ in women that are HR HPV positive. Given that risk what is the most efficient algorithm for using genotyping vs. cytology vs. a biomarker or all three? Does one test suffice or do we need multiple? Do we proceed sequentially or do we apply tests concurrently? The data presented will demonstrate the boundaries of the CIN3 + risk envelope and how that defines the yield of disease per colposcopy. The residual risk after colposcopy, which is not necessarily a gold standard will also be considered.

Conclusions: High Risk HPV status defines the majority of a patient's risk for CIN3+. Genotyping helps stratify that risk, perhaps more reliably than cytology but biomarkers like p16/ki-67 dual staining may present more efficient strategies for triage. However, there will always be imperfection and residual risk and balancing those risks may well drive triage test approaches.

MSS 5-2

INTRODUCTION OF PRIMARY HPV SCREENING IN ORGANIZED SCREENING PROGRAMS

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Already in 2008, primary HPV screening was recommended as an alternative to cytology-based screening if introduced into an organised, population-based cervical screening program in a controlled manner that allows stringent evaluation. The most stringent controlled and evaluable way to introduce a new policy is by means of a Randomized Healthcare Policy (RHP). We introduced primary HPV-based screening in Sweden as an RHP. In the organised program, all resident women are invited by letter to an appointment for cervical screening. In the RHP, the resident women are randomised 1:1 to either be invited to HPV testing or to cytology. . In the HPV screening arm (new policy), women were invited to HPV-screening with triaging by cytology. Among the 50% of resident women who are randomised to be invited to the old policy, there is primary cytology with HPV triaging for ASCUS and LSIL smears. HPV+/Cyt- women in the screening ages are referred to the next round of organised screening, whereas HPV+/Cyt- women aged 60 (who otherwise would have been acquitted from the programme) will continue to be screened. The primary evaluation is the sensitivity for CIN2+ detection and cost-effectiveness of the new policy in relation to the previously used policy.

So far, primary HPV screening was acceptable to the population, resulted in similar attendance rates, reduced the screening costs and there was also a tendency towards increased sensitivity for CIN2+. The results of the RHP thus supports continued implementation of HPV-based screening.

MSS 5-4

IMPLEMENTATION OF SCREENING: ITALY

Guglielmo Ronco

CPO Piemonte, Turin, Italy

In Italy, organised screening for cervical cancer covers 78% of the female population. A large multicentre RCT on HPV screening started in 2002. Following its results, several demonstration projects (randomised in 3 centres), aiming at evaluating feasibility, organizational impact, acceptability, and cost, were initiated. In 2012 a Health Technology report concluded that HPV-based screening, if appropriately performed, was more protective than cytological screening, with no substantial increase of undesired effects. Based on the data of pilot projects the report also estimated that, given prolonged screening intervals, the overall cost of screening women were lower with HPV than with cytology. Recommendations on protocols to be applied (start at age 30-35 years, 5-year intervals, stand alone HPV with validated tests and cytological triage), and on organisation (e.g centralisation of HPV testing), training of staff and communication to women were also given. In 2013 the Ministry of Health adopted such recommendations. HPV screening implementation, so as cytological screening, is monitored by annual surveys of performance indicators. In 2013 five Regions had officially decided to fully convert to HPV-based screening and prepared detailed transition projects. In 2012, 19 local programmes based on HPV were active and invited 311,840 women. Compliance to invitation was in general higher with HPV than with cytology. Protocols are highly applied, thanks also to the use of computerised systems. High variability in the proportion of HPV positive women judged to have cytological abnormalities was observed. However, in most cases, such proportion had an immediate increase but decreased after feedback of results.

MSS 5-5

IMPLEMENTATION OF HPV SCREENING IN GERMANY

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In 1971 opportunistic screening for cervical cancer was established in Germany with yearly Pap smears starting at 20 years (no upper age limit). This led to a reduction of cervical cancer incidence by about 60 – 70%. There are several disadvantages of the programme: no screening register, no information about participation rates, no standardized triage system, no standardized quality control. The yearly participation rate calculated from health insurance data is only ~45% but 65 -80% have at least one smear in a three-year period. In 2008, the Federal Ministry of Health launched the "Nationaler Krebsplan" and the Law on Cancer Screening and Registration (KFRG) was passed by the German government in 2013: organized population-based screening with invitations, adapted screening intervals and optimized quality assurance. A S3 guideline is currently developed based on current evidence of cervical cancer screening. In 2012, 21 scientific and professional societies joined the guideline group, financially supported by German Cancer Aid under guidance of the German Guideline Program in Oncology and the Association of Scientific Medical Societies (AWMF). One key question is the role of HPV testing in cervical screening. The Federal Joint Committee (G-BA) asked the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefits of an HPV test in primary screening. In 2014, IQWiG found an indication that HPV based testing leads to a reduction of CIN 3+ and invasive cervical cancer, however, no general recommendation for the G-BA was made which has to decide in 2015.

MSS 5-6

IMPLEMENTATION OF HUMAN PAPILLOMAVIRUS (HPV) SCREENING: NATIONAL VERSUS REGIONAL PROJECTS

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SUBDIRECCIÓN DE PROMOCIÓN DE LA SALUD Y PREVENCIÓN. CONSEJERÍA DE SANIDAD. COMUNIDAD DE MADRID. SPAIN.

Cervical cancer is one of the most important health problem in women over the word with nearly 500.000 new cases each year. Cervical cancer incidence is closely related to the level of development: while in developing countries is the second cancer (after breast cancer), in developed countries cervical cancer rates have dramatically decreased since the late 1980s.

Spanish cervical cancer incidence and mortality are estimated to be between the lowest in Europe: 7,6 new cases/100.000 population/year, with around 2.100 new cases diagnosed each year (3,3% of female cancer). Most of the cases are diagnosed in women between 35-50 years old. Primary prevention by prophylactic vaccination against the human HPV, from 2008, will change Spanish cervical cancer epidemiology in the next years.

The decrease in cervical cancer incidence follows the introduction of cervical screening programs. All Spanish Autonomous Communities currently offer cervical cancer screening to women, but in most of them it is an opportunistic screening, which take place in clinical setting and depends of the initiative of the individual woman or her doctor. Cervical cytology in the cornerstone of cervical cancer prevention programmes according to the Recommendations of the Spanish National Health System Cancer Strategy. The introduction of test systems to detect nucleic acids of oncogenic HPV is variable.

Opportunistic screening is less effective than population-based programmes and results in inequality because it is characterized by low coverage in some population groups with low socioeconomic status which increased risk for cervical cancer, coexisting with high covered in selected parts of the population which are screened too frequently which increased risk for adverse events.

Cervical cancer screening should be provided in organized, population-based programmes with information systems and quality assurance at all levels in order to maximize effectiveness, efficiency, equality and to permit evaluation. The success of the programme requires adequate communication with health professionals and women. All this applies particularly when HPV testing is included in screening due to the detection of HPV nucleic acids thus carries a risk of unnecessary colposcopies, psychological distress and possibly of overdiagnosis. Piloting with human HPV testing could be recommended if performed in an organized screening programme with careful monitoring of the quality and systematic evaluation of the aimed outcomes, adverse effects and cost.

MSS 5-7

MOVING FROM CYTOLOGY BASED SCREENING TO PRIMARY HPV TESTING IN THE US: TRIALS, TRIBULATIONS AND CONFUSION.

Lawson H

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Objectives: Describe the process of integrating primary HPV screening into a complicated web of published cervical cancer screening and management guidelines, while facing provider and patient resistance and confusion.

Methods: We used existing published information on risk based cervical cancer screening and management as the basis for developing interim guidance for primary HPV testing for cervical cancer screening. We also analyzed results from the ATHENA trial, conducted in the US, and used as part of an application for FDA approval of the cobas HPV test for primary cervical cancer screening.

Results/Conclusions: In 2011, the American Cancer Society, ASCCP, and the American Society for Clinical Pathology convened a global group of stakeholder organizations to participate in a process to update cervical cancer screening guidelines. One major component of that process was to consider primary HPV testing alone in the US for cervical cancer screening. At that time, there was little US-based evidence available, and while promising evidence was growing elsewhere, there was no consensus among participants for recommending primary HPV testing for screening. Nevertheless, the window was left open for pilot programs to test the effectiveness of the method. In April, 2014, the FDA approved the cobas HPV assay for this indication based on ATHENA trial data analyses showing it to be safe and effective. Some limitations of the clinical trial design and follow up led to a proposed algorithm that conflicts with recently published guidelines for screening and management. To bridge this gap and create simple and straight forward guidance, a panel of thought leaders reviewed existing evidence and posed questions that needed answers if the two systems are to coexist for the time being and can eventually be integrated. This presentation will provide details of this activity and the methods used to reduce barriers and engage providers and the public in conversations to facilitate understanding the value of risk-based screening and management for cervical cancer precursors, and other HPV associated disorders.

MSS 6-1

HPV-BASED CERVICAL CANCER SCREENING IN NON-VACCINATED WOMEN

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Cytology has been the mainstay for cervical cancer screening for decades. Our now-remarkable understanding of HPV and cervical cancer natural history has brought new tools for cervical cancer prevention, including HPV testing for cervical cancer screening. Two variations of HPV-based screening are currently being used: HPV-cytology co-testing and HPV testing alone without cytology. Compared to cytology, HPV-based screening approaches have higher sensitivity and higher negative predictive value over an extended period of time. Therefore, screening intervals can be safely extended with equal or higher program safety of HPV-based screening compared to cytology. In different health care programs, screening intervals for HPV-negative women have been proposed to be at least 3-5 years. Importantly, all HPV-based screening approaches require additional triage tests to decide who among the HPV-positive women needs to go to colposcopy. Current triage options for HPV-cytology co-testing include HPV genotyping or repeat co-testing for HPV-positive/cytology-negative women. For HPV-testing alone, cytology and HPV genotyping have been proposed as triage tests. With many different options available now, risk assessment, in conjunction with risk modelling and comparative effectiveness research plays a central role in determining the optimal strategies for cervical cancer screening.

MSS 6-8

THE ERA OF IMMUNOTHERAPY – ARE WE THERE YET?

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Massachusetts General Hospital, Boston, MA

Human papillomavirus (HPV) is a common virus that causes a wide range of human diseases, including a growing subset of head and neck cancers. Significant progress has been made within the past decade in designing and implementing preventive vaccination programs against HPV. However, a variety of societal and economic challenges impede the implementation of these vaccination programs, and the burden of HPV and its related cancers will continue until these challenges are overcome. Given the viral etiology of these cancers and associated expression of foreign immunogenic antigens, alterations in host immune function are responsible for the development of these cancers. Therapeutic vaccines are a potentially important tool to treat those individuals already infected and/ or diagnosed with established HPV-related diseases. However, a different set of challenges is uncovered with therapeutic vaccines based the tumor microenvironment into which the vaccine-induced T cells are recruited. As the field of cancer immunology matures, the obstacles to achieving activated tumor specific immune responses are being revealed and strategies are being applied to overcome these barriers. The unharnessed potential of immunotherapy in treating virus-related cancers, undoubtedly, is coming of age.

MSS 6-9

HOW HPV KNOWLEDGE HAS CHANGED OUR PRACTICE: SCREENING AND MANAGEMENT OF NEOPLASTIC LESIONS

Carole Fakhry
Head and Neck Surgical Oncology
Johns Hopkins School of Medicine
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This talk will review the requirements for development of screening tests. These requirements will be discussed in the context of oropharyngeal cancer to highlight the challenges for screening.
The clinic-demographic and prognostic implications of HPV-positive oropharyngeal cancer will be reviewed. Therapeutic options and clinical trials as a result of our changing knowledge base will be discussed.

MSS 6-11

POSITIONING THE VALUE OF THE NEW HPV VACCINE

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The two currently available HPV vaccines are safe and highly efficacious against HPV types that cause the majority of cervical cancer cases globally. However, various vaccine candidates that offer improvements over existing vaccines may become available in the future. Funders of vaccination and research on vaccination will need to address key questions about the value of the benefits offered by potential vaccines in order to make appropriate investment decisions, including:

- How higher-valency vaccines should be valued compared to existing 2-valent and 4-valent vaccines.
- What value should be placed on potential benefits such as therapeutic efficacy, thermostability, expanded age indications, reduced doses and broad spectrum protection.
- How considerations such as price, ease of delivery, breadth of protection and duration of protection should be traded off.
- How these considerations vary in different income settings.

MSS 6-12

UTILITY OF CERVICAL CANCER SCREENING IN THE ERA OF MULTIVALENT AND THERAPEUTIC VACCINES

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Cervical cancer screening has been the mainstay of global cervical cancer prevention programs for decades. While cohorts of young women receiving the bivalent and quadrivalent HPV vaccines are anticipated to have a much lower risk of invasive cancer in their lifetimes, current guidelines recommend continued screening for maximal cervical cancer prevention due to the limited type-spectrum in the current vaccine formulations. However, fully vaccinated cohorts will see a decline in prevalence of treatable cervical precancers, lowering the positive predictive value of screening. This will result in the potential for increasing the relative harms of screening by increasing the proportion of false positive to true positive screens and an overall decrease in the efficiency of screening – an effect that will increase substantially with the introduction of a nonavalent HPV vaccine. In this roundtable discussion, we will discuss factors to consider in choosing whether, when, and how to screen vaccinated populations. Issues to consider in this decision making include the costs and availability of screening and vaccination in different contexts, ability to identify vaccinated from unvaccinated women, age recommendations for screening vaccinated populations, relative performance of alternative screening methods in vaccinated individuals, and impact of nonavalent or broad spectrum next generation prophylactic vaccination on the decision to screen. These discussions will be benchmarked against the longstanding decision to NOT screen for low incidence HPV-associated cancers of the vulva and vagina.

MSS 7-1

COMPARATIVE EFFECTIVENESS RESEARCH ON DIFFERENT HPV VACCINATION/SCREENING STRATEGIES

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Background: High-risk (hr) HPVs cause precancerous/cancerous lesions in the uterine cervix, and in other anogenital and oropharyngeal sites. Bivalent HPV16/18 vaccine is efficacious against the hrHPV associated precancer, but neither the magnitudes of different vaccination scenario-associated herd effects nor how to screen HPV-vaccinated females, are known. A two tired set of comparative effectiveness trials (CRT) assess difference in the herd effect gained from vaccinating girls and boys vs. girls only, and how to screen vaccinated females.

Methods: In school-years 2007-8 and 2008-9, we invited 80.500 1992-95 born adolescents to a CRT in 33 communities a priori stratified by low, intermediate and high HPV16/18 seroprevalence. In 11 Arm A communities 90% of participating girls and boys received HPV16/18 vaccine, in 11 Arm B communities 90% of girls received HPV16/18 vaccine - boys received hepatitis B-virus (HBV) vaccine, and in 11 Arm C communities all received HBV-vaccine. HrHPV prevalence in vaccinated and unvaccinated girls was studied at age 18.5 years.

Since 2014 the 20.500 -vaccinated 1992-95 born females vaccinated at the ages of 13-15 in the above-mentioned trial have been randomized/invited to attend cytological screening at: 22/25/30 years (A1); 25/30 years (A2); or 30 years (A3) of age.

Findings: Enrolment of the four birth cohorts comprising altogether 32.176 adolescents: 20.515 girls (51-53% response) and 11.661 boys (22-32%% response) was identical. At the age of 15 years >98% of the participants were living at the study site communities. Smoking habits and alcohol consumption were similar in the different trial arms, also neither mean-ages of menarche (12.4 years) and 1st ejaculation (12.6 years), nor sexual behaviour (among those <25%, who had had sexual debut) did differ by arm. By 2015 this CRT will enable verification of modelled predictions on the indirect effectiveness (17 to 31% herd effect) of vaccinating both girls and boys with the moderate vaccine coverages.

The screening arms A1 and A3 will include at least 7000 females yielding 80% power for the demonstration a non-inferior accuracy (sensitivity) of A3 vs A1 screening strategy in the HPV16/18 vaccinees. An interim analysis of A1 vs Arm A2 (interventions at the ages of 22/25 vs at the age of 25) in 2018 will guarantee safety of the infrequent screening. At the age of 30 years all participating females will be offered both cytological and HPV test results.

Interpretation: Uniform life-style and sexual behavior characteristics indicate successful enrolment of the CRT. Quantifying effectiveness of vaccination strategies/verifying mathematical models the CRT will guide how to implement HPV vaccination programs.

The main screening study deliverable will be effectiveness of delaying the initiation of infrequent screening in the vaccinated females to 30 years of age.

MSS 7-2

THE EFFICACY RATES AGAINST CIN 3 OBTAINED BY THE QUADRIVALENT AND THE BIVALENT VACCINE PHASE III TRIALS WERE NOT IDENTICAL- WHY?

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End of study analysis of the Phase III trials of prophylactic HPV VLP vaccines in young women have already been completed. Two distinct vaccines were evaluated, Gardasil®, a quadrivalent vaccine containing VLPs or HPV 6,11,16 and 18, and Cervarix®, a bivalent vaccine containing VLPs of HPV 16 and 18. Two Phase III studies, FUTURE I and FUTURE II evaluated Gardasil® and two Phase III studies, PATRICIA and the Costa Rica HPV vaccine trial (CVT) evaluated Cervarix®. All trials were large, double blinded, randomized and controlled among young women, age range 15-26. These Phase III trials were large enough so that the best surrogate marker for invasive survical cancer, CIN 3 could be included as the most important trial end point. Both vaccines demonstrated excellent safety and immunogenicity profiles, remarkably similar efficacy against vaccine type related CIN3 lesions in women naïve to the corresponding types at vaccination. Gardasil® also demonstrated strong protection against genital warts and VIN/VAIN lesions associated with the vaccine types. Although the vaccine efficacies were almost identical in the HPV naïve populations and in the intention to treat populations against HPV 16/18 related CIN 3, the vaccine efficacies against any CIN 3 were significantly higher by the bivalent vaccine than the quadrivalent vaccine, in both populations. This suggests that the bivalent vaccine is more efficacious against non-vaccine high risk HPV types. The question of different cross protective efficacy has been under debate, and has several potential explanations. First, the vaccines are not identical and differ in several aspects including not only valency but also dose, production system and most importantly, the adjuvant. Furthermore, the study protocols differed in many aspects. At baseline, the trial subpopulations were much the same in terms of age and lifetime number of sexual partners and were cytologically normal, seronegative for HPV 16 or 18, and HPV DNA negative against 14 HPV types. However, differences exist in subpopulations. Incidence of infections was higher in the control group in FUTURE than in PATRICIA. In the FUTURE, cervical and vulvar or perianal samples were tested for infection outcomes whereas cervical samples only were tested in PATRICIA. There may have been differences in HPV DNA assay sensitivities and specificities as well. In addition, the colposcopy algorithms for obtaining colposcopy biopsies were different. Also the histopathological endpoint definitions were not necessarily the same. Neither vaccine demonstrated therapeutic efficacy. However it is reassuring that the vaccines did not alter the course of already established HPV 16/18 infection or disease. More data of the duration of protection and long term efficacy are essential. Simply, the duration of protection has not yet been established although so far there are no signals of waning protection. In conclusion, most difference observed between the vaccine efficacies may be explained or be attributable to significant differences in trial designs.

MSS 7-3

SCREENING APPROACHES FOR VACCINATED POPULATION: COMPASS TRIAL

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Objectives: Australia introduced HPV vaccination in 2007, with catch-up to age 26 years and 3-dose coverage of 73% in females 12-13 years. A recent review recommended transition to primary HPV for cervical screening. Compass is a randomised controlled trial of primary HPV vs. cytology which will inform program transition in Australia.
Methods: In Compass Phase I we recruited 5000 female residents of Victoria, aged 25-64, attending for screening at one of 47 practices from October 2013-September 2014. Liquid-based cytology (LBC) samples were collected and women were randomised in a central laboratory in a 1:2:2 ratio to: 1) 3-yearly LBC screening; 2) 6-yearly HPV with referral of HPV16/18 to colposcopy, and cytology triage of other oncogenic types; and 3) 6-yearly HPV with referral of HPV16/18 and p16/Ki67 triage of other oncogenic types.
Results: In preliminary analysis of the first 3290 participants randomised to HPV screening we found that in older unvaccinated cohorts (currently 33+ years), positivity rates for HPV16/18 were 0.5%(95%CI:0.3-0.9%) and 3.0%(CI:2.4-3.7%) for other oncogenic HPV. In younger cohorts offered vaccination (<33 years), positivity rates were 0.9%(CI:0.3-1.9) for HPV16/18 and 13.6%(CI:11.1-16.3)% for other oncogenic HPV.
Conclusion: Screen-positive rates for HPV16/18 in women aged 25-33 years are low and comparable to those of older women. This suggests that primary HPV screening with partial HPV16/18 genotyping starting at age 25 years will not result in high colposcopy referral rates in this vaccinated population.

Disclosure: Compass is conducted and funded by the Victorian Cytology Service (VCS), a government-funded health promotion charity. The VCS have received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana Inc USA.

MSS 7-4

HOW TO INTEGRATE HPV VACCINATION PROGRAMS AND ORGANIZED SCREENING PROGRAMS

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Organized screening programs have decreased the incidence of cervical cancer by 80% in some countries, e.g. in Finland. Opportunistic screening alone does decrease the incidence also, but not as much. Organizing a program includes many aspects, like defining the target groups, using population or other registries for drawing and sending the invitations to women. The invitations should preferably also contain the place and time for the sample taking. In conclusion the coverage and attendance rate are crucial for the success of a screening program. The same applies to vaccination programs as well.
Presently there is good evidence that we should move to use HPV-test instead of cytology (Pap-test) in the screening programs. HPV-test is more sensitive and in older age groups also more specific compared to the cytology, the negative predictive value (NPV) is also significantly better. Thus we will be able to use longer screening intervals, possibly up to 7-10 years and still prevent additional cases.
When vaccinated age groups reach the first screening age, which should be 25-30 years according the EU-guidelines, we will notice a significant reduction of cervical high-grade abnormalities and CIN lesions and thus referrals to colposcopy. The number of low grade abnormalities do not decrease so much, because the causal proportion of HPV 16 and 18 is lower in those lesions. However, the PPV of cervical cytology will drop dramatically in vaccinated cohorts. By then latest, we have to use HPV-test in cervical cancer screening, because of its better sensitivity. It may be possible to further increase screening interval, if vaccination programs have been successful in reaching a high coverage and the number of severe lesions continue to decrease.
To integrate vaccination and screening optimally each country or region has to define the HPV disese burden locally, i.e. find out the prevalence of HPV and CIN in each age groups, use the data of the present screening and vaccination programs and disease management. Using this data and simulation with mathematic dynamic models it is possible to produce the best scenarios to reduce the HPV burden with optimal cost-efficiency. In Finland this method produced a model to integrate screening and vaccination program, where the incidence of cervical cancer will continue to decrease dramatically as well as the precancer treatments. On top of that the total costs will be only approximately half of the present ones.

MSS 7-5

ADDRESSING AN UNMET MEDICAL NEED USING A 9-VALENT VIRUS-LIKE PARTICLE (VLP)-BASED HPV VACCINE

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Objective: VLP-based type-specific immunity is the basis for high vaccine efficacy. VLPs are manufactured for specific HPV types and quality-controlled for potency. VLP type-specific immunity and protection has shown long-term protection in numerous studies. While cross-protection has been described following vaccination, long-term effectiveness data are sparse. Cross-protective antibodies generated by licensed HPV vaccines appear to be short-lived and directed at non-specific viral sites. This presentation compares and contrasts data from long-term HPV type-specific and cross-protective effectiveness.

Methods: Data from publications and clinical trial data repository sites were reviewed to assess durability of protection using type-specific VLPs and cross-protection.

Results: Data from 4 extension studies of the original clinical trials in Scandinavia and Latin America suggest that both of the currently licensed VLP-based vaccines retain high effectiveness against HPV persistent infection (PI) and disease for up to 8 years for the types included in the vaccine. Early 6-month PI efficacy against cross-protective types shows that efficacy is neither as high nor as consistent as the efficacy against VLP-based HPV16/18. Additionally, data on longer-term PI efficacy against cross-protective types show that that efficacy wanes at 6 years.

Conclusions: HPV VLP-based vaccination has demonstrated a protective immune response that results in consistent and long-lasting type-specific clinical protection. In contrast, indirect protection via cross-protection has shown to be inconsistent across disease stages and of brief duration. In this regard, a 9-valent HPV vaccine could represent an important medical advance with VLP-based type-specific protection.

MSS 8-1

PROTECTION AGAINST NON HPV16/18 TYPES ON OVERALL VACCINATION IMPACT.

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Objectives: The impact of HPV vaccination on early endpoints is currently assessed in countries where vaccinated women enter screening age range. The results are re-assuring with regard to vaccine efficacy and support revision of screening guidelines. Available vaccines have also shown considerable cross-protection and future vaccines will target a broad spectrum of HPV types, further lowering the need for intensive screening. We explored the potential impact of vaccination on HPV16/18 and non-HPV16/18 infections and cervical lesions. For this purpose, we analyzed HPV genotype distributions observed in two trials over multiple rounds of screening.

Methods: We studied HPV genotype distribution of prevalent and incident high-risk HPV infections in Dutch (POBASCAM) and Italian (NTCC) population-based randomized controlled screening trials. Both countries are about to implement primary HPV screening. We estimated the cumulative probability of a screen-positive test result and screen-detected cervical lesion over multiple screening rounds, stratified by vaccination status.

Results: HPV16/18 vaccination was estimated to lead to a reduction in incident HPV infections of 29% in POBASCAM and 31% in NTCC. Estimated reductions in HPV incidence were higher when accounting for cross-protection or when vaccinating against HPV16/18/31/33/45/52/58, but HPV incidences did not reduce by more than 65 percent. The percentage reduction is expected to be stronger for disease endpoint than infection. In POBASCAM, the predicted cumulative CIN2+ risk was 7.4% in unvaccinated women but only 0.7% following HPV16/18/31/33/45/52/58 vaccination.

Conclusions: The development of screening recommendations for vaccinated cohorts will be an important challenge in the coming years. As vaccines may offer substantial cross-protection against non HPV16/18 types and future vaccines will protect against a broad spectrum of HPV types, new screening recommendations will need to be updated regularly in order to preserve a good balance between safety and screen-related burden.

MSS 8-3

EFFECTIVENESS AND COST-EFFECTIVENESS OF THE CANDIDATE NONAVALENT VACCINE

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Objectives: To compare the potential effectiveness and cost-effectiveness of the nonavalent and quadrivalent HPV vaccines.

Methods: We used HPV-ADVISE, an individual-based transmission-dynamic model of multi-type HPV infection and diseases (anogenital warts, and cancers of the cervix, vulva, vagina, anus, penis and oropharynx) in Canada. We calibrated the model to Canadian sexual behaviour and epidemiologic data. We obtained Quality-Adjusted Life-Years (QALYs) lost and costs ($CAN 2010) from the literature. We conducted the analysis from the health payer perspective, with a 70-year time horizon and 3% discount rate. We also performed extensive sensitivity analyses, including duration of vaccine protection and vaccine cost.

Results: Under base-case assumptions (80% coverage, 95$/dose, vaccine-type efficacy=95%, cross-protection for the quadrivalent vaccine, duration of vaccine-type protection (cross-protection)=20 (10) years), the cost-effectiveness ratios of vaccinating 10-year-old girls is predicted to be $15,528 [12,056;19,140] and $12,203 [9,331;17,292] per QALY-gained, using the quadrivalent and nonavalent vaccines, respectively. At equal price, the nonavalent vaccine is more cost-effective than the quadrivalent vaccine and remained more cost-effective even when assuming both shorter duration of protection (nonavalent=20 years vs. quadrivalent=lifelong) and lower vaccine-type efficacy (nonavalent=85% vs. quadrivalent=95%). However, the additional cost per dose of the nonavalent vaccine should not exceed $11 to remain more cost-effective than the quadrivalent vaccine, and $24 to remain a cost-effective intervention at the $40,000/QALY-gained threshold.

Conclusions: The nonavalent vaccine will most likely represent a cost-effective alternative to the quadrivalent vaccine, even in scenarios where nonavalent vaccine efficacy is 85%.

MSS 8-4

AGE-SPECIFIC SEXUAL ACTIVITY PATTERNS AND HPV INFECTION CONTROL.

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Objectives. The network within which sexual contacts occur affects much of the individual risk of acquiring sexually transmitted infections, such as carcinogenic HPV. We aimed at assessing the role of age-specific sexual activity patterns as determinants of the age-specific HPV prevalence and of the impact of HPV vaccination.

Methods. We adapted a transmission model of high-risk HPV transmission to investigate the effect of sexual activity patterns, i.e. age-difference between sexual partners and age-specific sexual activity rates, on age-specific HPV16 prevalence. Available data suggest that age-difference between sexual partners decreases as a function of measures of human development. Similarly, socio-economic transition was found to be associated with changes of gender- and age-specific sexual activity rates. We combined age-difference between sexual partners and age-specific sexual activity rates in an attempt to represent sexual behaviour in "liberal" and "traditional" social contexts. We then assessed the impact of women-only and gender-neutral vaccination in the two social contexts.

Results. We considered HPV16 prevalence in the US (NHANES 2003-2006) and India (IARC, 2005) as exemplification of HPV prevalence in "liberal" and "traditional" social contexts, respectively. We reproduced age-specific differences of HPV16 prevalence by accounting for only differences in sexual activity patterns. For any given coverage, vaccination was significantly more effective in the "traditional" context then in the "liberal" one, regardless vaccination status of the boys.

Conclusions. Countries undergoing rapid social transition are more likely to control carcinogenic HPV infections through an early introduction of vaccination before a shift from "traditional" to "liberal" sexual behaviours have occurred.

MSS 8-5

EFFECTIVENESS AND COST-EFFECTIVENESS OF VACCINATING MEN-WHO-HAVE-SEX-WITH-MEN

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Background and objective: Several economic evaluations have concluded that extending HPV vaccination to males may not be cost-effective because of substantial indirect (herd) protection from female vaccination. However, men-who-have-sex-with-men (MSM) benefit little from indirect protection from females despite having a high burden of HPV-related diseases. We examined the potential cost-effectiveness of targeted HPV vaccination of MSM attending genitourinary medicine clinics (GUM) in England.

Methods: We constructed (i) dynamic models of HPV 6, 11, 16 and 18 transmission via exclusive-male partnerships in an MSM population (stratified by age, HIV status, GUM attendance and frequency of same-sex partner change), (ii) natural history models of HPV-related anogenital warts, anal, penile and oropharyngeal (including tonsillar) cancers. We took into account reductions in potential vaccine impact due to existing HPV infections in MSM prior to their offer of vaccination at GUM attendance.

Results and Conclusions: Given the relatively high ongoing exposure to infection and risk of progression to disease (partly due to co-infection with HIV), HPV vaccination of GUM-attending MSM could have a substantial impact on HPV-related disease in these individuals. The cost-effectiveness of the programme will depend on the price of the vaccine and the groups of MSM who are offered vaccination.

MSS 8-6

IMPACT OF THE NONAVALENT VACCINE ON CERVICAL SCREENING PARADIGMS

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Objectives: Many countries are considering a transition to primary HPV screening, especially in the context of a widespread rollout of bivalent/quadrivalent HPV16/18 (2V/4V) vaccination. However, it is not known whether cervical screening will still be cost-effective in cohorts vaccinated with a new nonavalent (9V) vaccine.

Methods: Using Australia as an example, we modelled screening with cytology (current practice, 2-yearly cytology, 18-70 years), new Australian recommendations for HPV screening (5-yearly HPV, 25-70 years, partial genotyping and direct referral for HPV16/18) and once-, twice- and thrice-lifetime primary HPV screening (at 30 +/- 40 +/- 50 years), in cohorts who are (i) unvaccinated, (ii) 4V–vaccinated, or (iii) 9V-vaccinated (using Australian vaccine uptake).

Results: In unvaccinated women the cumulative lifetime risk (CLR) of invasive cervical cancer was 2.45% without screening, reducing to 0.65% with cytology screening. For 4V cohorts, CLRs were 0.22%, 0.19%, 0.49%, 0.39% and 0.32% for cytology, 5-yearly HPV, and once-, twice- and thrice-lifetime HPV, respectively; these fell to 0.16%, 0.13%, 0.34%, 0.27% and 0.22% for 9V cohorts. Thrice-lifetime HPV screening remained cost-effective in 4V cohorts (incremental cost-effectiveness ratio [ICER] $45,000/LYS, compared to indicative threshold $50,000/LYS) but only once- or twice-lifetime screening was cost-effective in 9V cohorts (ICERs $30,000/LYS and 48,000/LYS, respectively). Sensitivity analysis did not substantially change the relative outcomes for the screening strategies.

Conclusions: Since lifetime risk of invasive cervical cancer will be substantially reduced in 9V-vaccinated cohorts, only strategies that involve testing for HPV twice-lifetime or less frequently are likely to remain cost-effective in this group.

Declaration: The POLICY1 model platform was developed via grants from the National Health and Medical Research Council (NHMRC) Australia, government consulting contracts, and funding from other not-for-profits including Cancer Council NSW. KC is co-PI of an investigator-initiated trial of cytology and primary HPV screening in Australia ('Compass'), which is conducted and funded by the Victorian Cytology Service (VCS), a government-funded health promotion charity. The VCS have received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana Inc USA. However neither KC nor her institution on her behalf (UNSW Australia) receive direct funding from industry for this trial or any other project. No technology-specific issues were addressed in this modelled evaluation.

MSS 8-7

HPV-FRAME: A QUALITY FRAMEWORK FOR MODELS OF HPV PREVENTION

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HPV-FRAME is an initiative started in 2014 to develop a consensus statement and quality framework for modelled evaluations of HPV prevention. The overall intent of developing a quality framework is to enable a set of standards that ensure models contribute to an optimal decision related to the introduction of a new intervention or health program. Findings from the work done under this initiative will be presented.

MSS 9-1

L2-BASED SECOND GENERATION HPV VACCINE (RG1-VLP)

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Licensed bivalent (HPV16,18) and quadrivalent (HPV16,18; 6,11) HPV subunit-vaccines are comprised of virus-like particles (VLP), self-assembled from major capsid protein L1, that induce high-titer and long-lasting neutralizing antibodies, and provide mainly type-restricted protection against infection and disease induced by the included types. A nona-valent vaccine (V503), including additional 5 mucosal high-risk HPV31/33/45/52/58 VLP to the 4-valent vaccine is highly effective in clinical studies. However, more than 15 mucosal high-risk HPV types cause invasive cancer of the cervix and of other anogenital and oropharyngeal sites.

Papillomavirus minor capsid protein L2 contains type-common motives involved in key steps of early viral infection. Immunization induces low-titer antisera that are broadly (cross-)neutralizing against homologous and heterologous types. However, L2 is immunologically subdominant in the context of co-assembled L1 + L2 VLP.
We have generated chimeric RG1-VLP by genetic insertion of the broadly cross-neutralizing 20 amino-acid HPV16 L2 epitope RG1 within the immunogenic DE-surface loop of HPV16L1, resulting in an immunologically favourable 360-fold display of RG1 peptide on the assembled particle surface. Rabbit vaccination with RG1-VLP + alum-MPL induced high-titer antisera to HPV16 and (cross-)neutralization of mucosal high-risk types HPV26/33/35/39/68/59/68/73/69/53/34, mucosal low-risk HPV32/40/44/70, and cutaneous HPV2/27/3/76 in vitro. Passive serum transfer protected mice against experimental vaginal infection with phylogenetically divergent pseudovirions of mucosal high-risk types HPV16/18/31/33/35/45/52/58/73/59.

RG1-VLP are promising single-antigen vaccines against mucosal high-risk, mucosal low-risk, and cutaneous HPV.

MSS 9-2

ATTRIBUTION OF VACCINE TYPES IN MIXED INFECTIONS

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Objective: To give an overview on the attribution of the HPV types covered by the nonavalent HPV vaccine in preneoplastic lesions oft he genital tract.

Methods: Data are available for cervical and vulvar lesions in women and anal lesions in HPV positive men. The attribution of the various types was calculated with a proportional model (taking the frequency of the various types in account), a hierarchical model (for instance HPV 16/18 are more oncogenic than HPV 52). The number in lesions infected with a single HPV type gives the minimum estimate, the finding in any lesion including mixed infections the maximum estimate

Results: The attribution in low-grade lesions for the nine types was lower than in high-grade disease. It ranged in anal disease from 68.7-89%, in vulvar disease from 62.1-89.4%, in vaginal disease from 34.2-54.6% and in cervical disease from 43-55%. In the immediate precursors of cervical cancer (CIN 3/AIS) it ranged from 85-100%. In high grade lesions the results of the different models converged.

Conclusion: Independent of the mathematical model the attribution of the 9 types is in the order of 90% in high grade lesions of the genital tract. Compared with the attribution of HPV 16/18 a substantial improvement can be expected for both low and high grade lesions.

MSS 9-3

HPV VACCINATION IN THE IMMUNOCOMPROMISED

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There have been few studies to date examining the HPV vaccines in immunocompromised individuals and most publications have focused on HIV infected groups. No published study has examined efficacy. Only one of the vaccines, the HPV quadrivalent vaccine (HPQV), has been tested in HIV-infected children. Although it is likely that many perinatally infected children (PHI) will receive HPV vaccination, the protection elicited by the vaccine is unknown in this population. Data from IMPAACT showed that antibody titers after vaccination with QHPV for HPV 6 and 18 were 30% to 50% lower than those for non-immunocompromised children (aged 8 to 11). The safety profile of QHPV was similar to that previously reported for children. In addition, QHPV did not affect the CD4% or plasma HIV RNA however low CD4 nadir affected titers to HPV 18. At 72 weeks, 94% of children had antibodies to HPV 6, 11 and 16. However, only 76% had antibodies to HPV 18. Antibodies for all HPV vaccine types showed a rapid decay within the first 48 weeks after 3rd dose with slower decay thereafter. The study estimated that 50% of children would become seronegative for all the HPV types within 4-5 years after vaccination. At 72 weeks, a 4th dose of the QHPV was given and all subjects had a strong anamnestic response including those negative for HPV 18 antibodies. Studies of adolescents and adults of QHPV show that QHPV is also safe and immunogenic but also with lower seroconversion rates than general population. GMTs are lower in participants not taking ART particularly for HPV 6 and 18. A short follow-up study in HIV-infected MSM showed overall initial high seroconversion rates for all the HPV types with good safety profiles. One study compared the bivalent to the QHPV. The antibody titers to HPV 18 were higher among the bivalent group compared to QHPV however no differences were found for HPV 16.

Little is available regarding other immunocompromised groups. One study in Fanconi Anemia patients showed good response to all QHPV types and another showed that kidney transplant patients had equal immunogenicity as healthy controls whereas liver transplant patients showed significantly lower antibody titers to HPV 6 and16. In conclusion, data suggest that the HPV vaccines show relatively good immunogenicity for both vaccines with lower rates for HPV 6 and 18 among the HIV infected with low CD4 counts. However the durability of this response is unknown. Most importantly, there is no efficacy data to show that vaccinating is protective against HPV disease specifically among the sexually active adolescents and adults.

MSS 9-4

HPV VACCINES: EFFECTIVENESS & UTILITY OF FEWER DOSES

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As more experience is gained with HPV vaccination programs, we recognize that 3 doses can be challenging in terms of cost and difficulty completing the 3 dose series. A number of studies with the bivalent and quadrivalent vaccines have been undertaken demonstrating the immunogenicity of a two dose schedule in girls. These studies will be reviewed along with recommendations adopted in various regions of the world for the use of alternate dosing. The results of these studies have contributed to various organizations such as the World Health Organization endorsing a 2-dose schedule with an interval of at least 6 months between doses for girls aged <15 years. These recommendations will make completion of the vaccine series more affordable and increased flexibility in the intervals between doses will likely lead to an increase in vaccination coverage in both low income and industrialized nations.

MSS 9-5

IMPACT OF HPV16/18 VACCINATION ON GENITAL WARTS

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Objectives: No impact on genital warts (GW) was anticipated from the use of the bivalent HPV 16/18 vaccine in the immunisation programme in England. We have conducted detailed ecological analyses to investigate decreases observed in the number of GW diagnoses in England since 2008.

Methods: Data from Genitourinary medicine (GUM) clinics in England from 2008 to the end of 2013 were analysed to explore GW diagnoses by age, gender, year of diagnosis, and estimated immunisation coverage.

Results: There was a significant decrease of 28% (95% CI 26%-30%) in the number of GW diagnoses at GUM clinics per 100,000 population between 2008 and 2013 for females aged 15 to 19 years, and of 9% (95% CI 7%-11%) for females aged 20-24 years. A decrease of 17% (95% CI 13%-21%) was seen for 15-19 year old males over the same time period. The percentage declines lessened with increasing age, as does the estimated vaccine coverage and in females above the age eligible for HPV immunisation diagnoses rates showed no similar declines. Similar declines have been seen in diagnoses of GW in young females in data from General Practice.

Conclusions: Several factors might have contributed to declines in GW in England. However, the size and pattern of the declines among females strongly suggest that we are observing an unexpected, moderately protective effect of HPV 16/18 vaccination against GW, possibly via cross-protection. The smaller declines among young males are suggestive of some herd-protection to males. Similar findings from other countries are awaited.

MSS 9-6

CROSS-NEUTRALISING ANTIBODIES IN THE CROSS-PROTECTION AGAINST 16/18 BY BIVALENT & QUADRIVALENT VACCINES

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Two prophylactic HPV vaccines have been licensed for use in many countries, the bivalent vaccine Cervarix® against HPV 16 and 18 and the quadrivalent vaccine Gardasil® against HPV 16, 11, 16 and 18. End of study analysis of the Phase III efficacy trials have already been completed. Both vaccines exhibited excellent safety and immunogenicity profiles and also a strikingly high efficacy against vaccine type related CIN 3, the best surrogate marker for invasive cervical cancer, in the HPV naïve populations. The vaccines seem to differ in the cross-protective efficacy rates. Specifically bivalent vaccine seems more efficacious against non-vaccine high risk HPV types 31, 33 and 45 than the quadrivalent vaccine. Gardasil® demonstrated significant efficacy only against HPV 31. Cross-protection is important since approximately one third of the CIN 3 disease endpoints is caused by non-vaccine high risk HPV types. The most important immunogenicity data comes from the HPV naïve subpopulations which provide best estimates of the true prophylactic vaccine efficacy regardless of the assey used.Studies in these young women demonstrate consistent strong and durable antibody responses to each type in the vaccine and seroconversion rates approach 100%. Peak geometric mean titers one month after the third dose are at least 100-fold higher than after natural HPV infection, decline during the next three year, but the levels remain at high levels for several years. More data are needed to establish the exact duration of protection. A randomized observer blinded immunogenicity trial of Cervarix® and Gardasil® in 12-15 year old girls suggest that cross-neutralizing antibodies play a role in the cross-protection against HPV infection and disease caused by the vaccines. Neutralizing antibody responses against non-vaccine HPV types were broader and of higher magnitude in the Cervarix than in the Gardasil vaccinated individuals. Levels of neutralizing antibodies in genital secretions were closely associated with those found in the serum. There was a strong positive associations between cross-neutralizing between antibody seropositivity and HPV vaccine trial efficacy against non-vaccine types. Most of the HPV specific antibodies detected in the mucosa are antibodies that originate from the peripheral blood. Although both vaccines induce high titers of neutralizing antibodies against the vaccine types the response to HPV 16 is typically higher than the response against HPV 18 which is a common finding for both vaccines. Serum neutralizing antibody titers against HPV 31 and 45 were higher in the Cervarix® than Gardasil® vaccinated individuals. In conclusion, the cross-neutralizing antibodies seem to play a role in the cross-protection against HPV infection and disease reported for the current HPV vaccines.

MSS 10-1

NOVEL APPROACHES OF HPV AND NON-HPV BASED CERVICAL CANCER SCREENING: BIOMARKER TESTS

Magnus von Knebel Doeberitz, MD

Screening for cervical cancer aims to identify patients who develop HPV-induced high grade squamous intraepithelial lesions (HSIL). Due to the fairly high risk of HSIL to progress to invasive cancer treatment of these lesions is regarded mandatory. The aim of all screening programs is therefore to be as sensitive as possible to not oversee HSIL, but also at the same time to be as specific to not overtreat patients whose lesions would have regressed spontaneously or were not HSIL. These two aspects are usually expressed in the sensitivity and specificity ratios or receiver operator curves (ROC) for respective tests. Traditionally, the Pap-Test, a morphology based test aiming to assess the degree of genomic instability triggered by HPV oncogenes, was used to meet this aim. Due to its morphology based nature the Pap test is criticized as to insensitive and unspecific in comparison to more refined molecular tests. Based on recent discoveries of molecular alterations triggered by activated HPV oncogenes that are required to develop HSIL and eventually cervical cancer, more sensitive and more specific new tests were developed. These tests are based on either the detection of the essential risk factor to develop cervical cancer (i.e. the infection with certain types of the oncogenic HPVs) but also on the detection of its respective gene products on mRNA or protein level. In addition combinations of biomarkers like $p16^{INK4}$ and Ki67 that highlight functional consequences of the viral oncogenes appeared to be interesting technical alternatives. More recently also epigenetic changes of either the cellular or viral genome that come along with increasing dedifferentiation of the transformed cells were investigated as potentially useful diagnostic markers. At the conference we will review the more recent development of the identification and clinical validation of respective markers and discuss how they may be integrated into a refined screening algorithm to improve the sensitivity and specificity of future screening tests. This summary will be integrated into the molecular concept of what we know today, how HPV-infections trigger cervical carcinogenesis.

MSS 10-3

NEW STRATEGIES FOR HPV BASED SCREENING – USE OF GENOTYPING AND OTHER FACTORS

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HPV testing is more sensitive than cytology and has the advantage of being fully objective. However it is less specific, esp for younger women, so that if HPV testing is used as the primary screening modality, some sort of triage test is necessary to avoid excessive referral to colposcopy. At the moment reflex cytology is the most studied approach and when LSIL or higher results are obtained this can identify women at sufficiently high risk to warrant colposcopy. However there is still an appreciable amount of CIN2+ in women with normal or ASCUS cytology, and additional triage is needed for such women. Several tests now provide results for HPV type 16 and 18 separately and HPV 16 positivity indicates substantially greater risk than consensus high risk positivity, and esp for women over age 30-35y, it provides a basis for immediate colposcopic referral. HPV 18 is more problematic as most studies indicate the cross-sectional PPV is similar to that for other high risk types and it may not justify immediate colposcopy. It is suggestive of disease higher in the endocervical canal, and when found to be present on two consecutive tests more than 6 months apart is grounds for colposcopy and full evaluation of the endocervical canal by curettage, and careful surveillance. Similar management for HPV 45 may also be appropriate, but this is much less common and its significance is less well characterized.

It has recently become apparent that HPV 33, although much less prevalent than HPV16, carries a similar PPV when present and it may be appropriate to manage women positive for this type similarly, although it is not routine assayed by any of the well-studied HPV screening tests.

Other promising tests include p16 cytology and the methylation status of HPV L1 and some human genes, but both of these need further study before they can be recommended of routine use. A potential algorithm using all these approaches will be presented and discussed.

MSS 10-5

SELF-SAMPLING IN CERVICAL SCREENING: RESULTS OF PROHTECT STUDIES

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Offering cervico-vaginal self-sampling for human papillomavirus testing (HPV self-sampling) as cervical screening tool can lead to an improved protection as it may re-attract non-attendees into cervical screening. In two studies in the Netherlands (PROHTECT-1 and -2), in which HPV self-sampling was offered to non-attendees of the regular screening programme, about 30% of women responded by submitting a self-sample. Pooled data from these two self-sampling studies show that HPV self-sampling increases the efficacy of the screening programme by targeting a substantial portion of non-attendees of all ethnic groups who have not regularly been screened. The data indicate that HPV self-sampling reaches the women at highest risk of cervical cancer. In a third study (PROHTECT-3), an objective, non-morphological molecular triage assay directly applicable to self-samples of HPV-positive women was evaluated against cytology triage on a physician-taken follow-up cervical scrape. Molecular triage (i.e., DNA methylation analysis of *MAL* and *miR-124-2* genes) on HPV-positive self-samples was found non-inferior to cytology triage in the detection of CIN2+. This molecular approach obviates the need for a visit to a physician and reduces time to CIN2+ diagnosis, but at the cost of more colposcopy referrals. Altogether, our findings suggest HPV self-sampling combined with molecular triage opens the possibility of full molecular cervical cancer screening.

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MSS 10-6

NOVEL APPROACHES OF HPV AND NON-HPV-BASED CERVICAL CANCER SCREENING IN DEVELOPING COUNTRIES.

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Objective. Cervical cancer is, in theory, totally preventable and incidence has been dramatically reduced by screening programs in many developed countries. Further declines are expected as cohorts vaccinated against HPV16 and HPV18 reach peak ages of cancer incidence in coming decades. Unfortunately cervical cancer is out of control in much of the developing world with stubbornly high and sometimes increasing incidence. A multitude of factors underlie the lack of effective control with economic and social deprivation topping the list. Viable cost-effective solutions for cervical cancer control in developing countries are urgently needed and require exploration of realistic options.
Methods. Review of published scientific papers and consideration of research in the laboratory of the presenting author.
Conclusions. It is well known that infection with high risk or intermediate risk HPV types are necessary but insufficient for cervical cancer and play a direct role in the vast majority (>95%) of the cancers. This rather strict relationship encourages consideration of HPV testing and HPV vaccination as the main pillars of prevention most likely to be successful at the global level. There are many HPV tests with quite similar performance characteristics and screening can be adequately accomplished by different sampling approaches: 1) direct speculum-based sampling of the cervical os by clinicians, 2) vaginal self-collection by the women at home or in the clinic and 3) potentially by a test for HPV DNA in urine. Since HPV infection is rather non-specific all the screening options typically require triage of HPV+ women before referral to colposcopy and/or treatment. Costs of HPV testing have decreased but remain quite expensive for developing countries and consideration is needed for other approaches that do not rely directly on prevention or detection of HPV. Arguments favouring a non-HPV-based approach are that more than 95% of HPV infections are eventually controlled by the immune system and among persistent infections progression to cancer can take decades or may never occur. Although the lead time afforded by an HPV test may confer beneficial aspects and enhanced prevention it requires willingness for careful followup or treatment and acceptance of high costs related to over-treatment and patient anxieties. Non-HPV screening approaches can be considered if they are much more-specific for immediate risk of cancer than mere presence of HPV; they must also have acceptable sensitivity (not less than 70-80% of HPV) and be overall more cost effective. There are various options including: 1) p16 or p16/Ki-67 testing by immunochemistry or RNA, 2) DNA methylation testing for human genes, 3) micro-RNA panels; 4) improved automated cytology. Sophisticated screening at a local level requires self-contained robust equipment resistant to harsh environments and easily run by operators with modest education and training. Alternatively if expert central laboratories are available within reasonable distances with fast and efficient transportation then some genomics approaches are feasible where huge amounts of information are generated from pools of patient specimens, deconvoluted with bioinformatics and salient risk information returned to clinicians. Implementation of such advanced approaches is daunting and while demonstration projects may work in some locations it will take considerable finesse, effort and time to establish these as viable routine approaches across broad swathes of geography.

SS 1-2

IMMUNOTHERAPY OF HPV ASSOCIATED HEAD AND NECK CANCER

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Presence of oncogenic papillomavirus (HPV), mainly HPV16, has been associated with head and neck cancer especially oropharyngeal cancer (OC). HPV positive tumors have a better prognosis that non HPV head and neck, but are still treated with high dose chemo-radiotherapy regimen without taking into account the HPV status of these tumors. In this context, immunotherapy targeting HPV represent an alternative complementary approach which may allow a reduction of dose for conventional therapy avoiding unnecessary toxicity. Viral proteins such as E6 and E7 from HPV are considered as a good target for immunotherapy. Some clinical regressions of preneoplasic lesions associated with HPV have been observed after clinical trials based on the use of theapeutic HPV vaccines composed of E6 and E7 derived long peptides. However, despite these strong arguments supporting the development of an HPV therapeutic vaccines in head and neck cancer associated with HPV, some critical parameters have to be integrated in the design and clinical indications of the vaccines.

Intranasal route of immunization is required for vaccine-induced regression of head and neck cancer.

In a recent study, we set up in mice an orthotopic model of head and neck cancer expressing viral proteins (E6 and E7) from HPV 16. Using an HPV based vaccine composed of the B subunit of Shiga toxin, a vector targeting dendritic cells coupled to an E7 long peptide, we found that only the intranasal and not the intramuscular route of immunization was efficient to cure established orthotopic head and neck [1]. The intranasal mucosal route of immunization also led to a higher anti-E7 CD8+T cells infiltration than the intramuscular route. Lastly, we demonstrated that the intranasal route induced mucosal integrins (CD49a, CD103) on CD8+T cells and the blockade of CD49a both decreased the CD8+T cell infiltration and the clinical efficacy of the HPV vaccine administered by the intranasal route. This work identified a link between the route of vaccination and the induction of a mucosal homing program on induced CD8+T cells controlling their trafficking with a direct application on the efficacy of cancer vaccine to control head and neck tumors [1].

Counteracting the role of anergic PD-1+T cells and regulatory T cells in the tumor microenvironment of head and neck cancers.

We and other groups have shown that the tumor microenvironment of head and neck cancer is characterized by a state of inflammation with high levels of inflammatory cytokines along with high intratumor infiltration by suppressive T cells such as regulatory T cells and immature myeloid cells and anergic PD-1+T cells [2-4]. Although this suppressive and anergic T cell infiltration was paradoxically associated with a good prognosis, it has been shown that these cells keep their inhibitory role or their anergic state [3, 5, 6]. In preclinical models of tumors expressing HPV proteins, the combination of HPV vaccine combined with the blockade of regulatory T cells or the PD-1-PDL-1 interaction improved the induction of anti-E7 CD8+T cells and the regression of established tumors [3].

Conclusion : Development of an HPV therapeutic vaccines in oropharyngeal tumors makes sense due to the frequency of HPV detection and from preclinical data and encouraging preliminary clinical results.

SS 1-3

HPV-SPECIFIC IMMUNOTHERAPY (VGX-3100) INDUCES POTENT T-CELL RESPONSES AND REGRESSION OF CERVICAL INTRAEPITHELIAL NEOPLASIA IN A RANDOMIZED PHASE IIB STUDY

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Objectives: Assessment of the safety and efficacy of VGX-3100 in 167 women with biopsy-proven CIN2 or CIN3 with concurrent HPV16 and or HPV18 infection.

Methods: The randomized, placebo-controlled, double-blind study, was stratified by age and severity of CIN and evaluated cervical tissue changes after three 6 mg intramuscular doses of VGX-3100 followed by electroporation (EP) with Inovio's CELLECTRA®2000 device at weeks 0, 4, and 12.

Results: The study met its primary efficacy endpoint; the percentage of patients who had regression of CIN2/3 to CIN1 or no disease at 6 months post third dose was significantly higher in the VGX-3100 group compared to placebo ($p=0.017$). In addition, the trial demonstrated the ability of VGX-3100 clear HPV infection concurrent with regression of CIN lesions. The study also explored cell mediated immune responses to VGX-3100 in blood samples taken prior to the first vaccine dose and periodically thereafter. IFNγ ELISpot revealed higher responses in the VGX-3100 treated group than in placebo, suggesting that VGX-3100 was able to robustly engage the cellular arm of the patients' immune system.

Conclusion: The successful phase II results represent a significant milestone in the development of active immunotherapies to treat cancer and infectious diseases and have the potential to provide physicians an important alternative to surgery to treat CIN 2/3 disease. They illustrate the highly promising potential of therapeutic immunization with DNA followed by electroporation for the treatment of HPV-related precancerous cervical disease in women and present the possibility of treating HPV-associated cervical, head and neck, and anogenital cancers.

SS 1-4

A PRAGMATIC PROOF-OF-CONCEPT TRIAL OF LOPIMUNE (LOPINAVIR/RITONAVIR) AS A TREATMENT FOR HPV-RELATED PRE-INVASIVE CERVICAL DISEASE.

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Background: Cervical cancer is the most common female malignancy in the developing nations and the third most common cancer in women globally. An effective, inexpensive and self-applied topical treatment would be an ideal solution for treatment of screen-detected, pre-invasive cervical disease in low resource settings.

Methods and Findings: Between 01/03/2013 and 01/08/2013, women attending Kenyatta National Hospital's Family Planning and Gynaecology Outpatients clinics were tested for HIV, HPV (Cervista®) and liquid based cervical cytology (LBC -ThinPrep®). HIV negative women diagnosed high-risk HPV positive with high and low grade squamous intraepithelial lesions (HSIL, LSIL) were examined by colposcopy and given a 2 week course of 1 capsule of Lopimune (CIPLA) twice-daily, to be self-applied as a vaginal pessary. Colposcopy, HPV testing and LBC were repeated at 4 and 12 weeks post-start of treatment with a final punch biopsy at 3 months for histology. Primary outcome measures were acceptability of treatment with efficacy as a secondary consideration. Out of 821 women screened, 16 (1.95%) tested HIV positive. Of the remaining 805, 164 (20·4%) were positive for high-risk HPV of which 99 (60.3%) had normal cytology, 28 (17.1%) had HSIL, 11 (6.7%) LSIL, 21 (12.8%) ASCUS and 5 (3.0%) were diagnosed with invasive cervical cancer (ICC). A total of 23 women with HSIL and 17 women with lower grade cytology were treated with Lopimune during which time no adverse reactions were reported. Post-treatment cytology at 12 weeks on women with HSIL, showed 14/22 (63.6%) had no dysplasia and 4/22 (18.2%) were now low grade demonstrating a combined positive response in 81.8% of women of which 77.8% was confirmed by histology. HPV was no longer detected in 12/23 (52.2%) and a curative treatment response was also seen for women diagnosed with low grade cytology prior to treatment. These data are supported by colposcopic images, which show regression of cervical lesions.

Conclusions: These results demonstrate the potential of Lopimune as a self-applied therapy for HPV infection and related cervical lesions. Since there were no adverse events or detectable post-treatment morbidity, this study indicates that further trials are clearly justified to define optimal regimes and the overall benefit of this therapy. Trial registration No ISRCTN48776874

SS 1-5

GENERATION OF CHIMERIC P16INK4A HPV16 L1 PARTICLESFOR SECOND GENERATION HPV VACCINES

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Objectives: In HPV-induced neoplasia the cellular protein $p16^{INK4a}$ is strongly overexpressed, whereas in normal tissues barely any $p16^{INK4a}$ expression is detectable. Therefore, $p16^{INK4a}$ is considered to be an interesting target for therapeutic vaccination in HPV-associated cancers. We designed chimeric particles consisting of $p16^{INK4a}$ and HPV16 L1 with the aim of using the adjuvant-like effects of L1 particles to improve $p16^{INK4a}$ immune responses and at the same time generating a vaccine candidate with combined prophylactic (L1) and therapeutic ($p16^{INK4a}$) properties.

Methods: Three constructs were generated to evaluate the antigenic effect of different structural isoforms. The complete $p16^{INK4a}$ encoding cDNA sequence was cloned a) upstream and b) downstream of a modified HPV16 L1 sequence into a pGex4T2 expression vector. Additionally, the helix 4 region of L1 was replaced by $p16^{INK4a}$ (c). The GST-fusion proteins were inducible expressed in E. coli as inclusion bodies (IB). After IB purification, the proteins were extracted under denaturing conditions with N-Lauroylsarcosine and refolded by dialysis. The produced particles were evaluated for their structural properties and the in vivo immunogenicity of the capsomeres was tested in C57BL/6 mice.

Results: High protein concentrations and purity of chimeric constructs of HPV16-L1 and $p16^{INK4a}$ can be achieved with the developed advanced inclusion body purification protocol. Besides good stability characteristics, the capsomeres were found to be of rather heterogeneous structure. After vaccination of mice construct a) showed the best antibody response, b) seemed to induce the most efficient anti-p16 humoral immune response and c) induced highest L1- and $p16^{INK4a}$-specific T cell numbers.

Conclusions: The possibility to generate an effective immune response to $p16^{INK4a}$ opens new opportunities in the field of cancer immunotherapy and the developed chimeric particles are interesting new vaccine candidates.

SS 1-6

A PHASE I/IIA TRIAL TARGETING $P16^{INK4A}$ BY PEPTIDE VACCINATION IN PATIENTS WITH HUMAN PAPILLOMAVIRUS-ASSOCIATED CANCER

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Objectives: The $p16^{INK4a}$ protein is strongly overexpressed in HPV-associated cancers, while in normal tissues $p16^{INK4a}$ expression levels are low. Targeting this HPV type-independent antigen by vaccination could represent an interesting complementary therapeutic approach to E6/E7-based vaccination. We performed a phase I/IIa vaccination trial to monitor toxicity and immunogenicity of $p16^{INK4a}$ peptide vaccination (Vicoryx trial, ClinicalTrials.gov Identifier: NCT01462838, Sponsor: Oryx GmbH und Co KG).

Material and Methods: 26 patients with advanced $p16^{INK4a}$-overexpressing, HPV DNA-positive cancer (anogenital region, head and neck) were included. The protocol comprised a total of 12 subcutaneous injections of a synthetic $p16^{INK4}$ peptide mixed with Montanide® ISA-51 VG. Objectives of the trial were clinical safety and humoral and cellular immune responses against the $p16^{INK4a}$ peptide.

Results: No toxicity was observed that was regarded as related to vaccination with $p16^{INK4a}$ in any of the 26 patients. In the patients analyzed to date, pre-existing baseline T cell and antibody responses against the $p16^{INK4a}$ peptide were rare, but $p16^{INK4a}$-reactive immune responses were successfully induced in all patients that completed the study protocol, including two patients with CD8 response. To date four patients with advanced cancers are with stable disease for up to two years after they completed the study protocol.

Conclusions: This study demonstrates that $p16^{INK4a}$ peptide vaccination is safe and that immune responses against $p16^{INK4a}$ can be induced and are not accompanied by clinical autoimmune symptoms. Further trials will assess whether this approach may be an effective therapeutic strategy for patients with HPV-associated neoplasia.

SS 1-7

HUMAN PAPILLOMA VIRAL CLEARANCE FOLLOWING HPV TARGETED IMMUNOTHERAPY, TIPAPKINOGEN SOVACIVEC, IN PATIENTS WITH HIGH GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)

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Objectives: Clearance of HPV infections was monitored in a trial of tipapkinogene sovacivec (RO5217790), an MVA based therapeutic vaccine with modified HPV16 E6 and E7 genes as well as the gene for human IL2 in women with high grade CIN2/3

Methods: Patients with CIN2/3 associated with high risk HPV infection, were randomized in a 2:1 ratio to either RO5217790 or placebo. Patients received 3 subcutaneous injections on Days 1, 8 and 15, underwent conisation at Month 6, and subsequently returned for repeated follow up exams to Month 30.

Results: 206 patients were randomised; 136 to RO5217790 and 70 to placebo. At month 6, 24% (31/129) patients achieved histologic resolution in the RO5217790 and 10% (6/63) achieved histologic resolution in the placebo group. The histologic response (<CIN2) rate was 36% (46/129) in the RO5217790 and 21% (13/63) in the placebo group.

Patients treated with RO5217790 had higher clearance of baseline HPV infections at Month 6 than those on placebo (Table 1). The magnitude of the difference was higher in HPV16 monoinfected patients. By Month 30, the percentage of HPV clearance was high and similar in both groups, with a substantial loss to follow up, 38/129 patients from the RO5217790 and 27/63 from the placebo group.

Sustained viral clearance at Month 30 was achieved in 67/79 patients in the RO5217790 group and in 26 out of 30 patients in the placebo group. There were no long term safety issues with the HPV targeted immunotherapy.

Conclusions: Tipapkinogen sovacivec showed activity when compared with placebo in histologic assessment and viral clearance at Month 6. For the patients with HPV genotyping after Month 6, similar proportions in both groups had sustained viral clearance.

Table 1. HPV viral clearance by Roche linear Assay

		Month 6	Month 18	Month 30
HPV 16 Monoinfected	RO5217790 N = 55 (%)	52 20 (38)	48 44 (92)	42 41 (98)
	Placebo N = 27 (%)	23 2 (9)	17 15 (88)	15 14 (93)
	Missing	7	17	25
All genotypes	RO5217790 N = 129 (%)	121 45 (37)	101 88 (87)	91 86 (95)
	Placebo N = 63 (%)	58 8 (14)	42 39 (93)	36 34 (94)
	Missing	13	49	65

SS 1-8

VAXICLASE, A NEW ADENYLATE CYCLASE-BASED VACCINE VECTOR FOR MULTIVALENT HPV THERAPEUTIC VACCINATION

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Introduction: Vaxiclase is the first adenylate cyclase (CyaA)-based vaccine vector able to deliver large antigens > 300 amino acids (AA), with complex structures or with negative charges, to antigen presenting cells (APCs), leading to specific and effective immune responses. We report here on production, characterization and pharmacological properties of two Vaxiclase-based vaccines containing 3 HPV E7 proteins from HPV16, 18 and 45.

Methods: Vaxiclase was obtained from Bordetella pertussis CyaA deleted from 93 AA in its catalytic domain. HPV16, 18 and 45-E7 were cleaved and assembled as $HPV16E7_{C\text{-}term}$+$HPV18E7_{C\text{-}term}$+$HPV45E7_{C\text{-}term}$+$HPV16E7_{N\text{-}term}$ +$HPV18E7_{N\text{-}term}$+$HPV45E7_{N\text{-}term}$. Acidic portions of the E7 proteins were removed or not, and the two final antigens were genetically fused into Vaxiclase. The resulting two recombinant proteins were tested for their ability to bind their receptor (CD11b/CD18) and to induce E7-functional cytotoxic CD8+ T lymphocytes (CTLs; *in vivo* killing assay). Therapeutic efficacy (tumor rejection assay) was performed in C57BL/6 mice bearing TC-1 cells expressing HPV16E7 protein or a newly engineered LL2 cell line expressing HPV18E7 model treated with both adjuvanted Vaxiclase recombinant proteins. HPV45E7 immune response was not assessed due to inappropriate genetic background of mice.

Both Vaxiclase trivalent lead vaccines were able to bind to CD11b/CD18. Vaccination-induced CTLs killed syngeneic target splenocytes loaded with either HPV16E7 or HPV18E7 peptide libraries. Vaccination of TC-1 or LL2-HPV18E7 tumor-bearing mice led to long-lasting tumor eradication (113 days).

Conclusion: Vaxiclase-based vectors are suitable for therapeutic vaccination with large and negatively-charged antigens. These results are the basis for the next generation of multivalent HPV CyaA-based vaccines.

SS 2-2

ASSESSING RISK OF CANCER ASSOCIATED WITH HPV16/18

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Epidemiologic studies have been unequivocal in demonstrating across different populations that cervical infection with HPV16 has a greater risk of developing into cervical precancer and cancer than those with other carcinogenic genotypes of the alpha-9, alpha-11, alpha-7, alpha-5, and alpha-6 species. HPV18, a member of the alpha-7 species comes second and behaves differently in terms of tissue tropism and host cell lineage, being overrepresented in glandular lesions relative to HPV16 and other types. Cohort studies and cervical cancer case series are generally consistent in supporting the notion that HPV16 is the most carcinogenic type, not only in etiologic fraction but also in the speed with which an infection with that type progresses to lesions. The picture for HPV18 is less clear, however; to some extent perhaps because of the differences in host tissue distribution. HPV18 is the second most common type in invasive cancer but it is less common relative to others in precancer. This has led some to contend that HPV18 is associated with short sojourn times in the precancerous lesions stages. Are other carcinogenic types important in screening and management? Should genotyping be based on an expanded roster of types than simply HPV16/18? These questions acquire importance as molecular HPV testing has come of age and vaccination begins to disturb the HPV genotype distribution in populations.

SS 2-4

IMMUNE RESPONSES TO THERAPEUTIC HPV VACCINES

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Human papillomavirus (HPV) has been shown to be associated with several important cancers, including anogenital cancer, and a subset of head and neck cancers. This association has created an opportunity to control these cancers through vaccination against HPV. The existing preventive HPV vaccines are not effective in controlling pre-existing HPV infection and HPV-associated diseases. Thus, in order to accelerate the control of HPV-associated malignancies and to treat currently infected patients, it is important to develop therapeutic HPV vaccines. Two HPV oncogenic proteins, E6 and E7, are consistently co-expressed in HPV-associated cancers and are important in the induction and maintenance of cellular transformation. Therefore, immunotherapy that targets E6 and/or E7 proteins may provide an opportunity to treat HPV-associated malignancies. Among different forms of vaccines, DNA vaccines have emerged as an attractive approach for therapeutic HPV vaccine development due to its safety, simplicity and ease of preparation. Various innovative strategies to enhance DNA vaccine potency have generated impressive preclinical data, which have led to several HPV DNA vaccine clinical trials. Theoretically, a robust immune response in the lesional mucosa should induce more potent antitumor outcomes than that of a systemic response. Thus, we have attempted different strategies to elicit local immune responses. We found that local application of imiquimod, a TLR7 agonist, following therapeutic HPV vaccination results in trafficking of HPV antigen-specific CD8+ T cells into the cervicovaginal tract in a preclinical model. Furthermore, we observed that vaccination in the cervicovaginal tract of mice with therapeutic HPV vaccines generated potent local HPV antigen-specific CD8+ T cell responses. In human patients, it has been reported that heterologous prime-boost regimen with therapeutic HPV DNA vaccine prime followed by therapeutic HPV vaccinia boost leads to significantly increased infiltration of antigen-specific CD8+ effector and memory T cells into the cervicovaginal tract. Furthermore, the infiltrated tissue T cells in vaccinated patients form ectopic tertiary lymphoid aggregates that are associated with favorable prognosis. Therefore, additional studies should be done to further develop and investigate strategies that focus on inducing a more immunogenic environment in the sites of lesion. With continued progress in the field of vaccine development, therapeutic HPV vaccines provide a potentially promising approach for the control of lethal HPV-associated malignancies.

SS 2-5

PROCERVIX, A NEW VACCINE FOR HPV16&18 INFECTED WOMEN PRIOR TO DEVELOPMENT OF HIGH-GRADE CERVICAL LESIONS: FROM PHASE I TO PHASE II.

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With the progressive HPV testing implementation in cervical cancer screening programs, the number of women aware of their HPV infection will be increasing, without knowing whether they will progress to cervical lesions or clear the infection. Because prophylactic vaccines cannot eradicate prevalent infections, the only option for them is "watchful waiting". ProCervix is designed to fill the gap in HPV therapeutic solutions.

The Phase I study in HPV16 and/or HPV18 infected women with normal cervical cytology showed a good safety and tolerability of ProCervix adjuvanted with imiquimod 5% cream, allowing the selection of the appropriate vaccine dose and formulation for further clinical development. Exploratory investigations in this limited number of patients (n=47) showed vaccine T-cell immunogenicity and indicated that HPV16/18 clearance was higher in women vaccinated with ProCervix 600 μg plus imiquimod versus placebo plus imiquimod.

On the basis of the encouraging Phase 1 results, Genticel initiated a phase 2 trial in 39 European clinical sites. This randomized, double-blind, placebo-controlled study is designed to demonstrate that ProCervix plus imiquimod is superior to placebo in inducing viral clearance one year after vaccination. Sustained clearance will be assessed two years after vaccination. The study was initiated in January 2014 and enrolment was completed in November 2014 with 239 HPV 16 and/or 18 positive patients, with normal or ASCUS/LSIL cytology results, randomized. All patients underwent a colposcopy at baseline with biopsy of any visible lesion. Patients with CIN2+ were excluded at baseline.
The rationale and status of current clinical trials will be discussed.

SS 3-1

WORLDWIDE EPIDEMIOLOGY OF CERVICAL CANCEER: PREVALENCE, INCIDENCE, MORTALITY. RATES AND TENDENCIES

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Cervical cancer is the fourth most common cancer in women, and the seventh overall, with an estimated 528,000 new cases in 2012 estimations of Globocan. A large majority (around 85%) of the global burden occurs in the less developed regions, where it accounts for almost 12% of all female cancers. Cervical cancer remains the most common cancer in women in Eastern and Middle Africa. There were an estimated 266,000 deaths from cervical cancer worldwide in 2012, accounting for 7.5% of all female cancer deaths. Almost nine out of ten (87%) cervical cancer deaths occur in the less developed regions.

Cervical cancer was the cause of an estimated 7.8 million years of life lost (YLL) in women, third after breast and lung cancers.

While selected countries show a continuous decrease in cancer incidence, when there has not been a effective screening introduction, incidence of cervical cancer has increased in successive generations of women most likely as a result of changing sexual behaviour and increasing risk of persistent HPV infection.

The cancer projections indicate that cervical cancer incidence is estimated to increase by approximately 2% per annum to 770,000 new cases by 2030, with the vast majority of cases diagnosed in less developed regions of the world. It is estimated that unless massive preventive interventions take place, the beneficial impact of screening and vaccination observed in selected, generally rich countries, will be counter balanced by an increasing burden in poorer countries with unmeet prevention interventions and increase demography.

SS 3-2

REALITY OF HPV VACCINATION IN UNDER DEVELOPED COUNTRIES

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Human papillomavirus (HPV) vaccination has the potential to reduce cancer deaths by more than 60% in developing countries, where more than 85% of the mortality occurs. Successful planning for HPV vaccine introduction in developing-country settings requires a comprehensive approach that addresses individual, interpersonal, community, structural, and policy factors that positively enable HPV vaccine uptake. To date, 36 low- and middle-income countries have implemented small-scale pilots or demonstration programs of HPV vaccine delivery to young adolescent girls to learn feasibility mechanisms for delivery and effective methods to ensure community acceptability. Combined with 11 more country-level demonstration programs being considered for 2015, these experiences illustrate both a strong demand for and commit by governments and others to bring this life-saving vaccine to the areas of the world most heavily impacted by the devastating morbidity and mortality of cervical cancer. This presentation will summarize experiences of HPV vaccine delivery in developing countries, highlighting factors that have fostered success, challenges that have been encountered, and country and global level mechanisms in place to facilitate national introduction.

SS 3-3

AN EPIDEMIC WAITING TO HAPPEN: A REVIEW OF CERVICAL CANCER INCIDENCE IN SUB-SAHARAN AFRICA

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Cervical cancer is the second most common cancer amongst women of sub-Saharan Africa. Low-cost preventative measures are emerging, with a drive for national cancer control programmes. However, the reliability of surveillance data is questionable and population-based registries cover <1% of the population. The incidence of cervical cancer in sub-Saharan Africa is predicted to increase by 102% over the next 15 years. Unless action is taken, cervical cancer will be the next epidemic to dominate women's health. This must therefore be a public health priority post 2015, if we are to protect a vulnerable population from a preventable disease.

SS 3-4

EFFECT OF VIA SCREENING BY PRIMARY HEALTH WORKERS: RANDOMIZED CONTROLLED STUDY IN MUMBAI, INDIA

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Despite a large burden of cervical cancer developing countries are not in a position to set up organized cytology-based cervical screening programmes due to lack of infrastructure and trained personnel, and issues related to quality assurance and costs.

In the last one decade VIA and HPV testing have been tested in a number of developing countries. At least three randomized controlled trials have demonstrated a significant mortality benefit following cervical screening by either VIA or HPV testing. A single round of VIA screening performed by trained nurses in Dindigul district of southern India resulted in a significant 35% reduction in mortality from cervical cancer. A single round of HPV testing performed by technicians in Osmanabad district in western India, showed a significant 48% mortality reduction. Another RCT from Mumbai district also in western India demonstrated a significant 31% cervical cancer mortality reduction after 4 rounds of VIA screening performed by trained PHWs at 24-month interval.

These studies present 3 attractive options for cervical screening in developing countries:

1) In situations where only a single round of screening is feasible, the best option would be HPV-DNA testing
2) In situations where adequate number of trained nurses could be deployed to 'screen and treat', VIA testing followed by colposcopy and cryotherapy should be the choice
3) The third and most cost-effective and widely implementable strategy for cervical cancer control in developing countries would be four rounds of biennial VIA screening by PHWs.

The Indian States of Tamil Nadu and Sikkim have already started statewide organized cervical screening with VIA. Neighboring country Bangladesh is also piloting a VIA-based national cervical screening program.

SS 4-1

OVERVIEW AND UPDATE ON NTCC TRIAL

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Objectives. Provide evidence on relative benefits and costs of cytology- and HPV-based screening and best policies with the latter.

Methods. 94,370 women aged 25-60 years from 7 organised screening programmes in Italy were randomly assigned to conventional (conventional cytology) or experimental arm that followed two phases: the first with HPV and LBC co-testing, the second with stand alone HPV. Samples from HPV positive women were stored and tested for potential biomarkers.

Results. The relative detection of CIN3+ and CIN2+ was significantly higher in the experimental than in the conventional arm at baseline and lower at the second screening round, showing that HPV based screening allows earlier detection of persistent hgCIN than cytology. However, at baseline at baseline PPV was lower in the experimental arm. In younger women a higher cumulative detection of CIN2 over the first two rounds in the experimental arm, suggests larger over-diagnosis of spontaneously regressive lesions. Triage of HPV positive women by $p16^{INK4A}$ immunostaining increased cross sectional and longitudinal sensitivity vs. conventional cytology allowing prolonged re-testing. Analyses on genotyping and cytology (interpreted with knowledge of HPV positivity) as triage tests are on-going. A pooled analysis with other EU RCTs directly showed increased protection against invasive cancer and longer low-risk period after HPV-based screening.

Conclusions. NTCC, together with other RCTs, provided crucial information on the value of HPV-based cervical screening and on the best way to perform it. These results were the basis for Italian recommendation to convert to HPV-based screening and how.

SS 4-2

MANAGEMENT OF HPV+ WOMEN: RESULTS FROM RESEARCH TRIALS

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In some randomised trials only women who had abnormal cytology or persistent HPV infections were referred to colposcopy. In the New Technologies for Cervical Cancer screening (NTCC) study HPV-positive women had postcolposcopy follow-up every year until HPV clearance. Many new lesions were detected during such postcolposcopy clinical follow-up,but this approach is expensive and distressing for women. Identification of markers that would allow longintervals between testing for some HPV-positive women would therefore be useful.

In the NTCC trial women in the experimental arm were tested by HybridCapture2 (HC2). Residual cells were stored at -80°C. On DNA samples from women who were HC2 positive we performed PCR by GP5+/GP6+ consensus primers and typing by reverse line blot hybridisation. During phase 2 of the study HPV positive women were also tested for $p16^{INK4A}$ overexpression by immunostaining.

We followed-up 2399 HPV positive women with genotype determined and 1137 tested for p16 overexpression. Triage of HPV positive women by $p16^{INK4A}$ immunostaining increased cross sectional and longitudinal sensitivity vs. conventional cytology allowing prolonged re-testing.. Analyses on genotyping and cytology (interpreted with knowledge of HPV positivity) as triage tests are on-going

HPV positive women followed by cytology or partial genotyping need annual repeating test, women followed with p16 need annual test only if p16 is positive. However, longitudinal data for the subsequent risk of high-grade CIN in women by genotyping are needed to establish the appropriate frequency of retesting in HPV type specific persistent infection HPV-positive.

SS 4-3

UPDATE ON THE IMPLEMENTATION OF HPV PRIMARY SCREENING IN ITALY

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Background: Since 2007, in Italy started several pilot cervical screening programs adopting HPV as primary screening. The aim of these pilots was to assess: feasibility, organizational impact, acceptability, and cost.

Methods: the Italian Screening Monitoring Centre yearly conducts a survey on performance of all screening programs. For HPV pilot programs available indicators are: participation, HPV positivity, cytology triage results and referral rate.

Results: in 2012 19 HPV-based programs were active. All adopted a cytology triage algorithm re-inviting HPV+/cytology- women after one year to repeat HPV test. Twelve started HPV at 25 ad 7 at 35 years. The recommended interval for HPV- was 3 years and only in 2013 has been extended to 5 years. Three had a randomised design to compare with Pap test screening. Participation ranged from 13% to 65%, usually few percentage points over participation in Pap test screening. The HPV positivity ranged from 4% to 8.9% and from 4.6% to 21.8% in women 35-64 and 25-34, respectively. Positivity to cytology triage ranged from 12% to 53%, with 16 programs within 35% and 45%. Immediate colposcopy referral ranged from 0.5% to 4.4% and from 3.4% to 9.4%, for women 35-64 and 25-34, respectively, generally similar to cytology-based screening. Persistence of HPV at one year (8 programs) ranged from 42% to 58%. Total referral rate increased for both women 35-64 and 25-34.

Conclusions: Italian pilot projects sowed that HPV-screening is well accepted and feasible, even if it initially increases the burden of colposcopies.

SS 4-4

PERFORMANCE OF COMMERCIALLY AVAILABLE HPV TESTS (FROM STUDIES TO CLINICAL PRACTICE)

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Objective. Following the establishment of the causal association between high-risk human papillomavirus (hrHPV) infection and cervical cancer, hrHPV testing represents a new technology that can offer a more effective screening approach. As different systems have been developed to detect hrHPV in cervical specimens, it's of utmost importance to verify if their laboratory reproducibility/reliability and their clinical performance (in terms of sensitivity and specificity for ≥ CIN2 lesions) have been documented. Moreover, the degree of automation of the systems represents also a key point to be taken into account as these technologies must allow large-scale testing.

Methods. An analysis of the state of the art of different commercial systems has been performed, looking at the laboratory and clinical data related to the validation of the method, according to the European Guidelines [1] or to the data derived from studies in women undergoing screening.

Results. Although different systems are available today on the market, for many of them no data have been published demonstrating an adequate validation for the use in patients management.

Conclusions. Many commercial tests exist for the detection of hrHPV in cervical samples. As clinical guidelines governing the management of the patients are totally based on clinically validated tests, it is very important that any test which influences the management of the patients is validated before being introduced in clinical practice.

(1). Meijer CJLM, Berkhof J, Castle PE et al. Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. IJC 2009;124:516-20.

SS 4-6

PROGNOSTIC SIGNIFICANCE OF RLU VALUES IN HC2-POSITIVE ASC-US CASES

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Background: The risk of invasive cancer in patients with ASC-US cytology is low, ranging from 0.1% to 0.2% according to literature. However, 5% to 17% of these cases, and 24% to 94% of those with ASC-H will have high-grade precancerous lesions (CIN2/CIN3) at histology. The sensitivity of HPV DNA testing for the detection of CIN2/CIN3 in the triage of ASCUS cytology is reported as being in the range 83–100%. This high sensitivity is, however, often correlated with low specificity (63%) and low positive predictive value (PPV), determining high referral rates to second-level colposcopy and biopsy.

Methods: Our goal was to identify the prognostic significance of HPV viral load figures. We evaluated whether a correlation between viral load, expressed as relative light units/cutoff (RLU/CO), and the severity of cervical lesions existed in 614 consecutive ASC-US cases. Hybrid Capture 2 (HC2®) RLU/CO values, categorised into five classes, were correlated to clinical outcomes and statistically analysed.

Results: A significant correlation ($p<0.0001$) was observed between increasing RLU values and the prevalence of high-grade CIN (CIN2/CIN3). The mean RLU values for negative, low-grade and high-grade lesions were 68.1, 172.5 and 1,020.0 RLU/CO, respectively ($p<0.0001$). CIN2/CIN3 ranged from 4% for $0<RLU/CO\leq 1$, to 5% for $1<RLU/CO\leq 10$, to 9% for $10<RLU/CO\leq 100$, to 23% for $100<RLU/CO\leq 1{,}000$ and to 48% when RLU/CO values were $>1{,}000$ ($p<0.05$).

Conclusion: The HPV viral load in ASCUS cases significantly correlates with the severity of cervical cancer precursors. These data may have prognostic value, as they significantly correlate with the probability of a CIN2+ .

SS 4-7

COLPOSCOPY IN CYTOLOGY NEGATIVE HPV POSITIVE WOMEN

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Background: Based on evidence from large randomized control trials a significant improvement in the prevention of cervical cancer has been reached, from age 30 years, with HPV-based screening. No concordant clinical guidelines are provided to manage optimally women who test HPV positive and cytology negative.
Objectives: To estimated cumulative 5-year risks of cervical intraepithelial neoplasia grade 3 or worse (CIN 3+) among HPV+ PAP– women.

Methods: Review of the literature.

Results: Women aged 30 and older who test HPV positive, cytology negative represent less than 5% of screened women. Their 1-year cumulative incidence rate for CIN 2+ was found to be 2.83 (95% CI 2.55-3.12). However risks was greater for women who had a past HPV-positive, Pap-negative result compared with those who had HPV-negative, Pap-negative result. The 5-year cancer risk was 0.34% (95% CI = 0.26%-0.45%), being half of the cases adenocarcinoma. The majority of cancers were diagnosed following a single Pap-/HPV+ screen, suggesting the need of effective triage of these women.

Conclusions: HPV testing contributes to early cervical cancer diagnosis detection in women with negative Pap tests. The use of additional biomarkers, such as HPV genotyping16 or p16INK4a immunocytochemistry, can identify women at greater risk for CIN 3.

References: Castle PE, et al. Variable risk of cervical precancer and cancer after a human papillomavirus-positive test. Obstet Gynecol. 2011 Mar;117:650-6.
Katki HA, et al. Five-year risks of CIN 3+ and cervical cancer among women who test Pap-negative but are HPV-positive. J Low Genit Tract Dis. 2013;17: S56-63

SS 4-9

HPV-VACCINATION IN ITALY, AN UPDATE

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Italy has been the first European country that introduced a population based HPV vaccination strategy. In 2007 the Italian Ministry of Health added to the national immunization program the papillomavirus vaccine to be actively offered, free-of-charge, from the cohort of 1997, to the primary target: all girls between the 11th and the 12th birthday. Moreover, HPV vaccine was included into the list of Essential Levels of Assistance (LEA), whose purpose is to homogeneously provide key-services of the health care system (prevention, diagnosis and treatment) for all of the Italian citizens of the single Regions. However, the transfer of responsibility for health to regional authorities has resulted in a diverse (sometimes conflicting) situation within the country. All the 21 Italian Regions started the vaccination program only in 2008 for the primary target, offering also a catch-up for one or more other age cohorts of their population. Quadrivalent and bivalent vaccines are both available in Italy, and are subject of periodic tenders by public health services in all Regions. After seven years from the beginning of vaccination program, and a wide starting communication campaign, the national coverage rate (full three-dose, routine administered) of the primary target is less than expected (69% for the first and immediate subsequent cohorts), with heavy regional heterogeneity (not necessarily related to a north-to-south gradient), and slightly decrease in the last two cohorts of girls born in 2000 and 2001. Thus, there are many challenges in implementing and increasing the uptake of the vaccine. Parental opinions and attitudes probably play a key role in the success of any new vaccine, but particularly having to deal with such a sensitive subject: the fear of developing cancer and the sexual activity. Indeed, a wrong cultural judgment has often been translated the HPV vaccination as an encouragement of sexual activity among teenagers. Even the issues of vaccine safety play an important role as a cause of the unsatisfactory Italian coverage rate, along with the negative influence of some people strongly opposed (mainly through the use of frightening websites) to any vaccination practices and have helped to create a barrier against HPV vaccine. At last, there has been little awareness of some Italian physicians (gynecologists, pediatricians, general practitioners) about the importance of vaccination and, therefore, they not properly supported the national program. In a survey conducted in Italy, among a sample of parents of young girls, only 31% of the consulted healthcare provider recommended for HPV vaccination. Conversely, all of the health professionals should correctly inform parents and the primary target as well, thus increasing compliance by communicating the latest scientific data and dispelling misperceptions about the vaccine. These professionals are considered the most relevant sources of information about HPV vaccine by over 60% of Italian respondents to a specific survey. Data collected from the Istituto Superiore di Sanità (which is the Italian National Institute of Health) about national coverage rate from the first cohort of the primary target will be discussed, along with the variations of vaccine uptake by geographical site.

SS 5-1

ACCREDITATION IN COLPOSCOPY: THE AEPCC'S PROGRAM

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Spanish Association of Cervical Pathology and Colposcopy (AEPCC)

Since its beginnings in 1988 the Spanish Association of Cervical Pathology and Colposcopy (AEPCC) has ensured that Spanish gynaecologists are properly trained in colposcopy. The previous great work carried out by Spanish pioneers (Dexeus and Carrera, Calvo de Mora and Hernandez, Bonilla-Musoles and Balagueró, Mateu-Aragonese and Puig Tintoré) who all learnt from the foundations laid by Coupez and Brux1, was the seed of development of what must be called "Spanish School of Colposcopy" (SSC). The successive contributions of these authors, and other more recent, consolidated the idea of a dynamic colposcopy, highly related to clinical, cytology and pathology, an idea that should be considered the essence of the EEC, far from the German initial view of a virtually static photographic colposcopy.

The AECC, supported in its path by the European Federation and the International Federation of Colposcopy, was commissioned under the chairmanship of S. Dexeus to organize the 2002 International Congress in Barcelona. It was this congress that saw the presentation of the Terminology Classification of Colposcopic Images that largely welcomed the ideas of the SSC. This classification was not substantially modified in the 2011 congress in Rio de Janeiro and it is currently still valid.

The SSC believes that the colposcopist should not be a mere observer. His knowledge of the pathology of the lower genital tract (LGTP) should allow him to place colposcopy on the stage of the prevention of cancers of this location, next to other techniques available for this purpose. For this reason, ongoing training and quality control must be unavoidable strategies, procedures and targets. In order to achieve this, in 2005 the AEPCC decided to establish an Accreditation Program for Colposcopists, an instrument of self-assessment and quality control offered to the Spanish gynecologists.

Two paths were established for Accreditation:

1- Evaluation of curriculum vitae (CV) of the applicant, by applying a previously established scale, which also included certain conditions for access.

2- Applicants with insufficient CV achievements could be presented to a consistent test on a theoretical valuation practice, which currently consists of 100 multiple choice questions, covering all aspects of the LGTP in general and especially of colposcopy. To gain an accreditation, at least 80% of the questions should be answered correctly.

The Accreditation in Colposcopy is valid for five years, at the end of which the holder is requested to submit curricular activity in the field of colposcopy during those five years. The ad hoc Committee on Accreditation either renews the accreditation of the required level or if the accreditation is not renewed the applicant must take a new test.

In 2011 we presented our experience in the 1st Satellite Meeting on Quality Assurance in Colposcopy organized by the European Federation of Colposcopy (EFC) 2. The thesis defended was that the objective of quality in colposcopic procedures proposed by the EFC, based in the great experience of the Bristish Society of colposcopy, is fully endorsed, but the ways to achieve this goal do not necessarily have to be the same, given the different realities of health care and use of existing colposcopy among different countries of the Federation. That EFC overseeing these procedures and thus ensuring its quality, without going into the detail of its planning and execution, it was proposed as a reasonable and necessary alternative. This is the path we have followed. In the presentation we will show the number of accredited gynecologists, how they obtained their accreditation and the development of the procedures since its creation.

Conclusion A Self-Assessment and Quality Control Program (Accreditation) in Colposcopy is essential and should be implemented under the responsibility of the respective National Societies that decide their characteristics, guardianship and certification EFC.

SS 5-2

THE PER-OPERATORY SAMPLE OF HPV AS A MARKER OF RISK OF RELAPSE OR SECOND LESION

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Background: Protocols of post-conisation follow-up are based on serial cytology and HPV testing at 6 or 12 months after treatment. Nevertheless, an earlier identification of patients at higher risk of harbouring treatment failure might contribute to avoiding delays in the re-treatment, and would allow reducing unnecessary visits for women at very low risk of post-treatment disease.

Objective: To evaluate the feasibility and utility of intraoperative post-conisation HPV (IOP-HPV) testing and cytology to detect treatment failure in patients treated for HSIL.

Methods: A cohort of 132 women treated for HSIL was studied. An endocervical sample was obtained intraoperatively with a cytobrush from the cervix remaining after the conisation. The material was processed for Hybrid Capture 2 and cytology. Patients were followed-up for 24 months. IOP-HPV testing and IOP cytology were compared with conventional indicators of recurrence (cone margin, endocervical curettage, and HPV testing and cytology at 6 months).

Results: Treatment failure was identified in 12 women (9.1%). IOP-HPV testing sensitivity, specificity, and positive and negative predictive values for treatment failure were 91.7, 78.3, 62.2, and 96.0%, respectively, similar to HPV testing at 6 months (91.7, 76.0, 64.0, and 95.1%, respectively), and better than the values of other conventional predictive factors (cone margin, endocervical curettage, and cytology intraoperative at 6 months). IOP-HPV was strongly associated with treatment failure in the multivariate analysis (OR 15.40, 95% CI 1.58–150.42).

Conclusion: IOP-HPV testing is feasible, and accurately predicts treatment failure in patients treated for HSIL. This new approach may allow an early identification of patients with treatment failure.

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SS 5-3

INVASIVE CERVICAL CANCER QUALITY CONTROL IN SPAIN

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Introduction. The most common pitfalls in screening strategies to prevent cervical cancer are poor screen attendance and poor sensitivity of the cervical cytology.

Objective. To estimate proportion of false negatives smears in previous negative cytology of women with an invasive cervical cancer.

Methods: This retrospective study included 41 women with invasive cervical cancer diagnosed between 2000-2010 years in all Public Hospitals of Asturias (north of Spain) and negative cytology tests reported within 5.5 years of diagnosis. Retrieved cytologies were reviewed by a expert pathologist blinded to the case status and original cytology diagnosis.. Cytology tests performed within 6 months were assumed either to be tests leading to the diagnosis of cancer; these are excluded from the screening histories. 122 cytologies from women with no cervical cancer were included.

Results. Out of 41 women with cervical cancer, 61 previous smears with a negative result were reviewed. 61% bellowed to women with squamous tumors, 34,4% with a adenocarcinoma. An additional 122 negative smears from women without cervical pathology. Among the 61 smears from cancer cases, 46 were negative, 16 hadan abnormal results and 2 were inadequate. This resulted in a false negativy estimate of 27.1%. (Adenocarcinomas 52.6% vs. squamous tumors 16.2%, $p < 0.05$). All of 122/122 negative cytology test were confirmed as negative.

Conclusion. There is a need to reduce false negatives results to reduce invasive cervical cancer. Use of HPV tests may help.

SS 5-4

DO THE UNDERSCREENED WOMEN REMAIN THE PRINCIPAL CAUSE OF CERVICAL CANCER?

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Objective: Audit of women who have developed invasive cervical cancer (CC) is an important part of quality control within screening activities. We aimed to analyse the screening history in the 10 years preceding the study entry among women with and without CC in a predefined study area for the period 2000-2011.

Methods: 323 women with CC from six Pathology Departments in Catalonia (Spain) and 23,782 women with negative cytology were compared. Age, previous history of cytologies and histological type and FIGO stage were collected from the pathology registries. Logistic regression analysis was used to estimate odds ratios (OR) and 95%Confidence Intervals (CI95%).

Results: History of cytology was registered in 26.2% of CC cases and in 78% of the control women ($p<0.0001$) and its frequency decreased with increasing age. Compared to women with squamous cell carcinoma, adenocarcinoma cases were significantly more likely to have a cytology within the 3-year interval preceding cancer diagnosis (OR=2.6 CI95%:1.2-5.6) and to have normal cytology results in previous screenings (OR=2.4 CI95%:1.2-4.5). FIGO II-IV cases were more common among older women (older than 60 years).

Conclusions: Lack of screening is a major limitation in CC prevention. Efforts to increase population coverage of screening, especially in older women, in which a high number of non-screened and higher stages of cancer were observed, have to be paired with improving the sensitivity of the principal screening test for a better CC diagnosis, especially in the diagnosis of adenocarcinomas. Use of HPV based screening tests may significantly improve the efficiency of screening interventions.

SS 6-1

OPTIMAL SCREENING STRATEGIES IN THE ERA OF VACCINATION IN TERMS OF COST-EFFECTIVENESS - AUSTRALIA

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Objectives: By 2016, all women aged <35 years will have been offered HPV16/18 vaccination in Australia. This has prompted major review of the National Cervical Screening Program (which involves 2-yearly cytology from 18-69 years). The review took a linked evidence approach involving modelled evaluation of potential new screening strategies.
Methods: We used a comprehensive dynamic model of HPV and cervical screening, and estimated outcomes and cost-effectiveness of a total of 132 clinical management algorithms for cytology screening and for 5-yearly primary HPV screening in women aged 25-64 years. For HPV screening we evaluated cytology triage of pooled oncogenic types, HPV16/18 partial genotyping, and co-testing with cytology.

Results: The most effective strategies involved 5-yearly HPV with partial genotyping and direct referral of 16/18 positive to colposcopy. These are predicted to decrease cancer incidence and mortality by 13-18% and have cost savings of A$34-53M (16-25% of total program cost) in unvaccinated women; similar results are predicted in cohorts offered vaccination. With direct referral of 16/18 positive women, colposcopies would have increased by 12-25% compared to the present level if the population remained unvaccinated, but this would have been driven by referrals in women <34 years. In a population offered vaccination, by contrast, a decrease in the number of colposcopies (by 11-13%) is predicted. Screening until age 69 years increases the overall mortality improvement to 13-22%.

Conclusions: This work led to new national screening recommendations for 5-yearly HPV screening with partial HPV genotyping in HPV vaccinated and unvaccinated women, 25-69 years of age.

Declaration: The POLICY1 model platform was developed via grants from the National Health and Medical Research Council (NHMRC) Australia, government consulting contracts, and funding from other not-for-profits including Cancer Council NSW. KC is co-PI of an investigator-initiated trial of cytology and primary HPV screening in Australia ('Compass'), which is conducted and funded by the Victorian Cytology Service (VCS), a government-funded health promotion charity. The VCS have received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana Inc USA. However neither KC nor her institution on her behalf (UNSW Australia) receive direct funding from industry for this trial or any other project. No technology-specific issues were addressed in this modelled evaluation.

SS 6-2

OPTIMAL SCREENING STRATEGIES IN THE ERA OF VACCINATION IN TERMS OF COST-EFFECTIVENESS: THE NETHERLANDS

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Objectives: Primary HPV screening will be implemented in the Netherlands in 2016. The new program involves an extension of the screening interval from 5 to 10 years for high-risk HPV-negative women aged 40 or 50. For women between 30 and 40, the interval will remain 5 years. A further reduction in number of screening rounds is expected for vaccinated cohorts. We will re-assess the safety of the current interval extension to 10 years for HPV-negative women aged 40 or 50. For vaccinated cohorts, we will evaluate safety and cost-effectiveness of extending the screening interval to 10 years for HPV-negative women below 40 and will also explore extensions of the screening interval beyond 10 years.

Methods: Fourteen-year follow-up data of the Dutch POBASCAM screening trial have been collected. Projections of the impact of vaccination on screening outcomes are based on HPV genotyping of HPV positive women. A statistical model will be used to link the follow-up data to cancer registry data and to evaluate cost-effectiveness.

Conclusions: The interval extension to 10 years for HPV-negative women aged 40 or 50 in the new program does not lead to an increased cancer risk provided that precancerous lesions progress slowly to cancer. For vaccinated cohorts, 10-yearly primary HPV screening for all age cohorts seems cost-effective and may offer a good balance between between safety and colposcopy burden.

SS 6-3

OPTIMAL NUMBER OF HPV VACCINE DOSES IN TERMS OF COST-EFFECTIVENESS

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Objectives: To estimate the incremental cost-effectiveness of 2- and 3-dose schedules of HPV vaccination programmes, and identify the duration of 2- and 3-dose HPV vaccine protection necessary for a 3rd dose to be cost-effective.

Methods: We used HPV-ADVISE, an individual-based transmission-dynamic model of multi-type HPV infection and diseases (anogenital warts, and cancers of the cervix, vulva, vagina, anus, penis and oropharynx) in Canada. We used a 70-year time horizon and 3% discount rate and performed the analysis from the health payer perspective. We also performed extensive sensitivity analyses, including duration of vaccine protection and vaccine cost.

Results: Under base-case assumptions (80% coverage, 85$/dose) vaccinating girls with 2 doses of the vaccine (vs. no vaccination) produced cost-effectiveness ratios varying between $7,900-24,300 per quality-adjusted life-years (QALY) gained. The incremental cost-effectiveness ratio of giving the third dose to girls (vs. 2 doses) was below the $40,000/QALY-gained threshold when: i) 3 doses provide longer duration of protection than 2 doses and ii) 2-dose duration of protection is less than 30 years.

Conclusions: 2-dose HPV vaccination is likely to be a cost-effective strategy if its duration of protection is at least 10 years. Giving the third dose of HPV vaccine is unlikely to be cost-effective if 2-dose duration of protection is longer than 30 years.

SS 6-4

OPTIMAL HPV VACCINE IN TERMS OF COST-EFFECTIVENESS (BIVALENT, QUADRIVALENT, NONAVALENT)

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Background: Two vaccines against HPV are currently licensed (a bivalent and a quadrivalent vaccine), which differ in terms of their breadth and duration of protection against both vaccine and non-vaccine HPV types. A nonavalent vaccine is in development which may directly protect against the most prevalent oncogenic HPV types not already in current vaccines.

Objective and Methods: To compare the potential effectiveness and cost-effectiveness of bivalent, quadrivalent and non-avalent vaccines.

Results: Many head-to-head model-based comparisons find that protection against warts from the quadrivalent vaccine is economically more valuable than the potentially better cross-protection from the bivalent vaccine. The value of the bivalent vaccine compared to its competitors is affected by uncertainty around its possible partial protection against warts, the longevity of its cross-protective efficacy and the type of endpoint used to measure its protection against non-HPV 16/18 types.

SS 6-5

COMPARING IMPACT OF DIFFERENT VACCINATION STRATEGIES (GIRLS-ONLY, GIRLS AND BOYS, AND OLDER WOMEN CATCH-UP).

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Objectives. We aimed at comparing the expected impact of different vaccination strategies to up-scale the Swedish national programme of vaccination.

Methods. We adapted a transmission model to assess the impact of the following different vaccination strategies: a) rising the maximum age of women's catch-up from 18 to 26 year-old, b) adding a one-time catch-up vaccination of boys of 13-26 years of age, and c) introducing school-based vaccination of boys. Vaccination coverage of girls and boys was modelled using the current national estimates.
For each vaccination scenario, we have estimated the expected relative reduction (i.e. effectiveness) of HPV16 prevalence by birth cohort and over time and the reduction of HPV16 prevalence per number of people vaccinated. We also assessed the potential for vaccination of boys to mitigate a temporary (5 year) reduction by 50% of vaccination coverage in the population.

Results. The extension of catch-up had a faster impact on effectiveness, while the introduction of school-based vaccination of boys increased the overall effectiveness against HPV16. Faster effectiveness could be observed for approximately ten years after vaccine introduction among women above 20 years of age or older, whereas increased effectiveness was observed among younger cohorts after approximately 15-20 years since the introduction of vaccination. The shift towards gender-neutral vaccination approximately halved the ratio between the expected reduction of HPV16 prevalence and number people vaccinated. Finally, the 6% loss of effectiveness due to a temporary vaccination coverage reduction was reduced to 0.5% by vaccination of boys.

Conclusions. Catch-up of older women and vaccination of boys optimize vaccination effectiveness and mitigate the negative consequences of temporary reductions of vaccination coverage.

SS 6-6

INVESTIGATING THE IMPACT OF HPV VACCINE ON THE COST-EFFECTIVENESS OF CERVICAL SCREENING IN DENMARK

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Objectives: A quadrivalent HPV vaccine has been implemented into the Danish national vaccine programme in 2009. Recent research demonstrates that it has been effective and a reduced risk of cervical lesions can be observed both in immunised individuals as well as on population level[(1)]. The reduction in the prevalence of observed cervical lesions may impact on the cost-effectiveness of cervical screening programme. The extent of this impact and whether changes to the screening programme will be required is not currently established. The objective of this study is to investigate the impact of the vaccine on the cost effectiveness of the current screening programme and to assess a range of alternative screening strategies.

Methods: An existing Markov model [(2)] is being adapted to a Danish context. The model follows a hypothetical cohort of women through cervical screening and treatment pathways, investigating a range of screening strategies varied by the age at which screening begins and ends , as well as intervals between screens.

Results and conclusions: The effectiveness of the vaccine is likely to continue having a significant impact on prevalence of HPV infections, cytological abnormalities and cervical cancers. The findings of this study will help establish the most cost-effective scenarios for cervical screening in Denmark.

1. Baldur-Felskov B, Dehlendorff C, Munk C, Kjaer SK. Early Impact of Human Papillomavirus Vaccination on Cervical Neoplasia—Nationwide Follow-up of Young Danish Women. Journal of the National Cancer Institute. 2014.
2. Sopina E, Ashton T. Cost-effectiveness of a cervical screening program with human papillomavirus vaccine. International Journal of Technology Assessment in Health Care. 2011(27):290-7

SS 7-1

SCREENING AT THE EXTREMES: RISK IN WOMEN <30 AND >65

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Cervical neoplasia screening guidelines have been crafted to reduce patient risk for developing cancer by optimizing triage to and detection of treatable precancer. The principle of equal management for equal risk permeates US guidelines but such an approach historically was modified by patient age. The vast majority of cervical cancer risk is in the core age group 30-65, but what about the risk for women outside of this target core? For women less than 30 the risk of CIN2/3 may be high but invasive cancer quite low. And how does that risk vary across the decade 20-30? New data suggest that our historic approach of using cytology alone in young women for its specificity at the sacrifice of sensitivity may not have been optimal, particularly in women 25-30. Indeed given recent clinical trial data the argument can be made that HPV testing can perform very well in women 20-30 if only one tempers the response to a positive result.

At the other extreme current US screening guideline recommends women with adequate and negative screening histories stop screening at age 65. This too was based on the very low risk of cancer in women who have been repeatedly over time HPV negative and Pap negative. But there are many caveats based on residual risk of prior HSIL or Cancer, treatment, hysterectomy status, immune status, etc. Furthermore there is recent controversy regarding how those reassuring risk were derived. (Cancer. 2014 Jul 1;120(13):2032-8.) Despite this controversy, the question is whether in reality a sensitive screening or combination of tests at age 65 can be so reassuring as to allow women to no longer be screened for the final 2-3 decades of life expectancy?

Conclusion: Data from the recent literature predicts that for the women in the first decade and last decades of screening HPV testing can be applied to the benefit of both the patient and the health system and this view is contrary to many historic and even current screening guidelines.

SS 7-2

RATIONALE FOR THE DECISION TO REDUCE THE AGE TO START COTESTING FROM 30 TO 25

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Objective: To explain the decision to move the age to start cotesting (Pap plus cytology) for routine screening down to 25.
Methods: Review of cytology, HPV testing, and histology results by age over 2003-2012.
Results:

1) SEER cancer rate 25-29 is 5.1/100,000/year; our current all-ages rate is 5.0
2) 2012 CIN3 rates are highest at 25-34 and virtually identical at 25-29 and 30-34 on our Regional Lab.

AGE	PATIENTS	CIN III	% CIN III
21-24	30,805	1	0.003%
25-29	40,045	191	0.477%
30-34	42,746	222	0.519%
35-39	38,695	110	0.284%

3) HPV testing routinely turns positive before cytology in our population eventually diagnosed with AIS and adenocarcinoma. (data to be shown).
4) ASC-US triage "store and sort" is no longer necessary
5) Cotesting permits enhanced cytology QC (data on cancer effect to be shown)
6) Simplification of Guidelines aids compliance
7) Current management of abnormals changes at 25, not 30
8) Screening is going to stop under 25
9) Pap negative HPV positive rates at ages 30-34 are 6.1%, versus 10.1% at ages 25-29.
10) Colposcopy will not lead to overuse of cervical excisional procedures if CIN2 and CIN2/3 in 25-29 are observed and not treated, as we recommend. Data on cancer risk with observation will be shown.

Conclusions: Initiation of cotesting at 30 was a reasonable compromise with the information available in 2004. Information developed since that time informed the decision to decrease to 25, taken in June of 2012

SS 7-4

MANAGEMENT OF ASCUS/LSIL WOMEN UNDER 30: EVIDENCE FROM A NATIONWIDE AUDIT

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Objectives: ASCUS and LSIL are relatively common among women under 30, but most early lesions heal spontaneously and cervical cancer in this age group is rare. Results from a previous audit showed repeat cytology was an unsafe management of women with ASCUS/LSIL and that referral to colposcopy was necessary for adequate reduction in cervical cancer risk[1]. However, the proportion of ASCUS/LSIL smears in young women has increased dramatically in the last decade[2] making direct referral impractical. As part of a new, and much larger audit, that also has adequate power to analyse specific age groups, we re-evaluated the management of young women with ASCUS/LSIL and subsequent risk of cervical cancer.

Methods: All women in the screening ages resident in Sweden between1989-2011 were followed. Management of the ASCUS/LSIL diagnoses within 25 months was classified as repeat cytology, histology, or no further assessment. Incidence rate ratios (IRR) of subsequent cervical cancer within 6.5 years following the ASCUS/LSIL were estimated using Poisson regression for different age groups and management strategies.

Results: Incidence of cervical cancer among women with ASCUS/LSIL below 30 was low, although elevated compared to normal cytology. Repeat cytology within 3 months after an ASCUS carries a similar risk of cervical cancer compared to biopsy (IRR 0.9 (95% CI 0.3-2.5) among women aged 22-27. For LSIL, repeat cytology gave higher cancer risks than biopsy.

Conclusions: For women aged 27 or younger with ASCUS, repeat cytology was not associated with increased cancer risk. For women with LSIL, referral with biopsy had lower cancer risks than repeat cytology. This analysis represents an example of how the analysis of registry data can be used for incremental optimization of a cervical cancer screening program when specific issues arise.

1. Silfverdal L, Kemetli L, Andrae B, Sparen P, Ryd W, et al. (2009) Risk of invasive cervical cancer in relation to management of abnormal Pap smear results. American Journal of Obstetrics and Gynecology 201: 188 e181-187.
2. Swedish National Quality Register for Cervical Cancer Prevention (2013) Prevention of Cervical Cancer in Sweden: Annual Report 2013. Stockholm, Sweden: Swedish National Quality Register for Cervical Cancer Prevention.

SS 8-1

CANCER ASSOCIATED WITH HPV: THE CURRENT PICTURE
INTRODUCTION, OVERALL PICTURE AND GAPS

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Infection with human papillomavirus (HPV) is recognized as one of the major causes of infection-related cancer worldwide, as well as the causal factor in other diseases. Strong evidence for a causal etiology with HPV has been documented for cancers of the cervix uteri, penis, vulva, vagina, anus and oropharynx. Of the estimated 14.1 million new cancers occurring in 2012 worldwide, 4.8% were attributable to HPV infection, with substantially higher incidences and mortality rates seen in developing versus developed countries. The proportion of cancers attributable to HPV varies by anatomic site, with nearly 100% of cervical, 88% of anal and <50% of lower genital tract and oropharyngeal cancers attributable to HPV.

Massive introduction of safe and efficacious prophylactic vaccination against HPV infections need to be added to screening efforts to result in a major impact in HPV cancer burden. Regular screening remains limited to few countries worldwide, it is estimated that around 44 million women worldwide have been vaccinated against HPV (3-doses) through national HPV vaccination programs. This represents 1.3% of the total female population and 38.4% of targeted female cohorts.

While progress in our understanding of the natural history and prevention of HPV related cancers has considerably increased in the last decade many gaps remains. Particularly implement HPV-based preventive strategies need to be organized in a facilitating equity and acceptable ways. Scientifically sound advocacy to counter barriers facing the adoption of adequacy strategies are strongly needed.

SS 8-2

METHODOLOGICAL ISSUES

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What are the challenges we face in understanding the role of HPV infection in other anatomical sites? Is HPV infection also a necessary cause for cancers other than the uterine cervix? The answer is clearly 'no' but it has become increasingly clear that HPV infection plays a dominant role in anal cancer.
Does the discovery of HPV DNA in tumor specimens from non-anogenital, non-oral sites or tissues represent evidence that HPV is playing a causal role in these lesions? What are the causal criteria that one must consider in making causal inferences? What are the methodological limitations in advancing conclusions related to causality?
The presenter will review epidemiologic and other scientific criteria that serve to assign causality for policy decisions using research on HPV as example.

SS 8-3

CERVIX AND VAGINA

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Based on Globocan 2012 data, cervical cancer is the fourth most common cancer in women, and the seventh overall, with an estimated 528,000 new cases. A large majority (around 85%) of the global burden occurs in the less developed regions, where it accounts for almost 12% of all female cancers. Cervical cancer remains the most common cancer in women in Eastern and Middle Africa. There were an estimated 266,000 deaths from cervical cancer worldwide in 2012, accounting for 7.5% of all female cancer deaths. Almost nine out of ten (87%) cervical cancer deaths occur in the less developed regions. It has been estimated that cervical cancer accounted for 7.8 million years of life lost (YLL) in women. Almost all cervical cancer cases are attributable to HPV. When run in adequate conditions HPV DNA; HPV RNA and p16 overexpression are almost universally positive markers. A tiny fraction of cervical cancer cases of glandular origin may, however, turn to be negative to these markers and research is ongoing to disentangle their aetiology.
Cancer of the vagina is a much rarer entity than cervical cancer. In 2008 there were 27,000 new cases of invasive vaginal cancer worldwide. In the literature, HPV DNA ranged from 25 to 89%. Recent estimates from a large international study showed that HPV DNA was detected in 74.2%. Preliminary data suggest that RNA and p16 overexpression confirm this important HPV contribution.

The role of different markers to attribute HPV in cancer etiology will be discussed.

SS 8-3

THE CURRENT PICTURE OF VULVAR AND PENILE CANCER

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In this presentation, the current picture of vulvar and penile cancer regarding burden and HPV detection information will be reviewed.

Vulvar and penile cancers are rare entities with a global annual burden of 27,000 and 22,000 estimated new diagnosis, respectively. HPV infection is etiologically related to both of these cancers.

In a recent large scale worldwide analysis conducted at the Catalan Institute of Oncology (1), using a homogeneous protocol for HPV DNA testing (SPF10/DEIA/LiPA25) in paraffin-preserved tissue blocks, we reported an HPV DNA detection rate of 29% in vulvar carcinoma (out of 1,709 cases) and 87% in high-grade preinvasive intraepithelial lesions (out of 587 cases). Interestingly, when $p16^{INK4a}$ overexpression was considered, 25% of the vulvar carcinomas were both HPV DNA and $p16^{INK4a}$ positive. In penile lesions, the HPV DNA detection rate was of 33% in penile cancers (out of 877 cases) and 88% in high-grade preinvasive lesions (out of 83 cases).

HPV DNA positivity was higher in warty-basaloid cases compared to other pathology diagnosis, and variability on HPV detection by geography was observed in both cancer sites. HPV detection was higher in younger ages in vulvar cancer while this association was not found in penile cancers.

Like in other anogenital sites, HPV16 was the most common type detected both in vulvar and penile cancers with a relative contribution among HPV DNA positive cases of 73% and 68%, respectively. HPV16/18 vaccine's preventable fraction among HPV positive cases was of 77% in vulvar and 70% in penile cancers.

1. de Sanjosé S, Alemany L, Ordi J, et al; HPV VVAP study group. Worldwide humanpapillomavirus genotype attribution in over 2000 cases of intraepithelial andinvasive lesions of the vulva. Eur J Cancer. 2013 Nov;49(16):3450-61.

SS 8-4

CANCERS ASSOCIATED WITH HPV: THE CURRENT CLINCIAL PICTURE – THE ANUS

C Fairley

Melbourne Sexual Health Centre, 580 Swanston Street, Carlton, Melbourne, Victoria, 3053, Australia and Central Clinical School, Monash University Australia.

This presentation will discuss the current clinical picture of anal cancer. This will include discussion of the relatively low incidence of anal cancer in the general population and in high risk groups, including sexual risks, HIV infection and other immune deficiency conditions. The clinical presentation of anal cancer will be discussed including the long duration of symptoms before presentation to a health care worker in all risks groups. The importance of improving this substantially will be discussed because of the effect of early presentation and diagnosis has on the morbidity and mortality of the condition. The current treatment recommendations will be discussed in the context of a push for earlier diagnosis and the use of surgery for localised small tumours. The presentation will also discuss what steps should be taken in relation to patient and provider education if diagnoses are to be made substantial earlier than they currently are. The complex and relatively controversial issue of screening for anal cancer by cytology, high resolution anoscopy or routine regular clinical examinations will also be discussed. Recommendations will be made until the data large scale studies are available to answer these important questions

SS 8-6

HPV PERSISTENCE/P53 OVEREXPRESSION AND TREATMENT OUTCOME POST-ENDOSCOPIC ABLATION OF BARRETT'S ESOPHAGUS

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Background & Aims: We recently reported a potential role for high-risk human papillomavirus (hr-HPV) in the pathogenesis of esophageal adenocarcinoma (EAC). Thus, HPV and p53 [a Barrett's dysplasia (BD) progression marker] clearance/persistence was examined in relation to treatment outcome after endoscopic ablation of BD/EAC.
Methods: Forty patients with BD/neoplasia undergoing radio-frequency ablation (RFA)+/-endoscopic mucosal resection (EMR) were analysed. Pre/post-treatment biopsies were assessed for HPV DNA, viral transcriptional markers (E6/E7mRNA/p16INK4A) and p53 mutation.
Results: Post-ablation, 34/40 subjects eradicated dysplasia/neoplasia [squamous n=24, intestinal metaplasia, n=10]. 6/40 patients with detectable dysplasia/EAC post-treatment were positive for persistent biologically active hr-HPV (n=2) or p53 overexpression (n=4). Pre-ablation, 15 subjects were positive for biologically active HPV16/18 and 13 cleared the infection post-treatment of which 12 eliminated dysplasia/EAC. One patient who cleared the virus post-ablation subsequently developed p53 mutation with cancer progression. 10/13 subjects with p53 overexpression (pre-treatment) cleared the mutation after ablation and eradicated dysplasia/neoplasia, whereas 3/13 with persistent p53 mutation had ongoing dysplasia post-treatment (p=0.004).
Conclusions: Most HPV infected BD/EAC patients cleared the infection with endotherapy. Persistent dysplasia/neoplasia post-treatment was associated with HPV or p53 persistence.

SS 8-7

HUMAN PAPILLOMAVIRUSES AND SKIN CANCER – THE CURRENT PICTURE

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Human papillomaviruses (HPVs) infect squamous epithelia and can induce hyperproliferative lesions. More than 120 different HPV types have been characterized and classified into five different genera. While mucosal high-risk HPVs have a well-established causal role in anogenital carcinogenesis, the biology of cutaneous HPVs is less well understood. The clinical relevance of genus beta-PV infection has clearly been demonstrated in patients suffering from epidermodysplasia verruciformis (EV), a rare inherited disease associated with a high rate of skin cancer. In the normal population genus beta-PV are suspected to have an etiologic role in skin carcinogenesis as well but this is still controversially discussed. Their oncogenic potency has been investigated in mouse models and in vitro. The International Agency for Research on Cancer (IARC) has classified the genus beta-HPV types 5 and 8 as "possible carcinogenic" biological agents (group 2B) in EV disease.

Here, an overview on the knowns and unknowns of infections with genus beta-PV will be given and their potential impact on skin carcinogenesis in the general population will be discussed.

SS 8-8

HUMAN PAPILLOMAVIRUS (HPV) INVOLVEMENT IN OTHER CANCERS

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In addition to genital cancer, HPV has been implicated as a potential causal agent in benign, premalignant and malignant lesions at different anatomic sites. On the basis of the strength of evidence on this HPV association, we may distinguish different categories of HPV lesions: 1) established, 2) emerging, and 3) controversial HPV lesions. The global annual disease burden of all these HPV-associated malignancies was estimated recently by this author (Scand J Infect Dis, 41: Suppl. 107 and Suppl. 108; 2009). When all 3 categories are taken into account, the malignancies with established or suspected HPV association comprise almost 5 million cases worldwide, and over 8500 cases in Finland. There is no doubt that among all these malignant tumours attributed to HPV, HPV16 and HPV18 represent a major viral burden. Included in the list are squamous cell carcinomas in the following specific anatomic sites: eye and adnexal tissues, tongue, oral cavity, pharynx, nose and paranasal sinuses, larynx, bronchus, esophagus, anus and anal canal, skin (non-melanoma), uterine cervix, vulva and vagina, urinary bladder & urethra, and penis. The present survey implicates that a minimum of 7.859 to 8.316 new cases of HPV16- or HPV18-associated clinical lesions would be detected each in Finland. When adjusted for the European Standard Population, the respective age-adjusted incidence rates are 137/100,000 and 145/100,000. The implications of these data should be straightforward, but two impending challenges for designers of future HPV vaccination programs are: 1) the marked imbalance of HPV16/18 disease burden between the genders, and 2) HPV6/11 annual disease burden far exceeds that of HPV16/18.

SS 8-9

ECOLOGY OF HIGH-RISK HUMAN PAPILLOMAVIRUS (HR-HPV) INFECTIONS IN HETEROSEXUAL MEN (MSW), STUDIED USING EXPRESSED PROSTATE SECRETIONS (EPS) VERSUS ANOGENITAL SAMPLES

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Background: Detection methods and anatomical sites for optimal HPV sampling are of high interest. While the most of studies on HPV epidemiology employ "standard" genital (penile/urethral) and anal samples, prostate secretion obtained during a routine urological visit might represent an additional informative sampling material for the studies in men. HPV prevalence in the (ano)genital samples and EPS specimens was studied with a reference method from the WHO HPV LabNet global reference laboratory.

Methods: In total, β-globin positive complete sets (penile, urethral, anal swabs and prostate secretion) from 150 STI-negative Russian MSWs (age 20-58 years, sex debut 13-25 years, 1-700 life-time sex partners) attending a urology unit of a STI were collected in St. Petersburg. HPV testing and genotyping for 13 oncogenic HPV types (IARC WHO recommendations) was conducted, using a Luminex assay.

Results: Overall, the HR-HPV prevalence was 45.3%, and 10.0%, 14.7%, 20.7% and 19.3% for anal, penile, urethral and prostate samples, respectively. Compared to analysis of commonly used anogenital samples, studying EPS increased the HPV prevalence in this population by 7.3%. The most commonly detected HPV types were: 16, 45, 18, 59 and 51. Type 45 detection in a genital site sample was significantly associated with type 45 detection in the anus (any 1 or 2 genital sites: $p=0.0033$ and any 1 or 3 genital sites: $p=0.0067$).

Conclusions: HR-HPV infection is commonly detected in (ano)genital sites of low-risk Russian heterosexual men. Prostate samples should be a focus for HPV studies among high-risk groups.

The study was funded in part by Swedish Cancer Foundation. No pharmaceutical grants were received in the development of this study.

Table: The HR-HPV infection detected in (ano)genital samples from 150 heterosexual men

Anatomical sites tested, 150 men	Any HR-HPV, in total	HR-HPV prevalence
EPS, prostate	29	19.3%
G, penile	22	14.7%
U, urethra	31	20.7%
R, anal	15	10.0%
G or U or R	57	38.0%
G or U or EPS	59	39.3%
G or U or R or EPS	68	45.3%
All anogenital but not EPS, missed cases	11	7.3%

SS 9-2

CAN SELF-SAMPLING INCREASE SCREENING ATTENDANCE: A META-ANALYSIS AND SYSTEMATIC REVIEW

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Background: Suboptimal coverage for cervical cancer screening has been identified as an important contributor to incident cases of cervical cancer in many industrialised countries. With the introduction of high-risk HPV (hrHPV) testing as an effective primary screening option, the use of self-obtained samples (self-samples) has the potential to increase participation of hard-to-reach women in screening.

Methods: A systematic review and meta-analysis were performed to evaluate the response rate to invitations including a self-sampling kit for hrHPV-testing versus invitations for having a Pap smear taken by a clinician, sent to underscreened women or women who never participated in screening.

Results: Eleven studies were found eligible. In an intention-to-treat analysis, the pooled attendance rate was 25% (95% CI=20-29%) in the self-sampling arm, and 11% (95% CI=6-17%) in the control arm (relative attendance rate: 2.71 [95% CI=1.45-5.08]). When women were invited by a door-to-door approach, instead of by mail, the pooled attendance rate was 90% (95% CI=73-100%) and 64% (95% CI=19-100%) for women in the self-sampling arm and the control arm, respectively (relative attendance rate: 1.45 [95% CI=0.83-2.53]). The relative compliance to follow-up was 0.77 (95% CI=0.50-1.20) in the self-sampling arm compared to the control arm. The relative detection rate of CIN2+ was 3.05 (95% CI=1.76-5.28) in the self-sampling arm versus the control arm.

Conclusion: Considering invitation by mail, our analysis demonstrated that women who were never screened or underscreened, were more than twice as likely to undergo screening when offered a self-sampling kit, compared to an invitation for conventional screening.

SS 9-3

HOW TO TRIAGE WOMEN BEING HPV-POSITIVE ON A SELF-SAMPLE: DIRECT METHYLATION MARKER TESTING VERSUS CYTOLOGY ON AN ADDITIONAL SMEAR

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Objectives To identify HPV-test positive women associated with cervical intraepithelial neoplasia grade 2 or worse (CIN2+), cytology triage is accepted. However, direct cytology triage on self-sampled specimens is not reliable. We evaluated whether direct DNA methylation-based molecular triage on self-samples performs non-inferior in CIN2+ detection to cytology triage on extra physician-collected samples.

Methods We invited 46,001 non-responders of regular cervical screening to submit a self- collected sample for HPV testing. Women with an HPV-positive self-sample were randomised (1:1) over indirect triage by cytology or direct triage (on the self-sample) by methylation analysis of *MAL and miR-124-2* genes. Triage positive women of both groups were referred for colposcopy. Primary endpoint was CIN2+ detection (Trial register: NTR6026).

Results 12,819 women submitted self-sampled material; 1,024 tested HPV-positive and were randomised to either molecular (n=515) or cytology triage (n=509). CIN2+ detection was similar in the molecular (17.5%; 90/515) and cytology triage group (14.7%; 75/509) (RR1.19, 95%CI 0.90-1.57). Colposcopy referral rates were 55% (284/515) in the molecular group and 29% (149/509) in the cytology triage group ($p<0.001$). Mean time to CIN2+ diagnosis was 96 days (range 22-703) in the molecular triage and 158 days (range 42-580) in the cytology triage group ($p<0.001$).

Conclusions DNA methylation analysis of *MAL/miR-124-2* on HPV test-positive self-samples is non-inferior to cytology triage in CIN2+ detection. Women with molecular triage did not need an extra visit to the physician for triage testing, showed a better compliance and shorter diagnostic track, but a higher colposcopy referral rate than women with cytology triage.

SS 9-4

HPV DETECTION FROM URINE- AN ALTERNATIVE FOR SELF-SAMPLING

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Human papillomavirus (HPV) testing in urine offers a convenient approach for cervical cancer screening but has previously suffered from limited clinical sensitivity. Recently improved approaches for urine-based HPV testing suggest that it could achieve a performance similar to HPV self-sampling. We recently evaluated two HPV assays in urine samples from a pilot study of women undergoing colposcopy, the Linear Array test and the Trovagen HPV assay. The sensitivity and specificity for detection of CIN2 or greater was 96.2% and 40%, respectively, for HPV testing from cervical samples. In comparison, urine-based Linear Array testing had a sensitivity of 80.8% and a specificity of 53.3%, respectively, while the Trovagene assay had 92.3% sensitivity and 29% specificity, respectively. These results suggest that urine-based HPV testing may be an alternative approach for cervical cancer screening, especially in low resource settings with limited infrastructure for clinic-based collection of cervical samples. Larger studies are warranted to compare the performance of urine testing to established self-sampling and clinician-sampling approaches.

SS 9-5

SELF-SAMPLING IN CERVICAL SCREENING

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Studies have shown that offering self-sampling for HPV testing (HPV self-sampling) can improve the attendance to the cervical screening program. Pooled data from two self-sampling studies (PROHTECT-1 and -2) show that HPV self-sampling targets a substantial portion of non-attendees of all ethnic groups who have not regularly been screened. The data indicate that HPV self-sampling reaches the women at highest risk of cervical cancer. Several studies have reported that HPV self-sampling can have a similar sensitivity for CIN2+ as HPV testing on a cervical scrape obtained by a physician, although this may depend on the self-sampling device, HPV testing method and protocols used. In case the use of a given HPV test and self-sampler is clinically non-inferior to HPV testing on physician-collected cervical scrapes, HPV self-sampling may not only be used to complement current screening programs by increasing screening coverage, but may also be offered as alternative to all women invited for cervical screening. Self-sampled material is not suitable for cytomorphological analysis, and therefore cytology cannot be used as a direct triage method on HPV-positive self-samples. Alternative triage tools for HPV-positive women are available and feasible on self-samples, such as DNA methylation analysis, and clinically perform similarly as cytology triage testing on a physician-collected cervical scrape (PROHTECT-3). Altogether, HPV self-sampling combined with molecular triage opens the possibility of full molecular cervical cancer screening.

SS 10-4

EVIDENCE FOR LATENCY IN HIV-INFECTED WOMEN

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Natural history studies have consistently documented that 90% of HPV will become undetectable within 1-2 years of first detection. It remains unclear, however, whether the transition from HPV DNA positive to HPV DNA negative states in HPV natural history studies reflects viral clearance in the form of complete viral eradication, or immunologic control of the viral infection below limits of detection or establishment of latency. Even among immune competent women, a non-negligible proportion of type-specific HPV 'infections' which become undetectable are found to reappear; however methodological limitations preclude accurate estimation of what proportion of these 'recurrent detections' represent re-infection versus reactivation of latent infection. Data from several large natural history studies of HPV comparing HIV-infected to HIV-uninfected women demonstrate a profound influence of immune suppression on both HPV incidence detection, as well as HPV persistence, independent of sexual behavior differences. These data suggest that a proportion, perhaps a majority, of the relative increase in cervical HPV incident detection among HIV-infected compared with HIV-uninfected women results from a compromised ability to retain control of latent virus infection, rather than an increased susceptibility to new infection. The implications of virologic control rather than clearance on clinical care of the HIV-infected woman will be discussed.

SS 10-6

EVIDENCE FOR AND CONSIDERATION OF THE POTENTIAL IMPLICATIONS OF HPV LATENCY AND REACTIVATION IN OLDER WOMEN

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HPV infection is acquired rapidly following sexual debut, with a resulting peak in HPV prevalence in young adults in the United States. However, the pattern of age-specific HPV prevalence varies by geography and population, and a second peak in HPV prevalence around middle-age has been reported in several other countries. The causes of the second peak of HPV prevalence at older ages have not been elucidated, but have been suggested to be due to
(1) new sexual exposures,
(2) a cohort effect,
and/or (3) reactivation of latent infection.

Data will be presented to support that the variable presence and magnitude of the second peak of HPV prevalence at older ages may be due to a combination of all three of these factors. Given the mounting observational data to support the potential for HPV latency and reactivation in aging and older women, the clinical implications that this may have on cervical cancer risk, perception, and screening will be discussed.

SS 11-1

HPV IMMUNOLOGY, GENITAL VS ORAL

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OBJECTIVES: The human papillomavirus type 16 (HPV16) induces cancers in the cervix and in the oropharynx, which by nature is a stronghold of immunity. Here we compared the local immune response of both tumor regions in order to understand what part of the immune system is required for optimal therapy responses.

METHODS: Comprehensive cohort studies in which immunohistochemical, flowcytometric and functional data of isolated tumor-infiltrating immune cells were correlated to the clinical course of patients.

RESULTS: In both cervical and oropharynx squamous cell carcinoma's the presence of a dense infiltrate with CD8+ T-cells and low numbers of suppressive T cells is beneficial for clinical outcome and form an independent prognostic factor. While in cervical cancer a strong intraepithelial infiltration of matured M1 macrophages also is an independent prognostic factor for survival, the presence of M2 macrophages did not have a major impact whereas they were associated with poor outcome in oropharyngeal cancer. Analysis of the local T-cell response revealed the presence of HPV-specific T cells in ~50% of both cancer types. Notably, the detection of intratumoral HPV16-specific T-cell reactivity coincides with a better CD8 T-cell infiltration and a tumor-rejecting myeloid immune profile. Moreover, our preliminary data reveal that patients with HPV16-specific T-cell reactivity display a longer recurrence free period.

CONCLUSIONS: Intratumoral HPV16-specific T cells are associated with a stronger tumor-rejecting immune signature and clinical response to standard therapy. Thus, strategies to increase the number of HPV-specific T cells in the tumor are warranted to enhance clinical responses to standard therapy.

SS 11-2

IMMUNOLOGY OF REGRESSION VS PERSISTENCE.

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The host immune response is thought to be the key player in control of HPV infections. Innate immune responses are important initially whereas the development of a cell-mediated immune response is critical for clearance of a persistent infection and likely protection of future exposures. HPV has developed strategies to avoid detection by both the innate and adaptive immune arms. Key players in the innate arm include natural killer cells, dendritic cells (DC), Langerhans (LC) and keratinocytes. Most of these cell types promote cytokine-mediated pro-inflammatory responses. In addition, to the release of these pro-inflammatory cytokines, innate immune response can trigger the development of adaptive immune responses. One of the most criticial innate immune responses is linked to the activation of toll-like receptors (TLRs) which recognize imprinted pathogen associated molecular patterns. These allow for early non-specific recognition of pathogens. Numerous cells have TLRS including DC, LC and keratinocytes. TLRS are found on the cell surface as well as endosomal. The endosomal TLRS (TLR 3, 7, 8 and 9) play an important role for viral infections. Activation of these TLRs result in production of TNF alpha, IL-8, CCL2, CCL20, CXCL9 and type 1 IFN. HPV 16 appears to be able to downregulate TLRs as part of their ability to downregulate immune responses. We showed that persistence of an incident HPV 16 infection was associated downregulation of TLRs 3, 7,8 and 9.
We also showed that TLR expression was closely associated with the development of cytotoxic T cell response resulting in HPV clearance underscoring the importance of TLRS in developing cell –mediated immune response. We also have evidence that TLRs also may play a role in clearance of CIN 2/3 lesions.
Migration of antigen presenting cells (APC) are also important for immune responses. HPV can modulate these functions. E6 and E7 down regulated E-cadherin disrupting the adhesion of keratinocytes to LC. Severe dysplastic lesions show little to no expression of several adhesion/costimulatory molecules (e.g.CD11a, CD50) underscoring an environment with little ability to present antigen. In conclusion, HPV persistence is likely a combination of defective host immune responses and the ability of specific HPVs to downregulate the immune response. Further data that underscores the importance of immune responses and TLRs is the successful use of TLR agonists in therapeutic trials.

SS 11-4

NOVEL APPROACHES FOR THERAPEUTIC VACCINATION OF HPV-ASSOCIATED NEOPLASIA

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Therapeutic vaccines for patients with HPV-associated neoplasia are considered interesting strategies for improved treatment approaches. Classically the viral oncogene products E6/E7 have been used as antigens in clinical studies. Clinical responses have been reported in single studies from patients with precancer. The induction of successful treatment responses in cancer patients appears more challenging. The given room for improved therapeutic approaches motivated us to develop a strategy complementary to the frequently used viral antigens. The cellular protein $p16^{INK4a}$ is strongly overexpressed in HPV-associated precancers and cancers. The up-regulation of $p16^{INK4a}$ expression levels as an early consequence of HPV-mediated transformation renders the protein an interesting target for novel treatment approaches. Therapeutic vaccination using a $p16^{INK4a}$ peptide has been recently tested by us in a clinical phase I/IIa study. Vaccination of patients with advanced HPV-associated cancers was well tolerated and resulted in cellular and humoral immune responses against the $p16^{INK4a}$ peptide. Combined with the development of novel $p16^{INK4a}$-containing vaccine constructs aiming at a further improved immunogenicity, the approach is currently being translated into the next study phase to show clinical efficacy.

SS 11-5

THE ROLE OF NATURAL IMMUNE CONTROL IN THE EFFECTIVENESS OF NON-IMMUNE TREATMENT

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Control of HPV infections, persistence of disease, and natural regression are related to the immune system of an individual. Immunologically compromised patients (iatrogenically or by HIV infection) have a higher burden of disease and faster lesion development. HPV has evolved to maintain a low profile during its life cycle, avoiding to activate immunity, and in addition has immunosuppressive features that are tolerogenic to the viral antigens. Treatments based on specific or generic immunostimulation have shown some therapeutic success and can be enhancing clearance of infection. Basically an inflammation is induced and natural viral antigen is presented in an immunogenic context. Similarly, during non-immune treatment (e.g. cryotherapy, laser destruction, biopsy and surgery) inflammation can be induced and the immunosuppressive balance kept by the virus can be disturbed inducing immune responses. Such responses may be local and not measurable systemically. However, they may be important to support clinical regression and long lasting protection from recurrence or reinfection. Unfortunately, few evidence exists for the significance of these immune responses induced by ablative or surgical methods to date. Potential mechanisms will be reviewed.

SS 12-2

EPITHELIAL TARGET CELL IN CERVICAL CARCINOGENESIS – CURRENT CONCEPTS AND OBSERVATIONS

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Since decades it has been suspected that HR-HPV targets specific cells in the cervix but none have been unequivocally identified.
There are three types of cervical epithelia: the original squamous epithelium of vaginal Muellerian origin, and the metaplastic squamous epithelium and the columnar epithelium of uterine Muellerian epithelial origin. All types of epithelia can be infected by HR-HPV. Infection occurs when minor trauma exposes the cell membrane of reserve and basal cells of cervical epithelium to HR-HPV. Binding via a yet unknown cellular receptor leads to a conformational change of HPV with cellular uptake of HPV by presumed endocytosis. After infection, HPV genomes may persist in episomes in low copy numbers. According to the most widely accepted model, expression of viral genes in individual infected reserve/basal cells leads to lateral extension of the initial HPV-infected cell clone. Persistent HR-HPV infection is strongly associated with progression to HSIL, AIS and invasion.
2 major theories with respect to epithelial target cell of cervical carcinogenesis exist: The SCJ-cell theory and the reserve cell theory.
SCJ-cell theory: Most HSIL and SCC arise from a small cuboidal cell population at the SCJ characterized by a unique gene expression signature and expression of specific biomarkers (CK 7 and others). The transformation zone (TZ) itself is not considered a major site of HSIL/SCC development.
Reserve cell theory: Most HSIL and SCC are of reserve cells origin. Reserve cells are small cuboidal cells concentrated at the SCJ but also present in the entire columnar epithelium, although at lower frequency. They are characterized by expression of the p53 homolog p63 and cytokeratin 17. HR-HPV-infection of reserve cells produces a flat, immature appearing HSIL, erroneously referred to as atypical immature metaplasia. HR-HPV-infected metaplastic squamous epithelium of reserve cells origin gives rise to LSIL and HSIL. The SCJ and the entire TZ (uterine Muellerian origin) but not the original squamous epithelium (vaginal Müllerian origin) of the cervix are major site of HSIL/SCC development.
Further studies using HPV detection methods that preserve tissue morphology and tissue culture experiments may help to evolve these theories.

SS 12-3

POLYMORPHISMS OF THE HUMAN LEUKOCYTE ANTIGEN DRB1 AND DQB1 GENES AND HPV INFECTION IN THE LUDWIG-MCGILL STUDY

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Objectives: In 2002, we investigated whether polymorphisms in the human leukocyte antigen (HLA) class II loci HLA-DRB1 and –DQB1 were associated with the prevalence and persistence of human papillomavirus (HPV) infection in the Ludwig-McGill cohort in Southern Brazil. In this follow-up analysis with high-resolution HLA genotyping we investigated whether the polymorphisms previously shown to be associated with risks of prevalence and persistence were maintained in a subcohort of 1324 women from the original study.

Methods: Period-prevalence (ever positivity) of HPV infection was defined over the first year of follow-up on the basis of 4 visits every 4 months. Prevalence, persistence, and long-term persistence were defined for HPV16, low-risk HPV types, high-risk HPV types, and any HPV infections. The associations between HLA polymorphisms and HPV infections were estimated using unconditional logistic regression analysis adjusted for age and race.

Results: The DRB1*1601-DQB1*0502 and the DRB1*04-DQB1*301 haplotypes were associated with a 6-fold and a 1.5 fold increase, respectively, in risk for any HPV infection prevalence. Similarly, the DQB1*0502 allele was associated with an almost 8-fold increase in risk for persistent HPV infection.

Conclusions: These results support that previously demonstrated polymorphisms, although not all of the originally studied alleles were associated with risk of HPV infection and persistence.

SS 12-4

UNIQUE FUNCTIONS OF THE HIGH RISK HPV ONCOPROTEINS.

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Despite intensive investigation there are still major questions about why infection with so-called high-risk (HR) and low-risk (LR) alpha HPV types can give such different clinical outcomes. The roles played by the two major viral oncoproteins, E6 and E7, in the development and maintenance of tumourigenic phenotypes are critical. Biologically, E6 and E7 display activities consistent with their respective associations with cancer, with HR E6 and E7 inducing cell immortalisation and cancers in animal models, whereas LR E6 and E7 exert little effect in such assays. Biochemically the differences are often less well-defined. This is not surprising, considering the similarities in the respective viral life cycles.

Recent studies have used proteomic approaches to identify distinctive interacting proteomes for the HR and LR E6 and E7 oncoproteins. A group of cellular targets that are unique to HR E6 are cellular PDZ domain-containing proteins, many of which control diverse cellular processes, including cell-cell contact, mobility and polarity. Comparison of different HR E6 oncoproteins reveals specific patterns of PDZ protein recognition by different HR viruses, with prevalent types, such as HPV-16 and HPV-18 having a broader spectrum of targets than the less prevalent HPV types. Furthermore, PDZ recognition is regulated by post-translational modification of E6, indicating that alterations in E6-substrate interactions will occur during the viral life cycle, and may be important during HPV-induced malignancy. Intriguingly, these activities of E6 appear to offer an alternative means by which HR E6 oncoproteins can overcome p53 function.

SS 12-5

VIRAL GENE ACTION DURING HPV-INFECTION AND CARCINOGENESIS – IMMUNE EVASION STRATEGIES AND PERSISTENCE

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Human papillomaviruses (HPVs) infect squamous epithelial cells of skin or mucosa giving rise to hyperproliferative lesions. A subgroup of high-risk genus alpha HPVs induces human anogenital malignancies, i.e. cervical cancer. In contrast, genus beta HPV, such as HPV5 or 8, are associated with non-melanoma skin cancer in epidermodysplasia verruciformis (EV) patients. An important question is, how these HPVs escape local immune control during infection and at later stages of carcinogenesis allowing their persistence in the epithelium. Our studies demonstrate that HPV-infected cells substantially re-program the function of professional antigen-presenting cells, which are the bridge between innate and adaptive immunity. A striking observation in HPV lesions was the lack of Langerhans cells as well as a substantial reduction of the Langerhans cell attracting chemokine CCL20. Using molecular tools, we unraveled how the HPV E7 oncoprotein directly interferes with a novel pathway of CCL20 chemokine expression in the epithelium and with Langerhans cell recruitment. Of note, at later stages in cutaneous and cervical carcinogenesis we observed extensive stromal inflammatory infiltrates, predominantly with myeloid cells including dendritic cells. Although dendritic cells differentiated well in the presence of HPV-infected cells, they were functionally disturbed. Importantly, they lost their ability to migrate towards lymph node homing chemokines, which is necessary to initiate adaptive immune responses. Instead, recruited myelomonocytic and dendritic cells were instructed by the HPV-transformed cells to produce the tumor-promoting matrix-metalloproteinase MMP-9 locally in the tumor. Both, the suppression of immune functions and pro-tumorigenic activities of the myeloid cells were driven by interleukin-6, a cytokine produced by the HPV-transformed cells. In summary, our studies have unraveled novel molecular mechanisms of virus-host interactions critical for evading host immune defense and providing a microenvironment that is conducive to persistent HPV infection and carcinogenesis. They may provide the basis for novel therapy approaches.

SS 13-2

COMMERCIALLY AVAILABLE HPV TESTS: GLOBAL OVERVIEW AND FUTURE CHALLENGES

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Objectives: Testing for high-risk HPV is an invaluable part of clinical guidelines for cervical carcinoma screening, management and treatment.

Methods: As of October 2014, at least 150 distinct commercial tests for detection of alpha HPVs and at least 95 variants of the original tests are available at the global market. The available commercial HPV tests have been provisionally divided into six main groups: (i) hrHPV DNA tests, (ii) hrHPV DNA tests with concurrent or reflex partial genotyping for the main hrHPV types, (iii) HPV DNA full genotyping tests, (iv) HPV DNA type- or group-specific genotyping tests, (v) hrHPV E6/E7 mRNA tests, (vi) in situ hybridization based HPV tests.

Unfortunately, only a subset of commercial HPV tests has documented clinical performance for any of the standard HPV testing indications. For more than 70% of HPV tests on the global market, no single publication in peer-reviewed literature can be identified. It should also be stressed that in contrast to commercial kits for "classical" molecular microbiology targets, the great majority of HPV tests currently on the market does not contain sample extraction part and number of them don't even mention nucleic acid extraction methodology in their manufacturer's instructions.

Conclusions: Manufacturers of HPV tests are urged to put more effort into evaluating their current and future products analytically, using international standards, and for all standard HPV testing clinical indications, using internationally agreed standards and clinically validated endpoints. Since extraction of nucleic acids is an invaluable part of the whole HPV testing procedure we urge manufacturers of HPV tests to put substantially more effort into this initial and crucial step of molecular testing. Manufacturer independent evaluations of HPV tests and publication of the evaluation results in peer-reviewed journals is also crucial. We predict that the number of commercial HPV tests will continue to increase in the near future, due to promising marketing opportunities. Namely, in contrast to "classical" molecular diagnostic microbiology testing areas which are considered very mature with expected annual growth rates 2-5%, annual growth rates of HPV tests selling are expected to remain as high as 20% at least through 2016.

SS 13-4

CLINICALLY ORIENTED EXTERNAL QUALITY ASSURANCE PROGRAMMES FOR HPV DIAGNOSTIC TESTS: URGENT NEED.

Francesca Carozzi

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The introduction of the HPV test as a primary screening test causes important changes in the screening system based on cytology. In some countries, the standardization of cytology (Pap-Test) is difficult to implement and to maintain . Hr-HPV test is more easily standardized, easier to implement and to maintain of the guidelines for the hr-HPV testing are followed , if a HPV test ,clinically validated for screening purpose, is used and if internal and external quality assurance system is in place in the laboratory. Theoretically a strong reproducibility is achievable in all laboratories (developed and developing countries). In organised population-based screening programmes the interval after a negative primary HPV test is 5 years, so a HPV laboratory must produce robust results not only in order to avoid false positives but also false negative. In fact a HPV negative result means that a woman will not be invited by screening over the next five years. The HPV laboratory has to be in place an internal and external quality control system. HPV testing starts with sample collection so consistent method for collection and handling is needed to provide comparable results over time and between laboratories. Another important aspects are the time and temperature of storage the samples. Endogenous Quality control to control for cellularity and/or reaction inhibition become an increasingly pertinent question for HPV primary screening.

The laboratory involved in HPV screening program has to provide the infrastructure and environment to deliver the assay robustly, a demonstration of competence monitored through regular competency assessment, set up of quality system and framework to monitor performance longitudinally. Each laboratory must produce SOP identifying how a member of the staff or a new operator has to be trained including a competency test through 'Validation Panel'. Laboratories undertaking HPV testing must include in every run IQC samples in addition to required kit controls. The Lab has to participate in EQA clinically oriented and in the same medium used for collect the clinical samples. The EQA must consent to the community a comparison between the results form different validated HPV screening tests and able to evaluate all 12 HR HPV types in an annual cycle. There are several accreditate EQA for HPV but the results are not elaborated in a way to consent a comparison between different HPV screening validated tests and not include samples collected in the several collection medium available.

SS 13-5

INTERNAL QUALITY CONTROL REQUIREMENTS AND EXTERNAL QUALITY ASSURANCE PROGRAMS FOR COMMERCIAL AND IN-HOUSE HPV GENOTYPING TEST: CURRENT STATUS

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Objectives: Accurate and internationally comparable HPV DNA detection and typing methodology is essential both for research on HPV vaccines, and for effective monitoring and implementation of HPV vaccination programs as well as introduction of primary HPV screening. Accreditation of clinical laboratories normally requires participation in an external quality assurance program.

Method: The HPV LabNet regularly issues international proficiency studies of HPV DNA genotyping assays. Participating laboratories were asked to perform HPV typing using one or more of their usual assays on 43 coded samples composed of purified whole genomic plasmids of sixteen HPV types (HPV6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68a and 68b) in a background of human cellular DNA. Proficient typing required detection in both single and multiple infections of 50 International Units of HPV 16 and HPV 18 DNA/ 5μl and 500 genome equivalents in 5 μl for the other types, with at least 97% specificity.

Results: The 5th international proficiency study was distributed in the autumn 2014. In the study 2013 a continued trend towards increased sensitivity and specificity was seen compared to the proficiency panel results from previous years. In 2013, 44% (59 out of 136) of the data sets were 100 % proficient for detection of at least one type and 30% of the data sets were proficient for all sixteen HPV types. This is a definite improvement compared to the first panel results from 2008 when 23%, <25 data sets were fully proficient. More than 30 different HPV commercial genotyping assay methods were used 2013 as well as several in-house assays. Many commercial tests have an internal control making it easier to control the standardised performance. However there was no difference in proficiency in the 2013 study between commercial and in-house assays.
Conclusions: A continuing global proficiency program has documented an improvement in comparability and reliability of HPV genotyping assay performance worldwide.

SS 13-6

NOVEL HPV TYPES BEYONG HPV 150: AN OVERVIEW

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Established Human Papillomavirus (HPV) types, up to HPV202, belong to 49 species in 5 genera. International standardization in classification and quality standards for HPV detection is ensured by the International HPV Reference Center.
The center
i) receives clones of potentially novel HPV types, re-clones and re-sequences them. If confirmed, an HPV type number is assigned and posted on www.hpvcenter.se.
ii) distributes reference clone samples, for academic research, under Material Transfer Agreements agreed with the originator.
iii) provides preliminary checking of whether new sequences represent novel types
and iv) issues international proficiency panels for HPV genotyping.

The rate of HPV type discovery is increasing, probably because of metagenomic sequencing. The γ-genus today contains 79 HPV types and 27 species, surpassing the ∝ and β genera with 65 and 51 HPV types, respectively. The novel HPV types beyond HPV150 will be reviewed.

SS 13-7

GLOBAL GENOMIC DIVERSITY OF HPV6 AND HPV11

Jelen MM[1], **Chen Z, Kocjan BJ, Burt FJ, Chan PKS, Chouhy D, Combrinck CE, Coutlée F6, Estrade C, Ferenczy A, Fiander A, Franco EL, Garland SM, Giri AA, González JV, Gröning A, Heidrich K, Hibbitts S, Hošnjak L, Luk TNM, Marinic K, Matsukura T, Neumann A, Oštrbenk A, Picconi MA, Richardson H, Sagadin M, Sahli R, Seedat RY, Seme K, Severini A, Sinchi JL, Smahelova J, Tabrizi SN, Tachezy R, Tohme S, Uloza V, Vitkauskiene A, Wong YW, Židovec Lepej S, Burk RD, Poljak M**

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OBJECTIVES To investigate the global HPV6/11 genomic diversity and phylogenetic relationships among the most variable HPV6/11 complete genome (CG) variants.

METHODS In total, 530 HPV6 and 207 HPV11 isolates from the anogenital and head and neck anatomical regions were obtained from six continents. Isolates were analysed in regions: E5a-E5b-L1-LCR and the most divergent were selected for CG sequencing. We constructed maximum likelihood (RAxML) phylogenetic trees, assigned (sub)lineages, identified (sub)lineage-specific SNPs and statistically evaluated the geographical and clinical associations among HPV6/11 genomic variants.

RESULTS In total, 130 and 14 CGs were obtained for HPV6 and HPV11, respectively. Pairwise heterogeneities of 190 HPV6 CGs (130 from our study, 60 from GenBank) and 63 HPV11 CGs (14 from our study, 49 from GenBank) were 1.6% and 1.4%, respectively. Global phylogenetic trees revealed two lineages (A and B) and five sublineages: B1-B5 for HPV6 and two lineages A and B and four sublineages A1-A4 for HPV11. Among HPV6 variants lineage B prevailed globally, lineage A in Asia and sublineage B3 in Africa and Americas. Sublineages B1 and B3 were associated with anogenital infections and B3 showed higher odds for infection in females. Among HPV11 variants sublineage A2 prevailed globally, while newly assigned lineage/sublineages B, A3 and A4 consisted of one African, one North American and one European variant, respectively.

CONCLUSIONS This is the first extensive work on globally circulating HPV6/11 genomic variants. Preliminary results suggest the existence of novel HPV6/11 lineage/sublineages, with HPV6 variants exhibiting some degree of ethnogeographic, gender and/or disease predilection in their distribution.

SS 14-1

OVERVIEW OF THE COHEAHR CONSORTIUM AND SELF-SAMPLING FOR PRIMARY HPV SCREENING

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In the CoheaHr project funded by the European Committee (www.coheahr.eu), (cost-) effectiveness of different preventive strategies for human papillomavirus (HPV)-related cancers will be compared. The goal is to build a reliable and comparable evidence base on the (cost-) effectiveness of preventive policies implemented under country-specific preventive services conditions. The evidence base will enable policy makers to make informed decisions on HPV prevention strategies which will strengthen health systems in Europe.

To achieve this goal, a set of specific tasks will be carried out. Three randomized trials will be performed in organized screening settings to determine: i) whether self-collection of specimens for HPV DNA testing is an effective and feasible alternative for physician-based sampling, ii) whether screening intervals can be extended in women vaccinated at young age, iii) whether vaccinating women two years before entering the screening program will favor the use of HPV screening. Furthermore, a feasibility study will assess the acceptability of HPV vaccination among screen-eligible women aged 25-45 years. Finally, transmission models, longitudinal analyses of European screening cohorts as well as meta analyses will contribute to the evidence base on program impact on HPV infection, cancer rates and mortality rates.

The first of the three randomized trials, i.e. the HPV self-sampling screening trial, will be performed as a randomized pilot implementation trial in the Dutch and Finnish organized screening settings. The main aim is to determine whether self-sampling for HPV testing is non-inferior to physician-sampling in terms of detection of CIN2/3. In addition, screening uptakes of self-sampling and physician-sampling will be compared and the cost-effectiveness of self-sampling as an alternative to physician-sampling will be assessed.

SS 14-2

COMPARING HEALTH SERVICES INTERVENTIONS FOR THE PREVENTION OF HPV-RELATED CANCER

Berkhof, H., Dillner, J., Ronco, G., Baussano, I., Bosch, X., Arbyn, M., Veldhuijzen, N, Lehtinen, M.
on behalf of the CoheaHr consortium

Important progress has been made in the field of HPV-disease prevention with the development and implementation of HPV vaccines and HPV DNA screening. How the different modes of implementation affects the results is the subject of the CoheaHr European Union excellence project in Comparative Effectiveness Research. In CoheaHr, the (cost-) effectiveness of different European preventive strategies will be compared. The goal is to build a reliable and comparable evidence base on the (cost-) effectiveness of these policies implemented under country-specific preventive services conditions.
To achieve this goal, a set of specific tasks will be carried out. Three randomized trials will be performed in organised screening settings to determine: i) whether self-collection of specimens for HPV DNA testing is an effective and feasible alternative for physician-based sampling, ii) whether screening intervals can be extended in women vaccinated at young age, iii) whether vaccinating women two years before entering the screening programme will favour the use of HPV screening. The first and third randomized trials are multi-country trials whereas the second trial will be carried out in a cohort of Finnish women vaccinated in 2007. For unvaccinated, 25-45 year old women participating in screening, acceptability and general feasibility of HPV vaccination will be studied in a multi-country demonstration survey. Comparisons by transmission models are included to provide long-term projections for cancer incidence and mortality. Furthermore, the establishment of a standardized joint European data warehouse will be continued and extended for (continuous) evaluation of comparative effectiveness of screening and vaccination policies in Europe. Finally, there will be an ongoing effort for producing systematic reviews and meta-analyses which provide a sustainable resource for evidence.
CoheaHr will provide a strong evidence base to enable policy and other decision makers to make informed decision-making on HPV prevention strategies, thereby contributing to strengthening health systems and health services interventions in Europe.

SS 14-3

IHPV CLEARANCE RATES: IMPACT ON CERVICAL CONTROL STRATEGIES.

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Objectives. Estimating genotype-specific clearance and progression to high-grade cervical intreaepithelial lesion (hgCIN) of prevalent infections by papillomavirus (HPV) according to and time from detection. Studying the effect of women's age.

Methods. The analysis is based on the data of the NTCC randomised controlled trial. In the intervention arm of this study, HPV positive women were referred to colposcopy. If no CIN grade 2 or more was detected at colposcopy then women were recalled each year for new HPV testing and cytology. This procedure continued until two consecutive negative HPV tests were obtained. Women in follow-up were referred to colposcopy if cytology was ASCUS or more severe. Progression to hgCIN is considered to enhance viral persistence and, conversely, viral persistence is necessary for progression to hgCIN. Therefore data are being analysed according to a model for competing endpoints: progression and clearance. In addition, the presence/absence of HPV infection and of hgCIN can be observed only in the occasion of new HPV tests or colposcopies. Thus a model for interval-censored data is applied.

Results. Rates of infection clearance and of progression to hgCIN by genotype and by interval from in detection of the infection will be presented, together with variations of these rates by women's age.

Conclusions. These results will be relevant for knowledge of the natural history and for use in mathematical models for the evaluation of different screening and vaccination strategies.

SS 14-5

THE COMBINED VALUE OF HPV SCREENING AND HPV VACCINATION FOR MIDDLE AGED WOMEN

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n spite of the availability of cervical cytology and HPV screening technologies and more recently, of prophylactic HPV vaccines, cervical cancer remains amongst the three most common cancers in women and consistently the second most common in developing countries. In Europe, some 50,000 new cases of cervical cancer occur yearly with a 40 to 60 % mortality rate and great social inequality.

HPV screening has proven to be able to clear prevalent lesions / women at high risk with sensitivities greater than 90% and with technology adaptable to many environments. HPV screening is only slowly replacing cytology as the primary screening option.

Current HPV vaccination programs in most countries target single or few cohorts of girls and young women. Phase III clinical trials with vaccines against HPV 16 and 18 have recently shown that protection is also very high for adult women (to ages 45+) provided they are HPV DNA negative at the time of vaccination. A novel HPV vaccine (V503) is expected to be licensed in 2015/6 including antigens to 9 HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) that cover 90% of the infections that cause cervical cancer worldwide.

Extending the age of vaccination to adult women combined with an adequate HPV screening and triage algorithm should be able to dramatically reduce mortality in areas of high risk and moreover, these campaign type approaches have the potential to advance the reduction of cervical cancer incidence and mortality as compared to the time table in the reductions expected if only current programs of vaccination adolescent girls are maintained.

SS 14-6

A COCHRANE REVIEW ON PROPHYLACTIC VACCINATION AGAINST HUMAN PAPILLOMAVIRUSES TO PREVENT HPV INFECTION AND CERVICAL PRECANCER

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Objective A Cochrane review was conducted to evaluate HPV vaccine safety and efficacy (protection against cervical HPV16/18 infection as well as cervical precancer associated with these types and irrespective of HPV types). The following groups were distinguished: women without evidence of a high-risk HPV infection, without evidence of HPV16 and HPV18 infection, and all women regardless of HPV status at enrolment.

Methods Only randomised trials phase II and III were included. The Cochrane Collaboration's tool for risk of bias. Risk ratios and vaccine efficacy measures (vaccine versus placebo) were computed and subsequently pooled using random effects models and the inverse of the variance to weight each study into the meta-analysis. Meta-regression was used to assess the influence of covariates on effect measures. Protection against HPV infection is not reported in this abstract.

Results The efficacy of the HPV vaccines was excellent (>90%) among young women (15-26 years) without evidence of high-risk HPV infection or without evidence of HPV16 and 18 infection regarding protection, even among those who received less than three doses. Vaccine efficacy was moderate for the same endpoints for all women regardless of presence of HPV infection at enrolment.

The efficacy of the HPV vaccines among mid-adult women (24-45 years) without evidence of HPV16 and HPV18 infection regarding was good (86%) for protection against cervical precancer related to HPV16 or HPV18 when all three doses were administered. When all women were included, regardless of presence of HPV at enrolment, no statistically significant protection was observed.

The efficacy of the HPV vaccines varied from moderate to excellent among younger women (15-26 years) regarding protection against cervical precancer irrespective of presence of HPV types in women who were high-risk HPV negative or HPV16/18 negative at enrolment. Protection against cervical intraepithelial neoplasia grade 3 was higher for the bivalent vaccine (93%) than with the quadrivalent vaccine (46%), when women were high-risk HPV negative at enrolment. No significant protection against CIN2 was observed when less than three doses are administered. When all vaccinated women were included, regardless of presence of HPV at enrolment, the efficacy of HPV vaccines was moderate to poor. The efficacy of the bivalent vaccine against CIN3 was moderate whereas that of the quadrivalent vaccine was poor.

No results regarding protection against cervical precancer irrespective of HPV types were reported for mid-adult women without evidence HPV16/18 at enrolment. No protection was observed for all enrolled women regardless of presence of HPV infection.

More local effects at the injection site were observed in vaccinated subjects. Adverse effects are generally transient and well tolerated. Serious adverse effects were not more common in vaccine versus control arms. Congenital anomalies or adverse pregnancy outcomes were not more frequent in vaccinated compared to placebo subjects, who became pregnant during the trials.

Conclusions Among women who were high-risk HPV negative or HPV16/18 negative at enrolment, we observed excellent protection against cervical precancerous lesions associated with the vaccine types. For this reason, young teenage girls, before onset of sexual activity should be the first target of vaccination programs. Significant but lower protection against cervical precancer was also observed in women regardless of initial HPV status. Catch-up vaccination of adolescents or young women, where a considerable proportion may already be exposed to prior HPV infection, is also useful. In mid-adult women (aged 24 or older), HPV vaccination is effective when they are HPV16 or 18 negative and when all three doses are administered. HPV vaccination can be considered as safe. However, safety in pregnant women is not sufficiently documented

SS 14-7

THE REDUCED LIFETIME RISK OF SCREEN-DETECTED HIGH-RISK HPV INFECTION AND DISEASE IN VACCINATED COHORTS CALLS FOR A CHANGE IN CERVICAL CANCER SCREENING PROGRAMS

Nienke Veldhuijzen, Guglielmo Ronco, Chris Meijer, Johannes Berkhof

Introduction Since 2008, HPV vaccination programs have been implemented in many developed countries – offering highly effective, but not complete, protection against cervical cancer. Secondary prevention through screening remains necessary for vaccinated women. Optimal screening strategies in vaccinated and unvaccinated cohorts are however likely to differ. Moreover, because of the incomplete coverage of vaccination and the staggered replacement of unvaccinated by vaccinated cohorts, screening programs will face screening populations with differential risk on HPV infection and disease for the coming decades. Type-specific screen-detected high-risk HPV (hrHPV) incidence data obtained from population-based screening-trials can be used to explore the impact of vaccination on screening outcomes.
Method Using age- and type-specific hrHPV incidence and prevalence data, obtained from two large population-based randomized HPV screening trials in the Netherlands (POBASCAM) and Italy (NTCC), we studied the impact of vaccination on the lifetime risk of screen-detected infections (POBASCAM, NTCC) and cervical lesions (POBASCAM only). For bivalent (HPV16/18) vaccines and polyvalent (HPV16/18/31/33/45/52/58) vaccines two main strategies were evaluated: adolescent vaccination and adult vaccination. In sensitivity analyses we assessed the impact of cross-protection and waning.
Results Adolescent bivalent vaccination resulted in a 29% and 25% reduction in lifetime risk of hrHPV in POBASCAM and NTCC respectively. Including (lifelong) cross-protection to HPV types 31,33 and 45 resulted in a reduction of 43% and 36% respectively. In POBASCAM, reductions in lifetime risk of CIN2+ were 45% and 63% without and with lifelong cross-protection Slow waning of cross-protection of the bivalent vaccine (full protection first 20 years, waning over the next 20 years) had little impact on lifetime risk estimates, but rapid waning (full protection first 10 years, waning over the next 10 years) almost completely removed the benefit of cross-protection on lifetime risk estimates. The highest reduction in lifetime risk of hrHPV and CIN2+ was achieved with adolescent polyvalent vaccination, but only if lifelong protection was assumed.
Conclusion Vaccination more effectively reduces the (cumulative) risk of CIN2+ compared to the (cumulative) risk of a screen-detected hrHPV infection. The development of guidelines for integrated vaccination and screening programs will be an important challenge for the coming years.

SS 14-8

CHARACTERISTICS OF A RANDOMIZED SCREENING TRIAL OF HPV VACCINATED WOMEN

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Objectives: Post-vaccination era screening needs to be changed based on a hard evidence. We studied which strategy is: 1) at least as accurate/safe as repeat cytological screening, 2) most effective and 3) associated with the best quality of life.

Methods: The study was a comparative effectiveness study. 22.500 HPV16/18-vaccinated Finns born in 1992-95 and vaccinated at the age of 13-15 in a community randomized trial (EUDraCT 2007-001731-55) have been randomized into to attend cytological screening at the ages: 22, 25 and 30 years (A1); 25 and 30 (A2); or at age of 30 (A3).

Results: A1 and A3 include at least 7000 women yielding 80% power for the demonstration a non-inferior accuracy (sensitivity) of A3 strategy vs. A1 strategy in the HPV-vaccinees. An interim analysis of A1 vs. Arm A2 (no intervention at the age of 22 but at a round of smears taken at the age of 25) in 2017/18 will guarantee safety of the less frequent screening. At age 30 all participating women will be offered both cytological and unmasked HPV test results.
The study relies on an infrastructure validated in previous vaccine trials. Study deliverables are:
1) Successful enrolment by birth cohort to guarantee power (2014).
2) Safety of less frequent screening of HPV16/18 vaccinated females (2017/18).
3) Effectiveness of delaying the initiation of cervical screening in vaccinated women up to age 30 year.
4) Impact of less screening rounds on quality of life.

SS 15-2

HPV PREVALENCE AND CERVICAL CANCER SCREENING PRACTICES IN COUNTRIES OF THE FORMER SOVIET UNION.

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(Russian Medical Academy of post-graduate education, Moscow)

There is the hard burden of HPV and associated diseases in Russia and Western Countries of the former Soviet Union (Ukraine, Belarus, Moldova), Caucasus region and Central Asia (Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan). Both cervical cancer incidence and mortality have increased in these countries despite various cancer prevention initiatives. The review available data on HPV prevalence and on national policies of cervical cancer screening and HPV vaccination initiatives is presented.

Based on the data published in HPVcentre Monograph 2013 from the 12 countries, high risk HPV (hrHPV) prevalence ranges from 13.4% to 36.2% in women with normal cytology and being highest in younger age groups. The most common hrHPV type was HPV16, followed by HPV56, HPV31, HPV33, HPV18 and HPV45. In ASCUS and low grade lesions hrHPV prevalence varied from 29% to 33% and from 52 to 100%, respectively. HrHPV infection in women with high grade cervical lesions (HSIL) and cervical cancer ranged from 60.0 to 100%. HPV16 was the most prevalent HPV genotype in cervical cancer and HSIL, followed by HPV31, HPV33, HPV18, HPV39, HPV52 and HPV56. As the HPV profile in cervical diseases seems to be similar to that found in Western Europe the implementation of HPV testing in screening programs might be beneficial. Finally, HPV vaccination is currently not widely implemented in most of the twelve countries mainly due to pricing, availability, and limited awareness among public and health care providers.

Opportunistic screening programs, the lack of efficient call-recall systems, low coverage, and the absence of quality assured cytology with centralized screening registry are major reasons for low success rates of cervical cancer programs in many of the countries.

Country-specific research, organized nationwide screening programs, registries and well defined vaccination policies are continued and being discussed.

SS 15-3

CERVICAL CANCER SCREENING PRACTICES AND CURRENT STATUS OF VACCINATION IMPLEMENTATION IN CENTRAL AND EASTERN EUROPE

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Objective: To review current cervical cancer screening practices and the implementation status of vaccination against HPV in Central and Eastern Europe where the burden of cervical cancer is generally higher compared to Western or Northern Europe.

Methods: Data were collected by surveys conducted during August–October 2011 and in January 2013 in 16 Central and Eastern European countries: Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Montenegro, Poland, Romania, Serbia, Slovakia, Slovenia and the Former Yugoslav Republic of Macedonia.

Results: Opportunistic and organized cervical screening, mainly based on conventional cytology, is performed in nine and seven countries in the region, respectively, with the proposed age of the start of screening ranging from 20 to 30 years and the estimated coverage ranging from a few percent to over 70%. At least one current HPV prophylactic vaccine is registered in all central and eastern European countries except one. Six countries have integrated the HPV vaccination into their national immunization program and currently provide routine vaccination free of charge to the primary target population. Ten countries have not integrated HPV vaccination into the national immunization program. Vaccination of males is not recommended in any country in the region.

Conclusions: Even in the countries where only opportunistic screening is performed, well-prepared plans and strategies have been established for switching to organized screening in the near future. The key reasons for lack of implementation of HPV vaccination into the national immunization program are the high vaccine cost and negative public perception.

SS 15-4

COST-EFFECTIVENESS OF CERVICAL CANCER PREVENTION IN CENTRAL AND EASTERN EUROPE AND CENTRAL ASIA

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We studied the cost-effectiveness of cervical cancer prevention strategies in the Central and Eastern Europe and Central Asia (CEECA) region. The cost-effectiveness of human papillomavirus (HPV)16/18 vaccination of 12 year-old girls was calculated for 28 countries, under the assumption that vaccination prevents 70% of all cervical cancer cases and that cervical cancer and all-cause mortality rates are stable without vaccination.

At three-dose vaccination costs of I$ 100 per vaccinated girl (2005 international dollars), HPV16/18 vaccination was very cost-effective in 25 out of 28 countries according to the cost-effectiveness criterion of the World Health Organization. We also evaluated the cost-effectiveness of cervical cancer screening combined with vaccination in Slovenia, Poland, and Georgia. The screening interval was varied at 3, 6, and 10 years starting at age 25 or 30 and ending at age 60. In Slovenia and Poland, combined vaccination and 10-yearly HPV (DNA) screening (vaccination coverage 70%, screening coverage per round 70%) was very cost-effective when the cost of three-dose vaccination was I$ 100 per vaccinated girl. More intensive screening was very cost-effective when the screening coverage per round was 30% or 50%. In Georgia, 10-yearly Pap screening was very cost-effective in unvaccinated women. Vaccination combined with 10-yearly HPV screening was likely to be cost-effective if the three-dose vaccination cost was I$ 50 per vaccinated girl. To conclude, cervical cancer prevention strategies utilizing both HPV16/18 vaccination and HPV screening are very cost-effective in countries with sufficient resources. In low-resource settings, low vaccine pricing is essential for strategies of combined vaccination and screening to be cost-effective.

SS 15-5

RECOMMENDATIONS FOR CERVICAL CANCER PREVENTION IN CENTRAL AND EASTERN EUROPE AND CENTRAL ASIA

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Objectives: To develop recommendations for cervical cancer prevention in the Central and Eastern Europe and Central Asia (CEECA) region where 404 million of people are currently living in 28 different countries. In the region, burden of cervical cancer is substantially higher than in the rest of Europe with increasing trend of incidence and mortality.

Conclusions: Three different cervical cancer prevention strategies can be recommended for the CEECA countries:
(i) Countries which have implemented organized cytology-based screening should put substantial efforts into improving existing screening coverage in unscreened or under-screened women, in whom a significant proportion of invasive cancers occur. These countries should not maintain status quo but should strongly consider implementation of universal HPV vaccination into their national immunization programme and consider modification of the existing screening programme with HPV-based screening at larger screening intervals, at least for vaccinated cohorts.
(ii) Countries with opportunistic cytology-based screening and with an established network of functional cytology labs should put substantial efforts toward progressively modifying current opportunistic cytology-based screening with organized screening, preferably HPV-based or, alternatively, cytology-based. These countries should also immediately consider implementation of universal HPV vaccination into their national immunization programme.
(iii) Countries with non-functioning cytology-based opportunistic screening should be aware that creation of efficient cytology-based organized screening with the full complement of resources, expertise and infrastructure required for detection, management, follow-up and long-term quality control may be too costly an investment or even a totally unreachable goal because of the lack of a trained workforce, mainly experienced cytologists. Such countries should strongly consider implementation of universal HPV vaccination into their national immunization programme and de novo implementation of HPV-based screening with prolonged screening rounds instead of improving existing non-functioning cytology-based screening. (Poljak M et al. Vaccine 2013;31S:H80–H82.)

SS 16-2

UPDATED RESULTS FROM THE INDIAN HPV VACCINATION STUDY

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Objectives: To evaluate the effectiveness of less than 3-doses of HPV vaccination in preventing persistent HPV infection and cervical neoplasia in lower middle income setting

Methods: 20,000 girls aged 10-18 years were randomized to two groups to receive 3- or 2- doses of quadrivalent HPV vaccine. Unfortunately due to suspension of vaccination midway through recruitment due to events unrelated to our study, we ended up with four groups by default: 4,950 girls received one dose; 3,452 received 2 doses (days 1 and 60); 4,979 received 2 doses (days 1 and 180+ ATP) and 4,348 received 3 doses (days 1, 60 and 180+). These girls are followed up for immune response, frequency of persistent HPV infection and cervical neoplasia

Results: The immunogenicity of 2 doses was non-inferior to the standard 3 dose schedule (ATP) at 1, 24 and 36 months; immunogenicity of 1 dose was clearly inferior to that of 3 doses (ATP) at 12, 18, 24 and 36 months from the last dose. The frequency of incident infection based on cervical cells from 1288 married women and persistent infection (based on cervical cell samples from 171 married women) for vaccine targeted HPV infections were similar across the different dose groups. No persistent HPV 16 or 18 infection was found in the 171 girls from whom we have cervical cells.

Conclusions: Long-term follow-up of the vaccinated girls will clarify the preventive prospects associated with a single dose of HPV vaccination. Results following 2-doses (ATP) are consistent with published experience from elsewhere.

SS 16-3

CERVICAL CANCER PREVENTION IN HIV-INFECTED WOMEN

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HIV-infected women are living longer and are at a higher risk of acquiring cervical cancer. More data comparing cervical cancer screening and treatment strategies in these women are urgently needed. WHO guidelines on optimal methods to screen and treat cervical cancer are available, but there are limited data to inform their potential modification for HIV-infected women. Even fewer data are available which compare the efficacy of treatment methods (loop electrosurgical excision procedure (LEEP) and cryotherapy) and differences in cervical disease recurrence between HIV-infected and HIV-uninfected women.

HPV testing appears to be the most sensitive, although less specific for CIN-2+ detection than either VIA and cytology screening. Several studies of HIV-infected women have shown equivalent sensitivity of VIA and of cytology screening for CIN-2+, although there is variation in results. Consistently across studies, the specificity of cytology appears higher than either VIA or for high-risk HPV testing. Two studies in South Africa and Kenya have suggested that the specificity of HPV testing and VIA for detection of high grade lesions is lower in HIV-infected women with lower CD4 counts; more research is needed to examine if screening test performance varies for HIV-infected women with higher versus lower CD4 counts.

More research in HIV infected women is needed to examine if LEEP and cryotherapy treatment methods are associated with differences in HIV-viral shedding and in HIV transmission during or shortly after treatment.

HIV-infected adolescents have found to induce high-levels of neutralizing antibody titers following prophylactic HPV vaccination in bridging studies. Studies are not yet available on HPV vaccine efficacy in HIV infected women against either HPV-infection or clinical disease endpoints.

SS 16-4

INFECTION WITH C. TRACHOMATIS INCREASES HIGH-RISK HUMAN PAPILLOMAVIRUS INFECTION DURATION AMONG FEMALE SEX WORKERS IN KENYA

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Objectives To examine the association between sexually transmitted infections (STIs) - *Chlamydia trachomatis (CT), Neisseria gonorrhea (GC), Trichomonas vaginalis (TV), and Mycoplasma genitalium (MG)* – and the persistence of high-risk human papillomavirus (hrHPV) infection among female sex workers (FSW). HPV persistence is a major risk factor for developing precancerous lesions and invasive cervical cancer.

Methods Three hundred fifty FSW presented to the Korogocho clinic in Nairobi, Kenya every three months to complete a behavioral questionnaire and undergo HIV/STI and hrHPV testing. The APTIMA assay was used to detect hrHPV types expressing E6/E7 mRNA. Kaplan-Meier curves estimated the median duration of hrHPV infection, stratified by biological and behavioral risk factors. Accelerated failure time models computed time ratios (TR) for duration of hrHPV infection, based on presence or absence of STIs at baseline. Analysis was restricted to the 173 FSW who were diagnosed with hrHPV at any time during follow-up.

Results Infection with CT at baseline was associated with a significantly longer duration of hrHPV infection (TR: 1.68, 95% CI: 1.21, 2.55), adjusting for HIV status and age. When restricting to FSW with concurrent hrHPV and CT (co-infection status), the adjusted TR increased to 3.65 (95% CI: 2.46, 5.41).

Conclusions Infection with CT appears to increase the duration of hrHPV infection, particularly among women co-infected with CT and hrHPV. Infection with CT might exacerbate concurrent hrHPV infection through the recruitment of pro-inflammatory cytokines that promote cervical inflammation. Detection and treatment of CT should be prioritized to low-income settings in order to mitigate its effect on hrHPV persistence and development of precancerous and more severe lesions.

SS 16-5

DEVELOPING A SUSTAINABLE PROGRAMME OF CERVICAL SCREENING BY 'SEE AND TREAT' IN RURAL MALAWI

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Objectives: Although recommended by Government, there is no sustained programme of cervical screening in Malawi, with few trained practitioners, lack of cryotherapy for treatment or infrastructure for follow-up This programme aims to reduce cervical cancer morbidity in rural Malawi.

Methods: First steps included detailed planning for VIA (visual inspection with acetic acid) clinics, approvals from the Ministry, Regional and Village Chiefs and awareness sessions in hospital, health centre and village settings.
Local staff completed Malawian Ministry of Health VIA course, supplemented by training in VIA interpretation and treatment by cold coagulation from Scottish clinicians. A digital colposcope is available to aid recognition of abnormalities. Clinical support and competence assessment is provided through regular visits from Scottish staff.

Results: Cervical screening messages were delivered to 95% of Nkhoma staff and to >20,000 people. Spread of information by word-of-mouth and local radio led to large numbers attending clinics.
25 Malawians staff have been trained. Nkhoma Hospital provides daily 'see and treat' services with weekly clinics in 2 associated Health Centres. >3500 women attended in the first 9 months. HPV positivity is ~20%, VIA positivity is <10% and 75% of those requiring treatment received cold coagulation the same day. 18 advanced cancers were detected in 7 months. A digital colposcope provides an excellent teaching tool to develop and maintain clinical skills. Additional surgical skills have been acquired allowing treatment of early cancers.

Conclusions: The programme has reached more women, more quickly and from further afield than expected, confirming the great need. Plans are in place to extend access and roll-out across a population base of 500,000 in Central Malawi.

SS 16-6

RISK FACTORS FOR HIV POSITIVITY ACCORDING TO HPV STATUS AMONG TANZANIAN WOMEN

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Objectives: Human immunodeficiency virus (HIV) is highly prevalent in sub-Saharan Africa.
Several studies indicate that HIV seropositivity is strongly associated with human papillomavirus (HPV) prevalence but to date only few studies have evaluated HPV as a risk factor for HIV infection in women. We investigated risk factors for HIV positivity with a particular focus on the role of HPV.
Methods: From 2008-2009, a cross-sectional study was performed among 3715 Tanzanian women. Study participants were interviewed about socio-demographic and reproductive factors and sexual behavior. Blood samples were collected and tested for HIV and the women underwent a gynecological examination. HPV status was determined by Hybrid Capture 2 and HPV genotyping was performed using the Inno-LiPA test. We included 3424 women with known HIV and HPV status. Risk factors for HIV infection were analyzed using multiple logistic regression analysis estimating odds ratios (OR) and 95% confidence intervals (CI).
Results: The overall prevalence of HIV was 10.2%. Among HPV-positive women 23.1% were HIV-positive whereas this applied to 6.9% among HPV-negative women. HIV positivity was associated with lifetime number of sexual partners, time in present relationship, HPV status, and genital warts. Stratified analyses showed that HIV risk factors among HPV-positive and HPV-negative women were similar with the exception that genital warts increased the risk of HIV positivity markedly among HPV-positive women (OR = 6.07; 95% CI: 1.70–21.7) compared with HPV-negative women (OR = 1.21; 95% CI: 0.15–9.45).
Perspective: Further analyses on e.g. HPV type-specific patterns are ongoing.

CS 1-2

HUMAN PAPILLOMAVIRUS GENOTYPE ATTRIBUTION FOR HPVS 6, 11, 16, 18, 31, 33, 45, 52, 58 IN FEMALE ANOGENITAL CANCERS.

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Objective: HPV vaccines can potentially control cervical cancer and help to reduce other HPV related cancers. We aimed to estimate the relative contribution (RC) of the 9 types (HPVs 16/18/31/33/45/52/58/6/11) included in a new investigational nine-valent HPV vaccine in female anogenital cancers (cervix, vulva, vagina and anus).

Methods: Estimations were based on an international study designed and coordinated at the Catalan Institute of Oncology (Spain), including information of 10,575 invasive cervical cancer (ICC), 1,709 vulvar, 408 vaginal and 329 female anal cancer cases.
Consecutive and histologically confirmed paraffin-embedded cases were obtained from hospital pathology archives from more than 40 countries worldwide. HPV DNA detection and typing was performed by SPF_{10}-DEIA-LiPA25 system and RC was expressed as the proportion of type-specific cases among all HPV positive samples. Multiple infections were added to single infections using a proportional weighting attribution.

Results: HPV DNA prevalence was 84.9%, 28.6%, 74.3% and 90.0% for ICC, vulvar, vaginal and anal cancer, respectively. RC of the combined 9 HPV types was 89.4% (95%CI: 88.8-90.1%)-ICC, 87.1% (83.8-89.9%)-vulvar, 85.5% (81.0-89.2%)-vaginal and 95.9% (93.0-97.9%)-female anal cancer. HPV 16 was the most frequent type in all anogenital female cancer locations. Variations in the RC of HPVs 31/33/45/52/58 by cancer site were also observed, with RCs ranging from 7.8% (5.0-11.4%) in female anal cancer to 20.5% (16.1-25.4%) in vaginal cancer.

Conclusions: Although differences in HPV contribution were observed, the addition of HPVs 31/33/45/52/58 to HPV types included in current vaccines (16/18) could prevent almost 90% of female HPV positive anogenital cancers worldwide.

CS 1-4

CURRENT RADIATION TREATMENT MODALITIES AND INDICATIONS IN VULVAR CANCER.

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Gustave Roussy. Villejuif, France.

Vulvar tumours account for 5% of the female reproductive tract cancers. The standard treatment for vulvar SCC is surgery. External radiation therapy (ERT), brachytherapy (BT) and chemotherapy are either adjuvant treatment options or exclusive treatment options in advanced disease. Irradiation to the primary tumor or to the inguinal +/- pelvic nodes can be considered as adjuvant treatment after wide excision or as exclusive treatment in case of advanced and inoperable disease.

ERT to the primary tumor :

• as adjuvant therapy.

After wide local excision, ERT is indicated in case of positive margins or with margins < 3mm if re-excision is not possible, and is discussed in case of lymph vascular invasion. In this situation, a total dose of 45Gy-50Gy in 25-28 fractions controls potential micro-metastases. The technique usually mixes electrons and photons. Interstitial BT can be combined to external irradiation depending upon tumour location.

• as exclusive treatment.

In case of contra-indication to surgery or in advanced tumors, EBR has proven its efficacy. A total dose of 45 Gy is delivered to the pelvis, usually combined with interstitial BT to a total dose of 60 Gy-85 Gy. Concurrent chemoradiation consisting of cisplatinum or carboplatinum used alone or in combination with fluorouracil, has been shown to give a high response-rate even in the absence of randomized trials.

EBR to the groin as adjuvant treatment. In case of two or more inguinal node involvement, prophylactic external irradiation to the groin and to the pelvis compared to pelvic lymphadenectomy has been investigated in a randomized trial conducted by the GOG in 1986. The results evidenced a better prognosis in patients treated with external irradiation. A total dose of 45 Gy is generally recommended.

EBR to the groin as exclusive treatment. No randomized trial has been performed to compare groin dissection and groin irradiation. In a literature review, it has been shown that there was no evidence for a better control with external irradiation compared to dissection. In case of contra-indication to surgery, external irradiation represents an alternative to treat inguinal nodes. If external irradiation is to be performed prophylactically, a total dose of 45 Gy is recommended while this dose should reach 60 Gy-65 Gy in case of macroscopic nodes.

Treatment modalities. Radiation techniques have significantly evolved over the last years. Intensity Modulated Radiation Therapy (IMRT) allows radiation delivery in a more conformal manner than 2D or even 3D EBR. IMRT allows dose reduction in normal tissues, with a subsequent reduction risk of treatment-related toxicities. This technique also eliminates dose modulation across overlapping groin areas. IMRT potentially allows treatment intensification with the use of concomitant chemotherapy, as exclusive treatment or combined with surgery. BT technique allows high dose to limited areas. Image-guided adaptive BT has proven its efficiency in cervical and vaginal cancers. In vulvar cancers, the same technique can be applied integrating both clinical findings (and histopathological data if available) and imaging modalities. Interstitial techniques are usually integrated into the process of BT, aiming at increasing the tumor dose, while maintaining acceptable doses to organs at risk.

Conclusion. In vulvar cancers, radiation therapies (ERT/BT) are usually indicated either as complementary to surgery or as exclusive treatment in case of advanced disease. Recent advances in radiation techniques allow concomitant chemotherapy and reduction in side effects.

CS 2-1

TERMINOLOGY OF HPV AND PRECANCEROUS LESIONS OF THE VULVA: A CONTINUING CHALLENGE

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Objective. Diagnosis of vulvar diseases is complex, as the development of vulvar conditions results from multiple etiologies, the presentation of the lesions is different from other skin areas and from the cervix in that there is no transformation zone in the vulva and also the use of colposcopy with acetic acid application is controvesrial.

This is why during the last years, new terminologies have been introduced, for Vulvar lesion pattern recognition and for disease classification. However, there is still a debate concerning the application of the LAST terminology (Lower Anogenital Systematic Terminology) to vulvar intraepithelial neoplasia, since not all VIN are caused by HPV.

Materials and Methods. The terminology of the Vulva of the International Federation of Cervical Pathology and Colposcopy (IFCPC) and the classification of vulvar diseases of the International Society for the Study of Vulvovaginal Disease (ISSVD) are presented. Their applications to daily practice is discussed. The rationale for the evolution of the different VIN terminologies over the years, is analyzed (Table).

Conclusions. The approach to vulvar disease has been advanced considerably by the modern terminology and classification. A contemporary issue is the need for a comprehensive terminology of VIN that includes both HPV-associated (VIN) - low grade and high grade, and non HPV-associated (differentiated) variants.

CS 2-2

THE DISTRIBUTION OF 14 HPV TYPES DETECTED IN VIN AND VaIN LESIONS FROM WOMEN 15-26 YEARS OF AGE

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Objective: We estimated the fraction of vulvar and vaginal intraepithelial neoplasia (VIN and VaIN) attributable to HPV types targeted by the 9-valent HPV (9vHPV) vaccine (HPV6/11/16/18/31/33/45/52/58) among 10,656 women ages 15-26 enrolled in the placebo arms of two phase III clinical trials of the qHPV vaccine. We also evaluated the fraction attributable to five high-risk types, that are not targeted by the investigational 9vHPV vaccine (HPV35/39/51/56/59).

Methods: Subjects underwent genital examinations at baseline, months 7 and 12, then every 6 to 12 months for up to 48 months. Tissue from biopsies and excisions were tested for HPV DNA detection and genotyping via PCR. Lesions were diagnosed by a Pathology Panel consensus diagnosis. The prevalence of HPV types and type combinations was calculated using a proportional attribution method, whereby a fractional allocation for each individual HPV type was used when evaluating multiple infected lesions.

Results: A total of 41 and 47 LSIL(VIN1) and HSIL(VIN2/3), and 118 and 33 LSIL(VaIN1) and HSIL(VaIN2/3) lesions respectively were diagnosed during the 4 years of follow-up. The prevalence of HPV6/11/16/18/31/33/45/52/58 was 62.1% and 89.4% in LSIL(VIN1) and HSIL(VIN2/3) and 34.2% and 54.6% in LSIL(VaIN1) and HSIL(VaIN2/3), respectively. HPV6/11 were detected in 54.5% and 3.9% of LSIL(VIN1) and LSIL(VaIN1). Non-vaccine types HPV35/39/51/56/59 were present in 0% and 9.7% of HSIL(VIN2/3) and HSIL(VaIN2/3) respectively.

Conclusions: If 9-valent HPV vaccination programs are effectively implemented, a relatively large proportion of high-grade VIN and VaIN lesions worldwide could be prevented, in addition to approximately one-half of low grade VIN.

CS 2-3

PREVALENCE OF HPV TYPES IN VULVAR PRE-CANCER IN THE US

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Objectives. Warty and basaloid vulvar squamous cell cancers often arise from precursor lesions of characteristic histological types known as vulvar intraepithelial neoplasia (VIN). Prophylactic HPV vaccines targeting HPV-16 and HPV-18 appear to be efficacious against VIN 2/3 endpoints, but the efficacy of the 9-valent vaccine against VIN is yet to be determined. Our objective was to establish the pre-vaccine, type-specific prevalence of HPV in VIN3 in the United States.

Methods. Three cancer registries (Hawaii, Iowa, and Los Angeles County) submitted one representative, archival formalin-fixed paraffin-embedded tissue block from 68 cases of VIN 3 to the CDC HPV laboratory. Demographic and clinical information was available for all cases. All DNA extracts were tested with the Linear Array HPV Genotyping Test (Roche Diagnostics). Samples with negative or inadequate LA results were re-tested with the INNO-LiPA HPV Genotyping Assay (Innogenetics).

Results. HPV was detected in 97% of VIN 3. The most common types of HPV in VIN 3 were HPV16 (81% of specimens), followed by HPV33 (9% of specimens), and HPV59 (3% of specimens. All other types were presently in less than 2% of specimens. Four VIN 3 cases had multiple genotypes detected, and all included HPV-16. HPV was twice as common in cancers associated with warty/basaloid VIN than in those accompanying differentiated VIN.

Conclusions. This study supports the important role of HPV, especially HPV-16, in VIN 3 cases. Given the high prevalence of HPV in VIN 3 cases, prophylactic vaccines have the potential to decrease the incidence of vulvar neoplasia.

CS 2-4

VIN: DIAGNOSIS.

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The diagnoses of vulvar intra-epithelial neoplasia (VIN) are frequently difficult because of the different presentations of the pre-cancerous lesions. Whatever the presentation, biopsy(ies) is always mandatory before treatment.

The diagnosis is difficult because there is no "typical" VIN. We find different presentations: the lesions can be red, white, blue, brownish, and most of the time multi focal. It can presents like a "condyloma", hyperkeratosis or erosion. The differential diagnosis is between "flat" condyloma, extra mammary Paget's disease, psoriasis, and in case of a pigmented lesion, it is very important to rule out melanoma. Especially in post-menopause patients with a peri-anal lesion, multiple biopsies are important to make sure that there is no cancer.

Colposcopy and acetic acid can be useful when lesions are barely visible. In that situation, it is important to take more time for colposcopy because the lesions take more time to be well evaluated.

CS 2-6

IMMUNOTHERAPY IN VULVAR INTRAEPITHELIAL NEOPLASIA

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Objectives: Conventional surgical therapies for uVIN are nowadays increasingly replaced by immunotherapy developed to reinforce the immune response in both standardised (imiquimod) and experimental settings (photodynamic therapy and therapeutic vaccination). The clinical responsiveness to these therapies are promising but need to be improved. We studied the local immune composition to determine which components of the immune system play a major role in clinical outcome.

Methods: A cohort of 26 healthy controls, 43 uVIN and 21 HPV positive vulvar carcinoma was studied for the presence and phenotype of myeloid cells and T cells using a large array of antibodies and 3-color immunofluorescence and then related to clinical data.

Results: The vulva is intensely surveyed by different subsets of T cells and myeloid cells. The stroma is highly infiltrated with activated pro-inflammatory IFNγ-producing T cells, reflected by T cells expressing Tbet, TIM3 and/or NKG2A and Gal-9 expressing immune cells. High numbers of stromal CD8+TIM3+ T cells and CD3+ NKG2A+ T cells are associated with the absence of recurrences and/or a prolonged recurrence free survival. Furthermore, a dense intraepithelial CD14+ cell infiltration correlated with a high number of intraepithelial Tregs and is an independent prognostic factor for rapid recurrences.

Conclusions: Differences in the number of activated T cells and macrophages bear impact on uVIN recurrences and as such may also impact the response to immunotherapy. New studies on the innate and adaptive immune cell infiltrate in pre-immunotherapy samples are performed to determine the relevance for responses to immunotherapy.

CS 3-1

ADENOCARCINOMA IN SITU AND INVASIVE ADENOCARCINOMA OF THE CERVIX: AN UPDATE.

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Adenocarcinoma of the cervix is the second most common histology of invasive cervical cancer. Approximately 10 % of cervical cancers are invasive adenocarcinoma. The incidence of this type of cervical cancer is rising, and may become a larger portion of invasive cervical disease. Similar to invasive squamous cancer of the cervix, invasive adenocarcinoma has a precursor lesion. Adenocarcinoma in situ (AIS) is an equivalent lesion to severe squamous dysplasia. Also similar to invasive squamous cancer, human papillomavirus (HPV) infection is the underlying cause of invasive adenocarcinoma and AIS. Glandular lesions of the cervix are not easily detected by traditional methods of cervical cancer screening, such as cervical cytology and colposcopy. Also invasive adenocarcinoma and AIS may occur in the endocervical canal and are not easily detected in this location. Relatively higher prevalence of invasive adenocarcinoma is frequently found in countries and regions with cervical cancer screening. For example, more than 15 % of cervical cancers in northern Europe and North America are invasive adenocarcinomas. Because screening for AIS and adenocarcinoma is insensitive, HPV vaccination attractive strategy to prevent these diseases. This session will explore the association of various HPV types with AIS and cervical adenocarcinoma. Other topics include host immune responses, detection and prevention of this type of cervical cancer.

CS 3-2

HUMAN PAPILLOMAVIRUS TYPES IN GLANDULAR LESIONS OF THE CERVIX: A META-ANALYSIS OF PUBLISHED STUDIES

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Objectives In contrast to extensive information about HPV types across the complete spectrum of squamous cervical lesions, less is known about the pattern of HPV types in glandular preinvasive lesions, and how it compares to that in cervical adenocarcinoma (ADC). With the aim to improve understanding of the carcinogenic process for individual HR types from infection of glandular tissue to adenocarcinoma, we performed a systematic literature review of HPV type-specific prevalence data in preinvasive glandular neoplastic lesions, and compared to similar data on women with normal cytology and ADC.

Methods Medline was used to search for publications that (i) used broad-spectrum consensus PCR and (ii) reported overall and type-specific HPV prevalence, by strata of cyto- and/or histo-pathological cervical diagnoses.

Results 12 studies reported relevant data on atypical glandular cells (AGC) and/or adenocarcinoma in situ (AIS) from Europe (n=4), North America (n=5), Eastern Asia (n=1), Western Asia (n=1) and South/Central America (n=1l). HPV infection was detected in 10.5, 57.5, 99.1 and 84.6% of women with normal cytology, AGC, AIS and ADC, respectively. Among HPV-positive women, HPV16 positivity was similar in normal cytology (23.4%) and AGC (23.4%) but it increased to 48.7% in AIS and 45.7% in ADC. HPV18 positivity increased slightly between normal cytology (8.9%) and AGC (15.6%), but rose to 51.8% in AIS and 43.9% in ADC. HPV45 positivity was approximately 7% in all glandular lesions. ADC:normal cytology ratio was, therefore, higher for HPV18 (4.93) than HPV16 (1.95) and HPV45 (1.24). All other HR HPV types showed steep declines in prevalence between AGC and AIS. There were no substantial changes in prevalence between AIS and ADC for any HR HPV type. Furthermore, HPV18 was significantly higher in AIS than in similar data on high-grade squamous lesions (i.e., HSIL, CIN2, CIN3) Conclusions HPV16 and 18 are highly enriched in ADC and AIS compared to lower grades of diagnosis, confirming their higher potential to cause ADC than other HR-HPV types. Our present findings support the role of AIS as a true ADC precursor and suggest that findings from vaccination trials on prevention of AIS can be expected to hold for ADC. HPV-type distribution in AGC, on the other hand, resembled that in normal cytology, suggesting that, like its squamous-cell equivalent LSIL and CIN1, these lesions are more of a proxy of HPV infection than cancer precursors.

CS 3-4

OVERVIEW OF THE RELEVANT IMMUNOLOGICAL FACTORS FOR ADENOCARCINOMA OF THE CERVIX

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The role of local and systemic immunity in the control of HPV associated adenocarcinoma of the cervix will be discussed.

CS 4-1

TEACHING COLPOSCOPY IN THE ELECTRONIC AGE

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Background: Colposcopy has been taught in a traditional way using the apprenticeship system for many years. This method needs experienced teachers and adequate clinical throughput and increasingly is difficult to achieve and in most instances is an unrealistic aim .Didactic courses can achieve high quality teaching but again are limited to locations and teachers

Objectives: To examine alternate methods of teaching colposcopy especially in developing countries and in centers with minimal teaching facilities. With HPV screenings introduction there is an urgent increased need for guidance in safe usage of colposcopy .

Methods: Using latest electronic methods an e learning module based on the program used at the Whittington and University College London colposcopy courses over the last 30 years has been developed. It uses a combination of written and audio and is arranged in a foundation (basic) and advanced course. The former takes 9 hours to complete and is available on computer, smart phone or tablet. The time taken studying the course can be easily monitored. The introduction of a monocular light weight colposcope (Gynocular), extremely suitable for developing countries with facilities for smartphone adaption and cloud based electronic record maintenance will allow this e learning teaching program to be attached. With instant consultation ability worldwide it will enable supervised interactive long distance learning to become a reality

Results: Preliminary testing of the new e learning program has been well received with a number of national societies interested in its introduction to complement existing teaching methods. The ability to learn at ones own pace and avoid the expense in time and finance in attending formal courses, is attractive.

Conclusion: New electronic techniques allow high quality colposcopy teaching to be accessible to doctors worldwide.

CS 4-2

COLPOSCOPIC PERFORMANCE AND UTILITY TODAY

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Our contribution will not constitute a nostalgic overview of certain indications given to colposcopy in the past, it will be a demonstration of its full usefulness in todays pathology of the lower genital tract context.

Colposcopy was discarded as a screening tool due to a higher sensitivity and simplicity of cytology.

Defining Colposcopy just as a tool for guiding biopsies seems to us a very limited way of applying the multiple indications this technique can provide a gynaecologist in his every day practice.

It is quite astonishing to see how on one hand, the normal "manual" vaginal examination has practically been substituted by ultrasound, and on the other, how colposcopy has suffered a considerable set back in many countries.

In my opinion this is a consequence of the conditions in which many gynaecologists have been forced to develop their daily practice, that is, visiting a very large number of patients in a very short period of time. Other conditions such as the particularity of every country national health care system and the type of setting in which one is working will also be determinant. It seems reasonable to state that in a scenario in which LJTD is treated in special units, the "general" gynaecologist will loose interest in a area of gynaecology he will not be able to develop. In Spain, there are different health care providers other than the national health service.

We´ve been stating a increasing interest among Spanish gynaecologists in obtaining the colposcopic accreditation. This is achieved either by via cv in which experience has to be demonstrated or via the exam that takes place yearly in our annual meeting. The high and increasing attendance to the continuous medical education courses developed mainly by the AEPCC allows us to assert that colposcopy in Spain is still in good health.

CS 4-3

INDICATIONS OF COLPOSCOPY BASED ON HPV SCREENING

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There is a growing body of strong evidence to suggest that primary HPV testing is a reasonable approach to cervical cancer screening. In 2014, the US Food and Drug Administration (FDA) recently approved a primary HPV testing indication with the Roche Cobas 4800 HPV test. The primary objective of this lecture is to describe how colposcopy is integrated in a primary HPV screening algorithm and recently published data on the clinical value of random cervical biopsies at colposcopy.

CS 4-5

THE USE OF AN OBJECTIVE TEST FOR COLPOSCOPIC TRAINEES: A TEN-YEAR EXPERIENCE

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Background: Objective evaluation for residents in training is difficult. We want to report our experience using a computer-based test to assess the knowledge of our colposcopic trainees.

Methods: We performed an objective evaluation of each resident before and after their elective rotation in our colposcopy clinic, using a computer with DIMS programme (Denvu) and coloscopic pictures. The main aspect of the evaluation included: visualisation of the junctions, localization and description of lesions, colposcopic impression and site of biopsy (ies) were requested for 10 patients with 4 to 6 pictures each. Student paired T-test was used to compare the difference between pre-and post-rotation results

Results: Between September 2002 and August 2013, 50 residents chose a rotation in colposcopy. Three of them did not complete the post-test and were not included. The mean pre-test result was 69%±10% and the mean post-test result was 85%±14% ($p<0.001$). When comparing the results from the 2002-2009 cohort to those from 2010-2013, we observed that the last group had a better pre-test than the first group (74% vs 67%, $p<0.05$) but the improvement between pre-test and post-test remains significant ($p<0.001$) in both subgroups (14%±8% and 19%±11%, respectively, NS). We explained the difference over the time period by an increase of exposure to teaching presentations apart from the colposcopy clinic.

Conclusions: Our study showed that pre and post-rotation tests using high resolution pictures can be useful to evaluate the training in colposcopy. Our teaching model gave expected results.

CS 5-1

PATHOGNOMONIC SIGNS GUIDING BIOPSY AND THERAPY DECISION

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Objective: To demonstrate the morphologic spectrum of pathognomonic colposcopic criteria which have high accuracy for diagnosis of high-grade cervical intraepithelial neoplasia (hg CIN).

Methods: Using VITOM® videocolposcopy ridge sign, inner border sign, rag sign and/or cuffed gland openings were documented and analyzed prospectively in 100 women visiting our colposcopy institutes. Biopsies and loop specimen underwent immunohistochemical staining for p16, Ki 67 and stathmin. Colposcopic and histologic findings were topographically correlated.

Results: High grade CIN correlates significantly with ridge sign, inner border sign or rag sign. Accuracy of cuffed gland openings is lower due to less stringent colposcopic definition. There was excellent agreement between detection of p16, Ki 67 and stathmin with the presence of high grade CIN and these markers proved especially useful for evaluation of atraumatic scraping biopsies. High risk HPV types were detected in all patients.

Conclusion: We confirm the clinical validity of the pathognomonic colposcopic criteria inner border sign, ridge sign and rag sign for diagnosis and treatment of women with high-grade CIN.

CS 5-2

IS IT TIME TO CHANGE THE CONSENSUS ON CIN 2-3 LLETZ TREATMENT DURING THE FIRST TRIMESTER OF PREGNANCY?

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Background: Cervical Intraepithelial Neoplasia 2- 3 (CIN 2-3) is a premalignant lesion and Large Loop Excision of The Transformation Zone (LLETZ) is the recommended treatment. During pregnancy the consensus guidelines recommend observation and performing LLETZ only if invasive cancer is suspected. However, reports show that the risk of cervical malignancy following pregnancy is 11%, and that the LLETZ is safe during the first trimester.

Objective: The aim of the present study was to show our experience with pregnant patients with CIN 2-3 that were followed up and treated after delivery, or women who had LLETZ performed during the first 14 weeks.

Methods: 64 patients were diagnosed with CIN 2-3 in pregnancy between January 2006 and August 2014. 32 women were followed and 32 had LLETZ.

Results: 32 women were followed and 6 are still pregnant. In 26 women who were observed the final pathological results was: 2 women (7.7%) with cervical cancer, 18 (69.2%) had CIN 2-3 and 6 (23.1%) had CIN 1 or normal histology. Of the 32 women who underwent LLETZ during the first trimester invasive cancer was diagnosed in 4 women (12.5%) , CIN 2-3 in 26 women (81.2%) and 2 (3.1%)women had CIN 1 or normal histology. No complications were reported. 25 women continued their pregnancy, 17(68%) of them had term deliveries, three (12%) had late premature deliveries and 5 women (20%) are still pregnant.

Invasive cancer was the final diagnosis in 10.3% of the 58 women evaluated because CIN 2-3 during pregnancy.

Conclusions: LLETZ procedure performed during the first trimester appears to be safe and has advantage of diagnosing or preventing cervical cancer in 10.3% of the cases. Based on these results, we believe it is time to reconsider the indications of CIN 2-3 treatment during pregnancy

CS 5-3

MANAGING WOMEN 21-24 YEARS OF AGE WITH CIN

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The onset for starting cervical cancer (CC) screening ranges widely from as early as 18 to 35 years of age with most countries starting at 25 yrs. Those starting younger than 25 tend to be in countries without organized screening programs relying on passive screening. The management of abnormal cytology in this age group should be based on the same evidence that suggests screening does not need to start until the age of 25 years. In other words, these women need to be managed very conservately with observation. Rational for observation include: 1) >90% of infections including those with LSIL will regress spontaneously in young women underscoring the rarity of HPV persistence; 2) cancer in this age group is rare-the 1994-98 US data reported that 2 per 100,000 in women aged 20-24 had CC; 3) although HSIL in women 20-24 yrs is as common as found in women 25- 35, HSIL in women <24 yrs is more likely to clear --this is due to the fact that many of the HSIL in young women are due to recent infections, whereas in the older women, the HSIL reflects persistent infections which has a higher risk to progress to CIN 3. The new guidelinesin the US recommend that ASCUS (whether HRHPV positive or not) and LSIL be managed without immediate referral to colposcopy. ASCUS/LSIL should have repeat cytology in one year; if cytology remains ASCUS/LSIL, cytology can be repeated again in one year—colopscopy not required. HSIL/ASCUS-H at any visit, or persistent ASCUS/LSIL at 2 years requires referral to colposcopy—immediate treatment (see-and-treat LEEP) is unacceptable. If on colposcopy/biopsy, CIN 1 or less is found in those referred for ASCUS/LSIL similar follow-up is recommended with cytology only. If CIN 1 or less is found after cytologic HSIL or ASC-H, women should be observed with colposcopy and cytology every 6 months for up to 2 years until 2 consecutive negative Pap tests and no HG coloscopic lesions visible. If CIN 2 or CIN 2/3 is found on biopsy, women can also be observed with cytology and colposcopy every 6 months. If CIN 2/3 persists at 2 years or progression to a more severe CIN 3 is made, treatment is recommended. Treatment can also be more conservative such as using cryotherapy for smaller lesions and when colposcopy is satisfactory or a more targeted LEEP/LETZ procedure.

In summary, since most lesions regress in young women, over-diagnosis and over-referral are problematic and observation is considered best.

CS 5-4

ROLE OF BIOMARKERS IN THE MANAGEMENT OF HIGH GRADE CIN

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Correctly identifying cervical cancer precursors is central to the success of cervical cancer screening efforts. It is widely accepted that cervical histology evaluation of biopsy specimens has limited accuracy and reproducibility, especially for the CIN2 group. Molecular markers could improve the assessment of cervical histology. p16 staining has been proposed as a histologic marker for cervical precancer to improve accuracy and reproducibility. In a systematic review and meta-analysis evaluating inter-observer agreement p16-adjudicated histology, a significant increase in agreement for CIN2 endpoints was observed with p16 staining, while the increase in agreement was only modest for CIN3, for which diagnostic variability is less of a problem. In a recent update of cervical histology guidelines, p16 staining was recommended for adjudication of CIN2 lesions. According to the recommendation, a CIN2 without p16 staining is not considered to be a high grade CIN and is grouped with LSIL. p16-positive CIN2 and CIN3 are combined into a single group of HSIL. Several studies are currently underway to evaluate the effect of p16 adjudication on cervical histology practice. Apart from p16, there are currently no biomarkers routinely used that affect management of cervical precancers.

CS 5-5

NON-INVASIVE TREATMENT OPTIONS FOR CIN

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Objectives: Surgical intervention such as LEEP are the mainstay for CIN treatment, however, this may be associated with an increased risk of perinatal complications. Recent US management guidelines recommend conservative management in young women with CIN2/3. The American Association for Cancer Research Task Force underlined the urgent need for non-surgical therapy with an adequate safety profile. Results: Therapeutic vaccines have shown promise, but have not demonstrated definitive clinical efficacy and appropriate immunological responses for cervical neoplasia. The topical immune-response modulator imiquimod with self-applied vaginal suppositories achieved complete histologic remission in 47% compared with the placebo group in 14% ($P=.008$) with moderate side effects. In a randomized dose-finding photodynamic therapy (PDT) study that included a total of 262 women with biopsy-confirmed CIN1/2, patients received hexaminolevulinate hydrochloride (HAL) via an intra-vaginal photoactivation device which is programmed to deliver 125J/cm2 of red LED light at 629nm wavelength and is removed by the patient. A clear dose-response in the HAL 5% group of 95% (18/19 patients) compared to 57% (12/21 patients) in the placebo group ($p<0.001$) was observed at three months in women with CIN2, including an encouraging 83% (5/6 patients) clearance of HPV16/18 compared to 33% (2/6) in the placebo group at six months. The treatment was easy to use, well accepted by patients and gynecologists. Only self-limiting adverse reactions including discharge, discomfort and spotting were reported. Conclusions: HAL PDT is a novel promising therapy. More research for non-surgical therapies such as HAL PDT is needed.

CS 5-6

RISK FACTORS FOR CERVICAL CANCER AT COLPOSCOPY

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Objectives: Determine the risk of invasive cervical cancer at colposcopy based on the woman's age at colposcopy and associated cervical cytology.

Methods: Review of electronic medical records from colposcopy clinics followed by chart review of women with cervical cancer.

Results: Between 3/1/1996 and 4/23/2013, 816,000 cervical cancer screens resulted in 27,381 cervical colposcopies for evaluation of abnormal cervical cytology and/or positive high-risk human papillomavirus (HR-HPV) tests. Median age at colposcopy was 32 years. Biopsy at colposcopy or at subsequent Loop Electrocautery Excision Procedure, cervical conization, or hysterectomy diagnosed cervical cancer in 0.5%, 132/27,381) of women. At colposcopy, the risk of cervical cancer for women age 30 years or greater with high grade cervical cytology (cytology of Cancer, High Grade Squamous Intraepithelial Lesion, Adenocarcinoma In situ, Atypical Glandular Cells, or Atypical Squamous Cells r/o High) (7.2%, 82/1,134) was greater than for women age $<$ 30 years with high grade cervical cytology (1.5%, 7/468, $p<.001$). The risk of cervical cancer for women $<$ 30 years with high grade cervical cytology (1.5%, 7/468) was greater than for women age 30 years or greater with low grade cervical cytology (cytology of Low Grade Squamous Intraepithelial Lesion, Atypical Squamous Cells of Uncertain Significance, benign endometrial cells, or negative) (0.3%, 42/14,116, $p<.001$). The lowest risk of cervical cancer was among women age $<$ 30 years with low grade cervical cytology (0.009%, 1/11,663).

Conclusions: At colposcopy, cervical cancer is extremely rare in women age $<$ 30 years that present with low grade cervical cytology.

CS 6-1

MEN AND WOMEN: DIFFERENCES IN SERO-CONVERSION FOLLOWING HPV INFECTION – GENITAL, ANAL

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Objective: To estimate differences in percent seroconversion and rates of seroconversion to HPV 6, and 16 among men with infections at the anal canal, genitals, and oral epithelia and to compare this to sero-conversion rates observed among women.

Methods: Men who were sero-negative to HPV 6, 11, 16, or 18 at enrollment and who acquired genital, anal, or oral HPV while participating in the *HIM Study* were included. Serum specimens from the visit HPV was first detected and subsequent visits every 6 months for a median of 18.1 months of follow-up were tested for anti-HPV L1 capsid antibody IgG using a VLP-based ELISA assay. HPV genotype-specific analyses were restricted to men with infection at only one anatomic site who did not have that specific HPV type detected at a prior visit at another anatomic site. Seroconversion rates were estimated using the Kaplan-Meier method.

Results: HPV antibody prevalence is significantly higher among females compared to males with correspondingly higher antibody titers in females. Among adult men, sero-conversion following genital HPV 6 infection was significantly higher (18%) vs. sero-conversion following HPV 16 infection (10%) . Regardless of HPV type, a larger proportion (54-69%) of females sero-convert following genital HPV infection compared to men. While similar rates of sero-conversion were observed following HPV 16 infection at the genitals and anal canal (~10%), sero-conversion following anal HPV 6 infection was higher (~70%) compared to sero-conversion following genital HPV 6 infection (18%). Sero-conversion was not influenced by age or sexual orientation. Few men had an oral infection that was not preceded by a genital or anal infection; therefore, seroconversion to oral HPV infection could not be estimated.

Conclusion: Consistently lower seroconversion following HPV infection in men compared to women likely contributes to the high rate of HPV infection observed in mid-adult and older men.

CS 6-2

IMMUNOLOGICAL FACTORS THAT MAY BE COMMON OR DIFFERENT AT GENITAL, ANAL OR ORAL SITES OF INFECTION.

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Local immune control of HPV infection at genital, anal and oral sites will be discussed in terms of both innate and adaptive immune factors.

CS 6-3

HUMAN PAPILLOMAVIRUS INFECTION IN CHILDREN

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HPV has been detected in oral mucosa of infants and young children. The prevalence of oral HPV DNA in children aged from 0.3 to 11.6 years has varied from 0-47%. Current still limited evidence suggests that oral and recurrent respiratory papillomas have a bimodal age distribution, similar as in skin warts. The highest prevalence is found before one year of age, and the second peak at the age of 13-20 years. It seems that the risk is increasing by 3-5% each year.

Recent meta-analysis on 3128 women/children pairs showed a significantly higher risk for children born to HPV-positive mothers to acquire HPV. Plausible explanations include vertical mother-to-child transmission of HPV during pregnancy and/or at birth or a higher infection rate during the early nursing (Merckx et al. 2013). The Finnish Family HPV Study was designed to elucidate the dynamics of oral and genital HPV- infections within families. Our results have shown that newborn can acquire oral HPV infection during delivery. Although most of these infections clear, these can become persistent in a subgroup of children. HPV serology of the mother and father as well as mother's oral HPV status might be of importance in predicting the outcomes of oral HR-HPV infections in the infants. Importantly, we found that HPV DNA detection in cord blood and placenta (trophoblasts) increases the risk for newborn to be HPV+ve in oral mucosa (Koskimaa et al.2012). To conclude, all results support the view that HPV infection can be acquired early in life.

Reference

Merckx M et al. Transmission of carcinogenic human papillomavirus types from mother to child: a meta-analysis of published studies.Eur J Cancer Prev. 22:277-85, 2013

Koskimaa et al.(2012). Human papillomavirus genotypes present in the oral mucosa of newborns and their concordance with maternal cervical human papillomavirus
genotypes. J Pediatr 160:837–843, 2012.

CS 6-4

NATIONWIDE ASSESSMENT OF HPV IN CANCERS: IMPLICATIONS FOR MONITORING IMPACT OF CURRENT AND FUTURE (9-VALENT) HPV VACCINES IN THE US

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Objectives. Systematic surveillance to determine the type-specific prevalence of human papillomavirus (HPV) in the United States (US) cancers is needed to estimate the impact of current (16/18) and proposed (31/33/45/52/58) HPV vaccines.

Methods. The Centers for Disease Control and Prevention partnered with seven US population-based cancer registries to obtain archival tissue from invasive anogenital and head and neck cancers for HPV testing (n= 2670). Demographic, clinical, and pathologic data were evaluated by anatomic site and HPV status. We used current US cancer registry data and the relative contributions of the HPV types to estimate the number of cancers that could be prevented by HPV vaccine.

Results. HPV DNA was detected in cervical and anal cancers (91%), vaginal cancers (75%), oropharyngeal cancers (70%), vulvar cancers (69%), penile cancers (63%), oral cavity cancers (32%), and laryngeal cancers (21%). Removing HPV 16/18 from the population potentially could prevent 38,000 cancers, including the majority of cervical (66%), anal (79%), oropharyngeal (60%), and vaginal (55%) cancers as well as many penile (48%), vulvar (49%), and some oral cavity (22%) and laryngeal (8%) cancers. An additional 4% to 18% (8000) of these site-specific cancers may be prevented by the future vaccine. For most cancers, younger age at diagnosis was associated with higher HPV 16/18 prevalence. HPV 16/18 distribution was similar across racial/ethnic groups, with the exception of a lower prevalence among African Americans with oropharyngeal cancers.

Conclusions. The impact of current and future HPV vaccines on US cancers can be monitored using population-based cancer registries.

CS 6-5

HPV AND THE ENVIRONMENT

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HPV is not alone…certainly not in the vagina, skin or oropharynx. The microbiome and virome have shown that there are millions of microbes/viromes living with us, in us and on us. Compared to other organs such as the colon and oral cavity, the vagina appears to be more eclectic with less diversity. In a "healthy" environment, lactobacillus species are predominant however there remains numerous lactobacillus subspecies and not all are equal in health and disease. In addition to HPV types, there appear to be other non-oncogenic types including the beta and gamma HPV types known to be predominantly found in the skin and hair follicles. These types are thought to be commensal unless a person is immunocompromised. We now understand that many HPV types are commensal and are important members of the "microbial community". One study examined the HPV community using shotgun sequencing data generated from the NIH Human Microbiome Project. The overall HPV prevalence was 68.9% and was highest in the skin (61.3%), followed by the vagina (41.5%), mouth (30%), and gut (17.3%) with 48% of samples having multiple HPV types. These data underscore their likely role in health but their role in controlling the pathogenic HPV is not well understood but may be crucial. We recently examined the 25 young adult couples enrolled into a transmission study who were sampled for βHPV DNA from the genitals, hand, and mouth 5 times over a 6-week period. HPV5 was the most common with a prevalence of 56% and was found in 118 of 212 visits at any one genital site. Taking into account all 5 visits, 44% of couples shared at least 1 βHPV type in their anogenitals, 65% in their hands and 6% in their respective oral cavities. Transmission rate of βHPV between anogenital area was 0 - 16.7(CI=0.4-92.9) per 100 women months for MtoF at risk and was 0 for FtoM at risk. We also examined similar association with γHPV, although the rate of detection was much less common in the genital area. Few studies have examined the microbiome and HPV. In one study, women with vaginal microbes dominated with L. gasseri were more likely to have a negative sample and samples with low relative abundance of Lactobacillus sp (class IV) or class III (dominated by L iners) were more likely to be HPV positive. Another cross sectional study of women with normal cervical cytology found a greater biological diversity in the vaginal microbiota of HPV+ women then those HPV-. This study found that L. gasseri was higher in HPV + women than negative but none for L. gallinarum or L. iners. These data underscore the difficulty in examining the microenvironment and its influence on HPV persistence. Clearly it will be important to further examine the microbial influence on health and disease associated with pathogenic HPV.

CS 6-6

HPV PREVENTION: VACCINATION VERSUS EDUCATION

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Genital HPV infection is the most common sexually transmitted infection with millions of individuals newly infected each year. Persistent infection can cause cervical cancer as well as other anogenital malignancies, oropharyngeal cancer and genital warts. Approximately half of new infections occur in 15-24 year olds. The bivalent and quadrivalent HPV vaccines are extremely effective in preventing
incident and persistent HPV infection, CIN 2/3 and for the quadrivalent vaccine in preventing genital warts. Modeling studies have shown that vaccination of 12 year old girls with either vaccine is a cost effective use of public resources, as long as vaccine duration of protection is long term i.e. 30 years. Cost effectiveness estimates for females >12 years and for males is less certain and less precise.
Numerous models have found that the cost effectiveness of adding males to a female vaccination program depends on vaccination coverage in females and the cost of the vaccine.Prevention of HPV infection other than with vaccination includes educational messages of
consistent condom use, mutually monogamous relationships and limiting the number of sexual partners. Cervical cancer screening does not prevent HPV infection, but can prevent most cases of cervical cancer and deaths if women are screened and receive appropriate follow-up and treatment if screening results are abnormal. HPV vaccines are not 100% effective and sex education is far from perfect. However it would be incorrect to place all our emphasize on vaccination programs and ignore the contribution that appropriately delivered education programs can add to HPV prevention.

CS 7-1

CAN MEN HAVING SEX WITH MEN PERFORM SELF OR PARTNER-ASSISTED DIGITAL ANAL EXAMS? A STUDY PROTOCOL

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Objective: Digital anorectal exams are standard of care for persons with HIV in the US given high anal cancer incidence; however, they are underutilized. In order to increase utilization, we set out to determine if it is possible that men having sex with men (MSM) might be able to report accurate findings after performing a self or partner-assisted digital anal exam (DAE). Earlier detection of tumors should reduce anal cancer morbidity and mortality.
Methods: We will conduct a feasibility study among 100 single and 50 MSM couples, aged 27-80 years. A clinician skilled in performing DAEs will use a pelvic model to train participants in anal anatomy and the detection of abnormalities, i.e., hemorrhoids, warts, fissures, tumors, and skin tags. Next, the clinician will perform a DAE on the participant not only for diagnostic purposes, but also to model a correct DAE. The participants will then perform a self or partner-assisted DAE in private, record a normal or abnormal finding, and then complete a questionnaire that includes acceptability questions. The clinician's initial DAE findings will then be reported to the participant. Cohen's kappa will assess concordance between clinician and lay person's DAE results. Factors associated with concordance (e.g., waist circumference and age) will be assessed.
Conclusions: For persons at high risk for anal disease, the study will clarify if a single lay person can do a self-DAE, or perhaps the screening requires a partner, or if, in fact, the procedure requires a clinician for reasons of safety, accuracy, or acceptability.

CS 7-4

MANAGEMENT OF GENITAL WARTS : UPDATED GUIDELINES

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Objectives: compare current STI guidelines' recommendations for the treatment and management of genital warts (GW).

Methods: Review of 5 GW management guidelines frequently referred to by Canadian health professionals1-2-3-4-5.

Results: For diagnosis, most recommend visual inspection of the anogenital area but one recommended automatic proctoscopy for men but not for women.
Acetowhitening as a diagnostic method was not standard recommendations in all guidelines. Biopsy, cervical cancer screening and HPV testing recommendations were much alike across guidelines. Screening recommendation for other STIs is standard in all guidelines. Therapeutic agents for patient applied treatment at home differ in their availability but when available their recommended uses were quite alike. The evidence base to direct first and second line treatments is not strong.All guidelines discussed that treatments have significant failure and relapse rates and that treatment may involve discomfort and local skin reactions. Partner notification recommendations are alike across guidelines. The uses of HPV vaccines are mostly for the affected person for the prevention of infection by unexposed HPV types and not for prevention of recurrences. Recommendation for the use of HPV vaccine in partners was not very strong. The use and limits of condoms for the prevention of transmission were discussed in guidelines.

Conclusions: Many aspects of the management of genital warts are similar across reviewed guidelines but some are quite different such as availability of drugs, treatment schedules, diagnostic methods and use of HPV prophylactic vaccines.

1. http://www.bashh.org/documents/86/86.pdf
2. http://www.cdc.gov/std/treatment/2010/genital-warts.htm
3.https://www.inesss.qc.ca/fileadmin/doc/INESSS/Outils/Guides_ITSS/condylomes_GUIDE_ITSS_17jan_EN.pdf
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5. http://www.phac-aspc.gc.ca/std-mts/sti-its/cgsti-ldcits/section-5-5-eng.php

CS 7-6

GENITAL HIGH-RISK HUMAN PAPILLOMAVIRUS (HPV) INFECTION AMONG MEN IN DENMARK: PREVALENCE AND RISK FACTORS

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Objectives: It is crucial to understand the natural history of genital HPV infection in men including risk factors for HPV infection, to prevent the increasing male HPV-related disease burden. We investigated HPV infection in the general male population and identified risk factors associated with high-risk (HR) HPV infection.

Methods: Penile swab samples collected from 2460 male employees of the Danish army were tested for HPV DNA with two tests simultaneously, the Hybrid Capture 2 and a PCR assay, Inno-LiPAv2. The LiPA test was used for genotyping and identified 15 HR-HPV types and nine low-risk (LR) or non-classified HPV types. A self-administered questionnaire providing data on sexual behaviour, including self-reported STIs was completed. We used logistic regression to investigate the association between potential risk factors and HR-HPV.

Results: The overall HPV prevalence was 41.8% using the PCR test; 30.0% were HR-positive, 11.5% were LR positive and 7.5% were non-classified HPV positive. Factors significantly associated with HR-HPV were ever having had genital warts (self-reported) (odds ratio [OR], 3.5; 95% confidence interval [CI], 2.5–5.2), and number of female sexual partners within the previous year (OR, 9.0 for >10 partners versus 1-3 partners; 95% CI, 6.4–12.7). Circumcised men had a significantly lower risk of being HR-HPV positive (OR, 0.7; 95% CI, 0.4–1.0).

Conclusions: HPV infection is common among Danish men and risk factors for HR- HPV infection include genital warts, number of female sexual partners and circumcision status. Analyses of risk factors associated with type-specific HPV prevalence are ongoing.

W 1-1

SAFETY OF THE QUADRIVALENT VACCINE

S Garland[1-4]

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Objectives: Since 2006, a quadrivalent human papillomavirus (qHPV) type 6/11/16/18 vaccine (GARDASIL/SILGARD®) has been licensed in many countries worldwide (133 mid-2014). Indication for this vaccine is for prevention of cervical, vulvar, vaginal and anal cancers and their respective pre-cancers, plus external genital warts causally related to HPV types 6/11/16/18. Across the 5 phase 3 clinical trials (> 21,000 females aged 9–26 years and males 9–26 years), vaccination was well tolerated: vaccine and placebo recipients reported similar incidences of systemic adverse events, serious adverse events (SAEs) and new medical conditions potentially consistent with autoimmune phenomena, with only local injection site pain, swelling and redness being significantly greater in the vaccinated groups. With >161 million doses distributed worldwide and comprehensive national public health vaccination programs in several countries, it is important that ongoing post-licensure safety surveillance occurs. Ongoing evaluation of safety data in real world settings and in larger populations can signal rare and potentially serious safety issues related to vaccination not demonstrated in trial data. To date > 15 studies in over 1.6 million pre-adolescents, adolescents, and adults from various countries have been conducted for the qHPV vaccine.

Methods, Results, Conclusion: Various potential SAEs have been extensively studied: no increases in incidence of events were found compared with background rates. Along with the safety data from the pre-licensure clinical trials, these results confirm that the qHPV vaccine has a favourable safety profile. Key policy, medical, and regulatory organizations worldwide have also independently reviewed these data and continue to recommend routine HPV vaccination.

W 1-2

UNDERSTANDING THE TRICKS AND TROPES OF ANTIVACCINOLOGISTS

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Objectives: to analyse anti vaccine communication strategies.

Methods: review of anti vaccine websites, blogs and articles as well as of selected papers presenting rebuttal actions.

Results: Anti vaccine activists have made good use of the Internet. Web 2.0 media such as websites, blogs, social media and of more classical communication tools such as paper media articles in journals, television and publication in obscure scientific journals are easy to find on the internet and frequently come up first following a search on browsers. All this anti vaccine publications, interactions and user-generated content has become ubiquitous and foster a new postmodern paradigm of healthcare has shifted from doctors to patients, the legitimacy of science is questioned, and expertise is redefined. It is likely that anti vaccine websites can influence whether people vaccinate themselves or their children. The types of rhetoric used by the anti-vaccination movement can be convincing, despite lacking scientific support for their claims. This includes actions such as skewing science, shifting hypotheses, censoring dissent, and attacking critics[1]. Health professionals have little time to discuss these raised issues and will frequently skip the issue of vaccination over going in a long discussion explaining the safety and the reasons of vaccine further legitimizing those issues! Strong statements from health care professionals remain an important reason why parents decide on vaccination of their kids.

Conclusions: Recognizing disingenuous claims made by the anti-vaccination movement is essential in order to critically evaluate the information and misinformation encountered online.

1A. Kata. Anti-vaccine activists, Web 2.0, and the postmodern paradigm – An overview of tactics and tropes used online by the anti-vaccination movement. Vaccine 30 (2012) 3778– 3789

W 1-3

VACCINES, NOT JUST SCIENCE. THE ROLE OF THE HEALTHCARE PROFESSIONAL IN CRISIS COMMUNICATION

Bravo E.

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Introduction It is today unquestionable that vaccines are experiencing a crisis of confidence and credibility with regard to public opinion in different regions of the world. In this context, we have seen a flourishing of anti-vaccine groups – including those comprising healthcare professionals- whose arguments are gradually seeping into the media sphere. As a result of this, the fear, confusion and doubt over the true value of vaccines is progressively gaining ground among a large part of civil society in many countries. The example of the vaccine for human papillomavirus is definitely among those which best illustrate the issue raised here.

Consideration Should there be a response to all the attacks of the anti-vaccine groups? Before answering, let's think... Do we have a response? Will we be capable of transmitting it effectively? Do we really wish to transmit it? Do we understand that not everyone needs the same response? I also wonder whether we are prepared to renounce the rationale of science in order to communicate emotionally, which is what really influences the human being's habits, attitudes and behaviours either at an individual level or as a member of a community. These questions and others must be posed before implementing any strategy and action plan in the environment of what we call "crisis communication". Communication represents the essential tool for building reputation and destroying it and the reputation of vaccines is currently endangered.

Conclusions Healthcare professionals bear a great responsibility for popularising science as a basis for health education. Beyond the scientific forums where evidence is required to validate an argument, the transmission of a message that gets through to the public needs a painstaking strategic and tactical approach, especially in contentious and polemical contexts. For you, as healthcare professionals, to know and master the key questions so you can transfer your knowledge to all corners of society is vital to highlight to public opinion, not just something as prized as vaccines, but any other breakthrough in the world of medicine.

W 1-6

RESEARCH ON ATTITUDES AND ACCEPTANCE OF HPV VACCINE

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One way to gain a better understanding of different patterns of HPV vaccination uptake around the world is to carry out research examining attitudes towards the vaccine, and its acceptability, in the general population and among healthcare providers. Behavioural science research uses both qualitative and quantitative methods to measure psychological constructs that contribute to our understanding of behaviour. Using examples from the UK, the US and Japan, this paper will explore the contribution made by such research to our understanding of HPV vaccine participation and to intervention development, and will suggest future avenues of research to help increase informed participation in vaccination. Methodological issues as well as recent findings will be discussed.

W 2-1

INFORMATION: TRANSMISSION, RISK OF CANCER, PROTECTION CERVICAL CANCER

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Cervical cancer is a preventable disease. Armed with appropriate knowledge about HPV infection and risk of cervical cancer, women can make the most informed choices to minimize the risk in themselves and their daughters. It is first most important to recognize that HPV infection is an equal opportunity virus. While transmitted primarily through sexual intercourse, nearly all sexually active women will acquire at least one, and likely multiple, HPV infections over their lifetime. This is because HPV infections are very easily transmitted. Women rapidly become infected after they begin sexual activity, many from their first sex partner.

Wearing condoms is good advice, as it protects against many sexually transmitted infections, including HIV. Condoms also reduce the risk of HPV infection, though do not completely prevent infections since HPV can be transmitted through skin-to-skin contact not protected by the condom.

Therefore the best way to prevent cervical cancer is getting the HPV vaccine.

Because HPV is transmitted so easily and rapidly, girls and boys should be vaccinated before they start sexual activity.

Vaccinated women have lower chances of getting cervical cancer, but because a few cancers are caused by types not included in the current vaccines, they should still undergo routine cervical cancer screening. However, vaccinated women will have fewer abnormal Paps and will be less likely to have to undergo procedures such as colposcopy and LEEP.

W 2-3

INFORMATION: TRANSMISSION, RISK OF CANCER, PROTECTION OROPHARYNGEAL CANCER

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Commonly asked questions by patients with oropharyngeal cancer, their partners and family members will be discussed. This will include concerns regarding transmission to partners, risk of recurrence, change in sexual intimacy. Reactions to HPV-positive diagnosis will be covered.

W 2-5

PRINT MEDIA COVERAGE OF THE LINK BETWEEN HPV AND ORAL CANCER IN THE UK

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Objectives: The role of human papillomavirus (HPV) in some oral cancers has appeared in media publications, particularly following an interview with actor Michael Douglas discussing his cancer. Little is known about the content of these publications.

Methods: UK media publications (2001-2014) were searched using the terms 'oral cancer' and 'human papillomavirus' or 'HPV' in the database LexisNexis®. Of 252 articles, 67 were eligible (>100 words referred to the link between oral cancer and HPV) for content analysis to determine the main themes.

Results: No media publications reported the link between HPV and oral cancer until 2001. After this, the main topics included: HPV as a cause of oral cancer, the sexually transmitted nature of HPV (particularly oral sex), the need to vaccinate boys against HPV and Michael Douglas' claim that his throat cancer was caused by HPV. Many articles also referenced the link between HPV and cervical cancer. Peaks in coverage were found when research demonstrated an increase in mouth cancers (March 2012), when Michael Douglas discussed his cancer (June 2013), and following campaigns to vaccinate boys (February 2014). Some tabloid newspapers sensationalised the link between HPV and oral cancer, using phrases such as 'sex virus' and referring to the 'Big C'. Facts about HPV and references to research were provided in some articles.

Conclusions: The link between HPV and oral cancer has received coverage in UK media, but often without detailed information. Transmission via oral sex was regularly discussed which could potentially increase public concern about this sexual behaviour.

W 2-8

HPV VACCINATION IN EUROPE AND THE MULTIDISCIPLINARY APPROACH

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Vaccine Research Unit, Healthcare Research Institute of Santiago, Spain

The growth of real-life data supporting the success and safety of HPV vaccines is robust. However, the official HPV vaccine recommendations, and the actual degree of implementation and vaccine coverage in the different countries is variable. Active recommendation by a healthcare professional is key to any vaccine uptake, and this is not different for the HPV vaccine. All healthcare professionals who play a role in the information, training and application of correct HPV management and preventive strategies should, as far as possible, ensure that HPV reaches all the potential beneficiaries. At the same time, the potential recepients of HPV vaccines are varied, ranging from healthy prepubertal girls or boys, through healthy women or men, to adult oncologic patients. The so-called "vaccine experts" or those with the "know-how" do not necessarily have access to the entire target population. In contrast, those specialists with access to vaccinees don't always have the expertise and knowledge to proactively get them vaccinated. The solution to this riddle probably lies in a multidisciplinary approach. The "EUROGIN spirit", striving to bring together representatives of all the specialist areas concerned with HPV, is a good example of how the scientific voice behind HPV vaccines is quite solid and organized. However, the translation of this scheme into the patient realm is another story, and one which varies in different European scenarios.
The main reason behind the lack of actual commitment towards HPV vaccination shown by an important fraction of healthcare professionals is a lack of adequate education. Indeed information and education - EUROGIN Multilingual CME course, for example - are key tools to solve this problem. An essential step towards this aim is the coordination and integration of the scientific voice with those of other stakeholders and key players. This seems, at present, the weakest link of the equation. In this sense, bureaucratic advocacy, albeit slow, may be the most sustainable way forward.
HPV vaccines have fulfilled their expectations so far, and the next generation is here. We now have the duty to ensure that we actually achieve their full potential. There are also additional needs in the HPV patient environment - the HPV family burden - that require specific care: diagnostic, therapeutic, preventive and/or emotional care cannot be neglected. Integrated multidisciplinary HPV units may constitute the definitive response to this challenge, not only from the individual patient care perspective but also from the HPV leadership perspective at local/regional level.

HN 1-1

GLOBAL BURDEN OF HPV-ASSOCIATED HEAD AND NECK CANCERS

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Human papillomavirus (HPV) infection has emerged as an important etiologic factor for a subset of head and neck cancers, which arise from the oropharynx including the tonsil and base of tongue. Incidence rates for oropharyngeal cancers have significantly increased over the past three to four decades in the U.S. and other developed countries around the world. This rise in oropharyngeal cancer incidence is most apparent among men younger than 60 years of age. Recent molecular epidemiologic studies show that HPV infection is the cause of the rising oropharyngeal cancer incidence in recent calendar years and birth cohorts. It is believed that changes in sexual behaviors among recent birth cohorts have led to increased oral HPV exposure, and as a consequence, an increase in the incidence of HPV-positive oropharyngeal cancers. Contemporary estimates show that the proportion of oropharyngeal cancers caused by HPV infection is significantly heterogeneous worldwide, with high HPV-attributable fractions in North America and Northern/Western Europe (40-60%) and low HPV-attributable fractions in Asia and South/Central America (10-15%). An estimated 22,000 HPV-positive oropharyngeal cancers occur annually worldwide, and a majority of this burden is concentrated among men in developed countries.

HN 1-4

DEFINING RISK IN HPV-DRIVEN OROPHARYNGEAL CANCERS

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Eastern Cooperative Oncology Group: 1 Vanderbilt University, 2 Dana-Farber Cancer Institute, 3 Johns Hopkins University MD, 4 Ohio State University, 5University of Pittsburgh, 6 Northwestern University, 7 Colorado Cancer Center, 8 Stanford University, 9 North Memorial Health Care, 10 Fox Chase Cancer Center.

Objectives: Recognition that HPV-associated oropharynx cancer is treatment responsive has led to proposals to deintensify treatment for these cancers, minimizing late toxicity in patients with good long-term survival, given that treatment intensification was justified by in HPV-negative cancers. Accurate ascertainment of which patients are at low risk will be critical to successful pursuit of this goal.

Methods: E1308 was a phase II clinical trial of chemo-responsiveness as a dynamic biomarker of treatment responsiveness in locally advanced HPV or p16+ oropharynx cancer. Patients with clinical complete response (cCR) to 3 cycles of cisplatin, paclitaxel, cetuximab chemotherapy received reduced radiation dose of 54Gy, with concurrent cetuximab; patients with < cCR were treated with cetuximab and 69Gy. 71% attained cCR to induction. 62 patients received low dose radiation. 2 year progression-free survival (PFS) for this group was 80% vs. 65% for patients treated with full dose. T4a vs T1-3 had 2 year PFS of 54 vs. 84%; N2c vs. N0-N2b 77 vs. 82%; > 10 pack years vs. < 10 pack years tobacco 57 vs. 92%. Best prognosis nonT4, nonN2c, < 10 pack years patients had 2 year PFS of 96%.

Discussion: Appropriate patient selection is critical to the safe implementation of deintensification strategies. 96% PFS at 2 years is achieved with 54Gy in nonT4, nonN2c p16+ cancers and < 10 pack years when the tumor is chemo-responsive. This compares with 78.3% 8-year PFS for similar patients on R0129, in which patients received full dose cisplatin-radiation and were not selected by chemo-responsiveness.

HN 1-5

MODELLING THE NATURAL HISTORY OF HPV-DRIVEN HEAD AND NECK CANCERS USING CELL-BASED MODELS

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The molecular pathogenesis of HPV-driven head and neck squamous cell carcinoma (HNSCC) is distinct from HPV negative tumours and clinically the HPV positive tumours have a more favourable outcome. HPV-positive tonsillar cancer most likely occurs as a result of HPV infection of the tonsillar crypt. We have developed cell-based models of primary human tonsil keratinocytes transfected with HPV16 genomes, the most prevalent HPV type present in HNSCC, or HPV18, a high-risk virus strongly associated with adenocarcinoma of the cervix but whose prevalence is low in HNSCC cancers. Stable cell lines were established and the structure of the viral DNA was shown to be either episomal or integrated into the host genetic material. Upon long–term cell culture, episomal forms of the viral genome remained either episomal or integrated into the host DNA. Stratification of the cell lines by organotypic raft culture produced a stratified epithelium with a morphology that is typical of non-cornifying epithelium and expressed markers typical of the tonsillar reticulated crypt. Organotypic raft cultures of cells following long-term culture displayed a more dysplastic morphology. Investigation of these cell-based models will provide insight into the natural history of HPV driven tonsil carcinogenesis.

HN 2-1

ARE HPV H&N CANCERS PREVENTABLE BY SCREENING AND EARLY DETECTION AND IMMUNIZATION

Carole Fakhry
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This talk will discuss features of HPV-positive oropharyngeal cancer that are amenable to screening and early detection in the future. Limitations of present technology will be reviewed. The potential role of prophylactic vaccination upon HPV-positive oropharyngeal cancer will be discussed.

HN 2-4

COMBINED PROPHYLACTIC AND THERAPEUTIC VACCINATION STRATEGIES FOR HPV-HNSCC

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We have recently discovered that chemoradiation converts the tumor microenvironment into a site permissive for the activation of an adaptive immune response . This creates an opportunity to combining peptide or protein vaccines with chemoradiation therapy to elicit potent antigen-specific cell-mediated immune responses. Notably, chemotherapy with cisplatin or radiation therapy combined with peptide administration was sufficient to induce the accumulation of dendritic cells in tumor loci and elicit the priming and expansion of antigen-specific CD8+ T cells, leading to synergistic therapeutic antitumor effects compared to either treatment alone. Furthermore, this combination treatment leads to the presentation of antigenic peptides by immunosuppressive stromal cells of the tumor, which are rendered susceptible to antigen-specific CD8+ T cell-mediated killing. Together, this results in potent antigen-specific CD8+ T cell immune responses and antitumor effects. A particularly promising therapeutic HPV vaccine to use in conjunction with concurrent chemoradiation is TA-CIN, which is composed of HPV-16 L2, E6 and E7, as a single tandem fusion protein. TA-CIN has been clinically tested in healthy volunteers and shown to be safe and effective in generating T-cell immunity against HPV-16 E6 and E7. Our preliminary data indicate that administration of TA-CIN with an adjuvant, GPI-0100, generates antitumor effects in mouse models sufficiently promising to initiate a clinical trial in newly diagnosed, advanced stage HPV16+ head and neck cancer patients treated with concurrent chemoradiation therapy. This clinical trial exploits the temporally permissive tumor microenvironment induced by chemoradiation and administration of clinical grade TA-CIN/GPI-0100 to potentially enhance HPV-specific immunity and antitumor effects in HPV16+ HNSCC patients. The successful implementation of our clinical study may lead to a new platform technology, which not only benefit HPV16+ HNSCC patients, but may also be effective against other HPV-associated malignancies including cervical, vaginal, vulva, anal, and penile cancers.

HN 2-6

PERSONALIZED PATIENT COUNSELING - HPV AND OTHER BIOMARKERS FOR PREDICTION OF RESPONSE TO TREATMENT

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Objectives: To combine HPV positive status with other biomarkers to predict response to treatment to better personalize patient counseling

Methods: From 2000-2009 all 439 patients diagnosed with tonsillar or base of tongue cancer (TSCC and BOTSSC) at the Karolinska University Hospital with available FFPE pretreatment tumour biopsies and treated with intent to cure were included in the study. FFPEs were tested for presence of HPV and HLA class I, HLA-A2, numbers of CD8+ tumor infiltrating lymphocytes (TILs), LMP10, CD44 and other biomarkers and the data obtained - correlated to tumour stage, patient age, treatment strategy and clinical outcome, first one by one and then combined, using also a multinomial regression analysis.

Results: Absent HLA class I expression, high CD8+ TILs, as well as low CD44 expression and others were associated with a very good clinical outcome (<95% disease free survival for 20-40% of the patients. Using a multinomial regression analysis absent HLA class I expression and high CD8+ TIL counts and lower age remained positive prognostic markers.

Conclusion: By combining positive HPV status with different biomarkers and clinical markers and performing a multinomial regression analysis we have preliminary data suggesting that absent HLA class I and high CD8+ TIL counts remain interesting prognostic markers and may have bearing for future patient counseling and treatment.

HN 3-2

DECISION-MAKING IN MANAGEMENT OF OROPHARYNGEAL CANCERS (OPC) - TREATMENT – SURGICAL - ROBOTIC SURGERY?

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With the change in demographic and prognostic profile of patients with oropharyngeal cancer, there is increased interest in the role of transoral robotic surgery. Data on transoral surgery will be reviewed. The current role of transoral robotic surgery in present national comprehensive cancer network guidelines and clinical trials will be discussed.

HN 3-6

THE ROLE OF IMMUNOTHERAPY IN HPV+ HNSCC

Sara I. Pai, MD, PhD,
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HPV-associated head and neck squamous cell carcinomas (HPV-HNSCC) arise from the crypts within the lymphoid tissue of the tonsil and base of tongue and the majority of these cancers can be distinguished from tobacco-related head and neck cancers by the characteristic infiltration of lymphocytes within the stroma and tumor nests. Nevertheless, despite this profound inflammatory response within the tumor microenvironment, the virus and its associated cancer cells are able to evade immune surveillance, persist, and grow. Various mechanisms have been proposed for the resistance of human solid tumors to immune recognition and obliteration, including the recruitment of regulatory T cells (Tregs), myeloid derived suppressor cells (MDSC), and local secretion of inhibitory cytokines. Recent evidence that tumors co-opt physiologic mechanisms of tissue protection from inflammatory destruction through the upregulation of immune inhibitory ligands has provided a new perspective for understanding and overcoming tumor immune resistance. Antigen-induced activation and proliferation of T cells are regulated by the temporal expression of both co-stimulatory and co-inhibitory receptors and their cognate ligands. Coordinated signaling through these receptors modulates the initiation, amplification, and subsequent resolution of adaptive immune responses. In the absence of co-inhibitory signaling, persistent T cell activation can lead to excessive tissue damage in the setting of infection as well as autoimmunity. However, in the context of cancer, in which immune responses are directed against antigens specifically or selectively expressed by tumor cells, immune checkpoint pathways can represent major obstacles to the generation of clinically meaningful anti-tumor immunity. Therefore, efforts have been made in the clinical arena to investigate blockade of immune checkpoints as novel therapeutic approaches to cancer. The rationale for immune checkpoint blockade in HPV-HNSCC will be discussed.

JE 1-1

CURSO DE COLPSCOPIA - IMÁGENES NORMALES

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Colposcopy is a technique that allowes us to examine the lower genital tract and was first described by Hinselaman. The main indication for colposcopy is secundary prevention of lower genital tract cáncer.

Histology is the substract in wich the images observed by the colposcopist are generated. It is for this reason that the kwoledge of normal and abnormal histology is absolutely necessary.

The color reflected by the beam of light has its origin in the stromal vessels and the thickness of the epithelium. The glandular epithelium is a single layer epithelium colposcopically carcaterized by an intense reddish colour; The squamous epithelium is constituted by multiple layers so the reflected color will be pink or pale red.

The squamous-columnar junction (SCJ) is the histological spot in wich columnar and squamous epithelium collide. Locating, defining and Classifiyng this squamous-columnar junction is probably one of the basic objectives of the colposcopist. This junction hugely changes its position during a women´s life and it will do so depending on different life stages and hormonal status. The identification of this SCJ will allow us to classify the different tranformation zone types.
Classically the SCJ will be identified colposcopically as a thin White rim.

The transformation zone is constituted by a metaplastic epithelium in different maturation stages and is the region in wich almost all the pathological event will take place. The formation of the metaplastic epithelium follows two different pathways; The first one is a squamous re-epithelization originated from the original squamous eptithelium. The second one is via metaplastic transformation of the reserve primitive cells. These two mechanisms very often coexist.

JE 1-4

CRITICAL ANALYSIS OF THE COLPOSCOPIC CLASSIFICATION OF RIO DE JANEIRO 2012

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2 Department/Division of Gynaecology, Miguel Hernández University, San Juan Campus, Alicante, Spain.

The terminology of colposcopy, and colposcopic findings classification, has undergone a permanent change over 85 years with this technique. The reasons for these changes are the subjectivity of the physician at the time to describe the findings and notes the need to classify them according to knowledge of each era (which have changed very quickly).

The latest rankings as of Graz 1975, Rome 1990 and Barcelona 2002, for example, did not consider as important the size and location of the abnormal findings. Moreover, with the passage of time there have been studies that even establish the positive predictive value of some major abnormal findings recently were signs not described as the inner edge (inner border sign), the presence of nodules or ridges (ridge sign) in aceto-white areas and Rag sign (sign the flap or shred).

For these reasons the IFCPC again raised the need to review this issue and finally in 2010 in order to update both the terminology and classification colposcopic raised. The Nomenclature Committee of the IFCPC (J. Bornstein, J. Bentley, P. Bosze, F.Girardi, H. Haefner, M. Menton, M. Perrotta, W. Prendiville, P. Russell, M. Sideri, B. Strander, A. Torne and P. Walker) conducted a critical review of the last three terminologies through discussions "on line" discussion with National Society for Colposcopy and individual colposcopists and developed a proposal that was submitted and accepted at the World Congress Rio on July 5, 2011.

The objectives of the Committee was a critical review of previous classifications, consider medicine based on evidence to establish a modern terminology, include as new terminology techniques loop excision and description of the size of specimen and finally , include a parallel terminology to describe the colposcopic findings in the vagina, vulva and periano.
In this Paper a critic of the main sections of the new classification analysis also has limitations in clinical practice and the degree of implementation is carried out after two years of its publication.

JE 1-5

CASES REPORTS IN COLPOSCOPIC

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In this paper we present practical clinical cases of colposcopy. We present many images of colposcopy and its relationship with clinical.

We present nromal colposcopic findings. We also present abnormal colposcopic findings and other findigns as suspicious for invasión, miscellaneous findings, etc.

We include also cases with problems at the vagina and vulva (General assesment of vagina and vulva, normal colposcopic findings, abnormal colposcopic findings, etc.).

Finally we also include some clinical cases to highlight terminology cervical excision (excision treatment types, excision specimen dimensions, etc.).

JE 2-2

PRIMARY PREVENTION OF CERVICAL CANCER IN SPAIN: POST-LICENSURE MONITORING ACTIVITIES

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Spain made the decision to introduce human papillomavirus (HPV) vaccination into the national immunisation programme in October 2007 as part of its cervical cancer prevention strategy. The Interterritorial Council of the National Health System recommended the introduction of either the bivalent or the quadrivalent HPV vaccine for one cohort of girls aged 11-14 years before the end of 2010. All 19 regions of Spain implemented publicly funded HPV vaccination programmes according to their logistics between 2007 and 2008. The routine targeted age group, the type of HPV vaccine administered and the delivery strategy (school-based or primary care-based) varied by region. Initially, 6 regions chose the bivalent vaccine and 13 the quadrivalent vaccine; nevertheless, since the beginning of the program several regions have changed to use a different HPV vaccine.

HPV vaccine safety in Spain is monitored through passive surveillance while initiatives to monitor the impact of the HPV vaccines vary by region. Few regions have established vaccination registries. In addition to regular monitoring of HPV vaccine coverages and usual monitoring of cervical precancerous and cancerous rates by cancer registries or Public Health Directorates, there are ongoing or planned studies evaluating sexual behavior, trends in the incidence of genital warts and HPV type-specific prevalence at cervical or oral sites as well as in cervical neoplasia and invasive cervical cancer.

An overview of HPV vaccine post-licensure monitoring activities in Spain will be given and post-licensure surveillance studies conducted in Catalonia will be presented and discussed in detail in the presentation.

JE 2-3

SPANISH GUIDELINES FOR CERVICAL CANCER PREVENTION, 2014. CONSENSUS FOR SEGO AEPCC, SEAP, SEC.

Torne A[2], del Pino M[2], Cusidó M[1], Alameda F[4], D Andia[2], Castellsagué X[5], Cortes J[1], Granados R[3], Guarch RM[4], Lloveras B[4], Lumbrano A[2], Martínez-Escoriza JC[2], Ordi J[3], Puig-Tintoré LM[2], Ramirez M[1], de Sanjose S[5], Torrejon R[1], Bosch X[5], Piris MA[3], Rodriguez R[4], Comino R[2], Lailla JM[1], Ponce J[1].

(1) Sociedad Española de Ginecología y Obstetricia (SEGO), (2) Asociación Española de Patología Cervical y Colposcopia (AEPCC) (3) Sociedad Española de Anatomía Patológica (SEAP) (4) Sociedad Española de Citología (SEC) (5) Instituto Catalán de Oncología

Screening for cervical cancer in Spain is mostly opportunistic and different strategies are followed in the 17 Autonomic Regions. Recently, an update to the guidelines regarding the early detection of cervical precancerous lesions and cancer has been agreed based on a systematic review of the available evidence. The new screening recommendations address age-appropriate screening strategies, including the use of cytology and high-risk human papillomavirus (HPV) testing alone as a primary screening approach, follow-up (e.g., management of screen positives and screening interval for screen negatives), age at which to exit screening, and screening strategies for special population. Some prior guidelines were reaffirmed but important updates have been incorporated.

Target population and screening strategy

- Sexually active women ages 25-65. years
- Screening programs should ensure proper population coverage through effective recruitment and retention strategies.

Tests recommended and screening intervals

- Women under the age of 25: no screening.
- Women ages 25-30 years: cytology alone every 3 years.
- Women ages 30-65 years: 1) HPV testing every 5 years (preferred); 2) Co-testing (cytology and HPV testing) every 5 years (acceptable); 3) cytology alone every 3 years (acceptable).
- Women older than age 65: exit screening if adequate negative prior screening and no history of CIN 2+ within the last 20 years.

Screening in special populations

- Women who have undergone benign hysterectomy: no screening.
- Women with history of CIN2 +: screening for at least 20 years.
- Immunocompromised Women: 1) Cytology annually from age 21; 2) Co-testing from age 30 (every 3 years if CD4 ≥ 200 cl / uL or active antiretroviral therapy but annually if CD4 <200 cl / uL or no antiretroviral treatment).

JE 3-2

PROGRAM STRATEGY AND METHODOLOGY ONCO-GUIDELINES SEGO 2008-2016

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Onco-guidelines program conducted from the Section of Gynecologic Oncology and Breast Pathology of the Spanish Society of Gynaecology and Obstetrics (SEGO) is presented. The project Onco-Guidelines is part of the 5 strategic lines of the Section and act transversely on all of them: protocols and consensus building, teaching and spread, registration and accreditation, multidisciplinary participation and finally research and continuous improvement. The Onco-Guidelines were conceived as a tool used to achieve the cancer care equity in the SEGO sphere of influence, in order to develop specific improvement measures based on the best available scientific evidence and its applicability. This Onco-Guidelines must meet the basic requirements as equity, Protection, Reliability, Consensus and Transparency. Compared to other similar initiatives it has been worked in its implementation system, the registry data, the quality control and the clear need to review and update periodically the Onco-Guideline features. This has been prepared based on the premises of the European Quality Model (EFQM) and revised under the parameters of the Appraisal of Guidelines for Research & Evaluation Instrument (AGREE). Importantly, this is not a single protocol of action, not always exist enought evidence.

All Onco-Guidelines are made with the same format, a first methodological part that is common to all of them and a second portion of content structured algorithms work, tables and text developed accompanied in all cases of levels of evidence and level of consensus. It is essential consensus on definitions provided based on international terminology, consensus in developing a standardized pathological definitions and types of surgery report. This structure facilitates standardization, understanding and adapting to guide clinical practice becoming a pocket guide very easy to understand and therefore easy reference.

JE 3-3

GUIDELINES FOR THE MANAGEMENT OF ABNORMAL CERVICAL CANCER SCREENING TESTS AND CANCER PRECURSORS

del Pino M, Torne A, Cusidó M, Alameda F, D Andia, Castellsagué X, Cortes J, Granados R, Guarch RM, Lloveras B, Lumbrano A, Martínez-Escorizal JC, Ordi J, Puig-Tintoré LM, Ramirez M, de Sanjose, Torrejon R, Bosch X, Piris MA, Rodriguez R, Comino R, Lailla JM, Ponce J.

(1) Sociedad Española de Ginecología y Obstetricia (SEGO), (2) Asociación Española de Patología Cervical y Colposcopia (AEPCC) (3) Sociedad Española de Anatomía Patológica (SEAP) (4) Sociedad Española de Citología (SEC)

The recently screening recommendations raise new scenarios which claim new management strategies for women with abnormal screening tests.

Some of the most significant updates refer the selection of women with minor abnormalities in the screening tests using molecular markers, the observation without treatment of high-grade lesions with higher potential of regression and the post-treatment follow-up strategies.

Women with positive high risk human papilloma virus (hr-HPV) testing and a negative cytology could be evaluated using molecular biomarkers such as hr-HPV genotyping (types 16/18/45 carry a higher risk of cervical lesion development); E6/E7 mRNA testing (which has shown a similar sensitivity than hybrid capture test but a better specificity) or p16/Ki67 dual staining (a surrogate marker of cell cycle deregulation due to an hr-HPV infection).

On the other hand, recent studies show that up to 40-74% of the histologically confirmed HSIL/CIN2 lesion may regress spontaneously. Factors associated with the regression are: 1) age less than 25 years-old, 2) small lesions, 3) negative hr-HPV testing, and 4) cervical lesions caused by genotypes other than HPV-16. Thus, although treatment is recommended for high-grade cervical lesions, clinical follow-up is the preferred option in selected cases.

Regarding to patients treated for cervical intraepithelial neoplasia, compelling evidence shows that hr-HPV persistence or re-infection is necessary for development of post-treatment lesions. Current studies demonstrate that effective treatment eliminates both, the lesion and the causing hr-HPV. Therefore, in the last years, hr-HPV testing has been introduced into the post-treatment management protocols, and it is now considered the standard test for post-treatment follow-up.

JE 3-6

ONCOGUÍA CÁNCER ESCAMOSO INVASOR DE VULVA 2015

Sociedad Española de Ginecología y Obstetricia.
Presentada por J. Lombardía Prieto
- SESCAM (en excedencia). Toledo. España.
- Policlínica Madrid Parla Sur. Madrid. España.
- Hospital Nisa Pardo de Aravaca. Madrid. España.

OBJETIVOS:

La Sociedad Española de Ginecología y Obstetri¬cia (SEGO) a través de la Sección de Ginecología Onco¬lógica, ha elaborado el plan estratégico "PRO¬GRAMA ONCOGUIAS-SEGO 2008-2015" para el desarrollo e implantación de las principales guías de práctica clínica en el cáncer ginecológico y mamario.

Las oncoguías se conciben como la herramienta que utiliza la SEGO para lograr la equidad de atención oncológica en su ámbito de influencia, científico y territorial, con el objetivo de desarro¬llar medidas de mejora concretas, basadas en la mejor evidencia científica disponible y su aplica¬bilidad.

MÉTODOS:

La principal característica de la oncoguía debe ser su sencillez trasmitiendo el conocimiento de ma¬nera básica, clara y fácilmente inteligible.

Conscientes de las limitaciones para conjugar la evidencia científica disponible con la aplicabilidad a nuestro entorno sanitario, el proceso de elabo¬ración se basará en la evaluación y registro de 2 indicadores de estandarización fundamentales: nivel de evidencia científica disponible (sistema GRADE) y nivel de consenso entre los expertos.

RESULTADOS:

Se actualiza la Oncoguía de cáncer escamoso invasor de vulva del 2010, dando lugar a la Oncoguía de cáncer escamoso invasor de vulva 2015.

CONCLUSIONES:

Presentación de la Oncoguía del cáncer escamoso invasor de vulva 2015.

JE 5-1

LA EDUCACIÓN EN VPH DEL MÉDICO GENERALISTA / DE FAMILIA

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Especialista en Medicina de Familia y Comunitaria Centro de Salud Valdebernardo - Dirección Asistencial Sureste Servicio Madrileño de Salud

Los médicos de familia en nuestra práctica habitual y diaria estamos en contacto frecuente con la población, siendo la especialidad médica más accesible. Una característica de nuestra atención es ser longitudinal a lo largo de la vida de los individuos, lo que nos permite estar en un lugar privilegiado cuando se trata de enfermedades de larga duración como la infección persistente por virus VPH que a lo largo de los años puede originar un cáncer urogenital, principalmente de cérvix.

Los médicos de familia no nos limitamos a un área específica como ocurre en otras especialidades, tomamos parte de todas las disciplinas, actuando en todos los órganos y sistemas y ello implica tomar decisiones aplicables a un individuo concreto, la familia y la comunidad. El perfil del Médico de Familia hace que podamos y debamos desempeñar un papel fundamental especialmente en los aspectos preventivos y de educación para la salud y para poder llevar a cabo estas actuaciones es importante e imprescindible una buena formación. Así mismo, es igualmente importante que conozcamos todas las posibilidades y controversias sobre la vacuna del VPH, para de esta manera poder asesorar de una forma veraz y eficiente a nuestros pacientes.

La aparición y el desarrollo de vacunas seguras y eficaces significan un avance médico indiscutible. Además en el caso de la vacuna del virus del papiloma humano, no solo previene una infección, sino que además previene el cáncer de cuello de útero, entre otros cánceres genitales e incluso la papilomatosis faríngea y esto hace más importante la formación para poder llevar a cabo una prevención, de tal forma que no se limite exclusivamente a lo establecido en los calendarios vacunales fijados por la administraciones públicas.

JE 5-2

ROLE OF THE GENERAL PRACTITIONER IN THE PRIMARY AND SECONDARY PREVENTION OF CERVICAL CANCER

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Background: The incidence of cervical cancer in Spain is 7.6 cases per 100,000 women / year. Vaginal cancer is often diagnosed simultaneously with cervical cancer, and HPV16 contributes to 70% of these cancers.

Discussion: The family doctor plays an important role in making quality prevention. Start practicing good health education in their patients, both girls and boys. Primary prevention (vaccine) also depends heavily on the family doctor. It has demonstrated the effectiveness of the HPV vaccine in women aged 16-45 years, and men aged 16 to 26 years, and immunogenicity in children / girls and adolescents aged 9 to 15 years. It is indicated from 9 years for the prevention of premalignant and cervical cancer causally related to certain oncogenic HPV genital lesions. Public Health administers the vaccine to girls between 11 and 14 years, but recommending between 14 and 26. The main factor for better coverage rates of vaccination is a proactive attitude of the doctor on the recommendation of the vaccine. In terms of secondary prevention, cervical-vaginal cytology is the most useful method for its effectiveness and efficiency, and is done mostly in primary care.

Conclusions: The role of primary care is essential for primary and secondary prevention of cervical cancer.

OC 1-1

DETECTION OF CERVICAL DISEASE WITH THE APTIMA HPV AND COBAS 4800 HPV ASSAYS USING SUREPATH LIQUID CYTOLOGY SPECIMENS

M. Chernesky[1], **D. Jang**[1], **J. Gilchrist**[1], **L. Elit**[2], **A. Lytwyn**[2], **M. Smieja**[1], **B. Weinbaum**[3], **B. Kirkconnell**[3], **and J. Dockter**[3]

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3 Hologic, San Diego, CA

Objectives: To compare the performance of Aptima HPV screening and genotyping assays (AHPV and AHPV-GT) to the cobas 4800 HPV (cobas) test using SurePath liquid Pap specimens. Interim results from this study were reported previously and the final results reported here.

Methods: SurePath specimens were collected from consented women referred to colposcopy clinics. Colposcopy was performed and biopsies collected to ascertain disease status. SurePath specimens treated with Aptima Transfer Solution (ATS) were tested with the AHPV assay and AHPV-positive specimens were tested with AHPV-GT. Untreated specimens were tested with the cobas test per the manufacturer's instructions. The clinical sensitivity and specificity of each assay was calculated using a CIN2+ endpoint. Absolute and relative risks were calculated for various HR-HPV and genotype interpretations.

Results/Conclusions: There were 136 cases of CIN2+ from 1333 evaluable women (10.2% prevalence). The clinical sensitivity and specificity was 91.9% and 59.6% for AHPV and 94.9% and 54.9% for cobas. Specificity differences were significant (p-value <0.001), while sensitivity was not (p-value 0.2188). Women with genotype-positive results (16 and/or 18/45) were at significantly higher risk of disease (31.7% for Aptima assays and 30.2% for cobas) than women with other high-risk types (12.4% for Aptima assays and 10.9% for cobas). Women negative for high-risk HPV had low risk of disease (1.5% for Aptima assays and 1.1% for cobas). These results demonstrate sensitive detection of CIN2+ disease by the AHPV and AHPV-GT assays using ATS-treated SurePath Specimens, similar to cobas HPV testing of SurePath samples.

OC 1-2

DIRECT GENOTYPING FROM THE APTIMA® HPV ASSAY USING ANYPLEXTM II HPV28

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Objectives: In the APTIMA® HPV assay, 14 hr-genotypes (16,-18,-31,-33,-35,-39,-45,-51,-52,-56,-58,-59, -66 and 68) are detected, without type verification. During amplification of mRNA copies, double stranded DNA is produced as an intermediate step and the aim of this study was to evaluate if double stranded DNA could be used for genotyping, direct from the analyzed APTIMA tubes.

Methods: 108 samples were genotyped before and after APTIMA® HPV assay. Prior to analysis, 1 ml sample was used for DNA extraction. After mRNA analysis, APTIMA tubes were collected and 200 μl was DNA extracted for comparison. Pre- and post DNA was genotyped using the Anyplex™ II HPV28 (Seegene, Korea) detecting 28 different genotypes using real-time PCR and melting curve analysis at 30, 40 and 50 cycles.

Results: Sixty-three (58.3%) of the samples were positive for any of the genotypes included in the Anyplex™ II HPV28 prior to APTIMA® HPV assay and fifty-four (50.0%) samples were positive in the post analysis.

Sixty-five hr genotypes results were found prior to APTIMA® HPV assay, and fourteen hr genotyping results were lost at post analysis. Nine of the lost results were initially detected at 50 cycles indicating low viral load. When comparing detection levels before and after the APTIMA® HPV assay, thirty of all the genotyping results were detected at same cycle no and twenty of the results at a lower detection level. Interestingly, lr genotypes were detected in both pre and post analysis in 24 samples, where HPV-42 (n=9) and – 53 (n=6) were the most abundant genotypes.

OC 1-3

COMPARISON OF HC2 AND COBAS REALTIME PCR IN ROUTINE HPV TESTING

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Background: Long-time the HC2 test was the gold-standard in routine HPV testing. Meanwhile several new assays have been validated and received an FDA approval. Cytomol, a major German lab, until 2013 used HC2 and shifted to cobas 8/2013.

Methods: We compared the results with cobas from 5.8.2013 to 4.8.2014 when only this test was employed with the same period in 2012/13 (exclusively HC2). The profile of the users remained unchanged. Around 40% of the tests were performed as adjunct to cytology, around 60% as triage or test of cure.

Results: 22.5% of 27.429 tests were positive with the HC2 high-risk (HR) probe (13 HPV types including HPV16/18) compared to 31.8% in 27.246 cases tested with cobas 12 types HR and HPV16/18 probes, an absolute increase of 9.3% and a relative rise of 41.3%. In cases tested out of the Thinprep vial (mainly used for private patients with a lower rate of abnormalities and in adjunct testing) 16.1% were positive with HC2 and 26.1% with cobas. From the proprietary tubes (mainly used for public healthcare patients and as triage) this was 23.8% vs 33.0%.
46.5% of the cases positive with cobas for HPV16 and/or 18 were also positive for the 12-types-HR-HPV set. Comparable data for HC2 are not existing because here only secondary testing for a combined probe set of HPV16/18/45 is available.

Conclusions: First data from routine use of cobas HPV testing point to a higher positivity rate and hence a potentially lower specificity compared to the HC2 assay.

OC 1-4

DEFINITIVE SEPARATION OF HIGH GRADE FROM LOW GRADE DYSPLASIA USING THE COMBINED MORPHOLOGICAL AND MOLECULAR BIOMARKERS OF ONCOTECT 3DX

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Background: In prior studies, we have used 3Dx technology to demonstrate the ability to combine multiple measurable attributes with detection of E6/E7 mRNA to create a landscape capable of describing the cellular environment present in HPV infection. In an extension of this, we measured 13 cellular parameters to create a Logistical Regression Model taken from a compilation of 166 patients who were HPV DNA negative NILMs (negative for intraepithelial lesion or malignancy) and compared them to patients who were clinically defined as ASCUS (Atypical Squamous Cells of Undetermined Significance) n=37, or LSIL (Low-Grade Squamous Intraepithelial Lesion), n=29 taken from liquid based cytology specimens submitted for HPV DNA testing.

Materials and Methods: All submitted samples were processed using a semi-quantitative method designed to hybridize HPV mRNA and stain DNA using DAPI. The samples were collected on a Sony EC800 cytometer and the derived cellular parameters were tabulated with metadata in Excel and then ported into R, an open source language for statistics and graphics. Once in R, Random Forest analysis identified five parameters that differed from NILM and these parameters were used to derive the model designed to detect difference. The derived model was then tested by plotting true positives versus false positives to create an AUC (Area Under the Curve) and Boot Strapped 10 times to compare the initial accuracy of the model versus a cross validation of the model.

Results: The values of AUC (0.86-0.88) and Cross Validation Accuracy (0.851-0.861) reveal that the derived model is both highly specific and accurate in delineating ASCUS/LSIL from NILM in this small study. It is our goal to use similar concepts to objectively determine patients who should be referred to colopscopy from those who are merely infected. The use of highly specific cellular parameters using 3DX coupled with bioinformatic approaches appears to be a technique capable of highly accurate delineation beyond current standard of care.

OC 1-5

A NOVEL, SIMPLE AND SPECIFIC TEST FOR HPV INDUCED NEOPLASIA VIA DIRECT DETECTION OF E6 ONCOPROTEIN

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The unacceptably high mortality caused by cervical cancers in developing countries calls for screening technology that readily allows widespread implementation in settings of need. The Onco***E6***™ Cervical Test (E6 Test) has been developed to meet requirements specific to many low and limited resource settings; the test features lateral flow format and is void of cold chain requirements for storage or sample collection. The procedure uses low complexity equipment which is virtually maintenance free, and comparatively inexpensive. The E6 Test is compatible with several specimen types (dry swab, PreservCyt media), and it can accommodate very low to medium specimen throughput per run. The E6 Test can be performed by personnel with little to no laboratory expertise, and operator training can occur via training video, or by in person training following a trainer-trainee model. The time from sample collection to result is about 2.5 hours, reducing the risk of patient loss on follow-up, and facilitating screen-and-treat. Directly detecting elevated quantities of the cancer causing viral oncoprotein E6, the test delivers high clinical specificity and positive predictive value (98.9% and 40.8% for CIN3+, respectively, as found in the Chinese START-UP study), thus greatly reducing over treatment upon a positive test result. We will present a clinical performance summary for the Onco***E6***™ Cervical Test, present features relevant to use low resource settings, and discuss implications of its use as a triage or primary screen in a variety of settings.

OC 1-6

PERFORMANCE OF THE TROVAGENE URINE HPV ASSAY IN A REFERRAL POPULATION

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OBJECTIVE: Determine performance of the Trovagene Urine HPV test for the detection of high-grade cervical intraepithelial neoplasia (CIN) within a referral population.

METHODS: A total of 518 pairs of urine (in EDTA) and liquid based cytology samples in (ThinPrep Preservcyt medium) were collected. The Trovagene HR-HPV test was used for the detection of 13 high risk HPV types by consensus PCR amplification of the E1 region in both specimen types. Samples were anonymized, sent to Trovagene for testing with all urine specimens and currently 320 matching ThinPrep samples completed. This was part of the Predictors 4 study in which cytology samples were assayed by a range of other HPV tests in both ThinPrep and SurePath.

RESULTS: Sensitivity (SE) and specificity (SP) from cytology samples in ThinPrep medium was similar to other well established tests (SE=98.0% for CIN3+ and 95.7% for CIN2+; SP=22.8% for < CIN2). SE from urine samples was only slightly lower (90.5% for CIN3+ and 88.0% for CIN2+) with similar SP (24.7% for < CIN2). Positive/negative agreement between the 320 paired urine and ThinPrep samples currently analyzed was 84.4% (95% CI 79.8%, 88.2%) with 25 discordant pairs in each direction (kappa = 46.9%). 90.5% of the samples positive on cervical material were also positive in urine.

CONCLUSIONS: The Trovagene test had very good performance in ThinPrep samples - comparable to other established HPV tests, and good performance in urine that was slightly lower than for ThinPrep. Detailed performance from both urine and cervical samples will be presented.

OC 1-7

AUTOMATED VERSUS MANUAL PRE-PROCESSING OF SUREPATH LIQUID-BASED CYTOLOGY SPECIMENS: ASSESSING IMPACT ON THE PERFORMANCE OF THE REALTIME HIGH RISK HPV ASSAY

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Cervical specimens collected in liquid-based cytology (LBC) media are the only sample types used for cervical cytology in the UK. The Abbott RealTi*m*e High Risk HPV assay, a highly automated qualitative multiplex real-time PCR for the detection of 14 high-risk HPV (hrHPV) types with simultaneous typing of HPV16 and HPV18, has been approved by the English NHS Cervical Screening Programme for HPV triage of low grade dyskaryosis and test-of-cure. As per manufacturer´s instructions, pre-analytic processing of LBC samples involves manual mixing and liquid transfer of the original sample into a secondary tube used directly on the Abbott *m*2000 System. Future implementation of hrHPV primary screening increases the need for automation of pre-analytics. We evaluated a custom-configured work-table-setup of the TECAN EVO Freedom instrument designed to automate pre-processing of SurePath samples and patient-identification matching between original SurePath vials and secondary tubes comparing results from 415 specimens (primary screening population: N=260; triage and test-of-cure population: N=155) pre-processed manually and automatically. hrHPV was detected in 91 samples after manual pre-processing and 94 positive results were obtained after automatic pre-processing. Excellent agreement of overall-hrHPV results (98.3% [95%CI:0.92-0.99]; kappa: 0.95) and individual results for HPV16, HPV18 and other-hrHPV (≥ 98.6% agreement; kappa ≥ 0.89) was found following manual and automated pre-processing.

The TECAN EVO Freedom-configuration designed to automate pre-analytics required for preparing SurePath samples for hrHPV-testing resulted in assay performance comparable to that following the manufacturer-validated manual process, saves ~1.5mins hands-on-time per sample processed and allows for complete specimen identification tracking and documentation of process control.

OC 1-8

INTRODUCTION OF CEPHEID® HPV TESTS INTO CERVICAL SCREENING IN MALAWI

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2-Simpson's Centre for Reproductive Health , Royal Infirmary of Edinburgh

3-Department of Gynaecology, Stobhill Hospital, Glasgow

4-Nkhoma Hospital, Malawi

5-Centre for Population Health Sciences, University of Edinburgh

6-Women's Health Marketing, Cepheid, California

Objectives: Visual inspection with acetic acid (VIA) has a poor record in interpreting cervical abnormalities accurately and skills are readily lost. HPV tests could provide an objective primary screen with triage to VIA of positives. This project aims to test this in an unscreened population in rural Malawi

Methods: LBC samples were obtained from women attending VIA clinics within a new programme. Collection media included ThinPrep, saline and Cepheid®'s own collection medium. HPV tests were carried out on the same day as collection and later linked to clinic data.

Results: In the first 475 samples, HPV positivity was 20.2% overall and 31.8% in women known to be HIV positive. Of 90 positive samples, 17.8% harboured HPV 16, 19.6% HPV 18/45 and 56% HR-HPV other types. Comparison of collection media was available for 146 paired samples, with complete agreement in 133 (91%) and discordant or invalid results with one or more collection media in 13 samples. Results of HPV status linked with VIA results and clinical outcomes will be presented.

Conclusions: The Cepheid® HPV test proved easy to do with a turnaround time of 2 hours possible from clinic back to clinic. If the cost is acceptable, HPV testing may prove useful as primary screen in some settings in low resourced settings.

OC 1-9

GYNTECT®, A TRIAGE TEST FOR HIGH-RISK HUMAN PAPILLOMAVIRUS DNA-POSITIVE WOMEN, MAY HAVE PROGNOSTIC POTENTIAL

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Objectives: High-risk human papillomavirus (hrHPV)-DNA testing is frequently performed parallel to cytology for the detection of high-grade dysplasia and cervical cancer (termed CIN3+) particularly in women above 30 years of age. Although highly sensitive, hrHPV testing has only limited specificity. Furthermore it is well known that only a proportion of CIN lesions progress to cervical cancer. Therefore, markers with prognostic value would substantially improve cervical cancer diagnostics.

Methods: In a retrospective, cross-sectional study with two gynecological hospitals cervical scrapes from more than 500 patients with histopathology-confirmed diagnosis a panel of 5 promising DNA methylation marker regions comprising a newly developed test termed GynTect® were analyzed using methylation specific PCR. In addition, for 29 patients who attended the colposcopy clinic at least twice (up to nine previous visits) before obtaining the endpoint diagnosis CIN3, the GynTect® markers were determined and the results correlated to histopathological and cytological findings.
Results: High sensitivity and specificity was observed for the detection of CIN3+ if at least 2 out of 5 GynTect markers were methylated. In the longitudinal study earlier detection (up to six years) of the severe disease compared to histopathogy was obtained in 19 of 29 patients (66%), indicating that methylation of the GynTect® marker panel may show the likeliness of progression to severe lesions.

Conclusions: GynTect® may provide a promising diagnostic tool for identifying patients with CIN3+ among hrHPV-positively tested women. Furthermore there is strong evidence that these markers may be of prognostic value.

OC 1-10

VALIDATION OF NOVAPREP HQ+ LIQUID-BASED CYTOLOGY MEDIA FOR HR HPV DETECTION BY HYBRID CAPTURE 2 (HC2)

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Objective: To assess the suitability of Novaprep HQ+ Orange medium for the detection of HR HPV DNA by HC2.

Methods: Specimens were prepared with HPV16+ cells (SiHa and CaSki), HPV18+ cells (HeLa) and HPV- cells (C33-A) diluted in Novaprep HQ+ Orange medium and in STM as reference medium. Repeatability was evaluated by coefficient of variation (CV%) calculated on 14 determinations (three levels of HPV16 and HPV18 DNA concentrations). Reproducibility was assessed between 3 lots of Novaprep HQ+ Orange medium by CV% calculated on 14 determinations. A method-comparison study was conducted on HPV16+ and HPV- specimens diluted in Novaprep HQ+ Orange medium and STM. A study is ongoing to assess the stability of specimens stored at +4°C, +21°C and +40°C in 3 lots of Novaprep HQ+ Orange medium. Samples were tested with HC2 according to the manufacturer's instructions.

Results: Repeatability and reproducibility showed CV%<8% whatever the genotype (HPV16/18), or the lot was. The comparison study showed a 100% sensitivity and specificity for HR HPV detection from samples diluted in Novaprep HQ+ Orange medium. Furthermore, an excellent correlation was achieved (r^2>99%) between RLU/CO measured from cell samples diluted in Novaprep HQ+ Orange medium compared to those diluted in STM. Specimens are stable for at least 10 weeks at +4°C, +21°C and +40°C. In conclusion, Novaprep HQ+ medium adequately preserves HPV DNA and is suitable for HR HPV DNA detection by HC2.

OC 1-11

VALIDATION OF TWO METHODS OF COLLECTING INFORMATION ON HPV TEST: ELECTRONIC CLINICAL HISTORY AND MANUAL REGISTER ON CERVICAL CANCER SCREENING IN SPAIN.

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Objectives: In Catalonia (Spain) cervical cancer (CC) remain as the main screening tool the cytology and also introduced for the first time, the Human Papillomavirus (HPV) DNA test under some very specific situations (triage of ASC-US, underscreened women (women aged >40 years without screening history in the last 5 years) and post-surgery treatment) .The aim of this study was to examine the percentage and the reasons of each HPV test performed in CC screening for the period 2007-2011 using two methods of collection information: clinical history and manual register.

Methods: Two sources of information were available: a) electronic health record system used by 77% of primary care doctors of the public system in Catalonia for period 2008-2011, b) A specific form for collecting information about HPV tests including reasons, age, center for period 2007-2009 used by 100% of primary care doctors.

Results: Preliminary descriptive results indicate that from 2008 to 2011, 55.460 HPV tests (positivity of 16.8%) were registered in the electronic history. 54.8% were performed in underscreened women and 15% for ASC-US triage. In contrast, during the period 2007 to 2009, 66.486 forms for HPV testing were filled (positivity of 21.5%), 61.4% of which were performed in underscreened women and 22% for ASC-US follow-up.

Conclusions: Although preliminary descriptive results suggest that there may be some differences between the two methods of data collection, more comprehensive validation analysis adjusted for period and percentage of covered population are underway and will be presented at the conference.

OC 1-12

HIGH-RISK HPV mRNA IN RELATION TO FUTURE HIGH-GRADE LESIONS AMONG HPV-DNA POSITIVE WOMEN WITH MINOR CYTOLOGICAL ABNORMALITIES

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Objective: The aim was to determine the sensitivity and specificity of the APTIMA HPV mRNA assay (Hologic) in predicting future development of high-grade cervical intraepithelial neoplasia (CIN) among high-risk HPV-DNA-positive women with ASCUS or CIN1 cytology.

Methods: Archived SurePath cervical samples of women ≥ 35 years of age with high-risk HPV DNA-positive atypical squamous cells of ASCUS (n= 211) or CIN1, (n= 131) were tested by the APTIMA HPV assay, and the women were monitored for development of histopathologically verified CIN2+.

Results: Twenty-nine percent (61/211) of the women in the ASCUS group, and 34.3% (45/131) in the CIN1 group developed CIN2+ within 4.5 years of follow-up. The prevalence of HPV mRNA was 90.0% (190/211) among women with ASCUS and 95.4% (125/131) among women with CIN1. The presence of HPV E6/E7 mRNA was associated with future development of CIN2+ among women with ASCUS and CIN1 (p=0.02).

The APTIMA assay demonstrated high sensitivity in predicting future CIN2+ and CIN3 in the ASCUS (96.7% and 100%) and CIN1 (97.8% and 100%) groups. The corresponding specificity was low (5.4-12.7%). The negative predictive value of the HPV assay for detecting future CIN3 was 100% since no mRNA-negative woman developed CIN3 (0/27) as compared to 13.6% (43/315) of the mRNA-positive women (p=0.03).

Conclusion: The APTIMA mRNA assay demonstrated high sensitivity but low specificity in predicting future CIN2+ among women with minor cytological abnormalities. The assay had high negative predictive value for future CIN3, indicating that HPV-mRNA-negative women are at low risk of progression to high grade CIN.

OC 2-1

MONITORING THE IMPACT OF THE HPV VACCINATION PROGRAM AND CERVICAL CANCER CONTROL IN BHUTAN

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Objectives: Bhutan has started a national cervical screening program in year 2000 and a vaccination programme against human papillomavirus (HPV) in 2010 with coverage of >90% in girls aged 12-18. The collaboration between the government of Bhutan and IARC to monitor HPV prevalence over 10 years and pilot HPV-DNA-based cervical screening, offers an excellent opportunity to evaluate short- to medium-term impact of cancer control in LMICs.

Methods: We conducted a set of descriptive studies since 2011 to assess the burden of HPV infection and local screening program performances. A cytology-based and urine-based HPV prevalence survey were conducted among adult women and young female students, respectively; a case series of CIN3+ biopsies was assessed to quantify the fraction of cervical disease attributable to each HPV type; and finally, an assessment of screening coverage of women aged 25 years or more was performed in the capital, Thimphu.

Results: For the cytology-based and urine-based survey 2505 women and 1051 students were enrolled, respectively; for the case-series 323 biopsies were collected; and finally for the cervical screening assessment 1620 women were investigated. Among the general population and students HPV prevalence was 26% and 11%, respectively; 70% of cancers were attributable to HPV16/18; the screening coverage in the capital was 34%.

Conclusions: We will present detailed results of the baseline picture of HPV epidemiology in Bhutan prior to vaccination and will describe a 10-year IARC protocol for repeat surveys with which to compare future vaccinated cohorts of women to demonstrate vaccine impact.

OC 2-2

POSSIBLE HAND-GENITAL HPV INFECTION TRANSMISSION AMONG HETEROSEXUAL COUPLES: RESULTS FROM THE HITCH STUDY

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Objectives: HPV is transmitted by mucosal contact but other modes of transmission may exist. We analyzed the HITCH cohort study data to understand the role of the hand-genital route in transmission.

Methods: At enrolment and 4-month follow-up visits, we tested for HPV genotypes in genital and hand samples from 213 female university students (aged 18-24) and their male partners. We assessed genotype-specific concordance beyond chance between hand and genital sites within and between partners and genital-genital concordance between partners.

Results: Prevalence was higher in genitals (penile: 59.2%, vaginal: 57.8%) than in hands (male: 36.2%, female: 34.3%). Observed-to-expected ratios (95%CI) for hand-genital concordance within individuals were 8.7 (6.8-10.6) for men and 8.7 (6.7-10.7) for women, whereas between-partner ratios were 8.0 (6.0-10.0) for male hand-female genital and 6.7 (5.1-8.4) for female hand-male genital. The ratio for between-partner genital type concordance was 6.4 (5.3-7.5). Genital positivity was associated with the partner's same-type hand positivity, after accounting for the partner's genital HPV status. Mutually-adjusted odds ratios of vaginal infection were 7.40 (4.7-11.6) for male hand positivity and 55.2 (40.0-76.1) for penile positivity. The equivalent figures for penile infection given female hand and vaginal positivity were: 5.68 (3.5-9.2) and 55.80 (40.1-76.8).

Conclusions: In an individual, HPV types in the hand tend to reflect those present in the genitals, regardless of gender. Hand positivity is also correlated with a partner's genital positivity, even after taking into account the individual's genital types. Hand-genital transmission may be a significant influence in the epidemiology of HPV infection.

OC 2-3

AVAILABILITY OF TYPE-SPECIFIC DATA ON HPV INFECTION IN EUROPE FOR HEALTHY WOMEN AND WOMEN WITH CERVICAL, VULVAR OR VAGINAL DISEASE

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Objectives: To assess the availability of type-specific data on HPV infection in European women and identify data gaps.

Methods: PubMed/Medline and EMBASE databases were systematically searched to retrieve full publications reporting type-specific prevalence and incidence of genital infections in general European populations of women without clinically-manifested disease, as well as type distribution in histologically confirmed cervical, vaginal and vulvar intraepithelial neoplasms and cancers. Original studies and meta-analyses reporting on types 16 and 18 and at least one other high-risk type were included. Studies published before 2000, non-English publications, studies focusing on special populations (e.g., HIV-infected, pregnant), and small studies (N<50) were excluded. Key information, i.e., study type, country, population characteristics, sample type, HPV assay used, and HPV data, was extracted from each study.

Results: A total of 236 publications met the inclusion criteria: 126 for type-specific infection prevalence in general female populations, 107 for type distribution in cervical lesions or cancers, 23 for type distribution in vulvar or vaginal lesions and 5 for type-specific infection incidence. Five countries (Italy, UK, Spain, Sweden and Netherlands) contributed more than half of these studies. By UN sub-region, 107 studies originated from Southern Europe, 66 from Northern Europe (includes the UK), 51 from Western Europe and 17 from Eastern Europe (includes the Russian Federation).

Conclusions: There is a significant scarcity of published HPV type-specific data for Eastern Europe, representing a population of approximately 147 million women. Gaps also exist for HPV type-specific incidence in European women and type distribution in vulvar / vaginal lesions.

OC 2-4

CORRELATION OF VIRAL LOAD AND PERSISTENCE FOR HPV16 AND HPV18 IN A DUTCH COHORT OF YOUNG WOMEN

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Objectives: Persistent human papillomavirus (HPV) infection with an oncogenic high-risk HPV (hrHPV) type is necessary for the development of cervical cancer. Here we evaluate the association of viral load of HPV16/18 in persistent and non-persistent HPV16/18 infection in young women.

Methods: 3282 Women aged 16-29y supplied vaginal self-swabs in two rounds, one year apart. Samples were tested for HPV-DNA using the SPF_{10}-PCR DEIA $LiPA_{25}$ system. HPV16 and HPV18 load was quantified via an adapted RT-PCR protocol targeting the L1 gene. Values were normalized for cellular content by β-actin RT-PCR measurement. Only women that were HPV16/18-positive at baseline and participated in two rounds were included in the analysis.

Results: 271 Persisting HPV16 infections and 112 persisting HPV18 infections were found. Viral load was significantly higher in persistent infections than in clearing infections for HPV16 and HPV18 ($p=0.015$, $p=0.018$ respectively). HPV16 load was significantly higher in multiple infections (HPV16 + any HPV) than in single infections ($p=0.003$), but did not differ significantly for HPV18 ($p=0.136$). HPV16/18 loads in infections with or without α9/α7 HPV co-infections did not differ significantly ($p=0.926$, $p=0.092$). Integration of variables into logistical regression analysis showed significant contribution of viral load levels to HPV16 and HPV18 persistency status ($p=0.001$, $p=0.011$). Contribution of multiple and α9/α7 co-infection status was not significant for HPV16 and HPV18 (combined variables: $p=0.171$, $p=0.692$).

Conclusions: Viral load is a proxy for persistent HPV16 and HPV18 infections, but needs to be combined with other factors to predict persisting infections.

OC 2-5

SERIAL TYPE-SPECIFIC HUMAN PAPILLOMAVIRUS LOAD PREDICTS HISTOLOGICAL OUTCOME

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Objective: This retrospective study examined if HPV-specific changes in viral load measured in serial cervical smears are predictive for the natural evolution of HPV infections.

Methods: A cervical histology database was used to select consecutive women with biopsy-proven CIN in 2012 who had at least two liquid-based cytology samples before diagnosis of CIN. Before performing cytology, 18 different qPCRs allowed HPV type-specific load measurement. Changes in HPV-specific load between 2 and 3 measurements were assessed by linear regression. According to the degree of increase/decrease of viral load, 2 processes were considered 1) transient virion producing infections ±0.3 HPV copies/cell/day 2) basal cell transforming infections leading to CIN3+ 0.003 HPV copies/cell/day.

Results: 210 women were included, 80 had single type infections (80 infections with 2 measurements, 53 infections with 3 measurements) and 130 had multiple HPV types (382 infections with 2 measurements, 281 infections with 3 measurements). For 2 and 3 consecutive HPV specific viral load measurements there was a decrease in productive infections from CIN1 to CIN3+ and an increase in the number of transforming infections. We could clearly demonstrate regressing lesions with a persistent linear decrease in viral load (R^2>0.9;-0.003 HPV copies/cell/day).

Conclusions: The increase and/or decrease in HPV-specific viral load correlated with biopsy-proven diagnosis of CIN in 2, but even better after 3 consecutive measurements. Serial measurements allows triaging HPV-driven processes in transient virion productive and basal cell transforming, enabling prediction to high-grade CIN.

OC 2-6

THE EFFECT OF MALE CIRCUMCISION ON GENITAL HPV INFECTION AND EXTERNAL GENITAL LESIONS IN THE *HIM* STUDY

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Objectives: To assess the association between male circumcision (MC) and genital human papillomavirus (HPV) infection and subsite specific incidence of external genital lesions (EGL) among men in the *HPV Infection in Men (HIM) Study.*

Methods: The *HIM* Study is an ongoing prospective study of healthy men residing in the US, Brazil, and Mexico. The study enrolled 4,123 men, aged 18-70 years, followed every 6 months, up to 4 years. At each visit, men completed a risk factor questionnaire and underwent a clinical exam with swab sampling of the genitals for HPV DNA detection. Circumcision status was determined by a clinician. EGLs were biopsied and histologically diagnosed. Cox proportional hazards models were used to evaluate associations.

Results: Overall HPV prevalence, incidence and clearance rates did not differ by MC status, except for HPV types (6,11,16,33,39,40,42,51,58,61,64,68,71,81,IS39). In contrast, MC was associated with a significant reduction in the risk of any EGL at the distal penis only (adjusted hazard ratio for circumcised men to relative to uncircumcised men: 0.06 [95% confidence interval: 0.02-0.27]). Reduced risk associated with MC was consistent for all three types of EGLs (non-condyloma, condyloma and penile intraepithelial neoplasia).

Conclusions: Among men in the HIM Study, MC is not associated with prevalence, incidence or clearance of genital HPV infection when using a single sample of the genitals (penile head, shaft, and scrotum, combined). However, when considering specific genital subsites, MC is associated with a reduction in the risk of developing EGLs on the distal penis.

OC 2-7

WHAT CAN TWIN STUDIES TELL US ABOUT THE AETIOLOGY OF CERVICAL CANCER?

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O**bjectives:** To investigate environmental and genetic influences on variation in susceptibility to cervical pre-cancer in a classical twin study.
Methods: Pap smear histories were obtained from monozygotic (MZ) and dizygotic (DZ) adult twin pairs. Casewise concordance was estimated for 'history of atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesions or higher' (≥ ASC-H). Within-pair correlations were estimated for behavioural risk factors for ≥ ASC-H using a subset of participants for whom these data were collected.
Results: Pap smear histories were available for 2,095 pairs (1,324 MZ and 771 DZ). Mean age at most recent Pap smear was 42.9 years (SD 11.2), with no differences by zygosity. Overall, ≥ ASC-H was reported in 354 (7.8%) women. Casewise concordance for ≥ ASC-H was 0.24 (95% CI 0.16–0.32) for MZ pairs and 0.16 (95% CI 0.07–0.25) for DZ pairs, ($p=0.2$) for difference. In a subset (389 MZ and 238 DZ pairs), correlations were greater for MZ pairs for: age at first sex ($p=0.001$), lifetime number of sexual partners ($p<0.001$), years smoking ($p<0.001$), pack-years smoked ($p<0.001$) and Pap smear frequency ($p=0.04$).
Conclusions: Twin pairs were concordant for ≥ ASC-H suggesting a familial influence; although the estimate was higher for MZ than DZ pairs, the difference was not significant. Known cervical pre-cancer risk factors were more correlated for MZ than DZ pairs. Therefore, within the limitations of our sample size, we found no evidence that genetic factors explain variation in the development of cervical pre-cancer. The study concordance estimates guide the design of future pooled studies on this topic.

OC 2-8

48 MONTH INCIDENT HPV INFECTION RATES FOR WOMEN HPV NEGATIVE AT BASELINE: THE HPV FOCAL TRIAL

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Objectives: HPV FOCAL is a population-based randomized trial evaluating primary high-risk HPV DNA (HPV) testing plus liquid-based cytology (LBC) triage for HPV positives, compared to LBC screening with HPV triage for ASC-US. Reported are 48-month incident HPV infection rates and factors associated with incident infection in women baseline HPV negative.

Methods: In HPV FOCAL, women 25-65yrs randomly assigned to primary LBC (LBC arm) or HPV testing (Intervention arm (IA)). IA baseline HPVneg women exit trial at 48 months with LBC and HPV testing. Logistic regression analysis was conducted to determine factors associated with incident HPV infection.

Results: 9540 of 9553(99.9%) women in the IA had baseline HPV results: 770/9,540 (8.1%) were HPVpos [<35yrs: 334/1,862 (17.9%); 35-49yrs: 318/4,457 (7.1%); 50+yrs: 118/3,221 (3.7%)]; and 8,770/9,540 (91.9%) HPVneg. Of the 2709 baseline HPVneg women with a 48 month result, 111/2,709 (4.1%) were HPVpos [<35yrs: 33/334 (9.9%); 35-49yrs: 53/1,312 (4%); 50+yrs: 25/1,063 (2.3%)]. Of the 111 HPVpos, histopathology results available for 55(49.6%): 36(65.5%) negative; 13(23.6%) CIN1; 5(9.1%) CIN2; no >CIN3 identified. Logistic regression analysis found incident HPV infections were associated with age <35yrs (AOR 4.8; 95%CI 2.6, 8.9) and lifetime sexual partners (<6 partners: AOR 0.5; 95%CI 0.3, 0.9).

Conclusions: 48 month incident HPV rate in women initially HPV negative is 4.1%, compared to a baseline HPV prevalence rate of 8.1%. Women with incident HPV infections were likely to be younger, and have more sexual partners. In programs planning HPV primary screening, awareness of the incident infection rate will help to better plan for health services demands.

OC 2-9

TRENDS OF HOSPITAL DIAGNOSTIC DEMAND OF PAPILOMAVIRUS. 1996-2013.

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INTRODUCTION AND OBJECTIVES: HPV diagnostic is a technique of rising demand in clinical setting due to its value anticipating cervical pathology. The aim of this work is to analyze trends on diagnostic demand and positive results during last 18 years.

MATERIALS AND METHODS: Retrospective descriptive study of HPV diagnostic in samples from two different hospitals representing 500,000 habitants by means of molecular diagnostic based on hybridization, PCR and LIPA.

RESULTS: From 16,915 analyzed samples, 6,064 (35.8%) out of those were positive for any type of HPV. From these, 5,346 (32%) had high risk HPV type (HR-HPV), corresponding 736 (4.4%) to co-infections with low risk type HPV (LR-HPV). In 721 samples (4.3%) it was exclusively diagnosed LR-HPV, with minor differences in these percentages along the studied period. During 18 years, increasing trend in diagnostic demand fits a parabolic shape ($R^2$88.5%), while performance for HR-HPV slightly declined in a 0.9% yearly. Paradoxically, the sharpest slope in decreasing performance occurred in 2001-2004, when demand decreased too. In the last period (2009-2013) demand continues increasing in ~100 samples yearly, while HR-HPV diagnostic performance increases in a 0.4% yearly.

CONCLUSIONS: HPV detection is one of the most increasing techniques in the Microbiology laboratory. Despite that, percentage of positive and ARHPV/samples ratio remains being satisfactory, above 35 and 25% respectively during 18 years period. The outstanding performance could be related to milestone on scientific knowledge of HPV. Regarding registered trend in this study, it is expected a continuous increasing in the diagnostic demand of HPV.

OC 2-10

EPIDEMIOLOGY OF HPV 6, 11, 16, 18 ANTIBODIES AMONG ADULTS IN THE UNITED STATES ACROSS SIX YEARS: NHANES 2005-2010

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Objective: To assess the prevalence, distribution and trends of human papillomavirus (HPV) antibodies (Ab) contained in the quadrivalent HPV vaccine (HPV 6, 11, 16 and 18) among US adults.

Methods: The sample population consisted of 11,186 men and women ages 18-59 years with HPV antibody available data included in the National Health and Nutrition Examination Surveys (NHANES) 2005-2006 (pre-HPV vaccine), 2007-2008 and 2009-2010 (post-vaccine) . HPV type-specific Ab serostatus was established using the competitive Luminex Immunoassay of Antibodies to Neutralizing Epitopes on HPV 6, 11, 16 and 18 L1 VLPs. Both cervical and oral HPV types were assessed using the Roche Linear Array Assay. Data analyses consisted of weighted prevalence with 95% confidence intervals, accounting for complex sampling with the SVY module of Stata V13. A p value <0.05 was set for statistical significance.

Results: Prevalences of HPV Ab 6, 11, 16 and 18 were 16.4%, 5.9%, 12.4% and 4.8%, respectively. Among women, Ab prevalence increased from 15.7% in 2005 to 23.4% in 2010 (HPV16) and from 5.6% to 9.5% (HPV18) ($p<0.05$) with a dose response by number of vaccine shots.

Conclusions: Significant Ab prevalence increases were seen across survey years among women but not among men, likely attributable to the effect of HPV vaccination1.

1 Markowitz LE, Hariri S, Lin C, Dunne EF, Steinau M, McQuillan G, Unger ER. Reduction in human papillomavirus (HPV) prevalence among young women following HPV vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003-2010. J Infect Dis. 2013 Aug 1;208(3):385-93.

OC 2-11

ABUNDANCE OF PUTATIVELY NOVEL HPV TYPES IDENTIFIED IN EYEBROWS USING NOVEL CODEHOP PRIMERS AND A SINGLE TUBE NESTED 'HANGING DROPLET' PCR

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Objectives: Several PCR-based methods have been developed for simultaneous detection of a broad range of human papillomaviruses (HPVs) infecting skin. These traditionally include HPV-genera-specific single-round PCR using a single or multiple pairs of degenerate primers or nested PCR using two pairs of degenerate primers. In this study, an improved version of the original panPV CODEHOP primers for the broad detection of PVs across different PV-genera was used in combination with a single-tube nested 'hanging droplet' PCR to survey cutaneous HPVs.

Methods: DNA was extracted from 149 eyebrow hair specimens and amplified in a single-tube nested PCR reaction using a total of 70 cycles. Obtained amplicons were either directly sequenced or cloned and sequenced if they contained multiple HPV types or a novel type. Sequences were phylogenetically evaluated by the Bayesian algorithm using the BEAST package.

Results: HPV DNA was detected in 59.7% (89/149) of the analyzed eyebrow hair specimens. Multiple HPV types were found in the majority of 52 cloned PCR-amplicons. In addition to 32 officially recognized HPVs, a total of 35 putatively novel HPV types or subtypes were identified. Phylogenetic analysis revealed that all novel HPVs reside within the *Betapapillomavirus* (five types/subtypes) and *Gammapapillomavirus* (30 types/subtypes) genera, some forming novel viral species.

Conclusions: The panPV CODEHOP primers used with single-tube nested PCR are powerful tools for discovering novel HPV types. Continuous efforts to improve identification of novel cutaneous HPVs leads to a better understanding of their phylogenetic diversity and may eventually clarify their role in the development of skin cancer.

OC 3-1

SIGNIFICANT REDUCTION IN THE INCIDENCE OF GENITAL WARTS IN YOUNG WOMEN AND MEN 5 YEARS INTO THE DANISH NATIONAL HPV VACCINATION PROGRAM

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Objective: Denmark introduced the quadrivalent HPV vaccine into the vaccination program for 12–15-year-old girls in 2008/2009, which resulted in a prompt significant decrease in genital wart (GW) incidence in young women (1). In 2012, the program was supplemented with a catch-up program for women 19–27-years-old. We aimed to further extend our nationwide evaluation of the effectiveness of the vaccination program by increasing both the cohort size (with prescriptions of Podophyllotoxin) and follow-up time (until 2013) of the previous Danish cohort study.

Methods: Incident cases of GWs were identified from the Danish National Patient Register or through redemption of prescription for podophyllotoxin in the Danish National Prescription Registry in 2006–2013. Age-specific incidence rates (IR) were estimated and annual percentage change (APC) was calculated using Poisson regression.

Results: GW incidence was either stable or increased in both sexes aged 16–25 years in 2006–2009, with the greatest increase seen in 18–19-years-old men (APC=25.3%; 95% confidence interval (CI): 18.4; 32.7). After introduction of the vaccination program, GW incidence decreased significantly in both women and men aged 16–25 years with nearly elimination among 16–17-year-olds (IR_{women}: from 957 to 72 per 100.000 person-years (APC= –56.0%; 95% CI: –59.8; –51.4); IR_{men}: from 378 to 84 per 100.000 person-years (APC= –37.8%; 95% CI: –41.5; –33.9) in 2009–2013, respectively).

Conclusion: We find a near elimination of GW among women in age groups with high vaccination coverage. A similar pattern was observed for men indicating a substantial protection by herd immunity.

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OC 3-2

EFFECTIVENESS OF QUADRIVALENT HPV VACCINE ON GENITAL WARTS IN A REAL-LIFE SETTING IN BELGIUM

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Objective: To measure vaccine effectiveness (VE) of quadrivalent HPV (qHPV) against genital warts (GWs) in 16-23 year-old women in a real-life setting in Belgium.

Methods: We conducted a cohort study in women eligible for HPV vaccination in Belgium between 2007 and 2013 who were affiliated to a large Belgium sick-fund (MLOZ). Demographic and reimbursement data for insurees are recorded in their database. Women were considered as fully vaccinated 30 days after all three doses of qHPV vaccine had been reimbursed and as unvaccinated if no qHPV vaccine was reimbursed. Women vaccinated with bHPV vaccine were excluded from the primary analysis. A first agreement for reimbursement by the sick-fund medical advisor for imiquimod (the first line, most common GW treatment in Belgium) was used as a surrogate for a first GW episode. The incidence rate ratio (IRR) was used to compare GW incidence in unvaccinated and vaccinated women.VE was calculated as: VE = 1-IRR*100. Poisson regression was used to adjust for confounding factors.

Results: Among the 106,579 women (369,381 person-years) included, 33.6% were fully vaccinated at the end of follow-up. Overall, 274 GW treatment episodes were recorded. The age-adjusted VE for fully vaccinated women was 88.0% (95% CI: 79.4; 93.0). VE was higher in those who were <18 years than in those aged 18 to 23 years at vaccination.

Conclusion: High qHPV VE was observed in a real-life setting in Belgium. These estimates are consistent with the results from clinical trials and other effectiveness studies in different settings.

OC 3-3

EFFECT OF TIMING OF SECOND DOSE OF QUADRIVALENT HPV-VACCINE ON CONDYLOMA INCIDENCE

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Objectives: To assess the incidence of condyloma after 2 doses of qHPV-vaccine, by time since 1st vaccine dose, in women first vaccinated before age 20.

Methods: We established a national population-based cohort of 1.3 million women, aged 10-27, living in Sweden from 2006-2012. Women were identified through Swedish health care registers. The primary endpoint was condyloma, identified through the Patient Register (ICD10) or the Prescription Drug Register (prescriptions for Podofyllotoxin or Imiquimod). Exposure status was time-varying qHPV-vaccine dose, identified through the Prescription Drug Register and SVEVAC, the national register for HPV vaccination. Incidence rates of condyloma by time between 1st and 2nd dose were calculated. Women were censored at dose 3, emigration, death, or December 31st 2012, whichever occurred first.

Results: In Sweden, a total of 252,800 women received 2 doses of qHPV-vaccine from 2006-2012. There were a total of 185 condyloma cases and 110,866 person-years during follow-up. Between 0-9 months there is a fluctuating downward trend in condyloma incidence with a crude IR/100,000 range of 204 (95% CI 110-379) to 62 (95% CI 9-440). After >9 months between the 2 doses, there is instead a steep increase in incidence IR/100,000=746 (95% CI 388-1434).

Conclusions: Incidence rates of condyloma appear to decline with a longer time interval between qHPV-vaccine dose 1 and 2 with a maximum protection with 9 months between the 2 doses. With >9 months between doses, the incidence rate increases instead. However, no firm conclusions can be drawn at this time as further analysis is on-going.

OC 3-4

QUADRIVALENT HPV-VACCINE EFFECTIVENESS AGAINST CERVICAL LESIONS: POPULATION-BASED STUDY

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Objectives: This study aims to quantify the effect of quadrivalent HPV (qHPV) vaccination on incidence of CIN2 or worse (CIN2+) in the Swedish population of girls and young women.

Methods: An open cohort of all women ages 13-30 years living in Sweden between 2006-2012 (n=1,294,822) was linked to Swedish nationwide healthcare registers. These registers were used to obtain qHPV vaccination status of women vaccinated in the opportunistic HPV vaccination program (years 2006-2011) and cases with histologically confirmed CIN2+, respectively. The effect of qHPV vaccination on incidence of CIN2+ was analyzed using Poisson regression. Women previously diagnosed with genital warts or with an abnormal pap smear (ASCUS or worse) were excluded.

Results: Vaccination effectiveness against CIN2+ was 71% (95% CI 52-83%) among girls first vaccinated between ages 13-16. For girls first vaccinated between ages 17-19, vaccine effectiveness was 29% (95% CI 9-44%). No significantly decreased incidence of CIN2+ was found when comparing women first vaccinated between ages 20-29, with unvaccinated women (vaccine effectiveness= 7%, 95% CI -13-24%).

Conclusions: We show a significant reduction in CIN2+ following qHPV vaccination in women younger than 20 years at first vaccination. Vaccine effectiveness against CIN2+ increased with decreasing age at first vaccination.

OC 3-5

HPV VACCINATION IN YOUNG WOMEN AT 25 YEARS IN ITALY. EFFICACY, IMMUNOGENITY AND IMPACT ON SCREENING FOR CERVICAL CANCER

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Objective: Although teenegers are the main population for HPV vaccines, adult women who remain at risk of cervical cancer can also be vaccinated. To offer vaccination to 25-year old women at their first access to cervical cancer screening represents a good opportunity to evaluate the efficacy of vaccination at this age and to understand its impact on screening activity.

Methods: Women aged 25-years called to the Cervical Cancer Screening program were invited to this study (Grant from Tumour Tuscany Institute). Women were randomized in two groups: Study Group (Pap test, HPV test, Blood sample and free HPV vaccination) and Control Group (Pap test). After 3y, women in both groups perfomed Pap test and HPV test, and women in the Study Group also a second blood sample.

Results: 4481 invitation letters were sent in 2010. The compliance at enrolment was 18.6% (832/4481). In the Study Group the prevalence at enrolment for any HR-HPV type, HPV16 and 18 was 20.8%, 8.1% and 1.5%, respectively.
The prevalence for any HR-HPV, HPV16, HPV18 and HPV31,33,45 was statistically significant reduced in women HPV16/18 negative or HR-HPV negative at enrollment. A reduction in cytological abnormalities was observed in the Study Group compared to the Control Group .
After 3y, sero-conversion was 100% for HPV16 and 98.8% for HPV18. Moreover a strong increase of antibody response was observed also for HPV31,33,45.

Conclusions: The vaccination is effective in reducing the HR-HPV infections in 25-year old women, especially in HPV16/18 negative (12%) and HR-HPV negative (7.1%) before vaccine injection.

OC 3-6

MONITORING THE IMPACT OF THE HPV VACCINATION PROGRAM IN RWANDA

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Objectives: Human papillomavirus (HPV) vaccination is expected to offer an effective solution to the high cervical cancer burden in low- and middle-income countries (LMIC). However, reliable evidence of real-life effectiveness of vaccine programs is crucial to encourage national planners to implement and sustain cervical cancer prevention services. The government of Rwanda's introduction of a HPV vaccine programme in 2011 with a estimated 93% coverage among the target population offers an excellent opportunity to evaluate short- to medium-term impact of HPV vaccination in an early introducing LMIC.

Methods: In 2013/14, the baseline picture of HPV prevalence in Kigali, Rwanda was characterised among unvaccinated cohorts of women by collecting cervicovaginal samples from a population-based, age-stratified sample of 2,500 women aged 18–59 years and from urine samples from 1,000 18-20 year olds in high schools. HPV DNA detection and genotyping is underway using GP5+/6+ PCR.

Results: HPV genotyping results are available for the first 1,049 cervicovaginal samples. HIV prevalence was 23.1%, and high-risk HPV DNA prevalence 21.9%. The most common high-risk HPV type was HPV16 (6.2%), followed by HPV58 (2.9%). High-risk HPV prevalence decreased by age, from 30.7% among 16-24yrs, down to 14.3% for 55+yrs, and was higher in HIV-positive (31.2%) than HIV-negative (16.0%) women. Other significant risk factors for HPV positivity included lifetime number of sexual partners, marital status and receiving cash for sex. Complete HPV results for both the cervicovaginal and urine samples are expected by December 2014.

Conclusions: This survey confirms Rwanda to be a setting of cervical cancer risk with a background of high HIV prevalence. We will present the entire results on the baseline picture of HPV epidemiology in Rwanda prior to vaccination and will describe a 10-year IARC protocol for repeat surveys with which to compare future vaccinated cohorts of women to demonstrate vaccine impact.

OC 3-7

EFFECT OF CATCH UP VACCINATION ON HPV PREVALENCE IN ROUTINE CERVICAL SCREENING

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Objectives: Since 2008, Scotland has offered a national HPV immunisation programme to 12-13 year old girls which included an initial 3 year "catch up" for girls up to age 18. The "catch up" cohort are now of age to attend for cervical screening. The aim of this study was to determine HPV positivity in younger women and the effect of vaccination.

Methods: We enrolled 613 women (20 -24 years) attending for routine cervical screening. Samples were tested by the Cobas HPV test. HPV outcome was stratified by vaccination status and cytology. Follow up histology, where indicated, was also assessed.

Results: Fifty two percent (n = 321) were vaccinated. The Cobas HPV test was positive in 36.3% and 45.0% of vaccinated and non-vaccinated women respectively. Prevalence of HPV 16 /18 in the vaccinated was 3.7% compared to 13.7% in non-vaccinated women. Of these 58.3% and 65.0% respectively were co-infections. One in 10 infections in vaccinated women were due to HPV 16/18 compared to less than 1 in 3 in non-vaccinated women. There were 38 (11.9%) abnormal smears in vaccinated and 48 (16.6%) in non-vaccinated women respectively. We diagnosed 1 CIN2 and 1 CIN3 in vaccinated and 6 CIN 2 and 3 CIN 3 in non-vaccinated women.

Conclusion: Catch up vaccination changed overall prevalence by 8.7%. Positivity associated with HPV16/18 infection has been significantly reduced. We have preliminary evidence to suggest that catch-up vaccination has decreased the number of high grade lesions in the first round of screening.

OC 3-8

PROJECTING THE POTENTIAL PUBLIC HEALTH IMPACT OF A UNIVERSAL VACCINATION PROGRAMME WITH A NINE-VALENT HPV VACCINE IN THE UNITED KINGDOM

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Objectives: To estimate the incremental public health impact of a universal vaccination program with a nine-valent human papillomavirus vaccine (6/1/16/18/31/33/45/52/58) in the United Kingdom as compared to the current girls-only, vaccination program with a quadrivalent HPV vaccine (6/11/16/18).

Methods: A dynamic transmission model of HPV infection and related diseases was calibrated to the UK epidemiological data. Up to 70% of cervical cancer cases were attributed to HPV 16/18 for the quadrivalent vaccine, and an additional 20% to the five additional types included in the nine-valent vaccine. For non-cervical disease (vulvar, vaginal, anal and genital warts), the disease attribution assumption remained constant across both vaccines, producing conservative outcomes. In the base case, a two dose vaccination program with lifelong vaccine protection and a coverage rate of 87.5% was assumed for the 12-year age cohorts. Sensitivity analyses were conducted.

Results: The findings of the analyses indicate that universal vaccination with the nine-valent vaccine has the potential to:
i) reduce the incidence of HPV 16/18/31/33/45/52/58 -related cervical cancer by 99.9% after 100 years, relative to 76% for the quadrivalent vaccine and,
ii) prevent over 100 years, an additional 92,057 cases of CIN1, 227,344 cases of CIN2/3 and 33,988 cases of cervical cancer in females, 1,700 anal cases in total for females and males and, 365,393 and 969,469 genital warts cases in females and males, respectively.

Conclusions: The introduction of universal vaccination with a nine-valent vaccine in the UK is estimated to significantly reduce the public health impact of cervical and other HPV-related diseases.

OC 3-9

CHARACTERISTICS OF A CLUSTER-RANDOMIZED, PHASE IV HPV VACCINATION EFFECTIVENESS TRIAL

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Objectives Human papillomaviruses (HPV) causes anogenital and oropharyngeal cancers. While HPV-16/18 vaccine is efficacious against HPV-infections and associated precancers the herd effects of different vaccination scenarios are open. Our cluster randomized trial (NCT00534638) assesses the herd effects of vaccinating girls vs. girls and boys.

Methods In 2007-9 we invited 80.272 1992-95 born early adolescents to a CRT in 33 communities stratified by low, intermediate and high HPV-16/18 seroprevalence. In 11 Arm A communities 90% of participating girls and boys received HPV-16/18 vaccine, in 11 Arm B communities 90% of girls received HPV-16/18 vaccine - boys received hepatitis B-virus (HBV) vaccine, and in 11 Arm C communities all received HBV-vaccine. HPV prevalences were determined at age 18.5 years.

Results Equal enrolment of birth cohorts comprised 32.176 (40% response) vaccinees:: 20.515 girls and 11.661 boys. At age 15 years, 79.3% completed a questionnaire, 98% resided at study communities. Smoking and alcohol consumption were similar in the trial arms, also mean-age of menarche (12.4 years) or 1st ejaculation (12.6 years), and sexual behaviour (among $<$25%, who had had sexual debut) did not differ by arm. Mean-age at the sexual debut 14.3 and 14.4 in girls and boys, and proportions of those with $\geq$ 5 sexual partners (6.5% to 7.5%) were comparable. By the end of 2014 our CRT will verify predictions on herd effect (17 to 31% herd effect) of vaccinating both girls&boys with moderate vaccine coverage.

Conclusions Uniform residential, life-style and sexual behaviour characteristics indicate successful randomization/enrolment. Our CRT will guide HPV vaccination programs by verifying effectiveness of modelled scenarios.

Funding: GlaxoSmithKline Biologicals SA, Academy of Finland, Finnish Cancer Organizations

OC 4-1

EVIDENCE OF CROSS PROTECTION FOLLOWING USE OF BIVALENT HPV VACCINE IN THE NATIONAL HPV IMMUNISATION PROGRAMME IN ENGLAND

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Objectives: To monitor the changes in type-specific HPV prevalence since the introduction of national immunisation programme using the bivalent HPV vaccine in England.

Methods: Residual vulva-vaginal swab specimens from sexually-active young women undergoing chlamydia screening in community health services in England between 2010 to 2013 were tested for type-specific HPV DNA using a multiplex PCR and Luminex-based genotyping system. Prevalence of type-specific HPV infection was compared to a similar survey conducted in 2008 (before the introduction of the HPV immunisation programme). Prevalence ratios comparing the pre-immunisation and post-immunisation surveys were calculated using a multivariable log-binomial model, adjusted for demographic and sexual behaviour data. Estimated vaccination coverage was calculated using published national data.

Results: In the post-immunisation period, estimated vaccination coverage among women aged 16-18 years old was 60.2% in 2010-2011 and 73.4% in 2012-2013 (with 87% vaccinated over 12 years old). In this age group, the prevalence of HPV31, HPV33 and/or HPV45 was 8.6% in the pre-immunisation survey (n=1,054), 7.3% in 2010-2011 (n=933) and 5.4% in 2012-2013 (n=1,063). The prevalence of HPV16 and/or HPV18 was 19.1%, 8.7% and 3.7% in the pre-immunisation survey, 2010-2011 and 2012-2013, respectively. The adjusted prevalence ratio was 0.6 (95% CI; 0.4-0.9) for HPV31/HPV33/HPV45 and 0.3 (95% CI; 0.2-0.5) for HPV16/HPV18. No similar reductions were seen for other high-risk HPV types.

Conclusion: These ecological analyses suggest some evidence of cross protection following the introduction of a national immunisation programme using the bivalent HPV vaccine. This surveillance will continue, with attention to the duration of this protection.

OC 4-2

TWO OR THREE DOSES FOR PRIMARY HPV VACCINATION SCHEDULES? SYSTEMATIC REVIEW AND META-ANALYSIS

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Objective: The aim of this study is to estimate immunogenicity and efficacy of two-dose HPV vaccine schedules in adolescent girls.

Methods: We searched Medline, Cochrane Central and trials registers from their earliest dates to January 2014. We included controlled trials that randomised adolescent girls to either a two- or three-dose HPV vaccine schedule, or compared a two-dose schedule in girls with a three-dose schedule in women. We extracted immunological and clinical outcome data. We used meta-analysis to calculate weighted mean differences (with 95% confidence intervals, CI) for comparisons between geometric mean concentrations (GMCs).

Results: We screened 1,174 studies and identified eight eligible trials. GMCs were non-inferior (HPV16) or superior (HPV18) in girls receiving a two-dose schedule compared with women receiving the three-dose schedule but between study heterogeneity was severe (three trials in high income countries). In direct comparisons, GMCs in girls receiving the two-dose schedule were lower but non-inferior (HPV18) or inconclusive (HPV16) compared with girls receiving the three-dose schedule. All data showed non-inferior seroconversion and seropositivity for the two-dose compared with the three-dose schedule. GMCs were significantly higher for two-dose schedules with a longer (6 vs. 2 months or 12 vs. 6 months) interval between doses. We found no published clinical efficacy data.

Conclusions: Two-dose schedules in adolescent girls result in immunological outcomes that are as good as or better than three-dose schedules in women. The interval between doses is important. Two-dose HPV vaccine schedules for adolescent girls might increase vaccine effectiveness if they simplify administration and reduce costs.

OC 4-3

EFFECTIVENESS OF 3 VERSUS 2 DOSES OF QUADRIVALENT HPV-VACCINE ON INCIDENCE OF CERVICAL LESIONS IN A 3-DOSE VACCINATION SCHEDULE: A POPULATION-BASED STUDY IN DENMARK AND SWEDEN

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Objectives: This study aims to quantify the effect of quadrivalent HPV vaccination with three versus two doses on incidence of histologically verified CIN2 or worse (CIN2+) in girls and young women in Denmark and Sweden.

Method: A cohort of all women aged 13–30 years and resident in Denmark or Sweden in 2006–2013 was followed for HPV vaccination and first occurrence of CIN2+. Information on vaccination dates, number of doses, and dates of diagnoses were obtained from nationwide healthcare registers. Incidence rate ratios (IRR) with 95% confidence intervals (CI) were estimated using a Poisson regression model stratified on age at first vaccination (<20, ≥ 20) and adjusted for attained age with number of doses as a time-varying covariate.

Results: Preliminary results show that women vaccinated with three doses of the quadrivalent vaccine had significantly lower incidence of CIN2+ compared with two doses. For women vaccinated before age 20 IRR=0.54, CI=0.42;0.71, while for women vaccinated at older ages (≥ 20) IRR=0.57, 95% CI=0.52;0.62. Moreover, two doses of the vaccine did not result in decreased incidence of CIN2+ for women aged ≥ 20 at vaccination compared with unvaccinated women.

Conclusions: We observed a higher risk reduction of CIN2+ after three doses of quadrivalent HPV vaccine compared with two doses both in women vaccinated at younger and older ages. However, for women vaccinated at younger ages the result was based on few events.
Analysis of ASCUS+, the timing between first and second dose on disease incidence, and further adjustment for mother's education level is ongoing.

OC 4-4

MEMORY B CELL RESPONSES AGAINST HPV16, HPV18, HPV31 AND HPV45 IN 12-15 YEAR OLD GIRLS RECEIVING CERVARIX® OR GARDASIL® VACCINE

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Objective: To evaluate memory B cell responses against vaccine (HPV16/HPV18) and non-vaccine (HPV31/HPV45) types following immunization with Cervarix® or Gardasil® and compare with binding and neutralizing antibody responses.

Methods: Serum and peripheral blood mononuclear cell (PBMC) samples were from 12-15 year old girls following three doses of Cervarix® (n=42) or Gardasil® (n=46) vaccine. Binding titers were estimated by L1 virus-like particle (VLP) ELISA, neutralizing titers were estimated using L1L2 pseudoviruses and memory B cell responses were estimated by ELISpot following immune activation (R848/IL-2) of PBMC using L1 VLP as antigens.

Results: As expected, all individuals elicited high titer (ca. 104-105) vaccine-type binding and neutralizing antibody responses accompanied by a memory B cell response of around 1% of total IgG-bearing memory B cells. Responses against HPV16 were higher than HPV18 by all measures and Cervarix® vaccination elicited higher responses than Gardasil®. Neutralizing antibody responses against non-vaccine types were less frequent and orders of magnitude lower titer than for vaccine types, with Cervarix® eliciting higher titers than Gardasil®. However, this pattern was not reflected in VLP binding (*ca.* 10^3) or memory B cell responses (ca. 0.5% IgG-bearing cells) in which measurable responses against these types were common and similar between the vaccines.

Conclusion: The immunological effectors of cross-protection are unclear although the differential detection of neutralizing antibodies against non-vaccine types is at least coincident with the differential cross-protection bestowed by the current vaccines. These current data suggest that the magnitude of binding antibodies and memory B cells are poor surrogates of this functional neutralizing antibody response.

OC 4-5

CEL-MEDIATED IMMUNE RESPONSE AFTER HPV VACCINATION

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Objective: to evaluate the cell-mediated immune response to HPV after bivalent HPV vaccination, assessing cell proliferation and quantifying cytokines.

Methods: Cell Culture was performed with peripheral blood mononuclear cells (PBMC) from 30 patients one month after the total HPV immunization. Cell proliferation was assessed by MTT reduction assay. For the analysis of cytokine mRNA expression, cellular RNA was extracted from PBMC. Relative quantification of cytokines (IFN-β, IFN-γ, IL-12, TNF-α, IL-6, IL-17 or IL-10) in comparison to the transcripts of β-actin gene (endogenous control) was performed using "real time" PCR. Data were submitted to one-way ANOVA (nonparametric test) analysis followed by the Bonferroni's Multiple Comparison Test.

Results: The cell viability of the culture stimulated with the vaccine compared to the negative control was different (118% X 100%, $p<0.001$). The cytokines were upregulated in stimulated PBMC cultures following vaccination compared to in unstimulated cultures. The median n-fold increase theses cytokines were: IFN-β, 334.4-fold (95% CI, 37.49 to 706.3); IFN-γ, 12.64-fold (95% CI, 2.44 to 27.72); IL-12, 46.33-fold (95% CI, 4.29 to 96.96); TNF-α, 2.36-fold (95% CI, 0.69 to 4.03); IL-6, 9.07-fold (95% CI, 1.64 to 16.5); IL-17, 7.33-fold (95% CI, 0.73 to 15.40); IL-10, 6.47-fold (95% CI, 0.84 to 12.09). The cytokines expressions in stimulated cultures were different. IFN-β expression was significantly higher than IFN-γ, TNF-α, IL-6, IL-10 and IL-17 ($p<0.05$).

Conclusion: proliferative PBMC responses against HPV-16 and HPV-18 were detected in women who received the vaccine HPV immunization. HPV vaccine stimulates antiviral immune response, with robust induction of IFN-β production.

OC 4-6

THE EFFECT OF HERD IMMUNITY IN DIFFERENT HUMAN PAPILLOMAVIRUS VACCINATION STRATEGIES: AN ECONOMIC EVALUATION OF THE BEST II STUDY

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Objectives: Italian recommendations for HPV immunization target females aged 9 to 26 years. However, males can be vectors in virus transmission and are at risk of infection. The BEST II study was designed to evaluate the cost-effectiveness (CE) of different interventions targeting females as well as males.

Methods: We developed a dynamic Bayesian Markov model. Both genders were considered in a universal vaccination programme which was compared to screening-only and female-only vaccination. A range of HPV-induced diseases caused by HPV genotypes included in the quadrivalent vaccine were considered (cervical, vaginal, vulvar and anal cancer, and anogenital warts), and cross-protection effects were accounted for. The process of sexual mixing was estimated based on age-, gender- and behavioural-specific factors to estimate the force of infection dynamically. We considered several scenarios; the baseline assumed universal vaccination to be implemented for 12-year-old females and males. The follow-up period was 55 years.

Results: According to our analysis, universal vaccination was a cost-effective alternative when compared to screening-only (with an incremental CE ratio, ICER, of €1,200) and to female-only vaccination (ICER = €6,900). We performed extensive

Conclusions: Universal HPV vaccination of male and female cohorts is potentially cost-effective compared to cervical screening and female-only vaccination, when accounting for a wide range of HPV-related diseases. This is mainly due to the fact that universal vaccination increases effects of herd immunity and provides protection against HPV in males as well as in females.

OC 4-7

COMPARISON OF SAFETY STATEMENTS FROM NATIONAL AUTHORITIES AND INTERNATIONAL HEALTH BODIES FOR HPV VACCINE

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Objectives: Safety statements issued from outside of Japan are based on scientific evidence with transparency such as those from WHO, WMA, FIGO, Australia, the UK, the US, Korea and Canada, etc. In contrast, the Japanese Ministry of Health Labour and Welfare (MHLW) has decided not to resume proactive recommendation for the vaccine for more than 1 year. We investigated differences in scientific evidence and socio-political factors among other countries, governing bodies and Japan.

Methods: A comparison of statements and recommendations.

Results: In Japan, local governments, health professionals and parents were confused by the national government's suspension of recommendations for the HPV vaccine and as such uptake dropped from around 70% to below 8%. Safety statements issued from outside of Japan were based on scientific evidence with epidemiological surveillance both pre- and post-vaccination for analysis of causality between the vaccines and adverse events.

Conclusion: The Japanese government must issue strong recommendations with clear and honest communication to the public and the health professionals. Public health authorities should explain the effectiveness and safety of the HPV vaccine based on scientific evidence via mass media. Despite the presence of scientific evidence, immunization of an important vaccine has been suspended and this will have serious implications for the future in Japan. In 10-20 years, only in Japan, will there be may many patients suffering from cervical cancer globally.

OC 4-8

THE IMPACT OF NATURAL IMMUNITY ON THE EFFECTIVENESS OF HPV VACCINATION

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Objectives Population-level effectiveness of HPV vaccination has been estimated in models that all differ in assumptions on estimates regarding natural acquired immunity. We investigated the impact of different model assumptions on estimates of HPV vaccine effectiveness.

Methods We used STDSIM, an established microsimulation model with which we have previously studied mechanisms for HPV immunity, based on observed epidemiological trends with age. We considered two plausible mechanisms for naturally acquired immunity after infection: full immunity with variable duration (A), or cumulatively decreasing susceptibility to reinfection (B). Vaccine effectiveness was estimated using HPV-16, HPV-18 and cervical cancer incidence. The impact of naturally acquired immunity mechanisms was determined by comparing the vaccine effectiveness estimates between the two different naturally acquired immunity mechanisms. We also determined the impact of increased vaccine coverage (to 100%), the inclusion of boys, and lower vaccine efficacy (70% and 80%).

Results Model assumptions on acquired immunity mechanisms have a large impact on estimates of population-level vaccine effectiveness. While cervical cancer incidence decreases with almost 40% under mechanism A, this reduction is over 45% under mechanism B. The impact of model assumptions on cervical cancer reduction is even larger with a 10%-point difference between mechanisms when boys are included, and when assuming lower vaccine efficacy; and larger for the incidence of HPV-18 incidence compared to HPV-16.

Conclusions It is crucial to expand knowledge on naturally acquired immunity to accurately estimate population-level vaccine effectiveness, as well as to determine optimal vaccination strategies.

OC 4-9

LONG-TERM EFFECTIVENESS OF GARDASIL™ AMONG ADULT WOMEN IN COLOMBIA

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Objectives: The GARDASIL™ long-term follow-up (LTFU) study is an ongoing extension of the safety of the quadrivalent HPV vaccine (qHPV vaccine) and its effectiveness in preventing HPV6/11/16/18-related cervical intraepithelial neoplasia (CIN) or condyloma in 26-45 year-old women. Here, we present our data 8 years after vaccination.

Methods: The early vaccination group (EVG) who received qHPV in the base study included 804 Colombian subjects. The catch-up vaccination group (CVG) included 703 of the 806 eligible Colombian subjects who were vaccinated 5 years after the base (ages 31-50). Subjects underwent history, pelvic exams with Pap tests, and wart/lesion biopsy. Cytology and biopsy specimens were evaluated in a central laboratory with HPV testing, and endpoint adjudication performed by an independent panel. The primary analysis was for safety and effectiveness in the EVG but effectiveness data is available from the CVG as well.

Results: There were no cases of HPV 6/11/16/18-related CIN or condyloma in the EVG over the 8 years of LTFU. Additionally, there were no cases of HPV16/18 related CIN2 or worse or HPV 6/11 related condyloma. As there is no placebo group in the LTFU study, comparison to the two year incidence rates in the base study (HPV6/11/16/18 CIN or condyloma [0.4/100 person-years]; HPV16/18 CIN 2 or worse [0.1/100 person-years] and HPV6/11 condyloma [0.2/100 person-years]) shows maintained vaccine efficacy over the follow-up period.

Conclusion: The qHPV vaccine continued to be effective in this population of adult women. There were no new safety issues encountered in either arm of the study.

OC 4-10

A PHASE II STUDY OF GARDASIL IN HUMAN PAPILLOMAVIRUS RESEARCH THE MID-ADULT MALE VACCINE STUDY–THE MAM STUDY

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Objectives: To establish immunogenicity and safety of the Gardasil vaccine among mid-adult men ages 27-45 years. Specifically, to assess the proportion of HPV antibody sero-conversion one month post-dose three of the Gardasil vaccine.

Methods: The study population included subjects from Tampa, FL, US, and Cuernavaca, Mexico who met eligibility criteria (male, 27-45 years, completed 4 years of follow-up in our HPV natural history study). Subjects completed four visits over seven months, with Gardasil administered at months 0, 2, and 6. Sera, oral, anal, and genital specimens were collected, with computerized questionnaires completed at Months 0 (pre-vaccination) and 7 (post-dose three). Anti-HPV16 and HPV-18 IgG levels were determined by ELISA from sera collected at Months 0 and 7.

Results: 147 of the 150 participants enrolled completed all 4 visits. No serious adverse events were reported. The most commonly reported adverse events were injection-site pain and swelling, headache, and flu-like symptoms.
In an initial analysis of 51 U.S. participants, 11 (22%) and 15 (29%) men had detectable antibody levels for HPV16 and HPV18, respectively, at Month 0. At Month 7, all 51 (100%) had sero-converted for both HPV types. Median HPV16 and HPV 18 titers at Months 0 and 7 were 25.2 and 2296.57 EU/mL, and 13.6 and 705.84 EU/mL, respectively.

Conclusion: Vaccination of mid-adult men produced a robust antibody response against HPV16 and HPV18. As men are diagnosed at older ages with HPV-related cancers, vaccination may be an efficacious strategy these cancers in men beyond the currently recommended vaccination age group.

OC 5-1

UNDERSTANDING CERVICAL SCREENING NON-ATTENDENCE AMONG ETHNIC MINORITY WOMEN

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Objectives: Women from ethnic minority backgrounds are less likely to attend cervical screening than white women in England. This study explored the socio-demographic and psychological correlates of cervical screening attendance across ethnic groups.

Methods: Women aged 30-60 years were recruited from Indian, Pakistani, Bangladeshi, Caribbean, African and white British backgrounds (n=720, response rate = 65%). Participants completed face-to-face interviews with a multi-lingual interviewer.

Results: Half of the women had not been screened within 5-years (53%,n=374). Women from ethnic minorities were more likely to be unscreened than white British women, (44%-71% vs. 11%, p<.001). Migrating to the UK, speaking a language other than English and low education level were also associated with being unscreened. These socio-demographics reduced, but did not fully explain the association between ethnicity and screening attendance. Ethnic minority women were more likely to be scared of what screening might find (41%-65% vs. 25% of white women), to have low perceived risk of cervical cancer (22%-53% vs. 10%) and to think screening was not needed in the absence of symptoms (55%-63% vs. 7%). Psychological factors reduced the effect of ethnicity further, explaining some but not all of its influence on screening.

Conclusions: There are ethnic inequalities in cervical screening attendance in England and these are not fully explained by socio-demographics. Interventions for ethnic minority women should ensure they understand the meaning of a screening result, minimizing anticipated fear. Addressing perceptions of risk and beliefs about the efficacy of screening in the absence of symptoms may also be beneficial.

OC 5-2

BARRIERS TO AND FACILIATORS OF COMPLIANCE WITH CLINICAL BASED CERVICAL CANCER SCREENING

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Objective. This study aims to identify possible barriers to and facilitators of cervical cancer screening by (a) estimating time and travel costs and other direct non-medical costs incurred in clinic-based screening, (b) investigating compliance with screening and reasons for noncompliance, (c) determining women's knowledge of human papillomavirus (HPV), and (d) investigating correlates of HPV knowledge and compliance with screening.

Methods. Via self-administered questionnaires, data on sociodemographic characteristics, time and travel costs and other direct non-medical costs, mode(s) of travel, time, distance, companion's attendance, HPV knowledge and compliance with screening were obtained from 1 510 women attending the Swedish organized cervical cancer screening program.

Results. Mean total time and travel costs per attendance were €56. Over half (53%) of the respondents took time off work to attend screening (mean time 147 minutes). A large portion (44%) of the respondents were noncompliant, 51% of whom stated difficulties in taking time off work. 64% of all respondents knew that HPV vaccination was available; only 34% knew it was important to continue to attend screening following vaccination. Age, education, and income were the most important correlates of HPV knowledge and compliance. For compliance, these factors were additionally time off work, companion's attendance and HPV knowledge.

Conclusions. Time and travel costs of clinic-based screening can be substantial, may influence overall cost effectiveness of screening programs and constitute barriers to screening. Women with knowledge of HPV and who did not take time off work to attend screening were more likely to comply with screening.

OC 5-3

SMALL SCALE SCREENING – WORKING BESIDE COMMUNITIES TO CREATE A SUSTAINABLE SOLUTION TO CERVICAL CANCER SCREENING IN THE PERUVIAN AMAZON

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Background: *DB Peru* has worked with Amazonian communities in the Napo River for over 12 years. Health issues include remoteness, lack of resources, and poor health literacy. Reproductive healthcare - especially cervical screening - is complicated by the history of forced sterilization during Fujimori's government.
Provision of traditional pap-smears is difficult and often delayed in this region. 83% of women we surveyed did not seek pap-smears due to distance, lack of transport or funds, and environmental barriers.

Methods: We are employing a community-based participatory model. Our initial needs assessment and community consultation was performed in 2013 - 2014. We plan to implement a 4-phase 'screen-and-treat' program from April 2015, including baseline data collection, community education and collaboration, cervical screening and evaluation.

Results: Based on our needs assessment, review of current literature and international guidelines, we propose a single visit 'screen-and-treat' program incorporating education, HPV-DNA testing, visual inspection of the cervix with acetic acid (VIA), followed by cryotherapy where necessary. HPV vaccination will occur parallel to this. We will actively involve local health services and community health-workers during the program, with a vision to transitioning to locally-run services within ten years.
Initial responses from the community have been positive with over 80% of community members supporting sexual health education. 94% of women would participate in the 'screen-and-treat' program if offered. However, 63% of women interviewed felt embarrassed, anxious or scared about cervical screening, indicating that more community education to improve the acceptability of cervical screening must be included.

OC 5-4

ACCEPTANCE AND SATISFACTION OF CERVICAL CANCER SCREENING PROGRAM USING VISUAL INSPECTION WITH ACETIC ACID AMONG WOMEN IN MOROCCO

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Objective: The aim of the study is to explore the acceptance and satisfaction of cervical cancer screening via Visual Inspection with Acetic acid (VIA) at Meknes-Tafilalet Region. Method: A cross-sectional descriptive study was conducted using face-to-face interview of women attending health centers and meeting the inclusion criteria. A sample of 24 health centers, which represent 20% of total health centers that perform VIA screening in the region, were selected using a simple random sampling proportional to the number of health centers in urban and rural area in each of the 6 provinces of the region.

Results: A total of 324 women were included in the study. Result revealed low awareness about cervical cancer (19.6%) and a very high acceptability of VIA screening (94.5%). Of the 306 women who accepted to undergo VIA test, 99% stated going to recommend the VIA testing to their friends and relatives. All women screened negative intended to repeat the test every three years. Those that have a VIA positive test affirmed they will perform confirmatory explorations.96.3% of the women believed that screening using VIA test could save their live. Cervical cancer was the concern of 98.6% of the women. Only 11.6% of them say they feel anxious about repeating the VIA test. The majority of women (98.6%) were satisfied regarding the service received at the health center.

Conclusion: The study demonstrated that VIA screening program is acceptable by Moroccan women, despite their poor knowledge about cervical cancer. Awareness strategy is needed to increase their knowledge.

OC 5-5

AWARENESS OF HUMAN PAPILLOMAVIRUS BEFORE AND AFTER INTRODUCTION OF HPV VACCINATION: A LARGE POPULATION-BASED SURVEY OF SCANDINAVIAN WOMEN

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Objective: Population awareness of human papillomavirus (HPV) is crucial to ensure high coverage of HPV-vaccination programs. In this population-based questionnaire study, we assessed the proportion of Scandinavian women without awareness of HPV before and after introduction of HPV-vaccination. Furthermore, we investigated risk factors for non-awareness.

Methods: In 2004/05, before HPV-vaccination licensure, a random sample of women aged 18–45 years in Denmark, Sweden and Norway received a questionnaire on education, lifestyle, and HPV awareness (n=78,001; response rate 71.3%). In 2011/12, after HPV-vaccination licensure, the same questionnaire was administered to a new random sample in each country (n=83,720; response rate 60.6%). We calculated country- and age-specific proportions of women who had never heard of HPV. Country-specific risk factors for non-awareness were estimated by logistic regression.

Results: The overall proportion of women who had never heard of HPV decreased markedly from 2004/05 to 2011/12 in Denmark (from 75.8% to 25.1%), Sweden (from 74.8% to 33.5%) and Norway (from 62.4% to 33.0%). In 2011/12, the lowest awareness levels were observed in Norwegian women aged 18–19 and 20–24 years (60.4% and 48.9%, respectively, had never heard of HPV). In all countries, women with low educational level; virgins; and daily smokers were at increased risk of non-awareness, in unadjusted analyses and after adjustment for age and education.

Conclusion: HPV awareness has increased after introduction of vaccination, but 25%–33% of Scandinavian women have still never heard of HPV. Information campaigns targeting women with low educational level may be beneficial.

OC 5-6

KNOWLEDGE AND BELIEFS ABOUT HPV IN A VACCINATED COHORT OF YOUNG MEN AND WOMEN

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Objectives: Australia has provided free quadrivalent HPV vaccination to girls aged 12-13 years in a school-based program since 2007. Take-up rates are estimated to be around 80%, with significant variation between states. The program was extended in 2013 to include young men – a global first. This study examines knowledge and beliefs about HPV in this cohort of young men and women.

Methods: A national survey of Australian secondary students, aged 16 to 18, has been conducted regularly since 1992 and was most recently conducted in 2013 – data reported here. Students were recruited from all states and territories and from all school sectors. A total of 2,136 students (61% female) completed a paper based or online survey that examined their knowledge and practices concerning sexual practices and sexual health.

Results: Overall awareness of HPV remains low overall, with young women showing significantly greater awareness. Self-reported vaccination was lower than the known vaccination rates. There were significant gender differences on an HPV knowledge scale. Separate regression analyses for young men and women showed similar demographic and behavioural correlates of good HPV knowledge namely age, HPV vaccination status and sexuality significantly predicted greater knowledge of HPV.

Conclusions: A significant proportion of young men and women are under- informed about HPV and vaccination. For the vaccination program to be as successful for young men as it has been for young women, targeted health education and promotion is essential and must be based on current and relevant evidence of awareness and understanding.

OC 5-7

WEB-BASED SURVEY ON KNOWLEDGE FOR CERVICAL CANCER PREVENTION AMONG YOUNG WOMEN: COMPARISON IN JAPAN AND AUSTRALIA

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Objectives: Cervical cancer (CC) incidence and mortality among young women have been increasing in Japan. To develop effective measures to combat this, we conducted a knowledge and attitudes study about CC prevention.

Methods: Advertising banners targeting women aged 16-35 years in Kanagawa Prefecture, Japan, were placed on a social networking site (SNS), Facebook (FB), in a similar manner to an Australian (AUS) study conducted on 16-25 in 2010, and on our CC advocacy website. Eligible participants were emailed instructions for accessing our secure website where they completed an online survey including demographics and knowledge of human papillomavirus (HPV) and CC. Data for this study were compared with the preceding AUS study.

Results: Among 394 women who expressed interest, 243 (62%) completed the survey. Participants had high awareness and knowledge of HPV and CC, comparable to the AUS study participants. However, the self-reported HPV vaccination rate (22% among participants 16-25 years) and the recognition rate of the link between smoking and CC (31%) were significantly lower than in the AUS study (58% and 43%, respectively) ($P<0.05$). Significant predictors of high knowledge scores about HPV included awareness of HPV vaccine ($P<0.001$) and self-reported HPV vaccination ($P<0.05$).

Conclusions: SNS and websites are an efficient method to recruit young women into health surveys. The influence of several factors including the current suspension of HPV vaccine approval in Japan due to adverse reactions should be investigated as a next step, considering the HPV vaccination status in other developed countries including Australia.

OC 5-8

KNOWLEDGE AND PREVALENCE OF HPV DISEASES IN LATVIA

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Objective In last decade public health strategy in Latvia is focused on cervical cancer prophylaxis but not on prophylaxis of HPV diseases.

Aim Evaluate the knowledge and occurrence of clinical signs related to HPV diseases of Latvian inhabitants.

Methods In 2011 a population survey was carried out in Latvia sponsored by MSD company. The study sample consisted of 3050 randomly selected respondents aged 18 – 45 years. We compared knowledge and occurrence of clinical signs related to HPV diseases into three groups of patients: I - no sexual experience, II – having 0 – 1 partners during the last year, III – having two or more partners during the last year.

Results Among all respondents the frequency of incorrect answers to the knowledge questions was as follows: HPV infections is a rare disease - 52%, HPV infection is a sexually transmitted disease - 14%, can cause genital warts - 20%, may resolve without treatment - 72% and affects both man and women - 15%. Association between HPV infection and cervical cancer recognized 74% of the respondents of groups I and II but only 63% of group III ($p<0.001$). Genital warts more frequently have been noticed by respondents of the groups II (112/2347) and III (31/439) comparing to group I (2/224) ($p<0.01$). Precancerous lesions had no women of group I, 8.7% of group II and 16% of group III ($p=0.03$).

Conclusions Knowledge about HPV diseases in Latvia is insufficient. People with more risky sexual behavior are less aware about the consequences of HPV related diseases.

OC 5-9

A POPULATION BASED SURVEY OF SCHOOL NURSES' ATTITUDES TO THE IMPLEMENTED HPV VACCINATION PROGRAMME IN SWEDEN

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Objective: To investigate school nurses' attitudes to, and experiences of the school-based HPV vaccination programme, one year after its implementation in Sweden.

Methods: Data were collected using a web-based questionnaire in spring 2013, and 83.1% (851/1024) of the nurses answered the questionnaire.

Results: The majority (88.9%, n=756) agreed that HPV vaccinations should be the school nurses' responsibility, and most also agreed (81.5%, n=693) that boys also should be offered the vaccine. Two thirds, 66.9% (n=570), stated that they had experienced difficulties with the vaccination and of these 59.1% (n=337) considered the task time-consuming. Three out of four nurses, 76.1% (n=648), had been contacted by parents who raised questions regarding the vaccine. The most common questions were related to side effects. There were strong associations between the nurses' received education about the HPV vaccine and perceived knowledge about the HPV vaccine and a favourable attitude towards vaccination (both $p < 0.001$). A school nurse with a high level of received education was 9.8 times more likely to have a positive attitude to HPV vaccination compared to a nurse with a low level of received education ($p < 0.001$). Nurses with high perceived knowledge were 2.5 times more likely to have a positive attitude compared to those with a low level of perceived knowledge ($p = 0.006$).

Conclusions: HPV vaccination is a complex and time-consuming task and the school nurses need adequate knowledge, education, skills and time in order to address questions and concerns from parents, as well as informing about HPV.

OC 5-10

HUNGARIAN HIGH SCHOOL STUDENTS' ATTITUDE TOWARD THE HPV VACCINE

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Objectives: The study aimed to explore the attitude of high school senior girls – probably being at the dawn of their sexual lives - in Budapest, the Hungarian capital toward the HPV vaccine and their knowledge of cervical cancer.

Methods: 492 girls were recruited from 12 randomly selected establishments. We conducted a cross-sectional analysis by administering an anonymous questionnaire consisting of 54 multiple-choice questions concerning basic socio-demographic and lifestyle factors and questions assessing their knowledge about cervical cancer and HPV. We also tested their attitude toward the HPV vaccine and vaccines in general. Our sample was distributed almost evenly among grammar (52.6%) and vocational schools (47.3%)

Results: Only 33.7% of the girls were aware of the fact that cervical cancer was caused by an infection, though 74.7% marked that HPV caused cervical cancer. 70.1% knew HPV was an STD. 59.9% would make the vaccine compulsory and 79.5% would vaccinate their future children. 63.2% would give it to boys as well, significantly more girls from vocational schools. More than a fifth of the girls has been vaccinated already (23%) and 19.6% had family members who had also received the vaccine. 73.8% expressed their doubts regarding the efficacy of vaccines in general. 98.4% believed that attending cervical cancer screening was important.

Conclusions: The knowledge of the girls from our sample regarding cervical cancer and the HPV vaccine proved to be unsatisfactory. Girls in grammar schools seemed to have more thorough knowledge which corresponded with higher vaccine acceptance.

OC 5-11

PRIMARY PREVENTION OF HPV INFECTIONS FOR ADOLESCENTS(EDUCATION AND VACCINATION)

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The incidence of infection increases with the sexual onset in puberty and adolescence:
careless lifestyle, bad dietary habits and frequent change of sexual partners. The psychic and physical maturity are not strictly correlated in adolescent population. Why are adolescent social groups at increased risk? The need for sexual experimentation,poor knowledge on sexually transmitted diseases, hedonism as a value orientation,strong peer pressure,illusion of invulnerability,poor communication skills. We made our educational programme for adolescents:"Knowlwdge is pleasure". A week before the lectures/events, adolescents made:- web sites- theatrical performances (concerts, poems, plays...)- posters- lectures... on sexually responsible behaviour, and the prevention of youth violence and addictions Adolescents are actively involved in the project (making boxes, brochures, flyers, posters, organizing peers).We made research during 3 years of the project (2007 – 2010), 51 high schools, 2295 students. 68% uses condoms (of which 40% at their first sexual intercourse), 12% hormonal contraception.59% had first sexuall intercourse under the influence of alcohol, 13 % under the influence of drugs. 39 % have heard about HPV, 32% have heard that HPV presents a cancer risk factor. 70% estimate that their risk of contracting an STD is high. 85% know that condoms provide protection from both unwanted pregnancies as well as STD,45% have no knowledge about the role of hormonal contraception.HPV vaccination in Central and Eastern Europe(Croatia is part of this): Current HPV vaccines registered in 25/28 countries. Only 6 countries (Bulgaria, Czech Republic, Macedonia, Latvia, Romania and Slovenia) have integrated HPV vaccination into their national immunization programme and currently provide routine vaccination free of charge to the primary target population.The key reasons for lack of implementation of HPV vaccination into the national immunization programme:High vaccine cost or inappropriate pricing policy,low level of awareness among public,negative public perception,low level of awarness among health care providers,not high on political agenda.Parents perceive the vaccine as risky. The belief that the vaccine represents an experiment that uses their daughters as guinea pigs (serving the commercial intrest of pharmaceutical companies) The belief that the vaccine embodies a conspiracy theory that aims to reduce the world population. General mistrust in the ineffective health system. There are many reasons why people are not getting the HPV vaccine:one of the biggest reason is that physicians are hesitant to talk to 11- and 13-year-olds about vaccines when they feel compelled at the same time to talk about the sexual nature of the virus's transmission. I believe we should think of this vaccine as what it is: a cancer-preventing vaccine. Social media and text messaging can increase the amount of knowledge on the prevention of STDs. 80 % of teens report using social networking sites.

OC 5-12

HPV VACCINE CONCERNS IN JAPAN – SOCIAL AND POLITICAL BACKGROUND

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Objectives: Since June 14th 2013, the Japanese Ministry of Health Labour and Welfare (MHLW) has suspended recommendations for the HPV vaccine program after only 2 months from the start of NIP. We investigated factors influencing the suspension from a SOCIAL and POLITICAL perspective.

Methods: Initially, one newspaper reported without any medical proof that many girls suffered from severe chronic pain after HPV vaccination, based on information from an opposition group against HPV vaccine. It calls itself "The HPV Vaccine Victims' Group". Some politicians put these so-called victims in the forefront of the mass media, instigating tragedy and sympathy, and thus portrayed themselves as heroes who seek and obtain justice. Some politicians also gained the support of strange religious groups. "Vaccine Victims" were also extremely skillful at manipulating the mass media and social media by using very sensational video clips. Because the symptoms of all reported cases are so diverse, it is hard to find scientific causality between the vaccine and adverse events. The MHLW managed to dodge criticism by suspending positive recommendation of the vaccine without correcting false reports in the media.

Results: However, this measure failed because the concept of the HPV vaccine being dangerous has almost become fact and has spread widely. The situation is like a pandemic transmission of hysteria thorough both mass and social media. Many people misunderstand the causality. Consequently, the MHLW has not been able to resume recommendation of the vaccine due to protest by politicians. Thus, the issue is no longer scientific but political.

Conclusion: Poor governance of public health without scientific basis will have serious implications for the future.

OC 5-13

HPV VACCINE CONCERNS IN JAPAN – PUBLIC HEALTH AND SCIENTIFIC BACKGROUND

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Objectives: The Japanese Ministry of Health, Labour and Welfare (MHLW) has suspended recommendations for the HPV vaccine program for more than 1 year. We investigated factors influencing the suspension from the point of view of PUBLIC HEALTH AND SCIENCE

Methods: Although WHO (GACVS) issued a safety statement for HPV vaccine on the June 13th 2014, the MHLW decided to suspend recommendations for the HPV vaccine program on the 14th. Because the vaccine adverse reaction committee (VARC) was not able to assess whether there were indeed safety issues or not based on insufficient data provided by the Ministry, the VARC decided to suspend proactive recommendation of the HPV vaccine. On December 25th 2013, January 20th and July 4th 2014, the VARC investigated the alleged adverse effects of the HPV vaccine and reached the conclusion there was little evidence to suggest a causal link between chronic pain and the HPV vaccine (1.5 cases per 100,000 vaccine doses). It concluded that patients were suffering from functional somatic symptoms caused by a psychosomatic reaction. Although collaborative movements of Academia and advocate groups issued several statements for resumption of proactive recommendation, the media ignored them and the MHLW has not issued any statement.

Results: A poor surveillance system for adverse events cannot precisely analyze background incidence during both the pre- and post- vaccination period. The VARC has failed to submit their conclusions in a written report to the MHLW.

Conclusion: Epidemiological surveillance during both the pre- and post- vaccination period should be performed. Furthermore, a rapid high level scientific response is the best ways to prevent erosion of public confidence in immunization.

OC 5-14

CORRELATES OF UPTAKE IN SCHOOL-BASED ROUTINE HPV VACCINATION: A REGISTER-BASED STUDY OF 90,000 GIRLS AND THEIR PARENTS

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Objectives: To assess correlates of HPV vaccination of prepubescent girls in a free of charge, school-based childhood vaccination programme.

Methods: Individual demographic, socioeconomic and health data was merged from national registries for Norwegian girls born 1997-1999, eligible for HPV vaccination during the first three years of the programme (n=90,842), and for their registered mother (n=90,540) and father (n=88,565). Correlates of daughter initiation of HPV vaccination were analyzed by logistic regression.

Results: In total, 78.2% of the girls received the first dose of the HPV vaccine, 74.6% received three doses, and 94.8% received the MMR vaccine. Overall, the rate of initiation of HPV vaccination was similar across most levels of the potential correlates investigated. However, low parental education was associated with a relatively high likelihood of daughter initiation of HPV vaccination. In contrast, parental income level was positively associated with initiation. Parental age was negatively associated with initiation. The associations were similar for characteristics of mothers and fathers, although often less pronounced for fathers. The lowest likelihood for initiation of HPV vaccination was found among girls who did not receive the MMR vaccine. Daughters with relatively old mothers, or mothers in the lowest income category, also had relatively low likelihoods of initiation.

Conclusion: Many girls receiving the MMR vaccine did not get the HPV vaccine, thus indicating opportunities for improvements in HPV vaccine uptake. Routine school-based vaccination generally provides equitable delivery, yet some disparities still exist. These findings should be taken into account in attempts to improve coverage, and ensure equitable delivery of the HPV vaccine.

OC 5-15

PREFERENCE FOR 2- COMPARED TO 3-DOSE HPV VACCINE IN A GLOBAL SAMPLE OF ADOLESCENT VACCINE PROVIDERS

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Introduction: Highly effective prophylactic vaccines are available to prevent cancers associated with vaccine-preventable human papillomavirus (HPV) types. WHO's Strategic Advisory Group of Experts on Immunization recently revised its HPV vaccination recommendations to include a 2-dose schedule for girls who receive their first dose before 15 years of age. Understanding provider acceptance of a 2- versus 3-dose schedule will inform global implementation of HPV immunization programs. We investigated the acceptability of a 2- versus 3-dose schedule among adolescent vaccine providers in five geographical regions.

Methods: A total of 151 adolescent vaccine providers were recruited by non–probability convenience sampling in five countries: Argentina(n=30); Malaysia(n=30); South Africa(n=31); South Korea(n=30) and Spain(n=30). Univariate analyses were conducted using structured survey data from telephone or in-person provider interviews. NCT#:GSK117339

Results: Most providers said that they would recommend a 2-dose compared to a 3-dose schedule: Argentina:80%; Malaysia:76%; South Africa:45%; South Korea:90%; and Spain:86%. Most common reasons for preferring a 2-dose schedule were lower cost (Argentina:27%; Malaysia:53%; South Africa:16%; South Korea:60%; Spain:47%), fewer office visits (10%, 30%, 19%, 67%, 70%), higher series completion (67%, 3%, 19%, 50%, 63%), and less pain (37%, 10%, 10%, 33%, 53%).

Discussion: Adolescent vaccine providers reported preference for a 2-dose over a 3-dose HPV vaccine schedule for their female adolescent patients in Argentina, Malaysia, South Africa, South Korea and Spain. Benefits reported for a 2-dose vaccine schedule appeared to vary by country. Most providers (>50%) in 2/5 countries surveyed cited potential advantages of lower cost, higher series completion, and fewer office visits.

OC 6-1

LONG-TERM EFFECTIVENESS AND SAFETY OF GARDASIL™ IN THE NORDIC COUNTRIES

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Objectives: The GARDASIL™ long-term follow-up (LTFU) study is an ongoing extension of a pivotal study (Protocol 015) to investigate the safety, immunogenicity, and effectiveness of quadrivalent HPV vaccine (qHPV) on the incidence of HPV 16/18-related CIN2 or worse in 16-23-year old women. Here, we analyze the effectiveness and safety of the vaccine in this population of women up to 10 years after the start of vaccination.

Methods: All women in the trial are followed through different national registries (Denmark, Iceland, Norway and Sweden) for effectiveness and safety data. Effectiveness and safety analyses started approximately 2 years following completion of Protocol 015 and will occur approximately every 2 years thereafter. Cohort 1 included approximately 2,700 subjects who received qHPV vaccine at the start of Protocol 015. Cohort 2 consists of approximately 2,100 subjects who received placebo at the start of Protocol 015 and qHPV vaccine prior to entry into the LTFU.

Results: In an analysis of effectiveness after the first 10 years, there were 1,281 subjects that contributed to the follow-up period out of a total of 1,984 eligible subjects in the per-protocol population in Cohort 1. No new cases of HPV 16/18-related CIN 2 or worse were observed. There were also no cases of HPV 6/11/16/18-related CIN, vulvar cancer, and vaginal cancer observed.

Conclusions: qHPV vaccine shows continued protection in women through 8 years, with a trend towards 10 years. The qHPV vaccine continues to be generally safe and well tolerated up to 10 years following vaccination.

OC 6-2

PHASE II EVALUATION OF A MULTIVALENT HPV L1 VIRUS-LIKE PARTICLE (VLP) VACCINE

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Objective: To develop a multivalent prophylactic HPV vaccine that protects against infection and disease caused by HPV16/18 (oncogenic types in existing prophylactic vaccines) plus additional oncogenic types.

Methods: Three Phase II studies compared the immunogenicity and safety of several vaccine candidates with the licensed quadrivalent HPV6/11/16/18 vaccine (qHPV vaccine) in young women ages 16-26. Study 1 was conducted first. Studies 2 and 3 were conducted after analysis of results from Study 1. In Study 1, subjects received one of three dose formulations of an 8-valent HPV6/11/16/18/31/45/52/58 vaccine or qHPV vaccine (control). In Study 2, subjects received one of three dose formulations (termed low-, mid-, and high-dose formulations, respectively) of a 9-valent HPV6/11/16/18/31/33/45/52/58 vaccine (9vHPV vaccine) or qHPV vaccine (control). In Study 3, subjects concomitantly received qHPV vaccine plus 5-valent HPV31/33/45/52/58 or qHPV vaccine plus placebo (control). All vaccines were administered in at day 1, month 2, and month 6.

Results: In studies 1 and 3, anti-HPV6/11/16/18 geometric mean titers at month 7 were non-inferior in the experimental arms compared with the control arm; however, there was a trend for lower antibody responses for all four HPV types. In Study 2, this immune interference was overcome with the mid- and high-dose formulations of the 9vHPV vaccine by increasing antigen and adjuvant doses. In all 3 studies, all vaccine candidates were strongly immunogenic with respect to HPV31/33/45/52/58 and were well-tolerated.

Conclusions: Based on the totality of the results, the middle dose formulation of the 9vHPV vaccine was selected for Phase III evaluation.

OC 6-3

IMMUNOGENICITY AND SAFETY OF A NOVEL 9-VALENT HPV L1 VIRUS-LIKE PARTICLE VACCINE IN BOYS AND GIRLS 9-15 YEARS OLD; COMPARISON TO WOMEN 16-26 YEARS OLD

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Objectives: An efficacy study of the investigational 9-valent HPV (6/11/16/18/31/33/45/52/58) VLP vaccine (9vHPV) is not possible in sexually naive adolescents. Therefore, a study was conducted to provide immunological bridging from young women 16-26 years of age (the population used to establish 9vHPV vaccine efficacy) to adolescents 9-15 years of age. This report investigates whether the 9vHPV vaccine induces non-inferior serum antibody responses in boys and girls 9-15 years of age compared to young women 16-26 years of age.

Methods: Subjects (n=3,066) received 9vHPV vaccine as a series of injections administered at day 1, month 2, and month 6. Blood samples for anti-HPV serologic assays were obtained at day 1 and month 7. Systemic and injection-site adverse experiences (AEs) and serious AEs were monitored.

Results: At 4 weeks post-dose 3, over 99% of girls, boys, and young women seroconverted for vaccine HPV types; marked elevations in cLIA GMTs to HPV types 6/11/16/18/31/33/45/52/58 were elicited in all vaccine groups at 4 weeks post-dose 3. Non-inferiority of the GMT responses for each of the HPV types in both girls and boys, 9-15 years of age relative to GMT responses in young women was established. Administration of the 9vHPV vaccine was generally well tolerated. Only 2 vaccine-related serious adverse experiences were reported over the duration of the study.

Conclusions: These results support bridging the efficacy findings with 9vHPV vaccine in young women 16 to 26 years of age to adolescent girls and boys 9 to 15 years of age.

OC 6-4

IMMUNOGENICITY AND SAFETY OF A NOVEL 9-VALENT HPV VACCINE IN GIRLS 9-15 YEARS OF AGE COMPARED TO THE QUADRIVALENT VACCINE

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Objectives: Approximately 20% of cervical cancers are related to HPV 31, 33, 45, 52, and 58, and a 9-valent virus-like particle vaccine (9vHPV) containing antigens against HPV 6/11/16/18/31/33/45/52/58 has been developed. A double-blind study was conducted to assess immunogenicity and safety of 9vHPV vaccine compared with qHPV vaccine in girls 9 to 15 years of age.

Methods: Subjects (n=600) were randomized 1:1 to receive 9vHPV vaccine or qHPV vaccine (day 1, month 2, month 6), in 2 age-strata (9-12 and 13-15 years of age). Immune response to the 9 HPV types was evaluated by competitive Luminex Immunoassay. The primary objective was to demonstrate non-inferiority of 9vHPV vaccine compared to qHPV vaccine for both HPV 16/18, based on the lower bound of the 95% confidence interval (CI) for post-dose 3 geometric mean titre (GMT).

Results: Non-inferiority was demonstrated: at month 7, GMT ratios (9vHPV/qHPV) were 0.97 (95% CI: 0.85-1.11) for HPV16 and 1.08 (95% CI: 0.91-1.29) for HPV18. In addition, the GMT ratios were 1.07 (95% CI: 0.93-1.23) for HPV6 and 0.93 (95% CI: 0.80-1.08) for HPV11. After qHPV vaccine, all subjects seroconverted to the 4 vaccine types (HPV 6, 11, 16, 18) and a number of subjects seroconverted to non-vaccine HPV types (HPV 31, 33, 45, 52, 58), mainly HPV31 (73.5%) and HPV58 (54.8%).

Conclusions: The 9vHPV vaccine immune response was comparable to that of qHPV vaccine for HPV 6/11/16/18 and robust for HPV 31/33/45/52/58. Adverse experiences were comparable for both vaccines.

OC 6-5

SAFETY AND TOLERABILITY OF A NOVEL 9-VALENT HPV VIRUS-LIKE PARTICLE VACCINE

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Objectives: The investigational 9-valent HPV (6/11/16/18/31/33/45/52/58) (9vHPV) vaccine includes the 4 HPV types (6/11/16/18) in the quadrivalent HPV (qHPV) vaccine and 5 additional oncogenic types (31/33/45/52/58). Here we present the results of an integrated safety analysis from data gathered over multiple clinical trials of the 9vHPV vaccine.

Methods: The safety of the 9vHPV vaccine was assessed in 6 clinical trials (protocols 001, 002, 005, 006, 007, 009) conducted worldwide. These studies collectively were conducted in female subjects 9-26 years of age and male subjects 9-15 years of age. Temperatures were monitored for 5 days postvaccination. Systemic and injection-site adverse experiences (AEs) and serious AEs were monitored for 15 days post-vaccination using Vaccination Report Card. Non-prompted and serious adverse experiences (SAE) were also collected and reported.

Results: Overall, 92.2% of subjects who received 9vHPV vaccine reported an AE. Most adverse experiences were injection-site AEs (88.3%) and the most common were pain (85.3%), swelling (37.6%), and erythema (31.8%). The most common vaccine-related systemic AEs were headache (13.9%), pyrexia (6.6%), nausea (3.4%), dizziness (2.4%), and fatigue (1.9%). Five SAEs were determined to be related to 9vHPV vaccine. Few subjects (0.1%) discontinued due to an AE. There were no deaths related to the 9vHPV vaccine.

Conclusions: These analyses demonstrate that the IM administration of 9vHPV vaccine is generally well tolerated. Discontinuations were rare and no safety signals of clinical concern were identified.

OC 6-6

TOLERABILITY AND IMMUNOGENICITY OF A MULTIVALENT HPV L1 VIRUS-LIKE PARTICLE VACCINE IN 16- TO 26-YEAR-OLD MEN

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Objectives: This study is designed to evaluate the immunogenicity and tolerability of a prophylactic 9-valent HPV (types 6/11/16/18/31/33/45/52/58) VLP vaccine (9vHPV) in young men 16-26 years of age in comparison to young women 16-26 years of age. Safety and immunogenicity data from this study will be used to bridge 9-valent HPV vaccine efficacy findings in 16-26-year-old women to 16-26 year-old men.

Methods: This study enrolled 1103 heterosexual men (HM) and 1099 women who had not yet received HPV vaccination. In addition, 313 men having sex with men (MSM) were enrolled and were evaluated separately for immunogenicity (previous results showed that antibody responses to GARDASIL were lower in MSM than in HM). All subjects were administered a 3-dose regimen (Day 1/Month 2/Month 6) of 9vHPV vaccine. Serum samples were collected for anti-HPV assays. Safety information was collected for ~12 months.

Results: Administration of V503 to both 16-26-year old males and 16-26-year old females was generally well tolerated. The geometric mean titers (GMTs) for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 for 16-26-year old males (HM) were non-inferior to those of 16-26-year old females at Month 7. For all vaccine HPV types, Month 7 GMTs were numerically lower in MSM than in HM. Over 99.5% of subjects were seropositive at Month 7 for each vaccine HPV type.

Conclusions: These results support bridging the efficacy findings with 9vHPV vaccine in young women 16-26 years of age to men 16-26 years of age.

OC 6-7

END OF STUDY EFFICACY AND IMMUNOGENICITY OF A NOVEL 9-VALENT HPV L1 VIRUS-LIKE PARTICLE VACCINE IN 16-26 YEAR OLD WOMEN

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Objectives: An efficacy and immunogenicity study of an investigational 9-valent HPV (6/11/16/18/31/33/45/52/58) (9vHPV) vaccine was conducted in women 16-26 years of age to demonstrate immunological non-inferiority of HPV 6/11/16/18 response and efficacy against HPV 31/33/4/52/58-related persistent infection and disease. The report presents results through end-of-study (i.e. up to month 54).

Methods: 14,204 healthy 16-26 year-old women were enrolled into an international, double-blind efficacy and immunogenicity study of the 9vHPV vaccine. Subjects received 9vHPV vaccine or quadrivalent HPV vaccine (qHPV) as a series of injections at day 1/month 2/month 6. Primary analyses included subjects who were seronegative at day 1 and PCR negative from day 1 through month 7 for the HPV type being analyzed. Gynecological swabs (for HPV DNA testing) and Pap test were performed every 6 months. Subjects with abnormal Pap tests were referred to colposcopy.

Results: Anti-HPV 6/11/16/18 responses generated by 9vHPV vaccine were non-inferior to those generated by qHPV vaccine. Efficacy of 9vHPV vaccine against a composite endpoint of HPV 31/33/45/52/58-related high-grade cervical/vulvar/vaginal disease was 97.4% ([95% CI: 85.0-99.0] 1 case in the 9vHPV vaccine group and 38 cases in the qHPV vaccine group). Efficacy against HPV 31/33/45/52/58-related cervical/vulvar/vaginal disease (any grade) in the PPE was 97.7% (95% CI: 93.3, 99.4). Efficacy against HPV 31/33/45/52/58-related 6-month persistent infection in the PPE was 96.0% (95% CI: 94.6-97.1).

Conclusions: The 9vHPV vaccine was highly efficacious in preventing HPV 31/33/45/52/58-related persistent infection and disease up to month 54. HPV 6/11/16/18 immune responses were non-inferior to that of qHPV vaccine.

OC 6-8

POTENTIAL IMPACT OF A NINE-VALENT VACCINE ON HUMAN PAPILLOMAVIRUS (HPV) RELATED CERVICAL DISEASE IN WOMEN AGED 16-45 YEARS OF AGE, BY REGION

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Objectives: To examine the distribution of HPV types contained in an investigational 9-valent HPV (9vHPV) vaccine (6/11/16/18/31/33/45/52/58) in CIN2/3/AIS (i.e., CIN2+) from younger women (aged 16-26) and older women (24-45) using placebo data from three clinical trials of the quadrivalent HPV (qHPV) vaccine.

Methods: Protocol-mandated testing was conducted at regular intervals and included Pap tests and follow-up for abnormalities. Tissue from biopsies and excisions were tested for HPV via PCR. Lesions were diagnosed by a Pathology Panel consensus diagnosis. The prevalence of HPV types and type combinations in these lesions was calculated using a proportional attribution method whereby a fractional allocation for each individual HPV type was used when evaluating multitype infected lesions.

Results: A total of 945 CIN2+ lesions were detected. There was minimal regional variation for the 9vHPV vaccine types in CIN2+, with an overall prevalence of 82%, 83%, 82% and 69% for Europe, Latin America, North America and Asia. The contribution of the 5 additional oncogenic HPV types over that of the qHPV vaccine was 38%, 31%, 22% and 36% for these regions, respectively. According to literature, the annual incidence rate of CIN2+ per 100,000 women ages 18-39 is 265-533 in the US alone. Applying these rates and US female population estimates to our findings, we estimate approximately 120,000-241,100 of CIN2+ cases diagnosed in the US each year are attributed to HPV16/18/31/33/45/52/58.

Conclusion: A 9vHPV vaccine has recently been shown to be highly safe and efficacious. If future 9vHPV vaccination programs are effectively implemented, the majority (70-85%) of pre-cancerous cervical lesions could be prevented worldwide, in addition to approximately 90% of invasive cervical cancers.

OC 6-9

EVALUATION OF HPV CLEARANCE FOLLOWING PROCERVIX VACCINATION IN HPV 16 / 18 INFECTED WOMEN WITH NORMAL CYTOLOGY

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Introduction: In a Phase I study, ProCervix, a first-in-class adjuvanted bivalent HPV16/18 therapeutic vaccine was reported to promote increased and sustained viral clearance in HPV16/18 infected women with normal cytology1. Changes in cervical HPV virology were further examined to understand the influence of patient HPV history and characteristics on clearance.

Methods: A ProCervix dose escalation (100, 600 mcg/dose) was followed by a randomized evaluation of ProCervix600 with imiquimod or with placebo cream; and placebo vaccine+ imiquimod. Changes in cervical HPV virology were evaluated using 2 clinically validated real time PCR genotyping tests for HPV16 and HPV18, including one allowing for the individual quantification of 18 different HPV types, using fixed amount of HPV DNA.

Results: Six months post-vaccination, HPV positivity with both tests showed no difference between treatment groups. At final analysis (average follow-up of 16.7 months), ProCervix600+imiquimod led to more cleared patients (19/28) with more sustained clearance than placebo+imiquimod (3/7). Clearance, and protection against incident infections, appear to be HPV16/18 specific. Patient characteristics (age, pre-existing immune response, HPV 16 or 18 type infection, viral load, and multi-infections) did not appear to impact clearance and time to clearance. Most importantly, serial measurements of type-specific viral loads, including up to 5 years before vaccination, showed HPV16/18 clearance for patients with long term pre-existing infection (up to 4.3 years) and in CIN2/3 previously treated patients (4/4).

Conclusion: These encouraging HPV clearance results further support ProCervix clinical evaluation in women infected with HPV16 and/or HPV18.

References
1 Abstract SS9-4, Florence, Eurogin 2013S

OC 7-1

RISK OF HUMAN PAPILLOMAVIRUS-ASSOCIATED HEAD AND NECK CANCER FOLLOWING A DIAGNOSIS OF CERVICAL INTRAEPITHELIAL NEOPLASIA

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Objectives: Human papillomavirus (HPV) represents a necessary cause for the development of cervical cancer and its severe precursors (CIN2/3). Furthermore, HPV is associated with the development of a subset of head and neck cancers (HNCs). The aim was to investigate whether women previously diagnosed with CIN2/3 had an increased risk of developing HPV-associated HNC. Degree of HPV association was based on the current literature.

Methods: This nationwide register-based cohort study included all women born in Denmark between 1918 and 1990 (~2,900,000). Of these, 133,740 women were registered with a diagnosis of CIN2/3 in The Danish Cancer Registry or The Danish Pathology Data Bank. All women were followed from the age of 18 until date of HNC diagnosis, date of migration, date of death or December 31, 2012. Using Cox regression analysis with age as the underlying time scale, Hazard Ratios (HR) for the risk of HNC in women with previously diagnosed CIN2/3 were estimated (adjusted for birth year).

Results: A significantly increased risk of overall HNC of 93% (HR 1.93, 95% CI 1.68–2.21) was found for women with a previous diagnosis of CIN2/3. Restricting the analysis to include only highly HPV-associated HNCs (oro-pharynx) increased the risk (HR 2.12, 95% CI 1.66–2.71). The risk of medium HPV-associated HNC was (HR 1.67, 95% CI 1.30–2.13).

Conclusion: Our study shows a highly significant risk of HPV-associated HNC among women previously diagnosed with CIN2/3. At the conference further analyses e.g. on time between CIN2/3 and HNC will be presented.

OC 7-2

HUMAN PAPILLOMAVIRUS PREVALENCE AND GENOTYPE PROFILING IN HEAD AND NECK REGION: AN ITALIAN STUDY

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Objectives. Data on HPV prevalence in the head and neck region for the Italian population are scarce. The objectives of this study were to assess HPV prevalence and genotype distribution in oropharyngeal samples from individuals with: 1. squamous cell carcinoma (SCC); 2. benign lesions; 3. no clinically evident lesions. Additionally, we evaluated p16 overexpression in SCC.

Methods. Healthy mucosa samples were collected by cytobrushings in PreservCyt (Hologic); SCC and benign lesions were retrieved from the FFPE tissue archive of the Regina Elena National Cancer Institute. For DNA extraction we used: 1. DNeasy Blood and Tissue kit (Qiagen) for FFPE samples; 2. Amplilute Liquid Media Extraction kit (Roche Diagnostics) for cytobrushings. HPV testing was performed by the INNO-LiPA Genotyping Extra (Fujirebio) on FFPE samples, and the Linear Array HPV Genotyping test (Roche Diagnostics) on cytologic samples. p16 immunohistochemistry was performed using the CINtec® Histology kit (Roche Diagnostics).

Results. 132 SCCs, 44 benign lesions and 50 healthy mucosa samples were analyzed, with an HPV prevalence of 40.1% (45.0% in tonsillar and 44.1% in base of tongue SCC), 15.9% and 8.0%, respectively. Among SCCs only high-risk types were found, with HPV16 being present in 88.7% of the HPV-positive cases. p16 overexpression was observed in 97.8% of the HPV-positive SCCs, while only 14.7% of the HPV-negative SCCs displayed p16 staining.

Conclusions. HPV prevalence in all the groups analyzed is in agreement with data from the literature. HPV16 was confirmed as the most prevalent genotype in oropharyngeal SCC. Moreover, p16 overexpression seemed to be associated with HPV-positive SCC cases.

OC 7-3

FULL TITLE: THE INCIDENCE OF CERVICAL AND HEAD AND NECK CANCER AMONG INDIGENOUS PEOPLE IN AUSTRALIA, CANADA, NEW ZEALAND, AND THE UNITED STATES.

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Objectives: Indigenous people in four high-income countries, namely Australia (Aboriginal and Torres Strait Islanders), Canada (First Nations), New Zealand (Māori), and the Unites States (Native American/Alaska Native), have a higher burden from some cancers. We present here the incidence profiles of cervical and head and neck cancer, two cancers asso

Methods: Incidence data were derived from population-based cancer registries in three Australian states, namely Queensland (QLD), Western Australia (WA) and the Northern Territory (NT), New Zealand (NZ), the province of Alberta, Canada, and the US Contract Health Service Delivery Area (CHSDA) regions, including US Alaska and the four other US-CHSDA regions combined. We computed age-standardized incidence rates (ASR) by sex ethnicity for 2002-2006 using the SEGI world-standard population. Rates from Alberta were calculated directly by the registry; head and neck cancer rates were not available.

Results: Cervical cancer incidence was greater for indigenous women compared to all women in the population of each jurisdiction, including Alaska, but not for the rest of the US (Alaska Native7.8/100,000 vs US Whites 6.3/100,000). Head and neck cancer incidence was greater for indigenous men and women in the NT, WA, Qld, NZ and Alaska Natives.

Conclusions: Disparities exist in the incidence of cervical head and neck cancers, the former largely preventable through screening and HPV vaccination. HPV vaccination might also reduce the incidence of some head and neck cancers. Investigation of the risk factors for these cancer in Indigenous populations are needed, as are culturally-appropriate public health interventions that address barriers to screening and vaccination by indigenous people.

OC 7-4

STUDY OF HPV AND PRECANCEROUS LESIONS IN THE TONSILS ("SPLIT"): PRELIMINARY RESULTS

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Objective: The SPLIT study aims to understand the natural history of HPV infection in the tonsils.

Methods: Since 2012, tonsils from children and adults non-cancer patients are being collected in 20 centres in France. For each patient, half of the resected tonsils are extensively brushed to collect exfoliated cells for HPV detection and cytologic examination. A subset of nine centers are also collecting rinse/gargling samples before tonsillectomy.

Results: To date 500 out of 700 targeted patients have been included. Preliminary findings from the first batch of samples include the following: HR-HPV DNA was detected in 2 out of 170 tonsil brushing (of which one HPV16) and in 9 out of 68 gargles (6 HPV16). The two patients HPV-positive in tonsil brushing were also positive for the same HPV type in gargle. No cytologic abnormalities were found in exfoliated cells of the first 120 patients, of which 86 showed either inadequately high amount of lymphocytes, or low number of both lymphocytes and epithelial cells.

Conclusions: Preliminary results suggest that (1) HPV is rarely detected in tonsil tissue, although more frequently detected in gargles; and (2) extensive brushing of tonsil surface and crypt does not allow adequate diagnosis of cytological lesions due to low number and quality of epithelial cells. Updated findings for a larger number of patients will be shown.

OC 7-5

PREVALENCE OF HPV & P16INK4A IN MULTIPLE PRIMARY SQUAMOUS CELL CARCINOMAS OF THE UPPER AERODIGESTIVE TRACT

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Objective: The prevalence of HPV and p16Ink4a was investigated in patients with two or more primary HNSCCs.

Methods: A retrospective study was conducted in Royal Victoria Eye and Ear Hospital and St. James's Hospital, Ireland, between January 2000 and June 2012. p16 immunohistochemical staining was performed using purified mouse anti-human p16INK4A (BD Pharmingen™). The Qiagen DNA extraction kit was used to extract genomic DNA and it was tested for the presence of HPV using consensus SPF10 primers followed by gel electrophoresis. HPV genotyping was performed by TaqMan Real-Time PCR for HPV16, 18, 33 and 45.

Results: 72 (11.9%) out of 604 patients were identified with a second primary malignancy (SPM). Third primary malignancy prevalence rate was 3.0% (18/604) while a fourth primary malignancy rate of 0.5% (3/604) was established. Overall 57 males and 15 females between the ages of 36 to 78 (mean 58 +/- SD 9) were reviewed. The majority of SPM were located in the oral cavity (44%) and oropharynx (24%). Over 75% of these patients smoked and consumed alcohol. About one third of them (21pts) had HPV positive first primary tumour. Among them, nearly 50% (10pts) developed a HPV positive SPM. Majority of the patients were HPV16 positive (12pts). A low p16Ink4a positivity rate for both first primary (16.4%) and SPM (16.4%) was established.

Conclusion: HNSCC patients that were both HPV and p16Ink4a positive develop a SPM and these patients have a better survival compared to patients who did not harbour HPV infections and were $p16^{Ink4a}$ negative.

OC 7-6

ADULT ONSET RECURRENT RESPIRATORY PAPILLOMATOSIS: A RETROSPECTIVE REVIEW

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Background: Recurrent Respiratory Papillomatosis (RRP) is a disease caused by the Human Papilloma virus (HPV). Current literature suggests that the prevalence of adult onset-RRP is 1.8-2.3 per 100,000, that patients are from low socioeconomic backgrounds and that the median age of adult onset is 34. The evidence for malignant transformation is generally based on small series and case reports, a recent study found the malignant transformation rate to laryngeal carcinoma to be 2.7%.

Objectives: This retrospective study aimed to determine the demographics, prevalence and risk of malignant transformation of adult patients managed by an institution covering a population area of 800,000, between 2003 and 2014.

Methods: Patients were identified using pathology numbers. RRP history, demographics and outcome data were analysed using electronic clinical database. Socioeconomic status was determined using the National Statistics Socio-economic classification three class system. Age, gender and RRP history were analysed using measures of central tendency.

Results: 67 patients were identified, median age at diagnosis was 38 (range 19-92, mean 42.3). Socioeconomic status was determined: 3 patients were students or unemployed; 6 were class I (managerial, professional); 18 class II (intermediate); 7 class III (manual workers) and status was unknown for 33 patients. Three patients developed laryngeal cancer.

Conclusions: This study observed a RRP prevalence of 8.9 per 100,000. The malignant transformation rate was 4.5%. There appears to be an evolving pattern of RRP with older economically active patients being affected and a higher risk of malignant transformation.

0C 7-7

HPV IN ORAL SQUAMOUS CELL CARCINOMA IN INDIA: PATHOGENESIS AND CLINICAL IMPLICATIONS

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Objectives: Human Papilloma Virus (HPV) associated Oral Squamous Cell Carcinoma (OSCC) is increasingly being reported worldwide.The present study was done to assessHPV in OSCC along with associated risk factors, related biomarkers, histological features, clinical features and survival.

Methodology: HPV was detected in tumour biopsy by Real Time PCR in 250 histologically proven cases of OSCC and reconfirmed by Conventional PCR with L1 consensus PGMY09/PGMY11 primers and genotyped for High risk type 16 and 18. Immunohistochemical localization of p16 & P53 was done by standard protocol.

Results: HPV was present in 23/250(9.2%) OSCC cases, of which 56.52%cases had HPV 16 infection, 43.47% had HPV 18 and 26.08% cases were negative for both 16 and18. Six cases co-expressed DNA of both HPV 16/18 subtypes. p16 overexpression was observed in 40.90% while P53 in 65.2% of HPV positive cases. Of the 23 HPV positive cases association with Tobacco chewing was evident in 19 cases, smoking in 12 cases and alcohol in 7 cases.. Histological evaluation showed basaloid morphology in 2/23 cases, with a keratinizing squamous cell carcinoma in others. No significant difference in median survival of positive (16.5) vs negative (12.9) cases was observed (p=0.62).

Conclusions: Prevalence of HPV associated OSCC is low in India. Etio-pathogenesis of HPV associated OSCC in India may also be different due to association of multiple risk factors and activation of different biomarkers pathways. Basaloid histology and increased survival was not evident in all our cases.

0C 7-8

HUMAN PAPILLOMAVIRUS DETECTION IN ORAL MUCOSA CAN SUGGEST GENITAL INFECTION?

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Introduction: HPV is the etiological agent of cervical and anal cancer. However, little is known concerning the etiology of the oral infection and oral cancer.

Objective: To investigate whether oral infection could point out genital infection, determining the presence of HPV in both sites of infection.

Methods: Oral scrapes from healthy mucosa and genital smears of condylomatous lesions were evaluated by molecular methods. A hundred and ten samples from oral and genital sites were collected from patients attending the STD Clinic from Universidade Federal Fluminense. To screen and type HPV DNA, generic MY09/11 PCR and type-specific PCR, followed by restriction fragment length polymorphism (RFLP).

Results: HPV was detected in 85.5% of genital lesions (n=55) and in 43.6% of oral mucosa samples. In 13 of the 55 (23.6%) studied cases, both sites were infected. The agreement among genital and oral types were high: 9 cases showed the same infecting types in both mucosa. HPV 11 were the most prevalent (n=7), followed by HPV6 (n=2) and HPV45 (n=1). Two cases showed mixed infections infected by and HPV6/11 and one HPV11/45. Oral infection, separated by male and female showed statistical significance (p=0.004), with markedly higher prevalence of oral infection on men.

Conclusion: The oral detection of HPV can suggest genital infection in half of the cases but it further studies are required to elucidate the natural history of HPV infection, mainly in relation to oral lesions.

Keywords: HPV, oral cavity, genital tract, PCR

OC 7-9

MOLECULAR IDENTIFICATION OF HPV AND ITS RELATIONSHIP WITH THE PRESENCE OF PREMALIGNANT AND MALIGNANT LESIONS OF THE ORAL CAVITY IN A GENERAL HOSPITAL, AREQUIPA, PERÚ

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Objective: To establish the relationship between HPV with the presence of premalignant and malignant lesions of the oral cavity.

Methods: An observational, case-control study was conducted . During the months of October and November of 2013, there were attended 19 cases of patients with premalignant and malignant oral lesions in an oncology service (all confirmed by the pathology report), they were matched with 19 controls of similar age and sex. There were obtained two samples for each case and control by brushing of oral cavity and subjected to PCR RFLP (Polymerase Chain Reaction Polymorphism with the size of the restriction fragments).

Results: Oral malignant and premalignant lesions represented 26.76% of all head and neck care outpatient. Malignant lesions were mainly carcinomas (73.68%) and premalignant were mainly papillomas with foci of dysplasia (10.53%). The mean age was 51.82 ± 9.88 years and a predominance of females (63.16 %). Premalignant and malignant lesions were multiple. Premalignant lesions were elevated and without ulceration (15.79%), located in the cheek and tongue. Malignant lesions had ulcerations and located in the palate and lip. Patients with premalignant lesions showed HPV in oral cavity more frequently (66.66%).

Conclusions: The identification of HPV was linked with the presence of premalignant and malignant lesions of oral cavity ($p<0.05$). Cofactors such as oral sex ($p<0.05$) and consumption of tobacco (p 0.05) were also associated with the presentation of oral cavity lesions, both in the analysis of individual association and multivariate analysis.

KEYWORDS: HPV, premalignant lesions , cancer, oral cavity.

OC 8-1

THE ROLE OF THE STROMA IN TUMOUR INFILTRATING LYMPHOCYTES (TILS) IN OROPHARYNGEAL SQUAMOUS CELL CARCINOMA (OPSCC).

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Objective: HPV+ compared to negative OPSCC have a better clinical prognosis. The aim was to study density of TILs present in the tumour microenvironment of OPSCC and any relationship with patient survival.

Methods: Formalin-fixed paraffin-embedded tumours from 139 patients diagnosed with OPSCC between 2002 and 2011 at the Christie NHS Foundation Trust were investigated. HPV detection was by polymerase chain reaction, in-situ hybridisation and corroborated with P16 immunohistochemistry (IHC). TILS (CD3, CD4, CD8 and FoxP3 T cell subsets) were identified using multiplex IHC. Stained tumour sections were scanned and multispectral deconvolution used to delineate immune cells labelled with different chromogens. Myofibroblast transdifferentiation in the stroma was identified using antibody to smooth muscle actin (SMA). TILS density was performed using automated image analysis. TILS density, site and stromal activation status were analysed in relation patient survival.

Results: The density of CD3 T cells in tumours irrespective of HPV status was significantly higher in the epithelial versus the stromal areas. However, CD4 and CD4FoxP3 T cells were present at higher levels in epithelial areas whereas CD8 T cells were more prevalent in the stroma. Interestingly, significant differences in infiltration of CD4 and CD8 but not FOXP3 T cells were seen in the stromal sites of HPV positive compared to negative tumours. The higher T cell infiltration in the stroma of HPV+ tumours correlated with overall patient survival. A relationship with the stromal T cell infiltration, SMA expression and outcome is being evaluated.

Conclusions: Stromal infiltration of effector T cells correlates with better outcome in HPV+OPSCC.

OC 8-2

GENOMIC CHARACTERIZATION OF A NOVEL HUMAN GAMMAPAPILLOMAVIRUS GENOTYPE HPV-199 ISOLATED FROM NAZOPHARYNX

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Objective: To characterize and phylogenetically evaluate the complete genome sequence of a novel *Gammapapillomavirus* (γ-PV) HPV-199, isolated from a nasopharyngeal swab sample.

Methods: A partial HPV L1 gene sequence of 331 bp was obtained using broad-range FAP6085F/FAP64 primers (GenBank Acc. No. HG515499). A complete viral genome was amplified using inverse long-range PCR using primer set: KC82LNG-F (5'-GGCAATAAGGGTGATTGTCCT-3') and KC82LNG-R (5'-TTTTTTACAAGGTTCAGCAACATC-3'). The resulting amplicon was cloned into a plasmid vector and sequenced using a primer-walking strategy. The complete L1 nucleotide sequences from all currently completely sequenced γ-PVs were obtained from the PV genome database (PaVE), aligned and the maximum likelihood (RAxML) phylogenetic tree was constructed.

Results: The complete genome of HPV-199 has 7,122 bp and a G+C content of 36.5% (GenBank Acc. No. KJ913662). The genome contains five early (E1, E2, E4, E6 and E7) and two late (L1 and L2) open reading frames (ORFs), but no E5 ORF. The long control region (LCR) of 514 bp is positioned between the L1 and E6 ORFs. Phylogenetic analysis revealed that genotype HPV-199 clusters into the γ-PV genus, species γ12 and is most closely related to HPV-127 (nucleotide identity 77%). Systematic search in the GenBank database identified one more partial L1 sequence with 99% nucleotide identity (Acc. No. KC752084), isolated from the skin.

Conclusions: The cloning and full characterization of novel HPV genotype improves our knowledge of the diversity of γ-PV; however, the involvement of γ-PVs in clinical manifestations requires further investigation.

OC 8-3

COMPARATIVE ANALYSIS OF MICRORNAS IN HPV-POSITIVE AND NEGATIVE OROPHARYNGEAL CANCERS HIGHLIGHTS DIFFERENT ONCOGENIC MECHANISMS

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Objective: Human-papillomaviruses (HPV) type 16 is a causative agent in an increasing subset of oropharyngeal squamous cell carcinomas (OPSCCs). These tumors are different, at the clinical and molecular level, when compared to tumors caused by traditional risk factors. However, their specific oncogenic mechanisms are still poorly characterized. Analysis of their gene and microRNAs expression profile might provide valuable information.

Methods: mRNA and microRNA expression profiles were analyzed by micro-arrays in 38 OPSCCs (21 HPV-/ 17 HPV16+). A microRNA signature specific to HPV status solely was identified by analyzing a learning/training-set consisting of 16 OPSCCs (8 HPV-/ 8 HPV16+). Potentially confounding factors (stage, sex and tobacco) were equally distributed in both groups. The robustness of this signature was confirmed by blind case-by-case classification of a validation-set composed of 10 tumors.

Results: We have identified a 25 miRNA's signature, which discriminates HPV16-induced OPSCC from their HPV-negative counterparts. After the blind classification of the validation-set, the viral status was revealed: 8/10 tumors were correctly classified according to tumor etiology and 2/10 were misclassified. In silico analysis indicates that these 25 microRNAs play a potential role in Wnt and PI3K-pathways, cell-adhesion/cell-polarity and the cytoskeleton regulation. Analysis of the gene expression profile of 30 samples confirmed that genes related to these pathways/functions are differentially expressed according to HPV status.

Conclusions: Our study contributes to a better understanding of pathogenic mechanisms involved in the development of HPV-positive OPSCCs and in the identification of potential therapeutic targets. Further studies are needed to confirm these results.

OC 8-4

HPV CONCORDANCE BETWEEN NECK METASTASES AND PRIMARY TONSILLAR CANCER.

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Objective: To study possible HPV concordance between the primary tumor and the neck metastasis.

Background: Oncological treatment for HPV positive oropharyngeal cancer has proved to be successful worldwide and surgery can be avoided in most of these patients. Neck metastasis with unknown primary, CUP, was earlier treated primarily with neck dissection, but gradually, at many centers, neck dissection is if possible avoided. If the cytological diagnosis is certain and shows HPV positivity, the primary tumor can be assumed to be an undetectable tonsillar or base of tongue cancer and the patient can primarily be treated solely with oncological treatment.

Methods: Tumor biopsies from thirty-eight patients with tonsillar cancer and cytology from their corresponding neck metastasis were investigated. DNA was extracted using the Roche High Pure RNA Paraffin kit and HPV DNA detection was performed using Magpix instrument (Luminex Corporation, Austin,TX).

Results: In 33/38 patients there was a perfect concordance between the HPV status of the primary tonsillar cancer and the metastasis. In 23 patients both the primary tumor and the metastasis showed HPV 16 positivity and in 10 patients both were HPV negative. One patient presented HPV 56 in the primary tumor and HPV 16 in the metastasis. Among the remaining four cases, two patients showed HPV 33 and HPV 16 in the primary tumor, respectively, while the metastasis did not present any HPV DNA, which could possibly be explained by a secondary infection of the tumor. In two patients the metastasis showed HPV 16 and HPV 33, respectively, but no HPV was found in the primary tumor.

Conclusions: The finding of HPV 16 DNA positive cytology from a neck metastasis strongly indicates an HPV positive primary tumor.

OC 8-5

EXPRESSION OF APM COMPONENTS IN OROPHARYNGEAL CARCINOMAS IN RELATION TO HUMAN PAPILLOMAVIRUS (HPV) AND CLINICAL OUTCOME

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Objectives: Patients with HPV-positive, as compared to, tonsillar and base of tongue squamous cell carcinoma (TSCC and BOTSCC), respond relatively well to treatment with ~80% 5-year disease free survival after conventional radiotherapy/surgery. Treatment has lately been intensified, often resulting in serious side effects, and to avoid overtreatment there is a need for biomarkers to predict treatment response. Earlier studies have demonstrated a HPV-dependent correlation between HLA class I expression and clinical outcome. To further examine relations between components of the antigen processing machinery (APM), HLA class I, HPV and clinical outcome, the expression of LMP2, LMP7, LMP10, TAP1 and TAP2 was analysed in TSCC and BOTSCC.

Methods: Between 135 and 278 TSCC and BOTSCC biopsies, earlier examined for HPV DNA, from patients diagnosed 2000-2007 at the Karolinska University Hospital, were examined for nuclear and cytoplasmic expression of LMP2, LMP7, LMP10, TAP1 and TAP2 and the expression of these was correlated to each other, HPV status and clinical outcome.

Results: The expression of LMP2, LMP7, LMP10 and TAP2 was found to be absent/low in 42-88% of TSCC and BOTSCC and several correlations in the expression of the different APM components were found. In addition, a low nuclear expression of LMP7 or LMP10 was, for HPV-positive tumours, correlated to a successful treatment response.
Conclusions: Reduced expression of APM components is common in TSCC and BOTSCC and, for HPV-positive tumours and nuclear expression of LMP7 and LMP10 may potentially be used together with knowledge of tumour HPV status for prediction of clinical outcome.

OC 8-6

METHYLATION OF HPV16 URR SP1 AND E2 BINDING SITES 3 AND 4 IN MATCHED HPV16 POSITIVE PRIMARY / METASTASIS OPSCC PAIRS

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Objectives: Methylation of E2 binding sites (E2BSs) of the HPV 16 URR has been shown to play a crucial role in activating the expression of the HPV oncogenes E6 and E7 in cervical lesions that may progress to cervical carcinomas. During progression of transformed cell clones HPV 16 genomes often integrate into host cell chromosomes and become independent of the strict transcriptional control by the URR. Hence, integrated HPV genomes frequently lose methylation of E2BSs once they become integrated. Until now, this has not been investigated in detail for HPV genomes in OPSCCs. We assessed methylation patterns in pairs of OPSCC primary tumors and metastases to determine the extent of E2BS3 and 4 methylation in those distinct stages.

Methods: DNA extracted from FFPE tissue of 26 HPV16+/p16^{INK4a}+ matched pairs of OPSCC with metastases was bisulfite-converted and analyzed for methylation in CpGs in positions 31-58 of the HPV16 URR by pyrosequencing.

Results: Methylation levels were lower in metastases than primaries at CpGs 43 (E2BS3) and 52 (E2BS4) showing mean differences of 8.7 and 11.3 percentage points ($p<0.05$ for both) with similar trends for the remaining positions. Primary tumor samples' mean methylation levels covered the range from 0-100% with a distribution hinting at two subgroups with low and medium/high levels.

Conclusions: In line with observed changes in URR methylation patterns in cervical carcinogenesis in different stages of disease and states of viral genome integration, lower methylation in OPSCC metastases could be indicative of integration and associated demethylation of previously episomal genome copies.

OC 8-7

META-ANALYSIS ON P16^{INK4A} ACCURACY TO IDENTIFY HPV TRANSFORMATION IN OROPHARYNGEAL SQUAMOUS CELL CARCINOMAS

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Objectives: p16^{INK4a} immunohistochemistry (IHC) is applied as a surrogate marker of HPV-induced transformation in oropharyngeal squamous cell carcinomas (OPSCC), however, with considerable variation of accuracy among studies. We performed a meta-analysis on the accuracy of p16^{INK4a} IHC to identify a transforming HPV infection in OPSCC and compared the results to HPV DNA detection by PCR, by in-situ hybridization (ISH) and combined p16^{INK4a}/HPV DNA detection by PCR.

Methods: All available studies that assessed p16^{INK4a} IHC and HPV oncogene transcription by an amplification-based method in OPSCC were included in the analysis. Pooled sensitivity and specificity of the four tests were calculated.

Results: Eleven studies assessing for p16^{INK4a} IHC, four assessing for HPV DNA by PCR, five for HPV DNA by ISH and three assessing for combined p16^{INK4a} IHC and HPV DNA by PCR fulfilled the inclusion criteria. The pooled sensitivities of p16^{INK4a} IHC, HPV DNA by PCR, HPV DNA by ISH and combined p16^{INK4a}/HPV DNA by PCR in the oropharynx were 0.93 (95% confidence interval (CI), 0.86-0.98), 0.99 (95% CI, 0.91-1.00), 0.84 (95% CI, 0.71-0.94) and 0.95 (95% CI, 0.84-1.00), respectively. The pooled specificities were 0.84 (95% CI, 0.77-0.90), 0.91 (95% CI, 0.79-0.98), 0.91 (95% CI, 0.78-0.99) and 1.00 (95% CI, 0.96-1.00).

Conclusion: Our meta-analysis data indicate that p16^{INK4a} IHC alone is a very sensitive and moderately specific surrogate marker of HPV-induced transformation in OPSCC. Combined p16^{INK4a} IHC and HPV DNA by PCR testing considerably enhances specificity while maintaining high sensitivity and might thus provide a reliable diagnosis of HPV-transformed OPSCC.

OC 8-8

DETERMINATION OF HUMAN PAPILLOMAVIRUS SIGNIFICANCE IN ORAL PREMALIGNANT LESIONS IN ASSOCIATION WITH CLINICAL PARAMETERS AND P16^{INK4a} IMMUNOHISTOCHEMISTRY

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Objectives: Human papillomavirus (HPV) DNA and RNA is found in a proportion of oral cavity squamous cell carcinomas, indicating a transforming role of the virus in a subset of those cancers. HPV DNA has also been detected in some oral premalignant lesions (OPL), however, with unclear significance.

Methods: Formalin-fixed, paraffin-embedded biopsies of mild, moderate and severe OPL from the "Oral Cancer Prediction Longitudinal study" (OCPL), British Columbia, Canada, were analyzed for HPV DNA, genotype and semi-quantitative viral load applying Luminex technology. The results were correlated to various clinical parameters and p16^{INK4a} immunohistochemistry.

Results: Thirteen of 149 (8.7%) samples were HPV DNA-positive with a low mean "median fluorescence intensity (MFI)" as a semi-quantitative measure of viral load (high-risk(HR)-HPV16:204.6 and HR-HPV18:186.8 MFI). HPV DNA-positivity was associated with higher lesion progression risk ($p=0.038$). Half of the 149 samples demonstrated focal p16^{INK4a} expression (52%), 13% showed a diffuse pattern and 35% were p16INK4a-negative. No significant association between HPV DNA-positivity and p16^{INK4a} expression was observed. Progression occurred in 7 lesions: 0/78 focal, 6/52 negative and 1/19 diffuse p16^{INK4a} expression ($P=0.01$).

Conclusion: A higher progression risk in HPV DNA-positive OPL patients was demonstrated. HPV DNA-positivity in those lesions might represent a non-transforming bystander infection, particularly considering the low MFIs and the lacking association with p16^{INK4a} expression. Assessment of HR-HPV oncogene transcription in the HPV DNA-positive OPL will be performed to differentiate truly HPV-transformed lesions from potential bystander infections. OPL with focal p16^{INK4a} expression appear to have a low likelihood of progression independent of HPV DNA status.

OC 8-9

E6/E7 MRNA IN SITU HYBRIDIZATION IS SENSITIVE AND SPECIFIC TO PREDICT PATIENT OUTCOMES IN OROPHARYNGEAL SQUAMOUS CELL CARCINOMA (SCC)

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Introduction: The incidence of HPV-associated oropharyngeal SCC has increased rapidly and has been documented to have a significantly better prognosis. Various methods have been tested. P16, currently accepted as a surrogate immunomarker for HPV infection, is sometimes discordant with HPV16 DNA in situ hybridization (ISH). HPV DNA ISH is well-established and has excellent histologic correlation; however, interpretation can be difficult and sensitivity is low. RT PCR for HPV DNA is very sensitive; however, it lacks the histologic correlation and the specificity is compromised.

Methods and Results: E6/E7 expression is a hallmark of HPV-driven tumors; E6 and E7 proteins abrogate the functions of two critical tumor suppressors, p53 and RB respectively, to both initiate and maintain turmorigenesis. E6/E7 mRNA detection by a novel ISH (RNAscope) developed by Advanced Cell Diagnostics offers a both specific and sensitive method to detect transcriptionally active high risk HPV in patients with oropharyngeal SCC. Its high sensitivity is achieved through a robust signal amplification system which enables single-molecule detection. Its high specificity is due to effective background suppression to ensure extremely low noise, and the ability to correlate mRNA detection and morphology. The detection process can be performed on formalin-fixed and paraffin-embedded tissues on automated platforms. Compared to p16 immunostain and HPV DNA ISH, E6/E7 status is strongly prognostic and superior to p16 or HPV DNA alone.

Conclusion: E6/E7 mRNA ISH should be considered the gold standard method for high risk HPV detection and integrated in the molecular staging of HPV-associated oropharyngeal squamous cell carcinoma.

OC 9-1

ORGANIZED PRIMARY HPV SCREENING IN SWEDEN. COLPOSCOPIC AND HISTOPATHOLOGIC EVALUATION OF HPV++ WOMEN AGED 56-60.

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Objectives: To evaluate the colposcopic and histopathologic findings in HPV++women 56-60 years in an organized primaryHPVscreeningprogram.

Methods: The organized screeningprogram in Stockholm county randomised 50% of all resident women 56-60 years to either primary HPVscreening with cytology triage or to primary cytology and HPVtriaging for ASCUS/LSIL. In HPV screening, HPV+/Cyt-women had a repeat HPVtest 1 year later. Attendance rates were similar with the 2 policies (HPV screen: 5 979 women and cytology screen: 6087 women). HPV+/Cyt- women at base line and HPV persistence at follow up were invited to colposcopy, performed by the same expert gynecologist.

Results: So far, 65/80 Cyt-/HPV++ women have been HPV typed. 63% (41/65) were persistent for the same type, 34% (22/65) were ++ with "other"type (persistent with type persistence unknown) and only 3% had a new type. 49% (32/65) had atrophic epithelium. 45% (29/65) a transformationzone(TZ) type 3, 25% (16/65)type 2 and only 30%(20/65) had a type 1 TZ. 43%(28/65) had a colposcopic lesion, 15%(10/65) abnormal cytology from the endocervix and 23%(15/65) CIN2+ in the cervical biopsy or conisation following the colposcopy.

Conclusions: Primary HPV screening was acceptable to the population and resulted in similar attendance rates. Colposcopic evaluation of cytologically negative HPV ++ positive women resulted (so far) in a PPV for CIN2+ in histopathology of 23% (15/65). Atrophic vaginal epithelium and TZ type 3 are challenges in the colposcopic management in this group. Cytological endocervical evaluation, blind biopsies and diagnostic conizations as well as risk-assesment are options for this group of women.

OC 9-2

A NOVEL APPROACH IN CERVICAL CANCER SCREENING

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Cervical cancer is the second most frequent cancer . Pap smear screening has led to a substantial decrease in the mortality of cervical cancer over the last 50 years. Colposcopy evaluation done for abnormal smear patients, but it is expensive and requires considerable skill. Fluorescence spectroscopy measure fluorophores which might change according to preneoplastic and neoplastic tissues.

Objective: To assess performance of fluorescence spectroscopy in the diagnosis SIL and to compare this with colposcopy and Papanicolaou smear screening.

Materials & Method: Sixty five patients attending the outpatient clinic between June2013 to May14 with discharge per vaginum, low backache, pain in the abdomen, irregular bleeding and post coital bleeding were studied. After gynecological workup Pap smear and colposcopy done and Cervical biopsy was taken from normal and abnormal areas of the cervix and fresh tissue was sent to Saveetha school of Engineering for Fluorescence spectroscopy

Results: At 380 nm excitation of the tissue, SILs can be differentiated from normal columnar epithelia and inflammation with sensitivity of 79% specificity 74%, PPV 81%, respectively. At 460 nm excitation, high grade SILs can be differentiated from low grade SILs with an average sensitivity and specificity of 82% and 78%, PPV 74% respectively similar to that of colposcopy.

Conclusion: Fluorescence spectroscopy, a noninvasive, can be used by inexperienced health care personnel. This in vitro work can be implement it for in vivo using an optical fiber probe.

OC 9-3

WHEN SHOULD ENDOCERVICAL CURETTAGE BE DONE?

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Objectives: Determine the yield of cervical intraepithelial neoplasia (CIN) 2, CIN 3, or cancer (CIN 2+) attributed to endocervical curettage (ECC).

Methods: Review of electronic medical records from colposcopy clinics.

Results: Between 3/1/1996 and 4/23/2013, 18,537 cervical colposcopies with no missing results evaluated abnormal cervical cytology and/or positive high-risk human papillomavirus tests; median age was 32 years and median number of cervical biopsies was 3. CIN 2+ was diagnosed in 15.3% (2,840/18,537). Of 2,840 colposcopies with CIN 2+, cervical biopsy and ECC showed CIN 2+ in 19.9% (566/2,840), cervical biopsy had CIN 2+ with ECC not CIN 2+ in 67.0% (1,902/2,840), ECC showed CIN 2+ with cervical biopsy not CIN 2+ in 9.7% (274/2,840), and cervical biopsy and ECC had no CIN 2+ in 3.5% (98/2,840). Yield of CIN 2+ diagnosed by ECC of CIN 2+ with cervical biopsy not CIN 2+ was 1.5% (274/18,537); for women age < 25 years, yield was 0.5% (25/5,433) which was lower than for women age 25 years and older (1.9%, 249/13,104, p<.001). Of 274 women with ECC of CIN 2+ and cervical biopsy not CIN 2+; 90.9% (249/274) were age 25 years or greater; 28.8% (79/274) were age 50 years or greater; 24.8% (68/274) had cervical cytology of Cancer, High Grade Squamous Intraepithelial Lesion, Adenocarcinoma InSitu, Atypical Glandular Cells, or Atypical Squamous Cells r/o High; 8.8% (24/274) had colposcopic impressions of CIN 2+; and 20.7% (55/274) had inadequate colposcopy.

Conclusion: ECC should be performed at colposcopy in women age 25 and older.

OC 9-4

EQE OF CERVICAL DYSPLASIA: CYTOLOGY-BIOPSY EVALUATION IS MANDATORY FOR GOOD PATIENT MANAGEMENT

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Objective: HSIL on cytology is followed by cervical biopsy. A comparison of the biopsy findings in relation to the cytology has been carried out.

Methods: a comparative retrospective study called CBC (CytoBiopticControl) has been conducted on 20 patients whom abnormal Pap smear was followed by cervical biopsy.
The study was performed by a group of cytologists and pathologists. The following CBC results were possible: confirmative (biopsy confirmed the cytology), non-confirmative (biopsy findings did not confirm the cytology report). If findings were non-confirmative, cervical cytology and biopsy were re-evaluated. If necessary, additional sections from the available biopsy material were prepared and evaluated.

Results: Among the 31 cases (20 patients), conformity was reached in 11 cases (35%) and a non-conformity in 20 cases (65%). Re-evaluation of these 20 cases lead to conformity in an additional 11 cases (35%): 2 cases (18%) after re-evaluation of the cytology, 4 cases (37%) after re-evaluation of the biopsy, 1 case (9%) after re-evaluation of both cytology and biopsy, 2 cases (18%) when deeper sections from the biopsy material were analyzed and 2 cases (18%) required a new biopsy.

Conclusion: each HSIL cytology result should be followed by a cervical biopsy revealing and confirming the dysplasia. In cases for which non-conformity was present between cytological analysis and evaluation of the biopsy material several reasons were found. In 2 out of 31 cases (6%) the non-conformity was due to inaccurately performed biopsy or sampling error by the gynecologist and in 9 out of 31 cases (29%) due to evaluation errors by the pathologist. This quality control study demonstrates that the CBC is absolutely mandatory for exact patient management as 45% of the non-conformity results could be rectified in second time.

HPV TRIAGE OF LOW GRADE ABNORMALITIES IN IMMUNISED WOMEN – INSIGHTS FROM THE SHEVA STUDY

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Background and Objectives: In Scotland, women who received immunisation as part of an initial "catch up" phase have been invited for cervical screening since 2011. The SHEVa studies are designed to garner evidence on the clinical performance of HPV tests in immunised women. Here, we present preliminary data on the effect of immunisation on the performance of three HPV assays as a triage of low-grade (LG) cytology.

Methods: LBC samples from 1000 immunised and 1000 unimmunised 20 year olds collected between 2010-12 and stored in the Scottish HPV Archive were tested using three clinically validated assays [the rT HPV Assay (Abbott), the APTIMA HPV test (Hologic) and Onclarity HPV Assay (BD)]. A total of 245 (unimmunised) and 185 (immunised) women harboured low grade abnormalities; at time abstract preparation follow-up information is available for 152 and 98 of these (average length- 460 days).

Results: All assays detected all 23 cases of CIN2+ in the unimmunised women, 2/3 assays detected the 5 cases of CIN2+ in immunised women with one assay detecting 4/5 cases – this translated into high sensitivity: 80-100%, for all assays, irrespective of immunisation status. However, the PPV for CIN2+ for the rT HPV, APTIMA and Onclarity assay was 18.1, 17.8 & 17.7 in the unimmunised women compared to 6.5, 5.3 and 6.5 for immunised women.

Conclusions: Further data associated with outstanding follow up will be presented. However, these preliminary data indicate that the PPV of HPV testing for the triage of low grade abnormalities may reduce in immunised women.

OC 9-6

SPERANZA STUDY: PRELIMINARY RESULTS OF HPV VACCINATION AFTER LOOP ELECTROSURGICAL EXCISION PROCEDURE FOR CERVICAL INTRAEPITHELIAL NEOPLASIA

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Objectives: The aim of the study is to determine if HPV-vaccination post conization can decrease the rate of cervical disease recurrence in women treated with LEEP for CIN.

Methods: All women aged less than 46 years treated for CIN in our gynecology unit were enrolled in a double arm prospective study (case – control). Case group received HPV quadrivalent vaccine post LEEP while control group was submitted to follow-up alone. Follow-up was performed every 6-months by colposcopy, and cytology in the first year after LEEP, after annually. Abnormal findings were histologically confirmed and considered as recurrence if CIN2+. Statistical analysis was performed by Pearson's chi squared test.

Results: In January 2013 Azienda USL-1 Massa Carrara has approved a clinic for HPV-vaccination. The first project of the clinic has been the SperAnZA study (Sperimentazione anti-HPV zona apuana). We present data of 144 women undergoing at least 6-month follow-up period analyzed for recurrence-rate. Women were equally assigned to the 2 groups; 7 out of 72 patients in control group developed a cervical recurrence (9.7%) while only one of the 72 vaccinated women recurred (1.3%). The rate of recurrence was significantly higher in the control group, with a $p=0.03$ by Pearson's chi squared test.

Conclusions: Our preliminary results indicate that quadrivalent HPV-vaccination after LEEP treatment for CIN may be useful in preventing recurrence of the disease. HPV vaccination could prevent subsequent new infection and invalidate reactivation mechanism, Further data and longer follow-up are necessary to confirm our preliminary results.

OC 9-7

ECO-ROCS (EVALUATION OF CLINICAL OUTCOME AFTER REDUCTION OF CONIZATION SIZE), STUDY DESIGN

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Objectives: Cervical intraepithelial neoplasia grade 3 (CIN III) is the direct precursor lesion of invasive cervical cancer. Besides prophylactic vaccination, the only curative treatment is represented by conization. In correspondance with the definition of the LLETZ operation (LLETZ=large loop excision of the transformation zone) the lesion needs to be resected including the transformation zone. It is well known from the literature that the cone size directly correlates with the risk of preterm delivery in a future pregnancy. Therefore it would be highly desirable to keep the cone dimension as small as possible by maintaining the same level of oncological safety.

Methods: Aim of this ongoing study is to analyze if the resection of the lesion only without additional excision of the transformation zone is equally effective regarding oncological outcome. Therefore we perform this prospective, patient-blinded trial randomizing women who need to undergo a LLETZ operation because of CIN III at a ratio of 1:1 either into the group with additional resection of the transformation zone or into the group with resection of the lesion only. To evaluate equal oncological outcome we perform HPV tests 6 and 12 months postoperatively. Study is conducted in thirteen German study centers including 1000 women with CIN III. The study is designed to consider the "lesion only" operation as oncologically not inferior if the rate of HPV high risk tests is not higher than 5 percent compared to the HPV high risk rate of women undergoing classical LLETZ operation.

Results: First results will be presented.

OC 9-8

INFLUENCE OF GLACIAL ACETIC ACID ON HPV DETECTION - A STUDY OF 140 CASES OF CIN2+

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Objectives: Lysis of bloody liquid based cytology samples with glacial acetic acid (GAA) can aid cytological interpretation. Evidence suggests that while GAA treatment influences the quantitative read-out of HPV assays, it does not affect qualitative detection and associated performance. However studies which have reported this have been under-represented in terms of high grade disease. Consequently, we determined the impact of GAA on HPV detection in a prospective series of LBC samples enriched for high-grade abnormalities.

Methods: 207 LBC samples with high-grade cytology and treated with GAA were collated prospectively across two Scottish laboratories. A total of 140 had underlying CIN2+ (including 88 CIN3 & 10 cancers). All samples were tested with the Hybrid Capture 2 assay (HC2, Qiagen) and the rT HPV assay (Abbott). Any sample associated with a CIN2+ that was negative by either or both assays was genotyped.

Results: Sensitivity of the rT HPV for CIN2+ and CIN3+ was 92.8% (87.2, 96.5) and 94.3 (87.2, 98.1) respectively. Sensitivity of the HC2 for CIN2+ and CIN3+ was 97.2 (92.8, 99.2) and 96.6 (90.3, 99.2) respectively. "Missed" cases of CIN2+ were largely attributable to types outside the explicit analytical range of either assay.

Conclusions:. Although we do not have an untreated "comparator", the sensitivities reported above are comparable to published sensitivities in similar disease-enriched populations. The above data indicate that, in relation to the above assays, GAA treatment may have little impact on the detection of CIN2+.

OC 9-9

DYNAMIC SPECTRAL IMAGING FOR POST-TREATMENT TRIAGE

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Background: NHSCSP (National Health Service Cervical Screening Programme) recently implemented test-of-cure for patients treated for cervical intraepithelial neoplasia (CIN).

Objective: To assess the accuracy of colposcopy with and without the DySISmap in detecting CIN2+ for patients with post-treatment negative cytology and high-risk HPV positive.

Methods: This is an observational ongoing study (Mar-2013 onwards). Patients are examined using the DySIS digital colposcope. Initial colposcopic impression and biopsy sites are recorded before and after the DySISmap. Outcomes include sensitivity, specificity and negative predictive value (NPV) for CIN2+. The accuracy of the DySISmap in detecting CIN1 lesions that will progress will also be assessed once adequate numbers of patients with follow up cytology (1 year) is available.

Results: The study currently includes 97 women. Histology was available for 74, and these are analyzed. Overall, 5(6.7%) women had high-grade biopsy results. Of those, 1 wouldn't have been biopsied without the DySISmap, in 3 DySISmap indicated high-grade but the colposcopist would have biopsied the same area (regarded as low-grade lesion) and in one the DySISmap was normal. Colposcopy was normal/low-grade in all 5. Sensitivity of standard colposcopy for CIN2+ was 0% improving to 80% with the incorporation of the DySISmap. Using directed biopsy results NPV of colposcopy and DySISmap for CIN2+ was 98%. Sufficient numbers of patients with 1 year follow up, in order to assess outcomes for those with CIN1 biopsy results, are expected at time of presentation.

Conclusions: Incorporating the DySISmap as an adjunct to colposcopy might improve colposcopy accuracy for this population.

OC 9-10

REAL TIME IN VIVO MICROSCOPIC IMAGING OF THE CERVIX USING CONFOCAL LASER ENDOMICROSCOPY: PRELIMINARY OBSERVATIONS AND FEASIBILITY STUDY.

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Background: Confocal laser endomicroscopy enables in vivo, real time, imaging of living tissues with a micron scale resolution through a fiber optic probe.

Objectives: This study evaluates the technical feasibility and safety of CLE on exocervix and junctional area. The study also aims at creating a first cartographic atlas of normal and dysplastic squamous and columnar cervical epithelium.

Methods: In vivo CLE was performed on 9 patients scheduled for a cervical Loop Electric Excision Procedure (LEEP) for High Grade Cervical Intraepithelial Lesions (H-SIL). The CLE images were compared with standard hematoxylin and eosin analysis of LEEP specimens. Histopathological diagnosis on the surgical specimen was established as per standard of care. CLE images were then reviewed by pathologists to point out specific histopathological features.

Results: pCLE of exocervix and transformation zone was successfully performed on 7 out of 9 patients. Uninterpretable images were obtained the 2 other cases, one using the AlveoFlex and one using the GastroFlex UHD after the application of acetic acid 2%. 82.47% of the sequences recorded with the GastroFlex were suitable for interpretation. No adverse event nor complications occurred

C**onclusions:** CLE enables proper in vivo imaging of healthy and dysplastic cervical tissue. Images correlate well with histopathological features established through traditional histology. CLE could be of interest for the assessment and the treatment of cervical lesions by enabling fine margin delineation and extensive follow-up examination.

OC 9-11

OVERTREATMENT IN SEE-AND-TREAT MANAGEMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA; A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objective: To determine overtreatment rates in see-and-treat management of women referred for colposcopic evaluation because of suspected cervical intraepithelial neoplasia (CIN) grade 1-3, in order to define circumstances that justify, or indicate to avoid see-and-treat management.

Data Sources: MEDLINE, EMBASE, and the Cochrane Library were searched from inception up to 12 May 2014. Additional sources included references of retrieved papers and concept proceedings.

Methods of Study Selection: Studies were included that performed see-and-treat management in women with suspected CIN with a registered cervical smear result, colposcopic impression and histology result. The methodological quality was assessed with the Ottawa scales. We used the inverse variance method for pooling incidences, and a random effects model was used to account for heterogeneity between studies. Overtreatment was defined as treatment in patients with no CIN or CIN1.

Tabulation, Integration, and Results: Thirteen studies (n= 4,611) were included. The overall overtreatment rate in women with a high-grade cervical smear and a high-grade colposcopic impression was 11.6% (range 0-29.4%). The overtreatment rate in women with a high-grade cervical smear and low-grade colposcopic impression was 29.3%, and in case of a low-grade smear and high-grade colposcopic impression it was 46.4%. In women with a low-grade smear and low-grade colposcopic impression, the overtreatment rate was 72.9%.

Conclusion: The pooled overtreatment rate in women with a high-grade smear and high-grade colposcopic impression is at least equivalent to the two-step procedure, which justifies see-and-treat management in this subgroup of women.

OC 10-1

TECHNICAL EVALUATION OF THE XPERT® HPV ASSAY IN A GENERAL SCREENING POPULATION - AN ASSESSMENT OF THE CLINICAL PERFORMANCE

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Objectives: The Cepheid Xpert HPV Assay is a qualitative real-time PCR assay for the detection of 14 high-risk HPV types. A sample collected in PreservCyt is pipetted into a single use cartridge and processed by the GeneXpert® System. The result is available in 1.5 hours. The study evaluated the Xpert® HPV Assay in a screening population by comparing the results with cytology, histology and two established HPV DNA tests - Roche Cobas Test (primary comparator) and Qiagen hc2 Test (secondary comparator).

Methods : A prospective study using residual cytology samples for women aged 20-60 years attending routine screening in London, Bristol and Edinburgh. Residual specimens (minimum of 8mls after processing for cytology) were aliquoted in random order 1:1 for Roche Cobas and Xpert HPV assay. Qiagen hc2 was always third.

Results : Of the 3414 cases included in the analyses, 439 had referral cytology of borderline or worse. Xpert® Assay and hc2 were positive (to any high risk HPV type) in all cases where referral cytology was moderate dyskaryosis or higher (N=64) and Roche Cobas was negative in two cases. Histology is currently available for 107 participants (London only). 16 reported CIN2 or worse. Xpert® HPV Assay and hc2 were positive in all cases whereas Roche Cobas was negative for one case of CIN3.

Conclusions : The performance of the Xpert® HPV Assay in a general screening population is comparable to the established HPV tests and offers flexibility with non-batching and rapid turnaround time of individual samples.

OC 10-2

HPV TYPING FOR THE TRIAGE OF HPV-POSITIVE ASC-US WOMEN MAY REDUCE COSTS DUE TO AVOIDABLE COLPOSCOPIES

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Objective: High-risk HPV (HR-HPV) testing is commonly recommended as a triage strategy for ASC-US cytology. This study evaluated the potential impact of using extended genotyping as an alternate triage strategy.

Methods: The BD Onclarity™ HPV assay was used to genotype HC2 (Qiagen) positive ASC-US cytology samples from the PaP Cohort Study at Kaiser Permanente Northern California. Half of 640 CIN3+, 1/2 of 1,118 CIN2, and 1/10th of 12,020 <CIN2 cytology samples were genotyped to determine 3-year cumulative risks for CIN3+. Using genotype-specific risk and prevalence data, we estimated the number of colposcopies that could be avoided with extended genotyping, and quantified the cost savings using cost data from the Medicare 2014 Physician Reimbursement Fee Schedule. All assumptions and inputs will be detailed in the poster.

Results: Among HR-HPV genotypes, 3-year cumulative risk of CIN3+ ranged from 1.7% for HPV 39/68/35 to 21.3% for HPV 16, highlighting the risk variation among HPV genotypes. Rather than referring all ASC-US HPV+ women to colposcopy, we examined a strategy of referring women with HPV51, HPV59/56/66, HPV39/68/35 and those who were HPV- to 1-year follow-up. Preliminary analysis found this strategy could avoid approximately 250,000 colposcopies annually, saving nearly $48 million in healthcare spending. Results from alternate strategies will also be presented

Conclusions: Because ASC-US is so common and so often benign, it's worth exploring strategies that call for less invasive follow-up. Among certain HR-HPV types, the risk of CIN3+ might be low enough to avoid colposcopy, and help to reduce costs to the healthcare system.

Disclaimer: The views presented in this abstract do not represent those of the National Cancer Institute (NCI) or Kaiser Permanente Northern California (KPNC)

OC 10-3

DETECTION OF HIGH-RISK HUMAN PAPILLOMAVIRUS E7 PROTEINS

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on behalf of the PIPAVIR consortium (www.pipavir.com)

Objective: Persistent infection with high-risk human papillomavirus (hrHPV) types is a major prerequisite for development of precancerous lesions and cervical cancer. Upon integration of the virus into the host genome, Deregulation and overexpression of viral proteins E6 and E7 lead to loss of cell cycle control and, ultimately, neoplastic transformation.

Current cervical cancer screening methods rely mainly on cytological analyses (Pap smear) or detection of HPV nucleic acids. However, these tools fall short of discriminating between transient infections which can spontaneously regress and persistent infections, which have a greater chance to progress to high-grade squamous intraepithelial lesions.

A more effective and reliable screening approach may involve exploitation of the oncoproteins E6 and E7 for specific detection of cervical cancer and precancerous lesions. Development and validation of a new diagnostic test for progressive infectious diseases that allows detection, by ELISA, of HPV E7 proteins in cervical smears, could be an easy and beneficial solution for better diagnosis of cervical cancer and precancerous stages.

Results: After accurate characterization of the RabMabs, specific combinations of the antibodies were chosen to enable the set-up of the hrE7 ELISA system. The assay allows detection of the three hrHPV types 16, 18 and 45 with highest carcinogenicity. For validation purposes, the hrE7 ELISA system was validated with (i) recombinant E7 proteins as well as with (ii) cell lysates of HPV positive cell lines stored in ThinPrep buffer. The proof of concept was shown with HPV DNA negative and HPV16 DNA positive, clinical abnormal samples.

OC 10-4

CLINICAL VALIDATION OF E1-BASED "HPV EASY DNA ARRAY" GENOTYPING TEST DEVELOPED BY AID/GENID

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Objectives: Clinical validation of HPV Easy DNA Array, an E1-based genotyping test for identification of 18 high-risk (16,18,26,31,33,35,39,45,51,52,53,56,58,59,66,68,73,82) and 11 low-risk HPV types (6,11,40,42,44,54,67,69,70,85,97). It includes the GAP-DH control for verification of adequate DNA content.

Methods: Multiplex PCR is used to amplify E1 gene sequences. The PCR product is detected and genotyped by reverse hybridization to immobilized DNA probes spotted as tripletts together in single 96 well-plate wells and read by an AID ELISPOT reader. Clinical performance was assessed by using 563 cervical scrapings stored in PreserveCyte. Qiagen DNA extraction was used for DNA. Accuracy of the test was established by comparison with the reference test GP5+/GP6+ PCR with MPG-Luminex read out.

Results: We found complete match to the reference test in 30.6% (172/563), ≥ 1 HPV type match in 33.4% (188/563), and both tests HPV negative in 26.6% (150/563), with concordance of 90.6%. In 53/563 samples we found discrepant results: 5.7% (32/563) were MPG positive/HPV Easy negative, 2.7% (15/563) were MPG negative/HPV Easy positive and 1.1% (6/563) had discrepant HPV types. The sensitivity for HPV detection was 92% and specificity 88%, with positive predictive value of 95% and negative predictive value of 82%. The sensitivity for detection of high grade lesions (CIN2 or higher) was 97% and specificity was 67%.

Conclusion: HPV Easy DNA Array showed good concordance with MPG-Luminex Assay. It performs very well with regard to identifying high grade lesions. Due to simplicity and high throughput potential this method may be suitable for genotyping in HPV primary screening.

OC 10-5

CROSS-REACTIVITY TO UNTARGETED, LOW-RISK HPV GENOTYPES BY COBAS, APTIMA AND HC2

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3 University of Copenhagen, Department of Public Health, Copenhagen, Denmark

Objectives: Cervical cancer screening is increasingly changing from cytology-based to HPV-based testing. However, HPV screening displays lower specificity than cytology due to false-positive test results partly caused by cross-reactivity to low-risk genotypes. Cross-reactivity is costly as it may cause unnecessary follow up and anxiety in women. We studied cross-reactivity in three widely used clinical HPV assays with a full genotyping assay as a reference.

Methods: Within the Danish Horizon study, cross-reactivity to low-risk genotypes in consecutive routinely evaluated samples from 5,022 women was examined for HC2 (Qiagen), cobas (Roche), and APTIMA (Hologic-GenProbe) using CLART HPV2 (Genomica) as the reference assay. Complete histology follow-up was retrieved after 2.5 years.

Results: In total, 109 (2%), 62 (1%), and 35 (1%) of all included samples had a positive test result on HC2, cobas and APTIMA, respectively, where no high-risk genotype could be detected. When only samples with a positive test result on a particular assay were used as the denominator, cross-reactivity represented 11%, 5%, and 4%, respectively. Cross-reactivity was most common in young women, in women with abnormal cytology, and in follow-up samples. The most frequent cross-reacting genotypes were HPV70, HPV53, HPV82, HPV61, and HPV66 (the latter for HC2 only). Cross-reactivity was associated with low viral input. In total, 6 cross-reacting samples were associated with ≥ CIN2, but none from primary screening at age 30-65 years.

Conclusions: All three assays showed cross-reactivity to low-risk genotypes. Yet, cross-reactivity was not common and did not tend to be associated with ≥ CIN2 in primary screening.

OC 10-6

HUMAN PAPILLOMAVIRUS INFECTION CAUSED BY HPV TYPES 52 AND 58 AND ITS ROLE IN THE DEVELOPMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA

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Objective. The study of the prevalence and the role of different types of HPV in the development of CIN and cervical cancer, including HPV types 52 and 58.

Materials and Methods. Examined 548 women with abnormal cervical aged 18 to 60 years. Performed clinical-anamnestic, gynecology, extended colposcopy, molecular biological, morphological methods. Molecular biological techniques included a multiplex PCR detection results in real-time to determine the HPV type 21 (6,11,16,18,26,31,33,35,39,44 (55), 45, 51,52, 53,56,58,59,66,68,73,82) with the definition of viral load. Study group comprised 383 HPV - positive women.

Results. Frequent HPV types were 16, 58, 31, 52, 33, 44 (55). HPV types 52 and 58 were more prevalent in women under 35 years of age (88%). Cytology revealed: NILM - 169 (44.1%), ASCUS - 16 (4.2%), LSIL - 82 (21.4%), HSIL - 99 (25.8%), cervical cancer - 17 (4.4%). When NILM HPV types 52 and 58 occurred in 22 (13%) patients with ASCUS - in 1 (6.2%) with LSIL - in 20 (24.4%), and HSIL - in 25 (25.2%), and cervical cancer - the 2 (11.7%). Patients with HSIL, in the presence of the transformation zone with mild and severe changes, biopsy of the cervix. CIN was diagnosed in 145 of HPV - positive women: CIN I - 46 (31.7%) patients, of whom 11 (23.9%) identified HPV types 52 and 58; CIN II - 48 (33.1%), 12 (25%) identified HPV types 52 and 58; CIN III - in 51 (35.2%) 13 (25.5%) of them were found to HPV types 52 and 58.

Conclusion. HPV types 52 and 58 were more prevalent compared to previously submitted data, were the cause of the abnormal cytology in 22.4% of patients. Comprehensive analysis of the results of the extended colposcopy and histology of biopsy specimens of the cervix show a significant role of HPV types 52 and 58 in the development of CIN varying severity.

OC 10-7

DOES HUMAN GENOMIC DNA CAUSE FALSE POSITIVE HPV TEST RESULTS?

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Objectives: Hybrid Capture 2 (HC2) High-Risk HPV DNA Test (Qiagen), an in vitro nucleic acid hybridization assay with signal amplification and chemiluminescence for the qualitative detection of 13 types of HPV is routinely used to screen for cervical cancer. The Aim of this study is to examine whether human genomic DNA with HPV homologous sequences may anneal to HC2 RNA probes to produce false positive results.

Methods: HC2 positive and negative samples were PCR amplified using GP5+/6+ and MY09/11 primers from the L1 segment of the HPV viral genome. PCR amplicons were separated by gel electrophoresis, DNA excised and purified from agarose gel, and analyzed by Sanger sequencing and BLAST search.
Results: There were HC2 positive cases where although the ends of the PCR amplicon sequences matched for HPV, the internal sequence was not HPV viral DNA but Homo Sapiens genomic DNA sequences.

Conclusions: The results support the hypothesis that endogenous human genomic DNA with HPV homologous sequences can produce false positive HC2 results using cervical specimens. False positive HC2 results have been described previously with possible causes cited including contamination, cross-hybridization with low risk HPV strains, and a phenomena in which the reading of high viral load result affect neighboring samples during the HC2 process. Although as other FDA approved high-risk HPV assays, HC2 is a screening (not a diagnostic) test, its results can have profound implications on clinical care.

OC 10-8

POST-CONUS SAMPLES AND HPV TESTING WITH HC2 AND COBAS USING SUREPATH: RESULTS FROM TWO DANISH LABORATORIES

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Objectives: After conization, the risk of cervical cancer remains relatively high. In Denmark, women are followed after 6 months with cytology and HPV testing. In these women, we compared cobas (Roche) to HC2 (Qiagen), the most validated HPV test up to date. Cobas has internal controls and separate HPV 16 and HPV 18 typing, which HC2 does not.

Methods: Consecutive routine samples were collected from two Danish laboratories (Copenhagen University Hospitals in Herlev (n=234) and Hvidovre (n=177)). Testing on HC2 and cobas was undertaken according to the manufacturers' recommendations. Clinical outcomes were retrieved from the Danish Pathology Data Bank. We calculated positive agreement as a conditional probability that both assays returned a positive result if at least one did, κ-coefficients, proportions of ≥ CIN2 with a positive result on an assay (sensitivity), and of <CIN2 with a negative result (specificity).

Results: In Herlev, HC2 had a positive result in 58/234 (25%) samples, and cobas in 65/234 (28%). Positive agreement was 62% (95% CI: 0.50-0.73), and κ -coefficient was 0.68 (95% CI: 0.57-0.79). In Hvidovre, HC2 had a positive result in 56/177 (32%) samples, and cobas in 66/177 (37%). Positive agreement was a 69% (95% CI: 0.57-0.80), and κ -coefficient 0.73 (95% CI: 0.62-0.83). From 17 ≥ CIN2, HC2 detected 16 (94%), and cobas 17 (100%). HC2 returned a negative result in 233/325 (72%) <CIN2, and cobas in 223/325 (69%

Conclusions: Our study using SurePath samples suggested that in follow-up after conization, HC2 and cobas can substitute each other with similar clinical outcomes.

OC 10-9

VIRTUAL SCREENING OF HUMAN PAPILLOMAVIRUS ONCOPROTEIN E7

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Objectives: The objective of this work was to use "in silico" techniques, such as virtual screening assays and toxicity prediction, to search for inhibitors to human papillomavirus (HPV) E7 oncoprotein.

Methods: Four different types of HPV E7 oncoproteins (1A, 11, 16 and 18), previously modeled by Nicolau Junior & Giuliatti 20131, were submitted to virtual screening assays by using GOLD software and Chembridge molecular database. The highest scoring results were then visually analyzed, and their toxicity was predicted by Derek software.

Results: The 100 best scoring molecules were visually analyzed due to their molecular interactions with the active site of the E7 proteins. The most prone molecules to strongly bind to the E7 site were analyzed due to their theoretical toxicity to human beings, leading to compounds with good potential to become leads.

Conclusion: In silico search for potential E7 inhibitors has been shown to be a promising strategy towards the treatment of HPV infections and prevention of human cervical cancer.

"1 Nicolau N Jr, Giuliatti S. Modeling and molecular dynamics of the intrinsically disordered e7 proteins from high- and low-risk types of human papillomavirus.J Mol Model. 2013 Sep;19(9):4025-37. Epub 2013 Jul 18."

OC 11-1

HPV GENOTYPIC DISTRIBUTION IN PATIENTS WITH CERVICAL CANCER IN THAILAND

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Background: As Thailand's considering integrating HPV-16/18 vaccine into the National Immunization Program, this study aimed to determine the require data on HPV prevalence and genotypic distribution in Thai invasive cervical cancer patients.

Methods: The study was conducted during June 25, 2012 – September 11, 2014 at Chulabhorn Hospital, Bangkok, Thailand, 160 consecutively collected specimens of BD Surepath liquid-based cytology consecutively collected from pelvic examination for clinical staging and analyzed by linear array HPV genotyping tests (Roche, USA). Fourteen were excluded.

Results: Of 146 patients, mean age 55.0 years and range 26-78 years, HPV infection was detected in 140(95.9%), including 123(87.9%) single infections and 17(12.1%) multiple infections. HPV16 and HPV18 were the most common subtypes in 67(45.9%) and 25(17.1%), respectively, with HPV58, HPV52, HPV33, HPV45, HPV56, HPV59 and HPV31 found in 13(8.9%), 12(8.2%), 6(4.1%), 4(2.7%), 3(2.1%), 3(2.1%) and 2(1.4%), subsequently.

Conclusions: Differing slightly from the worldwide data, this study revealed lower prevalence of HPV16/18 and higher frequencies of HPV58 and HPV52. Currently available HPV vaccines against HPV16/18 could potentially prevent 63.0 % of cases. The next generation of 9-valent HPV vaccine (6/11/16/18/31/33/45/52/58) may be thus required for most Thai patients (88.4%).

OC 11-2

HLA-G POLYMORPHISM AND HPV TRANSMISSION AMONG HETEROSEXUAL COUPLES IN THE HITCH STUDY

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Objectives: Human leukocyte antigen (HLA)-G polymorphism influences innate and adaptive immune responses. Among heterosexual couples in the HITCH cohort study we examined the association between HLA-G alleles and genital human papillomavirus (HPV) infection in women and their male partners independently. We also analyzed whether allele sharing in a couple was associated with the likelihood that the partners had infections with the same HPV type, i.e., if allele concordance predicted transmission of HPV infection.

Methods: We tested genital samples from 274 couples for 36 HPV genotypes by PCR. HLA-G alleles were typed using direct DNA sequencing.

Results: The most common alleles among couples were: G*01:01:01 (95.6%), G*01:01:02 (60.1%), G*01:04:01 (33.9%), G*01:06 (21.4%), G*01:01:03 (19.6%), and G*01:03 (19.2%). The G*14bp deletion occurred in 86.1% of the couples. In gender specific analyses, only G*01:03 was associated significantly with risk (negatively) (odds ratio [OR] = 0.36, 95%CI: 0.17-0.76), among women exclusively. In the allele-sharing and HPV-concordance analysis G*01:03 was not a significant predictor of HPV positivity in either or both partners, nor was it a predictor that a couple shared a type-specific infection. The number of alleles exhibiting significant associations at the 5% level did not exceed what was expected under the null hypothesis taking into account the high number of associations examined. HPV-clade specific analyses also did not reveal any pattern of consistency concerning allele presence or sharing and risk, whether individually or in a couple.

Conclusion: We found no evidence for a role for HLA-G in acquisition and transmission of HPV infection.

OC 11-3

DO HPV 16 AND 18 PREDICT A HIGHER RISK OF CIN2+ THAN OTHER HIGH-RISK HPV GENOTYPES IN TRIAGE?

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Objectives: To estimate the positive predictive value (PPV) for CIN2+ of HPV DNA 16 and 18 versus other high-risk (HR) types, in single and multiple infections, in delayed triage among women aged 25-69 with ASCUS and LSIL cytology.

Methods: We included 6058 women with primary screen-detected ASCUS or LSIL cytology with a follow-up HPV test; Hybrid Capture II (Qiagen), between July 2005 and June 2010. The HPV positive cases were genotyped with in-house nmPCR(1), differentiating between the 13 high-risk HPV types covered by HCII. All women were followed-up for histologically confirmed CIN2+ within three years of index HPV test by linkage to the screening databases at the Cancer Registry of Norway.

Results: HC2 was positive in 46% of the women (2756/6058). HPV genotyping revealed single infection in 57% (1578/2756) and multiple infections with two or more genotypes in 32% of the cases (884/2756). In 11% of the cases (294/2756) we were not able to detect any genotype (HPV X). CIN2+ was confirmed by histology in 1191/2756 HPV test positive women (43%) and in 71/3303 HPV test negative women (2.1%). For single infection by HPV 16, we found the highest the PPV (61%) for detecting CIN2+, followed by HPV33 (53%), HPV35 (46%), HPV58 (41%), HPV31 (40%) and HPV18 (35%). Minor differences were detected for PPV in multiple infections which will be presented.

Conclusion: In this observational study we have shown that HPV16 and 33 predicts much higher PPV for CIN2+ compared to HPV18, both in single and multiple infections.

Reference:
1. Sotlar K et al. Detection and typing of human papillomavirus by e6 nested multiplex PCR. J.Clin.Microbiol. 2004;42:3176-84.

OC 11-4

"SAFETY IN NUMBERS" – HPV GENOTYPE-SPECIFIC VS. POOLED HIGH-RISK APPROACHES TO CIN3+ RISK STRATIFICATION

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Background: The widespread adoption of the Hybrid Capture 2 test (QIAGEN), which uses a pooled cocktail of probes to detect all high-risk HPV types, has led other investigators to continue to leverage this pooled assay design approach. It is now well established that genotyping HPV 16 and 18 provides improved risk stratification and 16/18 triage is an integral part of US screening guidelines. Nevertheless, all subsequent FDA-cleared assay designs utilize an all high-risk or 12-other pool approach.

Results: We present evidence that pooling of the 12 other high-risk types masks the real risk for CIN3+ disease in the same way that the Hybrid Capture 2 design underestimates the individual risk posed by HPV 16 and 18. This is a direct consequence of the fact that the 14 high-risk HPV types have different abilities to infect, persist and cause disease. This is evident from several published longitudinal genotyping studies and has recently been confirmed using the extended genotyping BD Onclarity™ HPV Assay.

Conclusions: Pooling of 12 high-risk types runs countercurrent to the recent recommendation to implement "equal management of equal risks" in making colposcopy referral decisions (1). If a pooled approach is used, the underlying individual HPV genotype risk may be masked by the pooled type result. We discuss the implications for national screening programs and suggest that this be part of the ongoing debate on future primary screening guidelines. Failure to learn from the HPV 16/18 "history lesson" may have important implications for informed management of HPV infected women.

(1) Katki HA, Schiffman M, Castle PE, Fetterman B, Poitras NE, et al. 2013. J. Low. Genit. Tract Dis. 17:S28-35

OC 11-6

SEXUALLY TRANSMITTED INFECTIONS AMONG HIV POSITIVE AND HPV HIGH-RISK PATIENTS IN NORTH TONGU DISTRICT, GHANA – AN ACCESSING* PILOT TRIAL

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**ACCESSING (Adequate Cervical cancer Capacity building, Education and Screening by new Scientific INstruments in Ghana): GIZ/ESTHER funded trial*

Objective: To determine the prevalence of 18 STIs among 100 HIV+ and 150 HPV high-risk women as part of the ACCESSING pilot study, taking place in the North Tongu District in Ghana.

Methods: Extracted DNA from vaginal lavage samples, taken with Delphi Screener, were tested with multiplex PCR followed by Luminex bead-based hybridization. This assay detects 18 sexually transmitted infections (STIP assay, Schmitt et al., 2014, J Infection 69:123). 250 Patients, aged 18 to 60 years, were selected for this pilot study with 100 HIV+patients 150 patients with a history of high-risk HPV positivity or cervical dysplasia (HPV-hr).

Results: Prevalence found for Chlamydia trachomatis was 0% and 4.3% among the HIV+ and HPV-hr patients, respectively. 2.1% and 0.7% were tested positive for Neisseria gonorrhoeae and 0% in both groups for Treponema pallidum. Prevalence found for Trichomonas vaginalis was 2.1% and 2.9%, for Herpes simplex type-2 8.3% and 3.6%. For Candidosis prevalence was 29.2% and 25.9% and for strong/very strong bacterial vaginosis 43.8% and 30.2%..

Discussion: For most STI the prevalence found among HIV+ patients was higher compared to HPV-hr patients, except Chlamydia trachomatis. Overall, the prevalence found for Chlamydia trachomatis among HIV+, Treponema pallidum and Trichomonas vaginalis in both groups was lower than stated in the 2005 WHO estimates for the African region among women 15 to 49 years old. Therefore, prevalence in our pilot study population seems lower compared to the WHO African region. Full epidemiological data of North Tongu District will be analyzed during the main ACCESSING study.

OC 11-7

PERSISTENCE OF HIGH RISK HPV INFECTIONS AMONG WOMEN IN THE NORTH TONGU DISTRICT OF GHANA - PARTICIPATING IN THE ACCESSING* TRIAL

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**ACCESSING (Adequate Cervical cancer Capacity building, Education and Screening by new Scientific INstruments in Ghana): GIZ/ESTHER funded trial*

Background: About 99.7% of cervical cancers are caused by persistent infection with high risk Human Papillomavirus genotypes (HR-HPV). However, data on persistence of HR-HPV is lacking for Ghana and most Sub-Sahara African countries.
Objectives: To determine the persistence of HR-HPV infections among women in the North Tongu District, Ghana.
Methods: As part of a cervical cancer study in 2010/2011, 500 patients were genotyped for HPV using nested multiplex PCR (Sotlar et al. 2004) from swab samples at University of Ghana School of Allied Health Sciences, Accra. A total of 104 women who tested positive for HR-HPV and remained untreated, were followed up in the current ACCESSING pilot study and re-tested for HPV. HPV genotyping in 2014 was done on cytobrush samples by GP5+/6+ PCR followed by Luminex-MPG readout at Charité Universitätsmedizin Berlin. Those who tested positive for HR-HPV were recalled for colposcopy and treatment.
Results: Out of 104 women who were identified as HR-HPV+ in 2010/2011, 71% had no high risk HPV infection after approximately 4 years, 7% had 1+ persistent HR-HPV type and 21% had cleared but acquired new HPV infections. Persistent HPV types were HPV 16, 18, 35, 39, 51, 52, 58, and 68. Complete clearance of HPV decreased with age, and older women acquired more new infections.
Discussion: This study represents rare longitudinal data on HPV infection in Ghana. The clearance rate observed does not vary greatly from other study populations. Further analysis by colposcopy will give insight into possible disease progression of the persistent HPV infections.

OC 11-8

PREVALENCE OF RISK FACTORS ASSOCIATED WITH HPV AND HIV POSITIVITY AND CERVICAL CANCER AMONG CAMEROONIAN WOMEN.

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Objective: To determine demographic and lifestyle factors associated with HPV and HIV prevalence and the presence of cervical precancerous lesions and cancer (CIN2+) in a community based HPV self-sampling.

Method: We report data from 838 women aged between 25-65 years, recruited in two sequential cervical cancer screening campaigns that took place in Cameroon. Demographic and historical information were obtained from all participants and specimens were self-collected for HPV testing (cobas®). HPV positive women were reexamined and underwent biopsy and endocervical curettage. Associations were determined using logistic regression.

Results: The overall HPV prevalence was 39.0% and the HIV self-reported prevalence was 9.2%. 18 CIN2+ lesions were found among the 194 women who underwent biopsy. Housewives had higher risk of being HPV positive (OR=1.60; 95%CI: 1.12-2.30; p=0.010). HIV co-infection (adjusted-OR (aOR)=3.44; 95%CI: 1.91-6.20; p<0.001) and hormonal contraception (aOR=1.97; 95%CI: 1.21-3.17; p=0.007) were associated with higher risk of HPV infection. Women with CIN2+ had higher probability to be infected with multiple HPV genotypes (aOR=7.23; 95%CI: 1.55-33.66; p=0.012). Housewives (aOR=4.72; 95%CI: 2.10-10.61; p<0.001) had higher HIV prevalence, as women having multiple sexual partners (aOR=10.29; 95%CI: 2.34-45.29; p=0.002). HPV positive women who wore condoms during sexual intercourse were at lower risk of CIN2+ (aOR=0.15; 95%CI: 0.03-0.82; p=0.029). HPV 16/18 positive women had 4.65-fold increased risk to develop CIN2+ (95%CI: 1.35-16.01; p=0.015).

Conclusion: Young single women and housewives are at higher risk of HPV and HIV infection and subsequently to develop cervical cancer. Condom seems to prevent cervical cancer in HPV positive women, although it doesn't protect against HPV infection. Screening strategies should target women at higher risk.

OC 11-9

THE EFFECT OF HIV INFECTION ON PENILE HIGH-RISK HPV INCIDENCE AND CLEARANCE AMONG MSM

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Objectives: Around 30% of penile cancers are caused by high-risk HPV (hrHPV) infections. Understanding the natural history of penile hrHPV is relevant for pathogenesis of penile cancer and to better understand penile-anal hrHPV transmission. Therefore, we aimed to compare the incidence and clearance rates of penile hrHPV infection between HIV-infected and HIV-negative MSM.

Methods: MSM aged ≥ 18 years were recruited in Amsterdam, the Netherlands, and followed-up semi-annually for 24 months. At each visit, participants completed risk-factor questionnaires. Penile-shaft self-samples were tested for HPV DNA and genotyped using the SPF_{10}-PCR DEIA/$LiPA_{25}$ system; HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 were classified as hrHPV. Effects on incidence and clearance rates were quantified via Poisson regression, using generalized estimating equations to account for multiple hrHPV types.

Results: 750 MSM with a median age of 40 years (IQR 35-48) were included in the analyses, of whom 302 (40%) were HIV-infected. The incidence rate of penile hrHPV was borderline significantly higher in HIV-infected compared to HIV-negative MSM (adjusted incidence rate ratio 1.45; 95%CI 1.00-2.11), whereas the clearance rate was non-significantly higher (adjusted clearance rate ratio 1.27; 95%CI 0.95-1.70). HrHPV incidence or clearance among HIV-infected MSM did not differ significantly by level of nadir CD4 cell count.

Conclusions: Increased penile hrHPV incidence rates and similar hrHPV clearance rates were found in HIV-infected compared to HIV-negative MSM, after adjusting for reported sexual behavior. Our findings suggest an independent effect of HIV infection on incidence of penile hrHPV infections.

OC 11-10

HIGH-RISK TYPES OF THE HUMAN PAPILLOMAVIRUS IN WOMEN DIAGNOSED WITH A PRECANCEROUS LESION

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Objectives: To assess high-risk types of the human papillomavirus (HPV) in women diagnosed with a precancerous lesion. To analyze high-risk types of HPV and their role in the development of cervical intraepithelial neoplasia (CIN).

Methods and Results: One hundred fifty seven patients were analyzed based on molecular tests and histopathological data. The frequency of HPV DNA type 16 and twelve high-risk oncogenic types, referred to collectively as human papillomavirus – high-risk (HPV-HR), in patients diagnosed with precancerous lesions suitable for treatment, was 54.8% and 53.5%, respectively. The difference between the HPV DNA type 16 and HPV-HR types is not statistically significant.

Conclusions: High-risk HPV infections are closely linked to the development of precancerous cervical lesions, and subsequently cervical cancer. This study shows that the incidence of type 16 of HPV is similar to the incidence of either one or more of the HPV-HR types: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, in patients diagnosed with cervical intraepithelial neoplasia suitable for treatment. Future studies could include the identification of specific HPV types of HPV-HR.

OC 11-11

EPIDEMIOLOGICAL STUDY OF HIGH-RISK HPV IN MIDI-PYRENEES (FRANCE) WITH ABBOTT HIGH-RISK HPV REALTIME PCR IN 2013

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Objectives: This work aims to obtain the second epidemiological data on the distribution of high-risk HPV in Midi-Pyrenees (France) after a first study in 2011.

Methods: Over a period of 12 months in 2013, 1476 patients were studied for high-risk HPV and positive samples were genotyped with Abbott High-Risk HPV Real-time PCR on an automated platform Abbott M2000.

Results: 492 samples were detected positive for HPV HR (33.3%) and 984 samples were negative (66.7%). The distribution of genotypes is as follows: HPV 16 in 25.2% and HPV 18 in 7.3% and others HPV HR (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68)in 73.6%. The distribution of the prevalence of HPV still depends of the matter of the prescription. In the 1104 samples of ASC-US women, 39.6% of the samples were positive. In the 304 women included for "screening" or "systematic", only 9.5% of the samples were positive.

Conclusions: HPV 16 and HPV 18 are still detected in less than 40 % of the positive samples. The others HPV HR group are mainly detected on more than 70% of positive samples.
The ASC-US patients have still a prevalence of HPV HR significantly higher with over 30% of samples detected positive while patients performing the test for "screening" have a prevalence of less than 10% of HPV HR. This study confirmed the 2011 data, the base point for following the evolution of HPV genotypes in Midi-Pyrenees with the advent of vaccination, which target genotypes 16 and 18.

OC 11-12

HUMAN PAPILLOMAVIRUS AND CHLAMYDIA TRACHOMATIS CO-INFECTION AND THE SEVERITY OF CERVICAL NEOPLASIA

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Objective: To correlate positivity for *Chlamydia trachomatis* (C. trachomatis) according to serology and polymerase chain reaction (PCR) assay with positivity for human papillomavirus (HPV) and to evaluate the relationship of these findings with the severity of cervical neoplasia in women with cytological abnormalities.
Methods: Between February 2007 and March 2009, 136 women were referred to a colposcopy clinic in Goiania, Brazil for cervical abnormalities. HPV-DNA was detected by PCR using PGMY09/11 primers and genotyping was performed by reverse line-blot hybridization assay. *C. trachomatis* positivity was evaluated both by enzyme-linked immunosorbent assay (ELISA) to detect IgG antibodies and by PCR-DNA detection using H1/H2 primers.
Results: The overall prevalence of HPV infection was 85.2%. Seropositivity for *C. trachomatis* was 25% (34/136). Thirty-one samples were simultaneously PCR-positive for HPV and seropositive for *C. trachomatis*. Although *C. trachomatis* seropositivity was higher in HPV-positive than in HPV-negative women, this difference was not significant. According to PCR analysis, 12/136 samples (8.8%) were positive for *C. trachomatis*. Again, the prevalence of *C. trachomatis* infection was higher, but not significantly so, in the women infected by HPV. Positivity for HPV, particularly HPV16 and HPV18, and seropositivity for *C. trachomatis* were significantly associated with the severity of cervical neoplasia (CIN 2 or worse). A significant association was also found after controlling for HPV16 and HPV18.
Conclusion: In this study, no statistically significant association was found between co-infection by HPV and PCR-detected *C. trachomatis* and the severity of cervical neoplasia, even after controlling for HPV type.

OC 12-1

LIQUID BASED CYTOLOGY (THIN PREP) AND COMPUTERASSISITANCE COMPARED TO CONVENTIONAL CYTOLOGY; SEVEN YEARS EXPERIENCE IN 310 203 CASES

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Objectives: Our goal is to compare the detection rate for pre neoplastic lesions in the cervical cancer screening with liquid based cytology versus screening with conventional cytology. We compared two similar groups of women who participate regularly to the cervical cancer screening program in Germany. One Group was screened computer assisted with Thin Prep- Imaging-System (TIS) and the other group with conventional cytology (CC). Here we report the performance of Thin Prep imaging System compared with conventional cytology under routine conditions over seven years.

Methods: Cytomol is a private commercial lab specialized in diagnostics for cervical cancer prevention. With Thin Prep since 2000 an experience with 340.000 cases has been achieved. Since 1.1.2007 all thin layer specimens have been processed by Thin Prep imaging system. Because in Germany liquid based cytology is reserved to privately insured and self-paying patients while public healthcare only reimburses conventional cytology. To avoid bias we limited this analysis privately insured patients. Finding rates of cytology abnormalities with TIS and CC were compared. Cytology diagnoses originally reported in the Munich nomenclature II (MN; with the use of the unofficial Pap IIK category. From 01.07.2014 we are using the new Munich III nomenclature), were translated to The Bethesda System.

Results: From 2007 to 2012, 310 203 slides have been analyzed among them 217731by TIS. Except of some bloody and very cell-rich samples 97.25% of the smears were accepted for analysis by the system. TIS had a rate of LSIL (=MN PapIIID/CIN1) of 2.05% compared to 0.48% for CC (92 472), an increase of 427%. HSIL (=MN Pap IIID/CIN2 + Pap IVa/b) was found in 1.14% with TIS versus 0.39% with CC (+292%). The ASC-US rate (MN Pap IIK + III) was 2.05% with TIS and 0.98% with CC. This increase of 209% is lower than the rise in LSIL and HSIL cases. It is suggestive that the higher sensitivity of TIS was achieved without lowering specificity. All these results remained stable over the years analyzed. With TIS 21.9 slides/h were screened, compared to 13.4 for manually read TPs and 8.5 with CC. However, the technical expenditure for TIS was much higher than for CC and also for manually read LBC.

Conclusions: In routine use of a commercial lab TIS provided improved screening quality and higher productivity at the cost of higher technical expenditure.

0C 12-2

NORMAL SMEARS AND SPECIMENS WITH BENIGN CELLULAR CHANGES: ARE THEY REALLY EQUIVALENT? DATA FROM 95 934 CASES

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Context: In Alsace, the cervical cancer screening programme distinguishes entirely normal smears from specimens with benign cellular changes, unlike Bethesda 2001 classification. Aim of this study is to know if this is clinically relevant in terms of CIN2+ detected within 10 years.

Methods: All normal smears and smears with benign cellular changes registered in 2001 inside the EVE screening programme, are included and followed for 10 years. Numbers in terms of person time are calculated. Increased risk of CIN2+ is assessed by cumulated incidence risk and Relative Risk.

Results: 95 934 smears are included, 65 021 normal ones (67.8%) and 30913 with benign cellular changes (32.2%).
In all, 729 CIN2+ are observed including 57 cancers.
After ten years the CIN2+ risk is increased by 30% (RR=1.36; IC95=1.17-1.58) for women with benign cellular changes compared to those with normal smears. But cancer risk is not significantly increased (OR=1.01; IC95=0.59-1.77)

Discussion: Management of the two types of smear was equivalent. For example, mean number of follow up smears is 4.0 in case of normal smears and 4.2 in the second group.

Conclusion: The increased risk observed for women with benign cellular changes justifies the cytological distinction made by Alsatian pathologists. Absence of increased cancer incidence supports an identical management.

0C 12-3

BENEFIT OF CERVICAL SCREENING IN YOUNG WOMEN – A MATTER OF ADHERENCE TO THE RECOMMENDED SCREENING INTERVAL

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Objectives: The benefit of cervical screening for women below age 30 is debated. We aimed to assess the benefit of cervical screening for women in this age group using a national Swedish case-control audit.

Methods: The first case-control audit of the Swedish screening program was performed in 2006 and included 1230 cases during years 1999-2001, with five population based controls per case. The number of cases below age 30 was 63 (309 eligible controls), and the number of cases with stage IB or worse (IB+) was 33 (158 controls). Cancers with a Pap smear within 6 months prior to diagnosis were considered screen detected. Conditional logistic regression models were utilized to calculate odds ratios (OR) with 95% confidence intervals (CI).

Results: The OR for cervical cancer was 0.45 (CI 0.26-0.78) for women below 30 participating according to the recommended screening interval (3 years). For stage IB+ cancers the OR was 0.64 (CI 0.30-1.34) and for women age 27-29 years the corresponding OR was 0.36 (CI 0.13-0.99). Allowing for an extended screening interval of 6 years gave corresponding ORs of 0.62 (CI 0.35-1.12), 0.96 (CI 0.40-2.28) 0.69 (CI 0.22-2.15). Women aged 23-26 years showed no benefit of screening within the last 3 years (OR 1.09, CI 0.32-3.68).

Conclusions: We found no evidence to support cervical screening below age 25, while women from age 27 and up have a benefit of screening, also against stage IB+ tumours. Six years seem to be a too long screening interval for ages below 30.

OC 12-4

AGE AT FIRST SMEAR AND CERVICAL CANCER RISK: RECENT UK INCIDENCE AND MORTALITY TRENDS

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Objectives: To assess the effects of the increase in age at first cervical smear in England.

Methods: The screening age increased from 20 to 25 year in England in 2004 but not in Scotland. Recent trends in incidence and mortality in England and Scotland were compared against the expected effects.

Results: Annual mortality rates for women aged 20-29 years increased in England from 0.37 per 100,000 in 2003-05 to 0.56 per 100,000 in 2010-2012 while rates remained stable in Scotland where the minimum screening age remained unchanged (0.21 and 0.19 per 100,000 respectively). Incidence rates of cervical cancer-in-situ (CIS) fell in women aged 20-24 but increased sharply in women aged 25-29, from 306 per 100,000 (2004) to 644 per 100,000 (2012). Annual CIS incidence per 100,000 women aged 20-29 increased by a third in England, from 263 (2004) to 349 (2012) compared to a 25% decrease in Scottish women from 472 to 356 per 100,000.

Conclusions: Interpretation is complicated by the introduction of Liquid Based Cytology and HPV triage and a transient increase in screening coverage in 2009 following the widely publicised death from cervical cancer of a 27 year old celebrity. Increases in CIS registrations in women aged under 30 could be due to lesser lesions remaining untreated and progressing to CIN3 before their first screen after age 25. Cervical cancer mortality has increased since 2004 in women aged under 30 but the causal link with raising the screening age remains uncertain.

OC 12-5

CERVICAL CANCER INCIDENCE AFTER A NEGATIVE SMEAR: COMPARING SUREPATH AND THINPREP WITH CONVENTIONAL CYTOLOGY

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Objectives. During the last 10 to 15 years, liquid-based cytology tests SurePath and ThinPrep have replaced conventional cytology as primary test method in the Dutch cervical cancer screening program. By comparing interval cancer rates (i.e. cervical cancer detected within 6 years after a negative primary smear); we examined the difference in sensitivity to detect clinically relevant cervical intraepithelial neoplasia (CIN)2+ lesions.

Methods. All negative primary smears taken from January 2000 until March 2012 within the Dutch screening program were retrieved from the nationwide registry of histo- and cytopathology (PALGA) with a follow-up until March 2013. The 6-year cumulative incidence per 100,000 negatively screened smears was calculated for each screen method. Cox regression analyses were performed to assess the hazard ratio (HR) adjusted for calendar time, age, screen region and socio-economic status.

Results. When comparing SurePath with conventional cytology, the 6-year interval cancer cumulative incidence was significantly lower (44.6 (95% confidence interval (CI): 37.8 to 52.6) versus 58.5 (95% CI: 54.6 to 62.7)), just as the hazard (HR of 0.83 (95% CI: 0.70, 0.98)). One interval cancer was prevented at the expense of finding 9 extra CIN lesions. When comparing ThinPrep with conventional cytology, the 6-year cumulative incidence (66.8 (95% CI: 56.7 to 78.7) versus 58.5 (95% CI: 54.6 to 62.7)) and the hazard (HR of 1.20 (95% CI: 1.01, 1.41)) were (non-significantly) higher.

OC 12-6

HYSTERECTOMY AND ITS IMPACT ON THE CALCULATED INCIDENCE OF CERVICAL CANCER AND SCREENING COVERAGE RATE IN DENMARK

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Objectives: The incidence rates of cervical cancer and the coverage rate of women in cervical cancer screening programmes are usually reported by including all women from the whole population. These rates are calculated without elimination of hysterectomized women from the population. We aimed to describe the incidence rates of total hysterectomy and its impact on the calculated incidence rate of cervical cancer, and screening coverage rate in Denmark.

Methods: Data were retrieved from five Danish nation-wide, population-based, health care registers. All total and radical hysterectomies undertaken for reasons other than cervical cancer between 1977 and 2010 were included in the analysis. The incidence rates of cervical cancer and the screening coverage rates for women aged 23-64 years were calculated with and without adjustments for hysterectomies.

Results: For year 2010, the prevalence of hysterectomy was estimated at 6% over the entire age span. The unadjusted overall cervical cancer incidence rate of 12.8 per 100,000 woman-years corresponded with the hysterectomy-adjusted rate of 13.5 per 100,000 woman-years. The difference between the two incidence rates was about 19% in women around age 70 years and above. The coverage rate of the women targeted by the screening program (23-64 years) increased from 76% (without adjustment) to 79% (with adjustment for hysterectomies).

Conclusions: In Denmark, hysterectomies do not have a large overall impact on the calculated incidence of cervical cancer and coverage rates. Nevertheless, in older women, adjusted rates would increase by up to ~20% compared to unadjusted rates.

OC 12-7

EVALUATION OF THREE STRATEGIES TO INCREASE CERVICAL CANCER SCREENING COVERAGE AMONG WOMEN AGE 30 TO 70 YEARS OLD. CRICERVA.

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Aims: To evaluate three strategies to capture women to cervical cancer screening with a poor history of cervical cancer screening(CaCX).
Methods: The CRICERVA study is a randomized controlled trial. Out of 32858 women aged 30-70 years old enrolled in SAP Cerdanyola area (Barcelona), 15963 with no history of cervical cancer screening in the previous three years. The study included three interventions (personalized letter(G1,N=4197); informative leaflet added(G2,N=3601), a telephone added call(G3,N=6088)) and a control group. (GNI,N=2079) (spontaneous visit). The participants were offered cervical cancer screening with Cytology, HPV and personalized interview on the reasons fro not attending to screening.
Results: The intervention increased the cervical screening in a 17.6% in the G1, an 16.7% in the G2, a 21.7% in the G3 and a 9.11% in the GNI. This represented a final coverage of the screening of a 82.8% in the G1, 83.3% in the G2, 82.8% in the G3 and a 53.4% in the GNI. The lack of information about the importance of the screening was the most common reason of non-assistance (58.1%).
Conclusions: Organized screening through a personalized contact and an informative letter and a fixed appointment resulted in important gains in coverage. Our data support the need for further effort to communicate the relevance of cervical cancer screening.

OC 12-8

IMPACT OF OVERSCREENING, DATA FROM A FRENCH ORGANIZED PROGRAMME.

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Objective: French Guidelines state that smears should only be repeated every three years after 2 normal tests. However physicians are afraid of interval lesions. Aim of this study is to assess the impact of overscreening in terms of detected lesions and costs.

Methods: A retrospective cohort is built based on data from the Alsatian cervical screening programme where all smears and further exams are registered. All women whose second normal smear occurred between 1998 and 2002 and are rescreened a third time are included and followed 9 years. Delay between the 2nd and the 3rd smear is considered to define 2 groups: one "overscreened" [6; 23] months and "correctly screened" [24; 43] months. The first criteria is CIN2+ lesions detected and the secondary ones cancers and CIN1. Costs of excess smears and CIN1 are assessed.

Results: 83346 women are followed. Incidence rate of CIN2+ is 12.7 per 10000 patients a year for the overscreened group (N=50350) and 10.6 per 10 000 patients in the correctly screened group (N=32996). The age-adjusted OR is 1.18 [1.01; 1.39]. Overscreening does not protect from invasive cancer but detects more CIN1 (OR=1.72; IC 95% [1.48; 2.00]). Considering only excess smears and CIN1, the excess cost of overscreening is 1 83301 € (+31%) and there is also an unnecessary obstetrical risk for the conized women.

Conclusion: Overscreening provides very low benefits in terms of detected CIN2+ and does not protect more from cancer. It is expensive and can be dangerous for young women, due to unnecessary CIN1 treatments.

OC 12-9

CERVICAL CANCER PREVENTED BY SCREENING: LONG-TERM INCIDENCE TRENDS BY MORPHOLOGY AND REGION IN NORWAY

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Objectives: We analysed 54 years of incidence trends of cervical SCC and adenocarcinoma in Norway in order to explain regional differences in cancer burden in terms of background risk and preventive effects of screening.

Methods: The Cancer Registry of Norway was used to identify and classify by morphology all 19,530 malignancies of the cervix diagnosed in the period 1956-2010. We used join-point analysis to describe trends in incidence rates by morphology and region, and to project annual SCC incidence in the absence of screening based on trends of adenocarcinoma.

Results: The the age-standardised (w) incidence rates (per 100,000 woman-years) of cervical SCC and adenocarcinoma were, respectively: 13.4 (95%CI:12.7,14.1) and 1.1 (95%CI:1.0,1.4) in 1961-1965; 14.9 (95%CI:14.2,15.6) and 1.0 (95%CI:0.9,1.2) in 1976-1980; 9.7 (95%CI:9.1,10.2) and 1.7 (95%CI:1.5,2.0) in 1991-1995; 7.1 (95%CI:6.6,7.5) and 1.9 (95%CI:1.7,2.1) in 2006-2010. The average annual percentage change was -1.3 (95%CI:-2.0,-0.5) for SCC, and 1.5 (95%CI:1.1,2.0) for adenocarcinoma. The projected age-standardised incidence rate of cervical SCC in Norway, assuming no screening, was 29 in 2009-2010, compared to an observed incidence rate of 6.7. The estimated proportion prevented by screening ranged from 67 to 79 % between regions.

Conclusions: Despite regional variation in the incidence rates of both types of cancer, the proportion prevented by screening was similar. Cytology screening has impacted cervical cancer burden in all regions of Norway to a higher degree than is evident by overall incidence trends. The simultaneous substantial increase in cervical adenocarcinoma is presumably associated with greater exposure to HPV over time.

OC 12-10

ESTIMATING THE CONTRIBUTION FROM UNSPECIFIED UTERINE CANCER TO CERVICAL CANCER MORTALITY

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Objectives: Monitoring effectiveness of cervical cancer prevention is feasible using population based registers. Data must be validated in order to effectively monitor changes in prevention strategies. All cervical carcinomas, but no other tumors should be included. Death certificates are issued using simplified diagnoses, causing a large proportion of endometrial carcinomas and sarcomas to be classified as unspecified uterine cancer. Algorithms have been developed to account for deaths due to cervical cancer, erroneously coded as unspecified uterine cancer. GLOBOCAN 2012 reports a cervical cancer mortality which is 35% higher than in the Swedish Causes of Death Register. One possible explanation is the attribution of unspecified uterine cancer deaths (ICD10 C55) to cervical cancer (ICD10 C53).

Methods: All deaths in the Swedish Causes of Death Register due to unspecified uterine cancer were linked to the Swedish Cancer Register from 1997-2011.

Results: 84% of all women with a reported cause of death "unspecified uterine cancer" already had a specific diagnosis in the cancer register (7% cervical carcinoma, 55% endometrial carcinoma, 3% non-uterine carcinoma, 19% uterine sarcoma). Less than 16% had an undetermined or no previous cancer diagnosis, some of which might be cervical cancers.

Conclusions: The contribution of women with a death certificate of "unspecified uterine cancer" (C55) but who actually died from cervical carcinoma is less than 10%, rather than 35%. Where possible, the Causes of Death and Cancer registers should be linked before applying reallocation algorithms to obtain valid data suitable for the evaluation of cervical cancer prevention.

OC 12-11

THE IMPACT OF CERVICAL CANCER SCREENING ON PRETERM BIRTH: A DECISION ANALYSIS

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Objectives: Although screening and early treatment has reduced cervical cancer incidence and mortality considerably, treatment of cervical intraepithelial neoplasia (CIN) might increase the risk of preterm birth (PTB). We assessed the impact of different screening strategies on the risk of PTB and subsequent neonatal outcome, relative to maternal life years gained (LYG).

Methods: We simulated six screening strategies, varying in start age (20, 25, and 30 years) and interval (3 and 5 years) using the MISCAN model. For every strategy, the model produced the age-specific number of CIN diagnoses and LYG. We assumed that 25% of CIN 1 and 100% of CIN 2 or worse was treated using loop electrosurgical excision procedures, which led to a relative increase of the age-specific PTB risk of 60%. Age-specific pregnancy data were used to estimate the increase in PTBs due to cervical cancer screening.

Results: Three-yearly screening from age 20 resulted in 10,448 LYG per 100,000 screened women, at the expense of 997 additional PTBs (i.e. 94 and 29 cases of neonatal morbidity and mortality, respectively). When the start age of screening was postponed to age 30, the number of LYG reduced with 0.3% to 10,419, while the number of PTBs reduced with 77% to 225 (i.e. 21 and 7 cases of morbidity and mortality, respectively).

Conclusions: Starting cervical cancer screening at age 30 instead of age 20 slightly reduces the number of LYG, for a substantial reduction in PTBs. Therefore, screening young women with a childwish may do more harm than good.

OC 12-12

EFFECT OF HR-HPV IMMUNISATION ON THE PERFORMANCE OF CERVICAL CYTOLOGY.

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Background. The ability of cytology to detect cervical precancer is fundamental to cervical screening programmes. Reduction of HR-HPV types and associated disease in immunised women is expected to adversely affect cytology. The first immunised women entered the Scottish Cervical Screening programme (SCSP) in 2010/11, at age 20. The SCSP uses Thinprep® with Image Assisted Screening® and can link immunisation status with cytology and histology results directly.

Methods. Data on first cytology test result, immunisation status and histology were obtained for women born between 1 January 1990 and 31 December 1993. The Positive Predictive Value (of HSIL+/ moderate and severe dyskaryosis or worse), the Abnormal Predictive Value (of ASCUS, ASCUS-H and LSIL/ borderline changes and mild dyskaryosis), and the Total Predictive Value (of all referrals for colposcopy), Referral Value (the number needed to refer to detect one case) and the Mean CIN Score (a weighted average of the severity of disease detected at each colposcopy) have been derived for CIN2+ and CIN3+..1 The PPV (CIN2+) is the primary analysis and statistical significance was assessed using Chi2 tests with a Bonferroni correction.

Results. Full immunisation is associated with significant reductions in PPV (CIN2+), and APV, TPV, RV and MCS for both CIN2+ and 3+, but not for the PPV (CIN3+). These findings suggest that high grade cytology carries the same significance with regard to CIN3 in both fully immunised and unvaccinated women but not for CIN2. Low grade abnormalities are probably less significant in fully immunised women, with implications for management.

	MCS		PPV%	APV%	TPV%	RV
All women	1.436	CIN2+	74.69	23.62	46.11	2.168
		CIN3+	37.06	6.77	20.29	4.950
Unvaccinated women	1.518	CIN2+	76.73	29.58	51.47	1.942
		CIN3+	37.97	9.43	22.97	4.353
Fully immunised women	1.286	CIN2+	69.30	16.44	37.32	2.679
		CIN3+	34.32	3.72	15.79	6.333

1 Achievable standards, Benchmarks for reporting and Criteria for evaluating cervical cytopathology, Third edition January 2013.

OC 12-13

CHARACTERISTICS OF GPS WHO DO NOT ENGAGE IN CERVICAL CANCER SCREENING IN FRANCE

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Objectives: In France cervical cancer screening (CCS) by Pap smear can be performed by general practitioners (GPs), and medical gynecologists. Medical gynecologists manage contraception, cancer screening, menopause, while deliveries and surgery remain to obstetricians. Women have direct access to gynecologists as primary care practitioners. Our aim was to measure GPs' involvement in CCS and investigate the characteristics of GPs associated with no practice of CCS.

Methods: Data came from 3 cross-sectional surveys conducted among representative samples of French GPs in 1998, 2002 and 2009 (n = 6213).We conducted univariate and multivariate logistic regressions stratified on GPs' sex to investigate the characteristics (age, solo or group practice, professional network, area of practice…) of the GPs associated with no practice of CCS ever.

Results: The proportion of GPs not performing CCS increased from 24.1% to 34.8% over the period ($\chi 2, p < 0.0001$). Women performed CCS increasingly more than men in all three years, from 8.7% more than men up to 17.1%. In multivariate analyses, female GPs with unregulated fees were more likely not to perform CCS (2.31, 95% CI: 1.50-3.56) as were male GPs belonging to no professional network (1.38, 95% CI: 1.15-1.66). Male GPs from the Paris metropolitan area were less likely to perform CCS until 2002.

Conclusions: Less and less GPs engage in CCS when the growing scarcity of medical gynecologists calls for more participation. Female GPs remain significantly more active in CCS than male GPs. The participation in CCS is determined differently according to the practitioner's gender.

OC 13-2

COMPLETE AGE SPECIFIC ROUND 1 RESULTS FROM THE CANADIAN POPULATION-BASED SCREENING TRIAL: HPV FOCAL

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Objectives: HPV FOCAL is a longitudinal population-based trial, evaluating the efficacy of high-risk HPV DNA testing, with Liquid Based Cytology (LBC) triage for HPV positives, compared to LBC testing with HPV triage testing for ASCUS, for detection of ≥ CIN3. Presented are the complete round 1 results comparing differences in CIN detection and colposcopy referral rates for women <35yrs and 35+yrs.

Methods: Recruitment occurred between January 2008 and May 2012 with 25,243 British Columbia women aged 25-65yrs consented. Participants randomized to either primary HPV (HPV arm) or LBC testing (LBC Arm) and followed for 2 or 4 years.

Results: Data presented for 25,151 participants with first round results (baseline and 12-month follow-up). Overall, CIN3+ detection rates for women all ages were not statistically different between HPV (6.6/1000) and LBC (4.4/1000) arms. In women ≥ 35yrs, overall detection rate for CIN2+ and CIN3+ were higher in HPV vs. LBC arm (CIN2+: 10.3/1000 vs. 5.4/1000. CIN3+: 3.7/1000 vs. 2.0/1000 respectively) and significantly higher for CIN2+ detection. In women <35yrs, CIN2+ rates were significantly greater for HPV vs. LBC arm (47.7/1000 vs. 31.7/1000 respectively) but as for women ≥ 35yrs, not for CIN3+. In all ages, HPV testing referred significantly more women to colposcopy (HPV: 59.0/1000 vs. LBC 30.9/1000).

Conclusions: For women all ages completing first round screening, primary HPV testing with cytology triage detects significantly more CIN2+ lesions and referred more women to colposcopy. Findings will inform for eventual paradigm shifts to primary HPV testing in organized settings (age to commence HPV testing and resource utilization).

OC 13-3

HUMAN PAPILLOMAVIRUS ASSAYS AND CYTOLOGY IN PRIMARY CERVICAL SCREENING OF WOMEN BELOW AGE 30 YEARS

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Objectives: Recent studies suggested that certain HPV assays, particularly those based on detection of HPV mRNA instead of DNA, might have a role in screening young women. Within the Danish Horizon study, we compared clinical outcomes of three DNA assays (HC2, cobas, CLART), one mRNA assay (APTIMA), and cytology in 1,278 women attending routine primary screening at age 23-29 years.

Methods: Testing protocols of SurePath samples were agreed upon with the manufacturers prior to the study. Women with abnormal cytology were managed according to routine recommendations, whereas HPV-positive/cytology-normal women were invited for repeated testing in 18 months as part of the study. They were followed through the Danish Pathology Data Bank for 2.5 years.

Results: In total, 406 (32%) of the women had a positive test result on HC2, 519 (41%) on cobas, 481 (38%) on CLART, 342 (27%) on APTIMA, and 95 (7%) on cytology. ≥ CIN3 was detected in 44 women. Sensitivity of HC2 for ≥ CIN3 was 95% (95% CI: 85-99), of cobas 98% (95% CI: 88-100), CLART 100% (95% CI: 92-100), APTIMA 82% (95% CI: 67-92), and cytology 59% (95% CI: 43-74). Specificities were 71% (95% CI: 68-73), 61% (95% CI: 59-67), 65% (95% CI: 62-67), 75% (95% CI: 73-78), and 94% (95% CI: 93-96), respectively.

Conclusions: In young women attending primary screening, HPV assays were highly sensitive but had low specificity. Although APTIMA was significantly more specific than the three DNA assays, its specificity was substantially lower than that of cytology, demonstrating that false-positive tests were frequent.

OC 13-4

REFERRAL POPULATION STUDIES IN EVALUATION OF HPV ASSAYS FOR PRIMARY SCREENING

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Objectives: Comparisons between HPV assays are dominated by studies of women with cytological abnormalities ("referral populations"), mainly for ease of execution and the high prevalence of CIN. However, referral populations represent a selected group within primary screening, where most women have normal cytology. Within the Danish Horizon study, we compared detection of HPV and ≥ CIN2 in women with normal and abnormal cytology.

Methods: Consecutive routine samples from 4,997 women had valid tests on HC2, cobas, APTIMA, CLART, and cytology. All women with positive screening tests were offered follow-up. The outcomes were retrieved from the Danish Pathology Data Bank. Differences in cut-off values, adjusted for women's characteristics, were assessed using a lognormal distribution.

Results: In total, 367 (7%) women had abnormal, and 4,630 (93%) normal cytology. The median cut-off values for HPV infections were lower (all p≤ 0.001) in women with normal than abnormal cytology: for HC2 (rlu/co), 11.0 (IQR: 3.3-52.6) vs. 124.2 (IQR: 22.9-506.9); cobas (CT), 33.6 (IQR: 29.6-37.5) vs. 26.9 (IQR: 23.7-31.3); and APTIMA (s/co), 10.2 (IQR: 5.8-11.3) vs. 11.1 (IQR: 9.4-15.5). The disagreement in detecting HPV infections (n=1,660) was more frequent with normal (67%) than with abnormal cytology (26%). Even in ≥ CIN2 (n=175), the disagreement between the four assays was twice as frequent with normal (26%) than with abnormal (15%) cytology.

Conclusions: Referral populations show higher concordance between HPV assays in detecting HPV infections and CIN than would primary screening populations. In choosing an HPV assay for primary screening, data from referral population studies should be used with caution.

OC 13-5

THE LONG-TERM PROGNOSTIC VALUE OF HPV TESTING AND PAP CYTOLOGY TO DETECT CERVICAL NEOPLASIA IN THE CANADIAN CERVICAL CANCER SCREENING TRIAL (CCCAST)

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Objective: To assess the long-term prognostic value of HPV DNA testing and Pap cytology to detect CIN2+ among women undergoing routine cervical cancer screening in Canada.

Methods: CCCaST was a randomized controlled trial designed to compare the performance of Pap cytology and HPV testing to detect CIN2+ among women attending routine screening in Montreal and St. John's, Canada (n=10,154). In this analysis, extended follow-up data (total=494,177.40 women-months) were evaluated for St. John's participants (n=5,754). Cervical screening-related procedures and outcomes occurring since study enrollment were retrieved from the provincial database for these women. HPV results with genotyping information and Pap cytology results determined at enrollment were correlated with detection of CIN2+ during the entire follow-up period using time-to-event analyses.

Results: The cumulative incidence rate of CIN2+ among women testing HPV(-)/Pap(-) at baseline was substantially lower during 120 months of follow-up [1.15%, 95%CI: 0.60-2.18] when compared with women testing HPV(+)/Pap(-) or HPV(+)/Pap(+) [12.17%, 95%CI: 6.71-21.52; and 26.05%, 95%CI: 15.34-42.13 (respectively)]. At approximately 60 months of follow-up, the cumulative incidence rate among HPV(-)/Pap(-) women began to notably increase. Of the four baseline HPV(+) participants developing CIN2+ following 60 months of follow-up, one was HPV16(+) and two were HPV18(+).

Conclusions: The consistently low rate of CIN2+ among women testing HPV(-)/Pap(-) at baseline suggests that double negativity confers a long-lasting protective effect (up to five years in this analysis). Determining the extent and duration of this effect may allow for enhanced efficiency in screening, while maintaining favorable outcomes and reducing potential harms of over-screening.

OC 13-6

EVALUATING THE POTENTIAL INTRODUCTION OF PRIMARY HPV DNA SCREENING IN ENGLAND

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Objective: Primary HR-HPV testing has shown high negative predictive value for cervical intraepithelial neoplasia stage 2 or worse (CIN 2+) in trials but has not yet been widely implemented. The aim of this study was to assess the health-impact and cost-effectiveness of primary HR-HPV testing, compared with primary cytology testing followed by HR-HPV-based triage, which is currently offered by the national cervical screening programme, to inform policy making in England.

Method: A novel stochastic model was developed to describe the transmission and natural history of HR-HPV infection, in which the competing hazards of CIN, invasive cervical cancer and natural clearance of infection vary as functions of time post-infection. The incidence of undetected cervical cancers was inferred using data from the Cervical Cancer Audit and Trent Cancer Registry. HPV type-specific infection parameters were identified for strains 16, 18, 31, 33, 45, 52, 53, 58 and 61 using data from Public Health England and the National Health Service Cervical Screening Programme (NHSCSP). Lifetime sexual activity and screening attendance behavioural patterns were characterised using data from a national survey on sexual behaviour undertaken in 2010 (Natsal-3) and the NHSCSP, respectively.

Results: The model predicts that primary HR-HPV testing leads to a net increase in total number of screening tests carried out annually. The model identifies increased detection of neoplasias by colposcopy. The benefit of primary HPV testing outweighs the cost of increased colposcopy and treatment. In conclusion, primary HPV testing is found to be cost-effective compared to existing cytology-based screening with HPV triage.

OC 13-7

HPV TESTING WITH CYTOLOGICAL TRIAGE VERSUS CONVENTIONAL CYTOLOGY IN AN ORGANIZED CERVICAL CANCER SCREENING PROGRAM

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Objectives: In 2012, HPV screening of cervical cancer was implemented for women aged 35 through 60 in Tampere (pop. 220,000). Conventional screening was continued in the surroundings (pop. 370,000).
Prospective population-based cohort study. All women aged 35, 40, 45, 50, 55, and 60 years in 2012 who were invited for screening in Tampere and its surroundings were included in the study.

Methods: Research arm (Tampere): Screening with Abbott RealTime HR HPV test. A PAP smear was taken at the same time but analyzed only if HR HPV test was positive.
Control arm (surroundings): Screening with conventional cytology only.

Results: 5,637 women were screened in HPV arm and 6,563 women in PAP arm. In HPV arm, 53 women (0.94 %) were referred to colposcopy, while the referral rate in PAP arm was 83 women or 1.26 %. Based on colposcopy-directed biopsies, the detection rate of CIN2+ and 3+ in HPV arm + was 2.8/1,000 and 1.8/1,000, respectively. The corresponding figures in PAP arm were 1.5/1,000 and 0.9/1,000.
A LEEP was performed to13 women in HPV arm and 12 women in PAP arm. The final histopathological diagnoses in HPV arm were: 1 adenocarcinoma, 2 SCC, 7 CIN3, 1 CIN2, 1 CIN1, 1 normal. In PAP arm, one SCC, 8 CIN 3, 1 CIN2, 1 CIN1, 1 inflammation were found in the LEEP specimens.

Conclusions: Primary HPV screening seems to be more sensitive in detecting CIN2+ and CIN3+ than conventional cytological screening.

OC 13-8

PERFORMANCE OF HPV DNA TESTING WITH INDIVIDUAL HPV 16/18 GENOTYPING FOR PRIMARY CERVICAL CANCER SCREENING AND TRIAGE, COMPARED TO CYTOLOGY

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Objectives. To assess the performance of the HPV DNA testing and individual HPV 16/18 genotyping using cobas® HPV test (Roche) as a method for primary cervical cancer screening compared with liquid-based cytology (LBC) in a population of Greek women.

Methods. Four thousand and nine women aged 25-55 years attending routine cervical cancer screening at nine Gynecology Departments in Greece were recruited between August 2011 and November 2013. Cytological evaluation was performed using LBC (ThinPrep®). An aliquot of each sample was used in order to detect HPVs 16 and 18 separately, and HPVs 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68, using the cobas 4800® system (Roche). Women found positive for either cytology or HPV were referred for colposcopy.

Results. Among 3,993 valid tests the overall prevalence of HR-HPV was 12.7%. Cervical Intraepithelial Neoplasia grade 2 or worse (CIN2+) was detected in 41 women (1.07%). Sensitivity of cytology [atypical squamous cells of undetermined significance (ASC-US) or worse] and HPV DNA testing for the detection of CIN2+ was 53.7% and 100% respectively (64.3% and 100% for CIN3+), and specificity was 96.8% and 90.3% respectively (96.5% and 89.7% for CIN3+). Genotyping for HPV16/18 only had similar accuracy to cytology for the detection of CIN2+ (sensitivity: 58.5%; specificity 97.5%) as well as for triage to colposcopy for HPV positive women (sensitivity: 58.5% vs 53.7% for cytology).

Conclusion. HPV testing with individual HPV-16/HPV-18 genotyping could represent a more accurate methodology for primary cervical cancer screening in comparison to liquid-based cytology.

OC 13-9

CLINICAL CHARACTERISTICS OF SAMPLES WHERE COBAS, HC2, APTIMA, AND CLART HPV ASSAYS RETURN DIFFERENT TEST RESULTS

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Objectives: From the Danish Horizon study comparing HC2, cobas, CLART, and APTIMA assays, and confirmed by other studies, we reported that the detection of HPV infections varies greatly by assay. In primary cervical screening at ≥ 30 years (n=2,859), only 29% of positive test results were in agreement on all four assays. Here, we studied the characteristics of the disagreeing samples.

Methods: Testing protocols of consecutive routine SurePath samples were agreed upon with the manufacturers prior to the study. Abnormal cytology was managed according to routine recommendations, whereas HPV-positive/cytology-normal women were invited for repeated testing in 18 months within the study. They were followed through the Danish Pathology Data Bank for 2.5 years.

Results: Women with a positive test result on only one HPV assay (n=258) were considerably less likely to have infections with HPV16 (6%), other high-risk genotypes (14%), and multiple genotypes (14%), than women with a positive test result on all four assays (n=188; 22%, 78%, 64%, respectively). Their samples were also more likely to contain only low-risk, or no genotype. The median cut-off values were substantially lower than for women with >1 positive test result, without overlapping IQR, indicating low viral load. Among women with ≥ CIN2 (n=50), no woman tested positive on only one assay.

Conclusions: Screening samples from HPV-positive women for whom the HC2, cobas, CLART, and APTIMA assays gave conflicting test results were systematically different and less likely to contain clinically important lesions than samples in which all four assays returned a positive test result.

OC 13-10

THE ADDED VALUE OF RESCREENING CYTOLOGY NORMAL SAMPLES WITH POSITIVE HPV MRNA TEST FOR THE DETECTION OF CIN2+ IN PRIMARY SCREENING

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Objectives. To estimate the increased detection rate of CIN2+ in women with normal Pap-smears by rescreening Pap-smears from HPV mRNA positive samples.

Methods. From April 4th, 2013, the Department of Pathology, Ålesund Hospital, introduced a study by rescreening all normal Pap-smears that had a positive HPV mRNA test (NorChip PreTect SEE) (types 16, 18 and 45) in women younger than 40 years. Within the SymPathy database, a study population of 3 947 women aged 23–39 years with no prior history of CIN1+ was established.

Results. 30% of women with normal cytology were tested via HPV mRNA (1060/3496), and 18 samples were positive (1.7%). After re-evaluation of the index cytology and subsequent follow-up smears, 10 women had colposcopy, resulting in four diagnoses of normal biopsies, 2 CIN1 and 4 CIN2+. The detection rate of CIN2+ among normal Pap-smears was 0.38% (95% CI: 0.32–0.44). In the ASC-US+ arm (n=318) of women without HPV sampling, 57 CIN2+ were detected. If we apply the CIN2+ detection rate among cytology normal / HPV mRNA-positive women (0.38%) to the arm of women with normal cytology without HPV testing, an increase in CIN2+ detection from 13.5–18.4% was estimated.

Conclusions. By testing all women with normal cytology with a specific HPV mRNA test, a significant increase in screening program sensitivity can be achieved. The volume of rescreened smears (1.7%) is very low. In addition, the study adds quality to educating the screeners by rescreening presumably false negative Pap-smears.

OC 13-11

EXPLORING THE VALUE OF A RAPID, ON DEMAND TEST FOR HPV AS PART OF CERVICAL CANCER SCREENING PATHWAYS

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Background: Rapid, on demand testing has been developed for HPV detection in cervical screening samples. This technology has the potential to change patient pathways. There has been no evidence presented yet around how such a test may impact upon a cervical screening programme.

Aim: To map patient pathways under the current NHS Cervical Cancer Screening Programme in England (HPV triage), and HPV primary screening, comparing standard currently available HPV testing platforms with a rapid, on demand test.
1. To compile experts' views on the value, opportunities and challenges of implementing a rapid, on demand test.

Methods: Semi-structured interviews with laboratory, epidemiology, policy, and clinical experts across England. To inform the mapping of the current screening pathway under HPV triage and HPV primary screening, and explore the potential value of introducing a rapid, on demand HPV test.

Results: Experts reported that using a lab based rapid, on demand HPV test on cytology samples qualifying for HPV triage could reduce the time to results by up to a week. Under HPV primary screening, a rapid near patient test in primary care could radically change the testing paradigm. Most HPV negative women could be notified within 1 day by the practice, and the proportion of samples sent for cytology could dramatically reduce. This could improve patient experience and reduce anxiety for women. Questions remain as to quality assurance, IT integration, and reimbursement, as well as potential logistical challenges to implementing this model of care.

OC 13-12

START-HPV FRENCH PILOT PRIMARY SCREENING PROGRAM FOR CERVICAL CANCER: PARTICIPATION RESULTS

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Background: START-HPV (STudy of primary screening in the ARdennes 'department' by Testing for HPV infection) is the first French primary screening pilot study using solely HPV testing. This study is supported by The INCa (French National Institute of Cancer). The objective is to evaluate the setting conditions of an HPV-based primary screening in France for the non-attending population, at the scale of a French 'department'.

Methods: The eligible population consisted of all women living in the Ardennes administrative area, aged 31-65, without any Pap-smear in the last 3 years. They received an invitation for having a cervical sampling to be analyzed by HPV testing (Hybrid Capture 2, Qiagen). Two recalls were scheduled. The second recall was randomized between cervical smear (1/3) or self-sampling (2/3).

Results: 30,365 women were eligible and gave their consent. Global participation rate was evaluate at 11.1%. The mean age of attendees was 51 years old. Samples were taken by gynecologists (43.0%), general practitioners (30.6%), self-sampling (24.2%) and other healthcare professionals (2.2%). Samples were tested HPV positive in 9.6% of cases. Among HPV positive women, triage cytology demonstrated to be abnormal (≥ ASC-US) in 39.2% of cases.

Conclusion: Participation rate is rather low in this population, despite a significant implication of general practitioners and self-sampling use. This probably reflects the difficulty to implement a new screening organization in France. A telephone survey is ongoing among 800 non-participating women, to identify the major reasons for non-attending. Results of the survey will be presented.

OC 13-13

INTRODUCING CAREHPV INTO A PUBLIC SECTOR SCREEENING PROGRAM IN EL SALVADOR

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Objectives: CAPE (Cervical Cancer Prevention in El Salvador) introduced a low-cost HPV-DNA test into a public sector program. El Salvador has one of the lowest screening rates in Latin America (19%). Coverage rates are poor and follow-up for abnormal cytology is inadequate. The aim, since October 2012, has been to implement a 3-phased program to screen 30,000 women. The true impact will be seen when the program is handed over to the government, and becomes the national screening program. Results of phase 2 are presented.

Methods: 8,035 women, ages 30-49, were screened. 6,737 had self- and provider-collected samples and 1,298 had provider-testing. The agreement between sampling methods was 83.6% (kappa of 0.71). HPV-positive women were referred to treatment using the strategy their community followed. Cohort A was referred to colposcopy; Cohort B had immediate visual triage and cryotherapy.

Results: 341 (12.5%) women were HPV positive in Cohort A; 325 (11.3%) were positive in Cohort B. 2,736 women in Cohort A (70.1%), and 2,889 women in Cohort B (77.9%) have completed 6-month follow-up. In Cohort A, all were referred for colposcopy—313 attended their appointment, and 243 were treated. 29.9% have not completed follow-up and were not included in the analysis. In Cohort B, 257/325 received treatment.

Conclusions: A program introducing HPV testing was successfully implemented in a low-resource setting. Requiring women to return for a colposcopy made them less likely to complete treatment. Outreach to women who had not been screened recently helped find women at higher risk for HPV.

OC 13-14

RANDOMIZED IMPLEMENTATION OF HPV-TEST IN PRIMARY SCREENING IN THE NORWEGIAN CERVICAL CANCER SCREENING PROGRAM

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Background: In 2015 Norway will implement hrHPV testing for primary screening in 4 counties as a randomized health service. Women will be allocated randomly to either HPV-test or Pap-smear based on their date of birth.

Methods: The Cancer Registry of Norway is responsible for the coordination of preparations prior to implementation. Two working groups were charged with defining and monitoring preparations. One group is focused on preparatory changes in laboratory infrastructure and routines, gynecological wards, and GPs, information to women and screening providers, necessary changes in the reminder routines and data handling in the Cancer Registry. The other group is focused on the academic safeguard along with developing protocols for the evaluation of the implementation project.

Results: Necessary IT-solutions for randomization in the laboratories are prepared. Protocols for the whole process from sampling to registration and reporting to the Cancer Registry are completed. A public tender for the purchase of a common HPV test platform and biobanking solution was initiated. There is an ongoing contact with the authorities for regulatory support and maintenance of HPV testing reimbursements. Likewise, information - and media strategies to reach out with understandable information to women, doctors, laboratories and population, have been prepared.

Conclusions: It is important to prepare a national implementation in close collaboration with all stakeholders. This is to ensure that the introduction takes place as seamlessly as possible with high quality. The goal is a robust implementation that provides security for individual women at all stages in the best possible way.

OC 13-15

CERVICAL CANCER SCREENING PROGRAM BASED ON CYTOLOGY AND HPV TEST: POSITIVE PREDICTIVE VALUE.

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Objectives: The aim of this study was to know the probability of undergo a disease given a positive result on cervical cancer screening (CCS), based on HPV test and cytology; this is, the positive predictive value (PPV), which is crucial both for health management and clinical counseling.

Methods: Castile and Leon is a Spanish region where CCS was established on 1986. Its female population is ~1.3 million women. Since 2008, HPV genotyping (CLART®HPV2) is conducted jointly with conventional cytology on women 35-64 y. Women 25-34 y. are screened only by cytology. Positive predictive values were calculated for different diagnostic outcomes during 2013.

Results: According to algorithm, 1,092 women out of 55,532 were positive (2.0%) and were recommended to attend to their gynecologist. Follow-up and histology was available for 496 women.
PPV for cervical pathology overall was 52.8% (IC95 48.3-57.3) given a positive CCS. The probability of undergo a low-grade dysplasia was 21.0%, 29.2% for high-grade and 2.6% for carcinoma.
Cytology (≥ ASC-US, any HPV test result) has a PPV of 58.3% (IC95 52.0-64.6) for cervical pathology: 19.0% for low-grade dysplasia, 35.3% for high-grade and 4.0% for carcinoma.
HPV-16/18 (any cytology result) has a PPV of 53.2% (IC95 47.2-59.3) for cervical pathology: 22.3% for low-grade dysplasia, 28.1% for high-grade and 2.9% for carcinoma.

Conclusions: There are no significant differences in PPV between cytology and HPV test, overall. HPV test has higher PPV for low-grade dysplasia, being an advantage for CCS in the earliest stages, consistently with natural history of infection.

OC 14-1

HPV PREVALENCE FINDINGS IN THE DANISH HPV SELF-SAMPLING IMPLEMENTATION COMPARED TO ROUTINE SCREENING

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Objectives: In Denmark, 45% of cervical cancers are diagnosed in screening non-participants. The on-going pilot implementation study in the Capital Region aims to improve the screening coverage rate by offering an HPV-based self-sampling test for free to non-attenders. Here we report on the HPV prevalence in the returned self-sampling brushes, with an age-stratified comparison to routine physician-taken samples from screening participants.
Methods: Non-attenders from the Capital Region (N= 54,585) were identified from the invitational module of the nationwide Pathology Data Bank. Women were randomly invited in batches of 1,000, and the recruitment is still on-going. Reminders were sent after 8 weeks. HPV prevalence was determined by testing with the BD Onclarity assay. For comparison, we used data from a BD Onclarity study on unselected routine samples, including predominantly primary screening samples.
Results: In 1,174 analyzed self-samples, the overall HPV prevalence was 15.3%. Age-stratified data showed that 20.7% of women aged 30-39 years had a positive test result; at 40-49 years, this was 13.3%; at 50-59 12.4%; and at ≥ 60 years 10.7%. For comparison, in a regular screening population (N=811), HPV prevalence was 20.4%, 13.2%, 7.5%, and 4.7% respectively.
Conclusions: HPV prevalence in women aged 30-49 years was similar between non-participants who accepted self-sampling and regular screening participants. In women aged ≥ 50 years, the prevalence rates were higher in the self-sampling group. These preliminary data suggest that the older self-sampling group has a higher risk of CIN, and might particularly benefit from self-sampling.

OC 14-2

COMPARATIVE EVALUATION OF TWO VAGINAL SELF-SAMPLING DEVICES FOR THE DETECTION OF HUMAN PAPILLOMAVIRUS INFECTIONS

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Objectives: To compare the performance of two devices for vaginal self-sampling of dry cell material (Evalyn Brush, Rovers Medical Devices; Qvintip, Aprovix) using a clinically validated high risk HPV (hrHPV) DNA test and evaluate their acceptability.

Methods: Both self-sampling devices (change of order with every patient) including instructions for use and a questionnaire were handed to 150 patients for self-collection prior to scheduled colposcopies with collection of cervical specimens by gynaecologists in a colposcopy clinic and a general gynaecological outpatient clinic. Matched self-collected and physician collected specimens were transferred to individual liquid-based-cytology vials (ThinPrep) and tested for the presence of hrHPV using the RealTime High Risk HPV assay (Abbott). Biopsies were taken if indicated by colposcopy.

Results: Data from 99 patients evaluated at date showed high agreement of overall hrHPV detection rates between self-collected (Evalyn:90.9%; Qvintip:88.9%) and clinician-collected specimens. In addition, high agreement of HPV16 (Evalyn:98.0%; Qvintip:97.0%), HPV18 (Evalyn:99.0%; Qvintip:98.0%) and non-16/18-hrHPV (Evalyn:91.9%; Qvintip:89.0%) was found between both self-sampledl and physician-collected specimens. Colposcopy and histological evaluation revealed 39 women without cervical intra-epithelial neoplasia (CIN), 24 CIN1, 26 CIN2 and 10 CIN3. Nine CIN3 cases collected with both self-collection devices and the reference smear were positive for hrHPV. So far women seem to appreciate the ease of use of the Qvintip device (63% versus 48%), while the majority of women (60%) favor a physician-collected smear.

Conclusions: High agreement of hrHPV results was found between self-collected (Evalyn, Qvintip) and physician-sampled specimens collected in ThinPrep vials. HrHPV detection rates in women with and without cervical disease and evaluation of the questionnaires will be reported upon completion of the evaluation.

OC 14-3

GOOD AGREEMENT OF HPV DETECTION BETWEEN SELF-COLLECTED DRY SAMPLES AND PHYSICIAN-COLLECTED SPECIMENS IN CHINA

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Objectives. To evaluate the effectiveness of self-collected dry specimens obtained with the Evalyn Brush (Rovers Medical Devices, KV Oss, The Netherlands) for the detection of high-risk HPV (hrHPV) using a clinically validated test.

Methods. 202 patients of the gynaecological outpatient clinic of a Chinese university hospital took vaginal self-samples prior to scheduled colposcopies. Self-sampled and physician-collected cervical specimens were tested for the presence of hrHPV using the Abbott RealTime High Risk HPV assay. HrHPV results were compared with cyto-and histopathology diagnoses.

Results. HrHPV was detected in 80/101 (79.2%) self-collected and in 82/101 (81.2%) physician-collected samples from women with cervical intra-epithelial neoplasia grade 2 and higher (CIN2+). Among 46 (45.5%) women in this group with CIN3+ hrHPV was found in 42/46 (91.3%) self-collected samples and in 43/46 (93.5%) physician-collected specimens. In women without cervical dysplasia, hrHPV was detected in 13/101 (12.9%) self-collected and in 15/101 (14.9%) physician-collected samples.
High overall agreement of hrHPV test results (96.5%%; kappa=0.93) was observed between both sampling methods. The overall sensitivity and specificity for CIN3+ by self-sampling was 91.3% (95%CI:79.2%-97.5%) and 87.1% (95%CI:79.0%-93.0%), respectively which was only marginally lower than by physician collection (93.5%;95%CI:82.1%-98.6% and 88.1%;95%CI:80.2%-93.7%). Similar detection rates for HPV16 (37.0% vs. 38.7%), HPV18 (5.4% vs. 3.2%) and non-HPV16/18 (72.8% vs. 72.0%) were observed in self-collected and physician collected samples.

Conclusion. Comparable hrHPV detection rates were observed with self-collected cervical specimens using the Rovers Evalyn Brush and physician-collected specimens from women with histology confirmed cervical status.

OC 14-4

HPV-BASED SELF-SAMPLING IMPLEMENTATION WITH AN OPT-IN STRATEGY TO IMPROVE CERVICAL SCREENING COVERAGE

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Objectives: In Denmark, 45% of cervical cancers are diagnosed in screening non-participants. The ongoing pilot implementation study in the Capital Region aims to improve the screening coverage rate by offering an HPV-based self-sampling test for free to non-attenders. Unlike in previous research studies, we rely on an opt-in strategy where invited women have to order the self-sample brush actively upon invitation. "Opt-in" was chosen to reduce the cost, and will probably be the most sustainable strategy for countries that will routinely roll-out self sampling. However, a concern is that an "opt-In" strategy might be potentially discouraging for participation. Therefore, we studied the actual response rates.

Methods: Non-attenders from the Capital Region (N= 54,585) were identified from the invitational module of the nationwide Pathology Data Bank. Women were randomly selected into batches of 1,000. They could respond by mail, webpage, mobile application, E-mail or phone. Reminders were sent after 8 weeks. Received kits are being analyzed with HC2, CLART, and Onclarity HPV assays.

Results: So far, 14,000 invitations have been sent. The overall response rate for the first batch was 41% in120 days after the invitation. Of the invited women, 36% chose to receive the kit and 63% of the latter returned a self-sample (mean age: 47.9 years). This increases the overall coverage rate by about 5-6%. So far, the overall prevalence of HR-HPV was 15.3% by Onclarity.

Conclusions: Self-sampling with an opt-in strategy was well accepted among non-attenders, and might be a good supplement to the regular call-recall screening program.

OC 14-5

CLINICAL VALIDATION OF SELF HPV TESTING IN ROUTINE SCREENING IN SCOTLAND.

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Background: Presence of HPV in genital epithelium is necessary for the development of cervical pre-cancer. Clinically validated HPV detection allows identification of women who will benefit from further screening or cervical assessment. Sampling has to be minimally invasive and universally accessible to women.

Objectives: We clinically validate self vaginal sample against previously validated cervical sample for HPV routine cervical screening (women from age20 years) using Cobas HPV detection.

Methods: 5330 women attending for routine smear between April 2013 and July 2014 consented to self-collect vaginal swab for Cobas HPV testing. The same Cobas HPV test was used for HPV detection in ThinPrep cervical samples. Women with abnormal smear results were referred to colposcopy as per routine protocol in Scotland. HPV positive participants with normal cytology where offered HPV re-testing in 4-6months. Those with two positive cervical HPV tests with HPV 16/18 were invited to colposcopy.

Results: HPV was detected in 14.7% of cervical and 16.5% of vaginal samples. Prevalence of HPV16/18 was 4.9% and 5.5% in cervical and vaginal samples respectively.
Sensitivity of cytology, cervical HPV testing and vaginal self testing for CIN2+ lesions was 79.7%, 96.5% and 94.3% respectively. Intra- and inter-laboratory agreement data will be presented.

Conclusion: It is reasonable to assume that the majority of women would prefer minimally invasive self HPV testing. Our results indicate that self vaginal HPV testing is as sensitive as cervical HPV testing in identifying CIN2+ lesions. This study is on-going with completion date in March 2015.

OC 14-6

ACCESSING*: SCREENING BY SELF-SAMPLING AND LOWER COST ARBOR VITA E6 ONCOPROTEIN TEST CAN DETECT DYSPLASIA IN HIGH RISK WOMEN

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Objectives: To demonstrate feasibility of self-sampling combined with usage of the low-complexity Arbor Vita OncoE6™ test, detecting elevated levels of the E6 oncoprotein of HPV types 16 and 18.
The ultimate aim of this feasibility study is to screen the most vulnerable women in remote areas for cervical cancer by taking advantage of resident community health nurses living in remote communities in Ghana.
Methods: 250 high risk women (100 HIV+, 150 HR-HPV detection or lesion) were recruited at Catholic Hospital Battor. Vaginal lavage (Delphi Screener) and swab samples were collected and tested with AVE6. Full HPV genotyping was done by GP5+/6+ PCR followed by Luminex-MPG readout at the Charité Universitätsmedizin. AVE6 positive and/or high risk HPV+ underwent colposcopy and treatment.
Results: 91% (228/250) self-sampled. 85% found this easy/very easy and comfortable/very comfortable. 63% of the HIV+ and 34% of formerly HR-HPV+ women were HR-HPV positive, respectively. 10% of HIV+ patients were CIN2+, compared to 2% of the HR patients. Of the 13 CIN2+, 5 were detected AVE6 positive by lavage sample of these 3 by the swab sample. Full MPG-Luminex genotyping revealed 9 CIN2+ patients had HPV 16/18. Of these 9, 4 were detected by lavage and 2 by swab.
Conclusions: Self-sampling was well accepted and not inferior in detecting dysplasia than swab sampling. Self-sampling in conjunction with AVE6 can be used in communities to detect and triage women with highest risk for severe dysplasia or cervical cancer and allow secondary cancer prevention 'on the doorstep' in remote locations.

OC 14-7

FEASIBILITY OF SELF-COLLECTION AND DRY SPECIMEN STORAGE FOR HPV MRNA TESTING TO DETECT CERVICAL LESIONS IN HIGH RISK WOMEN

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Objectives: High-risk HPV mRNA detection hold potential to improve cervical cancer screening in low resource areas. Studies reported comparable performance in detecting HPV between self-collected specimens stored in liquid media (stored wet) and physician collected specimens. Performance of HPV mRNA with self-collected specimens stored dry, which could enhance specimen collection and storage, is unknown. We compared HR-HPV mRNA testing on two self-collected specimens (stored dry versus stored wet) to detect high-grade cervical neoplasia or greater (≥ CIN-2) among women in Kenya.

Methods: We enrolled 200 female sex workers (100 HIV-negative; 100 HIV-positive) in Mombasa. Participants provided two self-collected specimens: one stored dry using a Viba brush (Rovers) and one stored wet with Aptima media (Hologic) using an Evalyn brush (Rovers); and physician-collected specimens using CSCT- for HPV RNA testing (APTIMA) and conventional cytology. Women positive on any screen underwent colposcopy with local biopsy reading.

Results: HPV RNA positivity was somewhat higher in physician (39%) and self-collected wet (39%) brushes than self-collected dry brushes (36%). Sensitivity estimates for ≥ CIN-2 detection (n=27) were similar in HIV-negative women: self-dry (82%), physician (82%), and self-wet (82%), yet differed in HIV-positive women: self-dry (69%), physician (94%), self-wet (94%). Overall specificity for ≥ CIN-2 were 61% for physician, 59% for self-wet, and 60% for self-dry sampling.

Conclusion: HR-HPV mRNA prevalence using dry self-collected specimens was somewhat lower than physician or wet self-collected specimens. Sensitivity of mRNA testing in self-dry samples for ≥ CIN-2 appeared comparable for the three sample types in HIV-negative women, yet appeared inferior in HIV-positive women.

OC 14-8

SELF-COLLECTED VS. PROVIDER-COLLECTED SAMPLING FOR HPV DNA TESTING IN A POPULATION-BASED CERVICAL CANCER PREVENTION PROGRAM IN RURAL EL SALVADOR

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Objective: To determine the efficacy of self-collected vs. health care provider-collected sampling among women participating in a public sector HPV-based cervical cancer-screening program in El Salvador.

Materials and Methods: Retrospective analysis was performed on data obtained during implementation of a cervical cancer prevention program Data was sought from women who completed Phases I and II of a phased implementation program. Phase I and II targeted 2,000 and 8,000 patients. Comparisons of self-collected versus healthcare provider-collected samples were analyzed for the first two samples.

Results: A total of 8759 women underwent self-collected and provider collected s. Overall agreement between self-collected and physician collected samples on 1,998 women in Phase I was 98% for a Kappa value of 0.75 while agreement on 6,761 women in Phase II was 93.7% fro a Kappa value of 0.71. Combining Phases I and II saw 1,031 women with positive HPV results in the provider collected group vs. 1,032 in the self-collected group. Biopsy results of the 203 provider collected HPV+s test in Phase I revealed 19 cases of CIN 2+. Of these 3 (16%), one CIN 2, one CIN 3, and one adenocarcinoma "in situ" had self-collected samples that were negative for HPV for an overall population detection success of 83%.

Conclusions: Our findings suggest that self-sampling has an excellent overall agreement with a provider collected sample. Implementation of a self-collected HPV sample strategy in areas with limited healthcare provider resources would have a high likelihood of success in detecting most cervical cancer precursor lesions.

OC 15-1

DIAGNOSTIC VALUE OF ANAL CYTOLOGY, HPV TESTING AND HIGH RESOLUTION ANOSCOPY (HRA) IN SCREENING FOR ANAL INTRAPEITHELIAL NEOPLASIA (AIN) IN HIV POSITIVE INDIVIDUALS.

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Objectives: HRA is the gold standard for the detection AIN. Our aim was to compare different screening strategies, including anal cytology and HPV testing

Methods: Data was prospectively collected from an AIN screening service for HIV-positive individuals over a 17-month period. HPV DNA testing was performed using Abbott real time PCR, detecting 14 high risk (HR) HPV types

Results: There were 179 attendances in 148 patients. 96% were MSM. The median age, time since HIV diagnosis and time on antiretroviral therapy were 48, 13 and 11 years, respectively. Median CD4 nadir was 215x109/L (range 0-828). 48% (85/178) had any HR HPV; 20% (36/178) had HPV 16 and 12% (22/178) had HPV 18. 35% (63/178) had other HR strains. There were no associations between presence of HR HPV and demographic factors. 41% (66/160) had abnormal cytology with 8% (12/160) identified with severe dyskaryosis. 23% (35/155) had abnormal HRA with changes suggestive of AIN. Of those biopsied, 8% (2/25) had ASCC, 16% (4/25) AIN3, 20% (5/25) AIN2 and 8% (2/25) AIN1.
There was not always good agreement between the three screening tests. 55% (45/82) of those with HR HPV had abnormal cytology, compared to 21% (16/77) of those without HR HPV. 53% (16/30) of those with abnormal anoscopy had abnormal cytology. Conversely, 29% (16/56) of those with abnormal cytology had abnormal anoscopy.

Conclusions: 48% were detected with high risk HPV, although the prevalence of type 16 and 18 was lower than expected. There was no predictive association between all 3 screening methods.

OC 15-2

PERSISTENCE, INCIDENCE, AND CLEARANCE OF ANAL HPV AMONG HIV-NEGATIVE MEN HAVING SEX WITH MEN AND MEN HAVING SEX WITH WOMEN AND MEN

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Objective: We assessed persistence, incidence and clearance of anal canal HPV among men having sex with men (MSM) and among men having sex with women and men (MSWM).

Methods: Genotyping for 37 HPV types was conducted for anal specimens from HIV-negative men, aged 18-70 years, from Brazil, Mexico, and the USA. A total of 406 men (125 MSM and 281 MSWM) provided evaluable specimens at ≥ 2 visits over 2 years. Persistence was defined as ≥ 12-month type-specific prevalent or incident infection at consecutive visits. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated by Cox regression.

Results: Median follow-up time was 2.1 years. HPV16 persistence was observed in 8% and 3% of MSM and MSWM, respectively. Of 12 MSM and 15 MSWM with prevalent HPV-16, a total of 42% and 20%, respectively, retained HPV-16 at 24 months. After combining MSM and MSWM groups, men who had multiple recent sex partners and always used condoms during the study had a 12-month incidence of high-risk HPV of 6.7% (95% CI 0%-19.3%) vs 19.5% (95% CI 12.7%-26.4%) among men using condoms inconsistently. There was significantly increased clearance among men in relationships of <1 year (HR 1.7, 95% CI 1.1-2.5) compared to single men and increased clearance among moderate alcohol drinkers (31-60 drinks/month, HR 1.6, 95% CI 1.1-2.4) compared to men who drank 0-30 drinks/month.

Conclusions: MSM with prevalent HPV16 infection should be considered at risk for HPV-associated anal disease. Condoms may help prevent anal HPV infection among men with multiple sex partners.

OC 15-3

THE EFFECT OF HIV INFECTION ON ANAL HIGH-RISK HPV INCIDENCE AND CLEARANCE AMONG MSM

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Objectives: The majority of anal cancers are caused by high-risk HPV (hrHPV) infections, which are especially common in men who have sex with men (MSM). We aimed to compare the incidence and clearance rates of anal hrHPV infection between HIV-infected and HIV-negative MSM.

Methods: MSM aged ≥ 18 years were recruited in Amsterdam, the Netherlands, and followed-up semi-annually for 24 months. At each visit, participants completed risk-factor questionnaires. Anal self-samples were tested for HPV DNA and genotyped using the SPF10-PCR DEIA/LiPA25 system; HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 were classified as hrHPV. Effects on incidence and clearance rates were quantified via Poisson regression, using generalized estimating equations to correct for multiple hrHPV types.

Results: 750 MSM with a median age of 40 years (IQR 35-48) were included in the analyses, of whom 302 (40%) were HIV-infected. The incidence rate of anal hrHPV was significantly higher in HIV-infected compared to HIV-negative MSM (adjusted incidence rate ratio 1.6; 95%CI 1.3-2.0), while the clearance rate was significantly lower (adjusted clearance rate ratio 0.7; 95%CI 0.6-0.9). HrHPV incidence or clearance among HIV-infected MSM did not differ significantly by level of nadir CD4 cell count.

Conclusions: Increased anal hrHPV incidence rates and decreased anal hrHPV clearance rates were found in HIV-infected compared to HIV-negative MSM, after adjusting for reported sexual behavior. Our findings suggest an independent effect of HIV infection on both incidence and clearance of anal hrHPV infections.

OC 15-4

CORRELATES OF HIGHER BURDEN OF ANAL HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS (HSIL) IN THE STUDY FOR THEPREVENTIONOF ANAL CANCER (SPANC)

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Objectives: Anal cancer precursor lesions (HSIL) are highly prevalent among homosexual men. In the cervix, larger HSIL size is associated with a higher risk of progression to cancer. Little is known about the relationship between burden of anal HSIL and demographic, behavioural and virological factors.

Methods: The SPANC study is a three-year prospective study of anal HPV and cancer precursors. Homosexual men aged ≥ 35 years undergo behavioural questionnaires, anal swabs and high resolution anoscopy (HRA)-guided biopsy (when required). Number of biopsy-confirmed octants with HSIL was used as a proxy for burden of HSIL.

Results: 450 participants were enrolled by June 2014 (median age 49 years; 29.1% HIV-positive). Among 368 participants biopsied, 139 (35.1%) had HSIL at baseline. Of those, 88 (63.3%) involved only 1 octant. In univariate analyses comparing 1 with >1 octant, more HSIL was associated with higher numbers of recent receptive anal intercourse with condoms (RAIC) partners (p=0.015), HPV16 (p=0.005), both having any, and having higher number, of high-risk (HR)-HPV types detected (p=0.049 and p=0.005 respectively). Age, HIV status, smoking, duration since first anal sex, lifetime and recent numbers of male sexual partners, prevalent low risk HPV types and prevalent HPV18 were not associated with higher HSIL burden. In the multivariate model, HPV16 (p=0.039) and higher numbers of recent RAIC partners (p=0.015) remained associated with HSIL burden.

Conclusions: Larger burden of anal HSIL was associated with prevalent HR-HPV, in particular HPV16, in this cohort. This suggests that larger burden of HSIL may be associated with increased risk of progression to cancer.

OC 15-5

STRATIFYING RISK OF DEVELOPMENT OF ANALCANCER – A PROPOSED CLINICAL ALGORITHM

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Objectives: Anal high grade squamous intra-epithelial lesions (HSIL) are highly prevalent among homosexual men and have a lower rate of progression to cancer than the cervical equivalent. There is currently no published proof of effectiveness of anal HSIL treatment, recurrence rates are typically 50% at one year and side effects are common. Targeting treatment towards those at highest risk of progression may be a preferable approach.

Methods: In the prospective Study of the Prevention of Anal Cancer (SPANC), homosexual men aged ≥ 35 undergo five visits involving anal cytology, HPV DNA testing and high resolution anoscopy with biopsy of visualised lesions. A clinical algorithm was developed which utilised age, detection and persistence of HPV16 and other high risk (HR) HPV types, anal HSIL and lesion size. At study completion, participants were stratified into low, moderate, elevated and highest risk of subsequent anal cancer.

Results: 450 participants had been enrolled into the study by June 2014 (median age 49, 29% HIV positive). Using the clinical algorithm, it is estimated that 16% of SPANC participants will be in the low risk stratum (no HR HPV or HSIL over time), 42% in the moderate risk, 35% in the elevated risk and 7% in the highest risk stratum (persistent HPV16 and/or HSIL).

Conclusions: Repeated testing can identify a small subset of homosexual men with persistent anal HSIL and HPV16. This subset of men is likely to be at greatest risk of progression to anal cancer and thus may benefit most from closer monitoring and potential treatment of their HSIL.

OC 15-6

ANAL CANCER SCREENING IN HIV POSITIVE CZECH MSM

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Objective: HIV positive men who have sex with men (MSM) have high prevalence of anal human papillomavirus (HPV) infection and are at an elevated risk of developing anal cancer. Preventive programs for anal cancer are worthwhile, as early detected lesions could be effectively surgically treated. Despite the high incidence and morbidity of anal cancer in HIV positive MSM, there are no official guidelines for how to effectively screen for anal cancer. More screening approaches are used in different countries based on experience and availability of examination and laboratory methods. Here we are presenting data from the anal cancer screening of HIV positive MSM from the Czech Republic using anal cytology and HPV testing.

Methods: Anal swabs from 45 HIV positive MSM patients were collected into a liquid-based cytological medium. Clinical and cytological findings were compared to HPV genotyping results and to the presence of E6E7 mRNA HPV transcripts.

Results: Cytologically, the most common finding included low-grade lesions. HPV genotyping revealed mixed infection of high risk, as well as low risk HPV types with HPV types 11, 6, and 16 being the most prevalent types detected. The presence of HPV mRNA was predominantly revealed in cytologically abnormal samples ($p<0.05$).

Conclusion: This is the first data about anal cancer screening in HIV positive Czech MSM. Laboratory finding are in concordance with clinical findings, however HPV mRNA testing seems to be more useful for anal cancer screening purposes because of an increased specificity for more advanced lesions, but follow-up data is needed.

OC 16-1

SEXUAL ACTIVITY AND FUNCTION IN PATIENTS WITH PREINVASIVE AND INVASIVE VULVAR LESIONS AFTER COMPLETED TREATMENT

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Background: Sexual activity (SA) and function (SF) are central outcome measures in women affected by preinvasive (VIN) and invasive vulvar (VC) lesions. Data on SA and SF after completed treatment are scares.

Methods: Validated questionnaires including the Female Sexual Function Index (FSFI-d) were provided to 166 women who were surveyed after completion of primary therapy for VIN and VC at the University Medical Center Hamburg-Eppendorf and Asklepios Medical Clinic Altona between March 2011 and June 2012. Furthermore patients could assess the questionnaires online via homepage of the Vulvar Cancer Support Group (n=14).

Results: With an overall response rate of 34.9%, 24 patients with VIN and 34 with VC were evaluable. Median age was 51.5 years, with 34 (58.6%) patients being postmenopausal. Median time since completion of treatment was 17 months. All women underwent vulvar surgery (laser/cold knife/combination). Overall, 14 (25.%) women reported no SA during the last 4 weeks. SA and SF was similar in patients with VIN and VC. Additional analyses contrasting surgical treatment methods yielded no significant differences. Time since surgery did not affect SA and SF. Age, however, was negatively associated to all dimensions of the FSFI-d [desire ($p=0.002$), arousal ($p<0.001$), lubrication ($p<0.001$), orgasm ($p=0.001$), satisfaction ($p=0.027$), pain ($p<0.001$)].

Conclusion: Women who regain sexual activity after treatment of vulvar lesions have a good overall sexual outcome; the results might however be biased by selection with a response rate of 32%. Age is one the most powerful factor influencing SA and SF.

OC 16-2

ROLE OF VULVAR CYTOLOGY VS COLPOSCOPY IN WOMEN WITH CHRONIC VULVOVAGINAL COMPLAINTS AND FUTURE ROLE OF HPV PCR AS A PRIMARY SCREENING MODALITY

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Objective: To evaluate the role of cytology, colposcopy and HPV PCR test in patients with chronic vulvovaginal symptoms.

Materials And Method: It was a cross sectional study conducted on 100 sexually active female with chronic vulvovaginal complaints > 6 months. Pregnant females, known case of malignancy of lower genital tract, patients with active bleeding per vaginum were excluded. A detailed relevant history was taken on preformed questionnaire. All patients were subjected to vulvar cytology ,HPV PCR test and vulvoscopy. Vulval biopsy was taken in patients who found to be positive on either on cytology or colposcopy.

Results: Mean age of patient was 39.1 yr. Most common complaint was pruritus vulva followed by discharge per vaginum. On inspection vulva , 18 patients had abnormality but cytology detected abnormality was found in 10 patients, colposcopic abnormality was positive in 30 patients(12 more subclinical cases) and HPV PCR test was positive in 18 patients. 34 patients were subjected to biopsy and abnormality found in 28 patients. Out of these 28, cytology was positive in 6, colposcopy positive in 28 ,HPV PCR in 12 patients. Sensitivity, specificity, PPV & NPV taking histopathology as a gold standard i.e. 33.3% ,97.5% ,75%, 86.95% of cytology,89%, 97.6%, 89%, 97.6% of colposcopy, 50%, 96.4%, 75%, 90% of HPV PCR respectively

Conclusion: Vulvovaginal cancers are on rise, thus increase the importance of early detection of premalignant and malignant lesions. Cytology vulva has a limited role but High sensitivity and specificity of colposcopy vulva and HPV PCR indicates its role in detecting cases which often missed on naked eye examination. Women with persistent vulvovaginal complaints should be screened and keep in scrutiny for follow up as they are the potential candidates for vulvovaginal malignancies.

OC 16-3

RANDOMIZED TRIAL OF TREATMENT AND FOLLOW-UP OF VAGINAL INTRAEPITHELIAL NEOPLASIA

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Objectives: The aim of the study was to evaluate the effectiveness, tolerability and success rates of different treatment options (laser or topical imiquimod) for vaginal intraepithelial neoplasia (VAIN).

Methods: The study was a randomized controlled three-arm trial enrolling patients (n=24) with histologically confirmed VAIN 2-3 or persisting VAIN 1. The study groups were A) expectant management (n=8), B) laser treatment (n=8) and C) topical imiquimod (n=8). Each group had follow-up colposcopy visits at 4, 8 and 16 weeks including high-risk HPV testing, cytology and punch biopsies.

Results: The preliminary results indicate a tendency for higher HPV clearance rates among patients treated with topical imiquimod (50%, 4 out of 8). In the other treatment groups HPV persisted. Treatment with laser or topical imiquimod was equally effective (normal histology at 16 weeks in 5 patients (63 %) in both groups). Nearly all patients experienced side effects such as pain or fever with topical imiquimod, but none of them discontinued the treatment.

Conclusions: Topical imiquimod appears to be as effective as laser treatment in VAIN, but in addition it may assist HPV clearance and thus promote permanent remission.

OC 16-4

RISK FACTORS AND OUTCOMES OF WOMEN WITH VAGINAL INTRAEPITHELIAL NEOPLASIA GRADE 2 AND 3 (VAIN 2/3) – AN ELEVEN-YEAR EXPERIENCE

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Objective: To evaluate the risk factors and outcomes of women with vaginal intraepithelial neoplasia grade 2 and 3 (VAIN 2/3).

Methods: The medical records of women with VAIN 2/3 in a tertiary hospital over an eleven-year period with a minimum follow up of 12 months were reviewed. Patients' demographic and clinical information related to the diagnosis, treatment and outcome were obtained and analyzed in an excel spreadsheet.

Results: A total of 120 women were diagnosed with VAIN 2/3 over an eleven-year period. After exclusions, ninety-seven women with VAIN 2/3 were analyzed. Median age at diagnosis was 53 years. Of these women, 59% were post-menopausal and 48% had previously undergone hysterectomy. Moreover, 80% had an abnormal PAP smear prior to the diagnosis of VAIN 2/3. Out of 20 women who had high-risk human papilloma virus (hrHPV) DNA test done, 75% had positive result. The diagnosis of VAIN 2/3 was mostly made after a biopsy of a suspicious lesion (73%). The rest were diagnosed on vaginal vault smear (16%) and on vaginal cuffs of radical hysterectomy specimens (11%). Of all these women, 79% underwent treatment and 31% experienced recurrence of disease, of which four women developed cancer of the vagina.

Conclusion: This cohort of women further delineates the demographics of VAIN 2/3. With the high number of abnormal PAP smear related to VAIN 2/3, careful evaluation of the vagina should be performed during colposcopy, as progression to cancer of the vagina in this cohort seems rather significant.

OC 16-5

TRENDS IN MORTALITY OF HUMAN PAPILLOMAVIRUS-RELATED CANCERS IN 1975-2012, FROM THE KANAGAWA CANCER REGISTRY, JAPAN

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Objectives: The impact on total mortality caused by HPV-related cancer in each country needs to be determined, because the prevalence of oncogenic HPV types varies between countries. We analyzed trends in age-standardized mortality rates (ASRs) of HPV-related cancer and age-specific mortality rates of cervical cancer and oropharyngeal cancer in a population-based study in a Japanese setting.

Methods: Using the Kanagawa Cancer Registry in Japan, we identified patients with cancers of the oropharynx, cervix, vulva, vagina, anus and penis between 1975 and 2012. We estimated the ASR of each cancer by sex- and age-specific mortality rates. In addition, we calculated average annual percentage changes (AAPCs) in ASRs using joinpoint regression.

Results: ASRs of oropharyngeal cancers increased among both males (AAPC 8.8% between 1980-2000, $p<0.05$; AAPC 1.3% between 2000-2012, $p<0.05$) and females (AAPC 5.9% between 1991-2012). For anal cancers, ASR increased among men (AAPC 1.8% between 1977-2012, $p<0.05$). Age-specific mortality rates increased for cervical cancer among females under 40 years old ($p<0.05$) and oropharyngeal cancer among males over 50 years old. ASRs of vulvar, vaginal and penile cancers decreased over the study period.

Conclusions: We observed increases in ASRs of cancers involving the oropharynx among males and females, and involving the anus among males. We also observed increases in age-specific mortality rates for cervical cancer among young females, and in oropharyngeal cancer among older males. Preventable deaths caused by HPV among both males and females have to be monitored carefully using population-based methods in Japan.

OC 16-6

HLA CLASS II ANTIGEN EXPRESSION IN CERVICAL INTRAEPITHELIALNEOPLASIA AND INVASIVE CANCER

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Objectives: Expression of HLA molecules on tumor cells is essential for the recognition of tumor antigens by the immune system. HLA class II antigens are expressed by professional antigen-presenting cells, but also by several tumors of non-lymphoid origin. Strong HLA class II antigen expression has been described for a subset of HPV-associated cervical cancers. To characterize HLA class II antigen expression during HPV-induced cervical tumor development, we examined HLA class II antigen expression in cervical precancers and cancers.

Methods: Biopsies of CIN2, CIN3 and invasive SCC were analyzed by immunohistochemical staining with a monoclonal antibody specific for HLA class II antigens (LGII-612.14).

Results: HLA class II antigen expression was absent in the normal cervical epithelium adjacent to lesions. In contrast, expression of HLA class II antigens was observed in all 9 CIN2 lesions (100%), in all 13 CIN3 lesions (100%) and all 19 cancers (100%). More than half of CIN2 lesions (5 out of 9, 55.6%) showed HLA class II antigen expression on all lesion cells while only 7 out of 19 (36.8%) invasive cancers had HLA class II antigen expression on all tumor cells.

Conclusions: Our results suggest that HLA class II antigen expression is commonly induced in precancerous stages of cervical tumorigenesis, with a potentially decreasing frequency in cancers. This observation supports the concept that HLA class II antigen-negative cell clones appear to emerge during tumor progression, possibly as a result of counterselection of HLA class II antigen-positive tumor cells.

OC 17-1

METHYLATION OF HUMAN PAPILLOMAVIRUS 16 L1 GENE IN CERVICAL INTRAEPITHELIAL NEOPLASIA AND CANCER

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Background: Transformation of HPV-infected cells is linked to a severe shift of HPV-gene expression patterns. It goes along with epigenetic activation of E6 and E7 oncogenes leading to p16 overexpression, whereas the late genes are usually silenced.

Objectives: We aimed to investigate the methylation status of all 19 CpGs in the L1-gene in productive p16 negative intermediate and superficial squamous cells versus non-productive but transforming p16-positive lesions and find out the impact of chromosomal integration of HPV genomes on the methylation levels of CpGs within the HPV 16 late genes.

Methods: 48 tissue sections HPV 16 positive samples were examined for $p16^{INK4a}$ and L1 gene expression as well as the presence of koilocytes in the specimens. 5 were diagnosed as CIN1, 9 as CIN 2, 25 as CIN 3 and 9 as squamous cell carcinomas (SCCs). Furthermore, 24 HPV16 positive fresh-frozen carcinoma samples were selected; 12 carcinomas with integrated and 12 with episomal HPV genomes. Methylation levels were obtained by pyrosequencing.

Results: L1-methylation levels were substantially higher in p16-positive transforming HPV-infections in comparison to the productive infections. Carcinoma samples with integrated HPV16 genomes had significantly higher methylation levels in the 3' region of L1, in particular at CpGs 9 to 15.

Conclusion: These data underline the hypothesis that the methylation of the L1 gene substantially increases during neoplastic progression. Methylation was lowest in p16-negative productive HPV-infections presumeably reflecting the active expression in these lesions. Methylation of the CpGs 9-15 may indicate integration of HPV genomes into the host cell genome.

OC 17-2

DICOVERY OF NEW METHYLATION MARKERS TO IMPROVE SCREENING FOR CERVICAL INTROEPITHELIAL NEOPLASIA GRADE 2/3

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Objectives: To identify new methylation markers for high-grade cervical intraepithelial neoplasia (CIN2/3) using innovative genome-wide methylation analysis and to assess their diagnostic performance in cervical scrapings.

Methods: Methylated DNA was enriched from normal cervices and CIN2/3 lesions followed by next-generation sequencing (MethylCap-seq) to identify differential methylation regions (DMRs). The 15 highest ranking differentially methylated genes were validated by MSP. For diagnostic evaluation, QMSP was performed in cervical scrapings from 2 cohorts: 1) cervical carcinoma vs. healthy controls and 2) patients referred from population-based screening with abnormal cytology in whom HPV status was determined.

Results: MethylCap-seq identified 176 DMRs comprising 163 genes. Nine of the 15 genes showed in the validation step significantly more methylation in CIN2/3 lesions compared to normal cervices ($p<0.05$). Subsequently, methylation levels of 8/9 genes were significantly higher in carcinoma compared to normal scrapings. For all 8 genes methylation levels increased with severity of the underlying histological lesion in scrapings from patients with abnormal cytology. In addition to the 8 new genes, also our previous four-gene panel (*C13ORF18/JAM3/EPB41L3/TERT*) was analyzed. The best combination of genes (*C13ORF18/JAM3/AL590705.4*) revealed sensitivity (74%) for CIN2+ comparable to hrHPV testing (79%), while specificity was significantly higher (76% vs 46%, $p\leq 0.05$) in a triage setting after abnormal cytology in population-based screening.

Conclusion: We identified new CIN2/3 specific methylation markers using genome-wide DNA methylation analysis. The diagnostic performance of our new methylation panel shows comparable sensitivity to hrHPV testing for CIN2+, but with higher specificity to prevent referral for unnecessary colposcopy. The next step before implementation in primary screening programs will be validation in population-based cohorts

OC 17-3

HPV ONCOTECT QUANTITATIVE E6, E7 MRNA AS A SINGLE TEST ALTERNATIVE TO HPV 16, 18 AND PAP REFLEX FOLLOWING PRIMARY HPV DNA SCREENING

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Background: HPV DNA has been approved for primary cervical cancer screening. Samples positive for HPV DNA are reflexed to HPV 16, 18 and if negative, the sample is reflexed to PAP.

Methods: In this substudy of samples from *Spathis et al PloS ONE 7:1-9, 2012*, 596 samples (including 196 CIN 2+) with HPV DNA, HPV 16/18, HPV Oncotect E6, E7 mRNA, liquid based cytology, and histology results were analyzed. Using the DNA alone screening algorithm, we compared the performance of HPV OncoTect Quantitative E6, E7 mRNA as a single reflex test with HPV 16/18 and PAP as utilized in the published algorithm.

Results: HPV DNA alone had a specificity of 42% for CIN 2+ while HPV reflex to HPV OncoTect had a specificity of 82% for CIN 2+. HPV DNA+/16, 18+ had a specificity of 87% for CIN 2+ but a sensitivity of 56% for CIN 2+ compared to a HPV OncoTect sensitivity of 86% for CIN 2+. The false negative rate of HPV OncoTect compared to PAP as a reflex to HPV DNA+ samples was the same at 3.3%.

Conclusions: HPV OncoTect is a viable reflex option in the HPV alone screening algorithm that could replace both HPV 16, 18 and PAP reflex using a single, automated, non slide-based test. The combination of HPV DNA and HPV OncoTect also provides a superior clinical laboratory workflow

OC 17-4

GENOME-WIDE METHYLOME ANALYSIS DISCOVERS NOVEL METHYLATION MARKERS FOR BOTH CERVICAL ADENOCARCINOMAS AND SQUAMOUS CELL CARCINOMAS

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Objectives: Cervical adenocarcinomas (ADC) are mainly diagnosed at advanced disease stage. In the last decade, the incidence of ADC increased in most developed countries and represents about 20% of cervical cancers. One explanation for the increase of ADC is the less effective cytomorphological detection of ADC and its precursors in population-based screening programs. Analysis of DNA methylation markers might improve the detection of ADC in earlier stages. The aim of this study was to discover novel methylation markers for cervical cancer detecting both ADC and SCC.

Methods: To generate a global methylation-profile, methylated DNA from 20 normal cervices, 6 ADC and 6 SCC was enriched followed by next-generation-sequencing (MethylCap-seq). Differential methylated markers (DMRs) were selected for verification and validation by bisulfite pyrosequencing or methylation specific PCR (MSP). Quantitative MSP (QMSP) was performed for the clinical evaluation on cervical scrapings from an independent cohort of 89 women with a normal cervix and 89 cervical cancer patients comprising ADC and SCC.

Results: Validation of the highest ranking 15 DMRs resulted in 5 markers exhibiting different methylation between normal and cancer tissues ($p<0.05$). Using QMSP analysis on cervical scrapings, the sensitivity of these 5 markers varied from 76.5% to 88.8% to detect both ADC and SCC with almost all normal scrapings negative (specificity: 94% -100%).

Conclusion: Using MethylCap-seq analysis, we identified 5 new methylation markers with a high sensitivity for both ADC and SCC in cervical scrapings. A large series of scrapings with ADC and its precursors is needed to validate its clinical relevance.

OC 17-5

COMPARISON OF MANUAL PROCESSING FOR P16/KI-67 DUAL STAIN

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Objectives: Immunocytochemical detection of overexpression of p16 is valuable for the triage of HPV-positive cytologically normal cases and borderline/low-grade abnormalities. Simultaneous detection of the proliferation marker Ki-67 significantly enhances its specificity. Meanwhile this test is also available in an automated staining system (Ventana Benchmark XT [VB]). In a routine lab with high-throughput testing we compared automated (VB) with manual (MS) staining.

Methods: 495 Thinprep specimens routinely collected for triage were each splitted. First two slides were prepared for p16/Ki-67 Dual Stain and secondly two slides for Pap cytology and another marker. Staining was performed according to the instructions of the manufacturer (Roche Ventana, Mannheim, Germany) and read by two cytologists. Positivity was grouped <3, 3-10 and >10 cells.

Results: With MS 236 smears were positive vs 247 with VB. About one third of the positives contained <3, 3-10 and >10 positive cells, respectively. Only 2 slides were rated invalid (one MS, one VB). In 19 of 495 cases (3,8 %) the results were discrepant: 4 cases MS-pos/VB-neg vs 15 cases MS-neg/VB-pos. In 18 of the 19 discrepancies <3 cells were rated positive. Only minimal differences between the two procedures were observed in the number of cells rated positive: in 9 of 232 cases positive with both approaches a minor difference was observed, only in one case a clear difference (<3 vs >10). Association with HPV status will be reported.

Conclusion: Automated staining with the Ventana Benchmark is slightly more sensitive than manual staining for p16/Ki-67. Only minor discrepancies are observed.

OC 17-6

ESTABLISHED AND NOVEL PROTEIN BIOMARKERS FOR EARLY DETECTION OF CERVICAL CANCER CELLS

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**on behalf of the PIPAVIR consortium (www.pipavir.com)*

Objectives: Early detection of cervical intraepithelial neoplasia (CIN) in cervical smears is key to efficient control of the disease. Current protocols, relying respectively on cytological assessment of cervical smears and detection of high-risk HPV DNA in such smears, fall short of reliably detecting CIN. Protein markers, such as viral oncoproteins and the host protein $p16^{INK4A}$ were proposed as more efficient tools for the detection of cervical precancerous and cancerous lesions.

Method: To assess the role, if any, of $p16^{INK4A}$ for maintenance of the transformed phenotype in established cervical carcinoma cells, we used shRNA-mediated knockdown of $p16^{INK4A}$ and followed cell proliferation and survival of $p16^{INK4A}$-depleted cells. We also developed a sandwich ELISA to detect E7 proteins in cervical smears in a routine screening setting.

Results: Depletion of $p16^{INK4A}$ from cervical cancer cells led to a significant reduction of E7 gene expression and otherwise yielded mixed results, ranging from induction of cellular senescence to no effect on cell proliferation. E7 proteins are detected by E7-ELISA in cervical smears derived from women with histology-confirmed CIN.

Conclusions: Our data suggest that $p16^{INK4A}$ is dispensable for the proliferation of several cervical carcinoma cell lines. Together with recent work showing that E7 drives $p16^{INK4A}$ expression in cervical cancer cells, our results provide a potential molecular basis for the observed high expression level of $p16^{INK4A}$ in most cervical cancers. The results reported here further warrant the use of HPV E7 proteins as biomarkers for cervical cancer detection.

OC 17-7

EPIGENETIC CONTROL OF HUMAN PAPILLOMAVIRUS LATE GENE EXPRESSION

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Background: L1 and L2 expression is restricted to intermediate and superficial layers of HPV infected squamous epithelia. Differential methylation of the viral genome has been proposed to control its transcription during the normal viral life cycle. In CaSki cervical cancer cells several hundreds of HPV 16 genome copies are integrated. The vast majority of these genome copies are methylated and not transcriptionally active. Only the E6-E7 genes of the most 3`located HPV genome are transcribed. This genomic and epigenomic structure of HPV 16 in CaSki cells resembles episomal HPV-genomes in infected basal squamous epithelial cells.

Objective: We were interested to test whether epigenetic inhibitors like 5-aza-2′-deoxycytidine (DAC) can activate the expression of the L1 gene in undifferentiated HPV-infected keratinocytes carrying episomal HPV genomes.

Methods: CaSki cells as model for the episomal genome configuration were treated with 5aza-dC in different dosages and over different time intervals. The expression of L1 gene was quantified by RT-qPCR and Western blotting. The methylation state of the L1 gene upon DAC treatment was determined by bisulfide conversion and subsequent pyrosequencing.

Results: DAC induced DNA hypomethylation within one week of treatment. After 2 weeks of DAC treatment expression of the L1 gene was substantially upregulated.

Conclusion: These data underline the hypothesis that treatment with DAC of HPV-induced lesions may activate the expression of L1 (and possibly L2) in HPV infected basal squamous epithelial cells. This may trigger a T-cell response and elimination of the HPV-induced lesions. The clinical validity of this therapeutic concept is currently under investigation.

OC 17-8

IDENTIFICATION OF NOVEL KEY MODULES REGULATING CELL CYCLE AND APOPTOSIS IN CERVICAL CARCINOMA.

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Objectives: Generation of pathogenetic insights into cervical carcinoma (CC), can lead to targeted therapies.

Methods: To this end, we performed an extensive study employing novel gene expression technologies from 5 CC patients and 5 matched controls.

Results: Gene Ontology and Gene-Signature Disease Databases revealed 1406 differentially expressed genes (DEGs) correlating with specific categories and pathways, and forming a network characterized by cell cycle and apoptosis deregulation. Specifically, upregulation of apoptosis-related genes (54 genes), and downregulation of most transcriptional factors involved in core developmental processes, was one of the key findings common among most of gynecological cancer (GC) studies. Additionally, a significant overlap (87 DEGs) was encountered in gene signatures between the recently identified region of squamo-columnar junction (SCJ) and CC patients. More significant was the correlation between CC and embryonic stem (ES) cell expression profiles, where transcriptional modules operating in ES cells, like Myc (35 genes) and the Polycomb (47 genes), were found also enriched in CC. Combining computational analysis of the promoter regions of DEGs with the binding patterns of known transcription regulators (TRs) in HeLa cells, we identified certain novel sets of modules regulating specific processes which characterized cervical cancer patients. The E2F/NFY module was enriched in the cell cycle process, while AP2 and JUN modules were documented as apoptotic regulating modules.

Conclusions: In summary, these data permit us to propose common features among CC, other GCs, ES, and pre-malignant (SCJ) states, where certain modules regulate the two key processes (cell cycle and apoptosis) aberrantly operating in CC.

OC 17-9

THE EPIGENETIC DRUG 5-AZA-2'-DEOXYCYTIDINE DOWNREGULATES THE VIRAL ONCOGENES E6 & E7 AND REDUCES PROLIFERATION IN HPV ASSOCIATED CANCERS

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Background: Epigenetic therapeutics are steadily increasing in importance for the treatment of various cancers. Several studies have so far indicated epigenetic mechanisms in the regulation of viral oncogene expression in HPV-induced cervical lesions. However, the effect of epigenetic drugs on HPV16 oncogene expression and growth patterns of HPV16-induced cancers remains unclear.

Objective: We examined the applicability of the DNA methyltransferase inhibitor 5-aza-2'-deoxycytidine (DAC) on HPV-16 transformed cell lines.

Methods: HPV-16 positive cancer cell lines of the cervix and head and neck were treated with various concentrations of DAC for 72 hours. Methylation levels were assessed using bisulfite treatment and pyrosequencing of the early HPV16 promoter and the long interspersed nuclear element-1 (LINE-1) as a marker for global methylation levels. mRNA and protein levels of the viral oncogenes E6 and E7 and related genes were determined via qRT-PCR and Western Blot. Proliferation and the level of differentiation were monitored.

Results: DAC treatment induced global DNA demethylation, as well as demethylation of CpG-sites in the upstream regulatory region of the HPV genome. This was linked to a significant decrease of E6 and E7 oncogene transcripts and E7 protein levels while p53 protein levels were upregulated. These findings were associated with dose dependent reduced proliferation and an induction of differentiation in the treated cell lines.

Conclusions: 5-aza-2'-deoxycytidine is a promising candidate substance in order to epigenetically suppress viral oncogene expression and proliferation.

OC 17-10

COFILIN-1 AND CATHEPSIN-D ARE PUTATIVE EARLY CERVICAL CANCER BIOMARKERS

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Objectives: Despite preventive measures, there is still a clinical need for reliable early cervical cancer biomarkers. Malignant transformation of the cervical epithelium is accompanied by qualitative and quantitative changes in protein expression profiles of the infected cells. The aim of our study was to identify proteins associated with cervical cancer by proteomic analysis and evaluate the potential use of these proteins as putative biomarkers.

Methods: In the present study, we undertook a systematic analysis for intracellular and secretome profiles of four cervical cell lines, i.e. HCK1T, a normal cervical epithelium cell line, HeLa [HPV18+], SiHa, [HPV16+], and C-33A [HPV-], exhibiting unique complementary molecular and phenotypic features, by employing 2D electrophoresis and MALDI-TOF mass spectrometry. Western blots and immunohistochemistry were performed on total cell extract and cervical tissue sections, respectively.

Results: 168 proteins in the total cell extract and 125 in the secretome were differentially expressed between normal (HCK1T) and cancer (HeLa, SiHa, C-33A) cell lines. The most significant group of differentially expressed intracellular proteins was related to cytoskeletal remodeling. Among these, the cytoskeletal protein Cofilin-1 was further analyzed. In both 2D electrophoresis and WB analysis, Cofilin-1 was significantly upregulated in HeLa and C-33A cells, compared to HCK1T. The secretome proteomic comparison has as prominent feature Cathepsin-D, a protease involved in cancer invasiveness, which was upregulated in SiHa cells compared to control HCK1T. The proteomic result was further validated by immunohistochemistry.

Conclusion: These novel data provide the impetus for further exploitation and validation of Cofilin-1 and Cathepsin-D as putative cervical cancer biomarkers.

OC 17-11

SECRETOME MAP STUDY OF NORMAL AND MALIGNANT CERVICAL CELL LINES

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Objectives: Cervical cancer is caused by sexually acquired infection with certain HPV types. Two HPV types (16 and 18) cause 70% of cervical cancers and precancerous cervical lesions. The aim of our study was to identify biological processes involved in malignant cell interactions with surrounding tissues by proteomic analysis of the secretome from control and cancerous cervical cell lines.

Methods: Secreted proteins were isolated from four cervical cell lines: HCK1T, a normal cervical epithelium cell line, HeLa [HPV18+], SiHa, [HPV16+], and C-33A [HPV-]. The secretome samples were analyzed by 2D electrophoresis and gels were stained with Coomassie Blue. Image comparison was performed by the PDQuest software. Differentially expressed proteins between normal and cancer cell lines (fold change >2) were identified by MALDI-TOF MS. Bioinformatic analysis was performed by the PANTHER software.

Results: A total of 125 proteins in the secretome (68 upregulated, and 57 downregulated) were differentially expressed between normal (HCK1T) and cancer (HeLa, SiHa, C-33A) cell lines. The percentage of secreted proteins identified in this list is 34.5%, which is much higher than the corresponding percentage (7%) in the total cell extract. The majority of differentially expressed proteins have catalytic activity and a significant number of upregulated enzymes in cancer cell lines are proteases implicated in extracellular matrix remodeling.

Conclusion: The proteomic analysis of the secretome from cervical cell lines indicates that the protocol used is effective for isolating secreted proteins. The proteases secreted by cancer cells are likely to play a role in the invasion of the surrounding tissue.

P 1-1

PREVALENCE OF HPV IN A PORTUGUESE POPULATION CENTRE LISBON

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Introduction: Several data confirms that HPV is the etiological agent of cervical cancer, with an incidence of 13.1/100.000 in Portugal (Globocan, 2012). There is substantial variation in HPV prevalence: according to the latest data, prevalence of HPV infection varies between 2% and nearly 30%. IARC has establishment the adverse effects of different factors, such as, long-term use of oral contraceptives, high parity, smoking and sexually transmitted infections.

Aim: Determine the HPV prevalence in a population selected from health care primary units of Lisbon.

Methods: 647 women, from 7 primary health care units (average: 39 yo), were randomly selected for the HPV detection. Samples were collected, processed and stained with Papanicolaou. The presence of HPV DNA was evaluated with an In House assay: using SPF primers, a 75 bp amplicon was amplified using Real Time PCR (SYBR Green dye). Samples with a positive result were genotyped using commercial kits (INNO-LIPA and Papillocheck). Under informed consent, data for the preparation of a descriptive analysis of the population were collected for different category variables (menarche age, onset sexual activity, contraceptive method, pregnancy's and vaginal flora. Prevalence of HPV were estimated by observation and retrospective analysis.

Results: HPV DNA was detected in 46,90% (287/612) of the samples against 53,19% (325/612) of negative results. Simple infection were represented in 64.4% (159/283), where the most prevalent genotypes detected were HPV16 40.7% (61/150), HPV56 7.3% (11/150) and HPV31 6.7% (10/150).

Conclusions: Our present study suggests a prevalence of HPV 47%, where the most prevalent genotypes are HPV16.

P 1-2

PREVALENCE OF INTRAEPTHELIAL LESIONS OF THE LOWER GENITAL TRACT IN PATIENTES <24 YEARS

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Background: Genital lesions caused by the Human Papilloma Virus (HPV) at the Lower Genital Tract (LGT) in the cervix, vagina, vulva and anus are frequent in women.

Objectives: This is a retrospective, observational study of the prevalence of HPV-related lesions in 2 groups of patients <24y (immunocompetent and immunosuppressed)

Methods: Data were collected from 1088 women < 24 years, attended in the Lower Genital Tract Unit. Hospital de Clínicas "José de San Martín" (January 2009 - July 2013) The gold standard diagnosis was the histopathologic study of the biopsy.

Results: HPV lesions were found in 171/1088 (15.7%).
Immunocompetent Group: Genital Warts (GW) vulva: 42.67% (67/1257); GW cervix: 14.01% (22/157); LSIL cervix: 12.73% (20/157); HSIL cervix: 2.54% (4/157) (CIN II: 1, CIN III: 3), LG-VAIN: 1.27% (2/157); GW Vagina: 0.63% (1/157); HG-VAIN: 1.27% (2/157) (VAIN II 1; VAIN III 1); Multicentric lesions: 24.84% (39/157)
Immunossuppressed Group: all patients had multicentric lesions. The predominant were GW vulva: 71.42% (10/14); LSIL cervix: 35.71% (5/14); LG-VAIN: 14.28% (2/14); HSIL cervix and anus: 7.14% (1/14)

Conclusions: LSIL lesions are common in patients <24y, multicentric lesions are very common in immunossuppressed women

P 1-3

DETECTION OF BETA AND GAMMA HUMAN PAPILLOMAVIRUSES IN ANAL SWABS OF HIV-INFECTED AND UNINFECTED MEN WHO HAVE SEX WITH MEN

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Objectives: Presence of cutaneous Human Papillomaviruses (HPV) has been demonstrated in mucosal samples. However, their presence in anal swabs has been rarely investigated. Here, we aimed to assess the prevalence, genotype diversity and determinants of cutaneous HPV anal infection in sexually active men who have sex with men (MSM).

Methods: Anal samples, obtained from 609 MSM (437 HIV-uninfected and 172 HIV-infected), were collected in PreservCyt (Hologic) using a Dacron swab. Beta and Gamma HPVs were revealed using a type-specific multiplex genotyping (TS-MPG) assay (IARC, Lyon, France), which combines multiplex PCR with a bead-based Luminex technology. Socio-demographic and behavioral data were also collected by face-to-face interviews.

Results: Overall, βHPV infection was detected in 166 out of 602 (27.6%) valid samples. The prevalence in HIV-uninfected and infected MSM was similar (27.2% vs. 28.6%, $p=0.73$). Additionally, gHPV infection was detected in 175 out of 597 (29.3%) valid samples (33.5% in HIV-infected MSM vs. 27.9% in HIV-uninfected MSM, $p=0.16$). β and γ-HPV co-infection was evidenced in 40/429 (9.3%) and 18/166 (10.8%) HIV-uninfected and -infected individuals, respectively ($p=0.57$). No significant association was found between β and/or γ HPV anal infection and viro-immunological characteristics, or socio-demographic and behavioral factors.

Conclusions: Both Beta and Gamma HPV types were detected in a significant and similar proportion of anal samples from MSM. In this population, neither HIV status

P 1-4

MOTHER-TO-INFANT TRANSMISSION OF HIGH-RISK HUMAN PAPILLOMAVIRUS

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Purpose: The presence of high-risk Human Papillomavirus (HR-HPV) in the neonatal oral mucosa supports the transmission of HPV from the mother to her newborn. The aim of this prospective study was to evaluate the rate of HPV infection in pregnant women and their neonates and to analyze the risk factors associated with vertical transmission.

Materials and Methods: The study included healthy pregnant women (n=5361; stage of gestation, 39.5±2.1 weeks). Cervical HPV testing was undertaken and mouth secretions and oral mucosa of neonates were tested for HPV immediately after delivery by means of polymerase chain reaction (PCR). HPV-positive neonates were rechecked 6 months postpartum. Kappa statistics and the Wilcoxon test were used to assess concordance.

Results: HPV deoxy-ribonucleic acid (DNA) was detected in 25.9% (1393/5361) of women who were positive for HPV DNA in pregnancy. At birth, 6.3% (338/5361) of neonates were HPV DNA positive. The HPV genotype-specific concordance rate of maternal and neonatal HPV DNA was 100%. Maternal HPV positivity was associated with primiparity (p=0.015) and abnormal cervical cytology (p=0.007). The rate of vertical transmission was estimated at 21.8% (1174/5361) and was positively correlated with vaginal delivery (p=0.050) and maternal multiple HPV types infection (p=0.003), but not with labor duration and premature rupture of membranes (PROM). Neonates with HPV showed a tendency for higher maternal total HPV copy number than neonates without HPV, but this difference was not significant (p=0.081). The neonatal HPV DNA found at birth were all cleared at 6 months after delivery.

Discussion/Conclusion: Vertical transmission is associated with vaginal delivery through an infected cervix and multiple HPV types in the mother. However, neonatal HPV infection through vertical transmission is thought to be a transient. The absence of persistent infection in infants at 6 months after delivery in fact may suggest temporary inoculation rather than true vertical infection.

P 1-5

PATTERN OF HIGH-RISK HPV VIRAL LOAD AFTER QUADRIVALENT HPV VACCINATION IN PATIENTS TREATED BY CONIZATION

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OBJECTIVE: Persistence of high-risk human papillomavirus (HR-HPV) is an essential factor in the progression of cervical intraepithelial neoplasia (CIN) after treatment. We analyzed a pattern of HR-HPV viral load after quadrivalent HPV vaccination in patients treated by conization.

METHODS: Cervical swabs from 122 women were collected before conization, at 6 months and at 12 months after quadrivalent HPV vaccination. The vaccination was performed at 6-12 months after conization. HR-HPV viral load was assessed by hybrid capture 2. The data of cohort was compared with those of vaccine-naive CIN patients who underwent conization and were represented by a historical cohort with similar age and CIN grade.

RESULTS: HR-HPV persistence rate was 14.8% (18/122) at 12 months after vaccination. Eight of these (6.6%) had HR-HPV negative after conization and were converted to HR-HPV positive after vaccination. One of 122 patients was diagnosed histologically more than CIN 2 after vaccination. Additionally, margin status was correlated with risk of HR-HPV persistence. Compared to the vaccine-naive cohort after conization, the rate of HR-HPV persistence or CIN recurrence was not significantly different in patients who underwent conization followed by quadrivalent HPV vaccination.

CONCLUSION: HR-HPV persistence was not related to whether quadrivalent HPV vaccination or not in patients who underwent conization. However, the rate of CIN recurrence in analyzed group was too low to speculate whether vaccination can prevent CIN after treatment. In addition, further studies are needed to evaluate whether HR-HPV viral load after conization can predict subsequent cervical lesion.

P 1-6

GENOTYPE DISTRIBUTION OF HUMAN PAPILLOMAVIRUS IN MEN FROM SALVADOR, BAHIA, BRAZIL

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Objectives: assess the distribution of HPV genotypes in men, describe the rates of multiple infections and demonstrate the association between HPV genotypes and male age in Salvador, Bahia, Brazil.

Methods: The study was conducted on 319 men who sought Studart&Studart Laboratory for performing the HPV genotyping in the period January 2011 to December 2013. Genotyping was performed using the technique PapilloCheck. Patients were divided into three age groups: less than or equal to 29 years; 30-49 years and greater than 50 years.

Results: From the 319 samples, 207 were positive for one or more types of HPV, 78 negative and 34 invalid. The most prevalent genotypes were HPV 06 (47%), HPV 11 (11.6%), HPV 16 (6.7%), HPV 44/55 (6.7%), HPV 42 (6.0%), HPV 53 (5.3%), HPV 56 (4.9%); HPV 18 was present in only 1.1% of the samples. HPV was detected in all age groups and was more frequent in the younger age group. HPV 06 was the most prevalent in all age groups. The HPV 44/55 was more frequent in the age group 30-49 years. Was observed more infections with a single HPV type compared multiple infections.

Conclusions: The most common HPV genotypes in the male population were HPV 06, HPV 11, HPV 16, HPV 44/55, HPV 53 and HPV 56, prevalence of infections by a single HPV type was observed and a higher incidence of HPV in young male population.

P 1-7

HPV TYPES PRESENT IN EXTERNAL GENITAL WARTS IN THE ARGENTINEAN POPULATION

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Background: Genital warts are a benign disease, with a very frustrating management due to its recurrent nature and frequent psicological harm in patients and it is one of the most common sexually transmitted disease. HPV types 6 and 11 are present in 90% of EGW all over the world.

Objectives: The objective of this study is to know which are the prevalent HPV types involved in genital warts in Argentinean population.

Methods: Women 15-45 years attending at outpatient consultation were enrolled between September 2012 and June 2014. Patients previously vaccinated with commercially available vaccines (Gardasil® or Cervarix®) were not invited to participate.
Biopsies from genital warts were taken through an excisional procedure under local anesthesia. After histological confirmation, a part of the specimen was sent to the laboratory to investigate the presence of HPV 6 and 11 by PCR analysis.

Results: 150/160 (93.75) had histological confirmation of GW and were analyzed by PCR to detect HPV type; we found HPV 6 in 120 patients (80%), HPV 11 in 19 patients (12.67%), coinfection with HPV 6 and 11 in 1 patient (0.67%). 6 patients were PCR negative for HPV with histological confirmation of HPV (4%), and 4 patients had other HPV types, HPV 16 in 3 cases (2%) and HPV 73 in 1 case (0.66%).

Conclusions: HPV Type 6 and 11 are present in 93.33% of genital warts in Argentinean population.

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P 1-8

DISTRIBUTION OF CERVICAL LESIONS IN SÃO TOMÉ E PRÍNCIPE DEMOCRATIC REPUBLIC - A MIDDLE AFRICA COUNTRY

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Objectives: Determination of cervical lesions distribution in S. Tomé e Príncipe Democratic Republic (STPDR).

Methods: A cross-sectional descriptive study was carried out between December 2011 and March 2014 in a total of 4569 patients in whom liquid based cervical samples (Turbitec©) were obtained. The cytological findings were classified according Bethesda system. A questionnaire with the following items: age, parity and age of first sexual intercourse was obtained from all women. In 4482 cases this information was complete.

Results: Epithelial cell abnormalities were seen in 12.0 % of the cases. Atypical squamous cells of undetermined significance (ASC-US) represents 5.11 % of the cases, low-grade squamous intraepithelial lesions (LSIL) represents 4.17 % of the cases atypical squamous cells: cannot exclude high-grade intraepithelial lesions (ASC-H) were 0.83 % of the cases, high-grade squamous intraepithelial lesions (HSIL) were found in 1.78 % of the cases, atypical glandular cell (AGC) in 0.089 % and squamous cell carcinoma in 0.022%. The age range of minor lesions (ASC-US and LSIL) was 18-57 years (median age 34 years) and 20-60 years (median age 36.59 years) for major lesions (ASC-H, AGC, HSIL and carcinoma).

Conclusions: This is the first attempt to document the epidemiological profile of cervical lesions in this country. The high percentage of epithelial cell abnormalities found in this study confirms the public health problem and the need for further epidemiological studies in order to define a National Cervical Cancer Prevention Program.

P 1-9

PERFORMANCE OF COBAS 4800 HPV TESTING AND GENOTYPE - SPECIFIC DISTRIBUTION IN OPORTUNISTIC CERVICAL CANCER SCREENING

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Objectives: We aimed to study the performance of the fully automated system cobas 4800 for the detection of HR HPV in cervical samples and the genotype-specific distribution in women with LSIL+ lesions undergoing opportunistic screening of cervical cancer in a Gynaecological Unit in the metropolitan area of Madrid.

Methods: 141 cervical samples with positive results by cobas 4800 system (Roche Diagnostics) were included. Fully genotyping was further carried out in cobas 4800 positive samples using Liner Array HPV genotyping test (Roche Diagnostics). Cytology results were also investigated. The same vial (Thin Prep) was used for cytology and HPV detection.

Results: Overall, 105 (74.5 %) women who tested positive by cobas 4800 had non-normal cytology. 26 (18.5 %) had ASC-US, 59 (41.8 %) had LSIL, 16 (11.3%) HSIL and 4 (2.8 %) invasive cancer. The more prevalent HR HPV genotypes detected in HSIL+ lesions were: HPV 16 (9, 56.2%), HPV 45(3, 18.7%), HPV 52 (3, 18.7%). In total, cobas 4800 detected 41 out of 43 HPV 16 and 8 out of 10 HPV 18 detected by Linear Array.

Conclusion: There was an excellent correlation in the detection of HPV 16 or HPV 18 between cobas 4800 and Linear Array in the samples associated to LSIL+ lesions. Our data also show that genotypes 45 and 52 play also an important role in precancerous lesions and are detected frequently in the absence of genotypes 16 or 18. Therefore the utility of identifying these genotypes separately requires follow up studies.

P 1-10

NATURAL HISTORY OF CERVICAL HPV INFECTIONS IN DIFFERENT GROUPS OF HIGH RISK WOMEN ENROLLED IN THE VALHIDATE STUDY

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Objective: to describe the natural history of HPV infection in HIV+ women (HIW), foreign-born women (FBW), and adolescent/young women (<26years) (AYW), compared to women attending PAP-screening program (SPW) enrolled in the VALHIDATE study [1].
Methods: longitudinal cytopathologic results in testing and control groups were defined as negative, low-grade (LG-SIL) or high-grade (HG-SIL) squamous intraepithelial lesion. The odds-ratio (OR) and 95%CI of SIL/HG-SIL development, and regression to negative cytology was assessed for each group. Probability of progression/regression was assessed by Kaplan-Meier plots.
Results: 860 women (510 HIW, 56 FBW, 67 AYW, and 227 SPW) accounting for 1516.9 person/years follow-up were included in this analysis. Progression to HG-SIL was observed in 17.9%, 10%, and 7.7% of HPV 16/18 infected HIW,FBW and SPW respectively. AYW had a 22.2% of persistent HPV 16/18 infections. The AYW and FBW groups had higher probability of disease regression (OR 3.5; 95%CI 1.8-6.8, and OR 2.4; 95% CI 1.2-4.9 respectively), while women in the HIW group had a lower probability of lesion regression (OR 0.5; 95%CI 0.3-0.8) if compared to the control group. The probability of SIL at 3 years from baseline evaluation was 28.1%, 13.2%, 11.7%, and 8.4% (logrank test $p<0.025$), and the probability of regression to negative cytology was 13.2%, 34.6%, 56.4%, and 19.9% (logrank test $p<0.0001$) in HIW, FBW, AYW and SPW.
Conclusions: The differences in the natural history of HPV infections observed underscore the need for specifically addressed screening programs.
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P 1-11

HPV GENOTYPES IN INTRAANAL SAMPLES OF IMMUNOCOMPETENT WOMEN AND CLINICAL AND LIQUID-BASED CYTOLOGY FINDINGS.

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Objectives: To identify genotypes of high-risk HPV in immunocompetent women and the associations with clinical and cytological findings.
Methods: This was an cross-sectional study of 148 women attended at the Federal University of Ceará (UFC) between August 2011 and June 2012. A sample of the residual material of liquid-based cytology (Surepath®) was used for RT-PCR on the Cobas 4800 (Roche) identifying 14 types of HPV (16, 18 and 12 others types) Clinical and cytological data were surveyed in records. Student's t tests and Fisher exact test were applied for a CI of 95%.
Results: Of the 148 tests 8 (5.4%) were invalid. In the 57 positive cases (57/140), the distribution was as follows: 16 (8 [14%]), 18 (3 [5.3%]) HPV-16 and others 12 (18 [34%]), HPV-18 and others 12 (8 [15%]). Associations between HPV genotypes occurred in 26 of 57 positive cases (45.6%). The average age was similar in both groups. The number of sexual partners referred was not significantly different between the two groups. The practice of anal sex did not differ between the groups. The HPV positivity was not associated to the presence of genital lesions nor the number of sites affected. However, among the positive cases atypical intra-anal cytology was significantly more frequent. Among the HPV positive = 17 (25%) and in negative = 12 (14.5%) (RR = 2.06, 95% CI = 1.06 to 3.98).
Conclusions: The presence of intraanal high-risk HPV is frequent and its presence is associated with an increased risk of abnormal intraanal cytology.

P 1-12

PREVALENCE OF CHLAMYDIA TRACHOMATIS INFECTION ON A COHORT OF SELECTED ASYMPTOMATIC YOUNG WOMEN IN MILAN, ITALY.

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Objective: To perform an epidemiological and microbiological monitoring of Chlamydia trachomatis (CT) infection in a cohort of young sexually active women aged 18-20 years.

Methods: Stored cervical samples from women who took part in the European Institute of Oncology (IEO, Milan) trial on HPV immunization program were used. We investigated demographic and behavioral risk factors associated with sexually transmitted infections: young age, smoking, multiple sexual partners, age at first intercourse, use of oral contraception or condoms, and co-infection with HPV. A nested PCR assay targeting cryptic plasmid of CT was performed as previously described by Jalal et al. 2006. The statistical significance of differences of studied variable between patients with different Chlamydia test outcomes was estimated.

Results: 518 girls (median age 18.7yrs, range 18–22) were included for this analysis. Twenty four (4.6%) resulted positive to Chlamydia test. Exact analysis didn't underline significant differences for variables included, except for HR-HPV infection ($p<0.001$, Chi-square test). CT was found in 12.9% within HPV-positive cases and in 3.4% of HPV-negative young women.

Conclusions: Despite data reported in literature we didn't find any correlation between the presence of Chlamydia and any behavioral risk factors considered with the exception of HR-HPV infection. This information on chlamydial asymptomatic infections could provide important consequences for patients to access to control programs and to reinforce sexual health education, and for clinicians to share with patients on the importance of screening to prevent *sequelae*.

P 1-13

HIGH PREVALENCE OF HUMAN PAPILLOMAVIRUS (HPV) IN VULVAR AND VAGINAL CARCINOMAS FROM BRAZIL

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Objective: This study aimed to evaluate the prevalence of HPV and HPV16 and 18 genotypes in a group of patients with vulvar and vagina invasive carcinomas.

Methods: The samples consisted of paraffin embedded specimens from 57 patients with primary invasive vulvar cancer and 20 patients with primary invasive cancer of the vagina. HPV detection employed the polymerase chain reaction (PCR) with SPF (short PCR fragment) 1/2 primers, and HPV 16 and 18 genotyping was performed by using specific primers designed for these genotypes. Differences between HPV positive and negative groups were analyzed by Fisher's exact test.

Results - Conclusions: The prevalence of HPV in vulvar cancer samples was 89%. HPV16 was detected in 42% and HPV18 in 24% of the HPV positive cases. HPV prevalence in vaginal cancer samples was 90%. Among these, 56% were HPV16 and 18% were HPV18. About 70% of HPV positive patients were over 50 years. Vulvar cancer was significantly associated with smoking ($p = 0.0110$) and lymph node metastasis ($p = 0.0304$). Tumor differentiation was significantly associated with the presence of HPV in patients with cancer of the vulva ($p= 0,0158$). A better prognosis was observed for HPV positive patients with vaginal cancer ($p = 0,0304$). Based on the results, it was estimated that HPV vaccine could prevent 58% of the vulvar cancer cases and 65% of the vaginal cancer.

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P 1-14

HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION IN AN ADOLESCENT: A CASE STUDY

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Objective: To report a case of high grade squamous intraepithelial lesion in the cervice of a 16 years old adolescent, showing that this lesion can appear in early ages and test what kind of HPV this adolescent was infected.

Case report: Patient ABX 5573, consulted the Public Health Service of Santo Angelo, Rio Grande do Sul, Brazil, complaining of pelvic pain. Cytology evidencing high-grade squamous intraepithelial lesion where colected in this ocasion. The hybrid capture tests used for the detection of high-risk and low-risk genital HPV-DNA types was positive for high-risk HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68 and low-risk HPV (LR-HPV): 6, 11, 42, 43 and 44. As it was a high grade lesion this patient was send to colposcopy with cervical biopsy. We also send material to PCR.

Final considerations: adolescent are precocious sexually ative nowadays, so we should think about initiating screening earlier with cytological smear. Citology, colposcopy, molecular tests and histopatological examination are all methods to diagnose and prevent cervical cancer.

P 1-15

IS THERE A CLINICAL PROFILE FOR PATIENTS WITH PERSISTENT HPV INFECTION AFTER CONIZATION?

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OBJECTIVE: To study the cofactors associated with persistence of HPV infection after conizations performed due to CIN 2+.

MATERIAL AND METHODS: retrospective study carried out by reviewing clinical records of all women with a conization performed after CIN 2+ diagnosis between January, 1st .2009 and December, 31st 2011 in the Lower-genital-tract unit of the Universitary Clinical Hospital of Málaga (Spain)

RESULTS: A total of 255 conizations were identified during the study period. The average age of patients was 36.1 years (21-66 years); 12.1 % were menopausal and 25.9 % presented viral persistence 6 months after of conization.
Colposcopy was positive in 83,3 % of cases. In a 44 %, the lesion was located in a single quadrant and at 12h. Histological diagnosis showed squamous lesion in 85% of cases and adenocarcinoma in 1.5 % (associated with genotype 18).
47% of cases were smokers and 10.6 % ex-smokers. 37.9 % of patients had used oral contraceptives (27.3 % for more than three years). 62.1 % had been pregnant at least once, and 44% had had one or more deliveries. 9.1 % were immunosuppressed (3% HIV).
Only 3% of the sample was vaccinated.

CONCLUSIONS:
1.- Our results show that parity, tobacco and oral contraceptives are cofactors strongly associated with the viral persistence after conization .
2.- It should be highlighted the low vaccination rate in this population.

P 1-16

HUMAN PAPILLOMAVIRUS (HPV) GENOTYPE DISTRIBUTION IN INVASIVE CERVICAL CANCERS IN MARTINIQUE (FRENCH WEST INDIES)

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Invasive cervical cancer (ICC) is a leading cause of cancer mortality in Caribbean countries. The present study was conducted in Martinique (French Caribbean island). An organized screening of cervical cancer by Pap smears has been implemented in the island since 1991. This program has contributed to a decline of ICC. However, the incidence remains higher than in mainland France. We evaluated the HPV type distribution in pathologic samples of ICC. A total of 131 formalin-fixed, paraffin-embedded tissues of ICC were analyzed. The specimens were cervical conization, biopsy, or hysterectomy piece. Basic information about patient's year of birth, year of collection, and original histological diagnosis were retrieved from medical records. HPV DNA detection and typing was performed using the Inno-Lipa Genotyping v2 test (Innogenetics, Gent, Belgium). The overall detection of HPV prevalence in our samples was 80%. The most prevalent genotypes were HPV-16 (47%), 35 (14%), 18 (10%), 33 (8%), 45 (6%), 51 (6%). HPV-16 was the most prevalent in squamous cell carcinomas as well as in adenocarcinomas. HPV-18 was more prevalent in adenocarcinomas. HPV-16 and 18 were associated with two-thirds of the cases. This rate is lower than in Europe but similar to several studies in populations of African descent. However, anti-HPV-16 and 18 vaccines are expected to significantly reduce cervical cancer associated deaths in our region.

P 1-17

ROLE OF QUANTITATIVE VIRAL LOAD AND PHYSICAL STATUS OF HUMAN PAPILLOMA VIRUS (HPV) TYPE 16 FOR PROGNOSIS OF EFFECTIVENESS OF CERVICAL CANCER TREATMENT

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Objectives Subjects of study were 69 patients with primary HPV16-positive cervical cancer.
Methods Quantitative load and physical status of HPV-16 was analyzed by multiplex real-time PCR assay. The degree of integration was evaluated by average ratio of virus gene targets E7/E2. Viral load was estimated by average ratio of genomic equivalents E7/β-globin. Results Virus integrated DNA HPV-16 was found in 31.9% of cases, in 68.1% of patients episomal form was observed. Relatively high viral load was found in 63.8% of patients.
In the group with integrated DNA HPV it was shown reverse correlation between the degree of virus DNA integration and the viral load ($p=0,001$). It was shown pronounced trend to higher frequency of the disease progression and mortality in patients with relatively low viral content. Analysis made by separate groups of patients with integrated and episomal forms showed direct correlation of the frequency of disease free survival with viral load ($p=0.05$) and inverse correlation with degree of virus integration into a cell ($p=0.02$) in the first group. In patients with episomal DNA HPV-16 form no correlation was found. It was not detected statistically significant differences of short-term results of treatment depending on the virus physical status ($p = 0.24$). However, analysis of long-term results showed a significant trend of lower frequency of disease remission in patients with integrated HPV DNA ($p=0.13$). The differences in disease-free survival were statistically significant only in the group of patients with a high degree of the virus DNA integration (>80%) compared to "episomal" group ($p=0.005$). It was also observed a statistically significant difference in the long-term results of treatment depending on the degree of integration viral DNA into cell's genome ($p=0.02$).
Conclusions Thus, according to the data it can be assumed that the quantitative load of HPV 16 does not related to prognosis of cervical cancer directly, the physical status of the virus is likely affect to the clinical outcome. The period following the main treatment requires special attention: although indicators of primary response to treatment of tumors with integrated and episomal viral forms were similar, indicators of diseases free survival in 3 years were statistically lower in the first group.

P 1-18

HUMAN PAPILLOMAVIRUS GENOTYPES IN SÃO TOMÉ E PRÍNCIPE DEMOCRATIC REPUBLIC - A MIDDLE AFRICA COUNTRY

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Objective: To characterize human papillomavirus (HPV) genotypes in São Tomé e Príncipe (STP).

Methods: A total of 461 cervical samples were analysed for the presence of HPV in two independent PCR reactions using general primers. HPV-positive cases were typed using DNA sequencing and qPCR.

Results: HPV was detected in 30% (104/346) of normal samples, 54% (19/35) of atypical squamous cells of undetermined significance (ASC-US), 76% (16/21) of ASC-H, 76% (13/17) of low-grade lesions (LSIL) and 93% (39/42) of high-grade lesions (HSIL). Overall, 34 types were detected: 12 high-risk (HPVs 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59), 4 probable high-risk (HPVs 53, 66, 68 and 82), 7 low-risk (HPVs 6, 42, 43, 54, 61, 62, and 81) and 11 unknown-risk types (HPVs 32, 34, 67, 70, 71, 83, 84, 85, 87, 90 and 114). The 5 most prevalent types detected were: HPV58, being detected in 16.5% of HPV-positive women, followed by HPV16 (10%), HPV33 (7.7%), HPV31 (6.9%) and HPV45 (5.8%). HPV58 was also the most prevalent type in HSIL samples (29.5%), followed by HPV16 (16%), HPV33 (11.4%), HPV31 (9.1%), HPV52 (6.8%) and HPV18 (4.5%).

Conclusion: This study provides the first view on the spectrum of HPV genotypes in STP. Although a larger study is needed to draw firm conclusions, our data suggest that HPV58 is the commonest type among HPV-positive women as well as in women with HSIL. Further studies including carcinoma samples will be important to evaluate the impact of HPV vaccines in STP.

P 1-19

SEXUAL BEHAVIOR AND HPV INFECTION IN ADOLESCENTS AND YOUNG WOMEN

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Background: The Human Papillomavirus (HPV) causes a sexually transmitted infection common among sexually active women.

Objective: To estimate the prevalence of HPV types in adolescents and young women and to relate it to the detection of cytological abnormalities and sexual behavior. Methods: This study included 280 adolescents and young women sexually active of 15 to 24 years of age. Cervical secretions were collected for conventional cytology. HPV-DNA was detected by the polymerase chain reaction (PCR) and genotyping was performed by reverse line blot hybridization assay. The population was stratified in two age groups: Group I (15 and 19 years old) and Group II (20 and 24 years old).

Results: The total prevalence of HPV infection was 46.1%. High risk HPV represented 82.9% and multiple types infections were observed in 44.2% of the positive cases. The most common types were HPV 16, 68, 52, 39 and 31. There was significant association between HPV infection and the detection of cytological abnormalities in adolescents and young adults. In bivariate and multivariate analysis, the variables associated with HPV infection were the number of sexual partners among adolescents and young women and the practice of anal sex in young women. Infections multiples types were independently associated with early sexual activity and with number of partners in adolescents and young women.

Conclusion: HPV infections are very common among adolescents and young women, especially those who have some type of cytological abnormality. Sexual behavior has a relationship to infection by HPV in adolescents and young women.

P 2-1

EVALUATING THE EARLY IMPACT OF QUADRIVALENT HPV VACCINE INTRODUCTION ON GENITAL WARTS IN BELGIUM

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Objective: To assess the early impact of quadrivalent HPV (qHPV) vaccine introduction on the incidence of genital warts (GWs) between 2006 and 2013 in Belgium.

Methods: We compared the incidence of GW before (2006) and after (2009-2013) qHPV vaccine introduction in a large Belgium sick-fund database (MLOZ). A first agreement by the sick-fund medical advisor for imiquimod reimbursement, which is the first line, most common GW treatment in Belgium, was used as a surrogate for a first GW episode. Women and men aged 16-59 years and affiliated to MLOZ were included. Change in GW incidence rate was stratified by age and gender and evaluated in different populations according to their likelihood of being targeted by the Belgian vaccination program. To adjust for potential changes in the MLOZ population over the study period, a direct standardization on age and gender was performed.

Results: Overall, 9,223,384 person-years of follow-up were included. In women aged 16 to 22 years, targeted by the qHPV vaccination program a reduction of 72.1% [95% CI: -77.9; -64.72] in the standardised incidence of GWs was observed between the pre- and post-vaccination periods, for a cumulative qHPV vaccine coverage of 48% in 2013. The decrease was 51.1% [95%CI: -67.7; -26.2] in men aged 16-22 years and 8.1% [95%CI: -15.3; -0.3] in the overall population aged 16-59 years.

Conclusion: We observed a substantial, early impact on the incidence of GWs, particularly in women targeted by the vaccination program and showed evidence of herd protection in younger men.

P 2-2

ASSESSING TYPE-REPLACEMENT FOLLOWING HPV VACCINATION

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Objectives: Control of HPV-related cancers by national vaccination programmes is likely to take place. One open question is replacement of the vaccine types with other high-risk (hr) HPV types in the vaccination era. We studied occurrence of HPV types in adolescent females participating in a population-based vaccination trial.

Methods: A total of 4,808 16- to 17-year-old females from Finland were enrolled in the 1:1 randomized phase III (PATRICIA) trial of the efficacy of vaccination with the AS04-adjuvanted HPV-16/18 vaccine as compared to hepatitis A virus (HAV) vaccine. HPV infection was assessed from cervical samples taken every 6 months for 4 years post-vaccination, by polymerase chain reaction (PCR) for genital oncogenic HPV types 16/18/31/33/35/39/45/51/52/58/59/66/68/73 as well as low-risk types HPV6 and HPV11. The HPV vaccination coverage ranged from 1 to 22% by age-cohort and study community. Odds ratios (OR) and Poisson regression derived incidence rate ratios (IRR) with 95% confidence intervals (CIs) for infections with HPV types in baseline PCR negative, and PCR positive vs. PCR negative women were calculated.

Results: The OR and IRR estimates for acquisition of any genital HPV types showed no excess risk in baseline HPV DNA negative HPV16/18vaccinated women compared to baseline HPV DNA negative HAV vaccinated women or in HPV16/18vaccinated baseline HPV16/18positive women compared to baseline HPV16/18negative women. In the HAV vaccinated, baseline HPV18positive women showed an increased risk of acquiring other clade A7 HPV types (39, 45, 59, 68) (IRR 1.8, 95% CI 5 1.01.-3.1).

Conclusions: We found no increased rate of non-vaccine HPV types suggestive of type-replacement 1–4 years post-vaccination among HPV vaccinated adolescents.

P 2-3

CANCER REGISTRY FOLLOW-UP OF HPV VACCINATION TRIAL COHORTS AND UNVACCINATED COHORTS

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Objectives: Vaccination against high-risk (hr) HPVs has been implemented in national vaccination programs. Due to long lag time between hrHPV infection and cancer development, data on vaccine efficacy against the most stringent end-point(s) from the programs emerges slowly. We report on 110.000 follow-up years of cancer registry-based surveillance of adolescents vaccinated at the age of 16/17 years and of originally 18/19 year-old unvaccinated women.

Methods: In August 2002 - April 2003, 875 and 874 Finns were enrolled in the FUTURE trial, and vaccinated with placebo or the quadrivalent vaccine. In May 2004-April 2005, 64 and 2.408, and 2.399 Finns were enrolled in a phase II (HPV-012) trial or the PATRICIA trial and vaccinated with the bivalent vaccine or with a hepatitis A-virus (HAV) vaccine. Cancer registry follow-up was established for the trial cohorts in November 2007 and 2009, respectively, 6 months after the active follow-up had been closed. In September 2006 and 2008 the cancer registry-based follow-up of the un-vaccinated cohorts was established in September 2006 and 2008. Overall 5-year surveillance results are now reported.

Results: We identified 85 cases of cervical intraepithelial neoplasia (CIN) grade 3 or cervical cancer in the unvaccinated cohorts in 78.500 years of follow-up. The CIN3+ incidence rate for the unvaccinated was 108 per 100 000 women years, which is identical to similar aged Finnish female population. Efficacy estimates against CIN3+ between 5- 10 years post vaccination will be provided for both the vaccines following on-line cancer registry linkages in December 2014. Long-term follow-up of the cohorts continues.

P 2-4

COST-EFFECTIVENESS OF HPV VACCINATION IN DEVELOPING COUNTRIES

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Objectives: Prophylactic human papillomavirus (HPV) vaccines represent primary cervical cancer (CC) prevention in countries where screening, diagnostics and treatment produce modest reductions in CC incidence/mortality. To understand priorities in low vs. middle income countries with high CC incidence pertinent cost-efficacy studies on CC interventions were compared.

Methods: We conducted a systematic review of cost-effectiveness studies including only countries with high CC incidence (>14.5) and GDP per capita below the high income group (<37,162 2010 international $).

Results: We identified 16 cost-effectiveness studies (with the bivalent 16/18 or the quadrivalent 6/11/16/18 vaccine) including 25 countries from Europe, Africa, Latin America, and Asia. CC incidence ratios vary from 14.8 (Kenya) to 38.3 (Mozambique) and GDP per capita from 913 (Mozambique) I$ to 27063 I$ (Slovenia). Sub-Saharan African countries excluded, the CC incidence rates were comparable in the middle- and low-income countries (median 18.5 vs. 22). The studies concluded that HPV vaccination of females is highly effective, especially when combined with screening, and also cost-effective assuming low to moderate vaccine cost at the same time. We emphasize that the commonly used cost-effectiveness thresholds do not always equal affordability.

Conclusions: HVP vaccination alone or a combination with screening is cost-effective in countries with high CC incidence and moderate to low GDP per capita. Affordability of the vaccination program is a crucial determinant for the success of cervical cancer primary prevention by country. This determines whether differences between the middle- and low-income countries in HPV disease burden are increasing or decreasing in the future.

P 2-5

PROJECTING THE POTENTIAL PUBLIC HEALTH IMPACT OF A 9-VALENT HPV VACCINE IN HUNGARY

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Objectives: To estimate the potential public health impact of a 9-valent HPV (human papillomavirus) vaccine (HPV9) in Hungary in preventing HPV-related diseases including cervical intraepithelial neoplasia grades 1 (CIN 1), grades 2 and 3 (CIN 2/3), and cervical cancer.

Methods: A mathematical model of the transmission dynamics of HPV infection and disease for the HPV9 vaccine was calibrated to Hungarian epidemiological data on cervical cancer. Based on global estimates, we attributed 70% of cervical cancer to HPV 16 and 18 for the quadrivalent vaccine (types 6/11/16/18: HPV4), and 20% to the five additional types in HPV9 (31, 33, 45, 52, and 58). Other inputs were from public data sources and published literature. Vaccine efficacy against the 5 additional HPV types was taken from phase III trial results for the HPV9 vaccine. We assessed the incremental public health impact of HPV9 over HPV4 based on vaccinating 85% of females by age 12.

Results: We projected that HPV9 vaccination of females could reduce the incidence of cervical cancer by 88% after 100 years, relative to 68% for HPV4. HPV9 vaccination relative to HPV4 vaccination could prevent an additional 22,000 cases of CIN1, 58,000 cases of CIN2/3, and 10,000 cases of cervical cancer in the Hungarian population, cumulative over 100 years.

Conclusions: Protecting the Hungarian population against HPV infection with an HPV9 vaccination program relative to an HPV4 vaccination program can have significant public health benefits in addition to the benefits provided by HPV4 vaccination.

P 2-6

BASELINE CHARACTERISTICS OF A RANDOMIZED SCREENING TRIAL OF HPV VACCINATED WOMEN

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Objectives: Post-vaccination era screening needs to be changed based on a hard evidence. We studied which strategy is: 1) at least as accurate/safe as repeat cytological screening, 2) most effective and 3) associated with the best quality of life.

Methods: The study was a comparative effectiveness study. 22.500 -vaccinated Finns born in 1992-95 and vaccinated at the age of 13-15 in a community randomized trial (EUDraCT 2007-001731-55) have been randomized into 3 arms to attend cytological screening at the ages: 22, 25 and 30 years (A1); 25 and 30 (A2); or at age of 30 (A3).

Results: A1 and A3 include at least 7000 women yielding 80% power for the demonstration a non-inferior accuracy (sensitivity) of A3 strategy vs. A1 strategy in the HPV16/18 vaccinees. An interim analysis of A1 vs. Arm A2 (no intervention at the age of 22 but at a round of smears taken at the age of 25) in 2017/18 will guarantee safety of the less frequent screening. At age 30 years all participating women will be offered both cytological and unmasked HPV test results. The study relies on a validated infra-structure validated in previous vaccine trials. Study deliverables are: 1) Successful enrolment by birth cohort to guarantee power (2014). 2) Safety of less frequent screening of HPV16/18 vaccinated females (2017/18). 3) Effectiveness of delaying the imitation of cervical screening in vaccinated women up to age 30 year. 4) Impact of less screening rounds on quality of life.

P 2-7

PREVALENCE OF HPV DNA IN ADOLESCENT MEN VACCINATED WITH THE HPV 16/18 VACCINE

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Objectives: Vaccine efficacy for the bivalent HPV16/18 vaccine in males is not known. We assessed HPV prevalence rates in vaccinated and unvaccinated adolescents four years post vaccination.

Methods: The study participants were enrolled in 11 study sites participating in a community randomized trial on the impact of different HPV vaccination strategies. Early adolescent boys between ages 12 to 15 had received either the bivalent vaccine (90%) or a hepatitis B-virus vaccine (10%) in 2007-2009. Screening for Chlamydia trachomatis was offered to young males at the age of 18.5 years starting from 2010. First void urine sampling kits for C. trachomatis testing were mailed on a webpage (rokotiitus.net) request. Extracted DNA samples were pseudonymized, however, retaining associated vaccination status. Altogether 305 samples (248 of HPV-vaccinees and 57 of HBV-vaccinees) were available for high throughput genotyping of HPV6/11/16/18/31/33/35 39/45/51/52/56/58/59/66/68, and by consensus PCR using the MGP primers followed by MALDITOF mass spectrometry on the SEQUENOM platform.

Results: The overall HPV DNA prevalence in the 305 samples analysed was 5.0 % (15 samples tested positive with both methods used). Overall, 11 samples from HPV-vaccinated individuals and 4 samples from HBV-vaccinated tested HPV positive (7.0 % vs. 4.4 %). No samples from vaccinated individuals tested positive for HPV 16/18 and 8 (3.2 %) tested positive for the vaccine covered HPV types 6/11/31/33/45/51. The differences in the prevalence rates were of borderline significance. Study limitation was the small sample size warranting further studies.

P 2-8

PREVALENCE OF GENITAL HPV INFECTION IN WOMEN AGED 18-29, IN THE POST VACCINATION PERIOD, QUÉBEC, CANADA

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Objective: An HPV immunization program was implemented in Québec in 2008 with the quadrivalent vaccine, targeting girls 9-10, with catch-up in high schools during the first years of the program. In order to evaluate the impact of the program, an HPV prevalence study was conducted.

Methods: Young women were recruited from March 2013 to July 2014, according to a multi-stage plan. Students were recruited through the school system and young workers through health institutions and pharmacies. A questionnaire including questions on sexual history and vaccination status was completed and women were asked to provide a self-taken vaginal sample for HPV analysis. Samples positive in a generic HPV test were genotyped with the Linear Array.

Results: 1998 women aged 18-29 completed the survey and provided a genital specimen for HPV analysis. Vaccination rates were 84.1%, 59.7% and 15.9% in women aged 18-20, 21-23 and 24-29, respectively. Globally, 35.4% tested positive for HPV, including 15.6% with a single type and 19.8% with multiple types. The main HR-HPV types identified were HPV51 (n=91), HPV59 (n=83) and HPV52 (n=80). HPV16 was less common, with only 53 cases (2.9% of participants) and its prevalence increased by age group. Other HPV vaccine types were infrequent. Data is being analysed according to self-declared vaccination status and age-cohorts for herd immunity effects.

Conclusion: The frequency of detection of HPV vaccine types is lower than those reported in unvaccinated populations of the same age in Canada and may represent an early impact of the vaccination program.

P 2-9

POTENTIAL IMPACT OF A NONAVALENT HPV VACCINE ON THE OCCURRENCE OF HPV-RELATED DISEASES IN FRANCE

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Background and aim: The objective was to assess the potential impact of a nonavalent HPV vaccine (HPV 6/11/16/18/31/33/45/52/58) on HPV-related diseases in France.

Methods: French HPV genotype distributions from 6 multicentric retrospective studies (EDiTH I to VI) were analyzed including 516 invasive cervical cancers (ICC), 493 CIN2/3, 397 low-grade squamous intraepithelial lesions (LSIL), 423 genital warts (GW), 366 anal cancer (AC) and 314 oropharynx and oral cavity carcinomas (OC). Low and high estimates of HPV vaccine impact were calculated as follows: low estimate was the prevalence of the 9 HPV genotypes alone or in association but excluding the presence of another HPV type; high estimate was the prevalence of the 9 HPV genotypes alone or in association possibly in the presence of another HPV types. For comparison, similar figures for the quadrivalent vaccine were calculated.

Results: Estimates of potential impact of a nonavalent HPV vaccine varied from 85% to 92% for ICC, 77% to 90% for CIN2/3, 26% to 56% for LSIL, 69% to 90% for GW, 81% to 93% for AC, and 41% to 44% for OC. Compared to the quadrivalent vaccine, the proportion of additional cases prevented by the nonavalent vaccine was 9.9%-15.3% for ICC, 24.7%-33.3% for CIN2/3, 12.3%-22.7% for LSIL, 2.1%-5.4% for GW, 8.5%-10.4% for AC, and 0.0%-1.6% for OC.

Conclusion: The nonavalent HPV vaccine showed significant increased potential impact compared to the quadrivalent vaccine for ICC, CIN2/3 and LSIL. Considering an ideal theoretical situation with a 100% vaccine efficacy and a 100% vaccine coverage rate, about 90% of ICC, CIN2/3, GW or AC cases could be prevented by a nonavalent HPV vaccine in France on the long term.

P 2-10

PROJECTING THE POTENTIAL PUBLIC HEALTH IMPACT OF A VACCINATION PROGRAMME WITH A NINE-VALENT HPV VACCINE IN NORWAY

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Objectives: To estimate the incremental public health impact of a girls-only, vaccination program with a nine-valent human papillomavirus vaccine (6/11/16/18/31/33/45/52/58) in Norway as compared to the current girls-only, vaccination program with a quadrivalent HPV vaccine (6/11/16/18).

Methods: A dynamic transmission model of HPV infection and the related diseases was calibrated to the Norwegian epidemiological data. Up to 70% of cervical cancer cases were attributed to HPV 16/18 for the quadrivalent vaccine, and an additional 20% to the five additional types included in the nine-valent vaccine. For non-cervical disease (vulvar, vaginal, anal and genital warts), the disease attribution assumption remained constant across both vaccines, producing conservative outcomes. In the base case, a three dose vaccination program with lifelong vaccine protection and a coverage rate of 80% was assumed for the 12 year age girl cohorts. Sensitivity analyses were conducted.

Results: The findings of the analyses indicate that girls-only vaccination with the nine-valent vaccine has the potential to: i) reduce the incidence of HPV16/18/31/33/45/52/58 -related cervical cancer by 87% after 100 years, relative to 66% for the quadrivalent vaccine, ii) prevent an additional 12,055 cases of CIN1, 28,867 cases of CIN2/3, 2,584 cases of cervical cancer in the female Norwegian population over 100 years.

Conclusions: The introduction of a nine-valent HPV vaccine immunization program in Norway is estimated to significantly reduce the public health impact of cervical and other HPV-related diseases.

P 2-11

PROJECTING THE POTENTIAL PUBLIC HEALTH IMPACT OF A 9-VALENT HPV VACCINE IN THE CZECH REPUBLIC

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Objectives: To estimate the potential public health impact of a 9-valent HPV (human papillomavirus) vaccine (HPV9) in the Czech Republic in preventing HPV-related diseases including cervical intraepithelial neoplasia grades 1 (CIN 1), grades 2 and 3 (CIN 2/3), and cervical cancer.

Methods: A mathematical model of the transmission dynamics of HPV infection and disease for the HPV9 vaccine was calibrated to the Czech Republic epidemiological data on cervical cancer. Based on global estimates, we attributed 70% of cervical cancer to HPV 16 and 18 for the quadrivalent vaccine (types 6/11/16/18: HPV4), and 20% to the five additional types in HPV9 (31, 33, 45, 52, and 58). Other inputs were from public data sources and published literature. Vaccine efficacy against the 5 additional HPV types was taken from phase III trial results for the HPV9 vaccine. We assessed the incremental public health impact of HPV9 over HPV4 based on vaccinating 65% of females by age 14.

Results: We projected that HPV9 vaccination of females could reduce the incidence of cervical cancer by 74% after 100 years, relative to 62% for HPV4. HPV9 vaccination relative to HPV4 vaccination could prevent an additional 33,000 cases of CIN1, 53,000 cases of CIN2/3, and 6,000 cases of cervical cancer in the Czech Republic population, cumulative over 100 years.

Conclusions: Protecting the Czech Republic population against HPV infection with an HPV9 vaccination program relative to an HPV4 vaccination program can have significant public health benefits in addition to the benefits provided by HPV4 vaccination.

P 2-12

CORRELATION BETWEEN LOCAL AND SYSTEMIC IGG AND IGA RESPONSES AGAINST HPV-16/18 VLP DURING HPV VACCINATION

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Objective: investigate pre- and post-vaccination antibody responses against 16/18 HPV by detection of IgG and IgA HPV-specific antibodies in serum and cervical samples.

Methods: controlled randomized trial 1:1 including 120 women. Subjects were given with the bivalent HPV vaccine -16/18 and controls no vaccine at the first day of vaccination (Day 0), at 1- and 6-month schedule and followed up until seven months. HPV was molecularly detected in the samples, and a specific assay was used to identify antibodies to HPV virus-like particles by ELISA. Samples were tested for HPV-specific antibodies An ELISA detecting IgA and IgG anti-HPV-VLP was carried out. HPV vaccine monitoring study cervical samples were available pre-vaccination, one month after the first dose, six months after the first dose and seven months after the first dose (Month 7).

Results: all subjects were initially seronegative in the vaccine group, and developed seroconversion for human papillomavirus-16 and -18 antibodies at Month 7. IgG and IgA antibody levels for HPV16/18 were quantified and compared pre and post each dose vaccination. In regard to vaccine immunogenicity, the seroconversion rate was increased in proportion to the number of vaccine doses.

Conclusion: the correlation of HPV16/18 antibody levels between serum and cervix suggests that the HPV antibodies transudate or exudate from the systemic circulation to the cervical mucosa to provide protection against HPV infections. IgG seems to play a key role, eclipsing IgA in the mucosal protection. Probably, the local and systemic antibodies work together, protecting against HPV infection.

P 2-13

PROVIDER INSIGHT INTO STRATEGIES TO INCREASE HPV VACCINE UPTAKE: A MULTI-SITE STUDY

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Objectives: Prophylactic HPV vaccine is available in many countries to prevent cervical and other HPV-associated cancers. The success of HPV vaccination campaigns has been variable across countries. Little is known about adolescent providers' perceptions of optimal strategies for vaccine implementation, and the barriers to overcome. Provider recommendation is the most important predictor of vaccine uptake among adolescents. Data are needed on providers' perspectives of HPV vaccine programs to identify optimal strategies. Our objective was to identify behavioral, structural, and cultural facilitators to HPV prophylactic vaccination from health providers' perspective in countries from distinct geographical regions.
Methods: Non–probability convenience sampling was utilized to recruit a total of 151 adolescent vaccine providers in five countries: Argentina(n=30);Malaysia(n=30);South Africa(n=31);South Korea(n=30) and Spain(n=30). Only providers authorized to administer adolescent vaccines were eligible. Semi-qualitative and quantitative data were collected through semi-structured surveys, and univariate analyses conducted. Funding was provided by GlaxoSmithKline (StudyID117339).
Results: Providers responded that the best way to vaccinate adolescent girls in their country was low cost vaccines or free access (Argentina: 53%,Spain: 60%, South Korea: 37%,South Africa: 32%) and school-located programs (Malaysia: 50%,Spain: 80%, South Korea: 33%, South Africa: 68%). Other factors frequently cited were mandatory vaccination (Argentina:40%); vaccination campaigns targeted at girls (South Korea:27%;South Africa:26%) and parents (South Korea: 37%). Cost of vaccination was cited as a notable barrier to HPV vaccination program success (Argentina: 20%, Malaysia: 57%, Spain: 37%, South Korea: 73%, South Africa: 29%).
Conclusions: Effective strategies identified by health care providers were largely similar across countries, although with some specific variations. Adapting these lessons to future HPV vaccination implementation programs could accelerate effective program design and enhance success across nations.

P 2-14

PERFORMANCE OF A TRIAL ORGANIZATION IN THE CONDUCT OF A LARGE CLUSTER-RANDOMIZED TRIAL

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Background: A community randomized trial on the effectiveness of different HPV vaccination strategies (boys and girls vs. girls only) was conducted between 2007-2014 in 33 communities. All 80.000 1992-95 born adolescents were invited and 32.500 received HPV16/18- or hepatitis Bvirus vaccination in 2007-2009 at 250 junior high schools by 88 study nurses. At the age of 18.5 years vaccinated and unvaccinated girls were invited to return for a follow-up visit during which cytological / HPV DNA samples were taken.

Objectives and methods: Following triangularization of the study/questionnaire content we asked all 88 study nurses to respond to a questionnaire (30 questions each comprising 5 likert-steps) on the performance of the trial infrastructure.

Results: Fifty-six (65%) of the study nurses responded. Interaction between the study nurses and the junior high-schools was favourable in 70% of the cases. Organization of recruitment by the University of Tampere was considered successful, GCP-proof and sustainable by 79 %, 74 % and 74 % of the study nurses. The professional substance knowledge and motivation of the study nurses were unanimously (97%, 100%) considered to excellent. Most (79%) of the study nurses considered that positive attitude towards the study aims and willingness to adjust for changes in the recruitment work were important for successful recruitment. The role of sponsor's clinical research associates (CRA) was considered supportive or helpful to the recruitment, by 47 % and 21 % of the study nurses, and 38 % felt that the CRA actions favoured the recruitment. Our study gives an insight into performance of a large intervention trial infrastructure.

P 3-1

MODIFIED PRE-PROCESSING METHOD FOR SUREPATH LIQUID-BASED CYTOLOGY: ASSESSING IMPACT ON THE PERFORMANCE OF THE REALTIME HIGH RISK HPV ASSAY

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Background: Cervical specimens collected in SurePath liquid-based cytology (LBC) medium are used for cervical cytology in England. The Abbott RealTi*m*e High Risk HPV assay is a highly automated qualitative multiplex real-time PCR for the detection of 14 high-risk HPV types and has been approved by the English NHS Cervical Screening Programme (NHSCSP) for HPV triage of low grade dyskaryosis and test-of-cure. Either the sample from the original SurePath collection vial or the remaining cell pellet sample after cytological processing can be tested using the Abbott assay. As per manufacturer's instructions, pre-analytic processing of the SurePath cell pellet sample requires adjustment of the sample to 6mls using SurePath preservative prior to manual vortexing and liquid transfer into a secondary tube.

Method: We evaluated testing the cell pellet sample (volume adjusted to 6mL in the original gradient tube) directly on the Abbott *m*2000*sp* instrument without the need to transfer an aliquot into a secondary tube, versus, the original procedure described by the manufacturer by comparing results from 200 samples run in parallel.

Results: hrHPV was detected in 89 samples using both methods with an excellent agreement of overall-hrHPV (98.5%[95%CI:0.94-1.00];kappa:0.97). Inter-laboratory reproducibility of the modified protocol was further investigated and excellent agreement was observed (98.5%[95%CI:0.94-1.00];kappa:0.97).

Conclusion: The modified protocol resulted in assay performance comparable to that following the manufacturer's validated manual process, saving hands-on time required for liquid transfer and labelling of secondary tubes. This method has been approved by NHSCSP for triage and test-of-cure samples.

P 3-2

COMPARISON OF HPV DIRECT FLOW CHIP SYSTEM WITH HYBRID CAPTURE II® METHOD FOR DETECTION OF HUMAN PAPILLOMAVIRUS IN WOMEN WITH PREVIOUS ABNORMAL PAP SMEARS

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OBJECTIVES: HPV Direct Flow CHIP is an automatic HPV screening and genotyping system based on PCR-reverse dot blot without the need of DNA extraction. In this study, the performance of HPV Direct Flow CHIP (DF, Master Diagnóstica SL) method for the detection and genotyping of HPV was evaluated in comparison with the Hybrid Capture 2® (HC2, Qiagen) method.

METHODS: Cervical samples (n=122) from women undergoing management for abnormal PAP smears were analyzed for HPV detection and genotyping by both HC2 and DF assays. Qiagen SMT transport medium was used directly for HC2, while total cell extracts were collected as PCR template for DF.

RESULTS: Rates for HPV detection were: HC2 46.7% vs DF 79.5%, with a positive agreement of 74% (k = 0.37). When only high risk genotypes were considered the rates were HC2 43.4% vs DF 68% with a positive agreement of 76.4%(k =0.5). DF was HPVHR+ for 68.6% of the patients with previous history of conisation, whereas only 37.2% were HC2 HR+. DF identified presence of HPV 16/18 genotypes in 57.1% (20/35) of the samples, which included six samples that were HPV HR- by HC2.

CONCLUSION: HPV positivity rates were significantly higher for HPV Direct Flow CHIP compared to HC2 (p <0.0001), in the subset of cervical samples included in this study.
High sensitivity of the HPV Direct Flow CHIP system makes it a useful tool in the follow-up of abnormal PAP smears and cervical cancer triage, allowing simple and rapid HPV detection and genotyping of multiple infections.

P 3-3

PRIMARY HPV TEST IN CERVICAL CANCER SCREENING IN LATIN (ITALY).

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Objective: human Papilloma Virus (HPV) plays a central role in cervical cancer development and its identification allows an early diagnosis promoting healing and reducing cervical cancer mortality. The Hybrid Capture 2 is a technique that allows the identification of 13 high risk HPV type. The aim of this study is to evaluate the impact and performance of the new algorithm in cervical cancer screening program in two years' experience of Latin (Italy).

Methods: the female population was divided into two group, 24-34 and 35-64, the first was referred to Pap test and the second to hr-HPV test according to national guidelines. In two years the participation rate increased among women 35-64 compared to women aged 25-34.

Results: the PAP test positive rate and hr-HPV test positive rate were 4% and 5.2% respectively. The PAP test positive rate among hr-HPV + decreased from 2012 to 2013. Women hr-HPV+/PAP+ were referred immediately to colposcopy and this rate was 3.8% and 1.2% in women aged 25-34 and 35-64 respectively. The predictive positive value for CIN2+ to colposcopy was 10.9% in 2012 and 9.1% in 2013 while the detection rate (DR) for CIN2+ was 1.66% in 2012 and 1.19% in 2013.

Conclusions: the adherence to the screening program has been satisfactory and the stratification of the female population into two aged groups led to a decreased of inappropriate therapeutic path and the combination of hr-HPV test with PAP test in woman aged 35-64 allows to obtain results with high levels of specificity and sensibility.

P 3-4

COMPARISION OF XPERT® HPV ASSAY VERSUS APTIMA® HPV ASSAY

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Objective: To evaluate the performance of the Cepheid Xpert® HPV Assay (Xpert) relative to the Hologic Aptima® HPV Assay (Aptima) and the Aptima HPV 16 18/45 Genotype Assay (Aptima GT).

Methods: 500 residual ThinPrep® specimens were tested for high-risk HPV (hrHPV) genotypes using the Aptima assay and were then tested using Xpert. The latter assay reports the overall hrHPV status and distinguishes genotypes 16 and 18/45. Specimens that were positive by Xpert were reflexed for genotyping by the Aptima GT assay. Specimens yielding discrepant results between the Xpert and Aptima assays were resolved by the Roche Linear Array® (LA) assay.

Results: Positive Percent Agreement (PPA) between the Xpert and Aptima assays was 89.1% (179/201) and the Negative Percent Agreement (NPA) was 95.7% (286/299). After LA discrepancy analysis, the PPA and NPA values were 97.4% (189/194) and 99.0% (303/306), respectively. HPV 16 agreement between the Xpert and Aptima GT assays was 79.1% (34/43), and the HPV 18/45 agreement was 71.4% (25/35). After LA discrepancy analysis, the HPV 16 and HPV 18/45 agreement values were 93.0% (40/43) and 97.1% (34/35), respectively.

Conclusions: The analytical performance of the Cepheid Xpert HPV Assay compares favorably with the Hologic Aptima assays. Most discordant results between the Xpert and Aptima assays were resolved with the Roche LA assay.

P 3-5

COMPARISON BETWEEN DIRECT SEQUENCING AND DIRECT FLOW CHIP FOR HUMAN PAPILLOMAVIRUS (HPV) GENOTYPING, IN FORMALIN-FIXED PARAFFIN-EMBEDDED (FFPE) BIOPSIES.

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Objectives: To evaluate the performance of Direct Sequencing compared to HPV Direct Flow CHIP, for HPV detection in cervical and oropharyngeal tumors.

Methods: Samples from FFPE biopsies were positives for HPV by Direct Sequencing. HPV (n=64) were blindly retested by the HPV Direct Flow CHIP. The cases were: 10 CIN-III, 4 mouth carcinomas, 10 condyloma acuminatum of the penis, 10 condylomas in anal region, 10 condylomas in vulva and 10 condylomas in perineal region.
DNA was purified by QIAsymphony SP® System and its quality was evaluated by amplification of a fragment of the Beta Globin gene.
HPV Direct Flow CHIP is a partially automatic HPV genotyping system of 36 different genotypes based on PCR followed by dot blot hybridization.
For Direct Sequencing, nested PCR was carried out using the MY11/09 and GP5+/GP6+ consensus primers. The amplicons were sequenced in the Applied Biosystems® 3130 Genetic Analyzer. In the cases of multiple infections, the superimposed sequences obtained after sequencing were analyzed using the Feoli-Fonseca database, which predicts the multiple genotypes contained in a sample by comparison to known sequences of the database.

Results: The overall agreement for HPV positivity was 98% for Direct Sequencing versus HPV Direct Flow CHIP. The results demonstrate a high agreement between HPV Direct Flow CHIP, Direct Sequencing and Linear Array, although HPV Direct Flow CHIP detected significantly greater rates of high-risk genotypes in multiple-infection settings.

Conclusions : Due to the high sensitivity and added advantages of quick sample processing, automation of hybridization and analysis, HPV Direct Flow CHIP test could become a new alternative for rapid and sensitive HPV genotyping in FFPE biopsies.

P 3-6

COMPARISON BETWEEN A REALTIME-PCR, DNA-BASED HPV TEST AND THE HPV APTIMA

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Objectives: In Örebro, Sweden, hrHPV test is used in the screening program for women over 35 with ASCUS and CIN1. Women testing hrHPV negative will go back to the normal screening interval, 3 years, while hrHPV positive women will be called for a new test after 1 year.
According to the national guidelines, the HPV test should be performed on DNA, but data supports RNA-based tests since only the active transforming infections are detected. Here, a DNA, HPV genotyping test, using real time PCR specific against E6 and E7 in 12 hr-HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) was validated against the HPV APTIMA test. HPV APTIMA detects 14 different hrHPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68), but gives no information about the genotype.

Method: In clinical routine, DNA test was performed on 409 consecutive samples on liquid based cytology samples. Following DNA test, HPV APTIMA was performed according to the manufacturer's description.
Results: Using the DNA-test, 195 of 409 (47,6 %) samples were positive for HPV compared to HPV APTIMA where 192 of 409 (46,9%) were positive. In total, 39 samples had deviating results; of these 22 were DNA positive and RNA negative while 17 samples were DNA negative and RNA positive.

Conclusion: In total, HPV APTIMA performed as excepted based on the literature. The test is more automated compared to the DNA-test that uses 8 PCR-reactions per sample, which results in several advantages for the lab.

P 3-7

IMPROVING LABORATORY EFFCIENCY BY AUTOMATION OF PRE-ANALYTIC PROCESSING OF THINPREP SPECIMENS FOR REALTIME HIGH RISK HPV TESTING

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Cervical specimens collected in liquid-based cytology (LBC) media are the most common sample type used for high-risk HPV (hrHPV) testing. The majority of molecular hrHPV tests are validated for processing a defined sample-input volume from the standard volume of medium contained in LBC vials supplied by different manufacturers. The Abbott RealTi*m*e High Risk HPV assay, a qualitative multiplex real-time PCR, detecting 14 hrHPV types and simultaneously discriminating HPV16 and HPV18 from the pooled signal from 12 other hrHPVs, is validated for use with cervical specimens collected in ThinPrep and SurePath LBC. A sample-input volume of400ul (plus tube-specific deadvolume) of LBC medium is required for testing. LBC vials are vortexed prior to sampling, followed by liquid transfer into a sample-input-tube (SPT) compatible with the highly automated Abbott *m*2000 System designed to carry out DNA-extraction, PCR reaction set-up, amplification, signal detection, and result interpretation. Pre-analytic steps required for pre-processing LBC samples prior to running the Abbott assay encompass vortexing and de-capping LBC vials, liquid transfer to an SPT with matching unique identifier and re-capping the original LBC vials. A custom-configured worktable setup for the Tecan Freedom Evo designed to automate, control and document these process steps for ThinPrep samples was used to evaluate the impact of automated vs. manual pre-analytics. Results from 99 samples pre-processed manually and automatically tested in parallel with the Abbott assay revealed 100% overall-agreement and comparable signal intensity of the cellular internal control (R^2=0.958) indicated appropriate distribution of cellular material. Reproducibility of test results observed with 23 randomly selected samples after automated pre-processing in triplicate was 100%. Automation of the pre-analytic processing of ThinPrep LBC samples with the Tecan Freedom Evo allows saving hand-on-time for specimen pre-processing and process documentation.

P 3-8

CERVICAL CYTOLOGY SPECIMEN STABILITY IN SUREPATH PRESERVATIVE AND ANALYTICAL SENSITIVITY FOR HPV TESTING WITH COBAS® AND HYBRID CAPTURE 2® TESTS

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Objectives: Evaluate specimen stability and analytical sensitivity for HPV testing with cobas (Roche) and Hybrid Capture 2 (HC2, Qiagen) assays using SurePath preservative.

Methods: Experiments were performed with residual, unprocessed cervical cytology samples. Pools of 5-7 samples (10-14 ml total) were prepared within 7 days of sample collection. HPV-positive pools (by cobas and HC2) were 3-fold serially diluted in negative pools and tested (1) with and without cytology processing (HC2, cobas) and (2) with (pretreated) and without (untreated) heat pretreatment 1:1 in pre-analytic buffer for 20 min at 120°C (cobas). Pools were stored for 2 weeks at room temperature followed by 4-10 weeks at 4°C.

Results: Highest dilutions with reproducible HPV detection were 27-fold (HC2), 2,187-fold (cobas, pretreated), and 2,187-fold (cobas, untreated). Positivity rates for 682 pools were 18% (HC2), 48% (cobas, pretreated), and 47% (cobas, untreated). Within and between run %CV were 0.2-11% (cobas) and 6-70% (HC2). After 6 weeks, mean HC2 RLU/CO ratios changed by -10 to +21 (SD 6), however high variability limited statistical power to detect trends. For cobas, mean Ct's differed over time between pretreated and untreated groups ($p \leq 0.0001$; other high-risk HPV n=110). After 6 weeks, mean Ct's increased by 2.1 for untreated samples and varied only by 0.3 for pretreated samples.

Conclusions: Cobas was analytically more sensitive. Pretreatment improved analytical performance for cobas by extending stability with comparable sensitivity and reproducibility. High HC2 variability rendered assessment of sample stability impractical. Large studies including cervical biopsies will be required to compare clinical performance.

P 3-9

QUALITY ASSURANCE OF HPV TESTING WITHIN THE NHSCSP

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Background: HPV Triage and Test of cure was implemented into the England NHS Cervical Screening Programme (CSP) in 2011. Implementation guidance states that, 'all laboratories providing HPV testing for the CSP must include positive and negative internal control (IQC) samples as well as all required kit controls in every run'. Only cervical specimens collected in Liquid Based Cytology either SurePath or ThinPrep are used for cervical cytology in the UK. Evidence suggests that HPV nucleic acid (particularly RNA) is less well preserved in SurePath medium compared with ThinPrep. This is a result of chemical linkages between proteins and nucleic acids generated by formalin present in SurePath preservative fluid during extended storage. Approved HPV tests for the CSP generally require more stringent criteria in terms of sample processing, transit storage and assay turn around time for SurePath compared to ThinPrep. The Abbott RealTi*m*e High Risk HPV test kit insert states that SurePath samples can be stored for up to 2 months at 15-30OC before testing.

Method: Commercial QC material in SurePath preservative for HPV is currently not available. Described is the preparation of in house IQC material using pooled positive samples prepared in sufficient quantities to determine the stability of HPV DNA in SurePath preservative maintained at ambient temperature over 6 months when using the Abbott test.

Conclusion: No decay in signal was observed during this time as shown using a Levey-Jennings chart with Westgard rules for QC procedures.

P 3-10

HPV DETECTION AND TYPING BY MOLECULAR DIAGNOSTIC MICROARRAY

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An accurate and reliable microarray based HPV test system for the simultaneous detection and typing of 30 relevant high- and low-risk anogenital HPV was developed. Each of these anogenital HPV constitutes an individual risk as they may contribute to the degeneration of epithelial cells of the cervix. The subtyping is of special importance for the distinction of a persistent infection from a new infection with another subtype.

This new test system is easy to use and reliable and therefore well suited for routine analysis of patient samples. The individual typing of the HPV subtypes provides a complete picture of the individual infection situation. The ability to distinguish between high and low risk types enables the physician to estimate the hazard for a progression of a HPV infection. The test system may also help to differentiate between new and persistent infections. This is a major advantage in comparison to test systems which only detect, but do not type or classify HPV. Primarily developed as a CE/IVD marked diagnostic tool for the identification and monitoring of a (multiple-) cervical HPV-infection it is also suitable to address a multitude of scientific questions, for example HPV detection in anal or penile smears or samples from head and neck.

P 3-11

TRIPLE NEGATIVE BREAST CANCERS (TNBC) AND MARKERS OF HPV INVOLVEMENT.

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Background: It is becoming apparent that infection with HPV may contribute to the natural history of various types of human cancers including head and neck, breast, lung, oesophageal and bladder cancer. Hence determining HPV status of breast cancer may be of clinical significance.
TNBC has an aggressive disease course and it is a challenge to treat due to lack of response to hormonal therapies and Her2 targeted treatments. It is, however, a heterogeneous disease. Bio markers predictive of response to treatment are important to decide on treatments to use. This subgroup provides the opportunity to identify if HPV has any bearing on the heterogeneous response to treatment.

Objectives: We will determine type-specific HPV prevalence in TNBC and how this correlates with P16, Ki-67 over-expression.
We will report if HPV/P16/Ki-67 status correlates with grade of cancer and outcome of treatment.
Methods: Tissue blocks of 50 clinically well described TNBC will be used for molecular and in situ studies. This will include DNA HPV PCR, P16/Ki-67 over-expression and RNA in situ hybridization method to determine E4, E6 and E7 expression.
Results: Study is ongoing. Results will be available and presented.

Conclusion: This will be, to the best of our knowledge, the first study looking at association between P16/Ki-67 over expression and evidence of HPV presence and activity in TNBC. Such information may be clinically significant in the light of preventive and therapeutic HPV vaccines.

P 3-12

STATISTICAL STUDY OF HPV GENOTYPES IN BARBASTRO AREA

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Objective: To study the prevalence of high risk human papillomavirus (HR-HPV) and the correlation with precancerous lesions and cervical cancer in Barbastro area. To study the interval time between positive HR-HPV test and negative test.

Method: A target population of 24,501 women between 30 to 64 years. The coverage of the screening programme was 50%. A total of 341 out of 3,858 HR-HPV tests were positive between 1st January 2012 and 31st December 2012. The patients came from primary care screening and from gynaecology service according to SEGO 2010 protocol, using co-testing. All HR-HPV tests were done with PCR in Cobas 4800 system.

Results: 225 cases (66.0%) from primary care were positive, the HR-HPV prevalence was 6.83% in the area. The age average was 38.60 years (CI 95%: 37.6-39.6) .The type specific frequency was 80 cases (23.5%) for 16 genotype, 22 (6.5%) for 18 genotype and 239 (70%) for others. 220 cases (64.5%) had a negative cytology result, 20 cases (5.9%) were HSIL and 3 (0.9%) were squamous carcinoma. The biopsy results were 41 cases (12%) for CIN 2+. The time average of these tests to be negative was 1.80 years (CI 95%: 1.61-1.99)

Conclusions: The prevalence in the area is lower than the prevalence average in Spain (14%). A 12% of positive tests have high grade histological lesions so there is a need to persist in HR-HPV positive control patients. A 43% of CIN2+ biopsies are 16 and/or 18 genotype positives.

P 3-13

COMPARISON OF TWO HPV GENOTYPING METHODS: HPV DIRECT FLOW CHIP AND GENOFLOW HPV ARRAY KIT.

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Objectives: HPV DIRECT FLOW CHIP (DF, Master Diagnóstica, Granada. España) is an automatic HPV detection and genotyping system based on PCR and reverse dot blot hybridization without the need of DNA extraction. In this study, the performance of DF was compared with GenoFlow HPV array Kit (GF, Diagcor Bioscience, Hong Kong. China).

Methods: Cervical samples from women attending routine HPV cervical inspection were analyzed for HPV detection and genotyping by DF and GF (n=42). DNA extraction was performed prior to HPV detection with the GF method, whereas crude cell extracts were used directly in the DF method.

Results: Positivity for HPV was: DF 66.6% vs GF 73.8%. The overall agreement between DF and GF for HPV positivity was 88.1% (Kappa=0.72). The results of DF and GF systems were concordant for 27 HPV positive and 10 HPV negative samples. The 5 discordant cases were all with diagnostic of NILM (n=3) or ASCUS (n=2). When comparing high risk and low risk genotypes detection rates, there was an agreement of 92.5% with both methods (kappa=0.63). Positivity for HPV 16/18 was: DF 35.7% vs GF 33.3% (Kappa=0.74; percent of agreement 88.1%). Individual differences for other specific HPV genotypes were observed.

Conclusions: HPV DIRECT FLOW CHIP and GenoFlow HPV array systems yielded comparable performances, proving to be reliable methods for HPV detection and genotyping. However, DF is an automatic system that does not require DNA extraction which results in reducing the overall hands-on time and thus optimizing the laboratory work-flow and creating an added-value.

P 3-14

COMPARISON OF FLOQSWABS FOR CERVICO-VAGINAL SELF-COLLECTION TO GYNECOLOGIST COLLECTED CERVICAL SPECIMENS FOR THE DETECTION OF HPV-DNA WITH ANYPLEXTMII HPV28 ASSAY.

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Objectives: Collection devices are essential for the diagnosis of sexually transmitted diseases (STDs). The aim of this study was to compare FLOQSwabs™ for SCV to gynecoligist collected cervical (GCC) sample for HPV-DNA screening.

Methods: Dual samples (n = 100) were collected, after informed consent, from patients attending the Milano ASL for HPV screening. FLOQSwabs™ (Copan) were used for patient SCV and GCC samples. A questionnaire was completed by each patient. The swab was placed in its tube and sent dry to the laboratory, than placed into a 2 ml tube of eNAT medium prior nucleic acids extraction on the NIMBUS IVD and testing for HPV-DNA with the AnyplexTM II test HPV (Seegene) that detects 28 HPV genotypes (19 HR and 9 LR).

Results: Self collection was prefered by 79% of patients versus gynecologist collection. Self-collected samples in eNAT had 59 positive and 11 negative HPV while gynecologist samples had 53 positive and 17 negative HPV. In the positive self-collected, 52% had to 2 genotypes, 37% had 3 to 5 and 11% had 6 to 8 with 13 HR (16 or 18). The positives gynaecologist collected, 44% had 1 to 2 genotypes, 26% had 3 to 5 and 6% had 6 to 9 with 11 HR (16 or 18).

Conclusions: The FLOQSwabs™ did not cause pain or bleeding and most patients prefered self to gynecologist collection. Similar number of HR HPV 16 and 18 were found by both sampling systems. FLOQSwabs™ can be used for cervico-vaginal self collection for HPV screening.

P 3-15

QUALITY OF LIFE OF PERSISTENTLY HPV DNA SCREEN-POSITIVE WOMEN

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Objectives: HPV infections/associated lesions adversely affect health-related quality of life (HRQoL). HPV vaccines protect against these conditions.

Methods: We investigated the impact of HPV vaccination on HRQoL in 22-23 year-old women 5 years after participation into two phase III HPV vaccination trials (FUTURE and PATRICIA). The FUTURE participants had been enrolled in an efficacy trial of the quadrivalent HPV vaccine at ages 16-17 (n=1749), or were unvaccinated females in the birth cohort above those eligible for participation in FUTUREII in Finland (n=7369). The PATRICIA participants had been enrolled in an efficacy trial of the bivalent HPV vaccine at ages 16-17 (n=4808), or were unvaccinated females in the birth cohort above those eligible for participation in FUTUREII in Finland (n=9602).

Results: All participants received a questionnaire consisting of two generic HRQoL instruments (RAND36 and EQ VAS) and a disease-specific questionnaire (CECA10).
In the former 4438 valid responses were received and analysed (463 HPV6/11/16/18 vaccinated, 417 placebo vaccinated, 3558 unvaccinated). In the latter 5196 valid responses were received and analysed (1143 HPV16/18 vaccinated, 980 HAV-vaccinated, 3753 unvaccinated). Unadjusted mean outcomes of the different QoL measures (RAND36 domains and EQ VAS) were similar. Multiple regression analysis found that reporting current or previous genital warts or cytological abnormalities was significantly associated with reduced QoL; but no significant differences between neither of the HPV vaccinated group and the control vaccine or unvaccinated groups were observed.

Conclusions: Five years post vaccination the health-related quality of life of HPV-vaccinated young adult women did not differ from controls representing the general population.

P 3-16

ORGANIZATION OF IN-DEPTH EXAMINATION OF THE ROSTOV REGION FEMALE POPULATION WITH THE AIM OF CERVICAL DISEASE DETECTION AT THE FACILITIES OF REGIONAL CLINICAL DIAGNOSTIC CENTER.

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Objectives: The use of clinically validated HPV test in screening allows to add precision in forming groups having risk of developing cervical cancer and to correctly determine the tactics of the patients in-depth examination. The main concern of HPV testing introduction in national screening program is the need for careful planning of financial costs and logistic solutions. Rationality of centralized management during all phases of screening in a specialized well-equipped facility was shown.

Methods: Since 2013, in Rostov-on-Don and the Rostov region a regional program of cytological cervical cancer screening with parallel HPV testing has been implemented. Liquid-based cytology BD TriPath and clinically validated test Abbott RealTime High Risk HPV are used for screening purposes in the specialized laboratory of the Regional Consultative and diagnostic center. The performance of all tests is automated.

Results: During the period of 2013-2014 cytology is conducted for 37135 women. HPV testing is conducted for 10892 females (29%). Pathological changes in the epithelium identified by cytology are detected in 6643 women (17%): LSIL - 6401 (17%), ASC-US - 113 (0,3%), HSIL - 123 (0.3%), the cancer is detected in 6 women (0.02%). Positive results in HPV testing with diagnosed pathology by cytological analysis contribute to 16%.

Conclusions: Complex approach to the diagnosis of cervical lesions and coordinated working process of medical institutions can significantly shorten the patients examination process and help to timely use high-tech testing and treatment methods in frames of one multi-disciplinary diagnostic center.

P 3-17

BIOCHEMICAL INVESTIGATIONS OF HUMAN PAPILLOMAVIRUS INFECTED CERVICAL FLUIDS

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Object: Cervical cancer is caused by persistent infection with high-risk types of human papillomavirus (HPV). The aim of this study is to determine the potential of Raman spectroscopy as a stand-alone analytical tool for clinical diagnosis of HPV infection using human cervical fluids.

Method: A drop-coating deposition surface enhanced Raman scattering (DCDSERS) method was identified as the most effective method of proteomic analysis in cervical biofluids. Using a 2-μL sample, the proposed DCDSERS method led to Raman spectra with high reproducibility, noise-independence and uniformity. Additionally, the produced spectra were independent of the volume of fluids used and detection zones analyzed with the central and the ring zones.

Results: The presence of HPV in cervical fluids could be detected more accurately regardless of the center and the periphery of the sample. There were different Raman spectra according to HPV type. Biomarkers with an intensity ratio of 800 to 1000 cm^{-1} achieved 100% sensitivity and specificity. The intensities of all Raman spectra from 417 cm^{-1} to 1782 cm^{-1} were different between the HPV-negative and -positive cervical biofluids. Therefore, all range of HPV-gated DCDSERS could be used as a marker to detect the presence of HPV infection.

Conclusion: The DCDSERS technique allowed for high chemical structure sensitivity without additional tagging or chemical modification, making it a good alternative for early clinical diagnosis of HPV infection. Therefore, we are hopeful that the DCDSERS method will be approved for use in obstetrics and gynecology clinics.

P 3-18

PERSISTENCE OF HPV AFTER CONIZATION IN A REFERRAL HOSPITAL IN SPAIN

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OBJECTIVE: To analyze the persistence of HPV infection after conizations carried out due to CIN 2+ in the Lower Genital Tract pathology unit.

MATERIAL AND METHODS: retrospective descriptive study by reviewing clinical records of all women with a conization carried out with diathermic loop between January, 1st 2009 and December, 31st 2011 and with positive HPV DNA test 6 months after.

RESULTS: A total of 255 conization were identified in the 3-years period, being 66 positive for viral persistence (25.9 %).
Average time of persistence was 27.9 months (12- 63 months) . Average age of patients was 36.1 years (21-66 years). Persistence rate was significantly higher in women ≥ 30 years of age. Average time of follow-up was 34.5 months.
Genotype 16 was the most persistent one (47% of cases), followed by types 31 (19.7 %), 51 (13.6 %) and 18 (7.6 %) . There were no cases of persistence by genotype 26. In 31.8% of cases (21/66) persistence was due low risk (LR)-HPV.
9.1 % of patients were immunosuppressed (3% HIV).

CONCLUSIONS:
1.- There was high frequency of persistence of high risk- HPV types after conization (25.9 %).
2.- The most persistent genotype in our environment was 16 (47 %).
3.- 31.8 % of cases of persistence were positive for LR- HPV that were not identified before conization.

P 3-19

COMPARISON BETWEEN HPV ONCOTECT AND NUCLISENS EASYQ ASSAY AND ITS POTENTIAL ROLE IN DETECTING PRENEOPLASTIC LESIONS OF THE CERVIX

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Objectives: This study compare the performance of NucliSENS EasyQ test (bioMerieux), a RT-PCR based method, or HPV OncoTect (IncellDx) a flow cytometry-FISH based method, in the detection of the E6/E7 mRNA expression of hrHPV. Moreover, we investigated the potential role, for the detection of high grade lesions, of the HPV OncoTect compared to pap smears to improve cervical cancer screening.

Methods: We enrolled 173 patients positive for HR-HPV DNA and/or pap smear and referred for evaluation by means of the NucliSENS EasyQ. All patients were tested with HPV OncoTect and 87/173 underwent a colposcopy and histological evaluation according to clinical protocol.

Results: HPV OncoTect displayed a reactivity of 25% in negative samples, 40% in atypical squamous cells of undetermined significance ASCUS, 48% in low-grade squamous intraepithelial lesion LSIL and 80% in high-grade squamous intraepithelial lesion HSIL. The corresponding results for NucliSENS EasyQ assay were 42, 60, 74, 90%, respectively. Histology analysis revealed that the sensitivity of HPV OncoTect compared to NucliSENS EasyQ was 20% versus 54% in normal specimens, 45% versus 69% in CIN1 and 87% versus 74% in CIN2+, respectively. Higher specificity was observed analysing CIN2+ samples with HPV OncoTect (69%) versus NucliSENS EasyQ (36%).

Conclusions: HPV E6/E7 mRNA Oncotect test is more specific than NucliSENS EasyQ in identifying women with CIN2+ but has a lower sensitivity. HPV OncoTect is a promising tool for early prediction of persistent HPV infection and seems to be an interesting method to evaluate the preneoplastic lesions of the cervix and improve cancer screening.

P 3-20

THE 16, 18 AND 45 HPV INFECTION TRIAGE IN PRIMARY HR-HPV TEST SCREENING PROGRAM

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Objectives: infection with high-risk human papillomavirus (hr-HPV) 16, 18 and 45 causes 94% of cervical carcinoma. The identification of these three subtypes in women resulted positive to hr-HPV test could lead to early identification of high grade lesions. In our screening center (Latin, Italy) we perform the hr-HPV test followed by Pap test to women aged 35-64 if they resulted hr-HPV+. We aimed to provide data about the genotyping test for HPV16, 18 and 45 and eventually to propose this test as alternative to triage cytology.

Methods: we used Digene HPV Genotyping PS Test to identify HPV16, 18 and 45 in 22 women with histological diagnosis of CIN2+, 22 women with histological diagnosis of CIN1 and 22 women hr-HPV+/Pap-.

Results: the group of CIN2+ showed the higher positivity to the test (64%) and the higher positivity to HPV16 (41%) than other groups. No woman of hr-HPV+/Pap- group showed positivity to HPV18 while this positivity was the same in the groups of women diagnosed with CIN1 and CIN2+ (9%). We observed a difference statistically different in test positivity between women with diagnosis of CIN2 + and the group of women with diagnosis of CIN1 plus women hr-HPV+/Pap (64% vs 36%). Analyzing the clinical performance of the genotyping test we observed that the specificity was 64%.

Conclusions: from these data we concluded that the identification of HPV 16 is predictive for high-grade lesions but this test could not be used alternatively to triage cytology.

P 3-21

CLINICAL VALIDATION OF THE ANYPLEX II HPV HR DETECTION FOR THE CERVICAL CANCER SCREENING IN KOREA

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Background: The AnyplexII HPV HR Detection (HPV HR, Seegene Inc, Republic of Korea) is a multiplex real-time PCR assay to detect individual 14 high-risk HPV types in a single tube for the cervical cancer screening.

Objectives: The clinical performance of AnyplexII HPV HR Detection was compared to that of Hybrid Capture 2 (HC2) using the noninferiority score test in a routine cervical cancer screening setting. The intra-& inter-laboratory agreements of HPV HR were also evaluated.

Methods: Total 1137 DNA were extracted from LBC specimens of Korean women who requested to Seegene Medical Foundation. The cytological grades of specimens were reviewed by the well-trained pathologists. 72 cases of HSIL and 1065 cases of <HSIL were tested. Total 504 specimens, of which 152 were positive by HC2, were used to assess inter-& intra-laboratory agreements.

Results: The overall agreement between two products was 92.4% (1051/1137) with a k value of 0.79(95% CI, 0.74 to 0.83). Clinical sensitivity and specificity of HPV HR were 94.4% (95% CI, 89.2 to 99.7) and 81.7% (95% CI, 79.4 to 84.0), and those of HC2 were 93.1% (95% CI, 87.2 to 98.9) and 81.8% (95% CI, 79.5 to 84.1), respectively. Clinical performance of HPV HR was noninferior to that of HC2 ($P<0.05$). In addition, inter- and intra-laboratory agreements of HPV HR were determined 97.4% (95% CI, 0.91 to 0.97) and 98.0% (95% CI, 0.93 to 0.98), respectively.

Conclusions: The AnyplexII HPV HR Detection is clinically comparable to HC2 and can be very useful for routine cervical cancer screening.

P 3-22

IMPROVED METHOD FOR HUMAN PAPILLOMAVIRUS DETECTION AND CHARACTERIZATION WITHOUT DNA EXTRACTION, USING A LOW DENSITY MICROARRAY TECHNOLOGY, CLART® HPV-4.

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AIM: Improvement of the Human Papillomavirus (HPV) detection and genotyping of the CLART® HPV2 assay by avoiding the DNA extraction step, increasing the sensitivity in the detection of high-risk types, and reducing labour time.

METHODS: Virus detection is performed via multiplex PCR for amplification and a low density microarray platform for detection. In this new version, new primers have been included to increase the sensitivity in the detection of the following HPV genotypes: 39, 42, 45, 54, 56, 62, 68a. Furthermore, an automatic faster system has been implemented for the visualization of results. Different clinical samples (swabs, LBC, biopsies) were amplified directly without the need for DNA extraction.

RESULTS: Analytical sensitivity was calculated by using recombinant plasmids, resulting in a range between 100 - 1000 copies/µl for all types. A 100% analytical specificity was obtained in all cases. This kit has been validated in collaboration with different hospitals (Clínico San Carlos University Hospital, Marqués de Valdecilla University Hospital, Guadalajara University Hospital, Germans Trias i Pujol University Hospital) adding up to 563 samples. Diagnostic sensitivity and specificity data was over 95%.

CONCLUSION: DNA extraction free CLART® HPV-4 simultaneously detects the most prevalent HPV types including those associated to high and low risk for cervical cancer with a sensitivity and reproducibility ≥ 95%, being useful in the clinical setting for rapid screening. Our data supports the use of this technology for clinical testing of HPV genotyping in any sample in a faster assay.

P 3-23

COMPARATIVE ANALYSIS OF CERVICAL CYTOLOGY AND HPV GENOTYPING BY 3 DIFFERENT METHODS IN ROUTINE DIAGNOSTIC SETTING

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OBJECTIVES: We compared HPV DNA results in view of the eventual development of a CIN lesion either determined on cytology or histology.

METHODS: A total number of 214 LBC samples were analysed. Three different HPV DNA methods were applied: Abbott RealTime High Risk HPV test, INNO-Lipa HPV Genotyping Extra and Full Spectrum PCR HPV Amplification and Detection/Genotyping System by Lab2Lab Diagnostic Service.

RESULTS: The comparison of these 3 methods revealed full concordance only for 49 samples (23%) and 27 (13%) of samples were discordant regarding revealing presence of high risk HPV type. Out of 214, 88 patients were selected presenting CIN or VAIN lesion in follow-up cytology or histology. In this group full concordance in HPV genotyping was present only in 19 (22%) of follow-up samples. Nine (10%) of follow-up samples showed discordant results for the presence of high risk genotype between 3 tested genotyping methods either by negativity for high risk HPV by one of the methods (n=6) or by failure to genotype HPV (n=2) or by combination of both (n=1). Discordance for the detection of HPV16 or HPV18 was observed between 3 HPV DNA genotyping methods used in 9 (10%) follow-up samples.

CONCLUSIONS: Major differences were found in genotyping results according to the HPV DNA method. Our findings accentuate the importance of careful interpretation of data from studies using different HPV genotyping methods and underline the need for standardisation by method validation in clinical laboratories especially in the foresight of primary HPV screening.

P 3-24

DETECTION OF HIGH-RISK HPV (HRHPV) GENOTYPES AMONG THE ECUADORIAN FEMALE POPULATION WITH COBAS 4800

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INTRODUCTION: While it is widely known that HPV 16 and 18 are responsible for approximately 70% of cervical cancer cases worldwide, limited information exists about the HPV genotype distribution in Ecuador.

OBJECTIVE: To detect the prevalence of hrHPV genotypes in the general Ecuadorian female population.

METHOD: Samples were taken from patients at the gynecology department at Hospital Luis Vernaza, Guayaquil, Ecuador from August 2012 to November 2012. Cervical samples were collected with Rovers Cervex brushes and then placed in PreservCyt Solution. Samples were then run on the cobas 4800 according to the manufacturer´s protocol.

RESULTS: Screening indicated the presence of an hr-HPV genotype in 63 of the 264 total cervical samples (23.8%). Of these samples, 9 (14.3%) were positive for HPV 16 only while 2 (3.2%) were positive for HPV 18 only. Interestingly, the remaining 52 samples (82.5%) were genotyped under the category of "Other," indicating the presence of a hrHPV genotype other than HPV 16/18. Three of these patients were also shown to be co-infected with HPV 16.

CONCLUSION: This study provides novel epidemiological data concerning the HPV distribution in Ecuador. While the sample size is small, it should be noted that very few of the samples were positive for HPV 18. Future studies are needed to further investigate this possible trend, which may have important public health implications for the implementation of the HPV vaccine, which solely covers HPV 16/18.

P 3-25

GENEXPERT® HPV ASSAY EVALUATION IN A LSIL SETTING

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Objectives: In the Eurogin 2012 we presented an evaluation of the new generation DNA and RNA tests, like the Roche cobas® HPV, the Abbott Realtime HR HPV, Cervista™ and the Aptima HPV, comparing it with Hybrid Capture 2. The high prevalence of HPV limits the usefulness of HPV DNA testing when deciding how to manage LSIL, however the study showed a better specificity of the new DNA and RNA tests, comparing to HC2, due to the lack of cross-reactivity with low risk types. This year, Cepheid developed a new HPV test for the GeneXpert® platform. We tested the samples mentioned above with this new technology in order to compare it with the other mentioned tests.

Methods: A total of 100 consecutive PreservCyt® Solution samples diagnosed with LSIL were selected from the routine screening at LAP. All results were compared with routine cytology and histology data generated for that sample. The gold standard is histological confirmed cervical intraepithelial neoplasia (CIN) grade 2+ or 3+. Sensitivity and specificity of each of the HPV screening tests were calculated based on disease defined as CIN 2+.

Conclusions: The new GeneXpert test achieve similar an excellent performance, comparable to the Roche cobas® HPV, the Abbott Realtime HR HPV, Cervista™ and the Aptima HPV, with significant better specificity than the HC2. In our perspective, this finding could re-launch the debate around HPV testing for triage of LSIL.

P 4-1

USING ACUTE ONCOLOGY TO DRIVE TRANSLATIONAL SCIENCE: IDENTIFYING POTENTIAL BIOMARKERS TO OVERCOME RESISTANCE MECHANISMS OF OVARIAN CANCER

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Objectives: We initiated an integrated Acute Oncology Service (AOS) in 2012 to provide rapid access for patients presenting with cancer related emergencies from Portsmouth, East Hampshire and the Isle of Wight. We use our AOS to drive translational studies to begin to identify ovarian cancer biomarkers which may prove viable targets for novel combined chemotherapies.

Methods: 2-4 patients per week presented to our AOS for drainage of malignant ascites due to ovarian cancer. With each patient's consent, we analysed excess ascitic fluids, performing molecular assays to identify targets known to influence cancer growth pathways, drug sensitivity and resistance mechanisms. Chemotherapy combinations were then tested in cellular assays, to evaluate promising targets. We also collected clinical data tracking CA-125, surgical, radiotherapy and chemotherapy interventions. As medical Oncologists, we are able to screen for available targeted biologics from primary cytology which may be used for ovarian cancer.

Conclusions: The development of our AOS service enables patients to gain rapid access to clinicians that they recognise and trust. Earlier specialist involvement improves clinician-patient contact, enhancing our access to valuable pathological samples, to empower translational studies such as this one. Thus far, we have identified two potential targets regulating growth pathways that appear sensitive to a combination of an EGFR inhibitor (gefitinib or erlotinib) and the PI3K inhibitor, ZSTK474. We aim to recruit 60 patients to extend this work over the next 12 months.

P 4-2

TYPE-SPECIFIC HPV PREVALENCE IN WOMEN AT HIGH RISK OF INVASIVE CERVICAL DISEASE: DATA FROM THE BASELINE OF THE ITALIAN VALHIDATE STUDY

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Objective: To evaluate the HPV type-specific prevalence at baseline of the VALHIDATE study(1) in 3 different cohorts of women at risk for cervical disease in Lombardy, Italy.
Methods: Between November 2010 and February 2014, three groups of high-risk women, HIV-infected women (HIW), recent migrant women (RMW), adolescent/young women (AYW), and, as a control group, women attending a spontaneous screening program (SPW), were enrolled in the study after providing a written informed consent.
Cervical specimens were collected to undergo HPV-DNA screening. HPV-DNA was detected by PCR amplification of a segment of ORF-L1. HPV-DNA positive samples were genotyped using the INNO-LiPA-HPV Genotyping Extra or RFLP, if untypeable.
Results: A total of 779 HIW, 423 RMW, 564 AYW, and 1422 SPW were recruited.
The overall HPV prevalence was 18.2% (95%CI:16.9-19.6): 27.9% (95%CI:24.8-31.1) in HIW, 19.9% (95%CI:16.3-24.0) in RMW, 19.7% (95%CI:16.6-23.2) in AYW, and 11.8% (95%CI:10.2-13.6) in SPW cohorts respectively. At least one HR-HPV type was detected in 82.8%, 90.1%, 92.8%, and 89.6% of HPV-DNA positive samples among HIW, RMW, AYW, and SPW cohorts, respectively. The highest positivity for HPV-16 and/or HPV-18, in HPV-positive women, was detected in the AYW group (30.6%), the lowest in the HIW cohort (20.9%).
Conclusion: High prevalence of HR-HPV types was detected in all HPV-positive women, regardless of the cohort analyzed. A higher prevalence of HPV-16 and/or HPV-18 infections was observed in the younger age-group. These data suggest the need for virological monitoring and the implementation of preventive strategies in women at high-risk.
(1) Orlando et al. BMC Cancer 2012,12:204.

P 4-3

STRTUCTURAL AND LEVEL ONCOGENICITY CORRELATION BETWEEN HUMAN PAPPILOMAVIRUS VARIANTS E7

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Objective: *In silico* analysis of HPV e7 electrostatic surface and active sites of the proteins (type 01 nonpathogenic (control); types 06 and 11, low risk; types 16 and 18, high risk), aiming to establish correlations between tertiary structures and oncogenicity levels.

Methodology: Characteristics analysis of proteins by PyMOL and active sites analysis by GHECOM 1.0 softwares.

Results: Proteins types 16 and 18 showed differences in size, composition and position of loops. They also have differences in composition and α-helices when compared to control. The main components of types 06, 11, 16 and 18 active site showed an increase to 5Å in the distance between them, compared to control. It is possible to observe correlation between the increase of the distance and the oncogenicity level. The analysis of sites and electrostatic surface revealed differences in format and sites sizes, confirming the observations of the measured distances of the sites elements, where larger sites, possibly more accessible to the substrate, were observed in the pathogenic variants.

Conclusions: From these results, it can be concluded that the sum of the variations can be related to the different degrees of oncogenicity of these proteins. The differences in specific amino acids in the active sites can directly affect their physicochemical characteristics[1] hence it can be expected higher protein-substrate affinity. Gathered with the presence of intrinsically disordered regions[2], results show a correlation between structural differences and virus oncogenicity. This study provides a basis for further experiments to a better comprehension of the oncogenicity of e7 variants.

1Tamarozzi ER, Torrieri E, Semighini EP, Giuliatti S. In silico analysis of mutations occurring in the protein N-acetylgalactosamine-6-sulfatase (GALNS) and causing mucopolysaccharidosis IV. GMR 4764, 2014.

2 Nicolau N Jr, Giuliatti S. Modeling and molecular dynamics of the intrinsically disordered e7 proteins from high- and low-risk types of human papillomavirus. J Mol Model. 2013 Sep;19(9):4025-37. Epub 2013 Jul 18.]

P 4-4

OVEREXPRESSION OF HPV E6/E7 mRNA: A MARKER FOR HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS PROGRESSION IN PUERTO RICAN POPULATION

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Objectives: HSIL carries a higher risk of progression to cervical cancer given that 40% to 50% of HSIL progress. The overexpression of HPV E6 and E7 oncogenes are associated with cell proliferation and cervical carcinogenesis. In this study, we want to demonstrate that overexpression of these mRNAs can be used as a progression marker for HSIL and also, to determine if age is a factor in disease progression.

Materials and Methods: A total of 87 HSIL samples, positive for high-risk type HPV were obtained from a pool of 3,621 liquid-based samples from OB/GYN clinics around Puerto Rico. Samples were rescreened and classified following TBS criteria for HSIL. The progression risk was established in each age range from 17 to 65 years old. To determine overexpression of HPV E6/E7 mRNA, each sample was submitted to OncoProbe assay test (IncellDx™) and was classified as positive in cases where >2% of cells showed overexpression of E6/E7 mRNA.

Results: From 87 HSIL cytology samples: 39 cases (45%) showed overexpression of E6/E7 mRNA and were classified as positive; and progression risk by age was: <30 (45%), 30-39 (44%), 40-49 (42%), >50 (46%). The risk of progression of HSIL is 40-50% and the overexpression of E6/E7 mRNA in our cases was 45%.

Conclusion: This study demonstrated that overexpression of E6/E7 mRNA is a powerful tool that could be used to determine the risk of progression in HSIL cases in Puerto Rican population and that age is not a factor for the risk of disease progression.

P 4-5

HUMAN PAPILLOMAVIRUS E6/E7 mRNA AS CERVICAL CANCER BIOMARKER

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OBJECTIVES: The aim of the present study was to study the relationship between HPV E6/E7 oncogenes mRNA expression and cervical cancer development in women population in The Basque Country (Spain).

METHODS: Samples were genotyped by Linear Array genotyping Test. RNA extraction was perform by NucliSENS Lysis Buffer and HPV16 ,18, 31, 33 or 45 high-risk genotypes E6/E7 mRNA was detected by NucliSens® EasyQ® HPV v1 Test (Biomerieux). Finally, E6/E7 mRNA and pathology were studied over time. Pathology was classified in three groups: 1) normal, 2) ASCUS (Atypical squamous cells of undetermined significance) and low grade cervical intraepithelial neoplasia (CIN1) and 3) High grade cervical intraepithelial neoplasia (CIN2/CIN3).

RESULTS: Thirty-eight women samples were analyzed. Their age average was 34.63±10.65 years old (age range 19-63 years). Presence of viral E6/E7 mRNA was detected in 63.15% (24/38) of samples. E6/E7 mRNA positivity rate was 55% in normal cytology samples, 70.58% in ASCUS/CIN1 specimens and 100% in samples with CIN2/CIN3. HPV16 E6/E7 mRNA was mainly detected (66.67%), followed by HPV18 (20.83%), HPV33 (8.33%), HPV31 (4.17%) and HPV45 (4.17%). Lesion progression study showed that mRNA detection was higher in samples in which pathology had worsen over time (86.66%) rather than in specimens with the same lesion (54.54%).

CONCLUSIONS: HPV E6/E7 mRNA positivity rate was higher in more severe lesions and in samples that had worsen over time. This finding means that E6/E7 mRNA may be considered as a potential cervical cancer prognostic biomarker.

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P 4-6

mRNA EXPRESSION OF GENES KI67, P16, PGR AND BCL2 AS MARKERS OF INCREASED RISK OF NEOPLASTIC TRANSFORMATION WITH HPV-ASSOCIATED CERVICAL DISEASE

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Objective: To identify features of changes in the level of mRNA expression of human genes in patients with HPV-associated cervical disease, to predict the risk of neoplastic transformation of the cervical epithelium.

Materials and methods. This prospective study included a comprehensive 225 women, aged 18 to 60 years (mean age 31,6 ± 0,5). Duration of follow-up of patients was 12,4 ± 5 months. Complex examination of women included: collecting complaints, anamnesis, gynecological status, colposcopy, molecular-biological methods of research, cytology, histological examination of biopsy material (if indicated). Molecular biological research methods included a multiplex PCR method with detection results in real-time quantification and typing of HPV (21 types: 6,11,16,18,26,31,33,35,39,44 (55) 45,51,52,53,56,58,59,66,68,73,82) and determination of mRNA expression of human genes (sets "NPO DNA Technology", Russia). MRNA expression of genes 67 MKI (KI67), CTSL2, CDKN2A (P16), ESR1, PGR, BCL2, BAX, BAG1, CD68, SCUBE2, PTEN was determined by quantitative RT-PCR in real time with respect to the expression of the reference gene TBP, B2M and GUSB .

Results. According to the obtained results were formed 5 groups: 45 (20%) - HPV-negative (I group - control), II group -56 (24.9%) with subclinical forms of HPV-infection (exophytic cervical warts, flat warts of the cervix), III group - 50 (22.2%) with LSIL, IV group - 55 (24.4%) with HSIL, V -19 group (8.5%) with cervical cancer.

According to a study in group II showed a significant increase in mRNA expression MKI67 (KI67) in 1.8 times ($p = 8.3 \times 10\text{-}3$), CDKN2A (P16) in 1.6 times ($P = 4.6 \times 10\ 2$), CTSL2 in 1.5 times($P = 3.2 \times 10\text{-}2$), compared with the control group. In group III, there was a significant increase in mRNA expression MKI67 (KI67) in 1.5 times ($p = 4.4 \times 10\text{-}2$) and CDKN2A (P16) in 2.9 times ($p = 2.2 \times 10\text{-}4$) in compared with the control group. In the IV group showed a significant increase MKI67 (KI67) in 2.5-fold ($P = 5.7 \times 10\text{-}6$), CDKN2A (P16) 5.9-fold ($P = 1.2 \times 10\text{-}7$), compared with control group. In group IV, an increased expression of mRNA is even more important: MKI67 (KI67) to 10.3 times ($p = 1.6 \times 10\text{-}7$), CDKN2A (P16) to 11 times ($p = 1.7 \times 10\text{-}5$). In this case, there is a decrease in BCL2 to 3.6 times ($p = 2.2 \times 10\text{-}4$), SCUBE2 2.5 times ($p = 2.5 \times 10\text{-}2$), BAG1 and BAX in 1.9 times ($p = 7.5 \times 10\text{-}3$, and $p = 1.6 \times 10\text{-}2$, respectively), PTEN 1.4-fold ($P = 1.4 \times 10\text{-}3$). Significantly (25-fold) reduced unit cell receptor - ESR1i PGR ($p = 3.2 \times 10\text{-}4$, and $p = 3.2 \times 10\text{-}5$, respectively) compared with the control group.

In order to develop a method for determining the samples with a high risk of malignancy tissue was performed regression analysis (binary logistic regression). The regression equation has the form: $Z = 0{,}8 * \ln(KI6 / PGR) + 1{,}6 * \ln(P16 / BCL2) - 4$, where KI67, PGR, P16 and BCL2 – is a mRNA expression of the corresponding genes.

Based on this function for each sample was calculated probability of neoplastic transformation of the cervical epithelium. To determine the critical probability value (point cut-off) was carried out ROC-analysis. In group with high risk for neoplastic transformation of cervical epithelium were 29 patients: 5 (8.9%) - from group II, 9 (18%) - from group III, 15 (27.3%) - of group IV. Common types of HPV in patients at risk were as follows: 16 (65%), 58 (24%), 31 (13%), 33 (13%), 39 (10%), 52 (6.8%), in 65.5% cases revealed the presence of two or more types of HPV. In terms of predicting the development and course of the neoplastic process is of interest patient groups II and III, which were in the high risk group. Dynamic observation was carried out in 6-12 months. After 12 months in all patients of group II remained HPV, ASCUS in 1 (11%), LSIL - 4 (44.2%). In group III - HPV maintained in all patients, cytology - LSIL - 6 (66.6%) changed to HSIL - 3 (33.3%). For comparison, in patients of group II, which were not included in the group of high-risk HPV elimination was observed in 24 (47%), 20 (39.2%) - remained HPV, cytologic conclusion - NILM. In group III in 16 (39%) survived LSIL; in 25 (60%) - cytologic conclusion - NILM. In 21 (51.2%) showed persistence of HPV. In group III elimination of HPV occurred in 20 (50%) cases. Thus, only high-risk patients observed the development and progression of the neoplastic process, which implies that the multivariate analysis to determine the increased risk of development and progression of neoplastic process of the cervix to changethe level of expression of mRNA of human (MKI67 (KI67), CDKN2A (P16), PGR and BCL2).

Conclusions: Increased mRNA expression of genes MKI67 (KI67), CDKN2A (P16), decreased expression of PGR, BCL2, combined with high risk HPV types (especially16, 58, 31, 33, 39), abnormal colposcopy can be considered as potential biomarkers of predicting the development and unfavorable course of neoplasia; multifactorial analysis to determine the increased risk of development and progression of neoplastic process of the cervix to change the level of expression of mRNA of human (MKI67 (KI67), CDKN2A (P16), PGR and BCL2). Further studies are required.

P 4-7

PROTEOMIC MAP STUDY OF CERVICAL CANCER CELL LINES

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Objectives: Human papilloma virus (HPV) represents the etiologic agent of cervical cancer in more than 90% of cases. The aim of our study was to identify biological processes involved in malignant cell transformation by employing proteomic analysis of the total cell extract from normal control and cancerous cervical cell lines.

Methods: The proteomic profile of four cervical cell lines, i.e. HCK1T, a normal cervical epithelium cell line, HeLa [HPV18+], SiHa, [HPV16+], and C-33A [HPV-], exhibiting unique complementary molecular and phenotypic features, was analyzed by employing 2D electrophoresis and MALDI-TOF mass spectrometry. The generated 2D gels were processed using silver staining in order to visualize protein spots, and image comparison was performed by the PDQuest software. Differentially expressed proteins between normal and cancer cell lines (fold change >2) were identified by MALDI-TOF MS. Bioinformatic analysis was performed by the PANTHER software.

Results: A total of 168 proteins in the cell extracts (93 upregulated, and 75 downregulated) were differentially expressed between normal (HCK1T) and cancer (HeLa, SiHa, C-33A) cell lines. The most significant group of differentially expressed intracellular proteins was related to cytoskeletal remodeling. Moreover, enzymes involved in the glycolytic pathway were upregulated in the cancer cell lines.

Conclusion: The proteomic analysis of cervical cell lines indicates that cytoskeletal remodeling could explain the increased motility and invasive character of cancerous cell lines.

P 5-1

OPTIMAL AGE FOR THE ONSET OF HPV-BASED PRIMARY CERVICAL CANCER SCREENING USING THE COBAS® HPV TEST (ROCHE).

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Objectives. To assess the optimal starting age for the implementation of the cobas® HPV test as a method of primary cervical cancer screening.

Methods. We recruited 4,009 women aged 25-55 years, undergoing Pap smear testing, between August 2011 and November 2013 at nine Gynecology Departments in Greece. Cytological evaluation was performed using Liquid-based Cytology (LBC) (ThinPrep®). An aliquot of each sample was used in order to detect HPVs 16 and 18, separately, and HPVs 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 using the cobas® system (Roche). Women found positive for either cytology or HPV were referred for colposcopy. Two separate analyses were performed concerning the cobas® HPV test performance for the detection of Cervical Intraepithelial Neoplasia grade 2 or worse (CIN2+) according to age. The first involved women aged 25-29 and the second women older than 30.

Results. Of the 4,009 women recruited, 3,993 were included in the analysis. The overall prevalence of HR-HPV was 12.7%, of HPV-16 2.7% and of HPV-18 1.4%. CIN2+ was detected in 41 women (1.07%). Sensitivity for the cobas test was 100% in both age groups, whereas specificity and positive likelihood ratio in older women were statistically significantly increased compared to younger ones (92.5% vs 79.1% and 13.4% vs 4.8 respectively). The absolute risk for CIN2+ among cytologically normal HR-HPV positive women was increasing with age.

Conclusion. HPV DNA testing should optimally be used as a method of primary cervical cancer screening in women over 30 years of age.

P 5-2

HIGH RISK HUMAN PAPILLOMAVIRUS POPULATION SCREENING AND INTRATYPIC VARIANTS DETECTION IN NORTHERN SPAIN

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OBJECTIVES: The objectives of this study were 1) to analyze the prevalence of high risk Human Papillomavirus (HPV) genotypes and 2) to detect HPV16 and HPV18 intratypic variants distribution in women during a population screening.

METHODS: Clinical samples from 912 women were tested for HPV Cobas Test (Roche Diagnostics), a real time PCR assay that analyzed 14 high risk HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). Then, HPV16 and HPV18 positive specimens were sequenced and compared with GenBank consensus sequences to determine intratypic variants.

RESULTS: Analyzed specimens mean age was 41.30±11.64 years and high risk HPV prevalence was 10.64% (97/912) in our area. HPV positivity showed that the 22.85% of women were infected with HPV16, 5.71% with HPV18 and 71.43% with other high risk genotypes. HPV positive women age average was 34.12±10.57 years. Moreover, it was observed that the majority of HPV positive samples are from younger women (<50 years) (96.15%) which showed a statistical significance ($p<0.05$). On the other hand, European variant was the predominant among HPV16 samples (84.21%) and Asian-American variants among HPV18 specimens (60%).

CONCLUSIONS: HPV population screening concluded that high risk HPV incidence is high (10.64%) in our area. Moreover, the virus infected above all young women. Thus, this study reveals the need of screening programs, variants detection and infected women follow-up by means of preventing HPV related lesions.

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P 5-3

IN SILICO MODELING OF HUMAN PAPILLOMAVIRUS TYPE 16 (HPV16) E6 PROTEIN

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Objectives: The aim of this work is to obtain in silico the complete structure of human papillomavirus type 16 E6 protein.

Methods: The protein was partly modeled by homology using as template the structure obtained by X-ray crystallography of HPV16 E6 oncoprotein in complex with the LXXLL peptide of E6AP protein (PDB ID: 4GIZ). The homology modeling was performed using MODELLER software implemented on the server @TOME2. The two regions, located at the N-terminal (residues 1-8) and C-terminal (residues 151-158), absent in the template, were modeled by Rosetta 3.1.

Results: After modeling, scoring functions such ModFOLD and QMEAN were used to classify the 1,000. The top ten selected by each software were reclassified by PROCHECK. The top 10 models resulting from this analysis were analyzed by multiple Model Quality Assessment Programs such as PROVE and Verify3D. The dynamics was performed using CHARMM27, implemented in NAMD 2.8 software.

Conclusions: The tertiary structure of the E6 protein was achieved by a combination of two approaches: homology modeling and ab initio modeling. This method allowed us to obtain in silico the complete structure of the E6 protein. Once known tertiary structure of the HPV E6, there is the possibility of carrying out virtual screening, searching for ligands as one of the possible strategies against HPV.

P 5-4

RESTRICTION OF CERVICAL CANCER IN LATVIA: OPPORTUNITIES AND CHALLANGES

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Objectives: Both primary and secondary cervical cancer preventation has been introduced by goverment in Latvia. Since September 2010 HPV vaccination has been integrated into the national immunization schedule. Cervical cancer screening programme was established in Latvia in 2009. In 2012 Latvia had 5th highestcervical cancer mortality among 40 European countries[1].

Methods: We analyzed some cervical cancer screening programme data obtained in 2009-2014(response rate for cervical cancer organized screening programme, screening cytology results interpretation,cancer audit,coverage of vaccination).

Results: The response rate for cervical cancer organized screening programme in Latvia is low :compliance to invitation in 2009 was 14,1%,in 2013-27,4% and opportunistic cytologies are still popular ,according to data up to 60% in 2012. Despite on free of charge HPV vaccinationt planned immunized population is still has not been reached,in 2013 1stdose has received 57,7%,but 3rd dose -55,9% of goal population. We should note that cytology material in Latvia is stained using Leishman's technique to compare other European countries where Papanicolau staining is used. The group of reactive changes is large (47%, in 2012 there were 23803 cases) with a high need for repeat cytologies and colposcopy referrals.Cancer;s cases are registrated,but cancer audit is not performed yet.

Conclusions: Monitoring, evaluation and coordination of the screening programme in Latvia are insufficient. Future development of quality assurance standards according to European guidelines on cervical cancer organised screening programme in Latvia will be required and regular audit of it will be provided .

1- Ferlay J., et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. European Journal of Cancer, 2013; 49: 1374-1403

P 5-5

CANCER SCREENING IN LOW RESOURCE SETTING

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In India first most cancer among women between 15 years and 44 years is cancer cervix. HPV 16 ,18 infection causes 82.5% of invasive cancer cervix and 7.9% women has HPV infection

Current estimates indicate that every year 134,420 Indian women are diagnosed with cervical cancer and Crude Incidence Rate of 23.5. In 2025 they expect new cervical cancer cases to reach 203,757 It is estimated that Women die due to cancer of the cervix approximately 72,825 at present and it will rise to 115.171.
HPV infection alone cannot cause cervical cancer there are other risk factors like low socioeconomic status, early marriage, poor genital hygiene, high parity ,smoking are necessary for progression of the disease. In India 80% of cancer cervix diagnosed from rural area. Hence well organized screening programme is essential to prevent , reduce the incidence and mortality due to disease.

Using the VIA / VILI method under magnification, all women within the age group 30 to 60 years of low socioeconomic women, irrespective of the presence of symptoms were screened for Cervical Cancer in Tamil Nadu at Govt RSRM Hospital for 6months. Using the visual methods as a screening tool, large number of women were screened. There are lot of advantages over Pap smear. This can be done even by Paramedic, can be performed as an op procedure, interpretation done on the spot, Highly sensitive, Positive cases immediately taken care by doing colposcopy and directed biopsy and early treatment started appropriately and they are not lost to follow up. It does not require cytotechnicians. This can be extrapolated to large scale.

P 5-6

MODELING TO IMPROVE: COVERAGE AND PARTICIPATION RATE IN AN ORGANIZED CERVICAL CANCER SCREENING PROGRAM.

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Objectives: The aim of this study was to know the participation rate in an organized cervical cancer screening (CCS) program in order to evaluate improvement opportunities.

Methods: Castile and Leon is a Spanish region where organized CCS was established on 1986. Since late 2008, its algorithm was reviewed. The participation rate was calculated as ratio between women attending the program in last 5-years (2009-13) and the optimal scenario. The optimal scenario was obtained by modeling the cohorts born 1945 to 1988 (data from municipal registry) through the algorithm applying different probabilities for outcomes and revision periods depending on age. Probabilities applied to population matrices were obtained from real data in 2009-13. Number of non-eligible women (because of ongoing cervical pathology or hysterectomy) was assumed to be negligible.

Results: Actual coverage of the CCS program is 100% which is a ~690.000 women aged 25-64 years. CCS results are positive (overall 2.56%, derived to gynecologist), non-determinant (8.82%, to be screened 1 year later) and negative (25-34 years are screened in a 3-years period –1-year period the first time– and women 35-64 years in a 5-years period). Participation rate was estimated to be 30.4%, from 37.0% in 30-34 years to 18.4% in 60-64 years, with a decreasing trend of 2.4% every 5-years of age.

Conclusions: Organized CCS can reach quite amount of target population. Nevertheless, personal invitation to participate in the CCS is needed to reach recomm

P 5-7

CERVICAL CANCER SCREENING: ALBANIA'S DILEMMAS AND PRELIMINARY RESULTS

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Background: Albania is facing a complex and unclear situation in relation to screening and prevention of cervical cancer. The said situation is conditioned by the lack of a formulated national strategy and of the ensuing national programs.

Objectives: Data collection and selection in view of identifying a proper method for the future construction of a national screening program in Albania.

Methods: After a two years (2011-2012) of a very low response to the invitation of IPH, for a routine HPV screening of aged 17 to 65 years women, a self-collected method was introduced in the year 2013. A number of 1580 women responded to the invitation on January 2013 - August 2014 period of time. Self collected samples were analysed with Hybrid Capture 2 Assay. All positive hrHPV women were advised for a cytological testing.

Results: HPV cervical infection was detected in 264 women presenting a high HPV prevalence (16.7%) despite of a relatively low incidence rate of cervical cancer in Albania (6 new cases/100,000 women per year).
Overall prevalence of infections with hr-HPV was found the highest among 25-34 years old women (36%) which were the most represented group. The cytological analyse showed that 75 % of hrHPV positive women were found with a normal cytology.

Conclusions: HPV self-collected test, significantly improved the participation in the screening. The results of this study provided useful information in relation to the future preselected methods for a wider screening program for cervical cancer in Albania.

P 5-8

COST-EFFECTIVENESS OF HPV DNA VERSUS HPV MRNA TESTING UNDER CURRENT UNITED STATES GUIDELINES FOR CERVICAL CANCER SCREENING

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Objectives: To compare the cost-effectiveness analysis of high-risk human papillomavirus (HR-HPV) DNA and HR-HPV mRNA testing under current US cervical cancer screening guidelines.

Study design: Markov model for stochastic cost-effectiveness analysis using published data.
We compared screening efficiency using HR-HPV DNA and HR-HPV mRNA testing for
1) co-testing with cytology of women 30-65 years, and 2) for triage of women with mild cervical cytological abnormalities (ASCUS) in the US. Screening endpoint is histologically-confirmed high-grade lesions (CIN 2+).

Methods: Sensitivity and specificity estimates of HR-HPV DNA testing with Hybrid Capture II (HCII) and HR-HPV mRNA testing with Aptima to detect CIN 2+ were from two published trials-the US CLEAR study for ASCUS triage, and the European FASE study for co-testing. Costs of Aptima and HCII were assumed identical. Costs of screening, diagnosis, and treatment of cervical neoplasia and cancer were from previously published estimates, adjusted to 2012 US dollars. Inputs were modeled as distributions for Monte Carlo probabilistic sensitivity analysis. Model outcomes were costs per life-year gained for each strategy, discounted at 3% annually.

Results: For both co-testing and ASCUS triage, Aptima cost less than HCII. Mean discounted life expectancy was slightly higher (0.00001 years) in both settings using HCII. The incremental cost-effectiveness ratio of HCII compared to Aptima was >$873,000 per life-year saved for co-testing, and >$1.9 million per life-year saved for ASCUS triage.

Conclusions: Based on the available data, HR-HPV mRNA testing for co-testing or ASCUS triage appears more efficient than HR-HPV DNA testing under current US cervical cancer screening guidelines.

P 5-9

SECONDARY PREVENTION OF CERVIX CANCER IN THE MADRID REGION: A PROPOSAL FOR A CHANGE.

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Goal: To replace the current cervix cancer screening system in the Madrid region by an updated screening, considering recent scientific evidence-based recommendations.

Methodology: In the Madrid region, and opportunistic Pap cytology-based cervix cancer screening is currently done. Samples are obtained both at primary and specialised health centres. Sampling is initiated at 25 years of age, and finishes at 65. In the age range 25-35 samples are taken at 3-year intervals, while 5-year interval sampling is done beyond the age of 36.
We propose herein a change towards a census-based wide screening of the subject population. Call phone system and self-sampling is contemplated. HPV-tests will be validated as primary tests, including first-line genotyping and 16/18 strain differentiation respect to other high-risk HPV strains.
Thus, women resulting positive for the 16/18 HPV test will be derived to colposcopy procedures, while those individuals positive for other high risk HPV-strains will be subjected to triage cytology. The covered age range will be 30 to 65 years, with samples taken every 5 years. HPV-test analysis will be performed at a centralised laboratory for the whole Madrid region, while the cytological samples taken at primary health centres will be sent and analysed at the corresponding Pathological Anatomy Unit of the referral hospital.

Conclusion: The new screening system will provide a larger coverage and, therefore, a bigger protection of the subject population against cervix cancer, with an expected 15% cost reduction compared to the current system.

P 5-10

P16/KI-67 DUAL-STAIN CYTOLOGY IN CERVICAL CANCER SCREENING: FUTURE IS NOW? OUR OWN EXPERIENCE IN A FIRST LEVEL HOSPITAL

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Objectives:

1. Evaluate the usefulness of dual stain cytology as a molecular marker in risk assessment in patients HPV (+) or abnormal cytology.
2. Compare our performance regarding Guidelines for the Screening of Cervical Cancer in Spain 2014.

Methods:

1. Literature review on new perspectives on cervical cancer screening (molecular techniques) versus conventional Papanicolau test.
2. Case series with dual staining (+) and medical action (therapeutic or preventive).
3. Comparison of our algorithm with the recommendations in the new guide.

Results:

1. The $p16^{INK4a}$ / Ki67 dual staining cytology (molecular marker) identifies premalignant lesions with high power progression, being proposed in secondary prevention of cervical cancer.
2. This marker of cell cycle deregulation induced by HPV help us improve the cytological diagnosis, eliminating the interobserver variability, serves as a prognostic marker and guides subsequent handling.
3. Our case series, n = 65 (18 months): If HPV (+) or cytology> ASCUS.
4. There is not unified protocols nor absolute agreement regarding the use of the dual stain cytology: according to the Spanish guide, apply if HPV (+) with normal cytology.

Conclusions:

1. Optimal screening behaviors are needed to identify precursor lesions to avoid overdiagnosis / overtreatment of transient infections without potential for progression (increase specificity screening).
2. There is no agreement on the management and monitoring of premalignant lesions, at every turn new strategies emerge, where molecular techniques take an important role.

P 6-1

RAMAN MICROSPECTROSCOPY FOR CYTOLOGICAL SCREENING OF CERVICAL CANCER

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Objective Although cytology-based screening programmes have allowed a decline in the incidence of cervical cancer, this decrease has recently reached a plateau and regular retesting is necessary to achieve adequate sensitivity for disease detection.
Over the past two decades, Raman spectroscopy has emerged as a promising new technology for cancer diagnosis due to its ability to detect pre-malignancy and early malignancy stages of the disease.
In this study we acess the viability of using Raman spectroscopy in the screening of cervical cytology samples.

Methods Negative, borderline and cervical intraepithelial neoplasia (CIN) ThinPrep® samples were used to establish the Raman spectroscopic profile of each group and assess the use of Raman spectroscopy on routine cytology samples. Raman spectra were obtained from the nuclei of the cells and subjected to multivariate statistical analysis.

Results Normal and abnormal cervical Thinprep samples were discriminated based on the biochemical fingerprint of the cell nuclei. The data suggest that Raman spectroscopy is able to identify biochemical features that allow a correct discrimination of the samples according to their clinical classification.

Conclusion This study has shown that Raman spectroscopy can be successfully applied to the study of routine cervical cytology samples from a cervical screening programme and this technology could be used in the future for cervical cancer screening.

P 6-2

APPLICATION OF 2-TIERED NOMENCLATURE FOR CERVICAL INTRAEPITHELIAL NEOPLASIA IN CLINIC

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Objective: To apply 2-tiered nomenclature of cervical intraepithelial neoplasia (CIN) in clinic, in order to unify the terminology of it and strengthen the knowledge of cervical precancer.

Methods: immunohistochemistry was used to examine the expression of p16 and ki-67 in cervical reactive changes with 111 cases, CIN1 with 81 cases and CIN2 with 39 cases.

Results: p16 expression was confirmed in 18.91%, 41.98%, 64.10% of cervical reactive changes, CIN1 and CIN2, respectively. Positive expression of Ki-67 was observed in 32.43%, 32.10%, 69.23% of cervical reactive changes, CIN1 and CIN2, respectively. There were significant differences in p16 among the various groups ($P < 0.05$)。No such finding was detected with Ki-67 among the groups($P > 0.05$). In cervical reactive changes, CIN1 and CIN2, the expression of p16(+) /ki-67(+) was 10.32%, 9.52%, 43.59%; p16(+)/ki-67(-) was 6.35%, 30.95%, 20.51%; p16(-)/ki-67(+) was 20.72%, 22.22%, 25.64； p16(-)/ki-67(-) was 60.36%, 35.80%, 10.26%, respectively. The expression characteristics of p16 negative and ki-67 positive are different in three groups.

Conclusion: p16 and ki-67 protein are very useful for 2-tiered nomenclature of CIN ； Accuracy of this classification relies on immunohistochemical interpretation standard carrying out. The different staining characteristics in the same grade maybe represent different biological nature, but it still needs large clinical validation.

P 6-3

ANOSCOPY COULD BE BENEFICIAL FOR WOMEN WITH EXTERNAL GENITAL CONDYLOMA?

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Background: Several studies considered external genital condyloma (GW) as anal SCC risk factor

O**bjective(s):** To determine prevalence of anal high grade squamous intra-epithelial lesion (HSIL) in women with GW and performance of anal cytology and HPV testing.

Methods: A high-resolution anuscopy (HRA) was performed to 93 consecutive women consulting for GW between January 1 and September 31, 2013. In the same time, anal smears for anal liquid-based cytology and for HPV genotyping with Linear array were collected and observed anal lesions were biospied.

Results: Clinical intra-anal lesions were found in 36 patients during HRA, corresponding histologically to LSIL in 24 cases (67%), HSIL in 4 (12%), not contributive in 4 and not biopsied in 4 cases. Intra-anal lesion during HRA correlated with anal sexual intercourse ($p=0.015$), abnormal anal smear ($p=0.03$) and anal HPV-HR detection ($p=0.007$). Satisfactory anal cytology findings (88/93) were normal (NILM) in 55 cases (61%) and abnormal (ASC-US, LSIL and HSIL) in 33 cases (37%). Sensitivity and specificity of abnormal anal smear to detect HSIL were 75% and 37.5%.Prevalence of anal HPV infection was 72% (50/66) with 68% (34/50) of oncogenic HPV and 42% (21/50) with more than 2 PVH. Anal HPV-infection correlated with age of first sexual intercourse ($p=0.03$), anal sexual intercourse ($p<0.001$), history of cervical or vulvar HSIL ($p=0.03$).

Discussion/Conclusion: Intra-anal HPV-induced lesions are frequent in women consulting for GW. Further prospective studies are needed to conclude if women with GW lesion should be routinely screened for identification of intra-anal lesion.

P 7-1

COLPOSCOPIC FINDINGS IN CERVICAL DYSPLASIA

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Background: A colposcopic examination is a cornerstone in triaging cervical dysplasia, but the sensitivity of colposcopy in diagnosing dysplasia is varying.

Objectives: The aim of this study was to assess the agreement between colposcopic findings and histology. Further to investigate if biopsy histology from colposcopically abnormal parts of the cervix reveals more dysplasia than biopsy histology from colposcopically normal parts of the cervix in the same patients.

Methods: From 2010 to 2012, we enrolled 305 women referred to Dept. of Gynecological at St Olavs Hospital due to abnormal cervical cytology. A specimen for liquid based cytology and HPV testing was taken before colposcopy. Cervical biopsies were taken from any abnormal areas of the cervix after the application of acetoacid. In addition biopsies were taken from all quadrants with no colposcopic findings. Biopsies from colposcopically normal and abnormal parts in the same cervix were examined separately. In addition a cervical scrape was obtained from all women.

Results: Will be presented.

P 7-2

INVESTIGATION OF THE BIOCHEMICAL SIGNATURE ASSOCIATED WITH HPV E7 ONCOGENE EXPRESSION USING RAMAN SPECTROSCOPY

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Objectives: The expression of the HPV oncogene E7 is necessary for the development of cervical cancer. Raman spectroscopy is a powerful tool that can generate a biochemical fingerprint of a sample in a rapid and non-destructive manner. The objective of this study was to define the specific Raman signature associated with expression of HPV E7.

Methods: Short interfering RNAs (siRNAs) were employed to target and silence the E7 oncogene in the SiHa cervical cell line model. TaqMan RT-PCR was used to verify the gene silencing. The control and treated SiHa cells were fixed after 96 hours. Raman spectra were then recorded from the nuclei, nucleoli and cytoplasm of 40 control and 40 treated cells. The data was subjected to multivariate statistical analysis.

Results: Distinct Raman spectral differences were detected between control SiHa cells and E7 silenced SiHa cells. Notably, peak shifts representing fluctuations in DNA/RNA levels were observable between the two spectral types. Principal component analysis showed an excellent discrimination between the two data sets.

Conclusions: Raman spectroscopy is a very powerful tool which can detect subtle changes between cervical cells, and may be useful for improved diagnosis of cervical dysplasia.

P 7-3

A SINGLE COLPOSCOPIST CAN IMPROVE DETECTION OF INVASIVE CERVICAL CANCER IN WOMEN WITH NEGATIVE CITOLOGY IN BRAZIL

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Introduction: Infection with Human Papillomavirus (HPV) is a necessary condition for the development of precursor lesions of cervical cancer. 15,590 new cases of cervical cancer are estimated in Brazil this year. The method of choice for screening, in Brazil, is the cytology by Papanicolaou technique. Colposcopy, along with cytology increases the sensitivity and specificity of detection of precursor lesions significantly, however, is an examiner-dependent technique.

Objectives: Demonstrate the importance of performing colposcopy by a qualified professional by detecting precursor lesions and/or cervical cancer in women with normal/inflammatory cytology in the public health system in Brazil.

Methods: Cross section of 176 cases where women had normal/inflammatory cytology for at least two years. All women were examined and was performed colposcopy with biopsy. The examinations were performed by the same professional and histological samples sent to the same laboratory.

Results: The mean age of patients was 33.5 years. The final histological results were: 152 (86%) normal/inflammatory; 16 (9%) CIN; 2 (1%) CIN2; 4 (2%) CIN3; 1 1 adenocarcinoma and squamous carcinoma *in situ*.

Conclusions: Colposcopy increases sensitivity and specificity for screening of cervical cancer precursor lesions. The qualified and trained gynecologist in a country with few resources in the public health system may be able to identify serious cervical lesions in patients with normal/inflammatory cytology who were not indicated for colposcopy at first. Thus, treatment might decrease the incidence of cervical neoplasia and also make the early diagnosis of this disease.

P 7-4

DYNAMIC SPECTRAL IMAGING FOR TRIAGE OF LOW-GRADES

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Background: Women with Low-Grade (LG) smears who are high-risk (HR) HPV positive are known to have a substantial risk of underlying CIN2+. In addition, for these women the 3-year risk for CIN2+ after a negative colposcopy is triple compared to the general population and colposcopy has shown poor outcomes in identifying which aceto-white lesions represent High Grade (HG) disease and should be biopsied.

Objective: To assess the adjunctive aid the DySIS digital colposcope in detecting or excluding CIN2+ for LG/HR HPV positive referrals.

Methods: This is an observational ongoing study, including the above population. Patients are examined using the DySIS digital colposcope. Initial colposcopic impression and potential biopsy sites are recorded before and after the DySISmap and histology is used to interpret results. Outcomes include sensitivity, specificity and negative predictive value (NPV) for CIN2+.

Results: The study currently includes 127 women. Histology is available for 102 and these are analyzed. Overall, 26(25.5%) women had CIN2+ histological result. The sensitivity of standard colposcopy for CIN2+ was 24% improving to 80% with the incorporation of the DySISmap. Specificity was 89% and 39% respectively. Although NPV cannot be accurately assessed, using directed biopsy histological results the combined NPV of colposcopy and DySISmap for CIN2+ in this population was 86%.

Conclusion: Incorporating the DySISmap as an adjunct to standard colposcopy may improve the sensitivity of colposcopy for CIN2+ among LG smear, HR HPV positive referrals.

P 7-5

NEW TECHNOLOGY FOR CERVICAL CANCER SCREENING AND HPV TESTING BASED ON RAMAN SPECTROSCOPY

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Objective: Cervical cancer is the second most common cancer affecting women worldwide but mortality can be decreased by early detection of pre-malignant lesions. Raman spectroscopy, which can provide a unique biochemical fingerprint of cells and tissues, has emerged as a promising new technology for cancer diagnosis. The objective of this study was to investigate the potential of Raman spectroscopy for detection of cervical intraepithelial neoplasia (CIN) and high risk HPV infection.

Methods: Raman spectra were recorded from a set of negative, low and high grade dysplasia ThinPrep® samples. After Raman analysis, the samples were Pap stained and the cytological classification was verified. HPV testing was also carried out on the same clinical samples. The data was subjected to multivariate statistical analysis.

Results: Negative, low and high grade cervical Thinprep samples were discriminated based on the biochemical fingerprint of the cells. HPV positive and HPV negative cervical Thinprep samples could also be discriminated based on their biochemical composition.

Conclusion: These results indicate that Raman spectroscopy could potentially be used not only to detect cellular abnormalities in cervical cytology samples but also to detect the presence of HPV infection.

P 7-6

TUMOR-CERVICAL TUBERCULOSIS: REPORT OF A CASE

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Tuberculosis is common in developing countries, particularly those in sub-Saharan Africa since the advent of HIV / AIDS. It usually affects young women in childbearing age.
The tubal, endometrial and ovarian locations are the most common.

The cervical spine is rare.

We report the case of Mrs. DN F, patient 36, VIIIG, IXP, in rural areas of unfavorable socio-economic conditions, plus history alive four healthy children, 4 children died. His surgical history is unremarkable.
This patient is referred by a colleague on suspicion of invasive cervical cancer in a context hydrorrhées and chronic pelvic pain.

Colposcopy has regained ulcerative budding tumor of the cervix with necrotic areas.

Colposcopic biopsy found a fibro-breaker cervical tuberculosis.

P 7-7

DIAGNOSTIC AND THERAPEUTIC MANAGEMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE 2 (CIN2).

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OBJECTIVES: The meaning of CIN2 reproducibility is unclear: 15-74% of the lesions regress, so only cases with high risk of progression should be treated (<5% develop invasive cancer) [1, 2].
Aim of this study is to find clinical parameters to select patients with high risk of progressive lesions, reducing the number of unnecessary treatments.
METHODS: We evaluated:
- correlation between histologically confirmed CIN2 at biopsy and LEEP.
- correlation between LEEP sample histology and clinical parameters: cytology, squamous-columnar junction, colposcopic grading, age.
RESULTS: 171/308 (55.52%) LEEP samples were confirmed as high grade lesions.
Initial cytology of patients with CIN2 at biopsy were: 6,17% negative, 48,70% L-SIL; 17,53% ASC-US; 16,56% H-SIL; 11,04% ASC-H.
Squamous-columnar junction was colposcopically visible esocervical in 216 cases (70,13%); endocervical in 70(22,73%); not visible in 22(7,14%).
235/308 patients (76,30%) had abnormal Transitional Zone grade1, 73/308 (23,70%) had abnormal TZ grade 2.
The age of treated patients ranged from15 to 64 years.
CONCLUSIONS: Our results didn't demonstrate close correlation between CIN2 at bioptical specimen and histological result at LEEP, indeed 44,5% of CIN2 at biopsy were not confirmed as high grade lesions at LEEP. This result justifies the hypothesis of reducing the systematic treatment of CIN2, as currently indicated by the international guidelines.
None of the clinical parameters reached statistically significant correlation with the LEEP histological sample.
It should be useful to identify predictive factors of progression, in order to recognize lesions with high risk of progression (10,7% progress to CIN3) and to avoid treatment if not necessary.

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P 8-1

DIFFERENCES IN RELAPSED PATTERN BETWEEN RADICAL HYSTERECTOMY AND RADICAL TRACHELECTOMY IN THE MANAGEMENT OF EARLY CERVICAL CANCER.

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Objectives: The objective of this study was to evaluate the oncologic and obstetrical outcomes of radical trachelectomy and to analyze the distinct relapsed pattern between radical hysterectomy and radical trachelectomy in the treatment of early cervical cancer without lymph node metastasis.

Methods: Forty-one patients with early-stage cervical cancer were treated by laparoscopic radical trachelectomy (LRT) from October 2004 to December 2009. Data regarding clinicopathologic characteristics, recurrence, and subsequent pregnancies were recorded. For the observation, 831 patients with early-stage cervical cancer were treated by laparoscopic radical hysterectomy (LRH) were analyzed.

Results: The median age at diagnosis was 29 years (range 22-37 years) and stage IA2 or IB1 cervical cancer were treated by LRT. Mean tumor size was 1.7 cm (range 0.4-3.5 cm) and there was no perioperative complication. Six patients were recurred after the initial treatment (14.6%); the recurrence rate was relatively higher than in patients treated with radical hysterectomy for early cervical cancer without lymph node metastasis (3.6%). The relapsed sites were all loco-regional locations, uterus stump or pelvic lymph node in LRT patients, whereas distant metastases including paraaortic lymph node, liver and lung were more common in LRH patients.

Conclusions: In conclusion, the relapsed pattern between radical hysterectomy and radical trachelectomy in the treatment of early cervical cancer without lymph node metastasis was obviously different. It is required to be cautious to prevent the dissemination of tumor cells in pelvic cavity.

P 8-2

CERVICAL CANCER STAGING: AN IMAGING REVIEW

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Objectives: Multimodality imaging with computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography with CT (PET/CT) plays a useful role as an adjunct to clinical staging of cervical cancers stages I-IV. Stratification at or below stage IIA is important for treatment, usually designated as appropriate for surgery. Stages higher than IIA are more often treated with combined chemotherapy and radiation. While ultrasound may provide some local detail, it is usually insufficient for accurate staging information. Cross-sectional imaging with CT, MRI, and PET/CT can evaluate the tumor as well as local extension and distant spread. MRI has superior soft tissue contrast resolution and is the preferred modality for assessment of tumor size, extent, as well as local and regional spread. Important reporting criteria in pelvic MRI include: tumor size, parametrial invasion, vaginal invasion, pelvic sidewall involvement or hydronephrosis, and bladder/rectal invasion. PET/CT is useful to assess distant disease and can be helpful in problem solving indeterminate findings detected on other cross-sectional modalities. It is useful to have multiple modalities available as contraindications, cost, and availability are variable. The objective of this presentation is to review imaging staging criteria and providing a multimodality imaging educational review of cervical cancer staging using CT, MRI, and PET/CT, displaying imaging examples of various stages of disease.

Methods: Anonymized images were retrieved from case collections and displayed for educational review.

Results/Conclusion: Multiple imaging modalities are useful for staging cervical cancer.

P 8-3

REDUCED GLYCOSYLATION LEVELS OF SERUM ANTI-HPV TYPE 16 E7 IMMUNOGLOBULIN ARE CRITICAL MARKERS INDICATING CERVICAL CARCINOGENESIS

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Background: Glycosylation changes of serum glycoproteins have been suggested to be a unique marker indicating cancer progression. It has been proposed that elevated level of serum immunoglobulin against E7 oncoprotein of HPV is associated with cancer progression in cervix. However, the immunoglobulin level against HPV E7 alone is not sufficient to specify the cervical carcinogenesis because considerable proportion of women with normal cytology or low grade CIN undergoes antibody responses against HPV E7.

Objectives: We hypothesized that the glycosylation pattern of immunoglobulin provoked in women with cervical cancer is different from that with normal or low grade CIN.

Methods: In the present study, therefore, we investigated the level of sialylation, galactosylation, fucosylation and mannosylation of serum anti-HPV type 16 E7 immunoglobulin from women with normal and CIN I and women with cervical cancer.

Results: The anti-HPV16 E7 immunoglobulin of cancer group showed significantly lower level of sialylation, galactosylation, fucosylation and mannosylation, compared to normal & CIN I group. Especially, the galactosylation level of anti-HPV16 E7 antibody from cancer group was confirmed to be remarkably lower than that of normal & CIN I group.

Conclusions: We suggest that the reduced glycosylation levels of serum anti-HPV16 E7 immunoglobulin are specific markers indicating cervical cancer progression. Also our results indicate that the antibody response against HPV16 E7 provoked in women with cervical cancer is significantly different from that with normal or CIN I. We anticipate that the reduced glycosylation levels of anti-HPV E7 immunoglobulin can be utilized as a new marker for diagnosis and prognosis of cervical cancer.

P 8-4

COMPARATIVE STUDY OF ROBOTIC RADICAL HYSTERECTOMY VERSUS LAPAROSCOPIC RADICAL HYSTERECTOMY IN CERVICAL CANCER

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Objective:
To compare surgical outcomes and complication rates of cervical cancer patients who underwent robotic radical hystereectomy and laparoscopic radical hysterectomy.

Methods:
Patients diagnosed with cervical cancer (FIGO stage I-IIA) who underwent robotic radical hysterectomy (N=36)at Dongsan medical center from september 2011 to december 2013 were compared with patients who underwent laparoscopic radical hysterectomy(N=95). Comparison was made with patients by age, stage, histologic type, node status, operation time. All information were collected retrospectively.

Results:
Operation time was significantly longer (340 versus 190 minutes) in the robotic radical hysterectomy. Blood loss was significantly reduced in the robotic radical hysterectomy. Recurrence were 4(11.1%) in the robotic radical hysterectomy and 12(12.6%) in the laparoscopic radical hysterectomy. The 3-year recurrence free survival was 88.9% versus 87.4%.

Conclusions:
Surgical outcomes of robotic radical hysterectomy for cervical cancer were comparable to those of laparoscopic radical hysterectomy

P 9-1

PREVALENCE AND EXPRESSION OF HUMAN PAPILLOMAVIRUS IN GREEK PATIENTS WITH HEAD AND NECK SQUAMOUS CELL CARCINOMAS

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Objectives: Human papillomavirus (HPV) infection is a potential risk factor for the development of head and neck squamous cell carcinomas (HNSCCs) and E6/E7 mRNA expression has been considered a necessary step for the onset of these HPV-infected cancers. The purpose of the present study was to investigate HPV infection and high-risk (hr) HPV E6/E7 mRNA expression in Greek patients with HNSCCs.

Methods: 102 biopsies were collected from patients with HNSCCs (58 from the oral cavity, 25 from the larynx, 16 from the oropharynx and 3 from the rhinopharynx) and tested for HPV DNA and hrHPV E6/E7 mRNA expression.

Results: The mean age of the patients was 55.5 ± 15.9 years. 76.5% (78/102) were male and 72.5% (74/102) were smokers and/or drinkers. The overall prevalence of HPV infection and E6/E7 mRNA expression was 14.7% (15/102) and 5.9% (6/102), respectively. HPV DNA detected in 10.3% (6/58) of cancers of the oral cavity, 18.8% (3/16) of the oropharynx, 16.0% (4/25) of the larynx and 66.7% (2/3) of the rhinopharynx. 6.9% (4/58) of oral cancers, 6.3% (4/16) of the oropharyngeal cancers and 33.3% (1/3) of the rhinopharyngeal cancers were positive for hrHPV E6/E7 mRNA expression, while none of the laryngeal cancers expressed E6/E7 mRNA. HPV 16 was the commonest genotype detected in HPV DNA and E6/E7 mRNA positive HNSCCs. No significant associations were observed between HPV infection and gender, age, tobacco and/or alcohol consumption.

Conclusions: The presence of hrHPV E6/E7 mRNA expression in our series suggests that HPV may be implicated in the pathogenesis of HNSCCs.

P 9-2

HIGH-RISK HPV-ASSOCIATED HYPOPHARYNGEAL CANCERS OCCUR FREQUENTLY IN THE PYRIFORM SINUS

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Background: High-risk human papillomavirus (HPV) is an oncogenic virus that causes oropharyngeal cancers, and it has a favorable outcome after the treatment. Unlike in oropharyngeal cancer, the prevalence and role of high-risk HPV in the etiology of hypopharyngeal squamous cell carcinoma (HPSCC) is uncertain. The aim of the present study was to evaluate the effect and prognostic significance of high-risk HPV in patients with HPSCC.

Methods: The study included 64 subjects with HPSCC who underwent radical surgery with or without radiation-based adjuvant therapy. Primary tumor sites were the pyriform sinus in 42 patients, posterior pharyngeal wall in 19 patients, and postcricoid area in 3 patients. High-risk HPV *in situ* hybridization was performed to detect HPV infection.

Results: The positive rate of high-risk HPV *in situ* hybridization was 10.9% (7/64). There was a significant difference in the fraction of positive high-risk HPV among pyriform sinus cancer (16.7%), posterior pharyngeal wall cancer (0%), and postcricoid area cancer (0%) ($p=0.042$). Significant correlations were found between positive high-risk HPV and younger age ($p= 0.050$) and tobacco consumption ($p=0.017$). HPV-positive patients had a significantly better disease-free survival ($p=0.026$) and disease-specific survival ($p=0.047$) than HPV-negative patients.

Conclusions: High-risk HPV infection is significantly related to pyriform sinus cancer.

P 9-3

18F-FDG PET/CT AND HIGH-RISK HPV IN HYPOPHARYNGEAL SQUAMOUS CARCINOMA

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Objective: We evaluated the association of preoperative ^{18}F-FDG PET/CT and high-risk HPV status in hypopharyngeal squamous cell carcinoma (HPSCC).

Methods: The medical records of 45 patients who underwent ^{18}F-FDG PET/CT for HPSCC before surgery were reviewed.

Results: High-risk HPV in situ hybridization was performed to detect HPV infection. The median SUVmax was 9.91 ± 4.91 and the positive rate of high-risk HPV in situ hybridization was 11% (5 of 45). The SUV_{max} values of negativity for the high-risk HPV subtypes (10.47 ± 4.87) and positivity (5.48 ± 2.45) were found to be significantly different ($p=0.030$). The SUV_{max} cut-off value for differentiating negativity for the high-risk HPV subtypes from positivity was 7.9. Patients with a SUV_{max} value higher than 7.9 ($p=0.005$) and high-risk HPV negativity ($p=0.047$) had decreased 5-year disease specific survival.

Conclusion: Median 18F-FDG PET/CT SUV_{max} cut-off values of 7.9 or greater were associated with high-risk HPV negativity in patients with HPSCC and we also found out the relationship of the poor survival rate with high SUX_{max} value.

P 9-4

THE BURDEN OF HEAD & NECK CANCERS IN IAȘI, ROMANIA

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Objectives: GLOBCAN 2012 rates Romania being on the second place in the first 20 highest countries in Europe, regarding the mortality (32.4/100,000) for larynx, lip, oral cavity and nasopharynx in male, all ages. Our aim is to evaluate the burden of the larynx, oropharynx, hypopharynx and oral cavity cancers in Iasi, North East of Romania.

Methods: hospital registry linkages from three surgical departments: plastic surgery - oncology, otorhinolaryngology and oral and maxillofacial surgery departments.

Results: between January 2010 – September 2014 we registered 226 cases of head & neck cancers: 119 cases of oral cavity cancers - lips and tongue, (39 - 80 years old), 1.68% (12/119) women; 56 cases of larynx cancers (47 – 58 years old), 3.57% (2/56) women; 15 cases of hipopharynx (54 – 67 years old), 26.66% (4/15) women; 36 cases oropharynx (41 – 71 years old), 2 women, 5.55% (2/36) women. The majority of anatomopathologic diagnosis were keratinizing and nonkeratinizing squamous cell carcinoma.
This is a pilot study which will be continued with all of these paraffin samples analysis for DNA/HPV and ARNm/HPV presence.

Conclusions: there is a high burden of head and neck cervical cancers in our area. This pilot study will continue to assess time trends in the incidence and mortality of HNC in North Eastern Romania and to determine whether HPV infections interact with additional HNC risk factors in our population.

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P 10-1

LONGTERM PREDICTION ACCURACY OF HPV TESTING FOR CERVICAL CANCER PREDICTION

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Objectives: The cervical cancer is the major cause of cancer for women worldwide. A tool providing good accuracy in long-term prediction was anticipated.

Methods: A female cohort (n=11923) were enrolled in 1991 in Taiwan from community. HPV genotyping was performed using EasyChip® HPV Blot to detect 38 types. The incident cervical cancer were ascertained by linkage with the National Cancer Registry until 2010. We compared the area under receiver operating characteristic curve (AUROC) using several Cox regression models which employed personal characteristics alone, Pap alone, cervical HPV infection alone and combined model to predict incident cancers in various period of follow-up.

Results: The AUROCs for personal characteristics alone, Pap alone, cervical HPV infection alone for cervical cancer diagnosed within one year were 0.60, 0.92 and 0.94. For predicting to incident cancer in 1-5, 1-10, 1-15, 1-20 years, the AUROC for personal characteristics alone were 0.69, 0.62, 0.63 and 0.65. respectively. The prediction for Pap alone was similar, where the AUROC were 0.66, 0.65, 0.60 and 0.58. The prediction accuracy increased for model employed HPV testing alone, and the corresponding AUROC were 0.82, 0.79, 0.80 and 0.77. For the model including both personal characteristics and HPV testing, there were only slightly increases on the AUROCs, they were 0.84, 0.76, 0.82 and 0.79, respectively.

Conclusion: The personal characteristics was unfavorable for cancer screening. Pap was only considered as a short-term tool. Using of HPV testing in cervical screening sustains by good prediction accuracy for 20 years.

P 10-2

UNCARIA TOMENTOSA AND TOPICAL USE IN GENITAL HERPES IN VULVA: CASE REPORT

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Introduction: genital herpes is a sexually transmitted infectious disease that affects people from many different social strata. Genital herpes is spread worldwide and is a frequent cause of painful genital sores in men and women.

Objective and Methods: to describe the case of adult women with clinical and cytologic clinical picture of a vulvar initial outbreak of genital herpes (2cm diameter) in which the lesion was treated with *Uncaria tomentosa* gel 50 mg/g three times a day for four days.

Results: the symptoms of pain and burning had rapid remission. During the consultation, about 25 minutes after topical application of the herbal medicine, the patient reported great improvement in genital pain. The clinical outcome was satisfactory and after six days the patient, whose lesion had already healed, reported having had vaginal intercourse without discomfort. We will present photos of patient injury completely healed and photo cytology, scraped the injury, showing cytological effects compatible with HSV infection.

Conclusion: application of *Uncaria tomentosa* topical gel in a vulvar initial outbreak of genital herpes was well tolerated, showed no side effects, and rapidly and significantly improved the clinical symptoms of disease.

P 10-3

PLACENTITIS CRYPTOCOCCAL PREGNANT PATIENT HIV + ASSOCIATED WITH OPPORTUNISTIC COMORBIDITES: CASE REPORT

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Introduction: HIV infection can promote severe immunosuppression[1]. The assault on the immune system leaves the patient vulnerable to various opportunistic infections [2]. In this case, a pregnant patient with HIV+ developed Placentitis cryptococcal. Cryptococcosis increased susceptibility due to immunological changes, especially in HIV+ pregnant women, and can lead to abortion[1]. If Cryptococcosis happen early can be associated with invasion of chorionic villi, or if it happens late can be associated with swallowing or aspiration of contaminated material[1].

Case Description: JPL, 19, female, AIDS, blood culture positive for C.*neoformans*. Biopsies of three lesions on the vulva (bullous, ulcerated, verrucous) with cytopathic changes suggestive of herpes virus, HPV, and molluscum contagiosum. Developed acute fetal distress, performing cesarean section at 29 weeks gestation. In examining placenta, there was marked chronic necro-proliferative, diffuse, without chorioamnionitis or funiculitis villitis, and histiocytes filled with rounded structures (7.0 microns), identified as yeasts of intermediate size and variable sizes with budding simple and positive to the PAS-Fungi, Mucicarmine and Grocott stainings, identifiable Cryptococcus sp.; presence of bacterial colonies in the intervillous space of intra and extracellular suggestive of Acinetobacter sp bacilli format. Compatible with fungal and bacterial hematogenous placentitis histology. Bronchoalveolar lavage performed with the finding of yeast identifiable Cryptococcus sp., inside cells.

Conclusion: The AIDS patient is very susceptible to opportunistic infections which should be diagnosed and treated in time[2]. Also, the patient is pregnant, which demands even faster in diagnostic and decision making in order to avoid potential harm to the fetus[2].

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P 11-1

EARLY DECREASE IN ANOGENITAL WARTS TREATMENT WHEN INTRODUCING A BROAD QUADRIVALENT HPV VACCINATION PROGRAM:

A STUDY FROM 3 NORDIC COUNTRIES

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Objective: Quadrivalent human papilloma virus vaccination (qHPVv) of females started in 2009 in Denmark (school program 11-12 years old and females ≤ 26 years old) and Norway (school program 11-12 years old). High vaccine coverage rates (VCR) of around 80% in school girls is reported in both countries, in addition of a 73% VCR for women up to 26 years in Denmark. During this period Finland did not offer HPV vaccination and was included as control. qHPVv protect against the human papillomavirus (HPV) types 6 and 11, which cause anogenital warts (AGW). We describe national trends in Imiquimod (IMQ) prescriptions as a surrogate for AGW treatments.

Methods: National public prescription information of IMQ was collected for the period 2008 - 2012 in Denmark and Norway, and 2008 – 2013 for Finland. Trends in absolute numbers of IMQ prescriptions for male/female age strata 15 – 19; 20 – 24; 25 – 29; 30 – 34 years were analyzed using linear regression.

Results: In Denmark, absolute numbers of IMQ prescriptions in women decreased ($p<0.0075$) while remaining stable for men ($p=NS$). In Norway, the vaccinated cohort is still too young to show impact on AGW numbers, and IMQ prescriptions increased for both women and men. In Finland values for IMQ prescriptions remained stable for both genders.

Conclusion: This study suggests that a broad qHPV vaccination program including catch-up with high VCR leads to an early decrease in AGWs incidence and therefore treatment. The study further indicates that herd protection to males is limited in a female-only vaccination program.

P 11-2

DYNAMIN II AS POTENTIAL THERAPEUTIC TARGET IN CERVICAL CARCINOMA

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Dynamin II plays an essential role in the completion of the final stage of mitosis and cytokinesis. MiTMAB (myristyl trimethyl ammonium bromides) and OcTMAB (octadecyltrimethyl ammonium bromide) are small-molecule inhibitors of dynamin that competitively interfere with the ability of dynamin to bind phospholipids and prevent receptor-mediated endocytosis. In this study, we investigated whether dynamin inhibitor could inhibit survival, proliferation, and invasion of cervical cancer cell lines. To evaluate the role of dynamin II in cell proliferation, we performed MTT assays with Hela and SiHa cells after incubation with various doses of MiTMAB or OcTMAB. To confirm the apoptosis after MiTMAB and OcTMAB treatment, active caspase-3 ELISA and FACS were performed. And to identify the role of dynamin II in cell invasion, we evaluated the secretion of MMP-9 after dynamin II inhibitor treatment by ELISA assay. We found that MiTMAB and OcTMAB had a growth-inhibiting effect at 2 or 3 day after treatment in both cells. Active caspase-3 expression and Annexin V intensity were increased by MiTMAB and OcTMAB. And the secretion of MMP-9 was increased after dynamin II inhibitor treatment. MiTMAB and OcTMAB are the first compounds reported to exclusively block cytokinesis without affecting progression through any other stage of the cell cycle. Cytokinesis failure induces cell death. These data revealed that dynamin II modulates cancer cell survival, proliferation, and invasion and suggest that dynamin II could be a key target for new strategies in cervical cancer treatment.

P 11-3

α2B-INTEFERON AND TILORONE IN THE TREATMENT OF CIN WITH LESIONS OF THE VAGINAL FORNIX AND WALLS

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Objective: To study the therapeutic efficacy of the use of α2b-interferon in in the form of vaginal suppositories, and tilorone in patients with CIN with extension to the fornix and walls of vagina.

Methods: In the study participated 62 patients with CIN with extension to the fornix and walls of vagina, of whom 36 were diagnosed with CIN II and 26 - CIN III. At the stage of etiological treatment the patients were divided into 2 groups (group A (31 patients) - 18 patients CIN II and CIN III 13 patients, group B (31 patients) - 18 patients with CIN II and 13 patients with CIN III)
In group A patients were prescribed a standard antibiotic therapy.
In Group B patients were appointed a standard antibiotic therapy plus α2b-interferon 500 000 IU suppositories twice a day every day for 14 days, and 125 mg of tilorone every 48 hours N10.

Results: Assessment of colposcopic features in patients with CIN II-III after treatment showed that patients from the study group significantly more often - 48,4 % (95%CI 39,4-57,4%) - compared with control group 9,7% (95%CI 4,3-15,0) - had a reduction of the area affected and displacement of the boundaries of CIN from walls of vagina to the cervix.

Conclusions: Decrease in the area of CIN and its displacement from the walls of the vagina allowed for the excision of the cervix within the healthy tissue.

P 11-4

HISTOLOGICAL CORRELATIONS IN CASES OF ASCUS OR ASC-H CYTOLOGY AND HPV CERVICAL INFECTION

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Objective: An anatomoclinical correlation between detection of an ASCUS or ASC-H cytology and the predictability of diagnosis of cervical dysplasia and HPV infection.
Methods: Prospective study was conducted in the IOMC Polizu Bucharest, between 2011-2013, for 126 women aged 21 to 58 years with ASCUS or ASC-H cytology. For 100 patients that had ASCUS cytology and 26 with ASC-H, HPV was tested and colposcopy was performed. Follow up was every 6 months by repeating cytology and colpscopy. HPV was tested yearly. At ASCUS or ASCH citology patients who remained positive at 1 year and had persistent HPV infection, excision of the cervical lesions and histopathological exam was performed.
Results: For ASCUS cytology, 68% were HPV positive compared to 62% in ASC-H group. Colposcopy revealed atypical transformation grade 1 areas (ATG1) in 64% for ASCUS, 69% in ASC-H group and ATG2 for 16% of ASCUS cytology and 31% in ASC-H group. We performed excizion at 42% of the patients with persistent ASCUS, HPV positive and 46% ASC-H, HPV positive. Histopathological results: 6% CIN1, 46% CIN2+, 4% invasive carcinoma (IC) were diagnosed for ASCUS group and: 8% CIN1, 39% CIN2+ and 8% IC were diagnosed in ASC-H group. HR-HPV 16, 31, 53, 51, 18 were correlated with CIN2+ in ASCUS and ASC-H groups.
Conclusions: HR-HPV positive with ASCUS and ASC-H cytology identifies a group at risk for significant histological abnormalities, almost half of them having CIN2+ and IC.

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P 11-5

FREQUENCY AND CHARACTERISTICS OF AFFECTED EDGES AFTER CONIZATION

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OBJECTIVES: To analyze the frequency of affected conization edges in our Lower Genital Tract Unit and evaluate related factors.
METHOD: retrospective study by reviewing of the clinical records of women conized due to CIN 2+ between July-2008 and July-2013.
RESULTS: 480 conizations were carried out during the 5-years period. There were affected edges in 16.7% of cases with high-grade lesions (HGL) and 3.1% of low-grade lesions (LGL). In 6.5% of cases, the edges were not assessable. Among HGL 30 % of cases had exocervical edge affection; 55 % had endocervical edge affection and in 15% of cases both edges were affected. In LGL 60 % of cases had affection of the exocervical edge, 20% had the endocervical edge affected and 20 % had both.
The average age of patients was: 40.8 years for HGL and 46.5 years for LGL.
Colposcopy showed grade 2 findings in 22.5 % of HGL. and in 21.4 % of LGL. The lesions affected two quadrants in 10% of HGL. and in 21.4 % of LGL.
61.3 % of women with HGL and 21.4 % with LGL were smokers.
The most frequent genotype in HGL. was HPV 16 (50 %).
CONCLUSIONS:
1.- A high rate (16,7 %) of affectation of edges in conizations done due to CIN 2+ were found.
2.- In HGL. the edge most frequently affected was the endocervical, while in the LGL was the exocervical.
3.- Cofactors of association more prevalent in our population were tobacco and HR-HPV 16 .

P 11-6

SUCCESSFUL TREATMENT OF A GIANT CONDYLOMA ACUMINATUM OF VULVA

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Objective: Giant condyloma acuminatum is a human-papillomavirus-induced cauliflower-like tumor of the genitoanal region. It is characterized by its size, capability of local infiltration and high recurrence rate. It is preferentially seen in men and immunocompromised patients. The purpose of our paper is to describe a case of a patient with this situation.
Methods: Description of a case-report.
Results: A 35-year-old women was referred to our department presenting with a large exophytic lesion extending across the vulva, and perineum, with 17-year evolution. Her remaining physical exam was normal. The past medical history was unremarkable. Biopsy of the lesion suggested condyloma acuminatum. Treatment included a simple vulvectomy followed by plastic reconstruction with thigh skin over denuded areas of the vulva and perineum. Small perianal remaining lesions were treated with topical Imiquimod 5% cream. Histopathology revealed a gyant condyloma acuminatum of Buscke-Lowenstein (BLT). Seven years later she remains free from the disease.
Conclusion: There is a lack of consistent trials regarding optimal treatment of BLT because of the infrequency of the disease. Radical surgery including full thickness excision of the affected areas represents the "gold standard" therapy. An adequate, long-term follow-up of patients with Buschke-Lowenstein conyloma acuminatum is highly recommended, because of the risk of recurrence.

P 12-1

THE AFFORDABLE CARE ACT: THE WOMEN WHO WILL BE LEFT BEHIND

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OBJECTIVES: Explore demographics/beliefs in those presenting in an underserved population with early stage vs local regional cervical cancer (CxCa).

METHODS: 138 women seen in a county (primarily uninsured population) with a new diagnosis of CxCa were surveyed. Demographics were collected as well as health beliefs and health locus of control survey.
RESULTS: Eighty-four percent reported an annual household income (AHI) of <=$35,000; 39% reported AHI of <=$10,000; 44% were born in the U.S., 21% in Mexico, 15% in Central America, and 2% in South America (n=110). When told they had CxCa, woman worried about " what others would say" (29.2%), "surgery making the cancer spread" (48%), "being contagious" (12.6%), "spiritual issues" (24%), and "guilty feelings" (35%) and not going to the doctor sooner (52.9%).
Comparing women with CxCa managed surgically (<=IB1) vs those requiring concurrent chemo-radiation (>=IB2) there were no significant differences in BMI, race, education, primary language, marital status, smoking, or Pap smear knowledge.
Higher stages were associated with more ER visits (p<.001) and transfusions (p<.001) prior to diagnosis. Compared to 88% with ≤ Stage IB1 disease, only 53% with advanced stage had a car (p=.003) Using the Multidimensional Health Locus of Control scale (MHLC), women with ≤ Stage IB1 had higher doctor LOC (17.0 vs. 16.0, p=.035) compared to women with advanced disease. The last 35 patients were asked whether they had vaccinated their children, 26 answered no, 18 had children who could have been vaccinated.
CONCLUSIONS: Cx Ca is almost totally preventable. Unfortunately, in the U.S., because of limited geographic and financial access and distrust in medical care, medically underserved women will continue to use the Emergency Room as primary source of health care. Consequently Cx Ca will likely be diagnosed in advanced stage, compromising chances at cure. Due to poverty or immigration status, as many as 25-33% of those living in the US may have limited access to prevention and screening services. Although the ACA may offer an alternative, in areas where Medicaid expansion was declined or immigration status prevents enrollment, Cx Ca will most likely continue to propose an unnecessary catastrophe for many.

P 9-5

HUMAN PAPILLOMAVIRUS DETECTION IN ORAL MUCOSA CAN SUGGEST GENITAL INFECTION?

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Introduction: HPV is the etiological agent of cervical and anal cancer. However, little is known concerning the etiology of the oral infection and oral cancer.

Objective: To investigate whether oral infection could point out genital infection, determining the presence of HPV in both sites of infection.

Methods: Oral scrapes from healthy mucosa and genital smears of condylomatous lesions were evaluated by molecular methods. A hundred and ten samples from oral and genital sites were collected from patients attending the STD Clinic from Universidade Federal Fluminense. To screen and type HPV DNA, generic MY09/11 PCR and type-specific PCR, followed by restriction fragment length polymorphism (RFLP).

Results: HPV was detected in 85.5% of genital lesions (n=55) and in 43.6% of oral mucosa samples. In 13 of the 55 (23.6%) studied cases, both sites were infected. The agreement among genital and oral types were high: 9 cases showed the same infecting types in both mucosa. HPV 11 were the most prevalent (n=7), followed by HPV6 (n=2) and HPV45 (n=1). Two cases showed mixed infections infected by and HPV6/11 and one HPV11/45. Oral infection, separated by male and female showed statistical significance (p=0.004), with markedly higher prevalence of oral infection on men.

Conclusion: The oral detection of HPV can suggest genital infection in half of the cases but it further studies are required to elucidate the natural history of HPV infection, mainly in relation to oral lesions.

LAST MINUTE ABSTRACTS

p 266 - 270

MTC 3-2

TRIAGE OPTIONS OF HPV POS WOMEN

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Although HPV testing has a very high sensitivity for CIN2/3+ its specificity is 2-4 % lower than cytology. If all these HPV pos. women would be send for colposcopy 3 times more women would be referred for colposcopy than by cytology. This might result in 1. a shortage of colposcopy capacity , 2. unnecessary treatments, 3.an increased risk of preterm births and 4. other cervical morbidity. Therefore triage testing for colposcopy of HPV pos women has been introduced. The objective of triage testing is to identify the women with HPV infections associated with CIN2/3+ lesions from women with a transient HPV infection. Thus triage testing increases the specificity for CIN2/3+ of the HPV test while keeping the high HPV sensitivity for CIN2/3+, thereby decreasing colposcopy referral rate. Presently cytology, HPV 16/18 genotyping or a combination thereoff have been tested as triage test for HPV pos. women in longitudinal studies. Cytology at baseline and repeat cytology after 6 month, and cytology combined by HPV 16/18 genotyping at baseline followed by repeat cytology at 6 months have proved to be safe strategies with with acceptable 5years CIN3+ risk (<2%) and with acceptable referral rates, but are associated with loss to f-up of women due to repeat cytology testing aftr 6 months. A single cytology combined by HPV 16/18 genotyping test at baseline does not have this loss to follow-up but this strategy has the disadvantage that its 5 years CIN3+ risk is around 2% in longitudinal studies. Depending of the quality of cytology and resources available health policy makers have to choose which triage test they will prefer.

New triage strategies are p16/Ki-67 dual staining and detection of hypermethylation of promotor regions of host genes involved in cervical carcinogenesis. p16/Ki-67 dual staining increases the specificity of CIN3+ detection in HPV pos. women triaged by cytology significantly, while keeping the high sensitivity. The results strongly suggest that the repeat cytology step at 6 month in triage testing may be postponed.

Hypermethylation of host genes CADM1, MAL and miR-124-2 has recently been shown to detect all cervical carcinomas and advanced CIN2/3 lesions with a high short term risk for cervical cancer .

In summary cytology at baseline and repeat cytology after 6 month, and Cytology combined by HPV 16/18 genotyping at baseline whether or not followed by repeat cytology at 6 months are presently the method of choice for triage HPV pos women. p16/Ki-67 dual staining and detection of hypermethylation of promotor regions of CADM1, MAL and miR-124-2 are new triage tests which are presently introduced in screening and diagnostic settings and will make cytology triage testing more reproducible and specific for CIN2/3+ (p16/KI-67 testing) or fully molecular (CADM1, MAL and miR-124-2 testing)

MSS 4-2

HOST METHYLATION AS TRIAGE TEST FOR HPV POS WOMEN

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The objective of triage testing is to identify the women with HPV infections associated with CIN2/3+ lesions from women with a transient HPV infection. Thus triage testing increases the specificity for CIN2/3+ of the HPV test while keeping the high HPV sensitivity for CIN2/3+. In this the colposcopy referral rate can be decreased. Presently cytology, HPV 16/18 genotyping or a combination thereoff have been tested as triage test for HPV pos. women in longitudinal studies.

Infection of cervical epithelium with high-risk human papilloma virus (hrHPV) may result in productive or transforming cervical intraepithelial neoplasia (CIN) lesions, the morphology of which can overlap. In transforming CIN lesions, aberrations in host cell genes accumulate over time, which is necessary for the ultimate progression to cancer. Recently it has been shown that on the basis of (epi)genetic changes, early and advanced transforming CIN lesions can be distinguished. Host methylation of promotor regions of genes involved in cervical carcinogenesis such as CDH1, DAPK1, EPB41L3, FAM19A4, PAX1, PRDM14 CADM1, MAL and miR124-2 has been proposed as a new triage tool for HPVpos women. Methylation levels of CADM1, MAL and miR124-2 have been shown to increase proportionally with the duration and severity of underlying cervical disease and being extremely high in cervical cancer. Consequently assays detecting of host methylation of CADM1, MAL and miR124-2 have been used for the triage of HPV pos women. Indeed combined methylation marker analysis of CADM1/ MAL for physician taken scrapes and of Mal/miR124 for self-collected lavage specimen have shown to detect with high accuracy cervical cancer and advanced cervical lesions with a high short term risk of cancer. The use and potential impact of these host methylation marker assays on the triage of HPV pos women will be further discussed.

MSS 5-3

IMPLEMENTATION OF HPV SCREENING: NATIONAL VS REGIONAL PROJECTS (ORGANIZATION, ASSESSMENT, PROBLEMS, SOLUTIONS, RESULTS, COMMUNICATIONS) – NETHERLANDS

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The present cytology based cervical screening programme in the Netherlands of which the last changes has been implemented in 1996 has done well. It is based on a call and recall system which make use of the municipal administration of the inhabitants. The target population is women 30-60 years. 7 rounds of screening with an interval of 5 years have been implemented. With attendancy rates of ~67% and a percentage of programme smears of over 80% both the incidence and mortality have been decreased with 1.1%/year, mainly based on a decrease in squamous cell carcinomas. Why then has the minister of health this year decided that in 2016 the cytology based population based cervical screening programme will be replaced by an HPV based screening programme? The reasons were that since 2004 the incidence and mortality of cervical cancer are not decreasing anymore. Attendency rates remain the same (~67%) Moreover the sensitivity of the HPV test for CIN2+ is much higher then that of cytology (95% vs 62%), although the specificity is 2-4% lower. Also the f-up from women with cervical lesions can be improved.

With the introduction of an HPV based screening programme support of stakeholders like patient organisations, screening organisation, Organisations of gynecologists , of general practioners and of cytotechnicians had to be obtained. Also a feasibility study had to be done documenting "how the primary programme, the organization , the quality policy, the communication, the monitoring and the evaluation has been set up." The total duration of this feasibility study and preparation time will take two years. The feasibility study has been finished and support of all the organisations involved have been obtained. The tenders for which HPV test will be used and for the selection of the 5 screeningslabs are out now. The preparation for the HPV based screening programme is on track and will be ready in 2016. In the presentation the expected gain in health and costs will be given also.

W 1-4

ARE ALL EXPERTS BANNED FROM SHARING THEIR KNOWLEDGE BECAUSE OF COLLABORATION WITH THE INDUSTRY?

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Marieke van Ham, Dept of Immunopathology, Sanguin research, Sanguin, Amsterdam, The Netherlands

Experts who are in the forefront of their research field are also often involved with industry, because they oversee best the potential clinical impact of their research findings. The research institutes where they are employed actively support their efforts for commercialisation, because they benefit from the revenues obtained by these experts. For the industry these experts working on the border of pure scientific research in a knowledge institute or university and the applied research of (pharmaceutical) industries are very important because they can guide and speed up the upscaling of production of new drugs or vaccines or the further development of new assays. The criticism made by outsiders and the public about these experts having industrial ties is that they may present to optimistic results and omit disadvantages or adverse effects from the products, vaccines or assays they are working on. Banning these experts from sharing their knowledge might seriously hamper the spread of knowledge and the translation of their findings into the diagnostic/therapeutic field.

Therefore peer reviewed journals always ask for transparency reasons to sign a conflict of interest form (COI) by the authors. Also in conferences the presenter should reveal his/her (COI) at the beginning of their presentation. In addition in conferences industrial support of symposia should always be revealed, which is at present common practice. To further show maximum transparency about the results we suggest that during presentations experts without industrial ties summarise or comment on the findings presented by experts with commercial ties. Only data from industrial work published in peer reviewed journals or presented at scientific meetings with COI statements can thus be used in forming an opinion about new products, vaccines or diagnostic assays.

MSS 6-7

Professor Mark Bower

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Results of longitudinal high resolution anoscopy (HRA) screening programme in asymptomatic HIV-positive men who have sex with men (MSM)

A pilot programme enrolled 368 asymptomatic HIV+ MSM to HRA screening. Over a median follow-up of 4.2 years (maximum 13 years), they had a total of 1497 HRA examinations. Following detection of AIN-2/3, patients were treated with trichloroacetic acid, imiquimod or referred for surgery as appropriate. Patients with AIN-2/3 underwent a repeat HRA at 6 monthly intervals whilst those with AIN-1 were screened every year. At first HRA: 36% had normal appearances, 16% had no dysplasia, 15% anal intraepithelial neoplasia (AIN)-1, 19% AIN-2 and 13% AIN-3. During follow-up, 5 patients (1.4%) developed invasive anal cancer (incidence 2.7 per 1000 person-years). The 5-year cancer rate is 0.3% [95% confidence interval (CI) 0–0.6%]. Progression to cancer was associated with: higher age (P=0.049) and AIN-3 (P=0.024). 90 patients had AIN-3 present at least at one HRA. The cumulative risk of cancer from first AIN-3 diagnosis was 3.2% (95% CI 0–7.8%) at 5 years. 171 patients had HSILs (AIN-2 or 3) present at least once. The cumulative risk of cancer from first HSIL diagnosis was 0.6% (95% CI 0–1.8%) at 5 years.

Despite screening and intervention, 5 patients (1.4%) developed invasive anal cancer and this was associated with higher age and AIN-3, although the tumours detected in screened patients were small localized, and generally the outcomes were favourable. In the absence of a control group, the value of the HRA screening cannot be accurately stated

Outcome of chemoradiotherapy for invasive anal cancer in people living with HIV (PLWH) including late immunosuppressive effects

From a prospective database 1986-2010 of 11,112 HIV+ patients (71,687 person-years of follow-up) we identified 60 (59 male) PLWH with invasive anal cancer. At anal cancer diagnosis the mean age was 44 years (range: 28-75) and half had a prior AIDS defining illness. The median CD4 cell count was 305/mm3 (range: 16-1252) and 41 (68% were on combination antiretroviral therapy (cART) of whom 32 had an undetectable plasma HIV viral load. The cancer stage at diagnosis were: 38% Stage 1, 27% stage 2, 10% stage 3A, 23% stage 3B and 2% stage 4. The tumour histologies were 88% squamous, 10% basaloid and 2% neuroendocrine. Of the 60 patients, 3 (5%) received best supportive care only, 1 (2%) was treated with radiotherapy alone, 6 (10%) were anal verge tumours treated with surgery alone, whilst 50 (83%) were treated with chemoradiotherapy, using the same schedules used in HIV negative individuals. Treatment interruptions were necessary in 4(8%) and CTC grade 4 toxicity experienced by 6 (12%). Thirty three (67%) achieved a radiological complete response, 13 (26%) a partial response and 4 (8%) patients had progressive disease.

Ten patients relapsed, 3/33 (9%) who had achieved CR and 7/13 (54%) who achieved PR ($p<0.0001$). The median follow-up was 6.5 years. The 5 year overall survival is 65% (95% Confidence Interval (CI) 51-78%). The median CD4 cell count fell by half during the first 3 months of therapy ($P<0.0001$) and remained below pre-CRT levels throughout a year of follow-up, although there was no change in HIV viral load for patients treated with CRT and cART. Nineteen (34%) patients died including 13 from anal cancer and 6 from HIV related illness while in remission. These deaths potentially relate to the immunosuppressive effects of the chemoradiotherapy (3 AIDS defining malignancies and 3 AIDS defining opportunistic infections). This series reports that the overall survival is similar to HIV-ve population (UKCCCR ACT I study of 292 patients treated with CRT 5yr OS= 58%), although CRT is associated with significant and prolonged suppression of CD4 despite HAART and suppressed viral load and this may cause late deaths in remission from Ois and AIDS defining malignancies.

Salvage surgery for persistent or relapsed invasive anal cancer in people living with HIV (PLWH)

Salvage surgery may be useful for patients with either relapsed disease or persistent residual cancer after chemoradiotherapy, typically evaluated after 3 months. Nine HIV positive men undewrwent salvage surgery. They suffered more complications (55%) including delayed perineal wound healing (median time to healing 4 months) than reported in HIV-ve patients. The median hospital stay was 29 days which is also longer than reported in HIV-ve patients. There were no peri-operative deaths and perioperative CD4 cell counts were sustained. However, the overall survival after salvage surgery was only 25% at 2 years. This is similar to published data from comparable HIV-ve cases

Persistence of anal intra-epithelial neoplasia following chemoradiotherapy for invasive anal cancer in people living with HIV (PLWH)

Twenty two HIV positive MSM have undergone screening high resolution anoscopy (HRA) following completion of chemoradiotherapy for invasive anal cancer. The median follow-up is 5.6 years. The findings at the most recent HRA were: 2 (9%) patients had no abnormal findings, 1 (5%) had persistent HPV infection, 12 (56%) had low grade dysplasia (AIN1/2) and 7 (32%) high grade dysplasia (AIN3). Interestingly, 2 patients with low grade dysplasia at last HRA, had previous normal HRA screening following CRT raising the possibility of reinfection with HPV rather than persistence of low grade dysplasia. Two (9%) patients relapsed 13 and 16 months after CRT and have died. They both had persistent dysplasia (1 high grade, 1 low grade) at follow-up HRA. These findings suggest that anal dysplasia persists following CRT and could result in disease relapse or development of a second primary anal cancer. Patients with invasive anal cancer who have been successfully treated with CRT should still be considered for screening HRA.

SS 14-4

HPV TRANSMISSION MODELLING IN OPTIMIZING PREVENTIVE STRATEGIES

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Objectives: The approach to prevention of infection-related cancers is shifting from cancer control to infection control, for example, vaccination and the detection of infected individuals. In support of this change, the use of infection transmission models has entered the field of infection-related cancer epidemiology. We have developed a compartmental, dynamic, population-based, transmission model of sexually transmitted carcinogenic HPV infections to investigate the epidemiology and natural history of HPV infections and to assess the impact of HPV vaccination.

Methods: We have calibrated our model to the data obtained from several European countries, we simulated different HPV vaccination strategies, and assessed the effect of changes in sexual behaviour on vaccination effectiveness (i.e. HPV prevalence relative reduction).

Results: Using our model we could show that a) catch-up significantly accelerates the impact of vaccination; b) gender-neutral vaccination increases the long-term effectiveness in case of suboptimal coverage (e.g. 40%) and c) mitigates the consequences of a time-limited (e.g. 5 years) interruption of a vaccination programme.
We also assessed the impact of HPV vaccination if a population transitions or not from traditional to permissive sexual behaviour. In absence of vaccination, transition to permissive sexual behaviour rises the HPV16 prevalence by about 2.5-folds; with vaccination before the transition, the rise in prevalence is rapidly stunt; with vaccination after the transition it would a few decades for prevalence to be reduced at a comparable level.

Conclusions: Overall, these results suggest that population specific information about sexual behaviour are crucial to correctly interpret empirical data collected to monitor the impact of HPV vaccination. Mathematical modelling is a precious tool to design realistic and feasible strategies for the control of infection-related cancers. The next step is to develop a model of cervical cancer natural history and screening to optimize the combination of vaccination and screening.

OC 13-16

HPV SCREENING IN THE NETHERLANDS: DETERMINATION OF HPV PREVALENCE USING 3 DIFFERENT AUTOMATED HPV SYSTEMS.

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Objectives. Primary HPV screening will be introduced in the Netherlands beginning of 2016. Our aim was to study the workflows of 3 currently available, automated systems for HPV analyses, including the sample processing solutions. Furthermore, HPV prevalence was investigated using these 3 HPV assays.

Methods. Approximately 12.500 residual PreServCyt cervical samples from the Dutch population based cytology screening program were randomized and tested for high risk HPV using the complete HPV testing solutions of Qiagen (QIAensemble decapper, HPV media/QiaSymphony, RCS and DML for Hybrid Capture 2 (HC2) testing), Roche (p480, Cobas X480 and Z480 for Cobas4800 HPV Test), and Hologic (TomCat and Panther for Aptima HPV Test). HPV results were exported to a local database for subsequent data analyses.

Results. The selected samples were representative for the population based screening program with respect to age distribution as well as cytology classifications. Analysis showed a higher high risk HPV prevalence than the previously reported 5% in Dutch screening populations using GP5+/6+PCR-EIA (POBASCAM, enrollment 1999-2002) and HC2 (VUSA-Screen; enrollment 2003-2005). This higher HPV prevalence was found with all three HPV tests studied. Additionally, a clear age-dependency was found, younger women showed a higher HPV prevalence. Final analyses of the complete cohort will be presented during the meeting.

Conclusions. Higher high risk HPV prevalence than 5% was found in this population based cytology screening cohort using the complete HPV solutions for HC2, Cobas, and Aptima. Possible consequences for the Dutch primary HPV screening program will be discussed.

HPV-FRAME: A QUALITY FRAMEWORK FOR MODELS OF HPV PREVENTION

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HPV-FRAME is an initiative started in 2014 to develop a consensus statement and quality framework for modelled evaluations of HPV prevention. The overall intent of developing a quality framework is to enable a set of standards that ensure models contribute to an optimal decision related to the introduction of a new intervention or health program. Findings from the work done under this initiative will be presented.

P 13-1

DEVELOPMENT OF POINT OF CARE AUTOMATED DETECTION PLATFORM FOR CERVICAL CANCER AND HPV USING MULTIPLEX PROTEIN BIOMARKERS

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Cervical cancer affects almost 500,000 women each year, with the highest incidence and death rates occurring in developing regions of the world where women have very limited access to routine gynecological exams [1,2]. The current process for cervical cancer screening is performed in a laboratory and involves the analysis of the Pap smear by highly trained cytologists who are not readily available in developing countries. Recently, a FDA Advisory committee unanimously recommended HPV Testing as an adjunctive test to primary screening tools for detection of women at high risk for cervical cancer. Although this announcement highlights a need for more objective and accurate molecular tests to replace the Pap test, it also raises significant problems with using HPV tests alone as a primary cervical cancer screening tool.

Cancer, being a complex and multifaceted disease, is caused by multiple genetic and biochemical abnormalities at the cellular level. Thus, the most effective way to fully characterize the cellular changes required for carcinogenesis, and to define the state of the disease, is to evaluate multiple biomarkers that reflect critical molecular changes associated with cancerous cells. We have developed a panel of biomarkers that characterize disease progression towards cervical cancers, including HPV status, and quantified these biomarkers in cells collected from a standard liquid cervical cytology sample. Evaluation of over 200 hundred cervical cytology samples with selected biomarkers showed statistically significant increases in the levels of biomarkers in HSIL when compared to normal or LSIL samples. These biomarkers are being integrated into a novel Point of Care platform that utilizes onboard sample preparation and a unique and sensitive molecular detection technology. Introduction of a low-cost and easy to use automated Point of Care system to sensitively quantify these biomarkers in cytological specimens will fulfill important clinical unmet needs and will significantly reduce the mortality rate due to cervical cancers.

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