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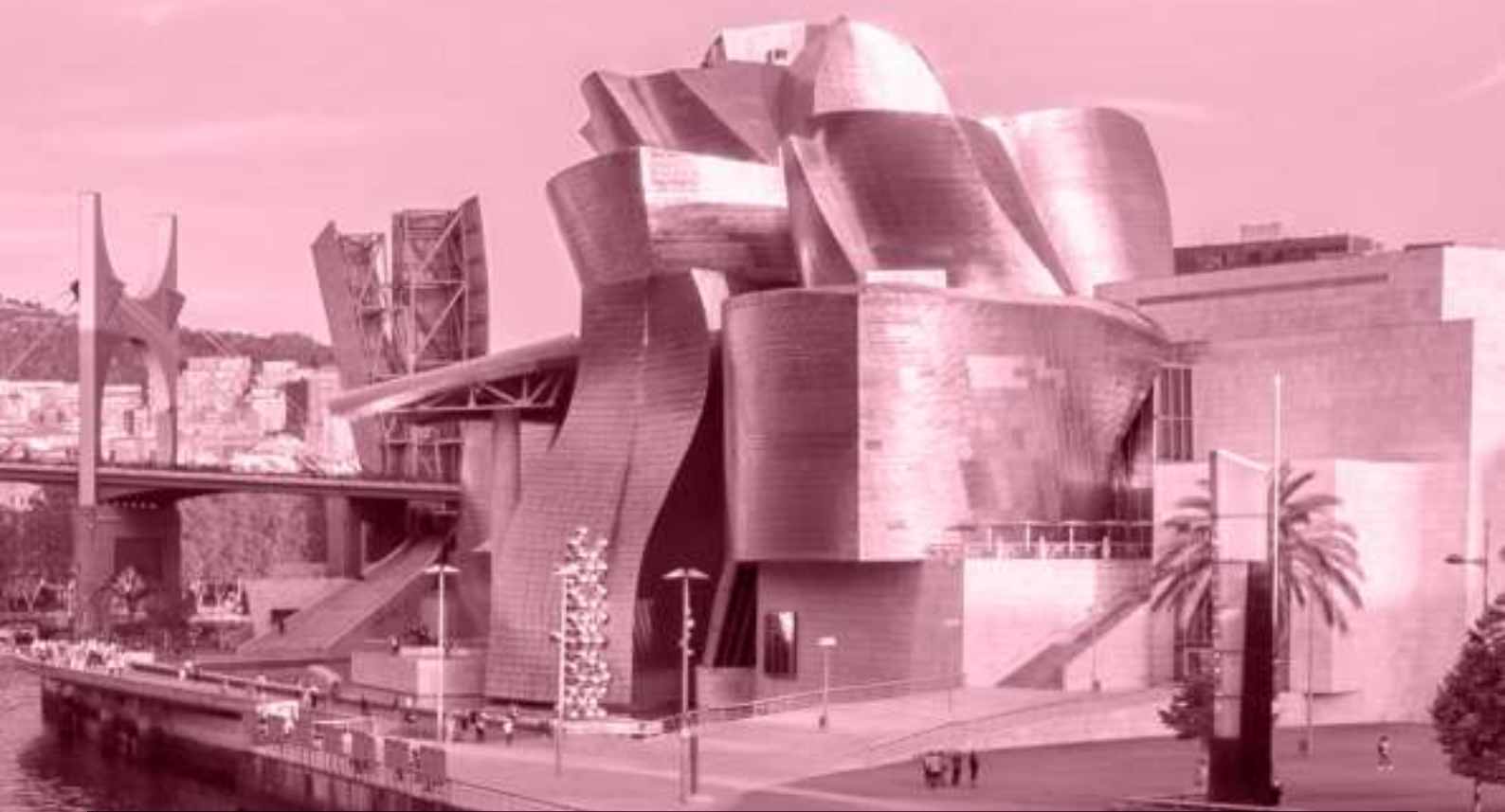
FEBRUARY 8-11
2023

SHARED CHALLENGES OF HPV DRIVEN CANCERS

FROM RESEARCH TO PRACTICE

Congress Presidents | **Jesper Bonde (Denmark) • Jennifer S. Smith (USA)**



ABSTRACTS

FREE COMMUNICATIONS SESSIONS

FC01- Free communications- Genotyping

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#4806

HPV genotyping in biopsies of HSIL and invasive cervical cancers in women living with HIV: A cohort- and a nested -case control study [1]

14 - Genotyping

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Background/Objectives: HIV infection constitutes an important risk factor for both acquiring HPV infection and for developing a persistence of this infection [2]. Consequently, the incidence rate of high-grade squamous intraepithelial lesion (HSIL),the direct precursor of ICC, is three times higher among women living with HIV (WLWH) than among HIV-negative women [3]. The pattern of HPV infection in WLWH is different from HIV-negative women [4]. We aimed to characterize HPV genotype distribution in HSIL and ICC- biopsies, of WLWH, in Europe, as compared to HIV-negative women.

Methods: A cohort- and a nested -case control study was conducted. We characterized HPV genotype distribution by performing PCR on HSIL and ICC biopsies from WLWH (n=170). We then compared the HPV genotype distributions in WLWH with those found in biopsies from HIV-negative women treated in the same institution, during the same period and matched for ethnic origin and stage of cervical lesion: 85 cases were compared to 85 HIV-negative matched controls. The proportion of patients that might be protected by HPV vaccines was estimated.

Results: Among WLWH (median age 36 years-old, median duration of HIV infection 70,5 months, 79% under cART): the most frequently detected HPV were HPV16 (30 %), HPV35 (16%), HPV58 (14,7%), HPV31 (13,5%), and HPV52 (11,7%). HPV16 was less frequently found in WLWH, originating from Central Africa (20,5%) compared to other African regions (35,5%) (p=0,05) or world regions (38,8%) (p=0,007). Multiple versus single high-risk HPV infections were associated with younger age (< 35 years)(odds ratio (OR) 2,65 (95%IC: 1,3-5,2,p=0,002), lymphocyte CD4 count < 350 cells / µL (OR 2,7 (95%IC: 2-8,5; p=0,005), use of cART for < 18 month OR 2,2 (95%IC: 1,1-4,5),p=0,04) or a cumulative time with undetectable HIV viral load of less than 12 months (OR 4,2 (95%IC: 2-8.5,p=0,001). HPV 31, 33 and 35 were more frequently detected in samples from WLWH than in HIV-negative controls (p<0,05). The 9-valent vaccine would increase HPV protection, in HIV-positive and negative women (p<0,001).

Conclusions: In conclusion, based on a large series of biopsies HPV-genotyping, we observed that HSIL or ICC in WLWH are more frequently due to high-risk HPV other than 16 and 18 than HIV-negative women, although HPV16 accounts for 30%. Multiple HPV causing HSIL or ICC in WLWH are frequent and are correlated with lower age, low immunity, and uncontrolled viral load. The use of 9-valent vaccine may prevent precancer cervical disease in up to 85% of women, whether HIV-positive or negative. Adding HPV35 to the HPV vaccine panel, might improve further vaccine effectiveness in WLWH especially originating from Africa.

References: Accepted in Vaccine Manuscript Reference No.: JVAC-D-22-01488R1 on the 13 th of october 2022 Liu G, Sharma M, Tan N, Barnabas R V. HIV-positive women have higher risk of human papilloma virus infection, precancerous lesions, and cervical cancer. Aids. 2018;32(6):795-808. doi:10.1097/QAD.0000000000001765 Denslow SA, Rositch AF, Firnhaber C, Ting J, Smith JS. Incidence and progression of cervical lesions in women with HIV: a systematic global review. Int J STD AIDS. 2014;25(3):163-177. doi:10.1177/0956462413491735 Clifford GM, Gonçalves MAG, Franceschi S. Human papillomavirus types among women infected with HIV: A meta-analysis. Aids. 2006;20(18):2337-2344. doi:10.1097/01.aids.0000253361.63578.14

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#5080

IMPACT OF JOINT HPV33/HPV58 PROBE ON REFERRAL RATES AND CLINICAL OUTCOME AFTER HPV POSITIVE SCREENING SAMPLE USING BD ONCLARITY HPV ASSAY

10 - HPV screening

Background/Objectives: In the Capital Region of Denmark women aged 30 to 59 are offered HPV screening with extended genotyping and cytology triage using a risk-based referral algorithm. In this algorithm HPV33 and HPV58 are placed in different risk groups with different follow-up procedures. However, using the BD Onclarity HPV assay, HPV genotypes HPV33 and HPV58 are by design bulked together in one channel and separation is not possible on the screening sample result, suggesting overtreatment of HPV58 positive women. We evaluated the impact of the joint HPV33/58 probe on referral for colposcopy, re-test rates and clinical outcome.

Methods: Women aged 30 to 59 years undergoing HPV screening from January to June 2022 with an HPV33/58 index sample result (BD Onclarity HPV assay) were re-tested for separation of HPV33 and 58 using the Anyplex II HPV28 (Seegene, South Korea). Data on cytology/histology follow-up was retrieved through the Danish Pathology Databank by October 2022.

Results: Of the HPV33/58 screening samples (N=161), 8% (N=13) carried a co-infection of either HPV16, 18 or 31 placing these in the direct colposcopy referral group. Of the remaining, 38% (N=56) were HPV33 positive, 2% (N=3) dual HPV33 and 58, and 60% (N=89) were HPV58 positive. For samples with concurrent high-grade cytology, 56% were HPV33 and 44% HPV58. For concurrent ASCUS or LSIL cytology, 28% were HPV33 while 69% were HPV58. For HPV33/58 positive women referred to colposcopy, resulting histology (N=53) showed higher ≥CIN3 rates amongst HPV33 positive women (62%, 13 of 21 cases) versus HPV58 positive women (10%, 3 of 31 cases). The only screening detected cancer in the cohort was HPV33 positive.

Conclusions: Currently HPV33/58 are analyzed jointly, thus women positive for HPV58 are unnecessary referred for colposcopy and biopsies instead of a re-test at 12 months. Though a limited dataset, it nevertheless seems reasonable to suggest that all screening index sample with an HPV33/58 positive outcome should be re-tested for full distinction between HPV33 and HPV58. Implicitly, this only account for samples without co-infection by the highest risk HPV16, 18, 31, 51 rendering the distinction between HPV33/58 irrelevant for referral recommendation. The benefit of applying a secondary HPV genotyping test to these samples are that 1) it is relatively few cases in the screening population, 2) it lowers the immediate referral rate for colposcopy and 3) there is limited screening detected severe dysplasia amongst HPV58 positive women, and even with a recommendation for a 12-month re-test, these will be followed up, however more conservatively.

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#4766

Real-World Evidence Using the BD Onclarity Extended HPV Genotyping Assay in Regional US Settings

14 - Genotyping

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Background/Objectives: The BD Onclarity HPV Assay received additional approval from FDA in 2021 to report extended genotypes, focusing on the 9-valent vaccine types (HPV 16, HPV 18, HPV 45, HPV 31, HPV 52, HPV 33_58) and pooling the majority of the other genotypes (HPV 51, HPV 35_39_68, HPV 56_59_66). A study protocol was submitted to central Institutional Review Board (IRB) to collect de-identified extended genotyping information from routine clinical use and link it to cytology and histology outcomes. The study was determined to be exempt from IRB oversight per 45 CFR 46.104(d)(4).

Methods: Data from patients undergoing routine screening or referred for abnormal cytology or HPV results were collected, de-identified and then linked through the Laboratory Information System (LIS) to cytology and histology results. The data was then analyzed to investigate the contribution to disease of specific genotypes, stratified by age, cytology, and histology outcomes.

Results: To date, over 30,000 HPV tests representing over 3,000 HPV positive outcomes and over 100 cases of CIN2/3 disease have accrued. The results confirm findings from the BD Onclarity national registration trial and underline the important of HPV 31, second only to HPV 16, representing approximately 20% and 30% all disease cases, respectively. The cross-sectional CIN 2/3 disease attribution in descending order was HPV16 > HPV 31 > HPV 52 > HPV 35_39_68 > HPV 56_59_68 > HPV 51 > HPV18 > HPV45 > HPV 33_58. Age-stratification analysis of all HPV+ patients revealed that HPV 56_59_66 channel positivity was approximately 2-fold higher in women < 30 versus women > 50 years of age and that HPV 16 infections increased with age, peaking in women 30-39. The other 9-valent vaccine types also followed this bell-curved genotype profile, reaching maximum prevalence in middle-aged (30-39) women.

Conclusions: The BD Onclarity extended genotyping results output allows clinicians to directly observe which high-risk types are contributing to disease and provide comprehensive risk assessment. HPV 31 was confirmed to be a major contributor to CIN2/3 disease and poses a sufficiently high risk to be referred directly to colposcopy based on the updated ASCCP CIN3+ risk threshold of 4%. 9-valent vaccine types tend to peak in incidence in middle-aged women. The assay enables monitoring of the impact of HPV vaccination and genotype-specific persistence, a key predictor of disease outcomes. The clinical utility of extended genotyping when combined with the ASCCP management principles of equal management of equal risk will be discussed.

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#4753

COMPARISON BETWEEN THE NOVEL ALLPLEXTM II HPV28 ASSAY, THE ANYPLEXTM II HPV28 ASSAY AND INNO-LIPA HPV GENOTYPING EXTRA II ASSAY FOR HPV DETECTION AND GENOTYPING

14 - Genotyping

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Background/Objectives: As genotyping of high-risk human papillomaviruses (hrHPV) is becoming increasingly relevant within cervical cancer screening programs, the optimization and comparison of novel and available HPV assays is currently of utmost importance. The recently developed Seegene AllplexTM II HPV28 assay is a novel qPCR HPV assay, designed to separately detect and quantify 28 distinct HPV genotypes in a fully automated and user-friendly manner. However, as a consequence of its novelty, studies comparing it with other more established and recognized HPV genotyping assays are yet to be published. This study therefore assessed and compared the performance of this newly developed HPV assay, with those of its Seegene forerunner, i.e. the AnyplexTM II HPV28 assay, and the INNO-LiPa HPV genotyping Extra II assay.

Methods: A total of 24 cervical samples (liquid PAP smears, ThinPrep® medium) were collected during routine screening at Ghent University Hospital and tested positive for at least one hrHPV genotype by the Abbott RealTime HR HPV routine assay. Samples were analyzed with all three HPV assays and HPV DNA positivity as well as coinfection rates were compared. Agreement in terms of HPV detection and genotyping was assessed by mean of the Cohen's kappa (κ) coefficient.

Results: Comparison of the HPV DNA positivity rates of different assays showed an agreement of 100% between the two Seegene assays, and of 91.6% when comparing the novel AllplexTM II HPV28 assay with the INNO-LiPa HPV genotyping Extra II assay. Moreover, coinfections were detected in 45.8%, 54.2% and 62.5% of the samples for the INNO-LiPa HPV genotyping Extra II, AnyplexTM II HPV28 and AllplexTM II HPV28 assay, respectively. Assay-wise comparison of all individual detectable genotypes demonstrated inconsistencies in 7 out of 28 genotypes when comparing the two Seegene assays and in 14 out of 28 genotypes when comparing the novel AllplexTM II HPV28 assay with the INNO-LiPa HPV genotyping Extra II assay. Furthermore, percentage agreements for all HPV genotypes were ≥96% (κ-agreement=0.00-1.00) when comparing the two Seegene assays, and ≥75% (κ-agreement=0.00-1.00) when comparing the AllplexTM II 28 HPV assay with the INNO-LiPa HPV genotyping Extra II assay.

Conclusions: This study shows good agreement in terms of HPV detection and genotyping between the results of included HPV assays. The current study can therefore be considered an important first step in the further evaluation and comparison of the novel AllplexTM II HPV28 assay with existing commercial assays, requiring larger sample sizes as well compatibility testing with other sample types, such as self-collected semi-cervical samples or urine samples, in the future.

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#4473

EXTENDED GENOTYPING, CYTOLOGY, AND SELF-SAMPLING: RISK-BASED ILLUSTRATIONS

14 - Genotyping

Background/Objectives: An analysis of published science was used to tabulate immediate risk of CIN3+ and 5-year cumulative incident risk of CIN3+ and then compare the risks to known thresholds for standard of care clinical actions.

Methods: MedLine was searched from 2001 through 2022 for relevant studies, supplemented by hand-searching of retrieved article reference lists. Eligible studies included prospective studies of women and retrospective studies of residual specimens from women that were tested using HPV genotyping tests. Outcomes were CIN3 or CIN3+ or invasive cervical cancer. Existing guidelines were used to establish clinical action thresholds in the USA and globally.

Results: Reporting genotyping provides stratification of both current and future CIN3+ risks. Genotyping combined with cytology improves risk stratification for Bethesda categories NILM, ASC-US, and LSIL. The risks were plotted for the general screening population, for follow-up 1-year after prior result of lesser abnormalities, for post-treatment follow-up, and for vaginal self-sample. By combining the published risks and the published guideline clinical action thresholds, extended genotyping informative illustrations were provided that support risk-based clinical action steps by the principle of equal management for equal risk.

Conclusions: Based on quality-evaluated studies that met inclusion criteria, genotyping combined with cytology stratifies risk. 20 annotated references are provided.

References: Citations: Demarco M, et al. A Study of Partial Human Papillomavirus Genotyping in Support of the 2019 ASCCP Risk-Based Management Consensus Guidelines. J Low Genit Tract Dis. 2020 Apr;24(2):144-147 Stoler MH, et al. Stratified risk of high-grade cervical disease using Onclarity HPV extended genotyping in women, ≥25 years of age, with NILM cytology. Gynecol Oncol. 2019 Apr;153(1):26-33 Bonde JH, et al. Clinical Utility of Human Papillomavirus Genotyping in Cervical Cancer Screening: A Systematic Review. J Low Genit Tract Dis. 2020 Jan;24(1):1-13 Monsonego J, et al. Prevalence of high-risk human papilloma virus genotypes and associated risk of cervical precancerous lesions in a large U.S. screening population: data from the ATHENA trial. Gynecol Oncol. 2015 Apr;137(1):47-54 Schiffman M, et al. A study of genotyping for management of human papillomavirus-positive, cytology-negative cervical screening results. J Clin Microbiol. 2015 Jan;53(1):52-9 Wheeler CM, et al. The influence of type-specific human papillomavirus infections on the detection of cervical precancer and cancer: A population-based study of opportunistic cervical screening in the United States. Int J Cancer. 2014 Aug 1;135(3):624-34 Data on File. Portability Study, Onclarity Results. See also citation #15 Schiffman M, et al. A cohort study of cervical screening using partial HPV typing and cytology triage. Int J Cancer. 2016 Dec 1;139(11):2606-15. Wright TC Jr, et al. Detection of Cervical Neoplasia by Human Papillomavirus Testing in an Atypical Squamous Cells-Undetermined Significance Population: Results of the Becton Dickinson Onclarity Trial. Am J Clin Pathol. 2019 Jan 1;151(1):53-62 Wright TC Jr, et al. Risk detection for high-grade cervical disease using Onclarity HPV extended genotyping in women, ≥21 years of age, with ASC-US or LSIL cytology. Gynecol Oncol. 2019 Aug;154(2):360-367 Schiffman M, et al. A study of HPV typing for the management of HPV-positive ASC-US cervical cytologic results.

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#4815

EVALUATION OF THE BD ONCLARITY HPV ASSAY FOR HPV-DNA DETECTION IN CERVICO-VAGINAL SAMPLES FROM THE ITALIAN NTCC2 STUDY

14 - Genotyping

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Background/Objectives: Different HPV genotypes are associated with different risks of having or developing a CIN2+ lesion. Therefore, several HPV assays now report extended genotyping. We aimed at investigating the performance of such an assay, the BD Onclarity HPV Assay, in a screening population from the Italian NTCC2 study, comparing results with those obtained with two other methods for HPV-DNA detection.

Methods: Cervico-vaginal samples from the NTCC2 study, already analyzed by Cobas 4800 (Roche) or HC2 (QIAGEN), were analyzed by the BD Onclarity HPV Assay for the qualitative detection of 14 high-risk HPV types (individual results for genotype 16, 18, 45, 31, 51 and 52, and pooled results for genotypes 33/58, 35/39/68 and 56/59/66).

Results: Overall, 3465 samples were analyzed by Onclarity Assay and only 3 gave an invalid result; 3129 were HPV-DNA positives with Cobas 4800 (n=1436) or HC2 (n=1693), hereinafter baseline-positives, and 333 were Cobas/HC2 HPV-DNA negatives, hereinafter baseline-negatives. Among the 3129 baseline-positives, the BD positivity reached 75.5%, whereas among the 333 baseline-negatives only 6 showed BD HPV positivity (1.8%; two for HPV16, one for HPV45, and 3 for the 35/39/68 pooled genotypes). Stratifying the BD positive results according to the cytologic triage report of the baseline-positives, we observed an increasing trend of positivity with increasing cytology severity (from 71.6% in NILM to 95.1% in ASC-H+ samples). Positivity for HPV16 also increased from 13.9% in NILM to 47.8% in ASC-H+ samples. Baseline-positives were triaged also by p16/ki67 dual staining; among them, 90.9% of the p16/ki67 positive samples were BD positive, of which 30% were HPV16 positive. Among the p16/ki67 negative samples, the BD positivity was 69.6% and the HPV16 positivity was 11.8%. The BD results stratified according to the baseline HPV-DNA test showed that a total of 87% (1250/1436) of the Cobas positive cases were concordant positive with the BD assay, versus only the 65.9% (1115/1693) of the HC2 positive cases. Moreover, as the Cobas assay is able to distinguish individually HPV16 and HPV18, we found that 95.2% of the Cobas HPV16 and 78.3% of the HPV18 samples were also positive for the relative genotypes with the BD assay. BD positivity was the highest among women with histologic confirmed CIN2 (75/78, 96.1%, of which 44.0% HPV16) and CIN3 (93/96, 96.9%, of which 60.2% HPV16).

Conclusions: Our study confirms high disagreement among different HPV assays used for screening. Nevertheless, the agreement is substantial for women p16/ki67 positive at triage, with high-grade cytology and histologically confirmed CIN2 and CIN3.

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#5041

COMPARISON OF ANYPLEXTM II HPV28 DETECTION AND LINEAR ARRAY GENOTYPING FOR PREVALENCE ESTIMATION IN EPIDEMIOLOGICAL STUDIES

14 - Genotyping

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Background/Objectives: Epidemiological HPV studies need methodologies able to inform the genotypes frequently distributed in the population. Additionally, it is important to have comparable methods in order to compare prevalence between countries/population. At least 254 commercial HPV tests are available on the global market currently. The Linear Array HPV Genotyping Test (LA, Roche) that was one of the most widely used tests was discontinued and replacement of methodologies can lead to misestimation of HPV frequencies and introduce potential errors in comparisons. So, we aimed to evaluate the specificity, reproducibility and sensitivity of the AnyplexTM II HPV28 Detection Test (Anyplex) compared to LA.

Methods: From a total of 6,388 DNA genital samples previously genotyped by LA test, 1,745 were randomly selected to be analyzed by Anyplex methodology. The nucleic acid extraction was done using LC DNA Isolation Kit III (Bacteria, Fungi) with MagNA Pure LC 2.0 System, Roche. Concordance was calculated by the percentage of agreement and Cohen's kappa (k) was classified as follows: 0.0 to 0.19, poor; 0.20 to 0.39, fair; 0.40 to 0.59, moderate; 0.60 to 0.79, good; 0.80 to 1.0, excellent.

Results: After genotyping the selected samples by Anyplex method and evaluating the Cohen's kappa score, it was possible to infer that the agreement between the two methodologies was good for HPV in general (k=0.78). The overall HPV agreement between the two techniques was 95.85%. False positive rate was 2.34% for general HPV and 2.57% for high-risk HPV genotyping. The sensitivity for overall HPV types and HR-HPV were similar: 97% (95% CI, 96% - 98%) and 96% (95% CI, 95% - 97%), respectively. HPV types 6, 42, 40, 68, 56 and 54 presented a difference higher than 5% points in the prevalence.

Conclusions: The validation process allows the replacement of LA by Anyplex in penile and cervical samples with a good agreement. Differences in sensitivity of detection for some specific types require a sample-balancing to correct estimation derived from technique differences in order to allow comparisons between populations. The comparison of prevalence between countries or studies carried out with different methodologies requires validations with different techniques and must be done with caution.

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#4914

IMPACT OF HPV mRNA TYPES 16, 18, 45 DETECTION ON THE RISK OF CIN3+ IN YOUNG WOMEN WITH NORMAL CERVICAL CYTOLOGY

14 - Genotyping

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Background/Objectives: Despite a well-established cervical cancer (CC) screening program in Norway, the incidence of CC in young women is increasing. 25% of all women diagnosed with CC had normal cytology three years prior to cancer diagnosis. To reduce cancer incidences missed by cytology, HPV-primary screening has been gradually implemented (2019), while cytology remains for women 25-33 years old. Research on how to further improve cytology readings seem quite limited. Given the high number of precancerous lesions in young women, an HPV mRNA reflex test following a negative cytology result could be used as a quality assurance measure to increase screening sensitivity. HPV-types (16-18-45) are shown to be the most prevalent types in cervical cancer among young women. This study investigated the detection rate of CIN3+ in women 25-39 years with normal cytology by using a 3-type HPV mRNA test as targeted quality assurance measure compared to cytology only.

Methods: During 2014-2017, samples from 13,021 women 25-39 yrs. attending screening were analyzed at Nordlandssykehuset, Bodø, Norway. Intervention group included 1,896 women with normal cytology and HPV-mRNA test (PreTect SEE, genotyping 16-18-45, PreTect AS, Norway). Index cytology for HPV-mRNA positive women was re-evaluated by a second cytology technician (re-examination of the existing slide) and revised cytological diagnoses were confirmed by a pathologist. The control group comprised 11,125 women evaluated with cytology only. All women were followed-up according to national guidelines throughout December 2021.

Results: 3.3% (429/13,021) had CIN3+ confirmed by biopsy, including 13 cases of invasive CC. In the intervention group, 2.6% (49/1,896) had positive mRNA-test. The cytology diagnoses were revised from normal to abnormal in 53.1% (26/49) of the HPV mRNA positive cases, while 23 cases remained normal after re-examination. The risks of CIN3+ among women with positive or negative HPV-mRNA test were 28.6% (14/49) versus 0.8% (14/1847). In the control group, 6.4% (712/11,125) had abnormal cytology (ASC-US+). The risks of CIN3+ among women with abnormal or normal cytology were 17.7% (126/712) versus 2.6% (275/10,413).

Conclusions: Applying a 3-type HPV-mRNA test as an adjunct to cytology will identify women at elevated risk, enabling targeted quality control of cytology readings, improving programme sensitivity by early detection of cell abnormalities. The volume of re-screened cytology samples is low. The risk of CIN3+ among cytology normal, HPV-mRNA (16-18-45) positive women during follow-up is high (28.6%) while double negative women remain at very low risk (0.8%).

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#5756

VALIDATION OF INTRA- AND INTER-LABORATORY REPRODUCIBILITY OF THE RIATOL QPCR HPV GENOTYPING ASSAY

09 - HPV testing

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Background/Objectives: Cervical cancer screening with assays detecting DNA of high-risk human papillomavirus (hrHPV) types is more effective than cytology-based screening. In order to be used in primary screening, HPV-assays have to meet pre-defined criteria. Clinical validation of hrHPV DNA assays requires demonstration of good reproducibility and non-inferior clinical accuracy for cervical precancer compared to a standard comparator assay. This study completes the diagnostic accuracy assessment conducted previously according to Meijer criteria (1) and within the framework of VALGENT-1 (2) and VALGENT-3 (3). The aim of this study is to determine whether the reproducibility of Riatol qPCR HPV genotyping assay is in line with international validation criteria.

Methods: In the scope of the international reproducibility criteria (4), 500 samples were evaluated of which 30% tested previously positive in a reference laboratory using a clinically validated assay. Each sample was subjected to an inter- and intra-laboratory comparative study. Agreement coefficients were statistically assessed to confirm meeting the predefined minimum criteria (not less than 87% agreement and a Kappa-value at least 0.5).

Results: The Riatol qPCR genotyping assay showed high intra-laboratory reproducibility with an overall positivity agreement of 98.9% [CI95: 98.0-99.8%] and a kappa-coefficient of 0.974 [CI95:0.953-0.995]. Inter-laboratory testing showed an identical agreement of 98.9% [CI95: 98.0-99.8%] with a kappa-coefficient of 0.974 [CI95:0.953-0.995].

Conclusions: With the reproducibility aspect confirmed, clinical validation of Riatol qPCR is completed. The Riatol qPCR genotyping HPV assay fulfills the test reproducibility requirements as outlined in international guidelines for use in primary cervical cancer screening

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FC04- Free communications - Epidemiology and natural history 1

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#5077

Women with cervical high-risk human papillomavirus: the ANGY cross-sectional clinical study

10 - HPV screening

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Background/Objectives: High-risk Human Papillomavirus (HR-HPV) cervical infection is an established risk factor of cervical cancer. The incidence of anal cancer is increasing, especially in women. Whereas the consequences of cervical HPV infection are well-known, little is known about the impact of anal HPV infection on the development of anal dysplasia and cancer. The aim of this study is to investigate the correlation between cervical and anal HPV, and also dysplasia.

Methods: The study was named ANGY for AnusGynecology. This is a prospective, cross-sectional, single-center study conducted at the University Hospital in Lausanne (CHUV), Switzerland. Patients were recruited and assigned to three groups : 1) patients from the general gynecology clinic, 2) patients from the specialized colposcopy clinic and 3) patients from the HIV clinic. They were calssified either in the cervical HR-HPV- positive group or in the cervical HR-HPV-negative group. Cervical and anal screening of HPV genotypes and cytology were performed in all patients. Biopsies were performed if needed according to the standards of care in colposcopy. Every patient was also tested for HIV.

Results: A total of 275 patients were enrolled. 102 (37%) had cervical HR-HPV. These patients compared to patients without cervical HR-HPV were significantly younger (39 vs 44 yrs, $p<0.001$), had earlier sexual intercourse (17.2 vs 18.3 yrs, $p< 0.01$), had more sexual partners (2.9 vs 2.2, $p<0.0001$), more dysplastic cervical cytology findings (42% vs 19%, $p<0.0001$) and higher prevalence of anal HR-HPV (59% vs 24%, $p<0.0001$). The HR-HPV group also reported more anal intercourse (44% vs 29%, $p<0.015$). Multivariate analysis retained anal HR-HPV as independent risk factor for cervical HR-HPV (OR3.3, CI 1.2-9.0, $p=0.02$).

Conclusions: The results of this study emphasize that when cervical HR-HPV is diagnosed, anal screening for concomitant HPV or dysplasia should be proposed as prevention tools of anal malignacy.

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#4873

Human papillomavirus prevalence in the European country with a high incidence of cervical cancer

40 - Public health

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Background/Objectives: Cervical cancer is caused by human papillomavirus (HPV) and is 4th most common cancer among females worldwide. Latvia implemented a screening program in 2009 that was based on cervical cytology. However, our country remains a European country with a high incidence of cervical cancer, which accounts for an 18.4 age-standardized incidence rate per 100,000 women and remains the 6th highest in Europe. By now, no population-based studies have been conducted in Latvia about the prevalence and determinants of high-risk human papillomavirus (HR-HPV) infection among Latvian women. This study aimed to provide this crucial data

Methods: The fieldwork of cross-sectional study was conducted from February 2021 to February 2022. The target population for HR-HPV testing was women aged 25-70 years who visited Riga East University Hospital (RAKUS) colposcopy unit (colposcopy population) because of the changes in their Pap smear and the general population who was enrolled from women visiting ten general practitioners' practices (2 practices per each of the five regions in Latvia). Women were asked to perform unsupervised HPV self-sampling using written instructions and, after the procedure, asked to fill in the questionnaire. Cervicovaginal samples were collected with a self-sample device - a dry cotton swab (FLOQSwabs) manufactured by COPAN. Samples were analyzed with Cobas 4800 System (Roche) for HPV 16 and HPV 18, along with a simultaneous, pooled result for other high-risk genotypes (HPV31/33/35/39/45/51/52/56/58/59/66/68). Statistical analysis of data was performed using SPSS 26.0. HPV-associated factors were identified by constructing a binary logistic regression model where all the factors showing statistical significance in univariate analysis (if $p<0.05$) were included.

Results: A total of 1313 women were invited to participate in the study, and 1274 participants provided a valid test sample. The prevalence of any HR-HPV was 34.2% (66.8% in the colposcopy population and 11.0% in the general population). In the colposcopy group (n=530), type 16 was present in 34.2%, type 18 in 4.0%, and other HR-HPV types were present in 42.0%. In the general population group (n=744), CPV 16 was present in 3.5%, type 18 in 1.2%, and other high-risk types in 7.5% of cases. In the final regression model, it was found that in the whole research sample, being positive for any type of HPV was significantly associated with being single, divorced, or widowed (vs. married/cohabiting odds ratio (OR) 1.8), being currently sexually active (vs. sexually inactive OR 2.0), with a higher number of lifetime sex partners (6+ vs. 1-2 OR 2.8, 3-5 vs. 1-2 OR 2.8), with last visit to gynecologist 1-5 years ago (vs. last year OR 1.9) and with belonging to the colposcopy study group (vs. general population OR 15.2). In the study-group stratified regression analysis, any type of HPV positivity in the colposcopy group was significantly associated with Latvian ethnicity (vs. other than Latvian) and with current smoker status (vs. never smokers). In the general population group being single, divorced, or widowed (vs. married/cohabiting), a higher number of lifetime sex partners and the last visit to a gynecologist 1-5 years ago (vs. last year) have shown significant associations with any type of HPV.

Conclusions: We documented a high HR-HPV infection burden in Latvia. Any type of HPV positivity was significantly associated with sociodemographic, sexual, and other health behavior as well as healthcare-seeking factors.

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The High-risk Human Papillomavirus Infection in eastern Ethiopia: Prevalence, cytological profile and associated factors

14 - Genotyping

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Background/Objectives: Cervical cancer is one of the major public health problems. It is a vaccine-preventable sexually transmitted disease. In the year 2020, an estimated 604,000 new cases and 342,000 deaths worldwide. Although its incidence is global, it is much higher in sub-Saharan countries. In eastern Ethiopia, there is a scarcity of information about the prevalence and genotype distribution of the virus. Therefore, this study was conducted to fill this information gap. The aim of this study was to determine the Molecular Epidemiology and cytological profile of hr HPV infection among sexually active women in eastern Ethiopia.

Methods: Socio-demographic and clinical data were collected by midwife nurses using a questionnaire. Visual inspection with acetic acid was used as an initial screening method for cervical cancer. From eligible women, cervical swabs were collected using L-shaped eNAT nucleic acid preservation and transportation vial. A Pap test was done to determine the cytological profile. An aliquot of the cervical swabs was extracted using STARMag 96 ProPrep Kit on SEEPREP32. A multiplex Real-time assay was performed to amplify the HPV L1 gene for genotyping using CFX96 PCR Deep well thermal Cycler. The data were entered into Epi data version 3.1 software and exported to STATA version 14 for analysis. Frequencies, proportions, and summary statistics were used for descriptive statistics. Binary and multivariable logistic regression models were used to identify associated factors and odds ratios with 95% CI were used to assess the degree of association. The p <0.25 were tested for multi-variable logistic regression and <0.05 was used to determine a significant association with the outcome.

Results: A hospital-based cross-sectional study was conducted from April 26 to August 28, 2021. A total of 901 (from 30 to 60 years, mean age =34.8 years, and SD= 5.8) women were screened for cervical cancer and 832 women had acceptable results for Pap test and HPV DNA testing. The overall prevalence of hr HPV infection is 13.1%. Out of 841 women with valid Pap test results, 88% of them had a normal and 12% (97% LSIL and 3% HSIL) had abnormal Pap test results. The detection rate of hr HPV was significantly higher among women with abnormal cytology (X2 = 688.446, p < 0.001). The prevalence of hr HPV infection decreased as the age increased (X2 =15.3408, p= 0.018.) while the highest prevalence (29.1%) was observed in women aged 30 to 35 years. Among 110 women whose hr HPV DNA was tested, 152 genotypes were identified. 80 (72.7%) women had a single genotype and 30 (27.3%) women had more than one (multiple) genotype. HPV-16 (31.8%), -31(19.1%), -52(11.8%), -58(10.9%), and -35(10%) were the most frequently detected genotypes. Single/never married (AOR = 9.39, 95% CI: 1.99 - 44.11, p <0.001) and women who had more than 1 sexual partner (AOR= 6.83, 95%CI: 2.92- 15.97, p<0.001) were more likely to have hr HPV infection.

Conclusions: The hr HPV infection continues to be a major public health problem and it mainly affects women in the age group of 30-35 years. HPV and Cervical cell abnormalities are highly correlated. In the areas where this study was conducted, some genotypes were found to be slightly different from other areas. Therefore, if a vaccine-based prevention program is to be effective, it is necessary to implement vaccine types that take into account the genotype distribution.

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#4827

CERVICAL HPV PERSISTENCE FROM A LARGE SCREENING COHORT OF HPV POSITIVE WOMEN IN THE DISTRICT OF FLORENCE

03 - Epidemiology and natural history

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Background/Objectives: Cervical HR-HPV persistence is one of the main risk factor for cervical cancer. We retrospectively investigated HPV persistence in a large cohort of HPV positive women who participated to primary HPV screening program in the district of Florence in the years 2013-2015. We also investigate the association between HPV persistence and two risk co-factors (age and smoking habits) which contribute to HPV persistence after one year since first HPV screening test.

Methods: We followed-up a cohort of 3511 women resulted positive at HPV screening test for an average of almost 8 years. The endpoint was defined as clearance of HPV, regardless of the HPV type. Women were divided into 2 groups depending on triage cytology outcome: C- if cytology was negative (2462/3511; 70.1%), C+ if cytology was ASCUS+ or unsatisfactory (1049/3511; 29.9%). The two groups were further stratified on age range [30-34 (n=72), 35-45 (n=987) and 46+ (n=2452)] and smoking habits [no smokers (n=1687), past smokers (n=516) and current smokers (n=1184)]. Median persistence time was calculated as median number of days between two consecutive screening tests. Age range and smoking risk analysis has been conducted on one-year persistence after baseline HPV test.

Results: At the second test, HPV persistence resulted 51.5% and 39.3%, in C- and C+ group respectively, and decreased to 22.3% and 20.5%, respectively, at the third screening test. HPV clearance overcrossed 90% starting from fifth test in both groups (92% C- and 91.6% in C+). HPV persistence also decreased under 20% from second test to the third one for age ranges 30-34 and 35-45 but not for 46+ (24.1% C-; 21.6% C+). Investigating the association between one-year persistence and age or smoking habits in C- group, odds ratios increased with both age [30-34 (OR=1), 35-45 (OR=1.10) and 46-67 (OR=1.29)] and current smokers [no smokers (OR=1), 35-45 (OR=0.96) and 46-67 (OR=1.26)]. Comparable results were found in the C+ group.

Conclusions: A well consolidated cervical screening program represents a useful source for HPV persistence investigation through years. In our cohort, about three quarters of women clear infection in 2 years from first test and persistence tends to reduce lower than 10% from the fifth screening test. Risk of one-year HPV persistence is greater in oldest age range (46+) and in current smokers than no smokers or past smokers, strengthing the importance to promote stop smoking within screening programs

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#4818

SURVEILLANCE OF HPV 16/18 INFECTION IN A POPULATION WITH HIGH VACCINATION COVERAGE (ENGLAND): FINDINGS, ISSUES AND FUTURE PRIORITIES

03 - Epidemiology and natural history

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Background/Objectives: The UK's National HPV Vaccination Programme began in 2008 offering routine vaccination to adolescent females aged 12-13 and catch-up to those aged 13-18. The programme initially offered the bivalent HPV vaccine before changing to the quadrivalent HPV vaccine in 2012. Ongoing surveillance has monitored the impact on type-specific HPV prevalence in young females. Here we summarise the findings for HPV 16/18, and consider the limitations of, and future priorities for, this surveillance, given the considerable impact of more than 10 years of high coverage HPV vaccination in England.

Methods: HPV DNA testing using an in-house multiplex PCR and Luminex®-based genotyping test was conducted on residual vulvovaginal swabs (VVS) collected from women aged 16-24 years old who were offered a chlamydia test as part of the National Chlamydia Screening Programme. Specimens were collected between 2010-2020 from 10 participating laboratories in 7 regions in England. Prevalence of vaccine types HPV 16/18 was analysed by age-group and calendar period.

Results: Residual VVS from 21,072 16-24 year old females were tested for HPV DNA. Large reductions in vaccine types HPV 16/18 were observed. In 16-18 year olds with the prevalence decreased sharply from 8.2% in 2010-11 to 1.1% in 2016-17 before plateauing to <1% in 2018-2020. The prevalence of HPV 16/18 is now <1% in females up to the age of 24 years who were all eligible for routine vaccination. Now that HPV16/18 prevalence is <1%, we would need to test at least 3,000 specimens per year (a 2-fold increase based on current targets of 1500) to detect a 50% change in prevalence between years as significant.

Conclusions: Given the huge success of the National HPV Vaccination Programme, and the direct and indirect protection resulting from 10 years of high coverage vaccination, surveillance in England now has limited power to detect small changes in HPV 16/18 infection prevalence. Continued surveillance is therefore unlikely to show the expected additional reductions due to extension of the National HPV Vaccination Programme to adolescent boys in 2019 or to detect any reduced protection should coverage or efficacy fall modestly (for example, as a potential outcome of a one-dose schedule). Our surveillance will adapt to this low prevalence endemicity (<1%) to ensure it has sufficient power to detect consequential changes, and to focus more attention on the fewer occurring vaccine-type infections in order to root out potential failures of the programme delivery (e.g. inequalities) and/or vaccine failures, that may have implications for the control of HPV, and elimination of cervical cancer.

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#5056

The annual recurrence risk model for tailored surveillance strategy in cervical cancer patients

26 - Cervical neoplasia

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Background/Objectives: Current guidelines for surveillance strategy in cervical cancer are rigid, recommending the same strategy for all survivors. The aim of this study was to develop a robust model allowing for individualized surveillance strategy based on patient´s risk profile.

Methods: A data of 4343 cervical cancer patients with pathologically confirmed early-stage cervical cancer treated between 2007 and 2016 were obtained from SCANN consortium centers of excellence. Only patients with complete key predictor variables and minimum 1-year follow-up data availability were included. Based on the prognostic markers, multivariable Cox proportional hazards model predicting disease-free survival (DFS) was developed and internally validated. A risk score, derived from regression coefficients of the model, stratified the cohort into significantly distinctive risk groups. On its basis, the annual recurrence risk model (ARRM) was calculated by conditional survival analysis.

Results: Five variables significant in multivariable analysis of recurrence risk were included in the prognostic model: maximal pathologic tumour diameter, tumour histotype, grade, number of positive pelvic lymph nodes, and lymphovascular space invasion. Five risk groups significantly differing in prognosis were identified; with 5-year DFS of 97.5%, 94.7%, 85.2%, and 63.3% in consecutive risk groups, while 2-year DFS in highest risk group equaled 15.4%. Based on ARRM, annual recurrence risk in the lowest risk group was below 1% since the first year of follow-up, and declined below 1% at year 3, 4, and >5 in 3 medium risk groups. Proportion of pelvic recurrences declined in groups with the growing risk. In the whole cohort, 26% of recurrences appeared at the first year of the follow-up, 48% and 78% until year 2 and 5.

Conclusions: ARRM represents a powerful tool for tailoring of the surveillance strategy in early-stage cervical cancer patients based on the patient´s risk status and respective annual recurrence risk. It can be easily utilized in routine clinical setting internationally.

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#4846

Association between sexually transmitted infections and abnormal cervical cytology: a prospective study based on cervical cancer screening cohort

34 - Sexually transmitted diseases and HIV infection

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Background/Objectives: Sexually transmitted infections (STIs) remain an important public health issue worldwide with a significant impact on female health. The association between STIs and abnormal cervical cytology has been seldomly evaluated.

Methods: This prospective study was conducted in 8,371women aged 21-64 years from cervical cancer screening cohort. The stored baseline cervical samples were tested by Next Generation Sequencing assay for high-risk human papillomaviruses (hrHPV), low risk HPV (lrHPV), and non-HPV STIs including Ureaplasma parvum (UP), Mycoplasma hominis (MH), Ureaplasma urealyticum (UU), Trichomonas vaginalis (TV), Chlamydia trachomatis (CT) and Mycoplasma genitalium (MG). Logistic regression analysis was used to estimate adjusted odds ratios (ORs) for incident atypical squamous cells of undetermined significance or worse (ASC-US+) associated with STIs.

Results: within 3 years follow-up, 771 incident ASC-US+ cases were identified.The adjusted ORs of hrHPV, lrHPV, UP, MH, UU, TV, CT and MG infections were 2.55 (95%CI: 2.14-3.04), 1.77 (95%CI: 1.41-2.23), 1.40 (95%CI: 1.18-1.65), 1.30 (95%CI: 1.09-1.55), 0.93 (95%CI: 0.76-1.14), 1.34 (95%CI: 1.01-1.78), 1.09 (95%CI: 0.68-1.75) and 2.00 (95%CI: 1.20-3.33), respectively.

Conclusions: Sexually transmitted infections, especially for HPV, UP, MH, TV and MG, were significantly associated with incident ASC-US+ among Chinese women.

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#4996

VARIATIONS OF THE MICROENVIRONMENT IN HPV ASSOCIATED LESIONS OF THE CERVIX-A HISTOLOGICAL STUDY OF THE SQUAMOUS AND GLANDULAR NEOPLASIA

04 - Pathogenesis

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Background/Objectives: Within the spectrum of sexually transmitted infections, HPV is the most prevalent cause, the severity of the disese ranging from non-detectable morphologically lesions to squamous and glandular neoplasia, in high risk HPV genotypes.

Methods: This was a retrospective study investigating a total number of 4873 PAP smears that have been registered in our department, out of which 9.24% showed a spectrum of cytological abnormalities from ASCUS to HSIlL, including AGC. All clinicopathological information related to age, tobacco smoking, abnormal vaginal secretion, paraclinical results and surgical interventions were retrieved from the medical records. A total of 23.7% of cases were followed by surgical intervention in our unit (from LOOP to hysterectomy). The histological slides of these cases were reevaluated in order to investigate the epithelial and stromal inflammatory reaction. Same parameters were applied regardless of the squamous or glandular origin of the lesion. Some patients were lost from investigation (did not present for follow up) and for others the therapeutic approach was "wait and see".

Results: In our study, the microenvironmental response showed differences, related to the histological subtype of the lesions and the HPV type involved, in what concerns the amplitude and extension of the inflammatory infiltrate, the cellular subtype, presence of angiogenic response and associated epithelial changes in the surrounding areas.

Conclusions: As tumor microenvironment has a well documented relationship to response to immunotherapies, further investigation in variables of the background of squamous and glandular lesions of the cervix are needed.

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#4968

THE ROLE OF BEHAVIORAL AND BIOLOGICAL FACTORS IN THE ASSOCIATION BETWEEN HIV PREVALENCE AND CERVICAL CANCER INCIDENCE IN SOUTH AFRICA: A MATHEMATICAL MODELLING STUDY

34 - Sexually transmitted diseases and HIV infection

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Background/Objectives: The perpetual high burden of cervical cancer (CC) in HIV-endemic sub-Sahara African countries is partly caused by the HIV epidemic. Women with HIV have a higher CC burden because of shared underlying risk factors (sexual behavior), increased susceptibility to HPV of HIV infected people, and increased CC disease progression in women living with HIV. However, it is poorly understood to what extent HIV contributes to the CC in sub-Saharan Africa, and how important the different behavioral and biological interactions between HIV and HPV/CC are. We extended an existing individual based STI transmission model (STDSIM) to incorporate the interactions between HIV and HPV/CC, and determine the role of HIV, and the relative importance of behavioral and biological risk factors in the CC burden in South Africa (SA).

Methods: We developed three different models, with increasing degrees of interaction between HPV/CC and HIV. Model 1 assumes no biological interactions between HIV and CC, and solely looks at behavior. Model 2 adds a co-factor for HPV acquisition in HIV infected men and women, and Model 3 adds heterogeneities in HPV, CIN and CC progression and regression. We calibrated each model to SA disease prevalence data. Using the models, we simulated the following four scenarios: Baseline (i.e. current HIV epidemic, ART scale-up, and risk behavior were simulated up to 2030); No HIV (i.e. we simulated the CC burden in the hypothetical scenario of no HIV in SA); No ART (i.e. no ART roll-out ever took place); and 95-95-95 (i.e. HIV treatment targets are met by 2030). For each scenario, we simulated the cumulative CC incidence in each of the three models.

Results: The models with increasing degrees of interaction between HPV/CC and HIV were more capable of reproducing disease prevalence data from SA, and our model estimates showed that roughly 25% of the increased risk in HIV infected women can be explained by behavior, and the remaining 75% by biological interactions. By analyzing the four scenarios, we found that the effects of the absence of HIV and ART are increasingly compensated for in Model 2 and Model 3, when biological factors are added. We also found that meeting the 95-95-95 targets will likely reduce the CC burden.

Conclusions: We have shown that to develop a representative model for the SA CC incidence, we need to account for both behavioral and biological factors in the interaction with HIV. Tackling the high CC burden will require "double-action' interventions that will take into account both behavioral and biological factors through a combination of both behavioral change actions and vaccination and screening interventions, preferably integrated with HIV services.

FC02- Free communications - Anal neoplasia

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#4953

Perianal Warts in HIV-infected MSM: Harbingers of Precancer and Cancer

28 - Anal neoplasia

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Background/Objectives: Genital warts are common lesions found in the perianal region of HIV-infected men who have sex with men (MSM). They are associated with low-risk HPV types and considered low-grade squamous intraepithelial lesions (LSIL) without malignant potential, although the risk of occult high-grade disease or cancer is not well known. We therefore sought to investigate the risk of precancer (i.e., High-grade squamous intraepithelial lesion, HSIL) and cancer associated with perianal warts in this high-risk population and to investigate their correlation with intra-anal lesions and oncogenic HPV types.

Methods: We retrospectively reviewed medical records of HIV-infected MSM who underwent high-resolution anoscopy (HRA) and concomitant biopsy of perianal warts and intra-anal lesions (when indicated) between 2018 and 2022. Patient age, histological diagnosis, concurrent cytological diagnosis and high-risk HPV testing results were recorded. Significance of risk factors for precancer and cancer were assessed using chi square and ranksum tests.

Results: 172 HIV-infected MSM met inclusion criteria. The median age was 50 years (range: 26-75). Histological diagnoses of perianal lesions were condyloma/LSIL (n=134, 78%), HSIL (n=34, 20%), and superficially invasive squamous cell carcinoma (SISCCA, n=4, 2%). Histological diagnoses of intra-anal lesions were benign (n=13, 8%), LSIL (n=92, 53%) and HSIL (n=67, 39%). Associated cytological diagnoses were inadequate (n=16, 9%), benign (n=14, 8%), ASCUS (n=67, 39%), LSIL (n=65, 38%), HSIL (n=10, 6%). High-risk HPV and HPV16 prevalence were 83% (n=143) and 30% (n=52). A total of 21 individuals (12%) had isolated perianal HSIL/SISCCA without intra-anal HSIL. As shown in Table 1, perianal HSIL/SISCCA was significantly associated with age ($p=0.007$) and HPV16 infection ($p<0.001$). Cytological ASCUS+ diagnosis, high-risk HPV unfection and intra-anal HSIL were not significant risk factors.

Conclusions: Perianal warts among HIV-infected MSM are associated with a substantial risk of concurrent precancerous lesions and occult cancer needs to be ruled out. HRA evaluation with histological diagnosis is warranted in this population, especially among elderly MSM with anal HPV16 infection.

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#4962

Anal cytology and Human Papilloma Virus genotyping of a population at increased risk of developing anal dysplasia and cancer

28 - Anal neoplasia

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Background/Objectives: Neoplasm of the anal canal are rare diseases in general populations but are more frequent in specific populations like men who have sex with men (MSM),HIV+ patients [1]and women with a history of cervical or vulvar dysplasia[2].The most common histology(80%)is squamous cell carcinoma(SCCA)and the anal preneoplastic lesions - i.e. the anal squamous intraepithelial lesions(ASIL) - are strongly related to human papilloma virus(HPV)infection,Several clinics or screening centers performs anal Pap tests to high-risk patients in order to early detect this type of malignancies;however,despite the growing number of new cases per year,to date there are no active screening protocols.We conducted a prospective cohort study aimed to explore the prevalence of anal high-risk(HPV-HR)and low-risk HPV(HPV-LR),the associated cytological pattern and eventual differences in men versus women.

Methods: During the period 2017-2021,550 anal swab specimen(436 of men and 114 of women with a mean age of 42.0 and 47.1 yrs,respectively),were collected at the Regional STD center of Florence.For each patients a unique sampling for Cytology(LBC ThinPrep) and HPV genotyping(Anyplex II HPV28 detection kit) was performed.All samples were analyzed at the laboratory of cancer prevention (LRPO) of ISPRO Institute.Cytology was evaluated according to the TBS system 2014.

Results: 315 patients out of 550(57.3%) resulted HPV-HR positive(HPV-HR+),of which 54/114(47.4%) women and 261/436(59.9%) men.Concerning anal Pap results,136 /315 (43.2%) patients had a cytology of ASC-US+;in this subgroup the incidence of HPV-HR+ was significantly higher(p=0.01) in men(121/261,46%) than in women (15/54,28%).Interestingly,227/261 men HPV-HR+ had a co-infection with one or more HPV-LR(87%), while this frequency resulted lower in women(41/54, 76%).Among the HPV-HR types, the most frequent were HPV16 (37%),HPV31 (21%) and HPV51 (25%).All patients(n=14) with a cytological interpretation suggestive of high grade squamous intraepithelial lesions(ASC-H/HSIL) were HPV-HR+ and 71.4% of these patients(10/14)resulted HPV16+.The distribution of the different HPV types was similar between men and women.

Conclusions: In HPV-HR+ patients,cytological alterations(ASC-US+)were more frequent in men than in women.Moreover,males showed more cases of co-infection with HPV-LR types compared to women;this finding could be the explanation for the higher frequency of ASCUS+ in the male group. Our data demonstrated that HPV genotyping test is characterized by a high analytical sensitivity for high grade squamous intraepithelial lesions;however,an high analytical sensitivity would reflect in a high referral rate for anoscopy(low clinical specificity).These findings support the hypothesis that anal cytology could be used as primary screening test for anal preneoplastic lesions,followed by HPV test(triage) to increase its specificity. The collection from high-resolution anoscopy and histology(when available) is currently ongoing to evaluate the clinical sensibility, specificity and the PPV of our approach, that could be proposed for the anal cancer screening in high-risk populations.

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#4650

HIGH PREVALENCE OF HPV, OTHER STI AND ANAL LESIONS AMONG MSM IN TOGO

39 - Low resource settings

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Background/Objectives: High prevalence of STI is a critical issue in Africa, especially in key populations such as MSM. Here, we present the baseli ne results of a 2-years longitudinal cohort study (ANRS DEPIST-H 12400) enrolling both HIV-positive and negative MSM.

Methods: MSM were included in Lomé (Togo) between June and december 2021, half of them living with HIV. High risk HPV (hrHPV) (Seegene) and HSV-1/2 (Altona) detection was performed on anal smears. Syphilis and HBs antigen were tested on sera samples on site. Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (NG) were tested (Cepheid) from urine, pharyngeal and anal swabs. A clinical genital examination was carried out by trained physicians.

Results: 200 MSM with a median age of 23 years (IQR=21-29) were enrolled. Prevalence of each STI is shown in Table 1. Only 1.5% of paticipants were positive for HBs antigen, while no HCV nor syphilis infection was detected. The prevalence of CT and NG was 6.5% and 3.0% in urine, 26.0% and 22.0% in anal swab, and 5.0% and 19,0% in oropharyngeal area, respectively. Anal herpes simplex virus (HSV) infection were detected in 9 (4.5%) of MSM (1 HSV-1 and 8 HSV-2). Overall, a high prevalence of anal hrHPV was detected (75.9%) and was significantly higher among HIV-positive MSM (84.0% vs 67.7%, p=0.008). The prevalence of hrHPV 16, 35, 51, 52, 58, 59 types was >15%. HPV35 and HPV52 were the most prevalent types (24%) among HIV-infected MSM. Multi-infections (>2 hrHPV) tended to be more common in HIV-infected MSM (69.0% vs 55.2%, p=0.08) . Two-thirds of hrHPV-positive MSM were infected with at least one hrHPV covered by the nonavalent vaccine. This proportion corresponded to 75% of HIV-infected MSM. More than a third of MSM (36.2%) presented an HPV-6 or -11. Anal lesions were detected at examination in 43.0% of MSM, with 19.5% of condylomas, 17.5% of marisks, 3.0% of anal fissures while anal ulcerations, gluteal abcess, hemorrhoid related pathology and anal fistula were diagnosed in 2.0% or less of participants. No anal cancer has been diagnosed.

Conclusions: These first data of the ANRS DEPIST-H emphasize the high burden of STIs among the key population of MSM in Togo. It also confirms the unusual distribution of HPV types in western Africa, with HPV35 being a highly prevalent hrHPV type non-covered by the nonavalent vaccine. A national strategy regarding STI screening and HPV vaccination in this key population is needed.

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#4590

AGREEMENT OF HPV GENOTYPES IN SELF- VERSUS CLINICIAN-COLLECTED ANAL SWABS AMONG MEN WHO HAVE SEX WITH MEN (MSM) IN MILWAUKEE, WISCONSIN, USA: THE PREVENT ANAL CANCER SELF-SWAB STUDY

13 - Self-sampling

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Background/Objectives: Home-based self-sampling, rather than clinician sampling, may be a viable option for anal cancer screening among men who have sex with men (MSM). Yet there is limited research comparing self-collected (SC) with clinician-collected (CC) anal swabs for HPV genotyping. We assessed prevalence of HPV genotypes and genotypic agreement in self and clinician anal swabs among MSM in a midwestern city.

Methods: The Prevent Anal Cancer (PAC) Self-Swab Study recruited MSM and transgender persons 25 and over in Milwaukee, Wisconsin, USA to participate in an anal cancer screening study. Participants were randomized to either a home or clinic-based arm. Home-based participants were mailed an anal self-sampling kit to complete and return via postal mail. They also were asked to attend a clinic appointment where they received a clinician-collected anal swab. Swabs were HPV genotyped using the SPF10-LiPA25 assay. We analyzed pairs of self- versus clinician-collected swabs to determine percent agreement. Adequate specimens with typable HPV taken ≤ 10 weeks apart were assessed (n=54). The median number of days between the home and clinic swab was 19.5 (range: 2 to 70 days).

Results: HPV was detected in 77.8% of SC and 75.9% of CC anal swabs with 87.0% agreement. Prevalence of any HPV, any high-risk HPV, any low-risk HPV, and types most associated with anal cancer (HPV 16, HPV 18, HPV 33, and HPV 52) did not significantly differ between SC and CC anal swabs. High-risk HPV was detected in 72.2% and 63.0% of SC and CC swabs, respectively, with 79.6% agreement. Self-swabs had similar prevalence of low-risk HPV (33.3%) to clinician swabs (35.2%), with 83.3% agreement. Among the types most associated with anal cancer, HPV 33 had the highest percent agreement between self and clinician swabs (98.1%), followed by HPV 18 (94.4%), HPV 16 (90.7%), and HPV 52 (88.9%).

Conclusions: Self-collected and clinician-collected anal swabs demonstrated high agreement for HPV genotyping among MSM. Percent agreement was above 88% for the types most implicated in anal cancer, and above 79% for any HPV, any high-risk HPV, and any low-risk HPV. Future research should assess level of agreement between self and clinician anal swabs collected on the same day.

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#4855

DNA HR HPV, mRNA HPV AND P16 TESTS FOR DIAGNOSIS OF PRECURSOR LESIONS AND ANAL CANCER: SYSTEMATIC REVIEW AND META-ANALYSIS

28 - Anal neoplasia

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Background/Objectives: Background / Objectives: Anal cancer prevention has two critical points: incidence is several fold higher for some groups, as people living with human immunodeficiency virus (HIV) and men who have sex with men (MSM), and there is not a well-defined guideline for its screening. This systematic review evaluates the accuracy of DNA HR HPV, mRNA HPV, HPV16 isolated and p16 biomarkers in anal canal smears to identify Anal Intraepithelial Neoplasia (AIN) 2 or 3, summarized as anal high-grade squamous intraepithelial lesions (aHSIL), and cancer.

Methods: Methods: Electronic databases search were conducted through Medline, VHS, Cochrane Library, Embase and Grey literature for papers published up to July 2022. Observational studies comparing biomarkers tests to a histopathology after HRA (High-resolution Anoscopy) as reference standard were included. We analyzed studies that both sexes were screened for anal cancer using DNA HR HPV, mRNA HPV, HPV16 and/ or p16 biomarkers. The analysis was done in pairs, for instance AIN2 or worse (AIN2+) versus AIN1, HPV infection and normal (AIN 1-).

Results: Results: We included 21 studies with a total of 6,643 patients. DNA HR HPV showed a higher sensitivity 93% (95%CI 86%-97%), specificity 39% (95%CI 31%-48%) and AUC 0.67, followed by mRNA HPV test, sensitivity 77% (95%CI 73%-81%), specificity 61% (95%CI 55%-67%) and AUC 0.78. HPV16 showed higher specificity 71% (95%CI 56 %- 83%), followed by p16 test, 66% (95%CI 53% - 77%). Sensitivity 56% (95%CI 39% - 72%) and AUC 0.69, 72 % (95%CI 52% - 86%) and 0.74, respectively. Subgroup analysis of MSM HIV+ (men who have sex with men, living with human immunodeficiency virus) with 12 studies and 4926 patients showed similar accuracy, with discreetly higher sensitivities and lower specificities.

Conclusions: Conclusion: DNA HR HPV can be useful tool for screening of aHSIL and anal cancer if followed to a biomarker with a higher specificity. As an isolated test, mRNA HPV had better performance, AUC of 0.78 for the whole group and 0.80 for MSM HIV+.

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#4674

Digital Anal Rectal Examination (DARE) utilization for anal cancer screening is very low among those most vulnerable to anal cancer: The Prevent Anal Cancer Self-Swab Study (NCT03489707)

16 - Screening methods

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Background/Objectives: In July 2021, an annual Digital Anal Rectal Examination (DARE) was recommended by the United States Centers for Disease Control and Prevention for early diagnosis of anal cancer among persons living with HIV and in HIV-negative gay and bisexual men. Given limited high-resolution anoscopy infrastructure, earlier detection of anal cancer using DARE may be many clinicians' only option for reducing anal cancer morbidity and mortality; however, there are no recent data on DARE utilization among the most vulnerable populations in the US.

Methods: Sexual minority men and transgender women (SMM/TW) with and without HIV, aged ≥ 25 years, were recruited into the Prevent Anal Cancer Self-Swab Study in Milwaukee, Wisconsin, USA. A total of 254 persons were consented and 241 self-reported their history of DARE. The proportion receiving DARE in the last year was estimated and factors associated with having a DARE in the last year were assessed in multivariable regression.

Results: Median age of enrolled participants was 46 years (interquartile range, 33-57 years). A total of 65.6%, 19.1%, and 12.9% identified as white, Black or Hispanic and 27.0% were individuals with HIV. Only 13.7% of these SMM/TW reported a DARE in the prior year and it was strongly associated with increasing age (p=0.002), for example, 5.6% of individuals 25-34 years reported a DARE in the prior year compared with 21.0% of those ≥ 55 years. DARE utilization did not vary by HIV status (p=0.98). In multivariable modeling, factors associated with DARE were age (aOR 1.04 95% confidence interval (CI) 1.01-1.08) and any history of a Pap test (aOR 2.48 95%CI 1.10-5.61 compared to individuals with no history of a Pap). Compared to persons mostly or always taking the insertive anal sex position, individuals taking the receptive position were more likely to have had a DARE in the last year (aOR 4.97 95% CI 1.18-20.88).

Conclusions: DARE utilization in the prior year is very low among persons who are most vulnerable to anal cancer. Current DARE utilization from a mid-sized US city is lower than 2017 data from Canada and consistent with older data from the US. Even among individuals aged ≥ 55 years, only 1 in 5 reported a DARE. While some characteristics of persons receiving a DARE were consistent with increased anal cancer vulnerability, e.g., increased age, any assessment for anal dysplasia, and mostly or always engaging in receptive anal sex, SMM/TW with HIV were no more likely to report a DARE than those without HIV. There is an urgent need to understand barriers to DARE not only among persons at risk for anal cancer, but also their health care providers.

Figure 1: DARE by age and HIV status

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#4988

EFFECTIVENESS OF A CORIOLUS VERSICOLOR-BASED GEL AS ADJUVANT TREATMENT FOR HPV16 POSITIVE ANAL INTRAEPITHELIAL NEOPLASIA: A CASE REPORT

28 - Anal neoplasia

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Background/Objectives: The incidence of anal cancer is 29,000 cases per year worldwide, from which about 90% are caused by Human Papillomavirus (HPV). This incidence has been increasing between 2-3% over the last decade. Anal Intraepithelial Neoplasia (HSIL/AIN2-3) is the precursor of anal cancer. Although the risk of progression to anal cancer is low, viral persistency is one of the main factors which can be modified to prevent anal cancer. Currently there is no consensus for the management of HPV-related anal lesions, and generally consists of clinical observation (wait and see). While there are available treatment options, such as surgical excision, none of these treatments is without problems. Therefore, access to safe, non-invasive treatment to help repair these lesions and promote viral clearance is needed. Recently, a Coriolus versicolor-based gel has become available for the treatment anal HPV.

Methods: In this clinical case, a 56-year-old woman, HPV16 positive in cervix 9 years ago and spontaneously cleared within a year, attended a consultation due to genital pruritus of few months of evolution that did not show improvement with hydrating treatment. Cervical cytology and colposcopy were both negative, but HPV test was positive for strain 16. Vulvar examination and biopsy showed moderate atrophy of the minor lips and the presence of lichen sclerosus. This was treated with 0.5mg/g Clobetasol which eliminated the lichen after 12 weeks. Nonetheless, the patient continued with intense pruritus in the perianal area. Further physical exploration with 5% acetowhite staining led to the identification of a 6-7 mm lesion in the anal genital area at 4h. Biopsy revealed HSIL/AIN2-3, positive result on p16 immunohistochemistry and anal HPV test was positive for HPV 16. The patient was treated with electrocauterization and a posterior adjuvant treatment with a Coriolus versicolor-based gel (1 cannula/day for 1 month + 1 cannula/alternate days for 5 months) for 6 months. Exploration at both 3 and 6 months, showed good reepithelization and clearance of HPV16 was achieved after 6 months of treatment.

Results: .

Conclusions: This clinical case illustrates the effectiveness of a Coriolus versicolor-based gel as adjuvant treatment following a destructive treatment, in a 56-year-old patient with HPV16 anal and cervical infection. Anal area good reepithelization and clearance of HPV16 were achieved after a single 6-month treatment period.

FC07 - Free communications - New technologies / Artificial intelligence

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#4673

USE OF AUTOMATION, DATA SCIENCE AND ARTIFICIAL INTELEGENCE-BASED ANALYSIS TO ENHANCE ACCURACY AND THROUGHPUT OF A QUANTITATIVE HPV-GENOTYPING PCR ASSAY

21 - New technologies

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Background/Objectives: With a clear aim towards the large-scale implementation of primary HPV screening worldwide, combined with a growing interest in genotype-specific knowledge, automation of data interpretation is gaining importance. Certainly, with higher demands on HPV assays, higher data resolution per sample is emerging. Historically, at AML 120,000 liquid-based cervical cytology samples are annually being tested using the in-house developed RIATOL wide-genotyping and viral-load quantitative RT-PCR assay [1]. Briefly, DNA extracts are amplified and tested simultaneously for 18 unique HPV types: 6E6, 11E6, 16E7, 18E7, 31E6, 33E6, 35E6, 39E7, 45E7, 51E7, 52E7, 53E6, 56E7, 58E7, 59E7, 66E6, 67L1, and 68E7. Beta-Globin expression is used as both internal cellular quality control and as viral copies normalizer on HPV-positive samples. The complexity of the assay used to involve manual labor-intensive analysis associated with long-TAT (1 dedicated full-time equivalent) and subjective results interpretation.

Methods: Here, we present a data science approach based on artificial intelligence (AI) (FastFinder, UgenTec NV) for the development, validation, and routine implementation of high throughput quantitative HPV-PCR analysis method. A core-script was initially developed and stepwise adjusted during a pre-validation phase, where results-driven fine-tuning of analytical Cq-cutoffs, baseline corrections, cross- or prevalence-driven contamination detection was achieved. After technical validation of the algorithm, empirical validation was performed by qualitative and quantitative head-to-head comparison between manual and automated analysis of 1040 samples.

Results: Qualitatively, a kappa coefficient of agreement of 0.98 between manual and automated analysis confirms an almost perfect agreement for a total of 20,800 observations. In fact, the automated algorithm outperformed the manual analysis remarkably in 96% of the non-concordant results. Quantitatively, the AI single-curve analysis method showed a higher accuracy when compared to traditional cycle-threshold analysis, especially for high viral load infections. Furthermore, automation of the analysis method resulted in a 90% reduction of hands-on-time from highly specialized staff.

Conclusions: FastFinder AI-based algorithm has demonstrated to be an all-in-one clinical grade platform providing automated data analysis, real-time results reporting and QC monitoring. Furthermore, it showed superior accuracy and lower TAT when compared with manual analysis for the RIATOL HPV-genotyping assay. Hence, FastFinder analysis has been fully implemented in the AML laboratory routine setting.

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#4824

3D-CATVIS: Development and validation of an open-source software-based workflow for 3D reconstruction of organotypic culture models

21 - New technologies

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Background/Objectives: Due to the more realistic representation of tissue architecture and context-dependent cell interactions, three-dimensional (3D) in vitro model systems are increasingly used in research. They allow for a more accurate approximation of the in vivo situation compared to classical 2D cell culture but require adapted imaging techniques to fully exploit their potential. We have previously established a 3D organotypic culture (OTC) model mimicking HPV-induced precancerous lesions enabling the simulation of new topical and systemic therapeutic approaches. To characterize treatment effects on tissue morphology and capture the additional spatial information present in 3D OTCs, we aimed to develop a 3D computer-aided visualization workflow using an open-source-software and employing digital image stacks of whole-slide-scanned serial tissue sections, apply it to our 3D OTC models and validate it using a different 3D structure.

Methods: A digital 3D computer-aided tissue visualization workflow (3D-CATVIS) was established comprising generation of serial, consecutive tissue sections of formalin-fixed, paraffin-embedded (FFPE) OTCs, high-resolution whole-slide-imaging (WSI; Hamamatsu S210) of Hematoxylin & Eosin (HE)-stained sections, region-of-interest (ROI) custom-trained classifier-based detection in QuPath [1] and registration, stacking and color-deconvolution with ImageJ [2,3]. This proceeding was followed by fusion and rendering with Fluorender [4] resulting in 3D representations of our OTCs. To evaluate generalizability of the developed 3D reconstruction approach, the workflow was adapted and applied to a serially-sectioned mouse lung sample.

Results: The newly established workflow allowed us to reconstruct and visualize the 3D morphology of our OTC model mimicking HPV-induced precancerous lesions and enabled structural insight as well as qualitative and semi-quantitative (i.e., volumetric) assessment of lesion burden. Machine-learning-based, automatic tissue segmentation using a pixel classifier trained on manual annotations was evaluated during workflow development and successfully used to isolate lesions from the surrounding matrix as 3D sub-volumes. The workflow proved to be adaptable to enable segmentation and 3D reconstruction of airways and parenchyma of an FFPE mouse lung sample with only very few modifications needed, validating our open-source-based approach as highly flexible and customizable.

Conclusions: We successfully developed a workflow that enables digital 3D reconstruction and visualization of OTCs mimicking HPV-induced precancerous lesions based on whole-slide-imaging of serial HE-stained tissue sections using readily available techniques and scriptable open-source software. This allows for qualitative and semi-quantitative evaluation of treatment effects in our model system of HPV-induced precancerous lesions. Ultimately, reconstruction of a mouse lung demonstrated the flexibility and easy adaptability of our approach, enabling evaluation of tissue morphology in a variety of sample types.

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#5008

COLPOSCOPY BASED ON ARTIFICIAL INTELLIGENCE: EXPERIENCE IN THE REPUBLIC OF UZBEKISTAN

25 - Colposcopy

Background/Objectives: Early detection of precancerous diseases and cervical cancer using AIDOT artificial intelligence.

Methods: The study included 200 women, aged 28 to 54 years (mean age 42.6±3.2 years). The colposcopy was performed using AIDOT artificial intelligence. Advantages of the method: ease of implementation, minimal preparation of the patient, portability of the device, speed of obtaining the result (about 30 seconds)

Results: In 118 patients with pathologies of the cervix, a biopsy was performed followed by a pathomorphological study, 82 women without pathologies of the cervix were recommended for further observation. In 92 (78.0±3.8%) cases, the results of colposcopy and pathomorphological examination were identical. A false positive result was noted in 10 (8.5%) cases, a false negative - in 16 (13.6%). Thus, the sensitivity of AIDOT in detecting CIN and cervical cancer was 67.9%, the specificity was 87.5%. The ability of the method to predict the presence of a disease with a positive result is 68.7%, the absence of pathology, with a negative test result, it can predict the correct result in 81.4%.

Conclusions: AI-based colposcopy AIDOT in the early detection of cervical cancer and as a triage method in cervical cancer screening can serve as an alternative to traditional colposcopy.

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#4871

Added value of electrical impedance spectroscopy in adjunction of colposcopy: a prospective cohort study

25 - Colposcopy

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Background/Objectives: To assess whether electrical impedance spectroscopy (EIS) with ZedScan combined with colposcopy increases the detection rate of cervical intraepithelial neoplasia (CIN2) in women with abnormal cytology.

Methods: We collected in Helsinki University Hospital colposcopy clinic a prospective cohort where EIS was used as an adjunctive technology for colposcopy and compared the detection rates of CIN2+ by referral cytology to a previously collected reference cohort with a conventional colposcopy. Detection rates of CIN2+ and diagnostic testing accuracy to detect CIN2+ with and without EIS and their relative differences between the two cohorts were calculated.

Results: A total of 647 women had a colposcopy with EIS while a conventional colposcopy was performed on 964 women. The detection rates of CIN2+ lesion varied between the cohorts, being 17.1% after ASC-US referral cytology in EIS cohort and 9.1% in the reference cohort, 16.5% and 18.9% after LSIL, 44.3% and. 58.0% after ASC-H, and 81.9% and 76.6% after HSIL, respectively. Sensitivity to detect CIN2+ was higher and specificity lower in the EIS cohort than in the reference cohort, regardless of referral cytology. The risk ratio of sensitivity was significantly higher with the use of EIS than without it in women with LSIL, RR 1.77 (95CI 1.30-2.41), ASC-H 1.57 (95CI 1.38-1.79) and HSIL 1.17(95CI 1.10-1.25) cytology.

Conclusions: A total of 647 women had a colposcopy with EIS while a conventional colposcopy was performed on 964 women. The detection rates of CIN2+ lesion varied between the cohorts, being 17.1% after ASC-US referral cytology in EIS cohort and 9.1% in the reference cohort, 16.5% and 18.9% after LSIL, 44.3% and. 58.0% after ASC-H, and 81.9% and 76.6% after HSIL, respectively. Sensitivity to detect CIN2+ was higher and specificity lower in the EIS cohort than in the reference cohort, regardless of referral cytology. The risk ratio of sensitivity was significantly higher with the use of EIS than without it in women with LSIL, RR 1.77 (95CI 1.30-2.41), ASC-H 1.57 (95CI 1.38-1.79) and HSIL 1.17(95CI 1.10-1.25) cytology.

FC03- Free communications - Self-sampling 1

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#4588

HPV self-sampling among long-term non-attenders to cervical cancer screening in Norway: A pragmatic randomized controlled trial

13 - Self-sampling

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Background/Objectives: Screening has reduced cervical cancer incidence and mortality substantially in Norway. However, coverage of the national cervical cancer screening programme has stagnated at a suboptimal 70%, and cervical cancer incidence has increased by 14% from the period 2009-2013 to 2014-2018. The Cancer Registry of Norway (CRN) is responsible for the national cervical cancer screening programme (CervicalScreen Norway), and invites women aged 25 to 69 years to attend screening. Under- or unscreened women have an increased risk of cervical cancer and being diagnosed at an advanced stage. We assessed whether human papillomavirus (HPV) self-sampling may increase screening participation among long-term non-attenders in Norway.

Methods: A pragmatic randomized controlled trial with participation as primary outcome was initiated in the national cervical screening programme March 2019. A random sample of 6000 women aged 35-69 years who had not attended screening for at least 10 years were randomized 1:1:1 to receive either (i) a reminder to attend regular screening (control), (ii) an offer to order a self-sampling kit (opt-in) for HPV testing, or (iii) a self-sampling kit unsolicited (send-to-all) for HPV testing. All women who returned a self-sample were informed about their test result per ordinary mail within six weeks after receipt of the self-sample in the lab. Women with an HPV negative result were encouraged to continue attending the regular cervical cancer screening programme at the recommended interval. Women with a hrHPV positive self-sample received the result together with a pre-booked triage appointment with a physician. To address feasibility and performance of alternative triage strategies that could be implemented in a screening programme, women were sequentially allocated to triage at their GP or a gynaecologist practicing in the largest city in their county. A total of 333 (5.6%) invited women, similarly distributed by intervention arm; 108 (5.4%) in the control arm, 103 (5.1%) in opt-in arm, and 122 (6.1%) in send-to-all arm; P = 0.4), were excluded from the study due to: (i) incorrect address, (ii) active refusal to participate in the study, or (iii) ineligibility for the study (living abroad/had prior hysterectomy/had a screening test between study sampling and invitation).

Results: Total participation was 4.8%, 17.0% and 27.7% among control, opt-in and send-to-all (P<0.0001; participation difference (%) send-to-all vs. control: 22.9 (95%CI: 20.7, 25.2); opt-in vs. control: 12.3 (95%CI: 10.3, 14.2); send-to-all vs. opt-in: 10.7 (95%CI: 8.0, 13.3)). High-risk HPV was detected in 11.5% of self-samples and 9.2% of clinician-collected samples (P = 0.40). Most women (92.5%) who returned a positive self-sample attended the clinic for triage testing. Attendance for women allocated to gynaecologist triage (irrespective of self-sampling intervention arm) for scheduled and any attendance was 75.6% and 90.2%, respectively, which was non-significantly lower than observed among women allocated to GP triage, who had corresponding attendance of 82.1% and 94.9% (P = 0.67 for scheduled attendance, P = 0.72 for any attendance Of the 933 women screened, 33 (3.5%) had CIN2+ (1.1%, 3.7%, 3.8% among control, opt-in, and send-to-all, respectively), and 11 (1.2%) had cervical cancer (0%, 1.2%, 1.3% among control, opt-in, send-to-all, respectively).

Conclusions: Opt-in and send-to-all self-sampling increased screening participation among long-term, higher-risk non-attenders.

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#5022

Self-sampling within routine cervical cancer screening in Region of Skåne, Sweden

13 - Self-sampling

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Background/Objectives: Year 2017 primary HPV screening was introduced in Region Skåne for women 30-70 years old. From September 2021, HPV testing of vaginal self-sampling was commenced as the first sample option for women aged 23-70 years. The aim was to analyze the performance of the newly introduced self-sampling screening program.

Methods: The performance of the self-sample program was analyzed by the use of data from September to December 2021, from the cytology-pathology database. HPV testing: About 51,000 self-sampling kits (Multitest Swab Specimen, Hologic), along with information were sent by mail. Self-samples were returned to the Department of Pathology in Lund. Self-samples were heated at 90°C for 1h and 15 min, cooled to room temperature and analysed by Aptima HPV mRNA assay. Self-sample-HPV-positive women were then invited for a follow-up within 3 months, where liquid based cytology (LBC) cervical samples were collected by midwifes. Renewed HPV analysis was performed, and reflex cytology were made from HPV-positive samples. Further gynaecological follow-up, due to cytology of atypical cells of undetermined significance (ASCUS) or worse, was done at outpatient colposcopy clinics where biopsy of abnormal tissues were taken and sent for histological assessment at Department of Pathology in Lund. Estimated costs for the self-sampling program (without cost for gynaecological colposcopy follow-up) was compared to that of the previous primary HPV-screening approach of midwife collected LBC samples among women 30-70 years of age.

Results: Among kits mailed from September to December 12th, the overall compliance for returning self-samples until end of December was 34% and 41% among women 23-29 and 30-70 years old, respectively. The HPV-prevalence was 33% and 16% among women 23-29 and 30-70 years old, respectively. Compliance of follow up at midwifes, after HPV-positive self-sample, was overall 86%. At follow up, 50% and 28% had HPV-positive LBC-sample among women 23-29 and 30-70 years old, respectively. Among these age groups, the LBC HPV-positive women demonstrated reflex cytology of ASCUS or worse in 86% and 77%, respectively. For women with cytology of ASCUS or worse, 7.3% and 9.8% had histologically confirmed high-grade squamous intraepithelial lesion (HSIL) or worse among women 23-29 and 30-70 years old, respectively. Among all the self-sample screened women (N=20,344) 0.5% had histology of HSIL or worse, including one invasive adenocarcinoma and one squamous cell carcinoma (SCC). Cost-estimations revealed that the self-sampling approach is about 70% of that of the primary HPV-screening program with cervical sampling provided by midwifes.

Conclusions: Upon summon for self-sample screening, compliance of returning self-samples was similar to the previous approach of attending to regular screening at midwife clinics. Although, efforts should be made to increase participation in screening by self-samples. As expected, the HPV-prevalence in self-samples was substantially higher among the younger age group. Although, histology of HSIL or worse at gynaecological colposcopy follow-up was detected at similar proportions (7-10%) among women 23-29 and 30-70 years old with cytology of ASCUS or worse. The proportion of histological HSIL (0.5%) among all the self-sample screened women was similar to that of previous regular primary HPV screening (0.5%) at midwife clinics in our county (Ref 1).

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#4764

Offering self-sampling method for HPV-DNA testing in an organized cervical screening program: an Italian experience

13 - Self-sampling

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Background/Objectives: From November 15th 2021 to April 05th 2022, as a recovery strategy for resuming organized cervical screening after COVID-19 emergency, the Local Health Authority of Bologna (the capital of the Emilia-Romagna Region-Northern Italy) offered to women aged 30-64 years overdue for screening the availability of self-sampling method for HPV-DNA testing as an alternative to a clinician appointment. The involved population was mostly women who historically did not participate in the organized screening. The study aimed to assess the ease of use and the acceptability of self-sampling method as well as its feasibility in the screening programme.

Methods: Self-collection was performed with self-vaginal FLOQSwabs® (Copan Italia SpA). Invited women were requested to collect and return the self-sampling device at their local pharmacy. Upon arrival at the laboratory, self-samples were eluted in 5 mL of ThinPrep PreservCyt® media (Hologic Inc) and high-risk HPV-DNA testing was performed by Cobas® 6800 System (Roche Diagnostics). The entire first-level procedure, from the self-sampling device collection to the laboratory result, can be tracked. Until March 2022 HPV-positive women were referred immediately to colposcopy, thereafter they were recalled to undergo cytology triage with the Pap-test and were managed accordingly. In case of sample inadequacy, women were recommended to undergo cervical sampling by a healthcare worker. Participants' screening attendance rates was evaluated till October 09, 2022.

Results: A total of 24228 women was invited, with an overall screening attendance of 15.4% (n=3725). Among these, 70.9% (n=2642) accepted self-sampling and 29.1% (n=1083) preferred clinician-sampling. The 15.6% (n=411) of the self-samples were HPV-DNA positive. The adherence to follow-up among women with a positive self-sample/cytology triage result was 89.1% and CIN2+ was detected in the 3.8% (n=10) of cases. Moreover, two inf40 years-old women received a diagnosis of adenocarcinoma in situ. The 1.2% of the self-samples were unsatisfactory. Due to technical-organizational issues, samples were not investigated in 0.5% of cases.

Conclusions: Offering self-sampling method allowed to resolve the backlog due to the pandemic. It proved to be an effective strategy for reaching women who historically did not participate in the programmed clinician-based screening given that they positively accepted this method; the low percentage of unsatisfactory self-samples reflected ease of use. Further evidence will be available, as HPV-based screening has been implemented in our Centre with the option of self-sampling for all women in the target population over 2022-2023 biennium.

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#5001

Cytological testing on cervical versus vaginal self-samples

13 - Self-sampling

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Background/Objectives: Cytological testing has been used for cervical cancer screening worldwide since the 1960s. HPV based cervical cancer screening has been proven to be more effective and provides longer protection against cervical cancer compared to cytology. Within the VALHUDES framework, we compared cervical and vaginal cytology for detection of CIN2/3+.

Methods: 454 (median age 41 years, range 21-72) women referred to colposcopy were included in the study with valid cytology, HPV result and clinical outcome. Vaginal samples were collected ether with Evalyn Brush (Rovers Medical Devices) (n=233) or Qvintip (Approvix AB) (n= 261) and cervical samples were taken by gynaecologists with a Cervex-Brush (Rovers Medical Devices). Cytological examination was performed on both sample types using Hologic's ThinPrep system. HPV testing was performed with Abbott Real Time HPV Assay. Abnormal cytology was defined as atypical squamous cells of undetermined significance and worse (AS-CUS+). We evaluated absolute and relative accuracy for CIN2+ of cytology on self- versus clinician-samples and of cytology versus HPV testing on both specimens.

Results: Sensitivity of cytology on vaginal samples was significantly lower than on cervical samples for CIN2+ (ratio=0.54 [95%CI 0.42-0.70]) and CIN3 (ratio=0.41 [95CI 0.25-0.66]), whereas specificity for <=CIN1 was significantly higher (ratio=1.22 [95%CI 1.14-1.29]). On cervical samples, cytology was less sensitive than HPV for CIN2+ (0.76 [95%CI 0.65-0.87]) and for CIN3 (ratio=0.67[95%CI0.53-0.84]), but more specific for <=CIN1 (ratio=1.41 [95%CI 1.26-1.57]). On vaginal samples, sensitivity of cytology was lower than HPV for CIN2+ (ratio=0.43 [95%CI 0.32-0.57]) and CIN3 (ratio=0.28 [95%CI 0.16-0.47]), whereas specificity for <=CIN1 was higher (ratio=1.62[95%CI 1.46-1.79]).

Conclusions: Vaginal cytology was less sensitive but more specific than cervical cytology. Sensitivity of cytology on both, cervical and vaginal self-samples was substantially lower than HPV but specificity was higher.

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#4915

THE VALUE OF 7-TYPE HPV mRNA E6/E7 TESTING IN SELF-COLLECTED SAMPLES AS TRIAGE OF ABNORMAL CYTOLOGY RESULTS: A MEXICAN MULTICENTRICENTIC STUDY

13 - Self-sampling

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Background/Objectives: Cervical cancer is a major health problem in Mexico. Only 40% attend regular screening, commonly conventional cytology. Self-sampling for molecular HPV testing is shown to be as reliable as clinician taken samples and increases access and screening-coverage. Most Mexican states have access to HPV-testing laboratories. Literature has shown advantages of E6/E7-mRNA detection over HPV-DNA test in triage of abnormal cytology, however few have evaluated the performance in self-sampled vaginal material. This study compared the performance of a 14-type HPV-DNA test to a 7-type HPV-mRNA test in triage of abnormal cytology with respect to PPV, sensitivity, specificity, and number of colposcopies per CIN2+ detected.

Methods: 418 Mexican women aged 25-65 years who were referred to colposcopy & biopsy after abnormal conventional cytology (ASC-US+) at the General Hospital of Mexico, Clinica Reina-Madre, and Clinica de la Colposcopia underwent self-sampling (XytoTest, Mel-Mont Medical) for molecular HPV-testing and completed a questionnaire evaluating the acceptability of self-sampling. Samples were tested for HPV-DNA (HPVm2000, Abbott) and E6/E7 mRNA (PreTect HPV-Proofer`7; individual genotyping of 16-18-31-33-45-52-58, PreTect AS, Norway). Study endpoint was histologically confirmed high-grade lesion (CIN2+).

Results: 93.1% felt confident performing self-sampling. 95.0% (397/418) had ASC-US+; 70.8% (296/418) low-grade (ASC-US/LSIL) and 24.2% (101/418) high-grade lesions. 55.5% (232/418) had positive HPV-DNA and 25.4% (106/418) positive HPV-mRNA test. Prevalence of CIN2+ was 12.0% (50/418) including 4 cases of cervical cancer. Sensitivity (CIN2+) for the HPV DNA test was 94.0% (47/50) versus 62.0% (31/50) for the mRNA-test, $p<0.001$. Both tests detected all cancers. The specificity was 49.7% (183/368) versus 79.6% (293/368), $p<0.001$, PPV was 20.3% (47/232) and 29.2% (31/106) for DNA versus mRNA-test, $p=0.09$. Low-grade cytology (ASC-US/LSIL) had PPV at 5.1% (15/296) compared to PPV for high-grade lesions at 30.7% (31/101). The number of colposcopies per CIN2+ detected by low-grade/high-grade cytology, HPV-DNA and HPV-mRNA was 19.7 and 3.3 compared to 4.9 and 3.4 respectively.

Conclusions: Self-sampling is suitable for HPV-testing and highly accepted by the women. The low PPV reported for low-grade cytology (5.1%) reflects the need for effective triage, reducing unnecessary colposcopies. A 7-type HPV-mRNA test has significant higher specificity, a PPV equals to high-grade cytology and lower number of colposcopies per CIN2+ compared to a 14-type HPV-DNA, effectively discriminating women warranted for immediate colposcopy/biopsy from return to follow-up.

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#4982

DNA METHYLATION TEST FOR DETECTION OF CERVICAL PRE-CANCER AND CANCER IN SELF-COLLECTED CERVICOVAGINAL SPECIMENS

13 - Self-sampling

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Background/Objectives: Clinician taken samples are the gold standard in cervical cancer screening but self-sampling may be a useful alternative for women who do not attend clinic at recommended intervals. Testing for high-risk human papillomavirus (HPV) infection using mailed, self-collected samples has already indicated a promising approach to increase screening programmes attendance. HPV testing is a very sensitive method, but not specific enough; thus, the choice of an appropriate triage strategy for high-risk HPV (hr-HPV) positive women remains one of the challenges facing the cervical screening community. In this study, we aimed to investigate the potential of using our DNA methylation test to identify cervical intraepithelial neoplasia grade 2 or higher (CIN2+/CIN3+) using self-collected samples in comparison to samples taken by clinician.

Methods: This study included 298 women undergoing clinically indicated colposcopy, 25 to 65 years of age, recruited between Nov 2016 and Jan 2019 in the study conducted at University of North Carolina to assess accuracy of hr-HPV testing in urine, self- and clinician collected cervical samples. Women with normal cytology and positive hr-HPV results were also recruited. For all 298 women we received self-collected cervicovaginal and clinician taken cervical samples accompanied by hr-HPV DNA test results and biopsy histological results. DNA was extracted from all of the samples, then bisulfite converted, PCR amplified for late regions of HPV16, 18, 31, 33 and host gene EPB41L3 and pyrosequenced as described previously (Brentnall et al, 2015). The DNA methylation score was calculated and its ability to identify CIN3+/CIN2+ in clinician and self- collected samples was evaluated.

Results: In preliminary data analysis our DNA methylation test showed a good and statistically significant separation between both <CIN3 and CIN3+ and <CIN2 and CIN2+ for clinician collected and cervicovaginal self-samples (Mann Whitney test, p=<0.0001). AUCs were significant for all pairwise comparisons of <CIN2, CIN2 and CIN3+ in both types of tested samples (p<0.001). In further analysis, performance of hr-HPV genotyping test (Onclarity assay, Becton Dickinson, Sparks, MD) and our methylation score for CIN3+/CIN2+ detection in both clinician and self-samples will be compared. We also received matching urine samples for a subgroup of 48 studied women to check if our methylation test can be successfully used in this type of self- specimen.

Conclusions: In this study, we demonstrated that our DNA methylation test can be successfully applied in cervicovaginal self-collected samples and that is able to correctly identify most of the CIN3+ and CIN2+ women. Self-sampling combined with our DNA methylation test may be a promising approach to improve cervical screening coverage especially in low and middle-income countries with limited access to health care.

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#4969

EVALUATION OF ALTERNATIVE SUSPENSION MEDIA FOR VAGINAL SELF-COLLECTED SAMPLES

13 - Self-sampling

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Background/Objectives: The introduction of self-collected vaginal samples in cervical cancer screening programs has been shown to improve coverage rates. Previous meta-analyses demonstrated that clinical accuracy of HPV testing of self-collected samples can be achieved using PCR-based assays. However validation of HPV assays in combination with self-collection devices needs to be performed. Moreover, pre-analytical protocols for the processing of vaginal self-collected samples, including medium and suspension volume, should also be evaluated. This study aimed to assess the clinical accuracy of OncoPredict HPV® Screening (SCR) and Quantitative (QT) assays (Hiantis) on self-collected vaginal swabs suspended in 5 mL of either ThinPrep® (Hologic) or of an alternative non-alcohol-based medium (eNat®, Copan), as compared to clinician-collected cervical samples.

Methods: Six hundred women were enrolled at 4 colposcopy centers as part of a clinical study conducted according to the European VALHUDES protocol (NCT04312737). A cervical sample (Cervex-Brush, Rovers) and a vaginal self-sample (FLOQSwab®, Copan) were collected from all participants. Cervical specimens were immediately suspended in 20 mL ThinPrep®, vaginal samples were transported dry to the laboratory. Hundred vaginal samples were suspended in 5 ml of ThinPrep® and 500 in 5 ml of eNat®. Nucleic acid extraction (Quick DNA/RNA viral MagBead, Zymo) and Real-Time PCR plate preparation were conducted using a totally automated platform (Fluent 480, Tecan), HPV testing performed with OncoPredict HPV® SCR and QT assays detecting respectively 13 and 12 hrHPV genotypes. The results from vaginal and cervical samples were compared, colposcopy findings and/or histology of biopsies were used to define disease status.

Results: 89.5% (k=0.786) and 87.9% agreement (k=0.751) for the detection of hrHPV positivity between cervical and vaginal samples were observed respectively with OncoPredict HPV® SCR and QT assays. Table 1 describes the different relative clinical sensitivity and specificity of vaginal samples suspended in ThinPrep® and eNat® as compared to cervical specimens. Since the overall specificity of vaginal samples was lower than that of cervical with both assays, the cut-off values for vaginal samples were adjusted (Table 2).

Conclusions: Vaginal self-sampling was demonstrated to be a valid alternative to cervical sampling having good clinical accuracy. The preliminary results suggest that medium composition and pre-analytical sample management should be taken into account when performing validation of new molecular assays on self-collected vaginal specimens.

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#5064

SCOPE2: A CLINICAL VALIDATION OF SELF-COLLECTION USING COPAN FLOQSWAB AND ROVERS VIBA-BRUSH ELUTED IN COPAN MSWAB MEDIA

10 - HPV screening

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Background/Objectives: The World Health Organization's Elimination Strategy includes the 2030 scale-up target of 70% of eligible people to be screened twice with a high -precision test. HPV-based cervical screening has created the opportunity for self-collection as a tool to increase access.

Methods: The Self-Collection or Practitioner-collection Evaluation 2 (SCoPE2) study recruited 400 participants attending for colposcopy. Participants who gave informed consent self-collected two samples, using a Copan FLOQSwab and a Rovers Viba-brush in random order, before a cervical specimen was practitioner-collected at colposcopy and eluted into a ThinPrep vial. The self-collected samples were shipped dry, stored for seven days then eluted in 5 ml of Copan MSwab media. All three specimens were tested on a range of clinically validated PCR-based HPV assays. Histological outcomes were available through to 6 months after recruitment.

Results: HPV positivity rates for the first 200 samples sets were 64.1% (mean across five HPV assays), 72.6% and 70.0% for the practitioner-collected, FLOQSwab and Viba-brush self-collected specimens. Preliminary data show the sensitivity for CIN2+ (n = 31) of HPV testing was 96%, 96% and 90% on practitioner-collected cervical and on self-collected FLOQSwabs and Viba-brushes; respectively. The average relative sensitivity estimates (self- vs practitioner samples) were 1.00 and 0.939, for FLOQSwab and Viba-brush, respectively.

Conclusions: Self-collection using cheap high-quality devices which can be transported dry are needed to increase accessibility both in low and middle-income countries and support screening in traditionally under- and never-screened populations in high-income countries. MSwab medium is cheap, non-toxic, does not contain alcohol and can be transported easily as it is not classified as a dangerous good. This validation demonstrates the clinical utility of two self-collection devices in combination with a non-toxic medium using a wide range of HPV assays.

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#4820

THE POTENTIAL OF FIRST-VOID URINE AS A SOURCE OF HIGH-QUALITY DNA FOR CERVICAL CANCER SCREENING AND TRIAGE

13 - Self-sampling

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Background/Objectives: Due to its non-invasive nature, urine is of great interest as a liquid biopsy in cervical cancer screening. It includes material derived from local shedding and debris of cervical cells. This ends up around the external female genitalia and is flushed away with the urine stream. Particularly the first part of the urine stream, the first-void urine (FVU), is known to collect this material and thus contains the highest concentrations of DNA. In this study, we looked at the quality of DNA that is detected in FVU and the effect of freezing, Amicon® filtration or gentleMACS homogenisation.

Methods: Two experiments were performed with each ten FVU samples that were collected from healthy volunteers with the 20mL Colli-Pee® device (Novosanis). In experiment one, the sample was divided over five 4 mL aliquots. One aliquot was used for fresh DNA extraction (NucliSens® EasyMag® (bioMérieux)) after centrifugation at 800 g (fresh_CF800), and the other aliquots were stored at -80°C prior to extraction using the same method (frozen_CF800) or after Amicon® filtration (frozen_AM). DNA concentrations and fragment patterns were determined using Qubit and Tapestation. In experiment two, the effect of gentleMACS dissociation was investigated. Here, fresh FVU samples were divided in two aliquots of which one was homogenised and both were subdivided in three 3 mL aliquots. The DNA extracts were used for analysis with Qubit, Tapestation and qPCR (GADPH).

Results: We observed no significant difference in average DNA concentration between fresh_CF800, frozen_CF800 and frozen_AM protocols (resp. 79 ng/mL, 99 ng/mL and 91 ng/mL FVU, $p=0.61$). Concentration differences between aliquots were not influenced by gentleMACS and were 25%, 28% and 23% (resp. Qubit, Tapestation and qPCR) with homogenisation and 25%, 24% and 21% without ($p=0.92$, $p=0.58$ and $p=0.38$). Yet, we observed a significant difference between DNA concentrations measured by qPCR and Qubit ($p<0.001$) and between qPCR and Tapestation ($p=0.015$).

Conclusions: Although the DNA concentrations vary greatly between measurement methods, our experiment shows that DNA concentrations are high in FVU samples. This study furthermore indicates that the DNA in FVU is mostly derived from local shedding - rather than per trans renal passage - as for most samples only fragments of 1000bp were observed. Moreover, there was no significant effect observed of freezing, Amicon® filtration or gentleMACS homogenisation on the DNA concentration, demonstrating the homogenous nature of FVU samples. Therefore, the quality and quantity of DNA extracted from FVU looks promising fur future screening and triage purposes.

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#4912

HPV Self sampling-Breaking barriers in cervical cancer screening

13 - Self-sampling

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Background/Objectives: India contributes to a huge burden of cervical cancer globally. We do not have an organized screening system and awareness of the availability of effective screening tests and the HPV vaccine is as low as 16%. Socio-cultural barriers prevent women from accessing health care services especially those that necessitate gynecological examinations.

Methods: HPV Self sampling was introduced to make cervical cancer screening more culturally acceptable. Project "Cervical Cancer Free Coimbatore" was initiated in January 2022 with an objective of screening 10,000 women. This was done with the help of NGO's and other organizations that already had a footprint in the community. Women in rural areas were approached, the importance of cervical cancer screening explained and the technique of self sampling taught by community health care workers. Women took the self sample in the privacy of their own homes. COBAS kit was used for HPV testing. The COBAS brush was initially used and this was switched to the Self FLOQ Swabs, Copan, Italy as we found this to be more woman friendly. After sampling, the swab was collected

Results: 3145 samples have been collected and results have been analysed for 2394 samples. Only 10% of women had a previous screening history. About 5.8% of women were HPV positive. Of these 16% were HPV 16 positive, 8.6% were HPV 18 positive, 66.9% were other High risk HPV positive and 7.9% had mixed infections. Of the 139 women who were HPV positive, 34% (N=48) had a colposcopy done. Majority of the colposcopies were negative (43.8%) while 14% were unsatisfactory. Two women had a diagnosis of LSIL, 1with HSIL and one had a diagnosis of cervical cancer. Twenty one women were treated with cryotherapy, 2 had LLETZ and 2 women had a hysterectomy

Conclusions: HPV self sampling is an effective tool in increasing cervical cancer screening as women find it more acceptable, less embarrassing and are more likely to recommend it to others.

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#4557

TARGETED RNA SEQUENCING OF VAGINAL SELF-SAMPLES VERSUS CERVICAL SMEARS

16 - Screening methods

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Background/Objectives: The Dutch population-based screening program uses hrHPV DNA testing on cervical smears followed by cytology triage of hrHPV positives. To increase response rates, self-sampling has been introduced for hrHPV-testing. The high sensitivity of hrHPV tests is accompanied by low specificity, resulting in high rates of overdiagnosis and overtreatment, despite cytology triage. Specificity of detecting CIN lesions can be improved by ciRNAseq, a new technology of multiplexed targeted RNA next generation sequencing that measures HPV-activity, HPV-genotype and HPV-induced human genes [1]. Because vaginal self-samples and cervical smears contain different cell populations, we here tested performance of ciRNAseq on self-samples and matching physician-sampled cervical smears.

Methods: Fifty women with a referral for treatment of a suspected CIN3 were included in this study. Prior to treatment a vaginal self-sample was taken with the Evelyn brush, followed by a regular cervical smear with a Cervex brush. RNA was isolated and subjected to ciRNAseq for measuring expression levels of 540 genes, including HPVE2 and HPVE6-7 genes for 15 high risk types. A previously established algorithm was used to calculate risk scores [1]. Gene expression profiles were compared and related to histopathological outcomes (≤CIN1, n=14; CIN2, n=7; CIN3, n=24; AIS, n=1; cancer, n=2).

Results: Good quality sequencing depth was obtained for all self-samples and cervical smears. Expression profiles in cervical smears and self-samples differed significantly (p3 for 164 genes). HrHPV RNA was detected in regular smears from 37/50 women (74%) and in 18 self-samples (36%). Concordance between genotypes detected in self-samples and matching regular smears was 94%. HPV RNA positivity alone in regular smears and in self-samples did not discriminate between ≤CIN1 and ≥CIN2. With a risk score cut-off of 0.5 in our algorithm [1], PPV of ciRNAseq to detect ≥CIN2 on regular smears was 0.58 and NPV was 0.79 (p=0.045). False negative rate was 0.5, false positive rate was 0.21. When doing the same exercise on self-samples, ciRNAseq could not differentiate between ≤CIN1 and ≥CIN2 (PPV=0.13 and NPV=0.92), false negative rate was 0.87 and false positive rate was 0.07.

Conclusions: CiRNAseq can be performed on self-samples and regular smears. To predict ≥CIN2, the ciRNAseq algorithm that we previously developed performs better on regular smears than on self-samples. Additional work is needed to optimize ciRNAseq and develop predictive algorithms for self-samples.

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FC05- Free communications- HPV prophylactic vaccines 1

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#4889

THE NCI-ACIB ONE DOSE VACCINE STUDIES IN COSTA RICA: A STATUS REPORT

06 - HPV prophylactic vaccines

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Background/Objectives: The Costa Rica HPV Vaccine Trial (CVT) provided proof-of-principle observational evidence of the efficacy of one dose of the bivalent HPV vaccine Cervarix (2v) against persistent HPV 16/18 infections, despite lower antibody levels compared to two doses (1). Vaccine efficacy (VE)estimates and antibody levels remain stable after 11 years follow-up (2). Other trials (IARC India, DORIS and KENSHE) have provided additional evidence that, together with CVT, led WHO to change its recommendation to "one or two doses' up to age 20 for both sexes. Current NCI/Costa Rica trials are expected to provide additional VE data for one dose of 2v and nonavalent vaccine (9v) in different age groups.

Methods: EXTEND is the 20-year follow-up of a selected group of about 1,000 CVT participants receiving different doses of AS04-adjuvanted 2v, designed to document a sustained antibody plateau. ESCUDDO is a RCT of one vs. two doses of 2v and 9v. In 2017-20 more than 20,000 girls 12-16 years old were recruited and randomized into 4 arms. Follow-up is planned for at least 5 years. ESCUDDO is designed to establish non-inferiority of 1 vs. 2 doses for each vaccine, and final results are expected in 2025. In addition, a cohort of 4,000 unvaccinated women 17-20 years old from the same study areas was recruited to directly estimate VE of one dose vs. no vaccination, and a second group is being recruited closer to the end of the study to take into account secular changes and potential herd immunity. PRIMAVERA is an immunobridging study of one dose of 2v in 620 girls 9-14 vs. 3 doses of quadrivalent Gardasil in 620 women 18-25 years, where efficacy has been demonstrated. The 3-year follow-up is near complete and results are expected in 2023. PRISMA is a RCT recruiting 5,000 women 18-30 years old randomized to 1 dose of 2v, 9v or a control vaccine, with 3 years follow-up to directly calculate VE against incident persistent HPV16/18 infections of the cervix, anus and mouth in this age group. Recruitment is ongoing and results will be reported in 2026.

Results: Accrual in our studies has achieved the goals established in the protocols and compliance with follow-up and specimen collection (including self-collected cervical, anal and oral specimens, as per study designs) has been at least 90%. The COVID-19 pandemic affected follow-up and may have changed sexual behavior practices during part of the studies, prompting protocol modifications that will be discussed. HPV testing will be done with NextGen Sequencing methods developed at NCI and transferred to Costa Rica. Preliminary assessments of HPV prevalence to validate study assumptions are being completed and will be discussed.

Conclusions: Our long-term joint research program (NCI-Proyecto Guanacaste-ACIB) has expanded and specialized to conduct large and complex intervention projects. We expect the current studies to provide irrefutable evidence that one dose is sufficient to prevent HPV infections up to age 30 and thereby accelerate elimination of HPV-related cancers worldwide.

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#4512

LONG-TERM EFFECTIVENESS OF THE 9-VALENT HUMAN PAPILLOMAVIRUS (9VHPV) VACCINE IN SCANDINAVIAN COUNTRIES

06 - HPV prophylactic vaccines

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Background/Objectives: A long-term follow-up (LTFU) extension (NCT02653118) of the 9-valent human papillomavirus (9vHPV) vaccine efficacy study in women aged 16-26 years (y) (NCT00543543) was initiated to assess effectiveness and immunogenicity for up to 14y follow-up. We report data from an interim analysis conducted at 8y post-vaccination for effectiveness and 9y for immunogenicity.

Methods: Participants from Denmark, Norway, and Sweden, who received 9vHPV vaccine during the base study and provided consent, continued into LTFU. National health registries were used to assess those attending screening and diagnosed with cervical (pre)cancers. Cervical tissue from biopsy and definitive therapy exams were retrieved from clinical biobanks for adjudication of pathology diagnosis and tested for HPV DNA by PCR. To assess effectiveness, observed incidence of HPV16/18/31/33/45/52/58-related cervical intraepithelial neoplasia-2 (CIN2), CIN3, adenocarcinoma in situ, or cervical cancer was compared with estimated incidence in an unvaccinated cohort (similar age and risk). A control chart method was used to detect signals indicative of vaccine effectiveness waning below 90%. Blood was collected at 9y from a subset of participants to assess antibody persistence by competitive Luminex immunoassay. Primary analyses were conducted in the per-protocol effectiveness (PPE) and per-protocol immunogenicity populations.

Results: Of 2223 participants who received at least 1 dose of 9vHPV vaccine at the start of the base study, 2029 continued into the LTFU study. Analyses were conducted based on median effectiveness follow-up post-Dose 1 of 6.8y (maximum 10.0y) among participants included in the PPE analyses (n=1799). No new cases of HPV16/18/31/33/45/52/58-related CIN2 or worse were observed during LTFU among 1448 PPE population-eligible participants (4084.2 person-years follow-up). Analyses based on a control chart method indicated no waning of vaccine effectiveness over at least 6y post Dose 1. There were also indications of continued effectiveness through 8y post Dose 1. Per-protocol immunogenicity analyses (n=150) showed that anti-HPV antibodies persisted through 9y post-vaccination. Effectiveness data ≥9y post-vaccination are not available.

Conclusions: The 9vHPV vaccine provides continued protection through at least 6y post-vaccination with a trend toward continued effectiveness for up to 8y, and persistent anti-HPV immunogenicity through 9y.

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#5740

HUMAN PAPILLOMAVIRUS (HPV) IMMUNIZATION AND SCREENING IN THE ITALIAN REGIONS: AN OVERVIEW OF THE CURRENT STATUS OF OPERATION

40 - Public health

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Background/Objectives: Vaccination against HPV (primary prevention) and screening tests (secondary prevention) can prevent the infection and early detect lesions, respectively. Despite the availability of national recommendations towards HPV diseases, the 21 Italian Regions have accountability for healthcare system and resources and some differences can be found in their strategies of prevention offer. The main objective of this study is to collect data on the offer of the HPV vaccination and screening in all Italian Regions (study funded by MSD[1] Italy, protocol number V9902).

Methods: A two-phase approach was adopted: a review of literature from official websites and documents of the Italian Regions released by the competent regional authorities in force on 31st December 2021; validatation of collected data through interviews with regional experts of primary and secondary prevention.

Results: For all regions the offer of HPV vaccination starts from 11 years old, both for females and males, but there is a different duration of gratuitousness. In addition, recommendations vary greatly among Regions in terms of other age cohorts targeted by vaccination. The offer is free of charge and actively carried out for cohorts of females born from 1993-97 and males born from 2001-06, depending on the region. For cohorts born before those to whom vaccination is offered free of charge, it is possible to receive the vaccination on request in co-payment. All regions have an electronic register for recording the vaccination status of the subjects undergoing the program. Only data collected on vaccine coverage rates (VCRs) in adolescents are sent by Regions to the Ministry of Health (MoH) for official publication. All regions have one or more public screening programs for cervical cancer. Programs usually include a PAP-test screening (women aged 25-29 years) and a DNA HPV test screening (women aged 30-64 years). PAP-test is performed once every three years, if there are no positive results. DNA HPV test is performed once every five years, if there are no positive results. All regions have an electronic register for recording the screening status of the subjects undergoing the program. Five regions have already developed an integrated system between registers of HPV primary and secondary prevention. All regions developed an outreach campaign for the HPV primary and secondary prevention strategy.

Conclusions: Data collected could inform properly the regional and national public health programs and strengthen resiliency of vaccination programs.

References: [1] Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, U.S.A.

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#4501

TYPE-SPECIFIC GENITAL HPV-INFECTION RATES AMONG SOUTH AFRICAN WOMEN 5 - 10 YEARS AFTER SCHOOL-BASED VACCINATION

06 - HPV prophylactic vaccines

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Background/Objectives: Results of two HPV vaccine implementation trials VACCS1 & VACCS2, conducted in 2010-2014, demonstrated successful school-based HPV vaccination combined with maternal screening in Gauteng & Western Cape, South Africa [1-3]. Current study forms part of follow-up trial performed 5-10 years later, aiming to evaluate genital HPV DNA status, self-reported sexual behaviour & attitudes, & HPV-immunity. Here we report & compare genital type-specific HPV-infection rates of vaccine recipients of one-, two- or three doses of either 2-valent (2vHPV) or 4-valent HPV vaccine (4vHPV), as well as unvaccinated girls.

Methods: Adolescent girls & young women, previously invited to VACCS1 and VACCS2, were eligible to participate in current trial. Demographic data & self-collected vulvo-vaginal swab specimens were collected & tested with PCR assay detecting 28 distinct HPV genotypes. Vaccine type, number & dates when vaccinated were collated from vaccination registers. High-risk HPV types were classified according to phylogenetic relationship as a-9 (HPV16, 31, 35, 33, 58, 52) and a-7 (HPV18, 45, 59, 39, 68, 70); low-risk HPV types classified as a-10 (HPV6, 11, 44, 40). Vaccine protection was defined according to WHO position paper 2014 [4].

Results: In total 111 participants were enrolled, mean age 19.5 [range 16-22] years; 52.3% (58/111) received 2vHPV, 39.6% (44/111) received 4vHPV & 8.1% (9/111) were unvaccinated. Mean age at vaccination was 11.0 [range 9-16] years. The majority 67.6% (75/111) were fully protected; 32.4% (36/111) were insufficiently vaccinated/unvaccinated. HPV DNA was positive in 47.7% (53/111) participants, no HPV16/18 occurred, & 5 cases of HPV6 infection occurred, all in 2vHPV recipients. In 2vHPV recipients, 89.7% (52/58) was a-9 negative, 8.6% (5/58) had infection with single a-9 type & 1.7% (1/58) multiple types; 82.8% (48/58) was a-7 negative, 13.8% (8/58) had single type & 3.4% (2/58) had multiple a-7 types. In 4vHPV recipients, 72.7% (32/44) was a-9 negative, 27.3% (12/44) had single a-9 and 0% multiple a-9 infection; 81.8% (36/44) was a-7 negative, 13.6% (6/44) had single a-7 & 4.5% (2/44) had multiple a-7 infection. Fully protected participants showed lower positivity for a-9 & a-7 types than insufficiently vaccinated participants [12.0% (9/75) v 27.8% (10/36); 16.0% (12/75) v 22.2% (8/36)].

Conclusions: The high prevalence of HPV-infection confirms early high-risk sexual behaviour. The absence of all vaccine types in vaccinated women is reassuring. Our data suggest better cross-protection against non-vaccine a-9 types for 2vHPV than 4vHPV, & cross-protection against both non-vaccine a-7 & a-9 types for fully vaccinated women compared to unprotected women.

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#4727

PUBLIC HEALTH IMPACT OF 2-VALENT, 4-VALENT, AND 9-VALENT HPV VACCINATION UNDER VARIOUS COVERAGE SCENARIOS IN CHINA - A SIMULATION STUDY

06 - HPV prophylactic vaccines

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Background/Objectives: Human papillomavirus (HPV) vaccination, currently not included in the Chinese national immunization program (NIP), is available in private market and provincial and city immunization programs. Previous modeling studies related to the vaccination focus mainly on quantifying the impact on cervical diseases under NIP-level vaccine coverage assumption (~90%). We aim to estimate more comprehensive health benefits of HPV vaccines under various coverage scenarios in China for cervical and non-cervical HPV related diseases.

Methods: Our previously published dynamic transmission model of HPV was calibrated to fit the latest cancer incidence and socio-demographic data for China. The model accounted for nine HPV vaccine-types (6/11/16/18/31/33/45/52/59), and sex- and disease-specific vaccine efficacies. For each type of vaccine (2-, 4- and 9-valent), we examined its impact under scenarios spanning across 8 coverage rates (20% to 90% in 10% increment) and 9 catch-up scenarios (0%, and 20% to 90% in 10% increment) in a time horizon of 100 years.

Results: The cumulative averted HPV related cervical (non-cervical, genital wart) cancer cases was > 2,000,000 (2*10^5, 2.5*10^5) in 77.77% (76.38%, 0.00%), 86.11% (73.61%, 97.22%), and 94.44% (87.50%, 97.22%) for 2-, 4- and 9-valent vaccine respectively for the 72 VCR scenarios. In high VCR scenarios, cervical (non-cervical, genital wart) averted cases was > 3,000,000 (3*10^5, 6*10^6) in 53.33% (70.00%, 0.00%), 96.66% (46.66%, 100.00%), and 100.00% (100.00%, 100.00%); in medium VCR, cervical (non-cervical, genital wart) averted cases was > 2,500,000 (2.5*10^5, 5*10^6) in 30.00% (30.00%, 0.00%), 66.66% (26.66%, 73.33%), and 100.00% (83.33%, 73.33%); in low VCR, cervical (non-cervical, genital wart) averted cases was > 2,000,000 (1.5*10^5, 1*10^6) in 0.00% (41.66%, 0%), 16.66% (33.33%, 100.00%), and 66.66% (66.66%, 100.00%) for 2-, 4- and 9-valent vaccine respectively.

Conclusions: In China, across multiple simulated VCR scenarios, the 9-valent HPV vaccine is projected to have much more significant reduction against all HPV related diseases, cervical and non-cervical, than the 4- and 2-valent vaccines.

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#4527

Modeling the implications of a single dose HPV vaccine regimen in a low/middle income country setting: an analysis in Indonesia

06 - HPV prophylactic vaccines

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Background/Objectives: While no HPV vaccine is indicated for single dose administration, some observational and short-term clinical trial evidence suggests that a 1-dose regimen might reduce the risk of HPV infection and offer comparable levels of protection against HPV infection as two or three doses. This study estimated the potential impact of implementing an off-label 1-dose HPV vaccination program, relative to the standard of care 2-dose program, with 9-valent vaccine (9vHPV) for adolescents in a low/middle income country, using Indonesia as a use case.

Methods: A previously published dynamic HPV transmission infection and disease model was adapted to the Indonesia population level data to compare the long-term health outcomes and cost-effectiveness of one-dose versus two-dose 9-valent HPV (9vHPV) vaccination programs in girls and boys aged 9-14. A probabilistic sensitivity analysis was performed with uncertainty distributions for the model degree and duration of protection of a single dose estimated from fitting data to interim KENSHE results. Scenarios analyses were run to show the impact of different coverage levels.

Results: For different coverage assumptions, 2-dose girls only (GO) or GNV program may avoid 70,000-1.96 million additional cancer cases, over 100 years compared to a 1-dose GO or GNV program. Compared to 1-dose, a 2-dose GNV program has nearly 100% probability of being cost-effective at a WTP of 0.5x Indonesian GDP ($1935/QALY) and none of the 1-dose scenarios had a probability of reaching cervical cancer elimination within next 100 years. Dose price, coverage, and 1-dose parameter uncertainty characterization sensitivity analyses led to similar results.

Conclusions: Our modeling shows adoption of the one-dose 9vHPV vaccination program resulted in more vaccine-preventable HPV-related cancer cases, introduced substantial uncertainty in both health and economic outcomes, and had a low to zero probability of being cost-effective compared to the two-dose programs. The health impact on a low/middle income country is substantially larger and more uncertain due to differences in attributes related to disease burden, vaccine coverage (including historical HPV immunization program), lack of screening practices and parameters related to socio-economic conditions.

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#4408

EARLY INITIATION OF HUMAN PAPILLOMAVIRUS VACCINATION AND SERIES COMPLETION IN EARLY AND MID-ADOLESCENCE

06 - HPV prophylactic vaccines

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Background/Objectives: The United States has an opportunistic, healthcare-based immunization delivery system. Routine HPV vaccination has been endorsed since 2006 for girls and 2010 for boys but rates remain sub-optimal. Two state-based studies suggest that initiation in late childhood at ages 9-10 rather than in early adolescence at the currently recommended ages of 11-12 improves series completion. No national study has explored the early initiation-HPV series completion relationship. This study addresses this knowledge gap and explores potential mechanisms through which early initiation may act.

Methods: A retrospective cohort of 19,575 15-17-year-olds who initiated HPV vaccination between ages 9-10 (early initiators) and ages 11-12 (later initiators) was assembled from National Immunization Survey-Teen 2017-2020 data. Three series completion endpoints were evaluated: complete by age 13 (UTD13), complete by age 15 (UTD15) and completion within 3 years of initiation (W3YR). Two potential mechanisms of action for early initiation were identified: increasing time to target completion ages (measures=UTD13, UTD15) and moving to an earlier developmental stage (measure=W3YR).

Results: 7.7% were early initiators. Series completion rose more than 2-fold between the ages of 13 (UTD13=34.5%) and 15 (UTD15=83.4%). Most completed within 3 years (W3YR=84.8%). In bivariate analyses, early initiators were more likely than later initiators to be UTD13 (78.3% vs 31.2%, $p<0.001$) and UTD15 (91.5% vs 82.7%, $p<0.001$), while early initiators were slightly less likely than later initiators to be W3YR (82.3% vs 85.0%, $p=0.006$). In multivariable analyses, early initiators had higher odds of UTD13 (AOR 6.17; 95% CI 5.46-6.96) and UTD15 (AOR 2.52; 95% CI 2.09-3.05) but early initiation was not associated with W3YR (AOR 0. 92; 95% CI 0.80-1.06).

Conclusions: By increasing time to target completion ages, moving routine HPV vaccination to ages 9-10 may improve vaccine coverage rates in early adolescence, increasing the likelihood of that vaccination occurs prior to sexual debut and maximizing the vaccine's public health benefit.

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#4864

HPV-related lesions after hysterectomy for high-grade cervical intraepithelial neoplasia and early-stage cervical cancer: a focus on the potential role of vaccination

06 - HPV prophylactic vaccines

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Background/Objectives: Adjuvant HPV vaccination after conization is associated with a reduced risk of cervical dysplasia recurrence. However, no data supported the execution of vaccination after treatment of hysterectomy for high-grade cervical intraepithelial neoplasia and early-stage cervical cancer. Here, we aim to evaluate the potential effect of vaccination after hysterectomy for high-grade cervical intraepithelial neoplasia and early-stage cervical cancer.

Methods: This is a multi-center retrospective study evaluating data of women who develop lower genital tract dysplasia (LGTD, including any grade of vulvar and vaginal intra-epithelial neoplasia) after having a hysterectomy for high-grade cervical intraepithelial neoplasia and FIGO stage IA1- IB1 cervical cancer (having surgery only without medical/radiation therapy). All patients included had HPV DNA testing at the time of LGTD.

Results: Overall, charts of 72 patients with LGTD were collected. The study population included 58 (80.5%) and 14 (19.5%) patients with high-grade cervical intraepithelial neoplasia and early-stage cervical cancer, respectively. Twelve patients had type B radical hysterectomy with or without nodal assessment. All patients achieved negative surgical margins at the time of primary surgery. Data on HPV status at the time of primary surgical treatment were available for 18 (25%) patients. The Median (range) time between hysterectomy and diagnosis of LGTD was 38 (range, 14-62) months. HPV16, HPV18, and HPV31 were the most common HPV types detected at the time of LGTD. Coinfections were detected in 41.6% of cases. Considering data from the whole cohort of 72 patients, HPV types covered by the nonavalent HPV vaccination would potentially cover 92% of the LGTDs. Then, we restricted our analysis to the 18 patients with available HPV data at the time of hysterectomy. The analysis of data from this population confirmed the potentially beneficial effect of nonvalent vaccination (efficacy: 16/18 (89%)). However, considering that patients with persistent HPV types (with the same HPV types at the time of hysterectomy and LGTD) would not benefit from vaccination, we estimated the potential protective effect of vaccination to be 72% (13 out of 18 patients; four patients had a persistent infection for the same HPV type(s)).

Conclusions: Our retrospective analysis supported the adoption of nonavalent HPV vaccination in patients having treatment for high-grade cervical intra-epithelial neoplasia and early-stage cervical cancer. Even in the absence of the uterine cervix, HPV vaccination would protect against LGTD. Further prospective studies have to confirm our preliminary research.

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#4796

Human Papillomavirus Vaccination Delivery Systems within National and Regional Immunization Programs: A Systematic Literature Review

06 - HPV prophylactic vaccines

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Background/Objectives: Human Papillomavirus (HPV) causes 4.5% of all new cancer cases. Efficient HPV vaccination programs are crucial to reduce the global burden of cancer. As of June 2020, 107/194 World Health Organization (WHO) Member States have introduced HPV vaccination, one-third of which are gender neutral whereby girls and boys receive vaccination. Globally, only 15% of girls and 4% of boys in the target age for HPV vaccination receive the full course. The objective of this systematic literature review was to describe HPV delivery strategies within national and regional immunization programs in low- middle- and high-income countries to identify strategies to increase HPV vaccination coverage globally.

Methods: We systematically reviewed studies within MEDLINE and EMBASE published between 2012-2022. Studies were included if they described immunization programs in which HPV had been included for >6 months. Key outcomes of interest were strategies utilized in the implementation of HPV delivery programs (e.g., vaccine delivery location, community awareness campaigns). Of the 2,549 articles retrieved, 168 met inclusion criteria and were included for final synthesis.

Results: Most (n=78) articles were from North America, 31 from Europe & Central Asia, 15 from East Asia and Pacific, 8 from Africa, 5 from Latin America & Caribbean, 2 from South Asia, and 29 included multiple regions. While most articles (n=121) focused on high-income countries, 19 focused on low- or middle-income countries and 28 spanned multiple income levels. The most frequently described strategies that had a positive impact on HPV vaccine coverage included selecting optimal delivery locations for the local context, such as school-based programs (n=51), multi-sectoral collaboration (n=47), community-awareness campaigns (n=42), systematic vaccine invitations and reminders (n=37), immunization information systems (n=26) and vaccine provider education and training (n=11).

Conclusions: Despite the diversity of countries included in this review in terms of geography and income, this review identified cross-cutting strategies that may improve HPV vaccine coverage.

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#4664

HPV Mallow Teens project - COOLTAS comics for young generation

06 - HPV prophylactic vaccines

Background/Objectives: The Mallow Flower Foundation works for HPV prevention and for gynecological cancers patient and caregivers in Hungary. The foundation also membert of ESGO-ENGAGe in Europe. The president, Icó Tóth/Ildikó NAgy-Tóth is a member of ESGO Prevention Committee. The foundation has several program to raise awareness about HPV and cervical cancer prevention, also other lesions and cancers caused by HPV. It has programs, campaigns for adults, parents, men (Gladiolus project www.kardviragok.hu) and for the young generation (Mallow Teens project). Each year we send online HPV educational packages for 2700 schools, information for the parents and separately for the young ones, girls and boys. WE organize online talks with HCPs. In Hungary, the HPV vaccine coverage is 84% at girls (national program has started in), at boys 60-70% (national program has started in 2020). It is crucial to talk about HPV in the appropriate channels, and languages regarding of the ages.

Methods: The foundation had a campaign 4 years ago on Musically (now TikTok) where we reached 90 000 young people, and collected 600 comments. We could see from it the knowledge of the human papilloma virus and also we could see the attitude of the families at the background. The following year we were running a campaign on Instagram, building on our last year experiements, and we have started to educate the young generation.

Results: From the results of the two campaigns, we have learnt that general HPV awareness campaign is not effective. We have to use different channels, languages. We invited some young people, girls and boys age 10-18 and established our Mallow Teens project. we gave them education, and we played. As a result, they all dreamed their avatar figures, and they told stories about HPV. Avatars went to a graphic designer, stories to a writer and comics was born: COOLTAS. Each day from 1 September 2022 one comic picture is shared on Instagram and also on Facebook channel too. Every month the gynecologist step out from the story and as live person shares a video. Comic is based on indirect information of HPV; the videos are based on direct information of HPV. We are also part of the Europaen Society of Gynecological Oncologist, ENGAGe network and ENGAGe Teens, so we can involve our teens community into european level too.

Conclusions: In order to achieve high HPV vaccination coverage, we must take into account generational differences, and in order to reach everyone, we must use own channels and languages.

References: Mallow Teens team: https://malyvavirag.hu/malyva-tinik-program Cooltas
Instagram: https://www.instagram.com/cooltas_malyva_tinik/ Cooltas Facebook: https://www.facebook.com/cooltasmalyvatinik

Cooltas

Hasche Daniel
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#4812

NEXT GENERATION L2-BASED HPV VACCINES CROSS-PROTECT AGAINST CUTANEOUS PAPILLOMAVIRUS INFECTION AND TUMOR DEVELOPMENT

06 - HPV prophylactic vaccines

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Background/Objectives: Licensed L1-VLP-based vaccines have been a great success in reducing anogenital cancers, but are limited regarding cross-protection against human papillomavirus (HPV) types not covered by the vaccine. Next generation vaccines induce broad cross-protection against highly conserved sequences of L2. We tested two novel L2-based HPV vaccine candidates, HPV16 RG1-VLP and CUT-PANHPVAX, in the preclinical model Mastomys coucha. These animals are naturally infected with the cutaneous Mastomys natalensis papillomavirus (MnPV), which induces cutaneous tumors.

Methods: In an exploratory setting, virus-free animals were vaccinated with HPV16 RG1-VLP, CUT-PANHPVAX, MnPV-VLPs (positive control) or PBS (negative control) prior to experimental MnPV-infection. Seroconversion against L2 peptides, presence of (cross-)neutralizing antibodies, viral load at the infection site and occurrence of skin tumors were examined. Microscopical examinations and immunofluorescent stainings were used to check the skin even for premalignant changes.

Results: Besides vaccine-specific seroconversion against HPV16 RG1 and CUT-PANHPVAX, the animals also developed cross-reactive antibodies against MnPV L2, which were cross-neutralizing MnPV pseudovirions in vitro. Like for the MnPV-VLP control group, both L2-based vaccines conferred in vivo protection since after experimental infection, viral loads in plucked hair were lower when compared to mock-vaccinated controls. Importantly, the formation of neutralizing antibodies, whether directed against L1-VLPs or L2, was able to prevent skin tumor formation. Consequently, while 83% of animals from the PBS group developed skin tumors, only 33% of the HPV16 RG1-VLP group, 17% CUT-PANHPVAX and 0% of those from the VLP group did so. Protected animals not even showed microscopical signs of MnPV infection in the skin.

Conclusions: For the first time, our study shows the proof-of-principle of two next generation L2-based vaccines that are currently entering clinical trials in an infection model with its genuine PV. Even across different PV genera, these L2-based vaccines have a promising efficacy to protect against HPV-induced skin tumors.

FC08- Free communications - Colposcopy / Management

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#5004

AGREEMENT AMONG COLPOSCOPISTS ON THE IDENTIFICATION OF THREE IMAGES MORE FREQUENTLY SEEN IN GLANDULAR CERVICAL PRECURSOR NEOPLASIAS

25 - Colposcopy

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Background/Objectives: To assess agreement among five colposcopists regarding the presence of three isolated colposcopic images more frequently seen in glandular cervical precursor neoplasias.

Methods: One colposcopist examined colposcopic images of patients treated between 2005 and 2018 and posteriorly revised the filed digital images with a second one. In this retrospective study, three independent colposcopists classified those colposcopic findings as normal, major, minor, or suspected of invasion, following international colposcopic terminology and evaluated the images for the presence of three isolated colposcopic images more frequently seen in glandular cervical precursor neoplasias, obstructed dilated grouped glands, aceto-white villi with invaginated borders, and atypical vessels in cylindrical epithelium area. The degree of agreement between the findings of the three colposcopists and the consensual findings of the two original colposcopists was assessed using the Kappa coefficient (κ).

Results: Images of 822 patients were evaluated, of which 67.4% had a diagnosis of cervical squamous intraepithelial neoplasias (CIN) grades 2 or 3, 6.8% of adenocarcinoma in situ, and 11.8% of CIN 1. The agreement for each isolated image ranged from κ 0.14 to 0.37 ($p < 0.001$). The highest agreements were found for aceto-white villi with invaginated borders (κ 0.15-0.37). The agreement among the degrees of colposcopic findings was higher for major (κ 0.29-0.46) and minor (κ 0.14-0.56) findings ($p \leq 0.001$).

Conclusions: The agreement among the three independent colposcopists and the consensual finding of two original colposcopists was statistically significant for the identification of three isolated colposcopic images more frequently seen in glandular cervical precursor neoplasias.

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Fig1, Tab1, Tab2, Tab3,Tab4

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#4719

Accuracy of colposcopy in the Swedish screening programme

25 - Colposcopy

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Background/Objectives: Colposcopy is an essential part of the screening programme aimed at detecting precancerous lesions and cancer in the cervix. The precision of this assessment is crucial as it determines whether and when biopsies should be taken. The issue of whether experience or professional background affect precision is debated. Several studies have shown similar sensitivity regardless of medical training background, and specially trained nurses, general gynaecologists, junior gynaecologists and colposcopists have been shown to perform equally well (1, 2, 3). Staff with shorter education or less professional experience, such as nurses and general gynaecologists, are prone to overestimate colposcopic findings and tend to compensate with multiple biopsies (1, 2). In contrast, a RCT showed that senior colposcopists performed better in detecting HSIL than junior colleagues (4). A retrospective German study yielded similar findings: the respective accuracy of colposcopists with < 2 years, 2-10 years and >10 years of experience in detecting HSIL was 87%, 85.3 and 90.2% (5). Studies on inter-observer agreement have reported low reproducibility (6, 7). The aim of this study was to investigate the accuracy of colposcopies in the Swedish screening programme, how accuracy has developed over time, the variability of assessment between colposcopists and how professional experience affects colposcopic accuracy in a routine setting.

Methods: We performed a cross-sectional study with data from the Process Registry in the Swedish National Cervical Screening Registry. All registered colposcopic assessments with a concomitant histopathological sample from women aged 18 years and up, performed between 1999 and September 2020 in Sweden was analysed. Accuracy of colposcopic assessments, calculated as overall agreement with linked biopsies, with three outcomes: Normal vs Atypical, Normal vs Low-Grade vs High-Grade Atypical, and Non-High-Grade vs High-Grade Atypical. A time-trend analysis was performed. Accuracy of identifiable colposcopists related to experience was analysed.

Results: In total 82 289 colposcopic assessments with linked biopsies were included for analysis of the outcome Normal vs Atypical; average accuracy was 63%. Overrating colposcopic findings was four times more common than underrating. No time trend in accuracy was noted during the study period. Accuracy in distinguishing High-Grade from Non-High-Grade lesions was better, 76%. Among identifiable colposcopists, overall accuracy was 67%. Some had significantly better accuracy than others, but no correlation to experience was found.

Conclusions: Colposcopy, including in a referral setting, has low accuracy in distinguishing Normal from Atypical. Increased experience alone does not lead to improvement. This is supported by the substantial differences in performance between colposcopists.

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#4720

MANAGEMENT AND STRATIFICATION OF PATIENTS WITH AGC-FN PAP SMEAR

18 - Methylation

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Background/Objectives: PAP-smears signed out as atypical glandular cells, favor neoplastic (AGC-FN) are rare (less than 0.1 %) and might be frequently associated with cervical precancer/cancer with the reported positive predictive value of 41-100%. Colposcopy/biopsy and diagnostic excisional procedures are routinely recommended as a management of patients with AGC-FN. However, AGC-FN reflects poor cytological reproducibility and specificity as it may be associated with benign conditions of the cervix and with cancers of other parts of the female genital tract. Therefore, this study explores the value of the HPV test and methylation test as a co-test in stratifying patients with AGC-FN cytology for further management.

Methods: We have been prospectively collecting AGC-FN PAP smears (both conventional (CC) and liquid-based (LBC)) signed out in Biopticka laboratory, Pilsen (BL), between 2017-2021. In the case of CC, it was supplemented by a subsequent LBC smear. Residual LBC material was used for HPV genotyping by a set of PCR targeting L1, E1, and E6/E7 regions and the methylation assay (QIAsure Methylation Test, QIAGEN). Patients were followed either at the Center of Oncological Prevention (COP) of the OBGYN Department, Medical Faculty Hospital, Pilsen, or by referring specialist and treated according to current Guidelines of the Czech OBGYN Society. In case of surgery (cone biopsy, hysterectomy), histologic results were obtained.

Results: There were 3 907 487 PAP smears performed in BL between 2017-2021. AGC-FN represented 0.08% (318). Seventy-three patients fulfilled the inclusion criteria of the study. All patients in HPV+/methylation+ subgroup (53 patients) presented some cervical pathology (10 [18.9%] invasive cervical cancer, 24 [45.3%] HSIL, 11 [20.8%] AIS, 6 [11.3%] AIS+HSIL, and 2 [3.8%] LSIL. HPV+/methylation- subgroup consisted of 11 patients. 6 of them (54.5%) presented AIS and/or HSIL, 1 had LSIL, and 4 (36.4%) were without dysplasia. There were six patients in the HPV-/methylation+ subgroup. Four of them (66.7%) had an invasive disease (3 endometrial cancer, 1 gastric type of cervical adenocarcinoma), 1 patient had ALEGH (atypical lobular endocervical glandular hyperplasia), and 1 was without dysplasia. HPV-/methylation- subgroup consisted of three patients (1 with HGSC - high-grade serous carcinoma - of the endometrium, 2 without dysplasia).

Conclusions: AGC-FN PAP smear is frequently associated with cervical precancer/cancer and cancer of other parts of the female genital tract. We show that the HPV co-test can identify patients with a high probability of cervical pathology (HPV+). In the HPV negative subgroup we recommend an examination of the uterine cavity and pelvic organs (hysteroscopy + endometrial biopsy; pelvic ultrasound) in addition to colposcopy/biopsy. In our experience, irrespective of HPV status, a positive methylation test predicts precancer or malignancy.

References: Funding: Study was supported by grant: FNPl 00669806/Ministry of Health of the Czech Republic

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#4882

Active surveillance of CIN2 in young women - a prospective cohort study

25 - Colposcopy

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Background/Objectives: With active surveillance of cervical intraepithelial lesion (CIN)2 the harmful effects of treatment might be avoided and the potential of spontaneous regression maximized in young patients. The purpose of this study was to investigate the regression and progression rates of CIN2 lesions in young women during two years.

Methods: This prospective cohort study at Helsinki University Hospital included 212 women aged 18-30 years with histologically confirmed CIN2 lesions, satisfactory colposcopy and lesion size less than ¾ of the transformation zone. At baseline, all women provided a cervical swab which was tested for 14 high-risk HPVs and for 20 low-risk HPVs. Women were followed at the colposcopy clinic every 6 months up to 24 months. The primary outcome was stratified into four groups: regression, progression to CIN3+, persistence of CIN2 and partial regression defined as histological or cytological low-grade squamous intraepithelial lesion (LSIL).

Results: The regression rate of CIN2 lesions was 60.9% (n=129) while 14.6% (n=31) of the lesions progressed to CIN3+. Stage IA cervical cancer was diagnosed in three women and one woman had adenocarcinoma in situ. Nearly half of the progressions (48.4%) were detected at the first 6-monthly visit. Partial regression was found in 20.8% (n=44) of the women and 3.8% (n=8) of the lesions persisted. The most frequent HPV-genotype at the baseline was HPV16 (42.0%) followed by HPV31 (31.2%) and HPV52 (9%). HPV16 was present in 58.1% of the women with a progressive lesion whereas 55.2% of the women with a HPV16-positivie lesion had their CIN2 regressed.

Conclusions: The majority of CIN2 lesions regress in young women and progressions appear to be detected mostly early on during follow-up. Adherence to follow-up is crucial and the patient has to be adequately informed on the risks of both local treatment and active surveillance to enable shared decision making.

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#4884

INTRAOPERATIVE HUMAN PAPILLOMAVIRUS TEST AS AN EARLY MARKER OF CERVICAL HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION TREATMENT FAILURE

23 - Diagnostic procedures / management

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Background/Objectives: Loop electrosurgical excision procedure (LEEP) is the standard treatment of cervical high-grade squamous intraepithelial lesion (HSIL). Despite treatment, approximately 15% of treated patients will present residual disease or recurrence after treatment. Current guidelines recommend a cytology with HPV test at 6 months given its high sensitivity and negative predictive value for the detection of disease recurrence. The aim of the study is to evaluate if the intraoperative (IOP) HPV test has the same prognostic value for the detection of disease recurrence at 24 months as the HPV test performed at 6 months. Here we present the preliminary results of women who have completed the 6-month follow-up.

Methods: Multicentre prospective cohort study of women diagnosed with cervical HSIL/CIN2-3 treated with LEEP at 22 hospitals in Spain between May 2020 and December 2021. Immediately after the LEEP, an HPV test was taken. Follow-up was performed according to the national guidelines at the time of the study. We compare the IOP-HPV test with the results observed at 6 months and the conization margins using multivariate logistic regression analysis.

Results: A total of 1884 women undergoing treatment for HSIL during the study period were included. At the time of diagnosis, cytology result was HSIL+ in 1078 (60%) of cases. HSIL/CIN2-3+ was confirmed by cervical biopsy and endocervical curettage in 1497 (80%) and 356 (19%), respectively. The HPV test was positive in 1591 (96%) of cases: 787 (49%) were positive for HPV16, 103 (6%) for HPV18 and 800 (50%) for non16/18 genotypes. A LEEP was performed in all cases and the conization specimen confirmed HSIL in 1405 (78%), adenocarcinoma in situ in 20 (1%) and invasive carcinoma in 39 (2%). The endocervical margin was involved in 292 (16%) of cases and the exocervical margin in 206 (12%). An optimal sample for IOP-HPV testing was obtained in 98% of cases and was positive in 712 (40%). Follow-up data at 6-months was available for 1249 women. Cytology result was negative in 1049 (83%), ASCUS/LSIL in 151 (12%), and HSIL+ in 29 (2%). The HPV test at 6 months was positive in 296 (24%) of cases: 97 were positive for HPV 16, (33%) 12 for HPV18 (4%) and 200 (68%) for non16/18 genotypes. The IOP-HPV test was associated to the 6-month HPV test (OR 2.16, 95%CI 1.63-2.86, $p<0.001$) and conization margin (OR 1.96, 95%CI 1.43-2.68; $p<0.001$) on multivariate analysis.

Conclusions: The preliminary results at 6-months confirm that the IOP-HPV test is a feasible test and could have a prognostic value to detect early recurrence of treated cervical HSIL.

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#4921

Practical application of modified ASCCP 2019 algorithms in the diagnosis and early detection of cervical pathology.

16 - Screening methods

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Background/Objectives: Objectives: We assessed the risk for the high-grade precancerous CIN 2 (+) in women with HSIL and ASC-H depending on HPV status.

Methods: Methods: A retrospective analysis of results of cervical cancer screening following the current ASCCP recommendations by co-testing (LBC and molecular HPV DNA HR) performed between 2018 and 2022 in the Laboratory of Cervical Pathology, Obstetrics and Gynecology Hospital of Poznań University of Medical Sciences. Patient ages ranged from 22 to 72 years.

Results: Results: The analysis of abnormal results of liquid-based cytology revealed the following: 1 suspicion of cervical carcinoma, 49 HSIL, 97 ASC-H, 95 LSIL, 92 ASCUS, and 4 AGC cases. Histopathological verification of the biopsy samples revealed a total of 288 abnormal results. CIN 2 (+) lesions were found in 127 women. ASC-H was the most common abnormal cytologic finding. Of the 338 molecular test results for HPV DNA HR, 85% were confirmed positive. A positive molecular signal confirming the presence of human papillomavirus on PAP smear was not homonymous with simultaneous histopathological diagnosis of cervical pathology.

Conclusions: Conclusions: There is a high risk for CIN 2 (+) in patients with HSIL and HPV 16 (+) and/or HPV DNA HR (+), as well as ASC-H and HPV 16 (+). HSIL is rarely observed in women with HPV 16 (-). The risk for CIN 2 (+) in women with ASC-H and HPV (-) is low.

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#4761

COMPREHENSIVE CHARACTERIZATION OF 751 VULVAR LESIONS, ORIGINALLY DIAGNOSED AS HIGH-GRADE VULVAR INTRA-EPITHELIAL NEOPLASIA

27 - Vulvar diseases and neoplasia

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Background/Objectives: High-grade vulvar intra-epithelial neoplasia (VIN) is categorized into high-grade squamous intraepithelial lesion (HSIL) and differentiated vulvar intraepithelial neoplasia (dVIN). Given the distinct cancer risk between HSIL and dVIN, adequate diagnosis is essential for optimal treatment but can be challenging. In this study we aimed to comprehensively characterize a large population-based series of vulvar lesions, originally diagnosed as high-grade VIN.

Methods: From a historical cohort, of 894 patients diagnosed with incident high-grade VIN without concurrent or history of vulvar cancer between 1991 and 2011, tissue blocks were retrieved and subjected to integrated analyses by revision of histopathology, immunohistochemical staining of p16INK4a and p53, and HPV DNA testing and genotyping.

Results: In total, 751/894 (84%) tissue blocks from vulvar lesions originally diagnosed as high-grade VIN (743 HSIL and 8 dVIN) were available. Histopathological categorization after revision with integrated analyses resulted in 665 (88.5%) HPV-associated lesions (87 (11.6%) viral/LSIL, 575 (76.6%) HSIL and 3 (0.4%) VSCC) and 76 (10.1%) HPV-independent lesions (31 (4.1%) non-dysplastic lesions, 44 (5.9%) dVIN and 1 (0.1%) VSCC). Inconclusive were 10 (1.3%) vulvar lesions. It was striking that 84% of dVIN was originally not reported as dVIN, while for HSIL this was 0%. Downgrading occurred in 118/741 (15.9%) of cases. In HSIL, HPV DNA was detected in 99.6% (including HPV type 16 in 81.1%). In accordance, 99.0% showed block type p16INK4a staining. In viral/LSIL, HPV DNA was detected in 90.6% (including HPV type 16 in 50.0%) and 33.3% showed block type p16INK4a staining. In HPV-associated lesions, a p53 mid-epithelial wild-type staining pattern was common (48.4%) while this pattern was not observed in HPV-independent lesions. One (0.2%) HSIL showed mutant p53 staining. Off all dVIN, 75.0% showed mutant p53 staining. One (2.3%) dVIN showed block type p16INK4a staining, only in combination with mutant p53 staining. Co-infection with HPV was observed in 15.2% dVIN (including HPV type 16 in 60.0%), only in combination with negative p16INK4a staining and mutant p53 staining.

Conclusions: To conclude, immunohistochemistry by p16INK4a and p53 is strongly recommended for optimal categorization of HPV-associated and HPV-independent vulvar lesions. One should be aware of the pitfalls when using those biomarkers. HPV-independent vulvar precursor lesions with a high cancer risk are poorly identified and show a wide morphological spectrum, emphasizing the need for diagnostic biomarkers.

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#5802

CERVICAL SMEAR EVALUATION BY RNA-BASED QUANTIGENE-MOLECULAR-PROFILING-HISTOLOGY ASSAY REPORTS DIAGNOSIS AND PROGNOSIS FOR LESION SEVERITY AND DEVELOPMENT

21 - New technologies

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Background/Objectives: Background: Nucleic acid-based cervical (pre)-cancer (CxCa) screening tests report risk for dysplasia but not dysplasia severity or prognosis for progression or regression. While sensitivity is high, specificity is low leading to overcalling, and overtreatment. Additional triage tests (cytology, p16/Ki6, methylation markers) need to be done. We developed and validated a multiplexed, quantitative, low-complexity, and cost-efficient HPV-oncogene and cellular-biomarker mRNA-detecting assay (QG-MPH) for molecular profiling of cervical smears. Algorithms calculate different risk scores (RS) for prediction of CIN2, CIN3, or cancer. The triage study (FACTS) aimed at resolving equivocal findings from standard screening methods and compared QG-MPH RS results to histopathology.

Methods: Methods: QG-MPH assay was done on 115 cervical smears from MPG-PCR high-risk (HR)-HPV positive women diagnosed with CIN3 by histopathology. Concordance and discordance of QG-MPH RS- and histomorphology-based diagnoses were investigated for HPV genotype composition and viral E7 mRNA expression-strength by QG-MPH. Methodically independent methylation marker test (Gyntect, Oncgnostics) and targeted RNA sequencing by ciRNAseq (Predica Diagnostics BV) were done to substantiate RS prognostic validity.

Results: Results: Of 115 patients with CIN3, 45 (39%) were correctly identified with a RS-CIN3 by QG-MPH but 34 (30%) were underrated having RS≤CIN2 and 36 (31%) overrated having RS-CxCa. HR-HPV genotype detection by QG-MPH E7 mRNA detection differed between RS classifiers. 19 (56%) in underrated RS≤CIN2, 4 (8.8%) in correctly identified RS-CIN3, but 0 in CIN3 overrated as RS-CxCa appeared E7-transcript negative. HPV16/18 prevalence in RS≤CIN2 was 8.8%, in correctly identified RS-CIN3 was 53.3%, and in samples overrated as RS-CxCa was 66.7%. The 7 most carcinogenic genotypes were present in 20.6%, 31.1%, 38.9%, while potentially carcinogenic genotypes in 14.7%, 6.7%, 8.3%, respectively. In the methodically unrelated methylation marker test the 6 target genes got progressively methylated reaching the CIN3+ cut-off in 22.6%, 56.5%, 77.8%, respectively. CiRNAseq analysis identified consistently progressively upregulated mRNAs from smears with RS≤CIN2 via RS-CIN3 to RS-CxCa, pointing at increasing level of cellular malignant transformation.

Conclusions: Conclusion: QG-MPH specifically detects and diagnoses cervical dysplasia severity. RS results differing from histomorphology may reflect lesion biology and malignant potential. Concordance of QG-MPH RS-classifiers with other progression risk markers suggests prognostic validity for dysplasia progression or regression, a unique feature. Longitudinal studies are warranted.

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#4833

"TIME IS ON MY SIDE" * DISEASE TRAJECTORY OF VULVODYNIA: A SYSTEMATIC REVIEW WITH A NARRATIVE SYNTHESIS

27 - Vulvar diseases and neoplasia

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Background/Objectives: Vulvodynia embraces in its etymology two health areas that are arguably neglected, i.e., external genitalia and chronic pain. It is defined as vulvar pain with a duration of at least three months, without a clear identifiable cause, which may have potential associated factors. The literature regarding this condition, which is scarce and discordant, reflects the secondary importance awarded to vulvodynia, despite its not negligible incidence of 7-15% in the general population. In fact, papers on the topic mainly consist of expert opinions or small sample size studies, which lack an adequate experimental design or a comparison with placebo. This results in a still unsatisfactory understanding of the disease's persistence, remission, and relapse rates. Addressing affected patients' distress holding such scarce knowledge constitutes a real challenge for physicians. The aim of this review was to shed light on the disease-trajectory of vulvodynia and identify potential risk factors which may affect such trajectory.

Methods: This systematic review (not registered in PROSPERO) was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A systematic literature search was conducted between March and April 2022 using the electronic database PubMed (last search conducted on April 25th 2022). The search strategy included terms combined with the Boolean operators "OR" and "NOT"; the final string research was the following: "vulvodynia OR vestibulodynia NOT menopausal NOT cancer NOT menopause NOT lichen". Non-original articles, abstracts and papers not written in English were excluded. Due to the exiguous number of retrieved studies and the heterogeneity in diagnosis modality and outcome measures, the data extracted from the included articles was summarized using a narrative approach, rather than a quantitative methodology.

Results: Five articles were included (total participants: 879 women with vulvodynia; 634 controls). Up to 50.6% of women reported remission at a two-year follow-up. Remission with relapse was observed in 26-39.7% at a two- to 25-year follow-up. Persistence throughout time occurred in 9.6% at a two-year follow-up. A decrease in pain was observed in 71.1% of patients (seven-year follow-up), while persistence occurred in 28.9%. Mean pain scores and depressive symptoms resulted lower at two-year follow-up, whereas sexual function and satisfaction were increased. Factors associated with remission of vulvodynia were greater couple cohesion, decreased reporting of pain after intercourse and lower level of worst pain. Risk factors for symptom persistence included marriage, more severe pain ratings, depression, obesity, pain with partner touch, interstitial cystitis, pain with oral sex, fibromyalgia, older age, primary vulvodynia, generalized vulvodynia, and anxiety. Recurrence was associated with: longer duration of pain, more severe ratings of the worst pain ever and pain described as provoked.

Conclusions: Symptoms of vulvodynia seem to improve over time, regardless of treatment. Considering the possible deleterious consequences of vulvodynia on women's lives, evidence regarding an improvement of symptoms over time is fundamental.

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#5643

Exploring the value of focused ultrasound ablation therapy for fertility protection in women of childbearing age with cervical lesions: protocol of a prospective cohort study

18 - Methylation

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Background/Objectives: Persistent high-risk HPV infection causes precancerous cervical lesions and subsequent progression to cervical cancer. HPV infection is very common in women of childbearing age with factors such as early onset of sexual activity. Treatment such as cold knife conization is usually used for women of childbearing age with CIN2+, which may cause delayed fertility, cervical insufficiency and other adverse pregnancy outcomes during subsequent pregnancies. Focused ultrasound (FUS) is a non-ionizing, non-invasive treatment method that is used to treat gynecological conditions such as cervicitis and vulvovaginal disease. The purpose of this study is to verify the treatmeat value of FUS and whether the PAX1m and JAM3m can be as the biomarker for follow-up after the treatments of CIN2+.

Methods: A protocol will be developed to evaluate the value of focused ultrasound in the treatment of women of childbearing age with cervical lesions and for fertility preservation based on statistical principles.

Results: This is an observation prospective cohort study with a 2-year follow-up, which will be conducted in The Third Affiliated Hospital of Zhengzhou University. The Institutional Review Board of The Third Affiliated Hospital of Zhengzhou University approved the study. All patients read and sign their written inform consent before enrollment. The data used in this study are collected from patients who meet the following criteria: (1) Patients over 18 years with histological CIN2 and CIN3 with TZ 1 and 2. (2) Have the need for family planning. The exclusion criterion is as follows: patients who are pregnant or lactating; who had cervical conization, LEEP and CKC within 6 months, who had vaginal lavage within 24 hours, and who were clinically observed obvious acute or subacute inflammation of the cervix or vagina are excluded. Patients will be randomly divided into two groups, each with a different treatment method. The treatment methods are (1) FUS treatment and (2) invasive treatment. The baseline and follow-up visits plan at before the treatments start, and 3, 6, 12, 18, and 24 months after treatment. If lesion progresses, terminate follow-up, and receive standardized treatment. All data will be obtained by the physician responsible for collecting the data. Participants undergo a full physical examination and basic information collection and psychological scale assessment is completed through a face-to-face interview. All biochemical test results (PAX1m and JAM3m detection,human papillomavirus test, thin layer liquid cytology test, colposcopy and pathology, etc.) will be obtained from recent medical records. Follow-up visits will take place at 3 months, 6 months, 12 months, 18 months, and 24 months.

Conclusions: The study also closely monitors the pregnancy status of patients with fertility needs and hopes to confirm through follow-up studies that there is no significant difference in the outcome of cervical lesion treatment with focused ultrasound ablation compared to the conventional invasive treatment group, that there is no negative impact on pregnancy in women of childbearing age, that there is no additional unnecessary waiting time, that pregnancy preparation can begin 1 month after treatment, and that there are fewer complications during pregnancy. This confirms the value of ultrasound ablation for fertility protection in women of childbearing age with cervical lesions and PAX1m and JAM3m can be as the biomarker for follow-up after the treatments of CIN2+.

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#4828

LONG TERM EFFICACY OF FAT GRAFTING IN VULVAR LICHEN SCLEROSUS: AN OBSERVATIONAL RETROSPECTIVE STUDY

27 - Vulvar diseases and neoplasia

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Background/Objectives: Autologous fat grafting has been used for several decades for the restoration of volume and function in various tissue disorders, also due to its regenerative and immunomodulatory proprieties and its negligible morbidity. Its effectiveness in the treatment of Vulvar Lichen Sclerosus (VLS) has been analyzed in few studies, which are mainly based on a short-term follow-up. The aim of our study was to evaluate middle-long term efficacy of fat grafting in the treatment of VLS.

Methods: A total of 85 women with a histological diagnosis of VLS received at least one treatment with autologous fat grafting between November 2010 and December 2020 in our institution. All women had received a standard three-month treatment with topical corticosteroids (TCS) prior to the fat grafting and were deemed eligible for surgery if they reported a persistence of symptoms despite treatment with TCS. We were able to contact 71 of the 85 women for a clinical re-evaluation between November and December 2021. At time of re-evaluation, patients underwent a vulvoscopic examination comprehensive of a vulvar biopsy and were asked to fill in validated questionnaires regarding their psychosexual health (FSFI and HADS questionnaires), their symptoms (NRS scale) and their satisfaction with the received treatment (Likert 1-5 scale). The main outcome of the study was patients' satisfaction. The secondary outcomes included modifications of symptoms, psycho-sexual wellbeing, vulvar trophism and histological findings following surgery.

Results: Patients' demographic and clinical characteristics are reported in Table 1. The mean follow-up time was 5.4 years (range 2-11 years).Overall, 63/71 (88.7%, 95%, CI 79.0-95.0) women were satisfied with the procedure, and the level of satisfaction remained remarkably high throughout the years (Table 2). Symptom-related questionnaires revealed a substantial reduction in pruritus, burning and dispareunia following surgery ($p<0.05$) (Table 3). At time of re-evaluation, all mean FSFI parameters for sexual function were significantly improved and depression and anxiety were significantly reduced ($p<0.05$). Pre- and post-surgery evaluations of vulvar architectural were not significantly different, while the need for TCS was significantly reduced at time of follow-up ($p<0.0001$). As what regards the histological analysis, the inflammatory infiltrate was stable or reduced in nearly two thirds of women, elastic fibers were comparable or restored in more than two thirds of women and estrogen receptor expression was stable or improved in around 90% of women. No cases of vulvar intraepithelial neoplasia (VIN) or invasive vulvar cancer occurred during follow-up.

Conclusions: In our case series, fat grafting was effective in the treatment of VLS following first-line treatment with TCS. Patients reported that fat grafting resulted in a reduction of symptoms, an increase in sexual function and wellbeing and a decrease in the need for TCS. Moreover, histological and structural modifications resulted stable or improved in the majority of women. The efficacy of fat grafting is detectable up to 11 years following the surgical procedure and as such we believe it may represent a valid therapeutic option in selected cases of VLS.

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#4483

HPV (GENITAL WARTS IN PREGNANCY)-DIAGNOSIS AND A NEW THERAPEUTIC APPROACH THE CAUSE OF LARYNGEAL POLYPS IN CHILDREN

41 - Fertility and HPV

Background/Objectives: HPV infection is an epidemic of modern age with the highest number of infected girls between 18 and 30 years of age and the most common diagnosis are genital warts in early or developed stage at first born women .Due to the alerted immune status during pregnancy the spreading of HPV infection is progressive .During the labor any retention of the child in the birth canal leads to aspiration of HPV particles witch further represents the most common cause of laryngeal papillomatosis in children.

Methods: The study involved 60 pregnant women between 18 and 30 years of age diagnosed with genital warts in early and advanced stages that were treated with RF technique which enables the smooth vaginal delivery with no signs of HPV infection on genito-anal region. Radio wave technique involves a special combination of radio wave access evaporisation and radio wave melting . Radio wave access evaporisation causes the evaporation of HPV infected cells and by radio wave melting we get the bloodless removal of condyloma.

Results: With Colposcopic examination we reveal subclinical stages of genital warts on the mucous membrane of the labia and the entrance to the vagina, and genital warts on the cervix which provides conditions for their immediate removal. The result of radio wave therapy is a bloodless surgical field with a precise and controlled removal of all forms of genital warts in one act throughout pregnancy. Operation is performed only under local anesthesia with a minimum damage to the surrounding healthy tissue , rapid recovery without accompanying infection, bleeding, recurrence, and a complete protection to the mother and fetus.

Conclusions: Genital warts during pregnancy represent a risk to the fetus during vaginal childbirth regardless of the severity of the clinical picture. Absence of colposcopic diagnosis, avoiding removing warts in the pregnancy, use of the wrong treatment leads to progress of condylomata as for outputting an infection of the fetus, by aspiration of HPV particles in the birth canal with later occurrence of laryngeal polyps in children up to 15 years. Radio wave technique removes genital warts without harmful effects on the course of pregnancy (mother -fetus) so as to avoid indicated caesarean section, and allows a smooth vaginal delivery, witch is the gold standard obstetrics.

References: 1. Patented the special technique of radiowave LOOP excision with radiowave vaporization as a method of treatment of choice with difficult cases of dysplasia on PVU (CIN I,CIN II, CIN III) 2. Patented the special technique of removal of condyloms on vagina and mucous membrane of labia (radiowave vaporization) 3. Patented the technique of removal of giant anal and intraanal condyloma, with the use of the mixed technique of radiowave vaporization and excision, without bleeding 4.Patented a special radio wave technique for the removal of condylomas during pregnancy

Condylomas in pregnancy

FC06- Free communications- Methylation 1

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#4929

CAN HPV GENOTYPING AND METHYLATION TRIAGE FACILITATE A PURELY MOLECULAR SCREENING OF YOUNG WOMEN 23-29 YEARS OLD?

10 - HPV screening

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Background/Objectives: In Denmark, women 23-29 years are offered cervical screening by cytology. Women <30 years has the highest HPV prevalence of all screening age groups (23-64 years), and the paradigm has been that introducing HPV screening for this age group will generate substantial over-referral. However, the first childhood vaccinated age cohorts are entering the screening program, and HPV prevalence is substantially reduced with HPV16 and HPV18 almost eradicated. Here we evaluate referral rates and clinical outcome using HPV testing with methylation triage as substitute to cytology.

Methods: An enriched cohort of 294 HR-HPV positive samples were collected from women aged 23-29 years attending the cervical cancer screening program in the Capital Region of Denmark. Routine cytology outcome was 184 NILM, 13 ASCUS, 17 LSIL, 6 ASC-H, and 66 HSIL; standard of care refers ASC-H and HSIL for colposcopy and biopsies. All samples were subsequently tested using the BD Onclarity HPV test (BD Diagnostics, Sparks, MD) and the QIAsure FAM19A4/miR124-2 methylation biomarker assay (Qiagen, Hilden, Germany). Data on routine cytology and histology outcomes were retrieved from the National Pathology Database. The study is a quality development study approved by AHH-Hvidovre Hospital.

Results: Of the 294 HR-HPV positive samples, 28% (N=82) were hypermethylation positive, 67% (N=196) hypermethylation negative and 5% (N=16) were invalid. Subsequent data analysis is conducted on all samples with a valid methylation test result (N=278). Overall, 39% (N=108) of the HP-HPV positive samples harbored one or more of the 5 highest risk HPV genotypes HPV16, 18, 31, 33, 51 and 39% (N=42) of these were hypermethylation positive. Of the HR-HPV positive samples, 34% (N=94) were referred for follow-up based upon the routine cytology. When modelling HPV testing combined with methylation, the referral of dual positives would be 30% (N=82). From cytology screening, 64 women were referred for colposcopy and biopsies with 60 resulting samples. Of these, routine cytology resulted in 58% (N=35) ≥CIN2 where 77% were methylation positive on the index sample.

Conclusions: HPV screening with methylation triage for women <30 years will not generate over-referral compared to the current cytology policy. Moreover, the majority of the detected ≥CIN2 are dual positive for HPV and methylation. As FAM19A4/miR124-2 is known to detect virtually all cancers, an HPV screening strategy for women <30 years combining HPV test and methylation could be both safe and result in lower referral rates than the current Danish cytology screening for this age group with a focus on those young women at highest risk for severe disease.

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#4950

ScreenYu Gyn® - cervical cancer screening triage based on a single DNA methylation marker

18 - Methylation

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Background/Objectives: Accurate clarification of women with HPV positive test results or abnormal cytology findings during routine screening is important in order to reduce both, overtreatment as well as long watchful waiting periods. Different strategies are discussed, among others DNA methylation markers show a high potential. Detecting DNA methylation is, however, not yet automated, and detecting a set of markers is still expensive and time-consuming. As a first step towards a simplified test, we developed and validated an assay, now CE IVD-marked as ScreenYu Gyn, based on a single DNA methylation marker, ZNF671, to detect cervical cancer and its relevant precancerous lesions using cervical scrapes.

Methods: ScreenYu Gyn is a duplex methylation-specific real-time PCR assay using TaqMan probes for the detection of the amplicons. ZNF671 and ACTB as quality control are amplified in a single tube reaction after bisulfite conversion (EZ DNA Methylation Lightning Kit, Zymo Research) of the clinical sample. One mL of a cervical smear collected in PreservCyt medium (ThinPrep, HOLOGIC) is used for bisulfite treatment, and 10µL of the 15µL eluate are used for the PCR. The analytical sensitivity and specificity of the assay was determined using in vitro methylated DNA as well as unmethylated DNA from healthy volunteers. Furthermore, a clarification cohort comprising >600 residual cervical scrapes was used to determine clinical performance of the ScreenYu Gyn assay.

Results: Using 20ng or 100ng DNA in total, ScreenYu Gyn has an analytical sensitivity of 0.1% methylated DNA in a background of unmethylated DNA. 100% unmethylated DNA does not show any signals up to 750ng template. Clinical performance was determined on the cobas z480 PCR cycler from Roche and the CFX96 Touch from BioRad. Sensitivity for CIN3+ was 65.2% on the cobas z480 and 64.8% on the CFX96. Specificity regarding healthy samples was 91.8% on the cobas z480 and 90.7% on the CFX96. In comparison to the GynTect assay, tested on different cohorts, GynTect sensitivity for CIN3+ is similar (62.5%), but specificity on healthy samples is slightly better for the six-marker assay GynTect (96.0%). Both assays detected all cancer cases.

Conclusions: The single DNA methylation marker assay ScreenYu Gyn shows good analytical and clinical performance. The test is CE IVD marked since 2022. Compared to the six-marker assay GynTect, ScreenYu Gyn is non-inferior regarding CIN3+ sensitivity, but shows slightly lower specificity on healthy samples. Reduction to only one marker seems to be promising, as a simplification is needed for a broader use of DNA methylation-based assays in routine screening.

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#4374

Comparing costs and diagnostic outcomes of replacing cytology with the QIAsure DNA methylation assay as a triage within HPV primary cervical cancer screening in the Netherlands

10 - HPV screening

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Background/Objectives: Detecting hypermethylation of tumour suppressor genes could provide an alternative to cytology within HPV primary cervical screening. In programmes with self-sampling, methylation detection removes the need to return to clinic after a positive HPV self-sample. The impact of using the QIAsure® Methylation Test (QIAGEN) to guide colposcopy referral on CIN3+ diagnoses, loss to follow up (LTFU), unnecessary colposcopies and programme cost/cost-effectiveness is unknown. The objective of this work is to assess the costs and diagnostic outcomes of using the QIAsure FAM19A4/hsa-mir 124-2 DNA methylation assay to guide colposcopy referral after an HPV-positive result compared to cytology (standard of care, SoC) in the Netherlands cervical screening programme.

Methods: The model structure (Excel decision tree) and input variables (probabilities, costs of sample collection, tests, colposcopy) were informed by published studies, manufacturer data and surveillance reports (Netherlands eligible cohort: 807,609 invited with 56% uptake). Outcomes for routine and follow-up screens were included (cost/clinical). The proportions self- (8.6% to 50%) and clinician-collected (91.4% to 50%) were varied. Two studies informed scenarios for the sensitivity/specificity of the QIAsure methylation assay versus cytology [1,2].

Results: Scenario 1 (higher specificity/sensitivity to detect CIN3+ for methylation than cytology [1], 50% self-sample). Using the QIAsure methylation assay resulted in a lower cost per screen (€55.85 vs. €58.67) compared to SoC, a 4% reduction in the total annual cost of the screening programme (€23.8m vs. €24.7m), a 36% reduction in LTFU (7,321 vs. 11,403), 17% more CIN3+ diagnoses (5,419 vs. 4,616) and 11% fewer unnecessary colposcopies in people with ≤CIN1 (6,082 vs. 6,808). Scenario 2 (lower sensitivity/specificity to detect CIN3+ for methylation than cytology [2]; 50% self-sample), methylation also resulted in a lower cost per screen than SoC (€49.95 vs. €50.11) and less LTFU (5,414 vs. 8,502) but led to 76 fewer CIN3+ diagnoses and more unnecessary colposcopies. In both scenarios, increasing the proportion of self-samples (from 8.6% to 50%), reduced the cost per screen by up to 17% (difference €8.51 to €9.86).

Conclusions: Although evidence supporting the clinical performance of the QIAsure methylation assay relative to cytology is limited, its use could result in more CIN3+ detection whilst reducing unnecessary colposcopies, LTFU and overall costs, making it a viable alternative to cytology to guide colposcopy referral within cervical screening.

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#4791

FROM HISTOLOGICAL CLASSIFICATION TO A CONTINUOUS SCORE: USING EPIGENETIC DATA TO ASSESS HETEROGENEITY OF CERVICAL LESIONS

18 - Methylation

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Background/Objectives: In cervical cancer screening, there is a substantial overdiagnosis that can lead to overtreatment [1]. It is therefore important to separate advanced from early lesions. Emerging technologies open possibilities for more effective and less harmful screening, taking into account the individual risk of developing cancer [2]. Epigenetic testing seems to be the next game breaker in term of cervical lesion diagnosis and several methylation sites have been proved to be linked to cancerous and precancerous lesions [3]. Previous work showed DNA hypermethylation status can be translated into a continuous probability for lesions to turn into cancer [4-5]. This work aims to construct a continuous score for the severity of cervical lesions based on hypermethylation data from cervical biopsies.

Methods: 126 cervical lesions biopsies from the Pathology Department (VU University Medical Center, Amsterdam, The Netherlands) [6] were categorized by 3 pathologists into no dysplasia/CIN1, CIN2, CIN3, or cancer by classical histomorphological grading criteria, and by an immunoscore grading system (cumulative value: 0-6) based on Ki-67 (score: 0-3) and p16ink4a (score: 0-3) expression. Lesions were analysed for hypermethylation of CADM1, MAL, miR124-2, FAM, PHACTR, PRDM, GHSR, SST_M1 and ZIC1_M2 genes (see figure 1 and 2) and categorized in 3 groups each. An Item Response Theory model (IRT) was applied to the methylation scores to obtain a latent score. Unidimensionality and monotonicity were checked and item selection based on item discrimination was applied to avoid local dependencies between the methylation scores. Results are displayed as a continuous score linked to the histological status. ROC curves are created to evaluate the accuracy of latent score for diagnosing cancer and precancerous lesions.

Results: An IRT model with three biomarkers GHSR, PRDM and ZIC1_M2 gave an adequate description of the data and unidimensionality and monotonicity assumptions were not violated. The association between the CIN classification and the latent score created is showed in figure 3. 21/22 cancer lesions had the highest latent score 1.20. 10/23 CIN3 lesions were scored the highest and ranged from -0.829 to 1.20 with a median at 0.577. CIN2 and CIN1/no lesion scores range were from -1.43 to 1.20 with a median respectively at -0.067 and -0.829. Diagnostic characteristics of the latent score to diagnose cancer and CIN3+ lesions AUC with CI95% are respectively 92.2% [88.5% - 95.9%] and 89.0% [83.1% - 95.0%] (figure 4).

Conclusions: IRT model using methylation data can be used to create a continuous lesion severity score. It showed good agreement with morphological histological classification. This score helps to assess the heterogeneity of precancerous lesions, especially CIN2 and CIN3. Further work should be done to validate our score in independent larger biopsy series.

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Figures

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#4721

MED-SEQ, A NOVEL METHOD FOR GENOME-WIDE DNA METHYLATION DETECTION, CAN BE USED TO CHARACTERIZE DIFFERENT GYNECOLOGICAL CANCERS AND ASSOCIATED HPV SUBTYPES

18 - Methylation

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Background/Objectives: DNA methylation and the presence of HPV subtypes serves as an important markers in cancer, is applied to classify tumors and can predict disease outcome and treatment options.

Methods: We developed a novel method that generates genome-wide methylation profiles associated with pre-cancer and cancer at very low cost. The assay involves isolation and purification of DNA from formalin-fixed paraffine-embedded (FFPE) or fresh biopsies (only 10-50ng DNA is needed). This Methylated DNA sequencing (MeD-seq) assay is very robust, allowing detection of DNA methylation at more than 50% of the 30 million CpGs present in our genome as well as detection of HPV integrated DNA. With respect to costs and sequencing depth MeD-seq is superior to all available technologies and requires no DNA bisulphite treatment.

Results: We compared MeD-seq profiles of different types of cancers from vulva, cervix, endometrium, fallopian tube and ovary between cancers vs controls and cancers vs other cancers. Identification of Differentially Methylated regions (DMR's) was achieved by comparing MeD-seq profiles using genome wide statistical testing using a sliding window approach. DMR's found were used to classify gynecological cancers and determine overlap in cell type of origin. In addition to DNA methylation data, MeD-seq generates sequencing data which enables the detection of Human Papilloma Virus (HPV) DNA incorporated in the genome of HPV-infected cells. Around half of the gynecological cancer types in our study are HPV-associated and we were able to detect HPV genomic integration and call HPV subtypes based.

Conclusions: MeD-seq is a reliable low-cost technology to establish genome-wide DNA methylation profiles. DNA methylation profiles of cancers and controls can be used to characterize cell type origin of different cancers. In addition MeD-seq is able to detect HPV integration in host genomes and able to call specific HPV subtypes.

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#4722

THE PROOF-OF-PRINCIPLE OF MARKER DISCOVERY FOR DIFFERENT GYNECOLOGICAL CANCERS BY A NOVEL METHOD FOR GENOME-WIDE DNA METHYLATION PROFILING (MED-SEQ)

18 - Methylation

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Background/Objectives: DNA methylation serves as an important marker for mis-regulation of gene expression in cancer, is applied to classify tumors and can predict disease outcome and treatment options.

Methods: We developed a novel method that facilitates genome-wide methylation marker discovery allowing successful identification of methylation changes associated with pre-cancer and cancer at very low cost. The assay involves isolation and purification of DNA from formalin-fixed paraffine-embedded (FFPE) or fresh biopsies (only 10-50ng DNA is needed). A DNA methylation dependent restriction enzyme digestion releases 32 base pair DNA methylated fragments that are sequenced by next generation sequencing. This Methylated DNA sequencing (MeD-seq) assay is very robust, allowing detection of DNA methylation at more than 50% of the 30 million CpGs present in our genome. With respect to costs and sequencing depth MeD-seq is superior to all available technologies and requires no DNA bisulphite treatment. MeD-seq is compatible with low amounts of DNA derived from solid tumor tissue enriched by laser capture microdissection (LCM) and liquid biopsies.

Results: We compared MeD-seq profiles of different types of cancers from vulva, cervix, endometrium, fallopian tube and ovary between cancers vs controls and cancers vs other cancers. Identification of Differentially Methylated regions (DMR) was achieved by comparing MeD-seq profiles using genome wide statistical testing using a sliding window approach, visualized through the Integrative GenomicsViewer (IGV) and subsequent identification of primer and probe regions for quantitative Methylation-specific PCRs (qMSP) to detect tumor-specific or general-tumor markers.

Conclusions: MeD-seq is a reliable low-cost technology to establish genome-wide DNA methylation profiles of FFPE treated laser dissected material of cancer and controls and can be used to call DMRs for development of PCR-based assays.

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#4775

EXPLORATION OF BIOMARKERS IN MULTIZONAL INTRAEPITHELIAL NEOPLASIA: UNDERSTANDING EPITHELIAL TRANSFORMATION (MINUET)

15 - Molecular markers

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Background/Objectives: Rates of lower anogenital tract (LAGT) squamous cell carcinoma (SCC), such as vulval and anal cancer, have risen steadily in women over recent years. All LAGT zones are susceptible to HPV-related dysplasia, and certain high-risk groups of women are vulnerable to persistent LAGT neoplasia and cancer. In some women, high-grade squamous intraepithelial lesions (HSIL) occur in more than one LAGT zone concurrently, designated multizonal intraepithelial neoplasia (MZN). Because all HSIL have the potential to progress to SCC without treatment, timely risk assessment and management of MZN is a clinical challenge. Although DNA methylation analysis has been useful in prognosing other LAGT HSIL, few studies have assessed this approach in MZN. Elucidation of the molecular nature of MZN is needed to determine if biomarkers can assist in MZN triage.

Methods: We conducted a study on 12 women with MZN where at least one LAGT HSIL progressed to SCC. DNA methylation of host gene EPB41L3 and late regions of HPV16, 18, 31, 33 was assessed in biopsies: from the cancer zone prior to progression to SCC; from the cancer zone at the time of SCC; and from other LAGT zones that did not progress to invasive disease.

Results: 123 multi-timepoint samples from 12 women were analysed in total, including 15 invasive SCCs in the anal canal (n=4), peri-anus (n=6), vulva (n=2) and vagina (n=3). DNA methylation profiling of SCC with respect to time and zone is currently in progress.

Conclusions: Multizonal disease is under-researched yet complex to manage clinically. DNA methylation has previously been useful to predict oncological transformation and disease progression, suggesting its usefulness in triaging cases of MZN. Future studies will conduct a full methylome analysis on qualifying samples. Identification of biomarkers and their application in the triage of HSIL may improve the objectivity of MZN treatment.

FC09- Free communications - Self-sampling 2

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#4758

ANALYTICAL AND DIAGNOSTIC PERFORMANCE OF HPV SELF-SAMPLES COMPARED TO CLINICIAN-COLLECTED SCREENING SAMPLES

13 - Self-sampling

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Background/Objectives: HPV self-sampling is gaining acceptance as an equal to clinician-collected cervical screening samples. Whereas HPV testing on clinician-collected samples has internationally recognized criterions for validated use, no such consensus is established regarding HPV self-collected samples. Differences in collection media, preanalytical volumes and the impact on analysis outcome is only sparsely described and may affect the diagnostic accuracy of HPV tests. Nevertheless, HPV self-sampling is today embedded into several screening programs including ours at the Capital Region of Denmark.

Methods: We conducted a registry-based retrieval of PCR Ct data on 20,567 HPV self-collected samples (Evalyn brush, 3 ml CBD media) and 39,701 clinician-collected samples (Combi-brush, 10 ml SurePath). All samples had been routinely analyzed as part of the cervical cancer screening program using the BD Onclarity HPV assay. Raw PCR Ct data on internal control genes (Human beta globin, HBB, cut off Ct 34.2) and all 9 different HPV genotype readouts (Cut offs: HPV16 Ct 38.3, others Ct 34.2) were collated. Furthermore, concordance between HPV positive self-collected samples and clinician collected follow-up (FU) samples were analyzed for 1,380 self-sampling HPV positive women.

Results: HPV prevalence was 15.1% and 8.5% for self-collected and clinician-collected samples, respectively. On all self-samples, the average HBB Ct score was 21.2 ± 1.8 compared to an HBB Ct score of 24.4 ± 1.5 for clinician-collected samples. Comparing HPV positive self-samples to the recommended clinician-collected FU sample, 60% (N=829) remained HPV positive, whereas 40% (N=551) were HPV negative. The index CtHPV score for consistently HPV positive at FU was 25.9 ± 4.7 versus 30.5 ± 3.5 for those FU negative.

Conclusions: We observe that we have almost twice as high positivity rate in self-collected samples compared to clinician-collected samples. Lower CtHBB scores indicate that the concentration of analytical human DNA is higher in self-collected samples using our protocol. We also note that women confirmed positive by clinician-collected FU sample had a lower index CTHPV score. Jointly, these observations indicate that preanalytical factors such as resuspension medium, volume, and brush type impacts the analytical test outcome on self-collected samples, and that protocols for these should undergo the same rigorous validation from the scientific community and manufacturers as has been performed for the clinician-collected samples.

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#4839

VALIDATION OF MSWAB® MEDIUM FOR THE ELUTION OF SELF-COLLECTED FLOQSWABS® FOR HUMAN PAPILLOMAVIRUS (HPV) DETECTION ON SIX COMMERCIAL PCR-BASED HPV ASSAYS

10 - HPV screening

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Background/Objectives: Vaginal self-collection has been promoted to improve women's participation to Human Papillomavirus (HPV) based cervical screening programs using PCR-based HPV assays. A dedicated protocol for devices, media type and volume is necessary for the elution of dry self-collected vaginal swabs instead of using vials of cytology alcohol-based media. MSwab®, a molecular medium that supports HPV stability and compatibility with clinically validated PCR-based HPV assays, can be used for the elution of self-collected swabs. The aim of this validation was to examine the compatibility of MSwab® for the elution of dry self-collected vaginal FLOQSwabs® (552C.80) for the qualitative detection of HPV using six commercial clinical validated PCR-based HPV assays.

Methods: Thirteen dual vaginal self-collected FLOQSwabs® (Copan Italia, Brescia, Italy) specimens were used for this evaluation. One swab was eluted in 3ml ThinPrep and analysed at zero-time using the Seegene HPV28 assay. The other swab, stored dry at 200 to 400C for 7 to 84 days, and PROCEEDxTM FLOQ® (HPV16, HPV18, HPV45 or Negative) (MicroBix, Mississauga, Ontario, Canada) were also analysed. All swabs samples and controls were eluted in 3ml MSwab® (Copan Italia, Brescia, Italy) medium by swirling for 20-seconds before removing the swab. Eluted samples and controls were assessed for the presence of HPV genotypes using Abbott Alinity m, Abbott Realtime, Qiagen NeuMoDx, Roche cobas 4800 and cobas, and Seegene HPV28 HPV assays. Testing was undertaken at VCS Pathology.

Results: In the thirteen self-collected vaginal specimens eluted in MSwab® , Abbott Realtime, Roche cobas 4800 and cobas detected 10 HPV positives and 3 HPV negative while Abbott Alinity, Qiagen NeuMoDx and Seegene Anyplex II HPV28 detected 9 HPV positive and 3 HPV negative. In comparison with the samples eluted in ThinPrep at zero-time, the dry self-collected sample in MSwab® had an intra-assay sensitivity and specificity of 100% ($k=1.00$, $p<0.001$). The PROCEEDxTM FLOQ®Swab controls also obtained 100% sensitivity and specificity with all six assays.

Conclusions: Data obtained in this evaluation, demonstrated that both dry self-collected FLOQSwabs® specimens and PROCEEDxTM FLOQ® Swab controls eluted in MSwab® medium had 100% intra-assay concordance with a reference sample.These data support the use of FLOQSwabs® eluted in MSwab® medium for detection of HPV using commercial clinically validated PCR-based assays for cervical cancer screening programs.

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#4948

VAGINAL SELF-COLLECTED VS CERVICAL CLINICIANS COLLECTED SAMPLES FOR CERVICAL CANCER SCREENING IN COVID-19 ERA

13 - Self-sampling

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Background/Objectives: Reduction in cervical cancer mortality is going to be realized through an effective HPV vaccination campaign and the implementation of cervical cancer screening programs.The COVID-19 pandemic has had an enormous impact on cervical cancer screening with the consequent blocking of screening and the reduction in the availability of access in the following months/years and reported disrupted cancer-treatment services(1).Proactive strategies are requires to expanded screening options and to maintain and improve screening coverage.An opportunity can be the self-collected HPV testing strategy.Several studies show that hrHPV testing on self samples appears at least as sensitive for CIN2+ as cytology or hrHPV detection on clinician-obtained samples, though less specific(2-5).Currently,however,there are no studies comparing samples self collectecd vs clinicians both for hrHPV test and for molecular analysis.

Methods: Women aged 34-64 years,residents in Florence will receive the invitation letter by the local Public Screening Program.2000 women will perform self collection (Self FLOQSwabs®, Copan Italia, Italy) before to undergone to clinician sample collection.Vaginal-swab is easy to use and acceptability will be evaluate by a questionnaire.In order to define the optimal management of HPV+ women the results obtained by different markers (genotyping,methylation and p16 status,microbiota composition,cytokines and chemokines concentration),will be compared,taking into account the multiplicity of comparisons.Cross-sectional and longitudinal accuracy obtained by combinations of markers will be computed and compared in women with hrHPV persistance or clearance and with and without hgCIN detected at recruitment.The PPV,NPV and the absolute risk of developing lesions during follow-up,will be computed as measures of individual risk.The study is founded by Regional Institute of Cancer and approved by Area Vasta Local Ethical Committees.

Results: The key issue for hrHPV testing in primary cervical cancer screening is to detect clinically relevant infections that are associated with or develop into CIN2 or higher and differentiate them from transient HPV infections to avoid redundant or excessive follow-up.

Conclusions: Self-sampling may be campaigns to raise awareness of opting in to cervical cancer screening, more research is needed on the added value and feasibility of integrated guidelines to evaluate the best triage markers to manage hrHPV+ women, implementation to assure women compliance and governance not to overburden health facilities.This strategy assumes particular relevance in the Covid-19 era,guaranteeing adherence to screening but limiting patients' access to points of care.

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#4896

Self-Collection for Cervix Screening in the British Columbia Organized Cervix Screening Population-Based Program: Preliminary Program findings

13 - Self-sampling

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Background/Objectives: HPV-based self-collection (HPV-SC) for cervix screening has the potential to improve screening coverage, not only for the never and under-screened, but also for those routinely engaged in screening. British Columbia (BC) is poised to transform its longstanding population-based cervix screening program using cytology to an HPV-based program. As part of the transformation, BC implemented a program offering HPV-SC to never and under-screened individuals and to those routinely screened, to assess feasibility and impact on screening coverage.

Methods: Under-screened (5 to 10yrs overdue) (CohortA) and those due for screening (3 to 4 yrs since last screen) (CohortB) in select communities in BC were invited to participate. In each cohort, individuals were randomly allocated 2:1 to: 1) Invitation by mail to request a HPV-SC kit (Opt-in) or 2) Invited and sent a HPV-SC kit (Opt-out). Rates of uptake; kits requested and returned were compared between cohorts; and risk ratios between Opt-in and Opt-out within cohorts are presented.

Results: Between Dec2021 to June2022, 22,156 potentially eligible participants were identified: CohortA, n = 14,676; CohortB, n=7,480. In CohortA 9,356 allocated to Opt-in, 1,476 (16%) requested a kit; 970(66%) returned kits for absolute return rate of 10% (970/9356). In Cohort A, 3,984 allocated to Opt-out, 952 (24%) returned kits. Opt-out participants were significantly more likely to return kits [RR: 2.31 (95%CI: 2.13, 2.50)]. In CohortB, 4,310 allocated to Opt-in, 1,018 (24%) requested a kit; 633 (62%) returned kits, for absolute return rate 15% (633/4310). In Cohort B, of 2,191 allocated to Opt-out, 654 (30%) returned kits. Opt-out participants were significantly more likely to return kits [RR: 2.03 (95%CI: 1.85, 2.24)].

Conclusions: The COVID-9 pandemic, in addition to a shortage of primary healthcare providers in BC has required the exploration of innovative approaches to cervical screening to ensure all those who require screening have access. This is the first North American HPV-SC implementation project fully embedded in an organized, population-based program offering HPV-SC not only to the under and never-screened, but also to routinely screened, engaged individuals. Our findings illustrate that mailed HPV-SC has the potential to increase screening coverage in under-screened and routinely screened groups. Across cohorts, the Opt-out approach has a higher return rate than Opt-in. Additional data on HPV results and follow-up attendance will be presented.

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#4485

RIDECA: A PROXIMITY-INCENTIVE STRATEGY BASED ON VAGINAL SELF-SAMPLING FOR CERVICAL CANCER SCREENING IN THE FRENCH DEPARTMENTS OF AUDE AND HÉRAULT

11 - Screening for women difficult to reach

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Background/Objectives: In France, participation to cervical cancer screening needs to be improved, currently reaching only 60% of the target population. Notably, menopausal women represent an important part of underscreened women (Barré et al. 2017) . Numerous studies suggest that proposing self-sampling for HPV testing to non-attendee women is a valuable strategy (Arbyn M et al. 2018). RIDECA - for Interventional Research for Cervical Cancer Screening - (ClinicalTrials.gov ID: NCT04716127) is an interventional study based on the proposal of immediate delivery of a vaginal self-sampling device (VSSD) for HR-HPV testing to underscreened women older than 50 years while attending health care centers.

Methods: Women aged 50 to 65 years with no cervical screening for 3 years or more and no history of cervical pathology are recruited by a midwife in 2 sites: a mobile unit for breast cancer screening covering the Department of Hérault and a Medical and Social Care located in a deprived area of Aude (Limoux-Quillan). The number of women to include is 300 per site. After information on cervical cancer screening, women are proposed a VSSD (Evalyn® brush) to use at home and send back by mail to the laboratory for HR-HPV testing, using the Cobas 4800 HPV DNA detection test. Primary objective of this study is adherence to this screening strategy (number of women accepting the VSSD among those offered it). Secondary objectives are completion of self-sampling for women who accepted the device and completion of follow-up for women with positive HR-HPV DNA test. During recruitment, women complete a questionnaire on their socio-economic environment, motivational determinants and their willingness to perform the vaginal self-sample. Semi-directive interviews are conducted in a sub-group of women to identify the barriers and levers of screening participation.

Results: RIDECA started in September 2021. By August 31,2022, 403 women had been recruited for both sites. Among these, 357 accepted the VSSD (88.6%) and 246 performed self-sampling (68.9%). 22/246 (8.9%) samples were HR-HPV positive. Among these, 13 women had adequate follow-up (59%). Recruitment was more efficient in Hérault, at the mobile unit for breast cancer screening (N=332), than in Aude at the Medical and Social Care Center (N=71). Women recruitment as well as semi-directive interviews, questionnaires analysis and follow-up of women with positive HPV test are still ongoing.

Conclusions: RIDECA preliminary results suggest that proposing a VSSD to 50 - 65 years old women while attending a mobile unit for breast cancer screening or a Health Care Center may be a promising strategy to increase cervical screening participation. However, differences in dynamic recruitments observed for both centers suggest that analysis of environmental factors and women motivational determinants will be important clues for future transferability.

References: Arbyn M, Smith SB, Temin S, Sultana F, Castle P and Collaboration on Self-Sampling and HPV Testing. 2018. Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. British Medical Journal 363(Dec 5): k4823. Barré, S., M. Massetti, H. Leleu, N. Catajar and F. de Bels. 2017. Caractérisation des femmes ne réalisant pas de dépistage du cancer du col de l'utérus par frottis cervico-utérin en France. Bull Epidémiol Hebd 2-3: 39-47.

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#4978

Self- and physician-collected high-risk HPV mRNA testing to detect high-grade cervical lesions among Thai women visiting a colposcopy clinic

13 - Self-sampling

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Background/Objectives: Human papillomavirus (HPV) self-sampling has the potential to increase cervical cancer screening uptake and coverage. The self-sampling methods were not popular and familiar among Thai women. Many women were concerned about the test's reliability. We compared the performance of High-Risk HPV (hrHPV) mRNA testing of physician- and self-collected specimens for detecting histological CervicalIntraepithelial Neoplasia grade 2 or more severe (CIN2+) in Women Visiting a Colposcopy Clinic in Thailand.

Methods: From January 2022 to April 2022, 500 females participated in this cross-sectional multicenter study; 494 had complete data and valid specimen results. Participants used a self-sampling Aptima Multitest Swab specimen collection kit (Hologic, USA) consisting of a dry cotton tipped swab to self-collected vaginal samples beforephysicians biopsied the cervix during the colposcopic examination. The self- and physician-collected specimens were tested for hrHPV mRNA using APTIMA nucleic acid amplification assays (Hologic/Gen-Probe Incorporated, San Diego, CA). Cervical tissues were collected during colposcopic-directed biopsy from the most severe lesion or a random biopsy and endocervical curettage specimen if no lesion was detected.

Results: We detected hrHPV mRNA in 75.4% of self-collected specimens and 70.6% of physician-collected specimens. The prevalence of CIN2+ from cervical histology was 25.1% (n=124). For self-collected, the sensitivity and specificity of hrHPV mRNA for CIN2+ were 87.0% (95% confidence intervals (CI), 79.7-92.4%; n=108) and 28.5% (95% CI, 24.0-33.4%). For physician-collected, the sensitivity and specificity of hrHPV mRNA for CIN2+ were 90.2% (95% CI, 83.6-94.9%; n=112) and 36.1% (95% CI, 31.2-41.3%).

Conclusions: Self-collected specimens for hrHPV mRNA testing demonstrated good sensitivity and negative predictive value for detecting CIN2+ in Thai females. Self-collected samples performed similarly to physician-collected ones.

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#4779

Perceived barriers to clinic-based cervical cancer screening and motivators for HPV self-sampling during the COVID-19 pandemic

13 - Self-sampling

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Background/Objectives: We aimed to describe perceived barriers to clinic-based cervical cancer screening and motivators to use at-home HPV self-sampling kits among underscreened women in a large urban safety-net system during the COVID-19 pandemic.

Methods: Data were collected as part of the PRESTIS (Prospective Evaluation of Self-Testing to Increase Screening) randomized controlled trial. Trial participants were women enrolled in a public safety-net health system, aged 30-65 years, and underscreened for cervical cancer. We conducted a telephone survey in English and Spanish among a subset of trial participants randomized to the self-sampling arm. We used descriptive statistics to assess barriers/motivators and evaluate differences between English and Spanish speakers.

Results: Of 233 surveys completed between August 2020 and September 2022, most (61.4%) were conducted in Spanish. Most participants reported that clinic-based screening (Pap test) is uncomfortable (67.8%), embarrassing (52.4%), and that they are uncomfortable with male providers (63.1%). Significantly more Spanish- than English-speaking participants found a Pap embarrassing (66.4% vs 30%, $p<0.01$) and were uncomfortable with male providers (69.9% vs 52.2%, $p<0.01$). Of the 153 survey participants who completed self-sampling kits, most found the kit less embarrassing (69.3%), stressful (55.6%) and more convenient (55.6%) than a Pap. More Spanish-speaking participants found the kit less embarrassing than a Pap compared to English speakers (79.6% vs 53.4%, $p<0.05$). The COVID-19 pandemic influenced most (59.5%) to participate in the trial. The most common reasons were fear of COVID, difficulty making appointments and convenience of at-home kits.

Conclusions: Discomfort, embarrassment and being uncomfortable with male providers were reported as major barriers to cervical cancer screening among participants (particularly among Spanish speakers). These barriers may be addressed by at-home self-sampling. Given that the COVID-19 pandemic hindered access to clinic-based screening, further research is needed to understand how barriers might be addressed with screening tools such as at-home HPV testing using self-sampling.

References: Montealegre JR, Anderson ML, Hilsenbeck SG, Chiao EY, Cantor SB, Parker SL, Daheri M, Bulsara S, Escobar B, Deshmukh AA, Jibaja-Weiss ML, Zare M, Scheurer ME. Mailed self-sample HPV testing kits to improve cervical cancer screening in a safety net health system: protocol for a hybrid effectiveness-implementation randomized controlled trial. Trials. 2020 Oct 21;21(1):872. doi: 10.1186/s13063-020-04790-5. PMID: 33087164; PMCID: PMC7580009.

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#4970

VALIDATION OF THE CLINICAL PERFORMANCE AND REPRODUCIBILITY OF THE NEUMODX HPV ASSAY SELF-SAMPLE WORKFLOW

13 - Self-sampling

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Background/Objectives: HPV testing on self-collected (cervico-)vaginal specimens (HPV self-sampling) has similar clinical accuracy for CIN2/3+ compared to clinician-collected samples when performed with a clinically validated PCR-based assay (Polman et al. 2019, Arbyn et al. 2022). The NeuMoDxTM HPV Assay targets the E7 region of 15 (probably) high risk HPV (hrHPV) types (HPV16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -67, and -68) and confers partial genotyping by individually reporting HPV16 and HPV18, and concurrently detects the 13 other common high-risk types as a pool. The NeuMoDxTM HPV Assay has been clinically validated for use in cervical screening on clinician-collected cervical samples collected in both PreservCyt and SurePath collection medium using the international guidelines for HPV DNA test requirements for primary cervical screening. Recently, the NeuMoDxTM HPV Assay self-sample workflow has been developed. In this study the clinical performance of the NeuMoDx HPV Assay self-sample workflow for CIN3+ has been validated for self-collected vaginal specimens collected with the Evalyn brush sampler.

Methods: Study design and acceptance criteria were based on the international guidelines for HPV DNA test requirements for clinician-collected samples (Meijer et al. 2009). In brief, from a population-based screening setting from women aged 30-60 years over 60 self-samples of women with CIN3+ and over 800 self-samples of women without evidence of CIN2+ were tested with the NeuMoDx HPV Assay self-sample workflow. Comparator assay, performed on the same sample, was the commercially available HPV-Risk assay, which was clinically validated for HPV self-sampling (Hesselink et al., 2014). For reproducibility analysis of the NeuMoDx HPV self-sample workflow over 500 self-samples were tested within and between different laboratories.

Results: The NeuMoDx HPV Assay self-sample workflow had similar clinical performance compared to the comparator assay. More details will be presented at the conference.

Conclusions: The NeuMoDx HPV Assay self-sample workflow had similar clinical performance compared to the comparator assay. More details will be presented at the conference.

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#4767

Democratization of HPV Self-Sampling: A New High-Throughput Workflow on the BD CORTM System

13 - Self-sampling

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Background/Objectives: The BD CORTM System is a unique high-throughput fully integrated pre-analytic and analytic system for molecular diagnostic testing and has obtained CE Marking for cervical cancer screening using self-collected Copan FLOQSwabsTM using a manual intervention step. Self-collected specimens are non-inferior to physician collected samples and have a proven ability to reach women who do not attend screening 1,2. The global COVID-19 pandemic has led to deferred testing and vaccination, significantly increasing the number of underserved women3. Self-collection offers a means to close this gap and reduce the burden of cervical disease, but to date, has lacked a high-throughput solution for large-scale implementation.

Methods: Standard validation methods were used to establish a new workflow on the BD COR System with a custom assay definition file (ADF) for dry-collected swab specimens.

Results: Samples are self-collected using Copan FLOQSwabs, broken at the score mark and the swab head placed directly into an empty barcoded BD HPV sample tube, sealed with a reclosing silicone septum cap. The dry samples are stable at ambient temperature and can be mailed to the laboratory. The samples are placed in racks and loaded directly onto the BD CORTM System. The system identifies and uncaps each tube individually, fills it with HPV diluent and replaces the cap. Specimens then cycle through the automated extraction and real-time PCR detection modules and extended HPV genotyping results are automatically uploaded to the laboratory information system (LIS). A single BD CORTM System can process up to 1,050 tests in a 24-hour period (~273,000 tests per year) .

Conclusions: The new BD COR System workflow requires no user intervention and represents the first true "load and go" workflow for self-collected vaginal specimens. This streamlined workflow can help enable national self-collection deployment, reduce program costs while increasing both disease detection and the number of women screened.

References: 1 Arbyn, M., Smith, S. B., Temin, S., Sultana, F. & Castle, P. Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. BMJ (Clinical research ed.) 363, k4823, doi:10.1136/bmj.k4823 (2018). 2 MacDonald, E. J. et al. Reaching under-screened/never-screened indigenous peoples with human papilloma virus self-testing: A community-based cluster randomised controlled trial. The Australian & New Zealand journal of obstetrics & gynaecology 61, 135-141, doi:10.1111/ajo.13285 (2021). 3 Wentzensen, N., Clarke, M. A. & Perkins, R. B. Impact of COVID-19 on cervical cancer screening: Challenges and opportunities to improving resilience and reduce disparities. Preventive medicine 151, 106596, doi:10.1016/j.ypmed.2021.106596 (2021). Note: The BD Onclarity HPV assay is currently not approved for use with self-collected vaginal specimens in the United States

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#4854

EVALUATION OF NEW STRATEGIES OF STORAGE AND EXTRACTION FOR THE IMPLEMENTATION OF SELF-COLLECTION IN CERVICAL SCREENING PROGRAMS

13 - Self-sampling

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Background/Objectives: Vaginal sel-collection is a convenient and economical method for cervical cancer prevention.New approaches in HPV screening, as rapid thermal nucleic acids extraction (RTNAE), proper sample storage and transport, could be useful in reducing cost and time of analyses.The aim of the present study was to evaluate the pre-analytical stability of dry self-collected samples FLOQSwab®, eluted in eNat® medium (Copan,Italia) for high-risk HPV detection at two different time points: at baseline and after storage at room temperature for ~1 month. Moreover, to further reduce time and cost of analyses associated with cervical screening process, the traditional DNA extraction was compared with Rapid Thermal Nucleic Acid Extraction Method (RTNAE) using a non-alcohol based medium (MSwab®, Copan,Italia).

Methods: A total of 392 women were enrolled, within the regional LILT (Italian League against Tumor) project. Dry self-collected FLOQSwabs® samples, were randomly suspended in 2 mL of MSwab® or eNat® media and processed at the Molecular Epidemiological laboratories of University of Sassari (Sardinia, Italy). The traditional DNA extraction was carried out by an automated system (Seegene AdvanSureTM E3) and analysed by AnyplexTM II HPV HR (Seegene). Moreover, vaginal samples resuspended in MSwab® medium, were simultaneously processed by rapid nucleic acids extraction (RTNAE), at 98°C for 5 minutes.

Results: A total of 185 (47.2%) samples were resuspended in eNat® medium, whereas 207 (52.8%) in MSwab® medium. The 17.1% (67/392) of women reported a positivity for at least one high-risk HPV genotype, with HPV-16, -56, -31, and -58. Diagnostic agreement was assessed with the Cohen's K between different extraction methods and McNemar test was used to evaluate the differences in HPV-DNA results at different time points. No substantial differences were observed between the results at different time points (17.3% (t0) vs 16.8% (t1); McNemar p-value=0.32) and an agreement of 99.5% (p-value<0.0001). Likewise, a total agreement (100%) was found comparing the HPV-DNA test between traditional and RTNAE extraction (Cohen K=1.0; p<0.0001).

Conclusions: Although the higher sensitivity of the HPV-DNA testing, the accuracy of the analysis is related to the stability of the swabs during transport and to the elution medium, particularly for vaginal self-collection. The present study confirmed that new approaches in HPV screening, as rapid thermal nucleic acids extraction (RTNAE), proper sample storage and transport, could be useful in reducing cost and time of analyses. For this purpose, these preliminary results show as MSwab® and eNAT®, are alternative non-alcohol-based medium for HPV detection in vaginal self-collected samples.

FC10- Free communications- Low income countries 1

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#5042

Barriers to Cervical Cancer Prevention and Control in Guatemala

39 - Low resource settings

Background/Objectives: to explore barriers to cervical cancer prevention and control in Guatemala where cervical cancer is the second-leading cause of cancer-related deaths among women

Methods: Four focus groups were held with female community leaders (N=43) in three different locations near San Raymundo in August 2022. Participants, who were primarily teachers, homemakers, midwives and nurses, were recruited by Refuge International, a non-profit organization with a local board that has maintained three health clinics in Guatemala for 20 years. Focus groups were held at the Refuge Internatnional Health Clinic, a local school, and a community center. Focus groups were facilitated by expert nursing faculty from the University of Utah in the U.S. who speak Spanish and have experience leading focus groups. Focus group leaders received additional assistance from a local translator. Focus group questions assessed the lived experience of participants' knowledge, practices and attitudes regarding cervical cancer prevention and control. Conversations that were recorded by audiotape concluded when saturation was reached. Field notes were taken to note significant statements, voice inflections, and agreement or disagreement among participants. The study team also shared related perceptions following each focus groups. Audiotapes were sent to a University of Utah-endoresed transcription services and translated into English. A preliminary mattrix of theses was derived from the English transcriptions.

Results: Focus groups lasted 46 to 75 minutes with an average of 62 minutes. Barriers to receipt of a Pap included not prioritizng prevention, but rather focusing on more immediate demands or symptoms. Additional barriers related to costs, embarrassment, fear the procedure will hurt, husbands who don't want other men looking at their wives, rural and indigenous disparities, illiteracy, lack of knowledge, and limitations of the health care system. Barriers to reciept of the HPV vaccine for daughters at the age of 11 included fear of harm, specifically infertility, lack of advertising about offerings, and limited availability. Barriers to HPV self-testing included fear of doing the test incorrecty, and needing someone they trust, such as a local nurse or lay midwife, to demonstrate the correct method of self-testing for HPV.

Conclusions: Our research indicates that Guatemalan women need more cultuturally-targeted information about cervical cancer prevention, screening, and treatment. HPV self-testing with a nurse of lay midwife may be an efficient approach to address some of the reported barriers, such as cost, embarrassment, fear of the procedure, husband reluctance, and limitations of the health care system. Outreach should focus on remote ares with low-literacy indigenou Mayans.

References: HPV Information Center, 2021

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#5048

LOW LEVELS OF LIFETIME PAP TEST RECEIPT AMONG VULNERABLE PATIENT POPULATIONS IN GUATEMALA

39 - Low resource settings

Background/Objectives: To assess demographic characteristics related to lifetime receipt of a Pap test in Guatemala where cervical cancer is the second-leading cause of cancer-related dealth among women

Methods: A 30-question survey was administered to Guatemalan female patients at two Refuge International Health Clinics in suburban San Raymundo and rural Sarstun in August 2021. Participants (N=139) included females age 18 to 65 who were recruited by a team of Spanish-speaking and indigenous-language-speaking members who also helped participants with low-levels of literacy answer survey questions. Participants reported demographic characteristics, cervical cancer knowledge, health care access, and self-reported behaviors. We hypothesized that women with receipt of at least one lifetime Pap test would be married, have more education, be more literate, identify as Hispanic, and have access to health care. Bivariate analysis and multivariable models examined associates of outcomes with predictors.

Results: Participants were primarily married (65.7%), spoke Spanish (65.7%), indigenous (58.0%) and lives less than 40 kilometers from a health clinic (60.1%). Most participants were illiterate (77.6%), however, 60.1% had only a primary or middle school education. Of the participants, 72% reported that they had received at least one lifetime Pap test, yet only 42.7% knew what a Pap test was, and only 20.3% knew that HPV causes cervical cancer. Hispanics were more likely than indigenous Mayans (91% vs 71%, $p = 0.01$), illiterate were more likely than illiterate persons (83% vs 55%, $p = 0.002$), and married people were more likely than unmarried people (84% vs 60%, $p = 0.004$) to have received of at least one lifetime Pap test. Hispanics were more likely than indigenous Mayans (74% vs 29%, $p < 0.001$), illiterate were more likely than illiterate persons (53% vs 23%, $p=0.01$), and those with at least some formal education were more likely than those with no formal education (65% vs 36%, $p= 0.001$) to have correct knowledge of a Pap test. Higher rates of knowledge of HPV was associated with being Hispanic (32% vs 17%, $p = 0.044$) and having higher education levels (42.3% vs 8.3%, $p < 0.001$). Multivariable models found significantly higher odds of receipt of at least one lifetime Pap test for married women OR: 10.89 [95% CI OR: 3.18. 37.4] and illiterate women OR: 7.09 [95% CI OR: 1.96, 25.65].

Conclusions: In Guatemala, cervical cancer is the second-leading cause of cancer-related death among women. Our research indicates that vulnerable populations, who are indigenous, illiterate, lack education, and are not married, were less likely to have received at least one Pap test in their lifetime. Culturally-targeted interventions are needed to improve cervical cancer prevention and control among vulnerable populations in Guatemala.

References: HPV Information Center, 2021

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#5053

The role of area-level socioeconomic status and health care access with advanced stage at diagnosis by race/ethnicity among women with cervical cancer in the United States: a case for improving cervical cancer screening access to the most vulnerable

11 - Screening for women difficult to reach

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Background/Objectives: In the US, cervical cancer is characterized by inequities with the large burden of adverse outcomes occurring among racial and ethnic minoritized populations, partially due to low access to screening. Racial and ethnic minoritized adults in the US are heterogeneous and experience disparate social determinates of health (SDOH) patterns in the context of access to health care. Our objective was to evaluate associations of SDOH measures with advanced stage at diagnosis among cervical cancer patients to gain insights into intervenable opportunities to improve screening uptake and cervical cancer care across the continuum.

Methods: We used data from the US National Cancer Database, which captures patients with cancer treated at a Commission on Cancer (CoC) certified facility, including 70% of cancer cases occurring in the US. Patients between the ages 18 and 89 years diagnosed between 2004-20019 with stage 0-IV cervical cancer (ICD-O-3 topography codes C530, C531, C538, and C539). Our main outcome was advanced stage at diagnosis, defined as stage 3 or above. Our main exposures included area-level socioeconomic measures, specifically % of adults without a high school degree by patient's zip code and median income quartiles within patient's zip codes. To account for similarities in patients treated at the same facility, we used hierarchical multivariable logistic regression models clustered by facility ID and estimated adjusted odds ratios with 95% confidence intervals. We stratified our models by race/ethnicity, [non-Hispanic (NH) White, NH-Black, Hispanic, NH-Asian, NH-American Indian/Alaskan Native, and NH-Pacific Islander], patient's insurance status (uninsured, Medicare, Medicaid, and private insurance), and cancer care facility type (community, comprehensive community, academic/research, and integrated network).

Results: Our study population included 156,952 women diagnosed with cervical cancer with 65% NH-White, 16% NH-Black, 0.5% NH-AI/AN, 0.3% NH-Pacific Islander, 4.0% NH-Asian, and 13.4% Hispanic. One-third of women were diagnosed with stage three or above cervical cancer, with higher proportions occurring among NH-Black (39%) and NH-PI (40%) women ($p<0.001$). NH-Black (46%) and Hispanic (62%) women with cervical cancer were more likely to live in a lower-education area compared to NH-Whites (20%) ($p<0.001$). Similarly NH-Black (49%), NH-AI (41%), and Hispanic (33%) cervical cancer patients resided in the lowest income quartile compared to NH-White (19%) and NH-Asian (12%) ($p<0.001$). After adjustment for age, calendar year of diagnosis, and Charlson-comorbidity score, lower area-level education (aOR:1.34; 95 CI: 1.29-1.40) and lower area-level median income (aOR: 1.33; 95% CI: 1.29-1.39) were associated with advanced stage at cervical cancer diagnosis. These associations were consistent across NH-White, NH-Black, Hispanic, and NH-AI patients. Further, these associations persisted across insurance status and cancer care facility type (excluding community cancer programs).

Conclusions: Area-level socioeconomic measures, specifically education and household income, are significantly associated with advanced stage at diagnosis regardless of insurance type and cancer care facility type. Our findings highlight the need for efforts to improve cervical cancer screening delivery by addressing social determinants of health (including financial and health care access factors) to improve cervical cancer outcomes across racial groups in the US.

Gunasekaran Geetanjali
India

Gunasekaran Geetanjali

#4908

SIGNIFICANCE OF CONVENTIONAL PAP SMEAR AS A SCFREENING TOOL FOR CERVICAL CANCER IN LOW SOCIOECONOMIC COUNTRIES

16 - Screening methods

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Background/Objectives: Cervical cancer is the commonest cancer cause of death among women in developing countries. Every year in India, 122,844 women are diagnosed with cervical cancer, and 67,477 die from the disease. India has a 432.2 million women aged 15 years and older at risk of developing cancer. It is the second most common cancer in women aged 15-44. By seeing this data cervical cancer has high morbidity and mortality. Many screening programs have been introduced and Papanicolaou (Pap) smear-based cytological screening programs are common in most of developing countries. Papanicolaou (Pap) smear remains the most available, feasible, and cost-effective tool for screening of cervix premalignant and malignant lesions. Via the pap smear, several premalignant lesions of the cervix including cervical dysplasia and inflammatory lesion could be diagnosed in the early stage of the disease. In this study, we have used Papanicolaou smears as the major tool of screening in JSS Hospital Mysore which serves as a main tertiary care center for the surrounding sub-urban places.

Methods: Study participants were recruited from the outpatients visiting the Obstetrics and Gynecology department in JSS Hospital Mysuru from January to June 2022. Samples were collected using Ayer's spatula from non-pregnant, non - menstruating, pre-and post-menopausal women who present with gynecological complaints. The fixed smears were transported to the pathology laboratory where it is submerged successively in 80% of alcohol,50%alcohol, and water for one minute. Stained with Hematoxylin Harris solution for approximately 5 minutes and immersed in water 6 times for 1 second. Dip the preparation in 95% Ethanol 10 dips and then Eosin dye was added and made to remain on the slide for 2.5 minutes and again the slide was dipped in 95% ethanol 10 dips for 2 changes followed by 100% Ethanol for 1 minute. Then the slide was placed in Xylene for 2 minutes and mounted with a permanent mounting medium.

Results: 1143 Papanicolaou smears were collected from the month of January to June 2022. Out of 1143 pap smears, the sample which was Inadequate for evaluation was around 48 (4.19%). Normal inflammatory smear with no infection was around 960 (83.9%). Pap smears with bacterial vaginosis cases were reported around 320 (27.9%) and Bacterial vaginosis with reactive changes was around 18 (5.62%). Candidiasis cases reported was around 21 (1.8%) and trichomonas accounted to 30(2.6%). Out of the premalignant conditions, Atypical Squamous cell of Undetermined Significance (ASCUS) was reported in around 3 (0.26 %) cases. Low-grade Squamous Intraepithelial Lesion and High-grade Squamous Intraepithelial Lesions constituted about 3 cases each (0.26% each). The Squamous cell carcinoma of the cervix constituted about 7 cases (0.6%).

Conclusions: From this study, we conclude that conventional pap smears, which has their own limitations such as obscuring factors, still remains a cost-effective method of screening in most developing countries. It is the most reliable method for rural populations and for screening on a large scale. It is also useful for early detection for premalignant and malignant lesions on a large scale.

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#4946

Introducing HPV self-testing in 4 resource-constrained countries to enhance existing cervical cancer screening programs: a preliminary field evaluation

11 - Screening for women difficult to reach

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Background/Objectives: An international consortium initiated an implementation research project (PRESCRIP-TEC) to study the feasibility of the WHO strategy for elimination of cervical cancer as a public health problem. The project introduces hrHPV self-testing as the primary screening approach for cervical cancer. We aim to evaluate the uptake and acceptability of self-collected specimens for HPV DNA testing.

Methods: The project plans to perform 32,000 hrHPV self-tests among eligible women from vulnerable groups (women in remote areas, minority groups, factory workers, living with HIV, and sex workers) with limited access to screening services in India, Bangladesh, Uganda and the Roma minorities in the Slovak Republic. Prior to introduction of the HPV testing, community mobilisation programmes were implemented. All eligible women at the project sites were invited to participate by specially trained community health workers and received vaginal swabs (Floqswabs®) for self collection at home. After collection, dried swabs were prepared for HPV DNA testing (GenXpert® or Cobas® 4800) with 3 ml Mswab® medium (Uganda, Bangladesh, Slovak Republic) or 20 ml Preservcyt® (India). hrHPV positive women were invited for Visual Assessment before Treatment (VAT) in Uganda, see and treat with Visual Inspection with Acetic acid (VIA) in India and Bangladesh, or Pap smear in Slovak Republic and referred for treatment if needed.

Results: Screening began in all four project regions between July and October 2021. To date, over 3160 women have been invited to carry out a self-taken hrHPV test. Preliminary results indicate high acceptance of the concept of HPV self-testing among communities. Early data suggests a range of 85 - 95% uptake across sites and over 98% performed the self-swab without assistance of a health worker. Testing results shows large differences in prevalence of hrHPV with low prevalence in Bangladesh (1-2%) and high prevalence in Uganda and in some high risk groups in India (respectively 21% and 25%). Data from Slovakia are not yet available.

Conclusions: This preliminary analysis shows the feasibility of hrHPV testing in vulnerable groups in four very different resource-constrained settings. The project will continue testing, analysing the feasibility of implementation, uptake, acceptability, and costs of the adapted screening strategy. Although costs of testing currently remain high, hrHPV testing can result in effective triaging of HPV positive women for further assessment and treatment. Offering women a home-based self-sampling may be a more cost-effective alternative than clinic-based screening in resource constrained settings with a strong community health network.

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#5032

BENCHMARKING CERVICAL CANCER CARE AT A TERTIARY ONCOLOGY FACILITY IN UGANDA AGAINST NATIONAL TREATMENT TARGETS ON CERVICAL CANCER CONTROL

39 - Low resource settings

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Background/Objectives: The treatment of cervical cancer patients in Uganda is hampered by late diagnosis due to the unavailability of timely screening and limited availability of advanced cancer care.1,2 This study evaluated the presentation and clinical management of cervical cancer patients presenting at the Uganda Cancer Institute (UCI) in Kampala, the tertiary oncology facility in Uganda.

Methods: We retrospectively analysed patient files of all cervical cancer patients presenting to UCI between January 2017 and March 2018. The clinical management of patients with early (FIGO 1A-2A) and advanced (FIGO 2B-4B) stage disease who completed treatment at UCI was evaluated using the national targets formulated in the Uganda strategic plan for cervical cancer prevention and control.

Results: Files of 583 patients were included, representing less than 10% of the annual estimated incidence in Uganda. The majority (86%) of patients presented with advanced stage of disease. More than half of patients (60%) never initiated or interrupted treatment. The treatment targets for surgery (10%) and palliative care (25%) were achieved for eligible patients at UCI, however, the target for chemo-radiotherapy (65%) was not met.

Conclusions: In Uganda cervical cancer is frequently diagnosed in advanced stage and the minority of patients reached the tertiary oncology facility UCI. Less than half of the patients presenting at UCI completed their treatment. Especially the availability of radiotherapy was limited, while most patients required chemoradiotherapy due to advanced stage of disease. After the study period a second radiotherapy machine was installed, leading to improved access to radiotherapy. Although the targets outlined for surgical treatment and palliative care were achieved at UCI, adhering to the national treatment targets still means that most patients do not receive the treatment they need. To decrease the burden of cervical cancer in Uganda, accessible prevention programs should be a public health priority and the focus of cervical cancer control, alongside investment in efficient referral pathways, oncological surgical capacity, chemotherapy, and radiotherapy.

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#5028

The Emerging Technologies in Cervical Cancer Screening 'ETiCCS' Initiative

39 - Low resource settings

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Background/Objectives: The roadmap towards global elimination of cervical cancer was launched by WHO in 2018. The short-term targets to be achieved by 2030 include a 70% screening coverage of 30+ years old women using a high-performance screening test. The ETiCCS initiative aims to contribute to this target in underserved regions of the world.

Methods: Our concept combines high-access community-grounded HPV testing with high-performance molecular and visual triage tests. A seamless cervical cancer screening continuum is ensured by a digital app which is hosted on a General Data Protection Regulation (GDPR) -compliant cloud platform (PAICON).

Results: The initiative was launched in 2015 by molecular oncologists, laboratory scientists, and public health specialists at Heidelberg University (Germany), Moi University (Eldoret, Kenya) and Gondar University (Gondar, Ethiopia). We have extended our partnerships to Namibia, Botswana and Cambodia supported by public and private funding sources. Our contributions towards the WHO vision of a cancer-free world include (i) analyses of epidemiological data to give a robust overview of cervical cancer screening prevalences in LMICs 1, (ii) real-world experiences on delivery options of HPV-based primary screening using community-based self sampling 2, 3, 4, 5, (iii) appraisal of the status and opportunities of laboratory services of molecular screening options for HPV testing and dual-stain cytology in our partner countries 6,7. We also (iv) compare different digital visual devices such as smartphone and colposcope as triage tools and their usage in different clinical environments, (v) collaborate with clinicians and researchers in Germany to develop computer algorithms for automated evaluation of digital cervical images and (vi) perform health economic evaluations to contribute to the design of cervical cancer programs by policy makers in our partner countries. We also share our vision and activities via our website (www.eticcs.org).

Conclusions: Our initiative provides an ideal stage to advocate, engage and collaborate with government and academic partners and to evaluate individual components of the screening continuum in different environments including HPV sampling delivery models, triage tools and economic impacts.

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FC11- Free communications- Low income countries 2

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#4335

Barriers and facilitators to cervical cancer screening among under-screened women in Cuenca, Ecuador: the perspectives of women and health professionals.

11 - Screening for women difficult to reach

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Background/Objectives: Background Cervical cancer screening is a cost-effective method responsible for a mortality reduction of 70% in countries that have reached high coverage through nationwide screening strategies. However, there are disparities in access to screening. In Ecuador, despite cervical cancer is one the most frequent cancer in women, only 58,4% of women of reproductive age have ever been screened during their lifetime. Objectives To describe and understand the experiences and perceptions of women and health professionals about the barriers and facilitators related to cervical cancer screening in Cuenca, Ecuador.

Methods: A qualitative study was performed from April 2020 until March 2021, in Azuay province, Ecuador. Focus group discussions (FGDs) were organized with health staff and under-screened women separately, as this method allows participants to interact with each other which enriches the generated information. Two FGD guides were developed, one for women and one for health personnel. Key topics addressed during the discussions were opinions about or experiences with cervical cancer screening, opinions about national cervical cancer screening practices or programs, barriers that inhibit screening uptake and suggestions to address these barriers. This study is based on Gadamer's hermeneutic phenomenology was carried out from an ecological approach.

Results: Overall, 28 women and 27 HP participated in the study. Both groups perceived different barriers for cervical cancer screening. For HP, barriers were mainly allocated at the policy level (lack of a structured screening plan; lack of health promotion) and individual level (lack of risk perception; personal believes). Women identified mainly barriers at operational level, such as long waiting times, lack of access to health centers, and inadequate patient- physician communication. Both groups mentioned facilitators at policy level, such as national campaigns regarding cervical cancer screening, and at community and at individual level, including: health literacy and women empowerment.

Conclusions: From women's perspectives, access to health services is the main limitation; while for health professionals lack of investment in screening programs and cultural patterns at community level constitute major obstacles. To address cervical cancer prevention integrally, the perspectives of both groups should be taken into account. Additionally, new strategies and technologies, such as HPV self-sampling and community participation, should be implemented to increase the access to cervical cancer screening.

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#4974

HUMAN-CENTERED DESIGN OF AN HPV RAPID TEST FOR CERVICAL CANCER SCREENING IN UNDERSERVED POPULATIONS

11 - Screening for women difficult to reach

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Background/Objectives: While cervical cancer incidence and mortality rates have dramatically decreased in high-resource settings that have invested in Human Papillomavirus (HPV) vaccination, screening, and treatment, significant disparities exist even in high-income countries like the United States (U.S.) in areas of poverty and marginalization. A single round of HPV testing is associated with a significant reduction in the numbers of advanced cervical cancers and deaths from cervical cancer over time compared to cytology, however laboratory-based HPV testing remains largely inaccessible to the most vulnerable U.S. and global populations and unsuitable for low-resource settings that lack the infrastructure, equipment, and trained personnel required to perform these tests. Furthermore, marginalized and underserved populations also face non-financial access barriers related to knowledge, health literacy, geography, language, culture, and social support that impede cervical cancer screening.

Methods: Our group previously designed, developed, and patented a simple, inexpensive, single-use, portable, and disposable rapid HPV DNA test that can be run in less than one hour by a minimally-trained operator in any setting. By employing community-based participatory research, we have engaged diverse stakeholders including clinicians, patients, community health workers, and policymakers in a mixed-methodology participatory design process to identify key requirements and inform the adaptation, acceptability, and translation of an existing high risk-HPV rapid diagnostic test (hrHPV RDT) prototype for cervical cancer screening in medically-underserved communities.

Results: We have operationalized diverse stakeholder feedback in redesigning a rapid HPV test prototype, and tailoring it to user- and stakeholder-informed target technical specifications. We have defined and will present the resulting concept target product profile (cTPP) for the hrHPV RDT that is informing ongoing device development.

Conclusions: This technology has the potential to facilitate cervical cancer screening programs by enabling home- or community-based HPV testing and circumventing many of the barriers of existing methods. Its further development and implementation must continue to be informed by target end-users and their communities, social structure, and cultural context, in order to address specific needs, increase screening coverage, and ensure linkage to follow-up care.

Gassama Omar
Senegal
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#5050

TREATMENT BY THERMOABLATION OF PRE-CANCEROUS LESIONS OF THE UTERINE CERVIX IN THE MEDICAL REGIONS OF TAMBACOUNDA AND KEDOUGOU (SENEGAL)

11 - Screening for women difficult to reach

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Background/Objectives: Describe epidemiological aspects, treatment of pre-cancerous cervical lesions by thermoablation, follow-up of clients

Methods: This was a prospective descriptive and analytical study that took place from March 1, 2020 to October 12, 2022 in the medical regions of Tambacounda and Kédougou and involved all eligible clients after cervical cancer screening by visual inspection after application of 3% acetic acid. The parameters studied were socio-demographic characteristics, thermoablation treatment (duration, surface area treated, pain sensation, complications) and client outcome. Data collection was done by Open Data Kit (ODK) software and analysis by Epi-info and SPSS software.

Results: Cervical cancer screening involved 6180 clients. Of these clients 307 (4.97%) had a positive visual inspection after application of 3% acetic acid and 27 women (0.44%) had a macroscopically suspicious cervix. VIA-positive lesions were located in 1 or 2 quadrants in 73.65% of cases. 150 (2.87) clients in our series had received thermoablation treatment. The majority (95%) of the clients had a pain score of 2 on the visual analogue scale. No side effects were noted and the postoperative course was simple in all patients.

Conclusions: Thermoablation can play an important role in the fight against cervical cancer in the "see and treat" strategy in the medical regions of Tambacounda and Kédougou

References: Cervical cancer screening, thermoablation, VIA, Tambacounda, Senegal

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#4880

IN MY HANDS: LEARNINGS FROM HPV-BASED CERVICAL CANCER SELF SCREENING APPROACHES IN REMOTE INDIGENOUS COMMUNITIES

11 - Screening for women difficult to reach

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Background/Objectives: Northern British Columbia (NBC) has 55 distinct First Nations and 13 Métis Chartered Communities over a vast geographic area. The NBC population has a significant percentage of Indigenous Peoples, many living in rural and remote communities with limited access to health resources resulting in health disparities. Given significant disparities in rates of cervical cancer among Indigenous compared to non-Indigenous women, there is a critical need to engage communities in ways that overcome challenges created by disparate geographies, health care provider shortages, and systemic anti-Indigenous racism within healthcare.

Methods: We used three different methods of engagement in three different settings. With extensive community engagement, health staff were trained to engage participants and support their involvement. All three projects involved offering mailed HPV-based self-collected (HPV-SC) cervical screening to under-screened women. Carrier Sekani Family Services (CSFS) integrated HPV-SC through established primary care centres. First Nations Health Authority (FNHA) offered HPV-SC screening as a parallel strategy to their community health engagement strategy. Both communities made screening kits available in participating health centres which were accessed through the support of trained health staff. Métis Nation British Columbia (MNBC) offered HPV-SC participation through kits mailed to the homes of participants once they registered through our project website. Considering the diversity of each community, health organization and geographical region, three unique approaches was essential. We will present HPV-SC uptake rates from each community approach.

Results: These projects work with; 11 CSFS, 3 FNHA and 3 MNBC communities. To date we have screened participants from CSFS (N=124) as of 02/2019, FNHA (N=43) 01/2021 and MNBC (N=44) 10/2020 and received results for all. 8.7% of total participants had positive results and were supported with follow-up care. Feedback surveys from CSFS (N=24) and MNBC (N=23) indicate an 83% acceptability rate.

Conclusions: Using precision implementation, these projects provide low-barrier access to cervical screening and are created upon a foundation of cultural safety, relationship-building, trust, and partnership indicating there is not a "one size fits all' approach to screening. Diversity in location and population necessitated unique approaches centered with a strengths-based lens. Using innovative technology and culturally appropriate engagement strategies, these screening projects are reducing barriers and supporting engagement of women in their health journey with the goal of reducing cervical cancer and pre-cancer rates.

Mhango Patani
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Mhango Patani
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#4684

ACCEPTABILITY, FEASIBILITY AND APPROPRIATENESS OF INTEGRATING HPV SELF-SAMPLING FOR CERVICAL CANCER SCREENING INTO VOLUNTARY FAMILY PLANNING SERVICES IN MALAWI

13 - Self-sampling

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Background/Objectives: Despite cervical cancer being preventable through screening and preventive therapy, it remains a burden for Malawi and other low income countries. The World Health Organization now recommends the use of human papillomavirus (HPV) testing for cervical cancer screening (CCS). We assessed the acceptability, feasibility and appropriateness of 2 models for integrating HPV self-sampling for CCS into family planning (FP) services in Malawi.

Methods: We randomised 16 health facilities to two models: Model 1 involved only clinic-based HPV self-sampling, whereas Model 2 included both clinic-based and community-based HPV self-sampling. We conducted a mixed-methods study through in-depth interviews (IDI), focus group discussions (FGD) and a Likert scale questionnaire. We purposely sampled 193 healthcare providers (nurses and clinicians), laboratory staff, clinic managers and community health workers (CHWs) at early, midline and final trial implementation phases. We audio-recorded IDIs and FGDs and then transcribed and analysed data using Nvivo 12 software and thematic content analysis. Quantitative data were entered directly into tablets using ODK software and analysed using Stata Version 16.

Results: We completed 171 IDIs, 22 FGDs and 272 questionnaires.Providers found both models acceptable because integrating CCS and VFP saved them time. Model 2 was acceptable due to trust the community had in CHWs. Availability of equipment and supplies, well-trained personnel, mentorship, staff commitment and teamwork made both models feasible. Workload was reduced for clinicians and nurses, but increased for CHWs and lab personnel. The models were also appropriate because HPV self-sampling was simple and ensured client privacy for those hesitant to undergo a speculum examination for screening. The integration also mitigated fears that women had about speculum exams and dispelled myths and misconceptions around family planning methods.

Conclusions: Both models of the integration of CCS into VFP were acceptable, feasible and appropriate, and provide a platform to rapidly increase the CCS uptake in Malawi.

Vega Bernardo
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#4220

Role of self-sampling for the diagnosis of human papillomavirus in rural areas from Cuenca Ecuador: Acceptance, sensitivity and specificity among urine sampling, self-sampling and clinician sampling.

13 - Self-sampling

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Background/Objectives: Background: During 2020, 1534 new cases of cervical cancer were reported in Ecuador and 813 women died from this cause. Pap smear has decreased mortality of (CC), however in Ecuador 41.6% of women in their reproductive age have been never screened. Different barriers for CC screening have been identified, among them: long waiting times, pain, embarrassment, lack of risk perceptions are related with this low coverage. High sensitivity tests for primary screening of HPV are useful for an early detection of cervical pathology. Self-sampling techniques could overcome barriers and increase participation in screening and participation. Objectives 1.- To compare the sensitivity and specificity of urine and vaginal self-sampling test versus clinician sampling test, for HPV diagnosis. 2.- To compare the acceptability of urine and vaginal self-sampling methods versus clinician sampling among rural women

Methods: A diagnostic test study was conducted in a rural parish of Cuenca, Ecuador. A total of 120 women participated. Each participant self-collected urine and vaginal samples and underwent clinician sampling for HPV testing. The latter was considered as the golden standard. All three samples were processed with the same amplification and hybridization protocol for HPV detection (Hybribio) following the manufacturer's instructions. After sample collection a questionnaire to qualify device and technique and individual acceptability was applied and additional overall preference of three sample tests was evaluated

Results: A total of 120 women participated main chracteristicas are: median age 35 years; 40.8% married; 46.7% had a primary level of education; median age of sexual onset, 17.6 years Sensitivity The prevalence of any type of HPV with clinician sampling was 15.0%, 17.5% with urine sampling and 18.3% with vaginal self-sampling. Self-sampling sensitivity reached 94.4% (IC 74.2-99.9), and specificity 92.1% (IC 85.2-95.9). Urine sampling had a sensitivity of 88.8% (IC 67.2, 96.9), and specificity 94.1% (IC 67.2-96.9). The negative predictive value was 98.9% (IC 94.2-99.8) for vaginal self-sampling and 97.6% (IC 92.6-99.4) for urine sampling. Conclusions: This study shows that vaginal and urine self-sampling methods have similar sensitivity and specificity compared with clinician sampling for the diagnosis of HPV. The correlation between HPV genotypes among the three tests is satisfactory. Acceptability Compared with clinician sampling, both vaginal self-sampling OR 20.12 (7.67-52.8) and urine sampling OR16.63 (6.79-40.72), were more comfortable, granted more privacy: vaginal self-sampling OR 8.07 (3.44-18.93); urine sampling OR 19.5 (5.83-65.21, were less painful: vaginal self-sampling OR 0.07 (0.03-0.16); urine sampling OR 0.01 (0-0.06) and less difficult to apply: vaginal self-sampling OR 0.16 (0.07-0.34) urine sampling OR 0.05 (0.01-0.17). Overall preference has shown an advantage for vaginal self-sampling 4.97 (2.71-9.12). No statistically significant preference was demonstrated with urine self-sampling versus clinician sampling.

Conclusions: This study shows that vaginal and urine self-sampling methods have similar sensitivity and specificity compared with clinician sampling for the diagnosis of HPV. The correlation between HPV genotypes among the three tests is satisfactory. Self sampling methods have a high acceptance in rural communities. Doubts on the reliability of self-sampling often appears to be a limitation on the acceptability.

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#4710

Systematic Review of Data Systems related to Cervical Cancer and HPV vaccination in Selected Middle-Income Countries

39 - Low resource settings

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Background/Objectives: Cervical cancer is the fourth most common cancer in women. About 90% of the cervical cancer cases are linked with Human papillomavirus (HPV). Multiple public health agencies, including the WHO, have made the call to action for the elimination of cervical cancer. To assess the progress towards the elimination goal, population-level studies that evaluate the disease burden, and the impact and effectiveness of HPV vaccination and cervical cancer screening are needed. To conduct these studies, robust data are required for continuous evaluation and tracking against established targets. The goal of our study is to examine whether there exist reliable data systems in middle-income countries (MICs) that can support HPV-related research.

Methods: Following the PRISMA checklist, we conducted a systematic literature review to summarize data systems that contain information on cervical abnormalities and cervical cancer, HPV vaccination coverage, and cervical cancer screening in nine MICs: South Africa, Mexico, Turkey, Kenya, Russia, Philippines, Vietnam, Brazil, and Indonesia. We developed relevant keywords and searched PubMed for studies published in the past ten years. Two reviewers independently screened the retrieved articles in two rounds of screening. In each round, disagreements were discussed to reach a consensus or resolved by a third reviewer.

Results: Fifty-three studies were included in the final information extraction. The numbers of studies by country are: Brazil (26), South Africa (10), Mexico (5), Turkey (5), Kenya (3), Russia (3), Vietnam (1), Philippines (0), and Indonesia (0). South Africa, Brazil, and Mexico had data systems related to cervical abnormalities and cervical cancer and cervical cancer screening. Turkey, Kenya, and Russia had data systems related to cervical abnormalities and cervical cancer. Vietnam had data systems related to HPV vaccination coverage. Philippines and Indonesia had no relevant studies.

Conclusions: There is a lack of data systems in MICs that can support HPV-related research.

HN03 - HPV and H&N Forum - Submitted papers 1

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#4898

Factors independently associated with oncogenic oral-HPV infection among men from Brazil, Mexico and USA participating in the Human Papillomavirus Infection in Men (HIM) Study.

29 - Oral HPV infection

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Background/Objectives: HPV-related oropharyngeal cancers are mainly caused by oral oncogenic HPV infection1. However, the risk factors associated with these infections are still understudied. We investigated the risk factors that are independently associated with oncogenic oral HPV, in the multi-national Human Papillomavirus Infection in Men (HIM) Study.

Methods: Men aged 18-70 years old provided at least two oral-rinse and gargle samples, at 6-monthly intervals. Data on sociodemographic and behavioral characteristics were collected using a computer-assisted self-interview. HPV was genotyped using the HPV SPF10 PCR-DEIA-LiPA25, (DDL Diagnostic Laboratory, Netherlands) line probe assay system. Factors associated with oral HPV incidence were assessed by multivariate Cox proportional hazard models.

Results: Among men from the USA (881), Brazil (1235), and Mexico (1021), factors independently associated with oncogenic oral HPV infection were education duration, lifetime number of female sex partners and number of male sex partners in past 6 months. Importantly, risk of acquiring a new oral oncogenic HPV infection did not vary by age but was significantly higher among men from the US (aHR 1.55; 95% CI: 1.02-2.36) compared to Brazil and Mexico. The risk of acquiring new infections was higher in men educated for 13-15 years (aHR 1.96; 95% CI 1.95 (1.33-2.88) and at least 16 years (aHR 1.47; 95% CI 1.47 (1.02-2.12), compared to those who completed 12 or less years. In comparison to men who reported having no female sex partners, those who had 3-7, 8-19 and >19 lifetime number of female sex partners in their lifetime, were at increased risk of infection (aHR 2.60; 95% CI 1.24-5.45, (aHR 2.77; 95% CI 1.29-5.95) and (aHR 2.80; 95% CI 1.29-6.07), respectively. Men who reported ^{3}2 male sex partners in the past six months had elevated risk of acquiring a new oral oncogenic infection (aHR 1.99; 95% CI 1.06-3.74).

Conclusions: Multiple sex partners, recent male and lifetime female, increase the risk of men acquiring oncogenic oral HPV infections. The interesting association of longer duration of education with new infections requires further investigation to guide prevention strategies and awareness campaigns.

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#4955

Laryngeal papilloma and presence of bacterial species.

29 - Oral HPV infection

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Background/Objectives: Laryngeal papilloma (LP) is caused by HPV6 or 11. The chronic LP-patients require regular surgical treatment and are considered non-curable. This provokes the question of how HPV can persist and express viral genes that drive proliferation without being uncovered and cleared by the immune system. We recently demonstrated that LP display an immune profile characterized by enhanced expression of neutrophilic markers (Ref 1). The normal function of neutrophiles is to respond and kill invading bacterial pathogens. The aim of the present study was to search for viable bacterial species in LP.

Methods: From the Earn Nose Throat Depts. in Lund and Umeå patients (N=23) had hitherto been invited. Swab samples from throat, healthy larynx and laryngeal papilloma (LP) were collected during anestesia just before routine surgery. Bacterial species was identified by standard methods at Clinical Microbiology Department of Region of Skåne, Lund. GBS serotypes was determined by PCR (Ref 2).

Results: We have hitherto cultivated samples from 23 patients comprising 17% (4/23) females and 83% (19/23) males. The mean age was 49 years (range 20 to 77 years). We observed respiratory pathogenic bacterial species in 35%, 26% and in 48% of throat, healthy larynx and LP, respectively. In bacterial cultivations performed from LP patients (N=21) positive for HPV6 or 11, Streptococcus agalactiae (Group B Streptococcus, GBS), was detected only among males and in 80% (4/5) of HPV11-positive LP, whereas GBS was present in only 6% (1/16) of HPV6-positive LP (P=0.004). Four patients had GBS serotype 1a, and one patient had GBS serotype 1c. Two patients with HPV11 positive LP, who had surgery 135 and 151 times, both had GBS serotype 1a. The frequency of bacterial species among 23 LP-patiens are shown in the supplementary file.

Conclusions: Linking GBS to LP with HPV11 is a new observation. Our study indicates that further studies of the bacterial flora among LP-patients should be performed.

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#4901

IMPACT OF CIRCULATING CELL FREE TUMOR TISSUE MODIFIED VIRAL-HPV DNA TESTING ON POST-TREATMENT IMAGING SURVEILLANCE PROTOCOL IN OROPHARYNGEAL CARCINOMA

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Post-treatment surveillance imaging recommendations for oropharyngeal squamous cell carcinoma (OPSCC) lack level I evidence, with significant variability in protocols by institution and providers. In addition to cross-sectional imaging (CSI), peripheral blood testing is available to detect circulating, cell free tumor tissue modified viral (TTMV)-HPV DNA in >90% of OPSSC. Given the paucity of data regarding radiologic surveillance with circulating tumor DNA (ctDNA) blood testing,1 this study aims to evaluate a novel post-treatment serologic surveillance pathway.

Methods: Retrospective review of post-treatment imaging in HPV-associated OPSCC was performed over 2-years at a single site. Frequency of CSI was compared between 2 groups: 1-year prior to ctDNA (control) versus 1-year after ctDNA (experimental). Eligible participants included patients treated for primary HPV-associated OPSCC with no evidence of disease on 3-month, post-treatment PET/CT. In-office exam and point of care ultrasound (POCUS) was used at each surveillance visit for all participants to assess for regional recurrence. The control group received CT neck with contrast every 6-months and CT chest at 6-12 months based on smoking history. The experimental group received ctDNA testing (NavDx, Naveris, Inc.) every 3-months; no additional imaging was obtained 1) unless there was concern for recurrence based on exam/POCUS/blood testing or, 2) deemed high-risk for metachronous lung primary per US Preventative Services Task Force (USPSTF) recommendations.2

Results: Among 81 participants, 25 controls (31%) underwent routine surveillance imaging and 56 (69%) received serologic surveillance. Over 12-months, all controls (100%) obtained at least 1 CT neck and chest. In the experimental group, 3 patients (5.4%) obtained a CT neck, yielding a 95% reduction in neck CSI. Of the experimental group, 26 (46%) were non-smokers (USPSTF low-risk); 30 (54%) were former/current smokers, of which 7 (1%) were considered USPSTF high-risk and received annual screening chest CT. Utilizing serologic surveillance, chest CSI was avoided in 100% of patients considered low-risk for metachronous lung primary (n=49, 88%).

Conclusions: ctDNA testing for OPSCC surveillance can decrease CSI neck and chest by 95% and 100%, respectively, in patients with low-risk smoking history. The impact of imaging reductions on health-system and individual-level costs, including patient financial toxicity, presents an area for future investigation. The potential to integrate surveillance ctDNA protocols may improve patient adherence to follow-ups and presents opportunities for novel remote tele-surveillance paradigms.

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#4935

FEASIBILITY STUDY ONCSALIVA - NON-INVASIVE SPECIMEN FOR THE DETECTION OF HEAD AND NECK CANCER VIA EPIGENETIC BIOMARKERS

15 - Molecular markers

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Background/Objectives: Head and neck squamous cell carcinomas (HNSCC) are mainly diagnosed at advanced tumour stages after the onset of symptoms. Timely detection would significantly improve the options for successful treatment of this disease. To that effect, sensitive diagnostic tools for early detection need to be established. Therefore, we want to leverage easy accessibility of non-invasive oral samples. A DNA methylation-specific qPCR-based assay was developed relying on five differentially methylated regions in HNSCC. It was previously validated using DNA from tumour and control tissue. Monitoring specific tumour markers in saliva could be useful for early diagnosis and postoperative recurrence risk assessment. The OncSaliva study is designed to determine the clinical performance of the multimarker panel in non-invasive specimen, such as oral swabs and saliva.

Methods: So far, study specimens were collected at the Department of Otorhinolaryngology at Jena University Hospital. Non-invasive specimens are collected pre-surgery and during post-surgical routine examinations. At the time of surgery fresh-frozen tissue samples from HNSCC patients and controls are collected. Isolated DNA is bisulfite-converted before use in methylation-specific multiplex qPCR. DNA methylation markers at the five genes ZNF671, ZNF833, ZIC1, PAX6-1, and HOXA9 and a bisulfite-specific reference locus at the ACTB gene were analyzed for the determination of diagnostic power. Analysis was based on valid samples only, referring to criteria for ACTB. The goal is to include 100 control individuals and 100 HNSCC patients. HNSCC patients shall be subjected to 2-year follow-up examination, until the end of 2024.

Results: Preliminary data of the OncSaliva study include 53 participants with HNSCC (53x tissue, 38x saliva, 7x swab samples) and 33 control participants (33x tissue, 22x saliva, 2x swab samples). Results of the multimarker panel in tissue showed 75% sensitivity and 100% specificity, if three of five markers were required to test positive. Single marker detection in tissue samples offered a diagnostic power of 83% sensitivity with 97% specificity for ZNF671. In saliva samples ZNF671 resulted in 71% sensitivity and 82% specificity. Analysis of all five markers in saliva resulted in 63% sensitivity and 91% specificity (three out of five positive). Comparing the multimarker panel results between tissue and saliva sample pairs yielded 49% to 78% agreement for the HNSCC group and 73% to 100% agreement in the control group. For an interim analysis of non-invasive specimen from post-surgery follow-up examinations we unblinded therapy courses for seven patients, for which data were available. For three patients we registered a persisting high DNA methylation in saliva samples, in agreement with a malignant event within the two years follow-up. Two patients showed low DNA methylation status during follow-up, consistent with the absence of recurrence. The DNA methylation pattern for two patients did not seem to correlate with therapy courses. Data from swab samples and individual patient follow-ups will be presented at the congress.

Conclusions: Preliminary results of the ongoing OncSaliva study support our hypothesis that DNA methylation analysis can robustly detect HNSCC in both, tissue and saliva. Offering a high diagnostic power in combination with simple sample self-collection methods, the evaluation of the HNSCC-specific epigenetic markers may provide the basis for a promising novel approach within HNSCC diagnostics.

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#4927

The Role of HPV in Determining Treatment, Survival, and Prognosis of Head and Neck Squamous Cell Carcinoma

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Human papillomavirus (HPV) infection has been identified as a significant etiological agent in the development of head and neck squamous cell carcinoma (HNSCC). HPV's involvement has alluded to better survival and prognosis in patients and suggests that different treatment strategies may be appropriate for them. Only some data on the epidemiology of HPV infection in the oropharyngeal, oral cavity, and laryngeal SCC exists in Europe. Thus, this study was carried out to investigate HPV's impact on HNSCC patient outcomes in the Irish population, one of the largest studies of its kind using consistent HPV testing techniques.

Methods: A total of 861 primary oropharyngeal, oral cavity, and laryngeal SCC (OPSCC, OSCC, LSCC) cases diagnosed between 1994 and 2013, identified through the National Cancer Registry of Ireland (NCRI), were obtained from hospitals across Ireland and tested for HPV DNA using Multiplex PCR Luminex technology based in and sanctioned by the International Agency for Research on Cancer (IARC). The Multiplex PCR uses HPV type-specific primers targeting the E7 region of 21 genotypes. A total of 19 of these are high-risk (HR) or possible HR (pHR) and include HPV16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68a, 68b, 70, 73, and 82. The remaining 2 are low-risk types HPV6 and 11. Independent variables, survival, and treatment data were provided for each patient case by the NCRI. These variables were then used to compare and contrast survival, prognosis, and treatment administered between HPVrelated and HPV-unrelated groups

Results: Overall HPV positivity rate was 17% (147/861), with the highest prevelance of HPV in the Oropharynx 41.1% (86/209),and lower positivity rates in Oral Cavity 10.9% (36/331) and Larynx 7.8% (25/321). Both overall and cancer-specific survival were significantly improved amongst all HPV-positive patients together, though HPV status was only a significant predictor of survival in the oropharynx. Amongst HPV-positive patients in the oropharynx, surgery alone was associated with prolonged survival, alluding to the potential for de-escalation of treatment in HPV-related OPSCC in particular.

Conclusions: Cumulatively, these findings highlight the need for continued investigation into treatment pathways for HPV-related OPSCC, the relevance of introducing boys into national HPV vaccination programs, and the relevance of the nona-valent Gardasil-9 vaccine to HNSCC prevention

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#5040

Prevalence of HPV infection in oropharyngeal cancer in Sardinian region

30 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Recently, it has been observed a dramatic increase in oropharyngeal squamous cell carcinoma (OPSCC) in Western countries, likely related to the Human Papillomavirus (HPV) infections. Globally, the burden of HPV-driven OPSCC has been estimated at 45% with significant variation by different geographical regions. Referred to the new AJCC staging system, which discriminates between HPV-positive and -negative OPSCC, the use of validated assay for the diagnosis of HPV-related cases becomes crucial. Our first aim was to assess the prevalence of HPV infection in North Sardinia (Italy) and, moreover, evaluate the reliability of p16 IHC alone for the diagnosis of HPV-driven carcinogenesis, comparing the combination with molecular test.

Methods: Patients with OPSCC diagnosed in North Sardinia, between 2017-2021, were enrolled. Demographic, clinical and epidemiological findings were collected from medical records, including information at follow-up. According to AJCC classification, FFPE samples were subjected to p16IHC for diagnosis of HPV-driven OPSCC. Moreover, HPV-DNA detection was performed using generic primers GP5+/GP6+ followed by detection of E6-mRNA RT-PCR for positive cases. The Cohen's Kappa coefficients were calculated to assess the HPV positivity agreement between p16 alone and IHC in combination with HPV-DNA test.

Results: A total of 62 cases were diagnosed, mainly in males (87%) with a mean age (±SD) of 64 (±10.2) years. 14.5% (9/62) of samples resulted positive at p16 IHC and HPV-DNA analyses, mainly caused by HPV-16 (6/9) genotype, followed by HPV-18 and -35. Sensitivity and specificity of p-16 alone was respectively 100% and 75%, with 3 HPV-negative cases stained positive for p16-IHC (Cohen's Kappa=0.83). No statistically significant difference was observed in disease-free-survival at 3 years between positive samples at p16/HPV-DNA combination vs p16 alone (100% vs 64%).

Conclusions: Our study showed a lower prevalence of HPV infection in OPSCC in comparison with national and international data, evidencing the need for more reliable and specific tests for the diagnosis of HPV-driven OPSCC in areas with lower prevalence of HPV infection, such as Sardinian region. In this scenario, the currently recommended standard by AJCC (p16 IHC alone) could provide a high rate of false positive results, with relevant implication in the choice of treatment (e.g., deintensification therapy), and consequently wrong prognosis of diseases.

FC12- Free communications - HPV prophylactic vaccines 2

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#4534

LONG-TERM EFFICACY, IMMUNOGENICITY, AND SAFETY OF THE QUADRIVALENT AND 9-VALENT HPV VACCINES: AN OVERVIEW OF CLINICAL TRIAL LONG-TERM FOLLOW-UP STUDIES

06 - HPV prophylactic vaccines

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Background/Objectives: Given the lifetime risk of HPV infection, prophylactic HPV vaccine clinical programs must demonstrate durable protection against infection and disease. Pivotal baseline clinical trials of the quadrivalent (qHPV) and 9-valent (9vHPV) vaccines were extended to assess long-term effectiveness against infection and disease up to 14 years (y).

Methods: Six long-term follow-up (LTFU) extension studies were designed to evaluate long-term effectiveness of the qHPV (NCT00092534, NCT00090220, NCT00090285, NCT00092547) and 9vHPV (NCT00943722, NCT02653118) vaccines in females (aged 9-45y) and males (aged 9-26y), with follow-up periods of 10-14y. Endpoint evaluation was carried out in a rigorous fashion throughout the studies. Tissue samples collected because of lesions suspicious for HPV-related disease were analyzed. Pathology panel adjudication was performed on all tissue specimens, and HPV typing was conducted to determine endpoint attribution. In some studies, participants randomized to placebo in qHPV vaccine trials who received catch-up qHPV vaccination at the end of the base study were followed during LTFU to evaluate effects of delayed vaccination at an older age.

Results: Across all studies, the qHPV and 9vHPV vaccine demonstrated durable effectiveness; no cases of high-grade cervical, vulvar, vaginal, and anal dysplasia or condyloma related to vaccine-targeted HPV types were observed during LTFU. Vaccine effectiveness was also observed in the catch-up qHPV vaccination groups. The LTFU studies included participants vaccinated at various ages (9-45y), of both genders, of various sexual orientations (heterosexual men and men having sex with men), and various countries across five continents, which supports the generalizability of the results.

Conclusions: Over 10-14y, qHPV and 9vHPV vaccines provided sustained protection with no breakthrough disease related to HPV vaccine types across studies in males vaccinated at ages 9-26y and females vaccinated at ages 9-45y. Catch-up vaccination was effective, suggesting that vaccination of adults not previously vaccinated may be beneficial.

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#4797

Gender-neutral HPV vaccination policies in the European Union and the UK: a matter of equity, the role of LGBT permissive societies and advocacy.

06 - HPV prophylactic vaccines

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Background/Objectives: In Europe, 2,5 % of all cancers is HPV-related and men account for an estimated 20 to 30% of these [i]. Men who have sex with men suffer a disproportionate disease burden, as they are considerably more at risk for anal cancer, driven by a different sexual behaviour and an ongoing HIV epidemic in their communities in Europe [ii]. Additionally, the incidence of HPV-related head and neck cancer is rising, especially in men[iii]. Although the European approval of the first HPV vaccine for boy's dates from 2006, the introduction of gender-neutral vaccination (GNV) for HPV in national immunisation programmes has been widely varied in the context of the European Union (+UK), raising equity issues towards men, and MSM in particular.

Methods: First, a country-level comparison was made between ILGA Rainbow Score, an indicator developed by ILGA (International Lesbian and Gay Association) of a LGBT friendly climate in a country, and HPV vaccination policy (girls-only vs gender-neutral). An additional comparison was made with another LGBT-specific health issue: PrEP (pre-exposure prophylaxis, in the context of HIV) accessibility for MSM and its public funding status. Secondly, two countries were chosen as case studies (one with early and one with late adoption of GNV) and stakeholders from policy-making side and advocacy side were interviewed to get their country specific perspectives on the policy-making process and perceived barriers and opportunities towards GNV.

Results: A correlation was found between high ILGA rainbow scores, signalling LGBT friendly countries, the implementation of gender-neutral HPV vaccination, and access to PrEP, although some outliers were notable. Stakeholder interviews revealed the importance of LGBT advocacy in reaching GNV in the two countries. Main barriers that were mentioned were that equity is typically not included in cost-effectiveness models, the relative high cost of the vaccine, the low awareness of HPV-related disease in men in the general public and LGBT communities as a health issue and the perceived reluctance to communicate about sex. For the UK, a well organised coaltion of different stakeholders, media attention and political involvement were identified as important opportunities. In the Dutch context, stakeholders mentioned the lack of a coalition between anti-cancer organizations and sexual health organizations, the tradition of austerity, normative thinking about sexuality and antivaccination lobbying as potential barriers.

Conclusions: In Europe, LGBT friendly countries tend to implement GNV earlier, mostly driven by LGBT advocacy. Context specific barriers apply and might explain discrepancies between scores on LGBT friendly legislation and the implementation of gender-neutral HPV vaccination. Coalition building between stakeholders, as was seen in the UK, might be a promising way to more efficiently advocate for GNV towards policymakers.

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Country-level association of ILGA rainbow scores and HPV vaccination policies

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#4900

Title: Safety and immunogenicity of Gardasil4® in females age 9-26 with juvenile idiopathic arthritis.

06 - HPV prophylactic vaccines

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Background/Objectives: Gardasil4® was first approved by the FDA in December 2006 in females age 9-26 for prevention of human papilloma virus (HPV) infection. However, rodent literature suggested that antigen-specific responses to this new type of recombinant vaccine comprised of vaccine-like particles (VLP) may be attenuated by inhibition of cyclooxygenase-2 (COX-2). At study start, children and young adults with juvenile idiopathic arthritis (JIA) of all forms were commonly treated with non-steroidal anti-inflammatories that inhibit both COX-1 and COX-2 or were selective for COX-2. We hypothesized that if COX-2 inhibition is a clinically relevant issue that JIA patients might not respond to Gardasil4â. Further concerns of vaccine-induced autoimmunity expressed in the lay literature might manifest as flare of JIA. Therefore, we proposed to determine the safety and immunogenicity of HPV vaccination in JIA.

Methods: Females with JIA age 9-26 (JIA is defined as arthritis onset at < age 16 years) were recruited from four centers. Patients who had controlled disease were immunized at baseline, 2 months and 6 months. Patients with systemic onset JIA (sJIA) with active systemic symptoms were excluded. The primary outcome variable was the presence of antibody directed against HPV 6, 11, 16 and 18 contained in Gardasil4â as measured by mean geometric titers (GMTs). Responses were dichotomized as positive or negative. Secondary outcome measures included GMTs at months 12 and 24 and disease flare over 24 months requiring intensification of NSAIDs, or addition of corticosteroids, new conventional DMARD or biological DMARD.

Results: 42/43 had a baseline visit, 39/42 a 7-mo. visit, 38/42 a 12-mo. visit including 2 patients with baseline antibody (ab) directed against HPV6, and 1 each against HPV 11 and 18. At 7 mo. 34/35 (97.14%) patients had detectable antibody to HPV 06, 35/35 (100%) to HPV 11, 16 and 18. The patient who had undetectable antibody to HPV06 did seroconvert and had ab directed at HPV06 at 12 months. At 12 months, 27/27 patients had ab detected against HPV06, 11 and 18 (100%) and 26/27 (96.3%) against HPV11. JIA flares after achieving inactive disease happened in 42.5% JIA patients(1). Vaccination was not associated with an excess of JIA flares. Gardasil®4 was not associated with any serious adverse events other than a pregnancy > 4 months after completing immunization. The protocol was modified to exclude pregnancy as an AE/SAE if conception occurred after the conclusion of the vaccine series.

Conclusions: The study met its primary endpoint in demonstrating that Gardasil4® was highly effective in inducing evidence of serological immunity against HPV serotypes 06,11,16 and 18 in females with JIA despite use of combinations of NSAIDs, low dose-steroids, methotrexate and tumor necrosis factor alpha inhibitors (TNFi). Gardasil®4 was not associated with any serious adverse events other than a pregnancy > 4 months after completing immunization. Immunization against HPV was not associated with an unusual number or pattern of flares. We conclude that Gardasil®4 is safe in females with JIA with the caveat that those with sJIA and systemic symptoms were excluded. Limitations of the study include that T-cell responses were not measured but also react to vaccine and contribute to resistance against HPV.

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#4535

PERI-TREATMENT USE OF PROPHYLACTIC HPV VACCINES IN PATIENTS WITH HPV-ASSOCIATED DISEASE: REVIEW OF THE MECHANISM OF ACTION

06 - HPV prophylactic vaccines

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Background/Objectives: Individuals with HPV-related disease remain at risk for subsequent HPV-related infection and disease after undergoing treatment for specific HPV-related lesions. Prophylactic HPV vaccines have shown benefits in preventing subsequent HPV-related disease when administered before or soon after treatment. However, the terminology used to describe vaccine effects in these populations is ambiguous, sometimes implying adjuvant or direct therapeutic effects, which would be considered off-label. In such cases, the terminology can become misconstrued and cause confusion about when vaccination can be effective and how it works.

Methods: We reviewed the published evidence for using prophylactic HPV vaccines in patients with HPV-associated disease before, during or after treatment, in the context of potential mechanisms by which individuals with HPV-associated disease may or may not benefit from vaccination.

Results: Based on the current understanding of the HPV life cycle and vaccine mechanism of action, prophylactic HPV vaccination is not expected to clear active persistent HPV infection or unresected HPV-associated dysplastic tissue remaining after surgery. However, vaccination may reasonably be expected to prevent new HPV infections caused by a different HPV type as well as re-infection with the same HPV type, whether from a new exposure to an infected partner or through autoinoculation from an adjacent productively infected site.

Conclusions: Given the reviewed virus biology and vaccine mechanism of action, vaccination should be termed prophylactic HPV vaccination regardless of past or present HPV disease. Precise terminology relating to use of prophylactic vaccines in this population is critical to avoid the incorrect expectation that prophylactic vaccines have direct therapeutic potential.

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#5841

VULVACCIN-trial: Adjuvant HPV vaccination in patients treated for vulvar HSIL, a Randomised Placebo Controlled Trial.

06 - HPV prophylactic vaccines

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Background/Objectives: Problem definition: HPV causes approximately 5% of all cancers worldwide. It is estimated that 30% of all vulvar carcinomas are HPV related. Vulvar carcinoma has a premalignant precursor caused by HPV, called vulvar High Grade Squamous Intraepithelial Lesion (vHSIL) with an estimated incidence of three in 100.000 woman and is rising over the last decades. The peak incidence of vHSIL is between 35 and 40 years of age and approximately 10% of women with (treated) vHSIL will develop vulvar cancer within 10 years of first diagnosis. Multiple treatment methods for vHSIL are available, including surgery, laser vaporization, and topical imiquimod, all with comparable treatment success. Despite treatment at least 30% of women will develop a recurrence within 2 years. This results in multiple treatments with disfiguring effects and is associated negative psychosocial and psychosexual impact. The economic burden of HPV related diseases are substantial. When additional HPV vaccination for vHSIL is effective this will reduce the costs. Patients wellbeing should be improve as well. To date, a successful strategy for reduction of recurrences has not been established. The available evidence of additional HPV vaccination at treatment of vHSIL is promising, yet insufficient to guide clinical practice. A retrospective analysis of pooled data of 2 RCTs showed a significant reduction of 35% (irrespective of causal HPV type) to 64% (related to vaccine type) for recurrences of vHSIL after adjuvant quadrivalent HPV vaccination. Recently, a case-control study was published showing a reduction over 40% of recurrences after quadrivalent HPV vaccination, due to small groups this reduction was not significant. There are no reports of studies on adjuvant nonavalent vaccination in woman with vHSIL. As all HPV variants that are linked to vHSIL are covered by the nonavalent vaccine,(8) we propose a prospective double blind randomized controlled trial investigating adjuvant nonavalent HPV vaccination compared to placebo for reduction of recurrence in women treated for vHSIL. Objective: The main aim of the proposed study is to determine the efficacy of additional nonavalent HPV vaccination in women who undergo treatment for vHSIL in preventing recurrence. There are currently two major trial on cervical HSIL and adjuvant HPV vaccination (VACCIN and NOVEL-trial). The evidence for prophylactic HPV vaccination is promising, but still in the research phase. We think the effect will be the same with vulvar hsil.

Methods: Randomized, double blind, placebo controlled trial in female patients treated for vHSIL. Patients will be randomized into two study groups: adjuvant vaccination with nonavalent HPV vaccine or placebo.

Results: Objective: To determine the efficacy of additional nonavalent HPV vaccination in women who undergo treatment for vHSIL in preventing recurrence within 24 months

Conclusions: This is a presentation on an upcoming intenrational trial on additional HPV vaccinations for vulvar HSIL. The study proposal is currently under review.

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#4801

Association of Child's Age, Parental HPV Vaccine Hesitancy, and HPV Vaccine Initiation

06 - HPV prophylactic vaccines

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Background/Objectives: HPV vaccination is now approved for ages 9-45, but the vaccine is only effective prior to exposure to the virus, so it is targeted to younger children and adolescents. CDC's Advisory Committee on Immunization Practices recommends vaccine initiation at ages 11-12, but in recent years, the American Academy of Pediatrics has shifted their recommendation earlier, targeting ages 9-12 for initiation. This analysis examined the association of age with parental HPV vaccine hesitancy and uptake.

Methods: An online Qualtrics survey was administered to parents of children aged 9-17 years in Arkansas, Mississippi, Missouri, Tennessee, and Southern Illinois in July 2021. Responses from 926 parents were summarized and analyzed using chi-square tests and multivariate logistic regression.

Results: 18.6% of parents with a child aged 9-12 and 23.2% of parents with 13-17-year-olds were categorized as HPV vaccine hesitant. The majority of parent reported that they believed the ideal age for HPV vaccination was between ages 12-15. 18.6% of children ages 9-12 had received at least one dose of HPV vaccine, while 52.3% of 13-17-year-olds had received at least one dose. Overall, 13-17-year-olds were 6 times as likely to be vaccinated as 9-12 year olds (OR: 6.01, 95% CI: 3.98-9.08).

Conclusions: Despite recommendations to initiate HPV vaccine at earlier ages (9-12), most parents still believed that 12-15 years was the ideal age to vaccinate their children. Overall, rates of vaccination are low in the states across this 5-state region for adolescents aged 9-17 (42.3%), but the uptake is less than half for 9-12-year-olds compared to 13-17-year-olds. Given that only 2 doses are needed for ages <15 and completion rates have been found to be higher when the series is initiated earlier, efforts are needed to educate both parents and providers on the benefit of earlier age of HPV vaccine initiation.

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#5065

HPV VACCINE PRESCRIPTION AND COMPLIANCE IN A COHORT OF WOMEN UNDERGOING AN EXCISION OF THE TRANSFORMATION ZONE

06 - HPV prophylactic vaccines

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Background/Objectives: In Portugal, HPV vaccination was included into the National Immunization Program in 2008. Since 2020, girls and boys are receiving two doses of 9-valent HPV vaccine at the age of 10. Coverage rate of this program is over 92%. However, most women who developed cervical lesions are not vaccinated, yet. Cervical pathology appointment seems to be a good opportunity to HPV vaccination counseling. Our aim is to evaluate the vaccination compliance and the reasons not to have been vaccinated in a cohort of women undergoing an excision of the transformation zone in our unit.

Methods: A retrospective analysis of data from women who have undergone an excision of the transformation zone, in our unit, between January 2018 and December 2019 was performed. Sociodemographic and clinical data and previous HPV vaccine status were evaluated. A telephonic questionnaire was carried out at least three years after the first appointment to assess vaccination compliance and the reasons for not having been vaccinated.

Results: A total of 236 women were included. The median age was 42 years old (minimum of 20 and maximum of 67 and the majority of women were not qualified workers. The histologic results of the excision were: carcinoma (3%); adenocarcinoma (2.1%); LSIL (25.4%); HSIL (64.4%); without dysplasia (5.1%). Only nine (3.8%) has already been immunized anti-HPV. Our preliminary results show that after vaccination counseling, almost 50% of women were vaccinated. Most women completed 3 doses. The main reasons for not having been immunized were lack of knowledge/counselling, planning to be vaccinated later, price difficulty and not to believe in vaccine benefits.

Conclusions: The choice to be vaccinated against HPV after excision of transformation zone is strongly associated with a proper recommendation by the health professional.

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#5034

HPV VACCINATION CHANGES OVER TIME IN YOUNG POPULATION IN BRAZIL: RESULTS FROM THE POP-BRAZIL STUDY

06 - HPV prophylactic vaccines

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Background/Objectives: Surveillance of vaccination coverage and the knolwdge about the people willing to vaccinated or not is critical to guide immunization policies and plan strategies to ensure immunization targets. We aimed to evaluate the changes in HPV vaccination rates and profile over time in Brazil.

Methods: The POP-Brazil study is a cross-sectional panel data that evaluates the impact of the vaccination in Brazil. The baseline was done in 2016-2017 and the second study started in 2021. Participants from 16-25 years from all 27 state capitals are invited to answer an interview and provided sample for HPV genotyping. Vaccination status was self-reported. Samples were processed in a central laboratory using Linear Array HPV Genotyping Test in the first study and Anyplex-II HPV-28 detection kit (Seegene®) in the second study.

Results: The vaccination coverage has improved from 7.45% in the POP-Brazil to 39.33% in the POP-Brazil-2 ($p<0.001$), without increasing in the coverage of boys that remains around 15%. There is a decrease in coverage according to age, with lower rates in younger ages (from 52.27% to 13.76%, $p<0.001$) and also a decrease of vaccination in higher educated people (from 21.96% to 4.87%, $p<0.001$) and in the very low educated participants (from 25.03% to 10.27%, $p<0.001$).

Conclusions: Although there was an expected increase in HPV vaccine coverage across time, the decrease in lower ages (16-17 years) denotes a decrease in vaccination rates in recent years. The changes in coverage according to educational levels can be associated to the rise of anti-vaccination movement in Brazil. The continuous surveillance on HPV coverage provide data to improve programme performance. Substantially improvement on vaccination uptake is needed to reduce the burden of HPV-associated cancers in Brazil.

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#4365

Sociodemographic Barriers to Human Papillomavirus Vaccination among Eligible United States Veterans

06 - HPV prophylactic vaccines

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Background/Objectives: Human papillomavirus (HPV) associated malignancy is increasing among US Veterans, and the current status of HPV vaccination at the VA is unknown, hindering any HPV vaccination programs. We aim to define HPV vaccination prevalence among young Veterans and to identify sociodemographic factors associated with vaccine adherence.

Methods: Design: Cross-sectional study Setting: Veterans Health Administration Corporate Data Warehouse Participants: Veterans 18-26 years of age with at least one primary care visit from 2018-2020 HPV vaccination status (any vs. no history of vaccination) was examined by age, sex, race/ethnicity, socioeconomic status, the branch of service, and geographic region. The National Health and Nutrition Examination Survey (NHANES) from 2017-2020 was used to compare HPV vaccination prevalence in the general US population. Odds ratios with 95% confidence intervals (95% CI) of vaccination were calculated with logistic regression. Geospatial differences in vaccination were represented by mapping vaccine prevalence in young Veterans by VHA Districts and Integrated Service Networks (VISNs) and states.

Results: Among Veterans ages 18-26 (n= 128,279), 30.2% of females and 18.7% of males had any history of HPV vaccination. In NHANES, the prevalence of any HPV vaccine was 62.4% and 37%, respectively. Geographically, VISN 5 (4.4% [95% CI: 3.7%-5.1%]) and VISN 17 (11.9% [95% CI: 6.65%-7.61%]) had particularly low prevalence. In an adjusted model, young male Veterans have lower odds of vaccination (0.52 [95% CI:0.50-0.53]) compared to young female Veterans. The odds of vaccination decrease with increasing age, and veterans living in low socioeconomic status zip codes had lower odds of vaccination than Veterans living in high socioeconomic zip codes.

Conclusions: Overall, HPV vaccination in the VHA population was considerably lower than in the general US population, suggesting barriers to vaccination extend beyond access to care. Since these Veterans have sought care through the VHA, we identified individuals that could benefit from directed vaccination efforts as an initial step to reducing HPV-related cancer incidence in this population.

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#5037

Knowledge and uptake of HPV vaccination and cervical cancer screening: preliminary data from an Italian Region

40 - Public health

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Background/Objectives: HPV vaccination is offered since 2009 in the Marche region of Italy, where one study on vaccine effectiveness suggested the presence of a herd-protection effect.(1) The interpretation of this finding would benefit from data on the prevalence of cervical cancer risk factors, on the characteristics associated with the uptake of vaccination and screening, and on the knowledge of these two preventive strategies among the pupulation in question.

Methods: The present cross-sectional study used an anonymous, web-based, self-administered questionnaire adapted from previous work on determinants of uptake of HPV vaccines and cervical screening, which targeted a convenience sample of young women aged 25-35 years from the Marche region. Descriptive statistics were then calculated.

Results: In the period between July and September 2021, 112 women answered the questionnaire, 66.1% of which were aged 25-27 years (mean age 27.5 years, standard deviation 3.1). 70.5% had a university degree, and about 6% and 5% perceived their socioeconomic status as lower or higher than average, respectively. Current and former smokers were 53.6%, and only 9.8% had at least one full-term pregnancy. Mean age at menarche was 12.4 years (SD 1.5), and excluding the 7.1% who did not have their sexual debut, mean age at first intercourse was 17.5 years (SD 2.6). Among the sexually active women, 26.8% had only one lifetime partner, 32.1% had 2-4 partners, and 33.9% had 5 or more. Considering only the last year, 11.6% did not have a partner, 73.2% had one, and 15.2% had 2 or more. Furthermore, 35.7% of the women declared that their main partner also had other partners. Partners were of the same age for 37.5%, older for 62.7%, and younger for 9.8% of respondents. Concerning the use of contraceptives in the last year, 19.6% and 5.2% used the pill and the vaginal ring, respectively, whereas only 25.9% consistently used barrier contraceptives, 39.3% used coitus interruptus (often in combination with condoms), and 5.4% used either nothing or coitus interruptus alone. The women vaccinated against HPV were 61.6% of the sample (95%CI 51.9-70.6), including 7.2% partially vaccinated. 2.7% requested an appointment but missed it, 15.2% did not think the vaccine would benefit them as they were already sexually active, and 20.5% had not heard of it at the time of the vaccination campaign. Indeed, 62.5% of the sample reported knowing of the vaccine since adolescence, with acquaintances, friends, family, and promotion campaigns as the main sources of information. Almost a quarter (24.1%) reported being taken to the vaccination appointment by their parents. Fear of adverse effects was cited by 7.2% of the women, and 76.8% had received at least one tetanus vaccine booster dose (3

Conclusions: The studies available to date identify fear of adverse effects and not receiving information from a healthcare professional as associated with vaccine refusal, and low schooling levels as associated with non-adherence to screening.(2-4) The present survey should be extended to a larger sample to explore these trends and potential others, and to guide the interpretation of estimates of vaccine effectiveness in the same population.

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#4987

After-conization HPV vaccination uptake: real-world data from Puglia (Italy)

07 - HPV therapeutic vaccines

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Background/Objectives: HPV is the etiological agent of epithelial lesions and cancers of various body sites in both genders. More than 100 subtypes of HPV exist. Subtypes 16 and 18 are mostly associated with high-grade squamous intraepithelial lesions (HSIL), a pre-cancerous lesion that involves vagina, vulva, anal canal and peri-anal skin. Nowadays, HPV-related cervical cancer is the fourth most common cancer in women. HPV infection is decreasing following implementation of vaccination programs. According to WHO's recommended "screen-and-treat" approach, screening tests should be the first approach to high-risk subjects, who should be treated immediately after a positive test. Available screening tests include HPV molecular testing, visual inspection with acetic acid and cytology (Pap-test). Treatments include cryotherapy, large loop excision of the transformation zone and cold knife conization. The earliest findings regarding the effectiveness of HPV vaccination in preventing recurrence of CIN2-3 lesions after surgical treatment date back to 2013. This scientific evidence has become widespread in clinical practice over the years. In Italy, HPV vaccination is recommended after conization since 2020, when guidelines on post-treatment CIN2-3 follow-up were published. This report aims to investigate the vaccination uptake in women who underwent conization in Puglia, a region in Southern Italy.

Methods: This is a retrospective observational study. Data about surgical procedures was obtained from the analysis of the hospital discharge records, using ICD-9 code 67.2 as key code for hospital discharge records and code PCA27 for inpatient care, while data regarding HPV vaccination was extracted from Apulian regional immunization database.

Results: From 2017 to 2020, 5,566 women underwent CKC. Their average age was 43.69 ±12,98 years. Among them, 6.9% (384/5,566) had received at least one dose of HPV vaccine before surgery. 15.1% (839/5,566) of women received at least one dose of 9-valent HPV vaccine after surgery. Among the latter, 9,7% (81/839) received at least one dose of 9-valent HPV vaccine before surgery. The average time between the day of surgery and vaccination was 309.8 days (1-1853).

Conclusions: The gathered data highlights how catch-up activities in Puglia are still far from the desirable values. Indeed, after-surgery vaccination uptake is lower than ideal, and vaccination is often offered with significant delay after surgery. It is therefore necessary to structure new communication and information strategies to increase both the patients' awareness about HPV-related diseases and their management and healthcare providers' knowledge about vaccination. This would lead to improved vaccination strategies and better healthcare for vulnerable patients.

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#4663

HPV vaccination uptake in men who have sex with men in Europe: a meta-analysis

37 - Advocacy, acceptability and psychology

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Background/Objectives: Most European countries currently enforce female-only HPV vaccination policies. However, gender-neutral vaccination is considered paramount, as it increases protection in all subjects while granting coverage for men who have sex with men (MSM). MSM are in fact a high-risk population for HPV. This meta-analysis investigates European MSM's HPV vaccination uptake.

Methods: Scopus, MEDLINE/PubMed and ISI Web of Knowledge were systematically searched for articles covering the topic of HPV vaccination willingness among MSM in the European Union and the United Kingdom. Studies published from 2018 to 2022 were included. The main outcome for the pooled analysis was the proportion of HPV-vaccinated MSM. Article selection followed PRISMA guidelines.

Results: 14 studies from the UK, France, the Netherlands and Greece were included, 7 of which were quantitative. The pooled analysis on 69.871 MSM (age: 16-45 years-old) showed a vaccination uptake of 37.1%, with the highest value in British studies (51.3%) and the lowest in French studies (13.6%). The systematic review of literature identified various vaccine uptake determinants among MSM. Attendance of sexual health clinics was especially relevant, as well as HIV positivity and a history of anogenital warts. MSM manifested a generally positive opinion of HPV vaccination. Acceptability was lower in MSM who neither use gay-oriented dating apps nor attend gay venues, while higher in HIV-positive subjects. No significant acceptability differences were identified between MSM and heterosexual men. The main weakness of vaccination campaigns is the low vaccine offer by HCPs. MSM's knowledge about HPV and HPV vaccination was found wanting, and high vaccine costs were reported as barriers. Finally, concerns about stigmatization were raised by a British study's participants.

Conclusions: Despite a low vaccination coverage, European MSM have a positive attitude towards HPV vaccination. Policies should facilitate the access to vaccination for people in economic disadvantage and promote knowledge about HPV and its vaccine.

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FC13- Free communications- Screening / HPV testing 1

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#4959

FOCUS ON ATYPICAL GLANDULAR CELLS LESIONS IN CERVICAL CANCER SCREENING: INDICATOR PERFORMANCES, CORRELATION WITH HPV TEST AND HISTOLOGY

10 - HPV screening

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Background/Objectives: The Bethesda System (TBS), conventionally used as classification system for the cervicovaginal cytology (Pap test), helps the professionals to interpret correctly all the morphological patterns, including the Atypical Glandular Cells(AGC). However,the cytological diagnosis of endocervical atypia or neoplasia could be difficult also for experienced cytologists. During the GISCi meeting (Italian Cervicocarcinoma Screening Group) in 2019, a specific working group has been settled with the aim of collecting data of all cases of AGC and other glandular diagnostic categories in order to evaluate the performances of these classes.

Methods: AGC data was collected from 7 screening centers with HPV test as primary test. All the participants compiled a shared excel grid. Data processing, carried out in LRPO of ISPRO in Florence, evaluated: % of AGC on the total examined triage cytologies (about 100,000 tests), the %of AGC by age group, correlation between AGC cytology and HPV genotyping, compliance to colposcopy, PPV for CIN2 +, overall DR for CIN2+ at baseline, correlation between histology and HPV type.

Results: In all the centers,less of 1% of all the triage Pap Tests were classified as AGC. The age group with the highest frequency of AGC was 40-44. Compliance to colposcopy of women with AGC cytology was very high. AGC categories showed a good PPV and DR for CIN2+ for squamous lesions (both LBC and conventional cases), but lower results for glandular lesions. A mild improvement of the performance for the identification of glandular lesions seems to be reached switching from conventional to LBC (from 6.9% to 21.7%), despite the small number of analysed cases. Glandular histological lesions appeared to be more related to HPV16 than HPV18 (respectively 67.9% vs 25%).

Conclusions: This study confirmed the "diagnostic trouble" of glandular atypia and lesions. Given the low amount of AGCs, an increase of case number should be needed. Moreover, the improvement of AGC classes could be deepened by collecting histologically confirmed Adenocarcinoma cases, re-evaluating cytological images and organizing specific training in order to improve the PPV and DR specific for histologically glandular lesions.

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#4958

HPV STATUS OF PATIENTS WITH HISTOLOGICAL DIAGNOSES IN THE FOLLOW-UP AFTER TWO YEARS OF CO-TETING HPV AND CYTOLOGY IN GERMANY

10 - HPV screening

Background/Objectives: The obligatory follow-up algorithms of the revised German cervical cancer prevention program in women >35 years since 2020 (applying HPV-cytology co-testing with liquid-based cytology (LBC) as an option every three years) require early expert colposcopy. E.g., after repeated HPV-HR-positivity or borderline cytology (according to Munich nomenclature III: Pap II-p/g; TBS: ASC-US/AGC) with and -if repeated- without HPV-HR-positivity. In Germany, colposcopy and, if biopsies are taken or conization is performed, histology are carried out decentralized in numerous practices and institutions. CytoMol, a leading lab specialized in cervical cancer prevention, intensively seeks to obtain the results of such examinations. From the HPV-negative co-tested group n= 370.394 (93,59%), we received n= 149 (0,04%) and from the HPV-positive group n= 25.365 (6,41%) we received n= 2.455 (9,67%) histology reports. Till 9/22 we received in summary n= 2.604 (0,65%) histologies from n= 395.759 screened cases

Methods: Histological diagnoses after co-testing in the years 2020/21 were associated with the results of HPV-HR-DNA-testing (cobas®, Roche Diagnostics, Mannheim, Germany) in the same patients on LBC specimens (ThinPrep®, Hologic, Wiesbaden, Germany) within at maximum six months before (n= 2.604). Histology was based on biopsy/curettage (n=1408; 54,07%), conization (n= 1035; 39,74%) or hysterectomy (n= 161; 6,18%). These findings are compared to the rates of HPV-HR-positivity in the LBC smears of all patients in the co-testing 2020/21.

Results: HPV-HR-positivity in the screened population (n= 395.759) was 6,41%. In the histological reports (n= 2604) it was 94,27%. In CIN I the HPV-positivity rate was 98,36% (n= 490), in CIN II 99,16% (n= 360), in CIN III 97,24% (n= 834), in squamous cell carcinoma 94,59% (n= 74), in AIS 100% (n= 14), in adenocarcinoma 85,71% (n= 21) and in cases without a histological abnormality 84,47% (n= 779) while in endometrial and other cancers it was only 18,75% (n= 32). In the preceding screening the HPV-positivity rates were as follows: Pap 0 (TBS: unsatisfactory) 6,0%, Pap I and Pap II-a (NILM) 3,9%, Pap II-p/g (~ASC-US/AGC) 83,6%, Pap III p/g (~ASC-H/AGC) 84,7%, Pap III D1 (LSIL) 88,5%, Pap III D2/Pap IVa-p/g (HSIL) 96,2% and Pap V-p/g (carcinoma) 70,1%.

Conclusions: In the follow-up of women >35 years screened with the new co-testing approach in the German cancer screening program 94,3% of lesions irrelevant for therapy (CIN 0,1,2) and 94% of relevant lesions for therapy (CIN III+) were HPV-HR-positive. An HPV only approach in primary prevention would miss the HPV-negative cases. Intermediate use of a biomarker would probably lower the rate of unnecessary colposcopies

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#4851

Introduction of Primary HPV Programs In Russia As A Means To Improve Quality of Cervical Screening

10 - HPV screening

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Background/Objectives: The roadmap to accelerate the elimination of cervical cancer as a public health problem in European Region was endorsed at a WHO Regional Committee from across Europe and Central Asia by 53 Member States accompanied by civil society representatives at its 72nd Session. What does really elimination mean? Is it a complete eradication of cervical cancer? Elimination could be realized in a case the so called 90-70-90 aspirational principle is completed before 2030 and literally means achieving the incidence rate less than 4 per 100 000 women. This principle can only be attained if 90% of girls by age 15 years are vaccinated against HPV, if screening of 70% of women with HPV test two times in a lifetime is done at 35 and 45 years of age and if 90% of women with identified cervical disease are duly treated. Hundred thousand women aged 30-49 are to be screened in Kaliningrad area commencing from 2021 in order to detect and treat women with high grade HPV lesions including patients difficult to reach as well as to ensure at least 10 year protection to HPV-negative women.

Methods: International golden standard technique, Hybrid Captue II was adopted as a HPV screening method and conventional cytology was used as a triage. ASC-US and higher positive tests were deemed abnormal. High-risk HPV and PAP positive patients were judged risky followed by referral for colposcopy and histological examination in the event of clinical requirements. A novel pre-cancer e-register was constructed and implemented for better data processing and higher quality of cervical screening.

Results: 32 201 women were enrolled into the screening and evaluated followed by invitations to 37 local centers of Female's Health. 90,5% of screened women(totally 29 145 women) demonstrated an adequate high-risk HPV status while 9,5% (or 3 056 patiens) appeared to be high-risk HPV-positive. High-risk HPV-negative women were excluded from the screening for the next 10 years interval and considered to be protected from HPV persistent infection. A survey was conducted to evaluate women's satisfaction comparatively to clinical outcomes and such protection. As a result of triage 2 140 high-risk HPV and PAP positive women were referred for colposcopy. Consequently histologically confirmed patients with CIN 2+ lesions were treated promptly while 33 patients with invasive cancer were conveyed to oncologists. A novel pre-cancer e-register demonstrated reliability both in patients data processing and in breaking up various patient's groups during COVID-19 pandemic in particular.

Conclusions: High-risk HPV-screening enhanced with a novel pre-cancer e-register proved to demonstrate substantial improvements in detection and treatment of patients with pre-cancer and cancer lesions during an organized cervical screening program in Kaliningrad area. Furthermore a long-term protection of high risk HPV negative women was achieved.

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#4679

Comparison of long-term colposcopy referrals by age groups in British Columbia's Cervix Screening Program among those who did or did not receive hrHPV-based screening in the HPV-FOCAL trial

10 - HPV screening

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Background/Objectives: Shifting from cytology to HPV cervix screening will initially raise colposcopy referral rates. The anticipated impact on health systems has been a barrier to implementing this shift. It is unclear if increased referrals persist past initial HPV screens or revert to new lower baselines due to earlier detection and treatment of precancer, as well as if this differs by age at screen.

Methods: Participants of the HPV FOCAL trial received one (HPV1, N = 6204) or two (HPV2, N = 9540) rounds of HPV screening. After trial exit, they participated to the BC cytology screening program, and screen results in this program were linked to trial data. A comparison cohort from the BC screening population (BCS, N = 1,140,745) was extracted, mirroring trial inclusion criteria. All participants were followed for up to 10 years through the provincial screening registry. Trial and post-trial referral rates per 1000 screens (totals- HPV1: 27,341; HPV2: 36,982; BCS: 5,076,312) were calculated for each group, stratified by age category (25-29, 30-34, 35-49, 50+), assuming that HPV positive participants were triaged with cytology and those with ASCUS+ were referred to colposcopy. A multivariate flexible survival regression model compared rates throughout follow-up.

Results: Among all age groups, referral rates were higher after an initial HPV screen versus cytology screening (HPV1: 8-100 per 1000 women depending on age group, HPV2: 10-100, BCS: 3-20). However, post-trial rates in HPV1 and HPV2 were significantly less than those in BCS during post-trial follow-up. Cumulative rates in HPV1 and HPV2 approached the cumulative rate in BCS by the end of follow-up (HPV1: 5-26 per 1000 women depending on age group, HPV2: 7-40, BCS: 5-25). Adjusted HRs for referral in HPV1 and HPV2 compared to BCS were <1 beginning 24 months post-final HPV screen.

Conclusions: Colposcopy referral rates decreased after HPV screening implementation reached a steady state across all age groups. After initial rounds of HPV screening, referral rates dropped below the current rates seen in a centralized cytology program. The expected early increase in referrals could be moderated by program implementation strategies.

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#5085

LOWER INITIAL COLPOSCOPY REFERRAL IN HPV SCREENING USING COMBINED GENOTYPE AND CYTOLOGY TRIAGE COMPARED TO LBC-SCREENING WITH HPV TRIAGE

10 - HPV screening

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Background/Objectives: HPV based screening is superior to cytology screening, and in 2021 Denmark initiated a phased implementation of HPV screening for women 30-59 old. In the Capital Region of Denmark, the HPV screening is carried out using extended genotyping and cytology to triage any HPV positive. Similarly, for those receiving cytology-based screening, HPV triage is used to qualify any ASCUS positive result before referral to follow-up. All HPV positive women not directly referred for colposcopy are recommended for a re-test after 6 (cytology) or 12 (HPV) months. A key concern is nevertheless whether HPV screening will result in higher direct rates of referral to colposcopy after the index screening round compared to the current cytology screening

Methods: All women aged 30 to 59 years participating in HPV or LBC-screening in 2021 with a valid index screening outcome were included. Data on HPV, cytology and resulting histology outcome were retrieved from the Pathology DataBank. Focus for this analysis were women who were referred for colposcopy after the index sample. The colposcopy referral criterion was either HPV+ and any of HSIL, ASC-H, AGC, AIS, CxCa or (ASCUS or LSIL) and any HPV16, 18, 31, 33, 52. For cytology, the colposcopy referral criterion was ≥ASCH or ASCUS/HPV positive. The study is a register-based quality study under the Capital Region of Denmark.

Results: In total, 80.540 women participated in screening with a valid sample in the period. Of these, 41.319 were screened by HPV versus 39.221 with cytology. For the HPV arm a total of 2.1% (N=874) were referred directly to colposcopy on the index sample versus 2.6% (N=1001) for cytology. The distribution of referrals in the HPV arm was 1.3% (N=520) with HPV+/≥HSIL and 0.9% (N=354) ASCUS or LSIL and any HPV16, 18, 31, 33, 52. For cytology, 1.7% (N=675) had ≥HSIL and 0.8% (326) had ASCUS/HPV+. At time of data retrieval, 94% of all referred to colposcopy in both arms had completed the procedure. Resulting histology showed 53% ≤CIN1, 47% ≥CIN2, and 33% ≥CIN3 for those referred in the HPV arm (N=771). For cytology (N=886), 61% were ≤CIN1, 39% ≥CIN2, and 26% ≥CIN3. For HPV, 22 Adenocarcinomas in situ and 9 CxCa were detected, versus 21 Adenocarcinoma in situ and 11 CxCa in the cytology arm.

Conclusions: We conclude that at the index round, HPV screening using an algorithm of extended genotyping/cytology reduce the initial colposcopy activity and increase the disease detection, compared to LBC cytology screening with HPV triage.

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HPV PRIMARY SCREENING WITH EXTENDED GENOTYPING IN THE SOUTH-EAST HEALTH REGION OF NORWAY

10 - HPV screening

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Background/Objectives: National implementation of HPV primary screening started in Norway in 2019 for women aged 34-69 and has a five-year screening interval. Following implementation, all cytology and HPV testing in the South-East Health Region were centralized from ten to three laboratories. In addition, a new platform for HPV DNA detection with extended genotyping and a new laboratory data system, Lab Vantage Medical Suite (LVMS)which is linked to the Cancer Registry of Norway's national databases for HPV, cytology and histology, were implemented.

Methods: In LVMS cervical samples were allocated to appropriate testing (either HPV or cytology, or both) according to the women's previous screening history and the current algorithms. Screening history from local and national databases for the last ten years was automatically acquired. The samples were collected in BD SurePath medium and the HPV-analyses performed using the BD OnclarityTM HPV assay. In 2019 on BD Viper, and from 2020 on BD COR, a fully automated, real-time PCR DNA assay targeting the E6/E7 region of the HPV genome. BD Onclarity detects six HPV genotypes individually (16,18,31,45,51 and 52) and eight genotypes collectively in three groups (33/58, 56/59/66 and 35/39/68).

Results: From May 2019 until March 2022 primary cytology screening was gradually replaced with HPV primary screening for women aged 34-69 years living in the South-East Health Region. The HPV prevalence among the 153,747 women eligible for a screening test was 6.6%. Triage cytology of the HPV positive samples revealed unsatisfactory cytology in 0,6%, normal cytology in 54.4 %, low-grade cytology in 31.8 % and high-grade cytology in 13.3 % of cases. Histological data was available for 2389 women. Normal histology was detected in 40.9%, CIN 1 in 15.1 %, CIN 2-3 in 38.5 % and AIS in 2.3 % of women. In women with normal or low-grade cytology the most prevalent genotype was HPV 16 (18.7%), followed by HPV35/39/68 (15,4%), HPV56/59/66 (14.8%), HPV31 (10.4%) and HPV52 (9.1%). In high-grade cytology the most prevalent genotypes were HPV16 (31.7%), HPV31 (12.8%), HPV18 (9.3%), HPV52 (9.1%) and HPV35/39/68 (8.3%). In women with histologically confirmed CIN3 or AIS, 3,4% tested negative with BD Cor in the screening sample. The most prevalent genotypes were HPV16 (43.5%), HPV31 (12.9%), HPV18 (10.3%), HPV52 (8.0%) and HPV33/58 (7.6%). Data on the invasive carcinomas is currently under review and will be presented.

Conclusions: The high-risk types with lowest odd ratio for cancer development that are not covered by the national HPV vaccination programme, were more prevalent in women with normal or low-grade cytology. When HPV primary screening is implemented for the entire screening population, extended genotyping will allow for further risk stratification and a more personalizied follow up for all women.

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#4931

A NATIONAL QUALITY ASSURANCE PROGRAM BASED ON RE-ANALYSIS OF "HPV NEGATIVE" HSIL+

09 - HPV testing

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Background/Objectives: High quality HPV screening should have a low risk of false HPV negativity. Detecting HSILs and invasive cervical cancer adequately is essential as any deficit will directly translate to an inadequate cancer prevention of the screening program. The Swedish National HPV Reference Laboratory (NRL) offers re-testing of all CIN2+/HSIL cases that have previously been classified as "HPV negative" by HPV laboratories throughout the country.

Methods: Specimens (LBC, FFPE, self-sampling material) from women with HSIL/CIN2+, that had been tested as HPV negative by routine HPV laboratories throughout Sweden were sent to the NRL for further investigation. After nucleic acids extraction (MagNA Pure LC Total Nucleic Acid Isolation Kit for LBC/self-sampling samples and Qiagen kit, DNeasy Blood & Tissue Kits for FFPE specimens), beta-globin detection tested specimen adequacy. Extracted material was then genotyped using MGP primers and Luminex with 37 different HPV types included. Specimens where HPV negativity was still found, were thereafter subjected to unbiased whole genome RNA sequencing, using the SMARTer® Stranded Total RNA-Seq Kit and the NextSeq 500 system (Illumina, USA).

Results: Since February 2019, the NRL has received 81 "apparently HPV negative" CIN2+ specimens belonging to 47 women. Luminex detected HPV in 46/81 (56.8%) specimens, with HPV 16 (n=11), HPV 18 and HPV82 (n=5 for each of the genotypes) being the most common types detected. Unbiased RNA Sequencing detected HPV in further 6/30 samples, with types 18, 26, 30, 33, 56, 58 and 82 being found. A total of 24/81 samples were still HPV negative even after the whole transcriptome sequencing.

Conclusions: A standard protocol for re-analysis of "HPV-negative" enables ensuring adequate performance of HPV testing services. The results of the re-analyses are used for continuous quality improvement work, aiming to have an increasingly higher probability of finding the HSIL+ cases in the screening.

FC14- Free communications - Epidemiology and natural history 2

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#5043

Examining cervical cancer screening patterns among women living with HIV in the US using a population-based sample: An analysis of the NIH's All of Us Study

34 - Sexually transmitted diseases and HIV infection

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Background/Objectives: In the US, most studies examining cervical cancer screening patterns among women living with HIV (WLH) were conducted among long-standing established cohorts of HIV-seropositive women who are more likely to be engaged in preventative healthcare and therefore aware of cervical cancer screening recommendations. Estimates from these reports may not reflect cervical cancer screening rates in the underlying population of women living with HIV in the U.S. By utilizing data from the All of Us survey program, we examined differences in sociodemographic factors associated with cervical cancer screening use in women living with HIV compared to those not living with HIV.

Methods: We conducted a cross-sectional analysis of data collected from participants enrolled in the The All of Us Research Program, stewarded by the US NIH, enrolled from 2018. Electronic health record data for enrolled participants were included starting in 2012, the calendar year HPV testing was integrated into routine recommended cervical cancer screening. HIV-positive women were identified using all relevant SNOMED (Systematized Nomenclature of Medicine) codes. To identify HIV-negative women, we matched on age of HIV positive women. Cervical cancer screening, specifically cytology (or Pap), co-testing, and HPV testing were identified using relevant procedure codes. We compared sociodemographics across HIV status and used descriptive statistics to identify significant differences among HIV seropositive and seronegative adults.

Results: In this sociodemographically diverse sample of n=7,608 women (n=1,268 HIV-seropositive and n=6,340 HIV-seronegative), 10.0% self-identified as Black, 35.3% as Hispanic/Latina, 2.3% as White; 21.3% reported < high school degree, and 23.5% reported an annual household income < $10,000. HPV and pap testing were reported by 2.8% and 50.5% of HIV-seropositive women and 2.5% and 14.3% of HIV-seronegative women. Among HIV-seropositive women, there were no statistically significant differences in cervical cancer screening by race/ethnicity, level of household income, health insurance status, employment status, sexual orientation or marital status. However, women with low levels of educational attainment (less than a high school degree) were less likely to report any cervical cancer screening. Among HIV-seronegative women, although marginally statistically significant, White women (p=0.0638) and women reporting annual household income >$75,000 (p=0.021) were more likely to receive cervical cancer screening (p=0.06) than no screening. Whereas HIV-seronegative women with a high school degree/GED (p=0.0345) and unemployed (p=0.0157) were less likely to report cervical cancer screening . In addition, health insurance coverage type was associated with cervical cancer screening among HIV-seronegative women. Women with private/employer based coverage or covered by Medicare were more likely to receive cervical cancer screening whereas those covered by Medicaid or another form of insurance (i.e. Indian Health Service, Veterans service, etc) were less likely to receive cervical cancer screening (p<0.001)

Conclusions: Women living with HIV in the US are regularly receiving cytology-based screening, based on their high-risk status and documented engagement in regular care as shown in prior studies. Our analysis suggests a missed opportunity to provide HPV testing to both women living with HIV and those without HIV, as recommended by national guidelines.

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#4944

CIN2/3 INCIDENCE DECREASE IN NORWAY: OBSERVATIONAL REGISTRY-BASED COHORT STUDY FROM 2004 TO 2020

03 - Epidemiology and natural history

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Background/Objectives: In Norway, a single-cohort school-based national HPV vaccination program with 4-valent Gardasil was initiated for 12-year-old girls in 2009, which was replaced by vaccination with 2-valent Cervarix in 2017. In 2020, the first vaccinated cohorts reached the age of 23 years. While the HPV vaccine coverage in the target birth cohort is over 80%, the single-cohort vaccination strategy has resulted in low overall vaccine coverage in the total population. The present observational registry-based cohort study estimates age-dependent incidence cervical neoplasia grade 2/3 (CIN2/3) trends from 2004 to 2020 in Norway.

Methods: Data on CIN2/3 incidence was obtained from the Cancer Registry of Norway. Annual incidence rates (IR) and average annual percentage changes (AAPC) with 95% confidence intervals (CI) in six age groups throughout 2004 to 2020 were calculated.

Results: Out of 1,161,833 females included, 75,388 had CIN2/3 diagnosis in the study period. The highest incidence was constantly in the age group 25-29, followed by the age group 30-34. The lowest incidence was among women under 20 years, which was also the only age group where the CIN2/3 incidence decreased (AAPC: -8.3%, 95% CI: -5.9 to -10.8). In other age groups, a significant increase was noted. The strongest increase was in the age group 25-29 (AAPC: 8.1%, 95% CI: 7.8 to 8.4), and the weakest increase was in the age group 20-24 (AAPC: 2.9%, 95% CI: 2.4 to 3.5).

Conclusions: The decrease in CIN2/3 incidence among women under 20 years is most likely induced by the school-based HPV vaccination, as the majority of these women have been vaccinated against HPV. An increase in CIN2/3 in the older age groups may be due to an increased HPV prevalence in the population as well as an increased use of more sensitive screening methodologies (liquid-based cytology and HPV based screening).

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#4844

P16 EXPRESSION IN INVASIVE ADENOCARCINOMAS OF MOZAMBICAN PATIENTS: A RETROSPECTIVE STUDY

26 - Cervical neoplasia

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Background/Objectives: Invasive adenocarcinoma (IAC) accounts for about 25% of invasive cervical carcinomas (ICC), a significant proportion of IAC are Human papillomavirus (HPV) independent. Thus, HPV vaccination and screening will not prevent nor detect some IAC. We aimed to investigate p16, a surrogate marker for hrHPV, in a series of IAC from Mozambique, a country where ICC is the most frequent cancer in women and with a high prevalence of HIV, in order to evaluate if the proportion of HPV associated and independent IAC may differ from a non-endemic HIV milieu.

Methods: Tissue micro arrays with material from 41 IAC diagnosed at Maputo Central Hospital (MCH) were stained for p16 by immunohistochemistry and classified in a four-grade scale as: strong diffuse (3+), strong focal/moderate intensity (2+), weak sporadic (1+) or no visible staining (0). Histopathological classification was done according to WHO 2020 into HPV-associated and HPV independent types. Ethical approval was received from relevant Mozambican authorities.

Results: 38/41 cases had HPV-associated morphology (usual type n=30, mucinous; NOS n=1, intestinal type n=5, signet ring cell type n=1 and villoglandular n=1). 3/41 presented with HPV independent morphology (serous n=2, mesonephric n=1). p16 was positive in all cases except in one (97.3%). Positivity was strong diffuse in 86%, strong focal or moderate in 11% and sporadic weak in 3% of the cases. The negative case was a serous carcinoma.

Conclusions: These data support the relevance of the present morphological classification system in a HIV endemic milieu. However, 2/3 cases with HPV independent morphology tested p16 positive, which needs to be further assessed by hrHPV analyses. Thus, since 97% of the IAC cases where p16 positive, our data supports the value of hrHPV based screening and HPV vaccination in Mozambican women with potentially an even higher potential to prevent IAC than in an HIV non-endemic setting.

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#4886

Comparison of cervical and anal cancer incidence trends by race and socioeconomic status in the United States, 2006-2018

03 - Epidemiology and natural history

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Background/Objectives: Most cervical (99%) and anal cancer (90%) cases are caused by oncogenic infections with human papillomavirus (HPV). Adherence to screening recommendations and HPV vaccination have contributed to an overall decrease in cervical cancer (CC) incidence. Despite shared viral etiology, anal cancer (AC) incidence has increased significantly over the past two decades. Understanding the populations most affected by AC may offer insights into possible public health strategies. To that end, we compared trends in incidence and survival for CC and AC.

Methods: We constructed a cohort of 38,285 CC and 16,018 AC cases diagnosed 2006-2018 using the Surveillance, Epidemiology, and End Results (SEER) database. Trends in age-adjusted incidence rates and survival were stratified by race and SES. Annual percent change (APC) in incidence was calculated using linear regression. Five-year overall survival (OS) was calculated using the Kaplan-Meier method.

Results: CC incidence was highest in low SES Black and Hispanic women (Figure 1). All demographic groups displayed a trend of decreasing incidence except low SES White women. High SES Black, Hispanic, and Asian women had the greatest decrease in incidence rates (APCs of -4.1, -2.9, and -1.9, respectively). OS for high and low SES Black women was lower than for their SES counterparts of other races (high SES Black 61.5% vs White 69.6%; low SES Black 52.8% vs White 62.8%) (Table 1). Smaller disparities by SES were observed in AC compared to CC. AC incidence was highest in low SES White women and Black men (Figure 2). All female groups displayed a trend of increasing incidence except Asian women (APCs of -2.8 and -0.5). All male groups showed a trend of decreasing incidence except low SES Black and White men (APCs of 2.1 and 1.5). OS for high and low SES Asian women was lower than for their SES counterparts of other races (high SES Asian 59.3% vs White 71.3%; low SES Asian 52.2% vs White 61.9%) (Table 2). Among low SES men, Asians had the lowest OS. Among high SES men, Hispanics had the highest OS.

Conclusions: There are significant ongoing disparities in both CC and AC. Black, Hispanic, and low SES women bear the greatest burden of CC, though a trend towards improvement for almost all groups is reassuring. AC continues to be a neglected disease with increasing incidence in all female groups except Asians. Despite decreasing incidence, Asian women experience worse OS than their respective SES counterparts of other races. Almost all male groups had decreasing incidence. These trends may be related to the inaccessibility of preventative healthcare, the inadequacy of public health messaging concerning shifting cultural sexual norms, and the ongoing HIV syndemic.

Figures 1 and 2

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#4471

Case series of HPV-independent cervical cancer: an increasingly important disease entity

26 - Cervical neoplasia

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Background/Objectives: Cervical cancer has the 4th highest incidence and cancer-related mortality in women worldwide. HPV infection is implicated in the majority of cases, but in recent years there has been increasing recognition of HPV-independent cervical cancer. The World Health Organization has updated their classification of cervical carcinomas in 2020 to include association with HPV as a differentiating criterion in addition to the morphological cell types. Increasing HPV vaccination rates and the move towards HPV-based primary screening are likely to increase the proportion of HPV-independent cervical cancer.

Methods: Gastric-type adenocarcinoma is the most frequently-encountered HPV-independent cervical cancer. Four such cases are described in Table 1. It presents typically in the older age group, and is more likely to involve the parametrium and/or vagina at presentation, compared to HPV-associated cancers. It has a preponderance to affect the upper endocervix instead of the ectocervix.

Results: Clinical manifestations include watery, profuse mucoid vaginal discharge, abnormal uterine bleeding and/or abdominal pain. Physical examination may reveal a bulky indurated cervix often without an obvious mass. Radiologically, it typically appears as a floret-like arrangement of small cysts known as the "cosmos pattern", but can be difficult to distinguish from nabothian cysts or lobular endocervical glandular hyperplasia. Histologically, gastric-type adenocarcinoma may exhibit varying degrees of differentiation. Gland confluence, cribriform architecture and luminal papillae may be observed. Immunohistochemistry may provide useful clues , including negative p16 immunoreactivity, positive PAX8 immunoreactivity and aberrant p53 staining. There are currently no separate management guidelines for HPV-independent cervical cancers, and treatment principles should follow that of HPV-associated cancer. Gastric-type adenocarcinoma exhibits reduced 5-year disease specific survival compared to HPV-associated disease, likely a reflection of the typically higher disease stage at presentation. In diagnosing HPV-independent cervical cancer, it must be understood that "HPV-independent" and "HPV-negative" are not always synonymous. In certain cases, HPV could be part of an initial trigger for carcinogenesis but subsequently becomes undetectable due to reasons such as sampling error, low viral load, technical factors with various HPV tests, or loss of HPV DNA fragments picked up by HPV tests.

Conclusions: HPV primary screening and HPV vaccination are two key pillars in driving down cervical cancer rates worldwide. However, clinicians must be aware of the rising prominence of HPV-independent cervical cancer. More research, especially in the field of molecular medicine, is currently underway to better define this condition, its pathogenesis and uncover molecular-based targeted therapy.

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#5114

Geotropism and oncogenic potential of HPV infections in cohort study populations in Vojvodina, north region of Serbia

03 - Epidemiology and natural history

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Background/Objectives: This study evaluates the prevalence of HPV infection in women from Vojvodina, north part of Serbia, according to cytological status and pathological changes of cervix, dysplasia and cancer. According to current estimates in Serbia, 1327 women get cervical cancer every year, and 551 die from cervical cancer. Cervical cancer is the 4th most common cancer among women in Serbia and the second most common cancer among women between the ages of 15 and 44. The aim of this study was to examine the prevalence and distribution of different HPV genotypes in a cohort of female patients with normal cytological findings, as well as the oncogenic potential of HPV infection genotypes in a group of female patients with histopathologically verified dysplasia and cervical cancer in Vojvodina, the northern region of Serbia.

Methods: The research was conducted as a retrospective study at the Oncology Institute of Vojvodina (IOV) and the Institute of Public Health of Vojvodina (IZJZV). It used data from the medical records of female patients treated for cervical intraepithelial neoplasia or cervical cancer at the Department of Gynecology, Clinic for Surgical Oncology, Oncology Institute of Vojvodina in Sremska Kamenica in the period from 2016 to 2021, as well as the laboratory findings of the IZJZV for a group of female patients with normal cytological results of the Papanikolau (PAPA) smear. The source of the material was the archival material of the IOV and IZJZV obtained from the medical documentation on the histopathological material from operation and cytological findings, the identified genotypes of the HPV and the age of the female patients. A total of 740 women, ranging from 20 to 82 years of age, with different cytological results were enrolled. 576 samples were classified as NILM, while 164 samples belong to a group of abnormal histopathology (LSIL/HSIL/cervical cancer). The HPV genotyping assay was performed using the EUROArray HPV test to detect 30 HPV genotypes.

Results: Twelve HPV genotypes classified as carcinogenic to humans were detected in 252 (55%) of NILM samples, while the same genotypes were detected in 125 samples (76.2%) classified as LSIL/HSIL/cervical cancer. In our study, the most prevalent genotypes were HPV 16, 31, 53, 51, and 18 in NILM cytological status. In the samples with the abnormal histopathology, the most prevalent genotypes were HPV 16, 33, 31, and 56, while 18 and 39 were equally verified. Genotype 16 was the most prevalent in the examined sample, with a higher prevalence in higher-grade histopathological findings: 18.8% in LSIL, 31.9% in HSIL, and 75% in cervical cancer samples. Infection with multiple associated genotypes of HPV is not correlated with histopathology. By comparing our female patients' histopathological diagnosis and age, we observed that older female patients had higher-grade lesions.

Conclusions: Based on the estimated oncogenic potential of HPV genotypes as well as their prevalence in our sample, we can conclude that the nine-valent HPV vaccine for genotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58 would have the potential to prevent HPV infection and the incidence of precancerous lesions and cervical cancer in about 85% of women.

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#4874

The Impact of Diet and Sleep Disorders on the Degree of Cervical Intraepithelial Lesions

24 - Risk management

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Background/Objectives: The objectives of our study was to identify the socio-economic and behavioural (diet, its pattern and habits of foodintake, sleep disorders) factors responsible for the development of low-grade and high-grade cervical squamous ntraepithelial lesions (CIL) and their impact on the degree of CIL.

Methods: Methods. A cross-sectional study using a consecutive non-probability sample of 893 women (age - 25-60 years;mean age - 40.56±8.97 years) of Adjara region (Western Georgia) have been studied by gynecological examination,PAP-test and colposcopically. Histomorphological study has been carried out in case of necessity. The specific structured questionnaire consisted of the lifestyle, socio-demographic and other characteristics of participants. Therisk-factors of cervical intraepithelial lesions (CIL) have been assessed by the determination of odds ratios (OR) and95% confidence intervals (95%CI). Control persons were randomly selected from non-CIL participants of same age and BMI. Case-control ration was 1:3.

Results: Results. CIL were diagnosed in 108 cases. Among them 76 cases (70.4%) were LSIL, 32 (29.6%) - HSIL. Theanalysis of demographic and socio-economic characteristics shows that the age, the family income, urban/rural habitants and educational characteristics did not significantly differed between groups. Compared to LSIL the requency of married patients was significantly lower in HSIL group (OR=0.30, p=0.018). Smoking and alcohol overconsumption comparison showed that the difference between groups was not significant. The distribution of study participants by diet pattern, dietary habits and sleep disorders showed that compared to LSIL group the odds of frequency of meal intake <3 (OR=4.35), low-protein diet (OR=4.60), breakfast skipping (OR=6.32), and discrete sleep (OR=4.42) are significantly higher in HSIL group. The analysis of cervical background diseases indicated that high percentage of cervical erosions found in HSIL cases compared to LSIL cases [15 of 32 (46.9%) vs. 16 of 76 (21.1%); OR=3.31, 95%CI - 1.36-6.96; p=0.004).

Conclusions: Conclusion. Study results indicated the possible impact of the degree of energy deficiency (the frequency of food ntake, breakfast skipping, low-protein diet, sleep disorders) and estrogen deficiency (cervical erosions) on the degree of CIL and its progression from LSIL to HSIL. However, the evidence of our results has to be confirmed by further valid randomized control trials to obtain the strong evidence-based conclusions.

FC16- Free communications - Health education – Advocacy – Public Health

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#4565

ATTITUDES TOWARDS HUMAN PAPILLOMAVIRUS VACCINATION AMONG ADULTS IN THE UNITED STATES

37 - Advocacy, acceptability and psychology

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Background/Objectives: The 2018 U.S. FDA approval of 9vHPV vaccine for mid adults aged 27 through 45 years was followed in 2019 by the U.S. Advisory Committee on Immunization Practices (ACIP) recommendation for shared clinical decision-making recommendation in that age group. It is essential, therefore, to understand the attitudes and beliefs towards HPV vaccination in this mid-adult population. However, data on attitudes and behaviors towards HPV vaccination are limited for mid-adults. The objective of this study was to assess knowledge, attitudes, and beliefs towards HPV vaccination of mid-adults in the U.S.

Methods: This was a cross-sectional survey of a national sample of 1445 U.S. adults aged 27-45 years drawn from a curated online panel and conducted between February and August 2021. Questions addressed demographics, health and sexual behavior, HPV vaccination status, and beliefs on HPV vaccination. Descriptive analyses were performed on the total sample and beliefs and attitudes compared across genders.

Results: Just over half (50.8%) of respondents were female, 72.7% of respondents were White and 58.6% had a bachelor's degree or higher education. Mean age was 36.2 years (SD 5.3years). More than half (55.6%) were married. Overall, 71% had heard of HPV vaccination and 51.5% had discussed HPV vaccination with a doctor; awareness was more common in females (77.8% vs 64.0%, $p<0.001$). Around one third respondents (32.7%) reported they were vaccinated, and vaccination did not differ between males and females. Among 10 reasons for non-vaccination, the most common reasons cited were being married (29.7%), not being at risk of getting HPV (23.8%), not having enough information about the vaccine (22.1%) and the least often cited was that the doctor recommended against it (4.3%). Males were more likely to cite lack of information (25.9% vs 18.3%, $p=0.007$) and females were more likely to cite inability to afford the vaccine (7.3% vs 4.3%, $p=0.049$). When asked about the relevance of HPV vaccination, 21.7% reported that the vaccine was extremely relevant while 20.5% of respondents reported it was not at all relevant. Relevance did not differ across genders. Importance of HPV vaccine to preventing genital warts ($p=0.006$), head and neck cancer ($p<0.001$) and anal cancer ($p=0.011$) was higher in males.

Conclusions: Mid-adult men and women have different beliefs and attitudes about the HPV vaccination, particularly about the importance of HPV vaccination in preventing HPV-related diseases beyond cervical cancer. These findings highlight the importance of patient education and engagement in this age group.

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#4994

HIGHER LEVELS OF HPV VACCINE HESITANCY AMONG RURAL HISPANIC YOUNG ADULTS IN THE WESTERN U.S., 2020-2021

40 - Public health

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Background/Objectives: To assess differences in HPV vaccine hesitancy by rurality and race and ethnicity among young adults in the western United States, during the era of COVID-19. Rural populations and Hispanics have higher cervical cancer incidence and mortality rates.

Methods: A convenience-sampled cross-sectional online survey was conducted among young adults (YAs) ages 18-26 years living in rural and urban communities across 12 western U.S. states (October 2020 - April 2021). Participants (N=2937) self-reported demographics and answered HPV vaccine hesitancy and healthcare trust questions. Factor analysis, using naïve and polychoric correlation, evaluated n=27 items to create individual coarse factor scores for three scales of HPV vaccine hesitancy, each demonstrating good internal consistency (Cronbach's alpha): HPV vaccine confidence (n=6, a=0.71[95%CI: 0.69-0.73]), HPV complacency (n=11, a=0.73[95%CI: 0.71-0.75]), and HPV vaccine complacency (n=3, a=0.81[95%CI: 0.78-0.82]). Differences were examined by race and ethnicity, rurality, and rurality among Hispanic young adults. Multivariate logistic regression estimated odds (ORs). Directed acyclic graphs (DAGs) identified scientifically meaningful and minimally sufficient covariates for estimating total effects.

Results: Compared with not-Hispanic White YAs, Hispanic YAs had significantly higher odds of HPV vaccine hesitancy across all scales: HPV confidence (OR=1.55 [95%CI:1.23-1.96]), HPV complacency (OR=1.53 [95%CI:1.22-1.93]), and HPV vaccine complacency (OR=1.28 [95%CI:1.01-1.61]). Significantly higher HPV vaccine hesitancy among rural YAs was observed in confidence (OR=1.66 [95%CI: 1.37, 2.01]) and HPV vaccine complacency (OR=1.79 [95%CI:1.48-2.17]) scales, but not in HPV complacency (OR=1.06 [95%CI:0.88-1.28]) compared to urban YAs. A similar and more pronounced difference among Hispanic YAs by rurality was observed; strong and significantly higher odds of hesitancy among rural Hispanic YAs for HPV vaccine confidence (OR=2.13 [95%CI:1.33-3.49]) and HPV vaccine complacency (OR=2.11 [95%CI:1.33-3.40]), but not HPV complacency (OR=0.84 [95%CI:0.54-1.32]) compared to urban Hispanic YAs.

Conclusions: Interventions are needed to decrease HPV vaccine hesitancy among rural Hispanic young adults in the Mountain West. Decreasing risk for HPV-related cancers among rural communities in the United States is a top public health priority.

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#5006

MISSED OPPORTUNITIES: LOW ENGAGEMENT OF HEALTHCARE PROVIDERS IN HPV-RELATED DISCUSSION WITH AMERICAN INDIAN & ALASKA NATIVES, BY US REGION, 2011-2020

38 - Health education

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Background/Objectives: In the USA, American Indian and Alaska Native (AIAN) people experience disparate HPV-related outcomes, including high incidence and mortality of several HPV-related cancers. AIAN-specific cancer burden shows unexplained, regional differences. We sought to describe regional variations in 13 HPV-related knowledge and HPV vaccination awareness indicators among AIAN. We hypothesized regional differences in HPV-related knowledge and HPV vaccination awareness, similar to observed regional variation in HPV-related cancers.

Methods: We used data from the Health Information National Trends Survey (HINTS), a weighted nationally-representative survey administered by the National Cancer Institute on knowledge of and attitudes towards cancer-relevant information. We pooled the AIAN population across 8 survey cycles (2011-2020) to estimate Census region-specific prevalence estimates for 13 HPV-related knowledge and HPV vaccination awareness measures. We used multivariable logistic regression to explore associations between socio-demographic and healthcare-specific characteristics and HPV-related knowledge and HPV vaccination awareness measures.

Results: Overall, 866 AIAN respondents were identified including 50% women, 33% below the age of 40 years, 57% with a household income less than $50,000, 60% reported having a regular provider, and 14% reported having no insurance. Only 17% (95%CI: 12-24%) of respondents reported having spoken to a health care provider regarding the HPV vaccine for themselves or their family members, with those residing in the South with the lowest prevalence (12%; 95%CI: 7-19%) and those in the Midwest with the highest (23%;95%CI: 12-40%) (p-value=0.37). Consistently across census regions, about 70% of AIAN respondents reported they did not know if HPV vaccine was successful at preventing cervical cancer. Also consistent across census regions, about two-thirds reported having heard of HPV and 55% reported having heard of the HPV vaccine. Adjusted models showed that the lack of regional variation in HPV-related knowledge and HPV vaccination awareness among AIAN remained after adjusting for sex, age, household income, educational attainment, marital/relationship status, smoking history, having a regular provider, health insurance status, and survey cycle. Women had higher odds than men of having heard of HPV, the HPV vaccine, and having discussed with their providers ($p<0.05$).

Conclusions: Although we did not observe statistically significant regional variations in our outcomes, we observed low engagement in provider discussions regarding HPV vaccination among AIAN adults, particularly men across the USA. Given provider recommendation is the strongest predictor of HPV vaccination, low engagement of providers with AIAN is of significant concern and suggests a missed opportunity to improve uptake of HPV related preventive measures.

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#5045

IMPROVING HPV VACCINATION THROUGH QUALITY IMPROVEMENT: COACH-BASED VERSUS WEB-BASED PRACTICE FACILITATION

40 - Public health

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Background/Objectives: Practice facilitation (PF) is an effective implementation strategy for improving adherence to clinical guidelines, but application to HPV vaccination has been limited. Health systems may consider providing in-person versus remote PF. We compared two formats for delivering PF to engage pediatric practices in quality improvement focused on HPV vaccination.

Methods: Community-based pediatric practices (N=21) in Tennessee, USA, were randomized to Coach-based or Web-based PF. Each practice selected four change options to implement over 12 months. Implementation outcomes included two measures of guideline adherence: receipt of HPV vaccine dose during well visits (patients ages 11-17) and bundling HPV with other recommended vaccines for 11-12 year-olds in the same visit. Clinical effectiveness outcomes included two practice-level HPV vaccination coverage measures: 1+ doses and all doses (patients ages 11-17). Interrupted time series analyses of logarithmic rates compared the practices' 12-month baseline to the 12-month implementation period. H1: Both arms will improve from the baseline period to implementation period. For implementation outcomes, we expected immediate improvement (positive change in level) followed by stability or gradual improvement (no or positive change in slope). For Effectiveness Outcomes, we expected gradual improvement only (positive change in slope). H2: Coach arm will improve more than Web arm on all measures.

Results: For the implementation outcomes, both arms showed immediate 11-17% relative improvements for doses received in well visits (Relative increase: Coach 1.11 fold [95%CI 1.03-1.20], Web 1.17 fold [1.06-1.30]) and immediate 16-19% relative improvements for bundling vaccines (Coach 1.19 fold [1.04-1.35], Web 1.16 fold [1.03-1.30]), all with stable slopes. These changes did not differ by study arm. For the effectiveness outcomes, only the Coach arm showed gradual improvements for 1+ dose coverage (1.006 fold [1.002-1.010]) and all dose coverage (1.006 fold [1.004-1.008]), which were significantly greater than Web. These positive trend changes for the Coach arm translated to 1+ dose and all dose coverage being 7.4% relatively higher by the end of the 12-month implementation period than they would have been without PF. Challenges included extraction of data reports from multiple electronic record systems.

Conclusions: Both formats equally improved implementation outcomes, while Coach-based PF yielded greater clinical effectiveness improvements. Further research should examine long-term effectiveness and cost differences between the two formats and explore data extraction options.

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#4960

CLINICIAN INSIGHTS ON THE USE OF ELECTRONIC MEDICAL RECORDS TO IMPROVE HUMAN PAPILLOMAVIRUS VACCINE UPTAKE

06 - HPV prophylactic vaccines

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Background/Objectives: Human papillomavirus (HPV) vaccination is universally recommended in the United States at ages 11-12 years to prevent HPV-associated cancers. Yet, the uptake of HPV vaccine is lower than other recommended vaccines given at the same age. We explored how providers document patient refusal of HPV vaccination, and if HPV vaccination documentation improved discussions with patients at subsequent visits.

Methods: Healthcare providers, medical staff and administrators from academic family medicine and pediatrics clinics in North Carolina, Missouri, and Oregon were recruited to participate in virtual focus group discussions. Guided focus group topics included clinic strategies for promoting and administering HPV vaccination; approaches used with vaccine hesitant patients and caregivers; and methods utilized for documenting patients' HPV vaccination refusal. Focus groups lasted 30-60 minutes. Audio recordings were professionally transcribed, a codebook was developed, and transcripts coded independently by two researchers (SAP and LMR). Interrater reliability testing was performed to determine consistency across coders. The research team discussed the findings and identified major themes that emerged using a thematic data analysis approach.

Results: Seven focus groups were conducted with 37 participants (18 providers, 12 nurses, 5 medical assistants, 2 administrators) from June to October 2022. Central themes that emerged in preliminary analysis included: 1) Providers are faced with multiple barriers from patients and caregivers regarding HPV vaccination; 2) Personalized conversations are key to increase HPV vaccine uptake amongst adolescents; 3) Offering additional HPV vaccination education will increase provider and nurse confidence in recommending HPV vaccination to patients and caregivers; 4) Providers frequently document HPV vaccination refusal in the "Notes" section of electronic medical record (EMR) systems to ensure a follow-up conversation with the patient at their next visit; and 5) Billing codes specifying vaccine refusal are rarely used in this context, and 6) there are no uniform guidelines to documenting HPV vaccine refusal.

Conclusions: Providers generally agreed that documenting HPV vaccine refusal in EMR was informative to guide future conversations. Yet, there was limited support for enforcing clinic-wide mandates or policies around documentation, particularly if individual providers had already developed strategies that worked for them and their patients. Alternative strategies to increase HPV vaccination included consistent messaging around HPV vaccination and personnel training on combating vaccine misinformation and hesitancy.

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#4484

THE QUALITY OF LIFE OF FREQUENTLY VS. INFREQUENTLY SCREENED HPV VACCINATED WOMEN

10 - HPV screening

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Background/Objectives: As the first birth cohorts of human papillomavirus (HPV) vaccinated women are entering the cervical cancer screening programs, there is a great need to design the most optimal future screening program for these women. A less frequent screening for the HPV vaccinated women is most plausible which would also provide improved quality of life (QoL) considering that medical examinations and possible abnormal screening test results are known to provoke anxiety among women.

Methods: A total of 594 HPV16/18 vaccinated women were included to the study. These women were part of an original study of four birth cohorts (1992-1995) of females who were vaccinated at the age of 13-15. At the age of 22, they were randomized to frequent (ages 22/25/28; n=2743) vs. infrequent screening (age 28; n=2883) groups. At the age of 28, questionnaires considering quality of life, CECA 10 (Spanish acronym for the Specific Questionnaire for Condylomata Acuminata) and EQ VAS (EuroQoL Visual Analogue Scale), were sent to subgroups of participants after their latest cervical cancer screening results (group 1 frequently screened; group 2 infrequently screened).

Results: In our study, group 1 consisted of 284 frequently screened and group 2 of 310 infrequently screened women. Our results show that women in both groups were equally satisfied in their life situation at 28 years of age. In a scale from 0 to 10, median was 8 in both groups. In EQ VAS questionnaire the median scores in a scale from 0 to 100 were 83,1 in group 1 and 79,3 in group 2, respectively. With a cut-off of 80 points, there was no significant difference between these two groups. CECA 10 questionnaire evaluating emotional and sexual aspects of QoL was used among women with a history of warts (n=44) or Pap cytology ≥ ASC-US (n=85). Comparing groups 1 and 2 and medians of their CECA 10 total points, we found no significant difference between these groups.

Conclusions: Our preliminary results show that there seems to be no significant difference in QoL between frequently and infrequently screened HPV vaccinated women. Vaccinated women may feel safe and taken care, and therefore frequent medical examinations and screening are not lowering their QoL in total.

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#4782

STOPPING HPV: A NATIONAL NETWORK TO DRIVE ELIMINATION OF CERVICAL CANCER AND OTHER HPV-RELATED CANCERS IN FINLAND

37 - Advocacy, acceptability and psychology

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Background/Objectives: Human papillomavirus (HPV) causes cervical cancer in women, as well as many other cancers and condylomata in women and men. WHO has stated that cervical cancer is a preventable disease which can be and should be eliminated. The European Union announced Europe's Beating Cancer Plan with the goal to eliminate all HPV-related cancers by 2030. However, high vaccination coverage rate (VCR) is a prerequisite to reach this goal. Approximately 300 HPV-related cancers occur in women and men annually in Finland. Strikingly, the VCR in Finland is much lower than that in the other Nordic countries, and with significant regional differences within the country.

Methods: This problematic situation led us to establish an HPV network to stop HPV, in order to eliminate cervical and other HPV-related cancers in Finland. Finland has been a global forerunner in organised cervical cancer screening. National screening program started in Finland 1963, with the attendance rate currently exceeding 70%. Implementation of the program rapidly led to significant reduction in cervical cancer rates. However, such secondary prevention of cervical cancer, although effective, only moved the focus from cancer to precancer, but the disease burden has not disappeared. Also, cervical cancer rates have recently increased in younger age groups, approaching the rate that existed before the organised screening program was launched. The goal of our network is to act now, in order to eliminate cervical cancer and other HPV-related cancers, following the goals set by EU and WHO. Our primary goal is to improve VCR of the HPV vaccination program to the level already reached in the other Nordic countries, and by recommending the so-called HPV-Faster strategy, i.e. combining adult HPV vaccination and HPV screening during the first round of the national organised cervical cancer screening program, at the age of 25. We will act by increasing public awareness and generating discussion in national media including medical journals and social media, on the critical importance of vaccination in prevention and elimination of cancers caused by HPV. Our awareness activities aim to support the Finnish Institute for Health and Welfare and government officials playing important roles in the development of national health programs. We will also proactively organise symposia and special sessions at the annual medical conventions taking place in Finland.

Results: The HPV network has already been covered in national media and has received positive attention by key stakeholders. In addition, editorials written by the HPV network members have been published in Finland's largest newspaper and in the Finnish Medical Journal Duodecim, and more is to follow.

Conclusions: We are convinced that by increasing awareness of HPV disease burden and HPV vaccination will evidently increase VCR in the Finnish population.

Paavonen et al abstract_suppl file 1

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#5556

Oral Health Providers' Human Papillomavirus(HPV) Health Education Training Expands Skills During Covid-19: A Case Study

40 - Public health

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Background/Objectives: Background: Many opportunities exist in the oral health environment to disseminate health information commonly given in medical settings. Increasingly, the dental field is embracing what is known as Level 1-6 integration of health services. Since 2018, the American Dental Association(ADA) has endorsed a policy urging dentists to advocate for and administer HPV vaccine(1). However, oral health providers have cited lack of knowledge about HPV as a barrier to educating their patients(2). Recommending the Human Papilloma Virus(HPV) vaccine provides an opportunity for integration between the two settings. Objective: To explore the details of a case study that identifies important themes from a training that propelled oral health providers into level 3 integration during the earliest months of the COVID-19 pandemic.

Methods: We disgned a module to train all clinic staff in the dental office to understand, endorse and recommend the HPV vaccine. Following 90 minutes of instruction, trained youth actors role-played an individual needing an HPV vaccine. Program participants volunteered to practice educating about and recommending the HPV vaccine. The training immediately preceded the onset of COVID-19 in Minnesota, USA, in March 2020. A qualitative evaluation study was conducted one year post-training, where the themes of this case study emerged. This training and evaluation were deemed exempt from the University of Minnesota IRB(Ethos Study ID STUDY00008406.)

Results: From the site where this case study emerges, 45 staff participated in the training. They self-identified as dentists, dental clinic administrators and support staff, a dental direct, hygienists and dental assistants. A separate evaluation of that training provided insight into the power of training to integrate the HPV vaccine into the oral health setting. For example, participants reported that the training gave them confidence in learning the relationship between the HPV vaccine and the prevention of cancer. Others described their comfort and ability to recommend the vaccine increased. Still others noted that previous to the training, HPV education and vaccine recommendation was a topic and skill they had assigned only to the physician community. Within weeks of the training, the COVID-19 pandemic began. Most dental clinics closed adn teh staff was furloughed. However, as a result of this training on HPV vaccination, the staff was primed for other activities in high demand, such as COVID-19 health education and vaccinators. Staff was redeployed, maintaining their employment, and immediately transferred their learning of the HPV information to use in the broader contect of COVID-19 education, testing and later vaccination.

Conclusions: This case study identified several themes. The value of integrating the topic of HPV education and vaccination recommendation into the oral health setting is supported by those trained. Integration of HPV vaccine education in the oral health setting can have broad-reaching impacts that can empower health care workers of all levels of training. Level 3 integration is acheivable and should be encouraged, beginning with education about of HPV with oral health clinic staff and providers.

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#4769

IMPACT OF THE COVID-19 PANDEMIC ON HPV VACCINATION IN PUERTO RICO

40 - Public health

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Background/Objectives: In August 2018, Puerto Rico (PR) became the 5th state or territory in the United States of America to adopt an HPV vaccine school-entry policy, requiring it for 6th graders starting in August 2018. This evidence-based strategy showed a significant marked increase in HPV vaccine initiation uptake among 11- to 12-year-old adolescents, from 58% in 2017 (pre-policy year) to 90% in 2019 (year post-policy initiation). While school-entry requirements effectively increased vaccination rates in PR, recent challenges due to the COVID-19 pandemic have negatively affected its full potential impact on sustained HPV vaccination rates. Targeted efforts are needed to restore PR's trend toward high HPV uptake. The objective of this study was to evaluate the impact of the COVID-19 pandemic in PR on HPV vaccine coverage among 11-16 years old youth.

Methods: A pre-post natural experiment was used. The study population included adolescents registered in the PR Immunization Registry during 2019-2021. We compared the HPV vaccine initiation and up-to-date (UTD) vaccine coverage of 2020 and 2021 with that of 2019 (pre-COVID).

Results: Vaccine data corresponding to a total of 172,940 adolescents was included in the analyses. In 2020, a decrease of 58% in HPV vaccine initiation uptake was noted compared to 2019. In 2021, a reduction of 25.4% was also observed compared with 2019.

Conclusions: From 2020-2021, a total of 66,550 HPV vaccine doses were missed due to COVID-19. This study demonstrated the impact of COVID-19 on HPV initiation and UTD coverage. It will likely take some time to reach pre-pandemic vaccination levels. Community and policy efforts enforcing the implementation of the school entry policy are still lagging due to the critical priority to optimize the impact of available COVID-19 vaccine supply among adolescents. This decrease could lead to increased cases of cervical cancer and genital warts in the upcoming years. Efforts such as catch-up HPV vaccination programs, community-based HPV vaccination promotion programs, provider training, and enforcement of the HPV school entry policy are needed to bring HPV vaccine rates to prior pandemic levels in PR.

FC15- Free communications - Economics and modelling

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#4708

Economic burden of cervical cancer in Mainland China: a systematic literature review

36 - Economics and modelling

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Background/Objectives: As cervical cancer is the fifth common female malignant tumor in China, it is important to assess disease burdens to inform early prevention like HPV vaccine. We aimed to estimate the economic burden of cervical cancer and cervical intraepithelial neoplasia (CIN) in China.

Methods: We conducted a systematic literature review of English and Chinese publications between 2001-2020. All costs and epidemiological data for cervical cancer and CIN patients in China were structurally extracted. The national total direct and indirect costs were estimated through incidence-based approach. Costs were discounted to 2020 Chinese Yuan (CNY) by local health care consumer price indices.

Results: A total of 155 studies were included, with 116 reporting costs from healthcare records/claims/surveys, and 39 from economic analysis. Estimated annual cost per cervical cancer was CNY 58,189 for incident patients and CNY 13,025 for prevalent patients in China. The per-capita annual cost increased from CNY 6,452 for CIN 2 to CNY 13,602 for CIN 3. Total economic burden of cervical cancer nationwide was estimated at CNY 9.69 billion, with 72% from direct medical cost. Cervical pre-cancer (CIN 2 and 3) imposed an additional burden of CNY 2.03 billion, with 48%-50% from direct medical cost. Using HPV attribution fraction, total costs preventable by nonavalent vaccine was CNY 8.72 billion and CNY 1.42 billion for people with cervical cancer and pre-cancer, respectively; by other HPV types 16/18 targeted vaccines (i.e., bivalent and quadrivalent vaccines), the preventable costs for cervical cancer and pre-cancer were CNY 6.88 billion and CNY 0.94 billion, respectively.

Conclusions: Cervical pre-/cancer is associated with significant economic burden in China. Scaling up HPV vaccination can reduce economic losses.

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#4976

COST-EFFECTIVENESS OF COMPUTER-ASSISTED CYTOLOGY IN A PRIMARY HRHPV-BASED CERVICAL CANCER SCREENING PROGRAMME

12 - Triage of HPV positive women

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Background/Objectives: The Netherlands has a primary high risk human papillomavirus (hrHPV) based cervical cancer screening programme with cytology triage for hrHPV positive women. Currently, cytology is fully manually performed. Previous studies have shown that the performance of computer assisted screening (COS) is similar to manual screening, although the results are heterogeneous. Furthermore, COS seems to be less costly due to personnel and costs savings through potential increased productivity of COS, and therefore also offering a solution for temporarily and structural capacity shortage. We evaluated the circumstances under which conditions COS will be cost-effective in comparison to manual cytology triage in a primary HPV-based cervical cancer screening programme. The parameters that will be varied are costs (due to increased productivity and/or reduced workforce) and the probability to detect (pre-invasive) cervical cancer.

Methods: Microsimulation model MISCAN was used to simulate a cohort of 10 million Dutch women born in 1992. Women underwent either manual- or COS-triage between ages 30-60 according to the current Dutch screening programme and were followed from birth until death. We simulated 198 different scenarios with varying test sensitivities compared to manual cytology for CIN1 (-10% to +10%, with 2% interval) and CIN3 (+0% to +4% with 2% interval) and reductions in costs (10 to 0 euros, with an interval of 2 euros). Test sensitivities and costs were based on literature and expert opinion. We calculated average cost-effectiveness ratios of the 198 scenarios compared to manual screening, in terms of costs per QALY gained.

Results: COS will be cost-effective (in terms of QALYs gained) in all scenarios, except for the following combinations: I) no cost reduction and increased CIN1 sensitivity (up until +10%), II) a cost reduction of 2 euros and increased CIN1 sensitivity from 4% onwards, or III) a cost reduction of 4 euros and increased CIN1 sensitivity from 6% onwards, compared to manual cytology. All COS scenarios with any reduction in CIN1 sensitivity (despite cost reduction or CIN3 test sensitivity change) or a reduction in costs from 6 euros onwards (up until 10 euros) seem to be a cost-effective strategy compared to manual screening.

Conclusions: Under realistic circumstances, COS seems to be cost-effective compared to manual cytology. Furthermore, we found that it is important to aim for reducing costs and not to increase CIN1 sensitivity of COS compared to manual screening. Our results can be used as a guideline when to choose for COS instead of manual screening.

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#4998

COST-EFFECTIVENESS OF HPV-BASED CERVICAL SCREENING USING HPV16/18 GENOTYPING AND CYTOLOGY AS TRIAGE TEST: A MODELLING STUDY

36 - Economics and modelling

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Background/Objectives: With the implementation of high-risk papillomavirus (hrHPV) testing followed by cytology in the Dutch population-based primary cervical cancer screening program (PBS), the colposcopy referrals increased three times compared to the previous cytology-based screening program [1]. To reduce the number of clinically irrelevant referrals, the PBS changed the triage from cytology alone to co-testing using HPV16/18 genotyping and cytology in July 2022 [2]. Since the impact of this change is still unknown, this study aimed to evaluate the cost-effectiveness of HPV16/18 genotyping and cytology triage testing compared with cytology alone in the Dutch-PBS framework using a Markov model.

Methods: We developed a microsimulation Markov model using published Dutch data. The previous Dutch PBS that used cytology alone as a triage strategy was simulated and validated using data from the Dutch cervical cancer screening monitoring report in 2019. The validation was performed using the number of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) detected in the direct referrals. As a next step, the co-testing triage strategy (HPV16/18 genotyping and cytology) will be simulated and compared with the cytology triage strategy regarding the number of colposcopy referrals, screen-detected CIN2+, related cervical cancer deaths, and life years gained (LYG). In addition, the incremental cost-effectiveness ratio (ICER) will be estimated. A univariate sensitivity analysis will be performed to evaluate the robustness of the model.

Results: The validation of the model indicates that the simulated number of screening-detected CIN2+ (3,994 cases detected per 1,000 direct referrals) corresponded well with the real-life data of the Dutch PBS in 2019 (3,673 cases detected per 1,000 direct referrals). More results will be presented within three months.

Conclusions: The microsimulation was validated and can be used to assess the cost-effectiveness of hrHPV-based cervical cancer screening. For the next step, we expect that the new screening program that uses HPV16/18 plus cytology would reduce the number of colposcopy referrals and, therefore, be more cost-effective than the previous screening program.

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#4937

Data Integration and Model Validation for Historical Cervical Cancer Screening in England.

36 - Economics and modelling

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Background/Objectives: The use of models to forecast cervical cancer (CC) incidence is well established in the literature. All models used for forecasting should be validated against historical data to lend credibility to those forecasts. To that end, we set out to validate a dynamic transmission model of HPV infection and cervical disease that was adapted to the English context. This validation exercise focused on recreating the changes in CC incidence that were associated with the switch from an opportunistic CC screening program to an organized CC screening program in England in 1988; a change which precipitated a nearly 50% drop in CC incidence by 1998. Such an exercise lends authority to our methods of integrating screening data into the model as well as model structure, particularly in capturing various methods of disease reporting.

Methods: We calibrated an HPV dynamic transmission model to age-specific CC incidence data in England prior to 1988. The change in the screening program was parameterized by integrating publicly available data on coverage from Public Health England. The model was then run from 1988 to 2008 and its outputs were compared to CC incidence data available for that time. Given the spectrum of data available of CC screening coverage (annual, 3-year, and 5-year coverage), we explored various methodologies for integrating different kinds of data into the model to simulate the change in the screening program, and how they affected the model's capacity to recreate the validation data.

Results: When parameterized with annual screening data, the model replicated the drop in CC incidence seen in the validation data. Consistent with validation data, there was no significant increase in CC incidence in model outcomes. This is evidence in support of the model's approach to disease reporting, which emphasizes CC identification through symptom recognition over screening. Integration of 3- and 5-year screening coverage data were less successful in replicating the drops in CC incidence.

Conclusions: Validating models against historical data is a key element in establishing credibility for the purposes of forecasting and future policy discussions. In this validation exercise, our model recreated the observed impact on CC incidence from 1988 to 2008 associated with a transition to organized screening in England. This evidence supports the validity of our model and increases confidence in our forecasts of CC incidence in England.

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#4793

PREVALENCE-INCIDENCE MODEL FOR THE CUMULATIVE RISK OF CIN2+ BASED ON INDIVIDUAL RISK-FACTORS

36 - Economics and modelling

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Background/Objectives: Moving from a "one-size-fits-all' cervical cancer screening approach towards a more efficient and effective personalized risk-based approach requires accurate risk assessment of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) in high-risk human papillomavirus (HPV) positive women. Risk assessment based on characteristics such as age, screening history, HPV genotype, and vaccination status can be used to inform risk stratification in screening programs. Some models exist for estimating the cumulative risk of CIN2+, however their parameters do not have a meaningful interpretation and risk estimates are poorly transferable to application in alternative settings.

Methods: We present a biologically-driven variant of a prevalent-incidence model with multiple-causes for interval-censored data to estimate the cumulative risk of CIN2+ in HPV+ women. Our model includes parameters for prevalent disease, progression from HPV+ to CIN2+, and viral clearance (all three of which can depend on baseline covariates). In addition, it takes into consideration that a woman remains at risk of CIN2+ also after her baseline HPV infection has cleared due to acquisition of a new infection during follow-up. The model parameters are estimated with the expectation-maximisation (EM) algorithm, which is implemented in our R package survmix. We validated the model with simulation studies and applied the model to the POBASCAM and VUSA-Screen studies - two population-based cervical cancer screening studies from different regions in the Netherlands with divergent HPV positivity rates (Amsterdam and Utrecht, respectively).

Results: We show that the HPV natural history parameter estimates of both studies are equivalent conditional on different risk factors, even though absolute risk predictions are different.

Conclusions: Cumulative risk of CIN2+ in HPV+ can be accurately predicted by our model that provides parameters that are relatively easy to interpret. Our model can be used to predict the impact of multiple rounds of screening and inform changes in the screening interval when moving towards a more personalised approach based on individual risk-factors.

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#4804

Potential impact of one-dose HPV vaccination in Low-and-middle-income-countries (LMIC): a modeling analysis using HPV-ADVISE LMIC

36 - Economics and modelling

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Background/Objectives: To help inform the recent 1-dose SAGE recommendations, we examined the population-level impact and efficiency of: 1) one- and two-dose multiple-age cohort (MAC) vaccination of 9-14-year-old girls and 2) one-dose routine vaccination of 9-year-old girls, both scenarios compared to two-dose routine vaccination of 9-year-old girls.

Methods: HPV-ADVISE LMIC is an individual-based, transmission-dynamic model independently calibrated to four epidemiology diverse LMICs (India, Vietnam, Uganda and Nigeria). All scenarios start in 2023 with the nonavalent vaccine and assume 80% vaccination coverage. We assumed that two doses provide 100% vaccine efficacy (VE) against vaccine-type infections and lifelong protection. We examined a non-inferior scenario for one dose vs two doses and pessimistic scenarios of lower one-dose VE (85%) or shorter duration of protection (20 or 30 years).

Results: For the four LMICs, our model predicts that, compared to no vaccination, two-dose routine vaccination with/without MAC would reduce cervical cancer (CC) incidence after 100 years by 79-86%. Adding MAC to two-dose routine vaccination would not impact long-term incidence but would accelerate CC incidence reductions and avert more cases. Adding two-dose MAC (or one-dose MAC with 100% lifetime VE) would avert 4-9% additional cases over 100 years. Adding one-dose MAC would provide a similar benefit (averting 2-7% additional cases) when assuming either 85% one-dose lifetime VE or 20-30-years duration. One-dose routine vaccination would reduce CC incidence after 100 years by 61-75% and avert 66-94% of the cases averted with two-dose routine vaccination under pessimistic assumptions (lifetime VE=85% or duration=30 years). One-dose in MAC and/or routine vaccination would be more efficient in terms of number needed to vaccinate than two-dose if duration is >20-30 years.

Conclusions: One-dose HPV vaccination, through MAC and/or routine vaccination, could facilitate HPV-related diseases prevention by increasing vaccine access and coverage, and potentially vaccinating more girls. Our results confirm that this strategy is likely effective and efficient if one-dose duration of protection is >20-30 years.

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HEALTH AND ECONOMIC EFFECTS OF NONAVALENT VERSUS BIVALENT HPV VACCINATION IN THE NETHERLANDS: A DATA-DRIVEN ANALYSIS

36 - Economics and modelling

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Background/Objectives: HPV vaccination in the Netherlands has recently been extended from a girls-only program to also include boys. The HPV vaccination program uses the bivalent vaccine, targeting HPV types 16 and 18, associated with 70% of the cervical cancers and a majority of other HPV-related cancers. An open question is whether the impact of HPV vaccination can be improved by using the nonavalent vaccine, targeting an additional seven HPV types. This study aims to compare these two vaccines within the Dutch vaccination program.

Methods: We performed a cost-effectiveness analysis for different scenarios with respect to cross-protection, herd-immunity and waning efficacy. We used a data-driven analysis to translate the uncertainty about data into uncertainty intervals for the outcomes. We analyzed data of the Dutch national cervical cancer screening program between 2017-2019 for detailed information on HPV testing outcomes and cytological and histological diagnoses per screening round. Type attribution of CIN2+ lesions were estimated from Dutch trial data. Cancer incidence data for the various HPV-associated cancers were collected from the Netherlands Cancer Registry, with type attribution obtained from the literature. Genital warts incidence data for girls were retrieved from a GP registry study and extrapolated to population level incidence. A type-specific HPV transmission model was used to project type-specific HPV incidence reductions resulting from reduced transmission.

Results: In the base-case scenario with life-long direct protection for the high-risk HPV types included in the vaccines, the nonavalent vaccine prevented an additional 650 CIN2+ diagnoses, 30 cervical cancer diagnoses and 14 other cancer diagnoses in a vaccinated cohort of 100.000 girls and 100.000 boys, compared to the bivalent vaccine with moderate cross-protection. This corresponds to an ICER that lies around the Dutch cost-effectiveness threshold of €20.000. Thus, the cost-effectiveness profile of nonavalent versus bivalent vaccination depends on the level of cross-protection assumed. However, when including the low-risk HPV types, associated with genital warts, the nonavalent vaccine is likely to be cost-effective irrespective of assumptions regarding cross-protection. ICERs remained below the cost-effectiveness threshold under various anticipated price differences and scenarios for herd immunity and waning vaccine efficacy.

Conclusions: Gender-neutral vaccination with the nonavalent vaccine is likely to be cost-effective compared to the bivalent vaccine when taking into account the total effects on screening, HPV associated cancers and genital warts.

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#4899

A new tool for conducting rapid assessments of the impact of interventions on the pathway towards global cervical cancer elimination.

36 - Economics and modelling

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Background/Objectives: In its Global Strategy to Accelerate the Elimination of Cervical Cancer, the World Health Organization has set ambitious goals for cervical cancer elimination, along with a set of intermediate targets for vaccination, screening, and treatment. However, given that the Strategy encompasses decade-long timelines, these targets will inevitably need updating over time as the landscape of available technologies for combating cervical cancer evolves. In this work, we introduce a new model that can rapidly evaluate pathways toward elimination under complex combinations of new and existing interventions.

Methods: We formulated a statement of need for an open-source HPV model, which identified three essential criteria: (1) ease of use, which demands simple and customizable analysis workflows, minimal computing requirements, and transparent documentation; (2) scientific rigor, essential if the model is to be used for policy; and (3) stakeholder acceptance through active and ongoing consultation and engagement across the modeling and policy landscape. Our team, with expertise in cancer epidemiology, software development, public health, and disease modeling, established processes for creating, sharing, evaluating, and updating the model.

Results: We created HPVsim, an agent-based model designed for rapid analysis of the resource requirements needed to meet targets around vaccination, screening, and treatment. HPVsim comes pre-loaded with country-specific demographics, sexual networks with genotype-specific HPV transmission, default parameter values sourced from literature reviews and expert advice, and genotype-specific disease progression calibrated to known aspects of cervical dysplasia's natural history. Given that so much of the model is pre-specified, analysis pipelines can be set up with very little effort. We demonstrate this by presenting an illustrative case study of using the model to estimate the savings that would result from adding therapeutic vaccination to existing cervical cancer intervention packages.

Conclusions: With the advances in computing power over the past decades, advanced mathematical models can now be run on personal computers, and used to provide comprehensive, evidence-based recommendations to policy makers along the pathway to cervical cancer elimination. We created a model with little to no time required for onboarding, installation, or running analyses, which can be placed directly into the hands of decision-makers. By improving access to cervical cancer modeling tools, our hope is that cervical cancer elimination targets will be more readily adapted and updated in response to changing technologies, and that cervical cancer elimination will therefore be a realistic, rather than strictly symbolic, target.

FC17- Free communications- Epidemiology and natural history 3

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#4925

HUMAN PAPILLOMAVIRUS TYPES IN INVASIVE CERVICAL CANCER IN RELATION TO CERVICAL SCREENING

14 - Genotyping

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Background/Objectives: Cervical cancer is caused by oncogenic Human Papillomaviruses (HPVs) and cervical screening programs are switching to HPV-based screening. However, different HPV types differ greatly in their prevalence and their oncogenicity, and the efficiency and effectiveness of cervical screening for each HPV type is undetermined.

Methods: We compared the incidence of invasive cervical cancer during 2004-2011 in Sweden by screening attendance in the past 10 years, in a population-based cohort of 3·5 million women. The screening-related reduction of incident cervical cancer was then stratified by HPV type, using HPV typing data of invasive cervical cancer from 2850 screened and non-screened cases, respectively. By further integrating HPV genotyping data from 362,000 women in the population cohort, we calculated number of women needed to screen (NNS), and number of women needing follow-up (NNF) to detect or prevent 1 cancer case.

Results: Attending screening was associated with a more than 70% reduction of cervical cancer incidence caused by HPV16 or by oncogenic types other than 16/18, and a 54% reduction of cancer caused by HPV18. The NNS and NNF were lowest for HPV16 but up to 40-500 times higher for some other HPVs commonly screened for. For women below 30 years of age, NNS and NNF for HPV16 were 4,700 and 288, respectively, but >220,000 and >16,000 for some other HPVs.

Conclusions: Although reasonable limits for NNS and NNF may differ between settings, the present estimation of NNS and NNF by HPV type should be informative for designing optimally effective cervical screening programs.

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#4934

HPV IN ATYPICAL GLANDULAR CELLS: ASSESSMENT OF NON-HPV16/18 SPECIFIC RISKS

24 - Risk management

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Background/Objectives: Atypical glandular cells (AGC) are associated with a higher risk for cervical cancer, in particular adenocarcinoma. Most human papillomavirus (HPV) positive AGC contain non-HPV16/18 HPV ("other HPV"), but the risk associated with specific "other HPV" types is not well known.

Methods: Registry linkages identified the women resident in the capital region of Sweden who had had an AGC during 2014-2018, where the index sample had been HPV tested and a subsequent histopathology existed during a follow-up until 2019. Cervical specimens that had been positive for "other HPV" were retrieved and HPV genotyped using general primer PCR with subsequent hybridization to type-specific probes. The 1 minus Kaplan-Meier function defined the cumulative incidence proportion of CIN3+, by specific HPV type. Hazard ratios (HR) for CIN3+ were generated using multivariate Cox regression.

Results: Overall, 341 women with AGC positive for "other HPV" were included. In subsequent histopathology, we found 139 CIN3+ cases (134 were CIN3/AIS and 5 were invasive cervical cancers (ICC)). Four of 5 ICC cases were HPV 45 positive, and one ICC was positive for HPV 31. The cumulative incidence of CIN3+ was highest (83%, 95% CI: 58-97%) among HPV 33 positive women with AGC. HPV 31 positivity conferred the highest HR for CIN3+ relative to other types, both in primary cytology and primary HPV screening (HR: 3.93, 95% CI: 1.12-13.73 and HR: 5.33, 95% CI: 1.55-18.34, respectively).

Conclusions: Among the "other HPV" types, HPV31, 33 and 45 constitute higher risk for CIN3+ among women with AGC, implying that extended HPV genotyping may be useful for AGC management.

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#4883

The HPV distribution in CIN2, CIN3 and Cervical Cancer lesions in the Autonomous Region of Madeira

26 - Cervical neoplasia

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Background/Objectives: Cervical cancer is the 4th most common cancer in the female population worldwide and virtually all cases are caused by sexually transmitted HPV infection. The aim of this work is to identify the distribution of HPV genotypes in CIN2, CIN3 and cervical cancer lesions in the Autonomous Region of Madeira (RAM).

Methods: Retrospective and descriptive study in the period from January to December 2021. 98 women who underwent excision of the transformation zone (LLEZT) in this period were included and 61 had HPV test (Anyplex II) prior to the procedure. We analyse demographic variables, pre-LLETZ citology, pre-LLEZT HPV test and histological results of LLETZ.

Results: Of the women who underwent LLEZT, 62% presented CIN2, CIN3 and cervical cancer on histopathological study. Of this group, 29% had CIN2, 66% CIN3 and 5% cervical cancer. Of the CIN2 cases, 61% of the women had HPV test prior to the procedure and the most common high-risk HPV types identified were HPV-16 (45%), HPV-31 (18%) and HPV-52 (18%). Regarding CIN3 cases, 40% of women had HPV test prior to LLEZT, with the most common high-risk HPV types being HPV-16 (38%), HPV-18 (19%) and HPV-45 (19%). All cervical cancer cases had HPV test prior to LLEZT, with the detection of high-risk HPV-16 (67%), HPV-31 (33%) and HPV-58 (33%). Regarding infection by multiple types of high-risk HPV, we identified 36% in cases of CIN2, 50% in cases of CIN3 and 33% in cases of cervical cancer. It should be noted that HPV-53, HPV-66 and HPV-68 were always presented in association and never isolated.

Conclusions: This preliminary study in the RAM has a parallelism with the Cleopatra II study carried out in Portugal. In our study we reported a higher rate of multiple infections (43% Vs 11.2%). Regarding the types of high-risk HPV, we showed similarities in the cases of CIN2, but in the cases of CIN3, although we also showed a higher prevalence of HPV-16, the other most common types in our study were HPV-18 and HPV-45 (Vs HPV-31 and HPV-33). The cervical cancer cases present genotypes similar to the Cleopatra II study. Our study shows slight differences compared to the national Cleopatra II study, imposing the analysis that we present: a smaller sample size, HPV test prior to LLEZT and data from the present time, where the vaccine available covers most of the genotypes involved in cervical dysplastic lesions.

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#4675

CHARACTERIZATION OF TYPE-SPECIFIC HPV PREVALENCE IN A POPULATION OF PERSISTENT CUTANEOUS WARTS IN FLANDERS, BELGIUM

31 - HPV and associated skin diseases

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Background/Objectives: Cutaneous warts are benign skin lesions caused by the human papillomavirus (HPV) with a worldwide prevalence of 0.84-12.9%.[1] Even though they are considered benign, they can have a huge impact on life quality and cause serious illness in certain immunocompromised populations. Studies have shown that the efficacy of a wart treatment is dependent on the causative HPV type.[2] Therefore, in this article we aim to determine the HPV genotype-specific prevalence in cutaneous warts of a Flemish population as part of the OVW-SA trial.[3]

Methods: Swab samples of cutaneous warts were collected during the enrollment phase of the OVW-SA trial. The DNA extraction was performed on the automated NucliSENS® easyMAG® system (bioMérieux).[4] The samples were analyzed with two separate in-house PCR assays capable of detecting the most prevalent cutaneous HPV types (i.e. wart-associated HPV qPCR) as well as the most relevant mucosal types (i.e. Riatol genotyping assay).[5][6] In total the type-specific prevalence of 30 distinct HPV genotypes was determined. The beta-globin gene was used as a cellularity control and for viral load quantification. Data concerning wart persistence, previous treatment, wart type and other relevant wart and patient characteristics was collected through a baseline questionnaire.

Results: The study population (n=269) consisted mostly of persistent warts considering that 92% (n=247) of the sampled skin lesions had undergone previous treatment and 98% (n=263) was older than six months. The most prominent wart type was the mosaic verruca plantaris (42%, n=113). Multiple HPV infections were detected in 79% [95%CI 74-84%] of the lesions, whit 53% [95%CI 47-59%] containing three or more HPV types. Only 2% [95%CI 1-5%] of the lesions remained HPV negative. The most prevalent HPV types were cutaneous HPV types 27 (73% [95%CI 67-78%]), 57 (63% [95%CI 57-68%]) and 2 (42% [95%CI 36-48%]). In only 7% [95%CI 4-10%] of warts other HPV types were found. Mucosal HPV types were also detected in 7% [95%CI 4-10%] of lesions, amongst which also HR-HPV types 31, 39, 51, 52, 59, 66 and 67. Highest viral loads were observed with HPV 2, 27 and 57 (i.e. 2,16x10^3 viral copies per cell).

Conclusions: Based on these findings, persistent warts are more likely to: (1) be mosaic verucca plantaris, (2) to be positive for multiple HPV types, (3) to be caused by HPV 2, 27 or 57 (a4 genus), and (4) have high viral loads. The high viral load of HPV 2, 27 and 57 can be an explanation for the high infectious potential and wide spread of these infections due to abundant viral shedding in the environment.

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#4952

HPV AND CYTOLOGY IN THE FOLLOW-UP OF CERVICAL CANCER PATIENTS WHO RECEIVED FERTILITY-SPARING SURGERY

26 - Cervical neoplasia

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Background/Objectives: The most effective follow-up strategy for cervical cancer patients receiving fertility-sparing surgery is unknown. Therefore, this study aims to evaluate the value of HPV testing and cytology to detect recurrences in the follow-up after fertility-sparing surgery.

Methods: From the Netherlands Cancer Registry, data were retrieved of FIGO 2009 stage I cervical cancer patients aged 18 to 40 years, who underwent fertility-sparing surgery between 2000 and 2020 in the Netherlands. These data were combined with the patients' cervix-related pathology records up to 15th September 2022, which are registered in the Dutch National Pathology Database (PALGA). The HPV and cytology results at 6, 12, 18 and 24 months +/- 3 months of follow-up were analysed. HPV status was considered positive if at least one HPV test was positive during a specific follow-up period. Cytology was subdivided into three groups (normal, mild dysplasia (MD), and moderate/severe dysplasia (SD)) based on the highest Papanicolaou classification during a specific follow-up period. The cumulative incidence of recurrent cervical intraepithelial neoplasia grade 2 or higher (CIN2+) lesions and of recurrent cervical cancer was calculated by performing Kaplan-Meier analyses in R (version 4.2.0). Patients were censored if they were lost to follow-up or if they received a hysterectomy.

Results: In total, 1,465 patients were included, of whom 19,583 pathological reports were available. The median age was 31 (interquartile range (IQR): 30-35) and, based on the tumour measurements in the pathological reports, the pathological FIGO 2018 stage was stage IA (n=128, 8.8%), IA1 (n=910, 62.1%), IA2 (n=216, 14.7%), IB (n=13, 0.9%), IB1 (n=111, 7.7%), IB2 (n=29, 2.0%), IB3 (n=3, 0.2%) or missing (n=54, 3.7%). The primary treatment was conisation/portio amputation (n=791, 54.0%), LLETZ (n=367, 25.1%) or trachelectomy (n=307, 20.9%) and the median follow-up was 6.1 years (IQR: 3.3-10.8). Recurrent CIN2+ was diagnosed in 128 patients (cumulative incidence: 15%), of whom 52 patients (cumulative incidence: 5.4%) had developed recurrent cervical cancer. The cervical cancer recurrences were located either locally (n=23, 44.2%), regionally (n=15, 28.8%) or distantly (n=14, 26.9%). Follow-up by cytology and/or HPV within the first 2 years of follow-up was available for 1,421 patients. Within the first 2 years of follow-up, 298 patients (21%) received one or two cervical scrapes, 838 patients (59%) received three, four or five cervical scrapes, and 285 patients (20.1%) received more or equal to six cervical scrapes. Table 1 describes the cumulative incidence of CIN2+ and cervical cancer recurrence, respectively, occurring within 6 months after the follow-up visits at 6, 12, 18 and 24 months. The cumulative incidence is stratified by cytology and HPV results, if available. The data demonstrated increased incidences of recurrent CIN2+ and cervical cancer, if the follow-up results at the specific time points show dysplasia or HPV positive status.

Conclusions: Cytology and HPV testing during the follow-up may identify recurrent CIN2+ lesions and recurrent cervical cancer occurring within 6 months after a follow-up visit. Recurrence rates of CIN2+ in HPV negative patients with normal cytology ranges from 0% to 0.7%, while the recurrence rates of HPV positive patients with moderate/severe dysplasia ranges from 25% to 100%.

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#4784

A two-year community-based follow up study of HPV infection in Ethiopia: Molecular epidemiology, genotyping, persistence, clearance, and re-infection rates among rural women

03 - Epidemiology and natural history

Background/Objectives: Cervical cancer (CC) is the second most common cancer among women world-wide and the highest burden of the disease is seen in low- income and low-middle-income countries (LMIC). In Ethiopia, cervical cancer is the second leading cause of morbidity and mortality from all cancers in women. Human papillomaviruses (HPV), the most common sexually transmitted viral infection globally, plays a key role in the development of cervical cancer. Persistent infection of the oncogenic HPV types and progression to precancerous lesions, and invasion is the most important step in the carcinogenesis process. This study aimed to determine the population-based prevalence of HPV infection and genotype distribution, their persistence and clearance rates within 2 years of follow up.

Methods: This population-based study was conducted among rural women aged 30-49 years in Butajira, south-central Ethiopia. A total of 893 samples were tested at baseline. A self-sampling device (Evalyn Brush®, Rovers, Oss, The Netherlands) was used for the first time in the country and HPV presence and genotype was determined using multiplexed genotyping (MPG) by BSGP5+/6+ PCR with Luminex read out. After the baseline screening, all the hr-HPV positive women were invited for follow-up testing at 6 and 24 months. Cervical examination using VIA, cytology, and colposcopy (if indicated) was done during the follow up.

Results: At baseline screening, the population-based HPV positivity rate was 23.2% (95% CI: 23.54-22.86%). Of these 20.5% (95% CI=20.79-20.21) and 10.3% (95% CI=10.52-10.08) women were hr- and lr- HPV positive, respectively. Fifty-five (7.2%) of the women showed multiple hr-HPV infections. Age-specific hr-HPV infection peaked in the age-group 30-34 years old (58.6%) and decreased in 35-39, 40-44, and 45-49 years to 20.4%, 4.5% and 3.8% respectively. The top five prevalent hr-HPV genotypes were HPV16 (57.1%), 35 (20.3%), 52 (15.8%), 31 (14.1%), and 45 (9.6%) in the Butajira district. At 6 and 24 months, 95 (60.5%) and 94 (59.9%) women attended follow up testing respectively with a loss to follow-up of 47 (30%) at the 6 months and 63 (40.1 %) at the 24 months follow-up visits. hr-HPV infection clearance was observed in 70 women (73.7%) within 6 months and among 77 women (84.6%) within 2 years. Among women who were negative at baseline, the hr-HPV incidence was 4.1% from the 74 tested women. HPV68, 82, 53, 52, 56 were the most persisted genotypes with 100%, 75%, 42.9%, 31%, and 25% persistence rates respectively after 24 months, while HPV 59, 68, 66, 52 and 16 were found to have persistence with 50%, 50%, 20%, 15.8% and 3.5% respectively. Twenty-nine (29.9%) of the 6 months follow up attended women were with abnormal cytology including ASCUS and HSIL constituted 10.3% of the tested women. Although HPV based cervical cancer screening is the way forward equally a triage test is needed for hr-HPV positive women to identify those women who may develop progressive disease.

Conclusions: This study provided new data on the overall prevalence of HPV infection and distribution of specific HPV types in rural Ethiopia. As a first population-based study in the country, our results can serve as valuable reference to guide nationwide cervical cancer screening and HPV vaccination programs in Ethiopia. HPV16, HPV35, HPV52, HPV31 and HPV45 were the most prevalent genotypes. Most of the hr-HPV infections among rural Ethiopian women were cleared within 2 years.

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#5225

EFFICACY OF A NEW SUPPLEMENTATION BASED ON EGCG, FOLIC ACID, VITAMIN B12 AND HYLURONIC ACID ON PATIENTS WITH HUMAN PAPILLOMA VIRUS (HPV) PERSISTENT INFECTIONS AND CERVICAL LESIONS.

24 - Risk management

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Background/Objectives: The persistence of the Huma Papilloma Virus (HPV) infection is the fundamental condition for the virus to exert a transforming action on the cervical epithelium to progress into cervical cancer. The lack of therapies and treatments for HPV persistent infections and related cervical lesions is the base of our project. We aimed to test the efficacy of a formula containing Epigallocatechin Gallate (EGCG), Folic Acid (FA), Vitamin B12, and Hyaluronic Acid (HA) in patients with HPV-related infections and cervical lesions.

Methods: Twenty patients with HPV infections and the occurrence of low-grade cervical lesions (chronic cervicitis, mild dysplasia) were divided into two groups. The ten women in the treated group received a tablet per day containing EGCG, FA, Vitamin B12 and HA for 12 weeks. As control, ten patients were untreated and evaluated over the same time scales as the treatment group. Adverse effects have been evaluated at four-week intervals. As measurement of treatment efficacy, we used: Pap-smear test, colposcopy, histology, and HPV DNA test. For instance, loss or decrease in the HPV-DNA content were considered as positive response to therapy. No detection of abnormal cells or decrease in the lesion extent were considered as positive response as well.

Results: Pap smear cytology test and HPV DNA test before the treatment showed that four out of ten patients in the treated group had chronic cervicitis (CC), while the remaining six had mild dysplasia. Moreover, five patients in the treated group displayed atypical squamous cells of undetermined significance (ASCUS), and three patients had low-grade squamous intraepithelial lesions (LSIL). Four out of five patients with ASCUS and two out of three patients with LSIL positively reacted to the therapy. In addition, four patients with CC and six patients with mild dysplasia displayed reduced HPV-DNA content after 12 weeks treatment. Eight out of ten patients displayed a total positive response to the treatment, namely the regression of HPV infected lesion. This contrasts with untreated control group in which only three out ten patients showed a positive response, namely the decrease in HPV-DNA content.

Conclusions: This study demonstrated that oral supplementation of a product containing EGCG, FA, Vitamin B12 and HA is effective for treating cervical lesions without any side effects. These data suggest that this new innovative formulation can be a potential therapeutic therapy for patients with HPV infected cervical lesions.

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#5036

Epidemiology of cervical adenocarcinoma in situ in the HPV vaccine era: an update

03 - Epidemiology and natural history

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Background/Objectives: Cervical adenocarcinoma in situ (AIS) is the only recognized precursor of adenocarcinoma, the second most common cervical cancer histology. Because most adenocarcinoma and AIS are caused by HPV 16 and 18, types targeted by all HPV vaccines, these lesions are highly vaccine preventable. Quadrivalent HPV vaccine was introduced for U.S. females aged 11-12 years in 2006, with catch-up through age 26. Previously, we described AIS reported to HPV-IMPACT, a 5-site cervical precancer surveillance system in the United States, for 2008-2015. Here, we compare AIS reported in 2016-2019 to those reported in 2008-2015.

Methods: Using active surveillance of all histopathology laboratories serving the catchment areas, site staff reported AIS diagnoses and demographics in women aged ≥18 years. Cervical cancer screening was estimated using site-specific data sources. Tissue specimens were sought for cases in women aged 18-39 years, and HPV typing was performed at CDC. Analyses were conducted comparing age, race, insurance, HPV vaccination, and HPV types detected for 2008-2015 and 2016-2019. We estimated age-specific AIS incidence rate ratios (IRR) and 95% confidence intervals (CI) among screened women by 2-year period, compared to 2008-2009.

Results: A total of 515 AIS cases were reported for 2008-2015; 255 cases were reported for 2016-2019. The median age was higher in 2016-2019 than in 2008-2015 [36 (IQR 31-42) vs 34 (IQR 29-41)]; no AIS cases were reported among 20-24-year-olds after 2016. In both periods, the majority of cases occurred among non-Hispanic White women (69%, 60%), and among those with private health insurance (75%, 68%). Overall, 32 (4%) AIS cases had documented vaccination before diagnosis at median age 24 years (range 17-30); vaccination and age did not differ by period. Among 275 typed cases, the proportion HPV16/18 positive was similar by period (90%, 89%); 57% and 54% had HPV16, and 36% and 40% had HPV18. Among 20-24-year-olds, AIS incidence declined from 11.7 per 100,000 screened women in 2008-2009 to 3.6 in 2014-2015 (IRR=0.31 [95% CI 0.09-1.07]), and to 0 in 2018-2019 (Figure). Among 25-29-year-olds, AIS incidence increased non-significantly from 14.2 in 2008-2009 to 18.5 in 2014-2015 (IRR=1.30, 95% CI 0.75-2.30), then declined to 7.8 by 2018-2019 (IRR 0.55, 95% CI 0.26-1.15). AIS rates increased significantly by 2018-2019 in age groups 35-49 years. In 50-64-year-olds, rates were low and no consistent trend was observed.

Conclusions: Twelve years after vaccine introduction, incidence of AIS was extremely rare among 20-24-year-olds and began to decline among 25-29-year-olds. These data provide further encouraging evidence on impact of the U.S. HPV vaccination program.

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Figure

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#4697

TRENDS IN HSIL AND CIN2-3 PREVALENCES AMONG COMMERCIALLY INSURED 15-39-YEAR-OLDS SCREENED FOR CERVICAL CANCER FROM 2007-2020, UNITED STATES

26 - Cervical neoplasia

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Background/Objectives: Administrative insurance claims databases have been used to monitor ecologic trends of abnormal cytological results and cervical precancers following implementation of the national HPV vaccination program in 2006. We extended previous analyses and estimated annual prevalence per 1000 person years (py) of cytologic high-grade cervical intraepithelial lesions (HSIL) and histologically-confirmed cervical intraepithelial neoplasia grades 2 and 3 (CIN2-3) among privately insured US women ages 15-39 years screened for cervical cancer from 2007-2020.

Methods: Using the IBM® MarketScan® Databases, we analyzed administrative claims for inpatient admissions, inpatient services, and outpatient services among continuously enrolled women ages 15-39 years with evidence of cervical cancer screening in each calendar year. HSIL and CIN2-3 prevalence /1000py were calculated among 15-19-, 20-24-, 25-29-, 30-34-, and 35-39-year-olds for each year of the study period.

Results: HSIL prevalence in 15-19- and 20-24-year-olds decreased by 71% and 62%, respectively from 7.22 and 10.44 HSIL/1000py respectively in 2007 to 2.06 and 3.93 HSIL/1000py in 2020 (Figure Panel A). Among 25-29-year-olds, HSIL prevalence increased 16% from 2007 to 2014 (7.36 to 8.53 HSIL/1000py), remained relatively stable through 2016, then decreased 12% through 2020 to 7.54 HSIL/1000py. HSIL prevalence increased 45% among 30-34-year-olds and 50% among 35-39-year-olds. CIN2-3 prevalence was lower than HSIL prevalence, however, trends were similar within each age group (Figure Panel B).

Conclusions: HSIL and CIN2-3 prevalences have declined over 60% among privately insured screened 15-19- and 20-24-year-olds since 2007 and 12% among 25-29-year-olds since 2016, suggesting protective impact of the U.S. HPV vaccination program. Continued monitoring can assess further impact of the vaccination program, including whether the decreasing trend among 25-29-year-olds is sustained and potential vaccine impact in older groups as vaccinated persons reach those age groups.

Figure

FC20- Free communications- Screening methods and self-sampling

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#4832

COMPARISON OF HISTOLOGICAL DIAGNOSES BEFORE AND AFTER TWO YEARS OF CO-TESTING HPV AND CYTOLOGY IN GERMANY

16 - Screening methods

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Background/Objectives: Since 2020 the German cervical cancer prevention program in women >35 years has replaced annual conventional cytology by HPV-cytology co-testing with liquid based cytology (LBC) as an option. The obligatory follow-up algorithms demand expert colposcopy already after twice HPV-high-risk-(HR)-positivity or borderline cytology with and -if repeated- without HPV-HR-positivity. CytoMol, a leading lab specialized in cervical cancer prevention, offers LBC (ThinPrep®, Hologic, Wiesbaden, Germany) with computer-assistance (IMAGER®, Hologic, Wiesbaden, Germany) with HPV-HR-DNA-testing (cobas®, Roche Diagnostics, Mannheim, Germany) as standard in co-testing.

Methods: In Germany colposcopy and histology are carried out decentralized in numerous practices and institutions. We therefore ask systematically for the results of such examinations. An estimated 80% of these data can be retrieved and stored. Here we compare the numbers of histological diagnoses after the first two years of co-testing 2020/21 with the respective numbers in 2018/19 when annual conventional cytology was the standard and no early colpocopy was required. The absolute numbers were referred to the numbers of cytological tests in the respective periods.

Results: In 2020/21 395.759 cytology/HPV co-tests were performed. From the same period we received 4.847 histology results (including cases after follow-up tests) while in 2018/19 with approximately the same number of patients 1.789 histology reports were retrieved. In 2018/19 29,5% of them were achieved by biopsy/curretage, 51,7% by conization and 18,8% by hysterectomy. In 2020/21 the rates were 53,4%, 41,4% and 5,2%.The rate of positivity for any grade of abnormality decreased from 2018/19 to 2020/21 from 75.5% to 69.7% because the number of cases without any abnormality in histology increased by a factor of 3.35. On the other hand all kinds of abnormalities were also more often detected: CIN I x6.15, CIN II x3.44, CIN III x1.97, squamous cell carcinoma x1.23 and AIS/adenocarcinoma x1.35. These data are limited by the incomplete recovery of the histology findings and the fact that there is no review of histology possible a large routine setting. However, these limitations were the same in both periods.

Conclusions: The shift from annual conventional cytology to co-testing LBC-HPV with the implementation of a strict follow-up protocol lead to a sharp increase of histologically confirmed abnormalities of all degrees. The higher increase of lower grade findings and cases without histological abnormality suggests that this rise in sensitivity may be compromised by a decline of specificity.

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#4783

ADHERENCE TO RECOMMENDED FOLLOW-UP IN OPPORTUNISTIC VS. NON-OPPORTUNISTIC CERVICAL SCREENING

23 - Diagnostic procedures / management

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Background/Objectives: A recent study found that adherence to recommended follow-up protocols was poor in the Danish population-based cervical screening program (1,2). The program integrates opportunistic screening in the organized program, and previous research have estimated that approx. one third of screening samples are performed opportunistically, which covers both delayed and too frequent screening, but it is unknown whether these women differed from non-opportunistic screened women in terms of adherence to follow-up (3). In this study we estimated the risk of non-adherence to the entire follow-up pathways among opportunistic screened and non-opportunistic women in the Danish population-based cervical screening program.

Methods: We included all women with non-negative screening samples, i.e. inadequate or abnormal cytology, between 1st January 2015 until 31st December 2017. Women were considered opportunistic screened if there was no record of an invitation to screening within a year before the inclusion sample. All follow-up samples registered until end of 2021 were then assessed in terms of how they were in accordance with the recommended in terms of timeliness, test type and provider. Adherence to follow-up was categorized into; i) full adherence, ii) insufficient follow-up, iii) no follow-up, iiii) more than recommended, but beneficial and iiiii) more than recommended with no gain. Binomial regression analyses were used to calculate relative risks of non-adherence to recommended follow-up for opportunistic screened women compared to non-opportunistic screened women. Analyses were adjusted for age, screening provider and previous screening abnormalities.

Results: In total we included 49,502 women with a non-negative cytology screening in this period. Of those, 17,144 (35%) was considered to be opportunistic screened. Overall, the proportions who had full adherence to the recommended follow-up were 39% in opportunistic screened women and 47% in non-opportunistic screened women. After adjustments, the relative risk of non-adherence to recommended follow-up was 1.12 (95% CI 1.10; 1.14) for opportunistic screened women compared to non-opportunistic screened women, while the corresponding relative risk was 1.65 (95% CI 1.48; 1.84) for no follow-up, 1.10 (95% CI 1.08; 1.13) for insufficient follow-up and 1.33 (95% CI 1.28; 1.38) for excessive follow-up vs. full adherence.

Conclusions: While adherence in general is poor after cervical screening, this study shows that it is even worse among opportunistic screened women. These results underscore the need for careful considerations in clinical practice when performing opportunistic screening, to secure that screening is followed up sufficiently.

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#4923

CERVICAL CANCER SCREENING ACTIVITY IN THE CAPITAL REGION OF DENMARK DURING THE COVID-19 PANDEMIC

01 - HPV disease and COVID-19

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Background/Objectives: We assessed the impact of the COVID-19 pandemic on cervical cancer screening activity in the Capital Region of Denmark. From March 2020 through January 2022, Denmark went through different levels of national COVID-19 restrictions including periodic lockdowns. Throughout the period, the Ministry of Health stipulated an unaltered continuation of all cancer screening programs. Yet, access to clinician collected cervical screening was at times limited due to difficulties in making non-acute appointments at primary health care providers.

Methods: Cervical screening activity was defined as screening by invitation, opportunistic screening, and screening participation by HPV self-sampling. The screening activity was monitored monthly during and after the COVID-19 pandemic (2020-2022) and compared descriptively to a 3-year pre-pandemic reference (2017-2019). Data was retrieved from the Danish National Pathology Database.

Results: The activity of cervical cancer screening by invitation was affected most in March-May 2020 with a monthly change in screening activity of -49%, -51% and -19%, respectively. This was offset throughout the remainder of 2020 resulting in a yearly screening activity reduction of 8% compared to the reference period. For 2021, <1% difference in activity of screening by invitation was observed compared to the reference period. Opportunistic screening activity was impacted more with an annual reduction of 14% in 2020 and 25% in 2021 compared to the reference period. In 2022, the trend continues with a reduction in activity of 31% in the evaluated period, even after lifting the last societal COVID-19 restrictions in January 2022. Participation in cervical screening by HPV self-sampling increased significantly from 17% (2017-2019) to 21% (2020-2021) and, in contrast to the pre-pandemic period, participation increased by age ($p<0.001$). The overall cervical cancer screening activity was reduced by 9% during 2020-2021.

Conclusions: The COVID-19 pandemic impacted the activity of cervical cancer screening by invitation most in 2020 and mainly during the initial lockdown periods, resulting in a screening activity reduction of 8% in 2020. In 2021, the impact was minimal, possibly reflecting societal adaptations to restrictions. Opportunistic screening activity decreased during the pandemic and a continuous decreasing trend is seen. Screening participation by HPV self-sampling was higher during the pandemic than in the pre-pandemic period, with a significant increase amongst women 40 years or older. Denmark has not instated any special initiatives to reduce the impact of the COVID-19 pandemic on cervical cancer screening activity.

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#4837

A NATIONWIDE TRIAL OF RISK-STRATIFIED CERVICAL SCREENING FOR FASTER CERVICAL CANCER ELIMINATION

40 - Public health

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Background/Objectives: As the era is approaching when vaccinations will have resulted in that HPV infection is no longer transmitted, design of effective campaign strategies for targeting of screening to find infected women at risk will become important.

Methods: We used the Swedish national quality registry of cervical screening to identify cervical cancer risk profiles based on screening history. Profiles with an invasive cervical cancer risk of >1% were for the whole Sweden found for 4,918 women and a self-sampling kit were sent to the registered address of these women. There were 76,653 women in Sweden who had not taken a cervical smear for 20 years or more and these women (as well as a group of 12,038 women with risk profiles between 0,3-1%) were by both online letters and physical letters sent a link to order a self-sampling kit. Piloting during 2019-2021 also used reminders by SMS.

Results: In the 2020 pilot, we invited 6,398 women with high risk profile and 20.0% responded and ordered a self-sampling kit. In the 2021 pilot, we invited 23,318 women (mostly long-term non-attenders) and 9.51% responded. The full scale campaign targeting 93,609 women all over Sweden was launched in September 2022. Direct send appears to have almost doubled the participation rate compared to the strategy with invitation to order a kit. HPV prevalences varied greatly by risk group, with a noteworthy finding being that almost one third of HPV positivities were HPV16/18 in the high risk groups. Positive women are referred to a regionally responsible gynecologist in the vicinity of the woman´s home.

Conclusions: Effective campaigns to reaching populations at high risk of cervical cancer with cervical cancer will be important for faster cervical cancer elimination. We find that a nationwide campaign using self-sampling and multiple contact strategies can be readily implemented in the whole country as a regular process for complementing the routing screening program.

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#4682

EXPLORING INVITATION STRATEGIES FOR HPV SELF-SAMPLING AMONG UNDERSCREENED WOMEN

16 - Screening methods

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Background/Objectives: Pap testing has significantly reduced incidence and mortality of cervical cancer. In Manitoba (a Canadian province), despite the availability of Pap testing through an organized screening program, screening participation is on the decline, and in some populations, has never occurred. Screening rates were further impacted by the COVID-19 pandemic due to temporary shut-downs of primary care services. In an effort to mitigate the decline in screening participation, an HPV self-sampling project was launched. Various invitation strategies were tested to determine the most effective way to enhance screening participation among women overdue for screening.

Methods: The study focused on the behaviours of women age 30-69 who had not had a Pap test in at least five years. Overall, 36,000 people who met the study inclusion criteria were randomized into three equal-sized study arms. People in intervention arm I (opt out) were directly mailed an HPV self-sampling kit, and if needed, a reminder letter. People in intervention arm II (opt in) received a letter inviting them to request an HPV self-sampling kit via paper form, online form, or telephone. The control group received no additional study-related correspondence. Screening participation rates and participant satisfaction were compared among the groups. Additional work was done with community health organizations to target people facing specific barriers to cervical cancer screening. About 2,000 self-sampling kits were either handed out or mailed in collaboration with these groups. The distribution process and screening participation were assessed.

Results: Preliminary results will be available in late 2022. Early indications show that more people completed an HPV test in the opt out group compared to people in the opt in group. Tailored interventions may be needed to ensure specific screening barriers are addressed for underscreened individuals.

Conclusions: Many lessons were learned in the development of resources, communication with participants, and work with community health organizations. Preliminary study results will be available in late 2022 and will be used to support decisions regarding the programmatic implementation of HPV self-sampling.

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EXPERIENCE FROM HPV SELF-SAMPLING AS PART OF A POPULATION BASED CERVICAL CANCER SCREENING PROGRAM IN THE REGION OF STOCKHOLM, SWEDEN

16 - Screening methods

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Background/Objectives: Globally, cervical cancer is the fourth most common cancer among women and affects 604,000 women every year. In Sweden, 40 years of implementation of population based cervical cancer screening, cervical cancer incidence has decreased significantly to around 550 women every year. Participation in the cervical cancer screening program is offered to all women between 23-64 years of age and participation is voluntary and free of charge. In recent years, there is a tendency to an increased cervical cancer incidence. During the COVID-19 pandemic, the cervical cancer screening program was paused during 9 months as part of the public health restrictions. To compensate for the screening gap in the Region of Stockholm, Sweden, the Swedish Board of Health and Welfare allowed for a temporary transition from provider taken liquid-based cytology (LBC) with analysis of HPV and reflex cytology to HPV self-sampling in 2021. There is a paucity in data globally regarding participation rate using HPV self-sampling and an opt-out approach as the main screening strategy among participating women in the cervical cancer screening program.

Methods: Descriptive statistics from the cervical cancer screening program was analyzed comparing participation rate by HPV self-sampling strategy during the period March - December 2021 and provider taken LBC in during 2018.

Results: During 2021, a total of 355,396 HPV self-sampling kits were sent by mail to eligible women of screening age in the Region of Stockholm. By comparison, in 2018 we invited 258,816 women for provider taken LBC with HPV analysis and reflex cytology. The participation rate was significantly higher with HPV-self-sampling strategy (51% as compared to 38 %; p-value <0.0001). The biggest gains in participation rate were seen among younger women 26-29 years (38% vs 54% ; p-value <0.0001) and 30-39 years (42% vs. 53%; p-value < 0.0001). The participation rate among non-participating women, defined as non-response despite 4 or more screening invites, doubled with HPV self-sampling (12% vs 23%; p-value < 0.0001). The participation in follow-up LBC with HPV analysis and reflex cytology among HPV positive women after self-sampling was 90%. The time span from HPV-self-sample and an appointment for a provider taken follow-up LBC was three months as per protocol.

Conclusions: Screening by primary HPV self-sampling in the Region of Stockholm has increased overall participation rate in the cervical cancer screening program, especially among younger women and non-participating women. Increasing the participation of follow-up testing among HPV positive women is crucial for early detection pre-cancerous lesions.

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#5055

Cervical cancer screening improvements with self-sampling precipitated by the COVID-19 pandemic

01 - HPV disease and COVID-19

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Background/Objectives: At the onset of the COVID-19 pandemic cervical screening in the capital region of Sweden was cancelled for several months. Several measures to preserve and improve the cervical screening under the circumstances were instituted, including a switch to screening with self-sampling to enable screening without crowding and risk for infection.

Methods: We describe the major changes implemented, which were i) nationwide implementation of HPV screening ii) switch to primary self-sampling instead of sampling by healthcare personnel iii) implementation of HPV screening in all screening ages and iv) combined HPV vaccination and HPV screening in the cervical screening program.

Results: A temporary government regulation allowed primary self-sampling with HPV screening in all ages. In the Stockholm region 330,000 self-sampling kits were sent to the home address of screening-eligible women, instead of invitation to screening by healthcare personnel. A rapid increase in population test coverage was seen. In addition, a national campaign for faster elimination of cervical cancer with concomitant screening and vaccination for women in ages 23-28 was launched.

Conclusions: The Covid-19 pandemic necessitated major changes in the cervical cancer preventive strategies, where it can already be concluded that the strategy with organised primary self-sampling for HPV has resulted in a major improvement.

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#4881

INTRA- AND INTER-LABORATORY REPRODUCIBILITY OF THE ONCOPREDICT HPV SCR AND QT ASSAYS USING THE VALGENT-2 FRAMEWORK

09 - HPV testing

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Background/Objectives: Background: Assessment of emerging HPV assays for their use in cervical cancer screening is vital. HPV OncoPredict® SCR and QT (Hiantis Srl) are two independent multiplex real-time PCR assays targeting HR-HPV E6/E7 DNA comprising a "partial" genotyping screening assay (SCR) and a "full" genotyping, normalized viral load (QT) assay. OncoPredict® SCR identifies HPV16 and HPV18 separately and 11 other hrHPV types in aggregate while Oncopredict® QT detects 12 high-risk (HR) HPV types independently. The assays can be used either alone or in combination, as a two-step reflex testing allowing HR-HPV genotype-specific viral load determination in screen-positive samples. Quality controls for sample adequacy, the efficiency of nucleic acid extraction and PCR inhibition are included in the testing. Objectives: To evaluate the intra- and inter-reproducibility of the HPV OncoPredict® SCR and QT using the international validation of HPV Genotyping Tests (VALGENT-2) framework.

Methods: The VALGENT-2 panel consists of 1,300 cervical liquid-based cytology (LBC) samples from women aged 20-60 attending the Scottish cervical cancer screening programme (1000 consecutive samples from routine screening enriched with 300 cytological abnormal samples). To assess the intra- and inter-laboratory reproducibility of the OncoPredictHPV SCR, a subset of 526 samples were randomly selected from the initial panel with 30% hrHPV positives determined with a standard comparator test (GP5+/6+ PCR enzyme immunoassay) as foreseen in validation guidelines. The reproducibility panel contained 157 hrHPV positive samples and 369 hrHPV negative samples established with the standard comparator test.

Results: Results for the intra-laboratory assessment for the OncoPredict® SCR showed an excellent overall agreement of 98.9% (95% CI=97.5-99.6%) based on a kappa value of 0.971 (95% CI =0.947-0.994). Analyses for the inter-laboratory resulted in an excellent overall agreement of 98.1% (95% CI= 96.5 - 99.1%) based on a kappa value of 0.951 (95% CI=0.920-0.981).For Oncopredict®QT: the intra-laboratory assessment showed an overall agreement of 99.2% (95% CI=98.1-99.8%) with a kappa value of 0.979 (95% CI =0.958-0.999). The inter-laboratory analysis had an excellent overall agreement of 98.7% (95% CI= 97.3 - 99.5%) based on a kappa value of 0.963 (95% CI=0.936-0.990).

Conclusions: HPV OncoPredict® SCR and QT assays fulfil the reproducibility validation criterion for use in cervical cancer screening.

References: Acknowledgements: HPV OncoPredict® assays were developed as part of a European Commission-funded SME Instrument Phase 2 Project (Grant agreement ID: 806551). SD and MA were supported by the Horizon 2020 Framework Programme for Research and Innovation of the European Commission, through the RISCC Network (Grant No. 847845)

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#4762

EVALUATING THE PERFORMANCE OF LSIL-H CATEGORY: COULD ITS INTRODUCTION IN THE BETHESDA SYSTEM BE USEFUL?

16 - Screening methods

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Background/Objectives: LRPO at ISPRO represents the reference laboratory for HPV test and cytology triage of whole Tuscany region. In order to increase the performances of cytology, Peer Review of positive or difficult cases is performed daily in blind mode; the evaluation of each cytologist is recorded using a home design software "Peer Review Cytology Plus" (PRCP) - and results are then collegially discussed to achieve a shared Final diagnosis (FD). PRCP includes an additional cytological class, as already hypothesized in TBS 2014, named LSIL-H, which comprehends cases where definite LSIL is present as well as some images referable but not sufficient to confirm an HSIL. Currently, majority diagnosis (MD) of LSIL-H flows conventionally into the LSIL category as FD.

Methods: In order to evaluate the usefulness of this interpretation class, we considered all cases recorded by the PRCP from 2017 to 2022, with at least one cytological interpretation of LSIL-H. Cases examined by less than 3 cytologists were excluded. We analysed MD and FD and a correlation with the follow-up histopathology, if available, was performed.

Results: Among the 2170 selected cases, 346 reported a MD of LSIL-H. 277/346 showed the suggested FD of LSIL, while ASCH or HSIL has been agreed for the remaining 69/346. HD was available for only 77 cases, 13 of which were negative for intraepithelial lesions. Among the remaining 64 cases, 44% showed histological diagnosis of CIN1 and 56% of CIN2. To increase the study population, we included cases in which the diagnosis of LSIL-H was attributed by at least 33% of cytologists. Even the 154/732 selected cases were 44% CIN1 and 56% CIN2.

Conclusions: Our preliminary analysis demonstrated the morphological usefulness of the LSIL-H category, which could be collocated between the LSIL and the HSIL classes. However, the clinical utility of this cytological category, especially in a screening context, should be assessed. Considering that more than 50% of LSIL-H showed an HD of CIN2, we could hypothesize to use HSIL as FD, in absence of an intermediate category.

FC23- Free communications- Molecular markers

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#4932

CONSERVATIVE MANAGEMENT OF WOMEN WITH CIN2 LESIONS ENROLLED IN A PROSPECTIVE MULTICENTRIC STUDY: CLINICAL OUTCOME AND PREDICTIVE BIOMARKERS.

15 - Molecular markers

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Background/Objectives: Excisional procedures for treatment of high-grade cervical lesions can pose a risk for subsequent pregnancies, thus conservative management of Cervical Intraepithelial Neoplasia grade 2 (CIN2) lesions should be adopted in young women. We describe a prospective multicentre study aimed at evaluating feasibility and efficacy of CIN2 conservative management and the role of different biomarkers.

Methods: Women attending organised cervical screening in four centres within the Veneto region, histologically diagnosed with CIN2 were enrolled between April 2019 and October 2021. Inclusion criteria were: age 25-45 years, transformation zone and lesion fully visible at colposcopy. Exclusion criteria were: pregnancy, previous treatment of a CIN2+ lesion, immunodeficiency, and presence of an endocervical lesion not completely visible at colposcopy. Women are followed for 24 months; treatment is delayed and subsequently performed in the case of lesion progression, or persistence for >12 months. At each visit, colposcopy and testing for several biomarkers (HPV genotyping, p16/ki67 dual stain, methylation status of FAM19A4/miR124-2 cellular genes and HPV late genes) in cervical cells are performed. The biomarkers' results at enrolment are evaluated in relation to the clinical outcome; the statistical significance is calculated by X2 test.

Results: Overall, 319 women diagnosed with CIN2 were enrolled; 44 women were lost to follow-up (FU) and 226 have completed 12-18 months of FU for ad-interim analysis, 76 of whom underwent excisional treatment. Overall, regression (<=CIN1), persistence (CIN2) and progression (CIN3+) were recorded in 54%, 33% and 13%, respectively; 15 CIN3, 4 adenocarcinoma in situ and 1 invasive carcinoma were diagnosed. At study enrolment, 16 samples were HPV-negative, while 27 and 14 were invalid for FAM19A4/miR124-2 and p16/ki67 assays, respectively. In Table 1, enrolment biomarkers are evaluated in relation to the clinical outcome.

Conclusions: The observed regression rate is in line with the scientific literature. A statistically significant association has been recorded for all the biomarkers evaluated in this ad-interim analysis; the strength of the associations indicates that these assays are mostly effective as regressive biomarkers.

Table 1

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#4961

LONGITUDINAL MONITORING OF HPV16 GENOMES IN CERVICAL INFECTIONS AND PHENOTYPIC IMPACT OF H78Y AND L83V MUTATIONS OF HPV16-E6 PROTEIN

15 - Molecular markers

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Background/Objectives: HPV16 genotype exhibits different lineages, sublineages and variants that may differ in their carcinogenic risk. The aim of this study was to identify some HPV16 high-risk variants, from a longitudinal cohort of HPV16-infected patients, and to describe the genetic variations harbored by these variants.

Methods: 34 HPV16-infected women longitudinally followed in our institution were classified in a "clearance" group ("C") if they had spontaneously cleared their cervical infection or in a "persistence" group ("P") if they had developed high-grade cervical lesions (HSIL) after a step of persistent infection. HPV16 whole genomes, obtained from the two groups of patients, were retrospectively sequenced (MiSeq, Illumina; in-house pipeline) and compared. Mutations of interest in E6 were reproduced by site-directed mutagenesis and explored phenotypically in an U2-OS cell model.

Results: Phylogenetic analysis revealed a low genetic intrahost variability contrasting with a larger interhost diversity. By comparing with a HPV16 reference sequence, 301 different single base substitutions were observed throughout the HPV16 genomes in our cohort but with a low frequency in E6 and E7 oncogenes, suggesting a high conservation of these genes. No APOBEC3-compatible mutation was observed in E6 and E7. The only statistically significant mutation between the 2 groups of patients was located in the L2 capsid gene (L330F). Two mutations in E6 were explored in vitro due to their position inside the protein: H78Y and L83V, located on an E6/IRF-3-binding domain and an E6/p53-binding domain, respectively. By stimulating the IRF-3-IFN-ß pathway [poly(i:c)] in the presence or absence of the H78Y mutation in E6, we did not observe any impact of this mutation on IFN-ß expression, suggesting that IRF-3 is not inhibited differently in the presence of this mutation. p53 degradation and p21 subsequent inhibition were equally observed in the presence or absence of the L83V mutation in E6. This mutation had no impact on cell viability (MTT assay), cell migration and proliferation (scratch wound healing assay), and apoptosis inhibition (Annexin-V-7-AAD staining) in our model.

Conclusions: Our results suggest a low longitudinal intrahost evolution of HPV16 sequences and a poor correlation between genetic variations and clinical evolution. In particular, the H78Y and L83V mutations in E6 had no impact on the IRF-3-IFN-ß pathway, and on the p53-mediated cellular effects, respectively.

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#4444

Early detection of locoregional minimal residual disease after surgery for HPV+ oropharyngeal cancer using a surgical drain fluid assay

15 - Molecular markers

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Background/Objectives: Plasma cell-free HPV (cf-HPV) assays have low sensitivity to detect postoperative minimal residual disease (MRD) in patients with HPV (+) oropharyngeal cancer. This largely precludes their use for adjuvant therapy decision-making in patients treated with primary surgical resection. In this study, we explored MRD detection in surgical drain fluid (SDF); an alternative analyte more proximal to the site of disease, collected 24-48 hours after tumor resection and neck dissection.

Methods: We used PCR and whole exome sequencing (WES) to quantify cf-HPV in 178 SDF samples and 48 matched plasma samples representing 74 oropharyngeal cancer patients.

Results: We are the first to show cf-HPV enrichment in post-op SDF, with 88% having detectable cf-HPV compared to only 15% of post-op plasmas. Strikingly, SDF cf-HPV burden was 11- fold higher in patients AJCC8th pN2 disease compared to pN1/N0 ($P = 0.01$) and 15-fold higher in patients with evidence of extranodal extension (ENE) ($P = 0.002$), demonstrating strong concordance between SDF MRD and individual aggressive pathological features. We then classified our patients according to composite pathological definitions of risk, derived from four HPV (+) oropharyngeal cancer clinical trials, and found SDF cf-HPV was consistently elevated in our patients with trial-defined high-risk disease (mean AUC=0.73). Lastly, SDF cf-HPV was detected in all of our cohort's recurrences, including the two locoregional cases, while paired plasma was cf-HPV negative in both cases. Beyond HPV (+) malignancies, we piloted a V600E BRAF cell-free DNA (cf-V600E) assay to show cf-V600E MRD detection in the SDF of high-risk thyroid cancer patients.

Conclusions: These findings demonstrate the potential for using SDF for early locoregional MRD detection and risk stratification in patients with HPV (+) oropharyngeal cancer.

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#4496

GENETIC EVENTS IN HPV-INDUCED AND HPV-INDEPENDENT PENILE SQUAMOUS CELL CARCINOMAS

02 - Viral and molecular biology

Background/Objectives: Squamous cell carcinomas of the penis (SCCs) account for up to 10% of male cancers in so-called high-incidence counties of South America, Africa and India. They are, however, rare in so-called low incidence areas of Europe, Russia and North America. The major cause of penile SCCs, particularly in the high-incidence countries, is a transforming Human Papilloma Virus (HPV)-infection. The role of HPV oncogenes in HPV-induced carcinogenesis is well established. In contrast, HPV-independent carcinogenesis is poorly understood, but linked to persistent chronic inflammatory dermatoses, such as lichen planus and lichen sclerosus. In this abstract, we report the results of a comparative analysis of driver gene mutations in HPV-induced penile SCC versus HPV-negative penile SCC from a single low-incidence country.

Methods: Invasive penile SCCs of 100 men from a single pathology institute of a low-incidence country were investigated. DNA was extracted from micro-dissected, formalin-fixed and paraffin-embedded tumor tissues, and analysed for the presence of 32 HPV genotype specific DNA using the LCD-Array Kit (CHIPRON GmbH, Germany) and for mutations in hot spot regions of 50 cancer genes by Ion Torrent Next-Generation Sequencing. Immunohistochemical overexpression of p16ink4a in HPV-associated SCC served as surrogate marker for a transforming HPV-infection.

Results: We identified 47/100 (47%) HPV-positive SCC; they all carried HPV high-risk genotypes and overexpressed p16ink4a. More than half of patients had a HPV-negative and p16ink4a-negative SCC (53/100 (53%). The majority of HPV negative SCCs arose in the background of a highly active, mostly untreated chronic inflammatory disease lichen planus. There was no age difference between these two groups at diagnosis of SCC. HPV-induced SCCs were mostly diagnosed in early stages (pT1), while HPV-negative SCC were predominantly large tumors (pT2 and pT3). The majority of HPV-positive SCC (31/47 SCC; 66%) was devoid of mutations in the 50 analyzed driver genes. Only 16/47 (34%) HPV-induced SCC carried driver mutations. In most cases, a solitary activating mutation was identified, predominantly in PIK3CA (5/16 SCC; 31%), PTEN (5/16 SCC; 31%), and FBXW7 (4/16 SCC; 25%). In contrast, a total of 48/53 (91%) HPV-negative SCC carried somatic mutations, mainly in tumor suppressor genes TP53 (33/41 SCC; 80%) and CDKN2A (24/41 SCC; 58%), but also in activating genes PIK3CA (11/41 SCC; 27%) and HRAS (8/41 SCC; 19%). Interestingly, 35/41 (85%) mutated HPV-negative SCC carried two or more gene mutations already in early tumor stage pT1 SCC.

Conclusions: Penile SCC arise via two distinct pathways. The HPV-related squamous carcinogenesis is driven mainly by actions of HPV oncogenes. Similar to cervical carcinogenesis, progression to invasive SCC was accompanied by additional activating mutations, e.g. in PIK3CA, only in a minority of cases. In contrast, HPV-independent penile carcinogenesis is strongly associated with chronic inflammatory lichenoid dermatoses, and early appearance of multiple driver mutations in tumor suppressor genes. Only a minority of penile SCC harbored targetable mutations. The role of long-standing chronic inflammation in penile carcinogenesis and development of the precursor lesion differentiated penile intra-epithelial lesion (dPeIN) preceding the development of an invasive HPV-negative SCC requires further investigation.

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#5005

EVALUATION OF CIRCULATING HUMAN PAPILLOMAVIRUS (HPV) DNA DETECTION IN BLOOD OF WOMEN WITH A RECENT HISTORY OF CERVICAL DYSPLASIA

15 - Molecular markers

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Background/Objectives: Recent studies suggested that high-risk Human Papillomavirus (hrHPV) dissemination via bloodstream may be associated with the oncogenic role of hrHPV. This ongoing longitudinal study aims to investigate hrHPV DNA detection in blood as a potential biomarker of cervical cancer progression.

Methods: A cervical swab (Endo/Eso L-Shaped, FloqSwab, Copan) and blood sample were collected from women attending the Colposcopy Clinic of San Gerardo Hospital (Monza, Italy) at baseline and at follow-up (FU) visits after 6/12/18 months depending on the clinical outcome. Cervical samples were resuspended into 20 ml of PreservCyt (Hologic) solution and analysed using the AnyplexTMII-HPV28 kit (Seegene). Peripheral Blood Mononuclear Cells (PBMCs) and plasma were separated using Ficoll gradient. Nucleic acids isolation from plasma was performed using the NucliSENS® easyMag® system (Biomerieux) starting from 1 ml of plasma and tested with OncoPredict HPV assay (Hiantis) able to detect and quantify 12 hrHPV genotypes.

Results: 324 women have been enrolled in the study and 66% (214/324) were found to be hrHPV positive, with HPV16 being the most prevalent genotype detected in cervical samples (71/342; 21.9%) followed by HPV31. Presently, 99 plasma samples collected at baseline and 32 samples collected at FU have been analysed; 14.1% (14/99) and 6/32 (18.7%) women respectively were found to be hrHPV positive in plasma with HPV16 being the most frequently detected genotype. In 4 of the 6 women hrHPV-positive in plasma at FU the same hrHPV genotype was detected in the cervical sample whilst in the other two cases the cervical sample resulted negative.

Conclusions: Preliminary results suggest that circulating hrHPV can be detected in a subgroup of women with a recent history of cervical dysplasia. Some women were found to have the same HPV genotype in both plasma and cervical samples suggesting a possible viral entry associated with cervical infection. HrHPV DNA was also detected in plasma even after clearance of cervical infection indicating a possible viral persistence and/or viral replication in the blood cellular compartment. Data obtained from samples collected at different follow-ups will permit to better understand the association between hrHPV detection in blood and cervical lesion progression. Moreover, analysis conducted on PBMCs will give further information about circulating hrHPV DNA.

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#4848

ARE TP53 MUTATIONS ASSOCIATED WITH HPV GENOTYPES IN WOMEN LIVING WITH HIV?

15 - Molecular markers

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Background/Objectives: More than 50% of human cancers are a result of somatic mutations in the TP53 gene. Polymorphisms in TP53 can be studied to establish a correlation between specific allele variants and cancer progression, however, there is limited research in Zimbabwe. The aim of the study was to determine the prevalence of TP53 codon 47 and codon 72 polymorphisms in women living with HIV (WLWH), with histologically confirmed cervical and vulvar precursor and cancer lesions.

Methods: A cross-sectional study enrolled 102 WLWH with confirmed cervical lesions (n=89) and vulvar lesions (n=13). Archived tumour tissue was retrieved for the extraction of genomic DNA for further analyses. The tumour tissue was genotyped for 15 high-risk and 2 low-risk HPV genotypes using the ATILA Multiplex HPV assay. Genetic polymorphisms in TP53 codon 47 and codon 72 were characterized using Sanger Sequencing and GraphPad Prism software was applied for data analysis.

Results: Mean age of the women was 43 years, ranging between 25-64 years. 87 cervical tissues were successfully genotyped for HPV. Overall HPV prevalence was 74.7% (65/87) in cervical and 84.6% (11/13) in vulvar samples. HPV16 was the most ubiquitous in both cervical (29.9%) and vulvar (53.8%) tissue. The prevalence of codon 47 and 72 polymorphisms in cervical tissues was 5.8% and 56.5% respectively, and in vulvar tissues 8.3% and 50% respectively. We found no association between codon 47 and codon 72 genotypes and HPV genotypes ($p>0.05$) as well as age with HPV genotypes nor histological diagnosis($p>0.05$).

Conclusions: This is the first Zimbabwean study to report on the prevalence of TP53 codon 47 polymorphism in cervical and vulvar tissues. This study supports the evidence that codon 47 and 72 polymorphisms are not associated with HPV genotypes or increased risk of cervical and vulvar precancer and invasive cancer, which is similar to reports from other African population studies. Taken together with the literature, data presented highlights that there is need to focus on other genetic targets such as immune response markers, that are yet to be explored in Zimbabwean populations. These findings are of significance to determine effective susceptibility, diagnostic, and prognostic biomarkers related to cancer risk and progression.

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#4857

HIV-1 Proteins Gp120 and Tat Promote Invasiveness of Neoplastic Genital and Oral Epithelial Cells

04 - Pathogenesis

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Background/Objectives: The incidence of human papillomavirus (HPV)-associated anogenital and oropharyngeal cancer in human immunodeficiency virus (HIV)-positive individuals is substantially higher than in HIV-uninfected individuals. However, the molecular mechanisms underlying HIV-1-associated promotion of HPV malignancy are not fully understood. Here, we showed that HPV-16-immortalized genital and oral epithelial cells and HPV-negative oral cancer cells that undergo prolonged contact with cell-free HIV-1 virions or with viral proteins gp120 and tat respond by becoming more invasive.

Methods: HPV-16-infected cervical CaSki, anal AKC-2, oral SCC-47, and HPV-negative cervical C-33 A cancer cells were treated with cell-free HIV-1 virions and viral proteins gp120 and tat, each at 10 ng/ml for five to seven days. Cells were evaluated for epithelial-mesenchymal transition (EMT) with H&E staining, and Western blot and immunofluorescence assays. Live EMT cells were also examined by phase-contrast inverted digital microscopy. In vitro invasion assays were performed using the collagen cell Invasion assay.

Results: The interaction of cell-free virions and gp120 and tat proteins with epithelial cells substantially reduced the expression of E-cadherin and activated the expression of vimentin and N-cadherin. EMT induced by the HIV-1 gp120 and tat proteins was accompanied by activation of the Snail transcription factor. EMT induced by gp120 and tat led to detachment of poorly-adherent cells from the culture substratum; these cells remained capable of reattachment, upon which they co-expressed both E-cadherin and vimentin, indicative of an intermediate stage of EMT. The reattached cells also expressed stem cell markers CD133 and CD44, which may play a critical role in cancer cell invasion and metastasis.

Conclusions: These results suggest that the interaction of HIV-1 with neoplastic epithelial cells may lead to their de-differentiation into cancer stem cells that are resistant to apoptosis and anti-cancer drugs. Thus, this pathway may play a critical role in the development of invasive cancer.

FC18- Free communications- Microbiome

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#4458

NEW PREDICTORS OF PERSISTENCY AND CIN2+ IN WOMEN INFECTED WITH HR HPV USING METAGENOMIC ANALYSIS OF THE CERVICAL MICROBIOME

04 - Pathogenesis

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Background/Objectives: Predictors of viral persistence and development of precancer in HR HPV infected women would allow better risk stratification in cervical cancer screening

Methods: Previously a prospective German cohort of 10,040 women was established and 411 test-positive (HPV and/or cytology) women were followed for up to six years with yearly intervals. Of 43 women that showed a persistent HPV infection with the same HPV type (> 24 months) including 10 women that developed histological findings of CIN2+ and 57 women that cleared their infections over time the DNA from the first cervical smears taken at the baseline were used to perform a shotgun metagenomic analysis.

Results: Six biomarkers allow to stratify women with a persistent infection from those that cleared spontaneously (OR=2.77; p=0.03) and a ROC-AUC of at least 0.96 and 5 biomarkers could stratify between women with incident CIN2+ or no abnormality (OR=15.5 ; p=0.001) and a ROC-AUC of 1.0. The machine learning classifier for the prediction of a persistent infection is based on the relative abundance of three bacterial taxa (2 genera: Catenulispora, Oleiphilus; 1 phylum: Chlamydiae), the relative abundance of two metabolic microbial pathways (UDPNAGSYN-PWY, PWY-621), and the relative abundance of the fungal genus Aureobasidium. The machine learning classifier for the prediction of incident CIN2+ is based on the relative abundance of two bacterial taxa (2 genera: Leisingera, Devosia), the relative abundance of a metabolic microbial pathway (PWY-2941), and the relative abundance of the two fungal genera Thermothelomyces und Marssonina. All biomarkers were investigated using a Ward-cluster analysis that demonstrated excellent discrimination of the respective groups. Further we found that HPV-positive women in whom the infection clears spontaneously have a significantly higher number of lactobacilli characterized by the PWY-621 metabolic pathway compared to those in whom the infection persists (OR 0.04, p = 0.03)

Conclusions: Using a shotgun metagenomic analysis of women infected with HR HPV for microbial and fungal infections it seems possible to predict the establishment of persistent HPV infections or clearance as well as an increased risk of incident CIN2+ by applying two machine learning classifiers.

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#4666

Age-stratified analysis vaginal microbiota dysbiosis and the relationship with HPV viral load in HPV positive women

19 - Microbiome

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Background/Objectives: This study evaluated the distribution of vaginal microbiota dysbiosis and the association with HPV viral load test in high-risk HPV positive women before and after 50 years old

Methods: For this cross-sectional study, 388 HPV positive women prior to referral to colposcopy in Peking University Peoples' Hospital were included and classified as younger than 50 years (n= 307) and aged 50 years or older (n=81), mid-vagina bacterial community composition was characterized by FlashDetectTM MAX vaginal microbes detection kit and BMRT-HPV reported type-specific viral loads/10,000 cells

Results: The community state types(CST) IV was the most common CST occurring in 148 women (38.1%). The proportion of CST IV in those aged 50 years or older was significantly higher than those younger than 50 years women (66.7% vs 30.6%), the difference was statistically significant (<0.001). CSTs distribution have no statistical difference in different grades of cervical lesion, regardless of the age (p=0.238 and 0.263). However, the women with high grade cervical lesion presented a more complicated trend and the abundance of vaginal microbiota dysbiosis than low grade lesion. HPV16/18 viral load was found to be significantly higher in CST III and CST IV than CST I/II/V(P□0.05).

Conclusions: In women younger than 50 years, higher HPV16/18 load was more closely associated with CST IV, however, it had no significant correlation in women aged 50 years or older.

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#4305

TEMPORAL COMPOSITION OF THE CERVICOVAGINAL MICROBIOME CORRELATES WITH HRHPV INFECTION OUTCOMES: A LONGITUDINAL COHORT STUDY

19 - Microbiome

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Background/Objectives: Persistent infections with high-risk human papillomavirus (hrHPV) can cause cervical squamous intraepithelial lesions (SIL) that may progress to cancer. The cervicovaginal microbiome (CVM) composition correlates with SIL development, but the dynamics of the CVM after hrHPV infections have not been fully clarified.1

Methods: To determine the association between CVM composition and infection outcome, we performed high-resolution microbiome profiling2 on a longitudinal cohort of cervical smears obtained from 192 hrHPV DNA-positive women with normal cytology at first visit, of whom 74 were diagnosed by cytology with SIL six months later.

Results: Here we show that women with Lactobacillus-dominated microbiomes have more stable microbial communities and associate with protection against SIL development, while women with the microbial community state type IV-A3 at first visit, characterized by high diversity and low Lactobacillus abundance, have a higher risk of developing SIL at second visit. Analyses at the species level demonstrate that increased abundance of Gardnerella vaginalis and Atopobium vaginae in the microbiome correlates with adverse infection outcomes.

Conclusions: Overall, we describe the temporal associations between the CVM and hrHPV infection outcomes, reinforcing the crucial role of the microbiome in cervical health. Our results suggest that the CVM can potentially be used as a predictive biomarker for cervical disease and SIL development after hrHPV infections.

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Graphical abstract

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#4985

Cervical microbiome associated to HPV vaccinated women who developed HSIL in twelve years post-vaccinated

19 - Microbiome

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Background/Objectives: The strong association between high-risk HPV and cervical cancer is well established and the vaccines against these viral infections have been implemented worldwide. Here we investigated the role of cervical microbiota among HPV vaccinated women with lesion progression.

Methods: Samples were collected from HPV-vaccinated women during the 12-year follow up of the Finnish HPV vaccine trial. Cervicovaginal swab samples were obtained from six HPV vaccinated women who developed cervical HSIL twelve years post-vaccinated and from 47 healthy controls of the same birth cohort. Both viral and bacterial microbiome was assessed using state-of-the-art bioinformatics.

Results: The virome showed that all the HSIL cases were associated to non-vaccine targeted oncogenic HPVs and the HPV type distribution differed significantly from the healthy controls. Furthermore, the cervicovaginal microbiome showed a significantly different bacterial taxonomic distribution for women with cervical HSIL compared to healthy controls. Altogether fourteen microbial taxa showed a significantly higher relative abundance among the women with HSIL compared to controls.

Conclusions: Our results indicate a shift in cervicovaginal microbial composition as a sequence from healthy cervical mucosa to HSIL. We speculate that combining the detection of a vaccine non-targeted oncogenic HPVs and cervicovaginal bacterial microbiome composition may improve cervical cancer screening in HPV vaccinated communities where the vaccine-targeted HPV genotyping may become inadequate.

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#4999

CHARACTERIZATION OF VAGINAL MICROBIOME IN CERVICAL SAMPLES FROM THE REGIONAL CERVICAL CANCER SCREENING PROGRAM OF THE NORTHERN REGION OF PORTUGAL

19 - Microbiome

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Background/Objectives: The vaginal microbiome has emerged as potentially influencing the natural history of HPV infections and their clinical impact. In this study we aimed to characterize the vaginal microbiome and correlate with HPV-status and cervical abnormalities.

Methods: We performed a cross-sectional study with samples from the Regional Cervical Cancer Screening Program from the Northern Region of Portugal (RCCU) processed between September 2021 to November 2021. A total of 807 women with mean age 41.45 ±10.79 years old (median age 41; range 24-64) were enrolled from the cohort of Hr-HPV positive cases with cytological evaluation and included all cases with ASC-H (n=114), LSIL (n=215), HSIL (n=47) and Adenocarcinoma (AdC, n=1), as well as randomly selected samples with NILM (n=319) and ASC-US (n=111). Microbiome analysis was performed using Allplex STI Essential Assay Q (STI), Allplex Genital Ulcer Assay (GU) and Allplex Bacterial Vaginosis Assay (BV) from Seegene.

Results: In our population, we found a prevalence of 8.2% for microorganisms from the GU (mGU), 68.1% for microorganisms from STI (mSTI) and 59.1% for microorganisms from BV (mBV). Overall, the most frequent microorganism found were U. parvum (52.5%), Gardnerella vaginalis (34.5%), Atopobium vaginae (32.6%), Lactobacillus spp. (30.7%) and M. hominis (23.5%) - Table 1. When analysing the association of microbiome with NILM vs any cervical abnormality, we found no significant differences on the prevalence of mGU (p=0.367) or mSTI (p=0.701), while we observed a protection associated with mBV (p<0.001; RR=0.12) - Figure 1. Similar results were found for NILM or ASC-US vs any cervical disease. In addition, we found that mSTI (p=0.021; RR=0.65) and mBV (p<0.001; RR=0.27) were associated with protection of developing HSIL or worse. Particularly, we found that the protection was associated with the presence of U. urealyticum (p=0.007), CT (p=0.022), Megasphaera Tipo 1 (p=0.048), Lactobacillus spp. (p<0.001), Gardnerella vaginalis (p<0.001), bacteria associated to bacterial vaginosis (BVAB2) (p=0.035), Atopobium vaginae (p<0.001) and Mobiluncus spp (p=0.005). The analysis of microbiome association with Hr-HPV status showed that mSTI was related with increased risk of multiple Hr-HPV infection (p<0.001; RR=1.85) and mBV with protection for HPV16/18 infection (p=0.003; RR=0.60). The individual analysis demonstrated that U. urealyticum (p<0.001; RR=1.94) and M. hominis (p=0.005; RR=1.63) are associated with increased risk of multiple Hr-HPV infections, while Mobiluncus spp. (p=0.028; RR=1.51) have a correlation with increased risk of infection by HPV-9val. On the opposite side, Lactobacillus spp. seems to be protective for either multiple Hr-HPV infections (p=0.026; RR=0.69), HPV 16/18 (p<0.001; RR=0.51) or HPV-9val (p<0.001; RR=0.50). Similar results were found for Gardnerella vaginalis for either multiple Hr-HPV infections (p=0.036; RR=0.71), HPV

Conclusions: Overall, these data showed that Lactobacillus spp. and Gardnerella vaginalis are associated with a protective effect for Hr-HPV-infection with development of cervical abnormality, while U. urealyticum, M. hominis and Mobiluncus spp. are more frequently associated with increased risk. This study provides important data to be used in the clinical approach and management of Hr-HPV positive women.

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#5252

The vaginal microbiota in cervical carcinogenesis; Findings from the Cervical and Self-Sampling in Screening study

19 - Microbiome

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Background/Objectives: Increasing evidence shows that the cervical microbiome plays an important role in cervical cancer development (third most common female cancer worldwide) and its precancerous lesion, cervical intraepithelial neoplasia (CIN). We investigated whether cervico-vaginal microbial species differ in CIN severity (CIN1-3) as possible markers of cervical cancer progression.

Methods: 186 women (54 non-neoplasia, 50 CIN1, 40 CIN2, and 42 CIN3) referred for colposcopy following abnormal cytology were selected. The vaginal microbial communities were assessed by sequencing two distinct 16SrRNA regions and using the high-resolution ANCHOR pipeline. Primer sets were integrated for annotation resolution enhancement. CIN bacterial diversities were measured and compared. Differential abundance analysis using statistical learning was performed to predict cervical carcinogenesis from bacterial diversity.

Results: 171 species were identified; 99.99% of counts attributed to 55 species from V3V4 primer sets and 99.93% of counts attributed to 116 species from V5V6 primer sets. Gardnerella vaginalis, Lactobacillus jensenii, and Lactobacillus crispatus species were significantly more abundant (False discovery rate, FDR<0.05, V3V4) in CIN2+ samples. Proteobacteria was significantly more abundant in CIN3 compared to controls (FDR<0.001, V3V4, V5V6).

Conclusions: Two primer sets show statistically significant species abundances across CIN severities, which are currently being used for classification in statistical learning algorithms.

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#4989

EFFECT OF A CORIOLUS VERSICOLOR-BASED VAGINAL GEL AND A REISHI-BASED FOOD SUPPLEMENT FOR THE TREATMENT OF HIGH-RISK HPV ASSOCIATED LESIONS: A CASE REPORT

23 - Diagnostic procedures / management

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Background/Objectives: Human papillomavirus (HPV) infection is one of the most frequently sexually transmitted infections worldwide. Although most infections are cleared spontaneously, viral persistence is associated with the development of cervical lesions. Importantly, as age increases, the spontaneous rates of HPV clearance and resolution of cervical HPV-dependent lesions are reduced. Currently, there is no established clinical approach for the combined treatment of couples, which might help to facilitate the viral clearance in both individuals. In this clinical case, a combined treatment involving the use of a Coriolus versicolor-based vaginal gel for her and a Reishi-based food supplement for the partner was used for HPV-clearance and cytology normalization.

Methods: A clinical case of an asymptomatic 54-year-old woman, with no relevant past medical history, who attended for a check-up visit because her sexual partner presented lesions in his genitals. In physical examination, normal external genitals and speculoscopy showing slight cervical erosion, were found. Additionally, relevant tests were performed: HPV test (positive to 26, 53 and 66 (HR-HPV), cytology (ASCUS), colposcopy (focal Lugol's at 6h negative lesion which was biopsied), biopsy (exocervical mucosa showed acute moderate cervicitis with reactive inflammatory changes which did not allow to discard the presence of dysplasia). Therefore, a conservative treatment with a Coriolus versicolor-based vaginal gel was prescribed (1 cannula/day for 1 month + 1 cannula/alternate days for 5 months). Moreover, her partner was treated with a Reishi-based food supplement (1 capsule daily also for 6 months).

Results: After 3 months of treatment, the patient returned to the clinic for testing without her partner. Cytology and speculoscopy test showed normalization, and clearance of HR-HPV types was confirmed. However, the patient now tested positive for low-risk HPV types 62 and 81. The patient continued the treatment with the vaginal gel and the partner with the Reishi-based food supplement for up to 6 months.

Conclusions: This clinical case shows the effectiveness of a combined treatment involving the use of a Coriolus versicolor-based vaginal gel for a 54-year-old patient and a Reishi-based food supplement for her partner, in the repair of HPV-related cervical lesions and the clearance of HR-HPV after only 3 months of usage.

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#4807

Prospective gut microbiome modulation with Microbial Ecosystem Therapeutic 4 (MET4) in the context of definitive chemoradiation in patients with Human-papillomavirus-related oropharyngeal squamous cell carcinoma (HPV+ OPC) (ROMA2 trial)

19 - Microbiome

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Background/Objectives: Gut microbiome modulation to boost antitumor immune responses in cancer patients (pts) is under investigation1. Several trials are evaluating antiPD-(L)1 agents in combination with chemoradiation (CRT) in HPV+ OPC2. ROMA-2 is the first interventional study evaluating the safety, feasibility and ecological effects of microbial ecosystem therapeutic (MET)-4, an oral mixture of cultured human stool-derived bacteria associated with favorable immune response, in combination with definitive CRT in HPV+ oropharyngeal cancer (OPC) pts (NCT03838601).

Methods: ROMA-2 is an investigator-initiated trial of MET-4 in HPV+ OPC pts treated with standard of care CRT. MET-4 was administered orally daily from weeks 1 -4 of CRT or unacceptable toxicity. Administration via feeding tube was not allowed. Tumor swabs, stool and plasma were collected at baseline (BL), week 4 (W4), week 8-10 (PostCRT) and at 2-month follow-up (FU). Co-primary endpoints were safety and change in stool cumulative MET-4 taxa relative abundance (RA) measured by 16S RNA sequencing. Secondary endpoints included evaluation of changes in tumor swabs and stool microbiome composition between BL and consecutive timepoints.

Results: A total of 30 pts were enrolled. Cohort characteristics are summarized in Table 1. 29 pts received at least 1 dose of MET-4 and were evaluable for safety. MET-4 related-adverse events (AEs) occurred in 8/29 (28%) pts: G3 diarrhea lasting 75% MET4 dosing and at least BL and W4 sampling). No significant change in cumulative RA of MET-4 taxa in stool was seen across timepoints, although there was a trend towards increased MET-4 RA at W4 in pts with stage III disease (p=0.06). There were no longitudinal changes in Shannon diversity index or taxonomic richness across timepoints. Cumulative MET4 RA at W4 and FU was higher in stage III vs stage I-II pts (p=0.002), with no differences postCRT. MET4 taxa were rare in tumor swabs at all timepoints. Overall tumor swab microbiome composition significantly differed by stage (III vs I-II, p=0.001) and sampling timepoint (PostCRT vs other, p=0.003).

Conclusions: MET-4 administration during CRT was safe, although intake was limited by CRT-induced toxicity. As ecological responses appeared limited to pts with stage III disease, further exploration of microbiome therapeutic interventions in this subgroup may be warranted. Plasma/stool metabolomics are on-going.

References: 1. D. Araujo, G. Watson, M. Oliva, et al. Bugs as Drugs: The Role of Microbiome in Cancer Immunotherapy Therapeutics. Cancer Treatment Reviews. 2021 Jan;92:102125. doi: 10.1016/j.ctrv.2020.102125. 2. Shamseddine AA, Burman B, Lee NY, Zamarin D, Riaz N. Tumor Immunity and Immunotherapy for HPV-Related Cancers. Cancer Discov. 2021 Aug;11(8):1896-1912. doi: 10.1158/2159-8290.CD-20-1760

Table1

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#4802

WILLINGNESS TO PERFORM ANAL PAP SELF-COLLECTION AMONG ADULTS LIVING WITH HIV IN PUERTO RICO

13 - Self-sampling

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Background/Objectives: Anal cancer screening is recommended by several professional organizations in high-resource settings (e.g., NY States, European AIDS Clinical Society) for persons living with HIV (PLWHIV). Similar to cervical cancer screening, self-sampling approaches could potentially help improve screening participation, particularly in low-resource settings (such as Puerto Rico) with acute personal (e.g., lack of transportation), system-level (e.g., long waiting time) and environmental (e.g., repeated disaster events imposing challenges to undergo screening) barriers. This study aims to assess willingness of anal pap test self-collection among Hispanic PLWH living in Puerto Rico.

Methods: A cross-sectional study was conducted in Puerto Rico among PLWHIV (n=212) from November 2020 to December 2021. A telephone-based survey was used to assess barriers, facilitators or anal cancer screening, and their willingness to perform self-collection. Logistic regression models were used to assess factors associated with willingness of self-collection.

Results: Median age of participants was 54 years (IQR: 46-58), 67.5% were men, 45.8% had high-school education or less, 71.7% had an annual income of less than $20,000 USD, and 20.8% had an AIDS diagnosis. The majority (60.4%) of the study population were aware of anal pap testing, but only over half (52.2%) had ever had an anal pap test. Over two-thirds (68.4%) indicated willingness to perform anal Pap self-sampling. However, the majority (57.1%) still preferred to undergo a clinician-conducted exam for their future visit. Preference to go to a health care provider (38.7%) and concern for not doing the test correctly (33.5%) were two main concerns regarding their hesitancy to perform self-sampling. In multivariate analysis, men who have sex with men were more likely to be willing to perform self-collection (OR: 2.53; 95% CI: 1.27-5.03) as compared to women; while higher odds were also observed for heterosexual men (OR=1.74, 95% CI=0.80-3.76), this finding was not statistically significant. No difference in preference was observed by age.

Conclusions: Willingness of anal self-sampling was high among PLWHIV, particularly MSM in Puerto Rico. While most participants were willing to perform self-collection, still over half prefer physician-performed collection as they were concerned about not performing self-collection correctly or believed that the healthcare provider could perform the test more accurately. These findings could have important implications to guide future educational efforts and research. Funding: NCI Grants 2U54CA096297-18 and 2U54CA096300.

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#4949

EFFECT OF A MULTI-INGREDIENT Coriolus versicolor-BASED VAGINAL GEL IN A HPV18+ PREGNANT WOMAN with CIN 2/3 LESIONS

41 - Fertility and HPV

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Background/Objectives: Human papillomavirus (HPV) infection is one of the most frequent sexually transmitted infections. Although most of the infections are short-lived, several factors such as pregnancy, increase the risk of persistent HPV infection, which is higher in pregnant women compared to aged-matched counterparts. HPV persistence increases the risk of cervical cancer. The current accepted approach during pregnancy consists in preventing the evolution to cervical cancer with the minimal intervention level, as surgical procedures are not recommended because they increase the risk of preterm birth and perinatal death. In this context, new conservative approaches to treat HPV lesions in the pregnant subpopulation are needed.

Methods: A clinical case of a 30-year-old pregnant woman, smoker, diagnosed HPV serotype 18, colposcopy and acetowhite staining revealed HSIL lesions, biopsy confirmed extensive CIN 2/3 lesions and intense positivity for Ki67 and p16. Given the patients' profile, a non-invasive treatment with a Coriolus versicolor-based vaginal gel has been decided (1 cannula/day for 1 month + 1 cannula/alternate days for 5 months) and a watchful waiting approach with periodic colposcopy control.

Results: After 11 weeks of treatment with the Coriolus versicolor-based vaginal gel, colposcopy images showed a clear regression of the affected area with a transformation zone 1, which was confirmed by cytology (CIN 1). The patient continued to be positive to HPV 18.

Conclusions: A conservative non-invasive treatment with the Coriolus versicolor-based vaginal gel for 11 weeks has shown to be effective for HR-HPV cervical lesion regression in a pregnant 30-year-old woman and no adverse events were observed in this clinical case.

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#4957

A CONSERVATIVE TREATMENT OF CIN 2 USING A CORIOLUS VERSICOLOR-BASED VAGINAL GEL: AN OBSERVATIONAL STUDY

23 - Diagnostic procedures / management

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Background/Objectives: Human papilloma virus (HPV) is behind 95% of cervical cancer cases and its precursor lesions. According to the American Society of Colposcopy and Cervical Pathology (ASCCP), 50% of CIN 2 cases managed conservatively spontaneously regress. The aim of this study was to evaluate the effect of a Coriolus versicolor-based vaginal gel in the conservative management of CIN 2 lesions.

Methods: A one-cohort, prospective, single-centre, observational study including ≥ 18 years-old women, with CIN 2 diagnosis were treated with 1 cannula/day for 1 month + 1 cannula/alternate days for 5 months of a Coriolus versicolor-based vaginal gel. Inclusion criteria have been based on the Spanish Society of Colposcopy and Cervical Pathology (AEPCC) guidelines for CIN 2 conservative treatment: colposcopy image with visible transition zone, completely visible lesion affecting less than 2 quadrants, non-affected endocervix and accepting cytology/colposcopy after 6 months. Baseline and 6-month biopsies were performed.

Results: A total of 44 women 35.5 years-old on average were included. After a 6-month treatment period, 68.2% of them showed a regression by biopsy, 11.4% persisted on CIN 2 and 18.2% progressed to CIN 3. Three patients were considered null and not included in the data analysis because they did not have a biopsy taken after 6 months.

Conclusions: The Coriolus versicolor-based vaginal gel 6-month treatment seems to increase the regression of the lesions (68.2% at 6 months) compared to spontaneous resolution (44% in women older than 30, at 24 months in a published meta-analysis1) and could represent a clinical advantage compared to the "wait and see" approach in patients meeting the conservative treatment criteria for CIN 2 lesions.

References: Tainio, Karoliina et al. "Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis." BMJ (Clinical research ed.) vol. 360 k499. 27 Feb. 2018, doi:10.1136/bmj.k499

FC21- Free communications- Triage of HPV positive women

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#4724

MULTIPLE HPV TYPE COMBINATIONS AMONG UNVACCINATED WOMEN WITH HIGH-GRADE CERVICAL LESIONS

12 - Triage of HPV positive women

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Background/Objectives: It is well established that cervical cancer cases are caused by human papillomavirus (HPV) infection. Previous studies suggest that infection with multiple HPV types might add the risk to develop cervical lesions compared to infection with single HPV type. The aim of this study was to determine which HPV combinations are more likely to cause high-grade intraepithelial lesions (HSIL).

Methods: This study comprises of 1360 unvaccinated women referred to the colposcopy clinic of Helsinki University Hospital, Finland. Cervical samples we genotyped with MALDI-TOF and pap cytology and cervical histology results were collected from the hospital records. Logistic regression was used to evaluate the association between different multiple HPV type infections in a variety of cervical lesions severity among the age groups of <30, 30-40, 40-50 and ≥50 years old.

Results: Of the 1360 women 1110 women tested positive for any HPV. Single HPV infection was the most common manifestation on 758 (68,3%) women, followed by two (n=257;23,2%), three (n=69,6;2%) and four to seven types (n=26;2,3%). The most common type of single infection was HPV16 (33,96%), followed by HPV31 (11,89%) and HPV52 (9,1%). Combinations between HPV types were diverse, the most common combinations were HPV16+52 (8,5%), HPV16+31 (3,9%) and HPV33+59 (2,7%). Across the different age groups the single HPV infection had the greatest association with HSIL, OR range of 6.24 to 11.69 (95%C range:2.38-45.89), compared to multiple infections. Interestingly only among older women (≥50) simultaneous infection with two HPV types significantly increased the risk of HSIL OR13.75 (95%CI:2.72 - 69.62). In other age groups the OR decreased as simultaneous HPV combinations were considered.

Conclusions: Preliminary results suggest that combination of two HPV types only increases the risk of HSIL among elderly women, but infection with single HPV type stays the most prominent risk-factor across the age groups in predicting cervical carcinogenesis.

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#4941

CERVIVA HPV PRIMARY SCREENING STUDY: 3 YEAR FOLLOW UP OF HPV DNA POSITIVE AND AND HPV RNA POSITIVE WOMEN WITH NORMAL CYTOLOGY

12 - Triage of HPV positive women

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Background/Objectives: Background: Management of HPV positive woman with normal cytology represents a major challenge in cervical screening programmes. This observational study aims to investigate the longitudinal clinical endpoints of women who test positive for HPV DNA by the cobas 4800 HPV test, and positive for HPV mRNA by the Aptima HPV Assay, and have NAD (No Abnormality Detected) on cytology. HPV 16/18 and HPV 16/18/45 genotype distributions are also compared.

Methods: Design: In partnership with CervicalCheck, The National Cervical Screening programme, CERVIVA are undertaking a longitudinal observational HPV primary screening study which is investigating triage strategies for management of HPV-positive women. Cervical cytology samples from approximately 13,000 women undergoing routine cervical screening were tested for HPV using the cobas 4800 HPV test and the Aptima HPV assay. Aptima positive women were further assessed with the Aptima genotyping assay for HPV 16/18/45. Baseline cytology and longitudinal follow up data has been collected for all women. The performance of the two assays in women with NAD on cytology has been examined both cross-sectionally and longitudinally over one screening round (to date) for detection of CIN2+.

Results: Results: From the overall study population, there were 10,150 with a valid Cobas, Aptima and cytology result. HPV prevalence was 15.7% (1592/10150) and 12.9% (1310/10150) for the Cobas and Aptima respectively. Cobas positive cases had a higher proportion of NAD cytology compared to Aptima positive cases, 66.7% (1062/1592; 95% CI 65.6-67.8) and 60.6% (794/1310; 95% CI 59.3-61.9). In those that tested positive with NAD cytology, 27.6% (293/1062) had HPV 16/18 detected by the cobas and 22.9% (182/794) HPV 16/18/45 detected by the Aptima Genotyping assay. Over a three year follow up period there was 31 cases of CIN2+ detected for both Cobas positive/NAD and Aptima positive/NAD. As the Aptima assay had a lower HPV detection rate compared to Cobas, yet detected the same number of CIN2+, the cumulative risk of CIN2+ in HPV positive/NAD was higher with the Aptima assay 3.9% (31/794; 95% CI 3.6-4.2) compared to the cobas HPV assay 2.9% (31/1062; 95% CI 2.8-3.1).

Conclusions: Conclusion: Here we present an update on the longitudinal follow-up of Cobas and Aptima detected HPV in women with NAD on cytology and the role of HPV 16/18 and HPV 16/18/45 genotyping.

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#4913

7-TYPE HPV MRNA TEST IN TRIAGE OF HPV-DNA PRIMARY SCREEN POSITIVE WOMEN

12 - Triage of HPV positive women

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Background/Objectives: A plethora of scientific data supports HPV-based screening to be the preferred strategy for cervical cancer prevention. The shift to a more sensitive first line test brings the need of effective triage up for discussion. In 2019, Norway implemented HPV-DNA testing in primary screening for women 34-69 years of age. Literature describes the seven genotypes included in the nonavalent vaccine to be the most oncogenic HPV-types, identified in >90% of cervical cancer tissue worldwide. We studied the performance of a 7-type HPV-mRNA test in triage of HPV-DNA screen positive women compared to cytology as the established reference method, focusing on the number of colposcopies per CIN2+ detected.

Methods: From 2019 throughout 2021, cervical samples from 17,684 women were enrolled HPV primary screening (Cobas 4800, Roche) at the department of Clinical Pathology, University Hospital of North-Norway. All screen positives were triaged by cytology and by a 7-type HPV mRNA E6/E7 test (PreTect HPV-Proofer'7, genotyping 16-18-31-33-45-52-58) and followed-up according to national guidelines. Study endpoint was histologically confirmed high grade lesion (CIN2+).

Results: 5.6% (990/17,684) had a positive HPV-DNA test, of whom 962 had a valid HPV-mRNA test. 55.5% (534/962) had abnormal cytology (ASC-US+) and 35.1% (338/962) had a positive HPV-mRNA test. Prevalence of CIN2+ was 9.8% (94/962). The sensitivity of cytology and HPV-mRNA was 83.0% (78/94) versus 76.6% (72/94), p=0.36. The specificity was 47.5% (412/868) versus 69.4% (602/868), p<0.001. The PPV for CIN2+ was 14.6% (78/534) for cytology and 21.3% (72/338) for the HPV-mRNA test, p=0.014. NPV was 96.3% (412/428) and 96.5% (602/624). The number of colposcopies per CIN2+ detected by cytology and HPV-mRNA test was 6.8 versus 4.7.

Conclusions: The 7-type HPV mRNA test was significantly more specific than cytology in triage of HPV-DNA screen positive women. Using this biomarker as a threshold for referral to colposcopy may better balance the benefits and harms of screening. Ensured by the triage test`s NPV, women with a positive HPV-DNA test and negative HPV-mRNA test safely can be followed up with repeat HPV-DNA testing after 12 months. Additionally, molecular triage by mRNA is applicable for self-collected samples, an approach having its impact on health care and cancer services to further increase screening participation and prevention of cervical cancer.

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#4835

Serial measurements with quantitative HPV genotyping in liquid-based cytology allows triage of HPV positive women

12 - Triage of HPV positive women

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Background/Objectives: HPV infections are common in women being screened with cervical cytology. While most infections are virion producing and infectious and will never lead to cancer, some of the HPV infections are clonal transforming, are not infectious but can in time lead to cervical dysplasia and cancer. By measuring and determining the different types of HPV infection (infectious/clonal) in women that are being screened with cytology, we wanted to assess the number of women with Cervical Intraepithelial Neoplasia Grade 2 or more (CIN2+) in this population during a 7-year follow-up.

Methods: The HPV status (clonal/infectious) for each of the following HPV types (6,11,16,18,31,33,35,39,45,51,52,53,56,58,59,66,67, and 68) was determined in liquid-based cytology leftovers of cervical samples. Cervical cytology was performed without knowledge of HPV status. Liquid based cytology leftovers (n=2783) were tested with quantitative polymerase chain reaction for 18 different HPV types. Serial measurement of the amount of type-specific HPV DNA present in consecutive smears allowed the calculation of the different infection(s) present. For each of the detected HPV infection we calculated if the type-specific HPV was infectious (± 0,3 HPV copies/cell/day) or clonal progressive (0,003 HPV copies/cell/day). During follow-up women had colposcopy with biopsy.

Results: From the 1941 women tested, 910 were HPV positive (46.9%), and 19 women had >=CIN2+ biopsies (0,98%). All women with >=CIN2+ were HPV positive. Most of the >=CIN2+ women (11/19; 57,9%) had only clonal HPV, and in 8 women (42,1%) both clonal and transient infectious HPV were detected simultaneously. In women with transient infections no >=CIN2+ were detected.

Conclusions: Serial quantitative HPV genotyping in liquid-based cytology leftovers allowed triage in women with infectious and clonal HPV infections. During follow-up >=CIN2+ detection only occurred in women with clonal HPV infections whereas women with infectious HPV cleared the infection(s).

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#4754

TIME AND AGE DEPENDENT HPV CLEARANCE AFTER HPV POSITIVE SCREENING INDEX SAMPLE: Health care policy implications for recommended follow-up

12 - Triage of HPV positive women

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Background/Objectives: In the Capital Region of Denmark, women aged 30 to 59 undergoing HPV screening are recommended a re-test 12 months later if the index sample is 1) HPV positive (any genotype) with normal cytology or 2) ASCUS or LSIL with any of HPV35, 39, 45, 52, 56, 58, 59, 66, 68. The aim is to allow viral clearance and thereby lower potential overtreatment. To evaluate this health care policy of a 12-month re-test, we present data on compliance to follow-up, as well as HPV clearance rates.

Methods: Women (30-59y) undergoing HPV screening from March to August 2021 with an index screening outcome of any HPV genotypes w./ normal cytology and ASCUS or LSIL w./ any HPV35, 39, 45, 52, 58, 56, 59, 66, 68, and not undergoing a follow-up course after recent screening positive sample were included (N=1317). All HPV testing was done with the BD Onclarity HPV test. The assay cut-off for HPV types other than HPV16 was Ct 34.2, the cut-off for HPV16 was Ct 38.3 (manufacturers specifications). Clearance was defined as a Ct score above the cut-off as well as a valid sample result. The association between clearance of HPV infection and age or time to follow-up was analysed by logistic regression.

Results: Compliance to HPV re-test recommendation was 61.5% and 75.5% within 12 and 18-months after index sample, respectively. Of all re-tested women, the median number of days until follow-up was 364 days. At re-test, 57% of the women remained HPV positive. Of these 12.7% had multiple infections. Of all HPV genotypes registered at index, 46% persisted with the same genotype at re-test, 9% were new types gained, 45% was cleared. Overall, 3% cleared the index type but gained a new type. HPV clearance was significantly associated with time until clinician collected follow-up sample, the longer period until follow-up the higher chance of clearance (p=0.035). We found no association between age and HPV infection clearance.

Conclusions: Women complying to the re-test recommendation did so on average very close to the indicated 12 months period, but with a large increase in compliance when evaluated within 18 months. The ability to clear an HPV infection was age independent, but time to HPV follow-up test was significantly associated with HPV clearance. To formulate a health care policy regarding the optimal follow-up time after an HPV positive index sample histology data remains still to be retrieved and analyzed. Yet, we are leaning towards suggesting that an 18-month follow-up time may be more optimal to allow most women time to clear the index sample HPV infection thereby reducing the number of unnecessary referrals after re-test.

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#5009

CAN REFLEX CYTOLOGY HELP IN THE MANAGEMENT OF WOMEN WITH HPV 16/18 IN THE CERVICAL CANCER SCREENING ?

10 - HPV screening

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Background/Objectives: Cervical cancer is the fourth most common cancer in women and virtually all cases are caused by high-risk oncogenic human papillomavirus (HPV), with subtypes 16 and 18 being responsible for most cases. In the central region of Portugal, since 2019, the national cervical cancer screening (CCS) program is based on primary HPV testing, which is more sensible and reproducible than conventional cytology as a primary screening method. We aim to estimate the prevalence of CIN2/3+ (high-grade lesions or cervical cancer) in women with HPV 16 and/or 18 in the CCS and to analyse the risk of CIN2/3+ according to the result of the reflex cytology. We intend to collect data that could support a prioritization based on reflex cytology of the patients referred from CCS to Colposcopy Units with HPV16/18.

Methods: Cross-sectional observational study of women referred to the colposcopy unit of a tertiary hospital due to a positive HPV test for subtypes 16 and/or 18 in CCS program, from Jan/2020 to Dec/2021. Clinical and demographic data were collected from the files in Siima-Rastreios and Sclínico softwares. Statistical analysis was performed using STATA v13.0.

Results: During this period, 441 women aged between 24 and 64 years (median 43) were referred with HPV 16 and/or 18. Only 9 women (2%) were vaccinated against HPV, all in the 30-39 years' group. Most women never smoked - 285 (64,6%), 112 current smokers (25,4%) and 44 ex-smokers (10%). Reflex cytology was performed in 355 cases (80,5%): NILM- 46 cases (13,0%); ASC-US-174 (49,0%); LSIL- 80 (22,5%); ASC-H/HSIL- 41 (11,5%); AGC- 14 (3,9%). All women underwent colposcopy. A biopsy and/or loop excision of the transformation zone (LETZ) was performed in 56,5% of the cases (n= 249). CIN2/3+ lesions were found in 34,1% of the cases (85/249). The age group with the highest prevalence of CIN2/3+ was 30-39 years (50,6%), which was statistically significant (OR 1,84; p=0,027). Concerning CIN2/3+ risk depending on the reflex cytology, we only found significant correlation in ASC-H/HSIL (OR 2,58; p<0,001) and ASC-US (OR -1,33; p<0,001); there were no cases in the NILM group; in LSIL and AGC results were not significant. The sensitivity and specificity of ASC-H/HSIL to predict CIN2/3+ for patients with HPV 16/18 was 49,2% and 93,2%, respectively.

Conclusions: In this analysis the prevalence of CIN2/3+ in women with a positive HPV test for subtypes 16 and/or 18 was 34,1%, which was similar to other studies. The results also suggest that HPV 16/18 with ASC-H/HSIL in reflex cytology increases 2,5 times the risk of CIN2/3+. ASC-US appeared to be protective in this analysis, which was probably due to the small sample size. We need more studies to validate if reflex cytology helps us prioritize the patients, as the volume of referred cases is increasing with this new and more sensible screening method.

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#5102

Diagnostic and clinical outcome at 12 months re-test after HPV+ index sample in HPV screening using extended genotyping and cytology as triage

10 - HPV screening

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Background/Objectives: In 2021, the Danish cervical cancer screening program initiated a phased implementation of HPV screening for women 30-59 years. In the Capital Region of Denmark, the HPV screening is conducted using extended genotyping and cytology combined to triage any HPV positive. The HPV screening algorithm employed is risk based where HPV positive index screening sample with concurrent ASCUS or LSIL in combination with HPV genotypes 35, 39, 45, 51, 56, 58, 59, 66 and 68 are referred to a re-test after 12 months. Likewise, HPV positive index screening samples with concurrent normal cytology are referred to re-test after 12 months. At the 12 months re-test, women with a test outcome of HPV+/ASCH, AGC, HSIL or AIS, HPV+/ASCUS or LSIL, or HPV16, 18, 31, 33,52 and NILM cytology are referred to colposcopy. Women with HPV35, 39, 45, 51, 56, 58, 66, or 68 with NILM cytology are recommended a 2nd re-test in 12 months. Here we evaluate the diagnostic and clinical outcome of the 1st 12 months re-test after HPV positive index sample.

Methods: All women aged 30 to 59 years undergoing HPV screening in March to August 2021 with a valid screening test and a recommended follow-up of re-test at 12 months was included (N=1317). For this analysis, data from 938 women with a completed re-test at 12 months were retrieved from the Pathology DataBank in October 2022.

Results: The re-test period resulted in 42% of the women clearing their HPV infection. At the re-test, 58% (N=545) of all referred women remained HPV positive. Of the re-test HPV positive women, 11% had concurrent ≥ASCH, 18% showed ASCUS or LSIL independent of HPV genotype, 39% had HPV16, 18, 31, 33, 52 and NILM cytology. All these were referred to colposcopy. The remaining 32% with HPV35, 39, 45, 51, 56, 58, 59, 66, or 68 and NILM cytology were referred to a 2nd re-test. At data retrieval, 263 women had completed colposcopy (71%). For HPV+/ASCH, AGC, HSIL or AIS, 41% showed ≥CIN2 and 27%≥CIN3; for HPV+/ASCUS or LSIL, 17% ≥CIN2 and 7% ≥CIN3, and for HPV16, 18, 31, 33, 52 and NILM cytology, 15% showed ≥CIN2 and 6%≥CIN3.

Conclusions: For those who remained HPV positive, the majority of disease was detected in the triage group of HPV+/≥ASCH. The triage groups HPV+/ASCUS or LSIL and HPV16, 18, 31, 33, 52 /NILM cytology yielded very few histology confirmed ≥CIN3, 7% and 6%, respectively. This leads to a cautious conclusion that the latter two triage groups potentially could benefit from a 2nd re-test recommendation rather than referral to colposcopy. This could benefit women by reducing overtreatment after the 12 months re-test and allow women additional time to clear the underlying HPV infection.

FC24 - Free communications- Serology and immunotherapy

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#4943

ABSENCE OF TOTAL AND NEUTRALIZING HPV18 L1 ANTIBODIES IN BIVALENT AND QUADRIVALENT VACCINE RECIPIENTS UP TO 12 YEARS AFTER 3-DOSE VACCINATION: A LONG-TERM FOLLOW-UP OF TWO PHASE 3 TRIALS

20 - Serology

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Background/Objectives: Long-term follow-up studies of HPV vaccinated recipients have reported that variable proportions of women have no detectable total and/or neutralizing antibodies against HPV16/18 after HPV vaccination with 3-doses. We further investigated the consistency of absence or presence of vaccine-induced HPV16/18 L1 antibodies over 12 years post-vaccination.

Methods: We conducted a follow-up study of two cohorts of Finnish women receiving 3 doses of either the bivalent or quadrivalent vaccine when aged 16-17, as participants of the PATRICIA and FUTURE II randomized phase 3 trials. The vaccine recipients comprising these cohorts were followed up in the Finnish Maternity Cohort, FMC, serum bank. The FMC serum bank contains serum samples from 96% of all pregnant women in Finland from 1983-2016. During up to 12 years of follow-up post-vaccination, 2046 serum samples were identified with the shortest lag (N=648) were analyzed both for total L1 binding antibodies to HPV16 and 18 via a pseudovirion-based Luminex assay and for HPV16 and 18 neutralizing HPV L1 antibodies via pseudovirion-based neutralization assay.

Results: A total of 648 vaccine recipients (328 quadrivalent vaccine recipients, QVR and 320 bivalent vaccine recipients, BVRs) were eligible and included in the study. Among QVR and BVR, 4.0% and 0.0% respectively were seronegative for both neutralizing and total binding HPV16 antibodies, Cohen's Kappa coefficient (comparing the results from the two assays), $\kappa = 0.93$ (95% confidence interval, 0.83-1.00). Whilst 14% and 0.0% were seronegative for both neutralizing and total binding HPV18 antibodies respectively, $\kappa = 0.72$ (95% CI, 0.63-0.81).

Conclusions: Among women vaccinated in late adolescence with 3-doses of the quadrivalent vaccine, 1 in 25 recipients may have no measurable antibody response to HPV16, whilst 1 in 7 may have no response to HPV18. Observations of HPV16- or HPV18- vaccine non-response as measured via a pseudovirion-based neutralization assay were replicable when measuring total-binding antibody response. However, continued long term non-response does not provide evidence of limited efficacy.

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#4902

THE HPV SEROLOGY STANDARDIZATION INITIATIVE: AIMS AND PROGRESS TO DATE AT THE FREDERICK NATIONAL LABORATORY FOR CANCER RESEARCH

06 - HPV prophylactic vaccines

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Background/Objectives: Protection against Human Papillomavirus (HPV) infection after vaccination is believed to be mediated by HPV-specific antibodies. However, the lack of standardized assays, procedures, and reagents accessible to the scientific community has precluded the comparison of different studies evaluating immunogenicity of HPV vaccines. With an increase in the number of trials relying on immunobridging for approval of new dosing schedules or vaccine formulations, there has been a critical need for standardized measurement and reporting of immunogenicity to reliably assess non-inferiority of antibody responses and improve overall comparability between studies.

Methods: The HPV Serology Standardization Initiative led by the HPV Serology Laboratory (HSL) at the Frederick National Laboratory was established in January 2017, working with the National Cancer Institute (USA) and The Bill & Melinda Gates Foundation to lead standardization and harmonization efforts for HPV serological testing within vaccine trials. The main goal has been to expedite serology assay standardization by assisting with the development of primary serology standards for HPV-6, 11, 31, 33, 45, 52, and 58, as well as testing samples from several one dose vaccine studies and immunobridging studies. Furthermore, standard operating procedures are also accessible on our laboratory website.

Results: HSL developed secondary standards calibrated against available WHO international standards, reference HPV Virus Like Particles (VLP) and a serology-based proficiency panel for the 9 HPV types included in licensed vaccines. Reference materials have been shared with 19 unique serology labs worldwide via Material Transfer Agreements. Furthermore, HSL co-led efforts for WHO international standards production by NIBSC for HPV-6, 11, 31, 33, 45, 52, and 58.

Conclusions: Achievement of these aims will enable comparisons of data across different HPV vaccines and different studies and, therefore, it will facilitate vaccine development and implementation of new vaccine recommendations.

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#5020

OPTIMISATION OF THE LABORATORY WORKFLOW FOR IMPROVED EFFICIENCY AND QUALITY OF HPV VACCINE SURVEILLANCE DATA

14 - Genotyping

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Background/Objectives: To monitor vaccine effectiveness, the Norwegian HPV reference laboratory performs HPV genotyping on tissue samples from cervical cancers, ACIS and CIN2/3 obtained from all pathology departments in Norway. This work, administered by the National Institute of Public Health, has been ongoing since 2017, analysing approximately 1400 samples per year. As part of the responsibilities of the reference laboratory, optimisations of the laboratory protocol and workflow are regularly considered.

Methods: After DNA extraction from formalin-fixed paraffin-embedded tissuesamples, HPV genotyping is performed using MGP-PCR followed by hybridization to type-specific probes (Luminex technology), detecting 37 HPV-types. For Luminex negative samples, additional testing with Anyplex II HPV28 (Seegene) and type-specific E6/E7 PCR against the 14 high-risk (HR) types (in-house) is performed. To improve the laboratory workflow, the following has been assessed: Evaluation step 1: Today, HPV-negative Luminex samples with concentration >30ng/µl are diluted and reanalysed in duplicate before further analysis; might this step be replaced by direct analysis using Anyplex? Evaluation step 2: Some samples are positive for non-HR types after Luminex genotyping; might HR-types be hidden in a background of other genotypes, resulting in a non-representative result associated with the stochasticity in PCR amplification?

Results: Preliminary results evaluation step 1: In 2021, 23 samples gained a positive Luminex result after dilution and retesting. Anyplex analysis of the undiluted sample confirmed the results in all 23 cases. Preliminary results evaluation step 2: Of 22 samples positive for non-HR types by Luminex, four were positive with an additional HR-type by Anyplex. These will be validated with E6/E7 type-specific PCR.

Conclusions: The whole laboratory workflow will be presented, including a complete dataset verifying the following improvements: 1. Direct Anyplex analysis of HPV negative Luminex samples with concentration >30ng/µl will replace duplicate reanalysis on diluted samples, being both time and cost-efficient, and 2. To minimize unsuccessful detection of HR-HPV types, additional analysis with Anyplex, a technology more robust for multiple infections, will be implemented for samples found positive exclusively for non-HR types by Luminex. In addition, the value of E6/E7 type-specific PCR as a third detection assay, will be evaluated and presented.

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#4680

SERUM IGG ANTIBODIES TO HPV6 L1, E2, E4, E6 AND E7 PROTEINS AMONG NEONATES FOLLOWED-UP FOR THREE YEARS

20 - Serology

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Background/Objectives: Current knowledge implicates that human papillomavirus (HPV) infection can be acquired already at early age. However, the role of HPV-specific passive immunization from mother to neonate is nearly unexplored especially against the HPV early proteins. Here we analyzed IgG antibodies against HPV6 early (E2, E4, E6, E7) and late (L1) proteins in neonates followed-up for three years. The further knowledge on HPV6 infection is crucial as it is known to cause laryngeal papillomas especially in neonates and young children.

Methods: A total of 272 neonates and their mothers from the Finnish Family HPV study were included to these analyses. Serum samples were obtained from pregnant mothers at their 3rd trimester and from neonates at 1-, 2-, 6-, 12-, 24- and 36- month visits after birth. Antibodies to the early proteins E2, E4, E6, E7 and late L1 protein were analyzed by multiplex serology based on glutathione S-transferase fusion protein capture to fluorescent beads. Cut-off value for seropositivity required a value of at least 100 MFI for E2, E4, E6 and E7 and at least 200 MFI for L1.

Results: Maternal antibodies against all five different HPV6 proteins (E2, E4, E6, E7 and L1) were transferred to the neonate and the individual antibody levels were significantly correlated with each other ($p<0.001$). Seropositivity of the neonates especially for HPV6 L1 declined during the first six months of life from 32% to 19% while changes in antibodies to early proteins were less obvious. The children seroconverted first to HPV6 L1, with a mean time of 17 months, and later for the early proteins E2, E4, E6 and E7 between 19-29 months. A significant association in the infants' sera was seen between L1 antibodies and the E4 and E6 antibodies at the 6-month and 12-month follow-up points ($p=0.004$ and $p=0.005$).

Conclusions: IgG antibodies against HPV6 early and late proteins are transferred from the mothers to their neonates. These results indicate that maternal IgG-antibodies against HPV6 are waning by the age of 6 months but supports the view that new HPV6 infection is acquired in early life either vertically or horizontally which will result in infant's later seroconversion.

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#5046

IMMUNE INFILTRATES AMONG WOMEN WITH CERVICAL PRE-CANCER AND CANCER

26 - Cervical neoplasia

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Background/Objectives: Virtually all cervical cancers are caused by HPV infection. Host immune factors likely play a role in disease outcomes, however, these have not been defined, data needed to inform the development of therapeutic vaccines targeting HPV. A study of tumor immune infiltrates of archived cervical interepithelial neoplasia and carcinoma was conducted.

Methods: This case only, cross-sectional study of cervical dysplasia and cancer using FFPE tissue archived at Moffitt Cancer Center included patients aged ≥18 years with a diagnosis of squamous cell carcinoma (SCC), adenocarcinoma (ACC), or intraepithelial neoplasia grade III (CIN 3) of the cervix. Four (4 micron) slides were cut from each FFPE block. Slides underwent dual staining for the following markers: CD3/CD20, CD4/Foxp3, CD56/CD68, and CD8/CD33. Three regions of interest (ROI) were identified per slide. The percent of positive cells for each marker was calculated for each ROI. Patient medical charts were reviewed and data on patient demographics, diagnosis, and treatment were abstracted. Patient and tumor data were combined and the mean percent of cells positive for each immune marker for the three ROIs was calculated for each case.

Results: Twenty-five patients were included. Median age was 42 years (range 19-57 years). Eleven (44%) patients were diagnosed with CIN 3 or carcinoma in situ (CIS), four (16%) with SCC and 10 (40%) with ACC. Seven (28%) patients were treated with surgery and chemotherapy and/or radiation, all of whom had invasive cancer, and 18 (72%) were treated with surgery only. The highest percentage of CD3, CD4, Foxp3, CD20, CD33, and CD68 cells were observed in CIN 3/CIS specimens. Those markers were lower in invasive cancer, with lowest levels in ACC. Among ACC, CD3, CD4, Foxp3, CD20, CD33, and CD68 were 30%, 90%, 60%, 83%, 44%, and 82% lower respectively compared to CIN III/CIS cases. Proportions of CD8 and CD56 were similar across all specimens. All patients had a complete response to treatment; however, among CIN/CIS cases, two (18%) recurred, and one case of ACC (10%) recurred. Immune infiltrates were similar between cases which recurred and those which didn't, except those which recurred had almost double the percent of CD4 and Foxp3 infiltrates.

Conclusions: ACC cases had the lowest level of immune infiltrates, and cases which recurred had higher levels of CD4 and Foxp3 infiltrates, which suppress cancer clearance by immune cells. Larger studies examining the relationship between the tissue immune landscape and cervical disease treatment outcomes across diverse geographic and immune deficient (e.g., HIV) settings are needed to inform therapeutic vaccine development.

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#4964

5-Aza-2'-deoxycytidine in combination with the cytidine deaminase inhibitor tetrahydrouridine significantly improves survival in a preclinical mouse model of HPV-induced cancer

08 - Immunotherapy - Immuno-oncology - New treatments

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Background/Objectives: Malignant transformation of HPV-infected cells is functionally associated with aberrant methylation of both the HPV and the host genome. In this project, we are developing a novel treatment approach for HPV-induced carcinomas targeting this aberrant methylation. To this end, we are utilizing DNA methyltransferase (DNMT) inhibitors, such as 5-aza-2'-deoxycytidine (DAC). To achieve therapeutically relevant plasma levels, DAC generally needs to be applied in relatively high doses when administered systemically, since the drug is unstable in aqueous environments and subject to degradation by the enzyme cytidine deaminase (CDA). We aim to reduce DAC degradation by combined administration with the CDA inhibitor tetrahydrouridine (THU) and to thereby increase the therapeutic effect of DAC when applied systemically at lower, non-cytotoxic doses. In the course of this study, we investigated whether the combined systemic administration of DAC and THU can prolong survival in a mouse model of HPV-induced cancer and further determined the treatment outcome with regard to the induction of cell death, senescence and differentiation.

Methods: Mice of the immune-deficient NOD scid gamma (NSG) strand were injected with HPV-transformed cells of the CaSki cell line. Systemic treatment was performed on three consecutive days per week with either PBS (control group), low-dose DAC of 0.1 mg/kg, or DAC 0.1 mg/kg+THU 10 mg/kg, until preset stopping criteria focusing on general animal welfare and tumor size were reached. Endpoint analyses comprise survival, tumor size and biological treatment effects assessed in tumor tissue. Treatment effects on DNA methylation within the tumor tissue are assessed via determination of DNMT1 expression using immunohistochemistry (IHC) and via LINE-1 methylation determination using bisulfite pyrosequencing. Evaluation of further biological treatment effects focus on the qualitative and quantitative assessment of cell death mechanisms, senescence and differentiation via qRT-PCR analysis of different molecular markers, immunofluorescence (IF), and IHC approaches.

Results: Mice of the control group treated with PBSshowed a median survival of 59 days, while DAC only-treated mice survived significantly longer, demonstrating a median survival of 66 days. Mice treated with the combination of DAC+THU showed the longest median survival of all observed treatment groups of 98 days, significantly differing from both PBS control and DAC only-treated groups. Preliminary results from tumor tissue analyses further provided indications that DAC+THU treatment induced cell death and differentiation of tumor cells. None of the mice did show indications of clinical toxicity as a consequence of treatment with DAC or DAC+THU.

Conclusions: Our results indicate that combinatory systemic application of DAC and THU results in a biologically relevant treatment outcome in a mouse model of HPV-induced cancer, while showing good tolerability.

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#4956

EFFECTS OF LOW-DOSE 5-AZA-2´-DEOXYCYTIDINE (DAC) TREATMENT ON DIFFERENTIATION OF HPV-TRANSFORMED CELLS

08 - Immunotherapy - Immuno-oncology - New treatments

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Background/Objectives: Epigenetic therapy with demethylating agents, such as 5-aza-2'-deoxycytidine (decitabine, DAC), is a new causal therapeutic concept for HPV-transformed lesions. HPV-induced transformation in cervical epithelium is characterized by overexpression of the viral oncogenes E6 and E7, resulting in uncontrolled cellular proliferation and de-differentiation. DAC has been shown to lead to demethylation of aberrantly methylated sites in the HPV and host genome and decreased expression of E6/E7. We previously demonstrated a dose- and time-dependent induction of apoptosis and senescence in DAC-treated HPV-transformed cells. In acute myeloid leukemia (AML), for which DAC is already clinically approved, expression of key terminal differentiation genes is epigenetically repressed. DAC treatment has been demonstrated to revert the epigenetic repression of terminal differentiation genes, leading to an induction of terminal differentiation in the treated AML cells. In this work, it was of major interest to investigate if DAC treatment at low doses may also induce differentiation of HPV-transformed cells.

Methods: A comprehensive search on PubMed was conducted to identify a panel of markers that can indicate the induction of differentiation in HPV-transformed cervical cells. Formalin-fixed paraffin-embedded (FFPE) sections from high-grade vulvar intraepithelial neoplasia (VIN) samples of 8 patients (1 sample per patient) were assessed by immunohistochemistry /immunofluorescence applying the identified differentiation markers and comparing expression patterns to that of p16INK4a as a marker of HPV-induced transformation. HPV-transformed cervical cell lines SiHa and CaSki were cultured and treated with different concentrations of DAC (0.01 µM, 0.05 µM, 0.1 µM, 0.5 µM and 1.0 µM) over one and two weeks and were subsequently assessed for the potential treatment-related induction of differentiation by immunofluorescence and real-time quantitative PCR using the identified marker panel.

Results: Keratin 10, involucrin, filaggrin, loricrin, and cornifelin were identified as potentially eligible markers of differentiation in the target cells based on the comprehensive literature search. A clear inverse relation between p16INK4a and keratin 10 and between p16INK4a and involucrin expression was observed in HPV-transformed VIN, supporting the suitability of the identified marker panel to indicate cellular differentiation. DAC treatment considerably reduced cellularity and caused cell death in a dose- and time-dependent manner in treated SiHa and CaSki cells. Further, a dose- and time-dependent positive effect of DAC on differentiation was observed morphologically and on protein and mRNA level in the remaining vital cells at treatment doses between 0.1 µM and 1.0 µM.

Conclusions: Low-dose DAC treatment induces a variety of biological treatment consequences in HPV-transformed cells that at least partially comprises the induction of cellular differentiation. Treatment with low doses of DAC has the potential to induce biologically meaningful treatment effects in tumor cells while reducing the risk of toxicity to normal cells.

FC19 - Free communications- Methylation 2

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#4947

CIN3+-specific methylation marker analysis to improve the triage of hrHPV-positive self-samples in the Dutch population-based cervical cancer screening programme

18 - Methylation

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Background/Objectives: The Dutch cervical cancer screening programme consists of primary high risk human papilloma virus (hrHPV) testing with cytology as triage test. To increase participation, women are offered self-sampling. As triage cytology is not feasible on this self-sampled material, women with a hrHPV-positive test need to visit their GP for cytology. We aim to identify a methylation marker panel as an alternative triage test to detect CIN3 or worse (CIN3+) in hrHPV-positive self-sampled material.

Methods: Fifteen methylation markers, selected from literature with high sensitivity and specificity for CIN3+, were analysed using quantitative methylation-specific PCR (QMSP) on 208 hrHPV-positive self-samples of women with a CIN2 or less (<CIN2) and 96 with CIN3+. The diagnostic performance was determined by area under the curve (AUC) of receiver operating characteristic (ROC) analysis. Self-samples were divided into a train and test set. Model-based recursive partitioning and robustness analysis were applied to identify the best marker panel.

Results: QMSP analysis of these individual markers showed discriminative DNA methylation levels between <CIN2 and CIN3+ for all markers ($p<0.05$). ROC analysis for CIN3+ showed an AUC of ≥0.7 ($p<0.001$) for 9/15 markers The most promising and robust panel consisted of three methylation markers with an AUC of 0.83 in the training set and 0.84 in the test set. The sensitivity to detect CIN3+ was 82% in the training and 84% in the test set, with a specificity of 74% and 71%, respectively. Furthermore, all five cancer cases were identified.

Conclusions: In this study we identified a methylation panel, consisting of three methylation markers, which revealed good diagnostic performance. This panel of methylation markers shows clinical applicability to replace cytology and avoid the extra GP visit after a hrHPV-positive self-sampling test. Currently, we are performing external validation of this optimized panel in a large cohort of hrHPV-positive self-samples.

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#4842

DNA methylation markers for optimal detection of vulvar intraepithelial neoplasia with a high cancer risk

27 - Vulvar diseases and neoplasia

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Background/Objectives: High-grade vulvar intraepithelial neoplasia (VIN), the precursor of vulvar squamous cell carcinoma (VSCC), constitute a heterogeneous group of premalignant lesions. These include human papillomavirus (HPV)-associated and HPV-independent precursor lesions with a varying cancer risk (1, 2). There is a clinical need for objective molecular biomarkers to aid in cancer risk stratification of patients with VIN. Host cell DNA methylation is already appreciated as a biomarker for detection of lesions with a high cancer progression risk in cervical and anal neoplasia (3-6). Previously we have shown that several genes showed higher methylation levels with increasing severity of disease in a well-defined cross-sectional series of vulvar lesions (7). The aim of this study was to evaluate the accuracy of previously identified methylation markers for detection of VIN with a high cancer risk.

Methods: A population-based series of 751 high-grade VIN lesions, retrieved from the Dutch Pathology Databank, were reassessed and included in the study together with 113 healthy vulvar controls. Archived tissues of high-grade VIN cases were reassessed and categorized into HPV-associated or HPV-independent vulvar disease categories. Healthy control tissues were collected from patients undergoing aesthetic or reconstructive genital surgery. DNA methylation levels of 12 genes were determined in relation to disease category and cancer progression. The performance of all individual markers and selection of an optimal marker panel for detection of high-grade VIN was determined by univariate and multivariate logistic regression analysis, respectively.

Results: Significantly higher methylation levels were found with increasing severity of vulvar disease. All markers showed a moderate to good individual performance to distinguish high-grade VIN from healthy controls. AUC values ranged from 0.67 to 0.90, with nine markers showing an AUC above 0.80. SST was the best performing individual marker (AUC 0.90), detecting 80% of high-grade VIN cases, with excellent detection of HPV-independent VIN (95%), known to have the highest cancer risk. Merely 2% of controls were tested methylation positive. Selection of a marker panel, including ZNF582, SST and miR124-2, resulted in a comparably high accuracy for detection of high-grade VIN (AUC 0.89). SST and the marker panel detected over 90% of cases which progressed to VSCC within five years.

Conclusions: This study validated the accuracy of 12 DNA methylation markers for the detection of high-grade VIN. SST, as a sole marker or in a panel, provides an optimal diagnostic tool to distinguish high-grade VIN in need of treatment from low-grade or reactive vulvar lesions. Future perspectives include further exploration of methylation biomarkers as a prognostic tool for cancer risk stratification of patients with VIN. Such biomarkers, in combination with other clinical parameters, have the potential to optimize the identification of vulvar lesions with a high cancer risk, allowing personalized management for affected patients.

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#5002

TOWARDS ELIMINATION OF CERVICAL CANCER - INCREASED USE OF BIOBANKS ENABLES RAPID ASSESSMENT OF EMERGING BIOMARKERS IN SCREENING

18 - Methylation

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Background/Objectives: To achieve the WHO goal for global elimination of cervical cancer, Norway and other countries have implemented human papillomavirus (HPV)-based primary screening. Optimal follow-up of high risk (hr)-HPV positive women remains a challenge and molecular biomarkers which can increase screening accuracy are needed. DNA methylation analysis is a promising biomarker for separating between HPV-positive women with progressive potential disease and those with harmless infections. However, determining predictive accuracy of biomarkers in real-life is difficult, due to long follow-up required and ethics. Our objective is to determine the optimal GynTect DNA methylation assay protocol for individual biobank sample types, assessing effects of storage duration and sample processing on assay performance and determine minimal amount input needed for optimal assay outcome.

Methods: The biobank: Residual cervical screening samples (LBC Thinprep) collected from consecutive 4242 participants who attended to National Cervical Cancer Screening Program in Norway between 2007 and 2013. Sample types: 1) Cells sedimented in Thinprep (Hologic); 2) cells resuspended in specimen transport medium (STM; QIAGEN) and 3) nucleic acid extracts Magna pure (Roche). The study: samples from 60 participants were selected, and the samples anonymized (year of sample donation only known variable). Ethical approval granted from Regional Ethics Committee of Southern Norway #2011/2341. As self-sampling is being introduced into screening, similar analyses are on the way for this sample type. Bisulfite conversion: Different protocols were performed using EpiTect Fast DNA Bisulfite Kit (Qiagen). GynTect DNA methylation analyses: Eluate from bisulfite treatment was filled up with ddH2O to 90µl, and 80µl were used to perform GynTect according to the manufacturer's protocol using cobas z480 Analyzer (Roche).

Results: Cervical screening samples stored long term at -80° displayed excellent GynTect DNA methylation assay performance. Optimal performance with 100% valid results was observed for cells stored in Thinprep. No difference in GynTect performance was observed between Thinprep samples stored for 14 years or for 10 years. In comparison, assay performance was reduced for cells stored in STM (65% valid samples) and further for nucleic acid extracts (40% valid samples).

Conclusions: Stored cervical screening samples combined with known HPV status and clinical outcome (enabled by personal linkage with screening registries) are a resource for rapidly assessing diagnostic accuracy of emerging biomarkers. Data from retrospective cohort studies using biobanks will inform policy makers and speed up the process of implementations into the screening program. Studies to adapt protocols for individual biobanks is essential to ensure optimal assay performance and minimal sample use. Specifically for this pilot, we have demonstrated excellent assay performance with 100% valid GynTect results when using LBC cervical cells stored at - 80° in Thinprep. Fruitful collaborations between private sector and public institutions enable full exploitation of existing biobanks and emerging technologies.

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#4942

VALIDATION OF METHICA CC KIT AS TRIAGE TEST FOR CERVICAL CANCER SCREENING

18 - Methylation

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Background/Objectives: The introduction of high-risk human papillomavirus (hrHPV) testing as the primary screening tool created a full molecular screening for cervical cancer. This is even more emphasized by the increased use (5% in 2017 to up to 30% in 2022) of self-sampling in the Netherlands. Although hrHPV screening is very sensitive for the detection of cervical abnormalities, the specificity is low and additional triage of hrHPV positive women is required. Analyzing promoter methylation of tumor suppressor genes with quantitative methylation specific PCR (mQMSP) is a promising molecular triage method. The Methica CC Kit enables detection of promoter hypermethylation of C13ORF18, JAM3 and ANKR18CP identifying high-grade cervical intraepithelial neoplasia and cervical cancer (CIN2+) lesions in physician-taken cervical samples and importantly also in self-sampled samples. Here, we analyzed the evaluation of the repeatability and reproducibility using the Methica CC Kit.

Methods: Cervical scrapings were selected from 20 hrHPV-positive women, from the Dutch population-based screening cohort. DNA methylation analysis was performed using the Methica CC Kit using bisulfite-converted DNA extracted from these cervical samples. Ten cases were selected to be methylation negative for all three markers and 10 cases were selected to be methylation positive (e.g., for at least one of the three markers). These bisulfite-converted DNA samples were analyzed with the Methica CC kit at 3 centers (UMCG, JBZ and Radboud). Concordance was determined for both repeatability and reproducibility resulting in 24 and 40 separate runs per sample, respectively.

Results: The methylation-negative samples showed a concordance of 99.1% and 99.3% for the repeatability and reproducibility, respectively, whereas in the methylation positive samples the concordance was higher (100% concordance for both repeatability and reproducibility). Including all 20 bisulfite-converted DNA samples, the concordance for the Methica CC kit was 99.6% for the repeatability and the reproducibility.

Conclusions: The Methica CC Kit showed a high concordance for both repeatability and reproducibility in a selected series of DNA samples. This suggests a reliable method for the detection of clinically relevant CIN lesions. Large-scale validation of the Methica CC Kit is currently being investigated.

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#5010

COMPARISON OF THE PERFORMANCE OF THE DNA METHYLATION MARKER TEST GYNTECT® AND THE CINtec Plus CYTOLOGY ASSAY

18 - Methylation

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Background/Objectives: Reliable triage methods are essential in cervical cancer screening settings in order to avoid overtreatment and higher screening costs. Among the screening triage options discussed, specific DNA methylation patterns may provide a suitable tool especially with respect to keeping false-positive rates low. In this study we compare DNA methylation and p16/Ki-67 as triage marker for women showing cytological abnormalities during primary screening.

Methods: Surplus cervical scrapes collected in PreservCyt® from women with cytology findings ≥ Pap III were assessed for methylation of the marker regions ASTN1, DLX1, ITGA4, RXFP3, SOX17, and ZNF671 (GynTect® assay; Schmitz et al., 2017). For all samples data for p16/Ki-67 dual staining (CINtec Plus® test) were available.

Results: Cytology is given according to the Munich nomenclature III, as is obligatory in Germany, and translated as far as possible to the Bethesda system. 1000 surplus cervical samples from women with the cytology findings Pap III (n=51; 43 ASC-H, 8 AGC endocervical favour neoplastic), Pap IIID1 (n=527; LSIL), Pap IIID2 (n=304; HSIL), Pap IVa (n=114; HSIL), and Pap IVb (n=3; HSIL susp. for invasion) were collected for the study. Among these, a high proportion were positive for the CINtec PLUS test (Pap III 90.2%; Pap IIID1 79.9%; Pap IIID2 97.7%; Pap IVa and Pap IVb each 100%). For a part of the samples (> 50%), also histopathology findings were available. Currently GynTect analyses of the samples are underway, and the data will be presented at the EUROGIN.

Conclusions: DNA methylation analysis is discussed as a promising option for cervical cancer triage. We assess the performance of the marker panel (GynTect® test) in cervical scrapes with abnormal cytology findings to further evaluate their clinical validity in cervical cancer diagnostics.

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#4954

NMPA approval trial of Gong An Li (GynTect®), a DNA methylation assay using six biomarkers for detecting cervical cancer and its precancerous lesions

12 - Triage of HPV positive women

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Background/Objectives: HPV testing as the primary screening assay has been discussed for several countries, among them also for China. The current triage method for all HPV positively tested women is cytology, but also partial HPV genotyping, especially for the main cancer-causing HPV 16 and 18 is discussed to be included in screening algorithms. The aim of this study was to show the clinical value of the methylation panel consisting of the markers ASTN1, DLX1, ITGA4, RXFP3, SOX17, ZNF671, comprising the test Gong An Li (GynTect®) in the triage of HPV positively tested women during cervical cancer screening in China.

Methods: Four clinical centers in China (Nanjing Drum Tower hospital; Peking University First Hospital; Maternal and Child Health Care Hospital Hunan; The First Affiliated Hospital of Anhui Medical) participated in the trial. Women at the age of 21-65 having a positive hrHPV test (70-80% cobas HPV, domestic HPV typing test, Nanjing: HC2, if positive cobas HPV test) were included. All women with positive HPV test were referred to colposcopy for taking a smear for cytology and the methylation marker assay, and, if indicated, a biopsy. Sensitivity, specificity, PPV, NPV, PLR and NLR was calculated for cytology, HPV 16/18 typing and the methylation assay on the total cohort as well as for cytology and methylation on the non-HPV 16/18 cohort.

Results: In total, 1660 participants tested hrHPV-positive could be included in the study. Of these 546 were HPV 16 or 18 positive and 1114 were positive for a non 16/18 HPV type. Sensitivity, specificity, PPV, NPV, PLR and NLR was calculated for cytology, HPV 16/18 typing and the methylation assay. In almost all aspects regarding the calculation for CIN2+ and CIN3+, methylation assay performance was superior compared to cytology. Detailed numbers will be presented at the conference.

Conclusions: The NMPA trial demonstrated a superior clinical performance of the methylation assay compared to the current standard, cytology. In China, Gong An Li (GynTect) is therefore now approved for the triage of non HPV 16/18 positive women to distinguish who is going directly to colposcopy and who will go back to regular HPV testing after one year.

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#4776

HPV VACCINATIONS ASSOCIATION TO PREGNANCY AND CHILDBIRTH PREVALENCE

06 - HPV prophylactic vaccines

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Background/Objectives: Prophylactic human papillomavirus (HPV) vaccines have proven to be highly efficacious against cervical cancer and its precursors. The data on HPV vaccination impact on women's fertility and pregnancy outcomes are scanty. The objective of this registry-based study was to determine whether HPV vaccination affects fertility.

Methods: The study population comprised HPV vaccinated women born 1992-1993 and a reference cohort of unvaccinated women born 1990-1991. Age-aligned data was collected up to age 28 for both cohorts. The subcohorts comprised vaccinated birth cohorts: 6200 and 2266 women who had received HPV16/18 vaccine at the age of 13 to 15 or 18.5, 1744 women who had received hepatitis B-virus (HBV) vaccine at age 13-15 and 19476 unvaccinated women. We compared the rates of pregnancies and births among the HPV-, HBV- and unvaccinated women by cluster randomized intervention arms (A, B and C) using nationwide Finnish Medical Birth Registry data.

Results: During the follow-up mean age of women at first childbirth was 23,8 years among the HPV and HBV vaccinated and 23,6 years among the unvaccinated women. At age 28 the cumulative numbers and proportions (%) of childbirths by non-vaccinated birth cohorts (BCnon) and vaccinated birth cohorts (BCvac) in the different intervention arms were: Arm A 2825 (31.4%, 1990-91 BCnon) and 1241 (31.1%, 1992-93 BCvac); Arm B 2926 (32.5%, 1990-91 BCnon) and 1368 (34.3%, 1992-93 BCvac); Arm C 3248 (36.1%, 1990-91 BCnon) and 1381 (34.6%, 1992-93 BCvac). As for the first childbirths comparable observations by birth cohort and intervention arm represented approximately two thirds of the above numbers and percentages.

Conclusions: Our results indicate that in the intervention arms A and B HPV vaccinated women have identical pregnancy and childbirth prevalence compared to unvaccinated women in adjacent birth cohorts. In the control arm C the prevalence were somewhat higher probably due to geographic and behavioral differences.

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#4869

COMBINED HOST AND VIRAL METHYLATION PANEL IN DETECTING HIGH-GRADE CERVICAL LESIONS AMONG HPV-VACCINATED WOMEN

06 - HPV prophylactic vaccines

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Background/Objectives: There is a great need to re-design cervical screening programs including triage tests as HPV-vaccinated women are entering the programs. We investigated the ability of a DNA methylation panel to identify high-grade cervical lesions among vaccinees.

Methods: The study comprised 9242 women, who had received three doses of HPV16/18 vaccine at age 12-15 (6958) or 18 (2284) in a community-randomized trial during 2007-2014. In 2014-2018, the vaccine recipients were re-randomized into a trial on (ages 22/25/28) vs. infrequent (age 28) screening. During 16 years of post-vaccination follow-up 39 histopathological confirmed high-grade squamous intraepithelial (HSIL) and 41 low-grade (LSIL) cases were identified. For this study 16 HSIL and 15 LSIL cases identified at the age 25+, and 370 age-matched HPV16/18 vaccinated controls were eligible. Methylation analyses were done with cervical samples obtained at the age of 25. DNA methylation of viral late regions in HPV16/18/31/33 and host gene EBP41L3 was measured with pyrosequencing assay. Cervical HPV genotyping at ages 18/22/25 was generated with Luminex technology.

Results: Persistent HPV types 33/51/52/59 at ages 22 and 25 were found in 8 of 16 HSIL and 3 of 15 LSIL cases. No HPV16/18/31/45 were identified. The mean age of HPV vaccination was among both HSIL and LSIL cases 15 years. A predefined methylation panel of host and viral genes for the detection of HSIL was comparable to ROC AUC against those of pap-cytology or HPV 33/51/52/59 genotyping. Evaluating only viral genes a few samples with HPV33 methylation only was detected.

Conclusions: Current methylation panel provided only slightly better triage than pap-cytology or HPV 33/51/52/59 genotyping for HPV-vaccinated women. The true progression potential of HSIL among HPV-vaccinated women warrants further investigations.

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#5508

EPIGENOME-WIDE ASSOCIATIONS BETWEEN METHYLATION AND PROGRESSION TO HIGH-GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN2+): A PROSPECTIVE CLINICAL COHORT STUDY

18 - Methylation

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Background/Objectives: Methylation levels at CpG sites throughout the human genome may serve as clinical biomarkers to predict progression of precancerous cervical lesions. Few studies have prospectively assessed methylation-associated progression risk in screening-detected cervical abnormalities, which could improve screening algorithms. We conducted an epigenome-wide association study (EWAS) of CpG methylation and progression to high-grade cervical intraepithelial neoplasia (CIN2+) in individuals with normal or low-grade (CIN1) histology after an abnormal screening test in the United States (US).

Methods: A prospective, multiracial US cohort of 291 colposcopy referral patients with normal (n=188) or CIN1 (n=103) enrollment histology was assessed. DNA in baseline cervical samples was analyzed with the Illumina Human Methylation 450K (n=77) or EPIC 850K (n=214) array. Participants returned at provider-recommended intervals and were followed for up to 5 years via medical records. "Progression to CIN2+" was defined as CIN2 or 3 histology or—in the absence of histology—high-grade or "cannot exclude high-grade" cytology. We assessed associations between continuous methylation M value of CpGs of 9 pre-selected genes and time-to-progression to CIN2+. We estimated CIN2+ hazard ratios (HR) for each CpG with Weibull accelerated failure time (AFT) models for interval-censored data, adjusted for age, race, and 2 constructed surrogate variables. We conducted an exploratory EWAS with similar AFT models. Significant CpGs (Benjamini-Hochberg $p<0.05$) were mapped to genes, biologic functions, and phenotypes using Illumina annotation, National Library of Medicine Gene, and EWAS Catalog.

Results: Median age was 29.2 years at enrollment; 63.9% were high-risk HPV-positive, and 54.3% identified as a non-White race. During follow-up (median 24.1 months), 20 participants progressed to CIN2+. Two pre-selected CpGs were associated with faster times to CIN2+: Each 1-unit increase in PAX1-related cg07213060 M value was associated with a 16-fold hazard of progression (HR 16.7; 95% CI 2.6, 109.5), and each 1-unit increase in DAPK1-related cg14286732 M value was associated with a 3-fold hazard (HR 3.1; 95% CI 1.0, 9.5). The EWAS found 39 novel progression-associated CpGs; of these, 21 mapped to genes that have associations with other cancers.

Conclusions: Our study confirmed previously reported associations between PAX1 and DAPK1 CpGs and cervical disease progression with prospective time-to-event data, and we found novel CpGs associated with time to CIN2+. Methylation biomarkers may help identify individuals with normal or low-grade histology who have different progression risks and inform risk-based cervical cancer screening guidelines.

FC22- Free communications- Screening / HPV testing 2

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#5000

A nationwide trial of rapid elimination of HPV and cervical cancer

10 - HPV screening

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Background/Objectives: LS Arroyo Muhr, E Hultin, E Yilmaz, C Lagheden, M Vikström, A Ure, R Martinez, M Elfström & J Dillner Aim: To achieve an as rapid extinction of circulation of the major oncogenic HPV types as possible. Setting: Sweden. School-based vaccination has a 90% coverage of girls and 85% coverage of boys. Catch-up vaccination up to age 18 has had a 60% coverage. Cervical screening uses HPV testing starting at age 23, with very high coverage (>90%) in the younger ages. Pre-vaccination HPV prevalences (14 types) in ages 23-29 were close to 30%, with 6% HPV16 and 3% HPV18.

Methods: Design: All women in the country ages 23-28 are offered no-cost nonavalent HPV vaccination and concomitant HPV screening with extended genotyping. Women positive for vaccine HPV types are followed-up in the screening program. All women are invited for a repeat visit 3 years later. Hypotheses: At follow-up, we will assess i) whether the oncogenic HPV types covered by the vaccine are still detectable in the Swedish population and ii) whether there has been a decline in cervical cancer.

Results: Preliminary results: The population-based HPV prevalences at enrolment (concomitantly with vaccination) were 2.1% HPV16, 0.5% HPV18, 3.9% HPV45, 11.6% HPV31/33/52/58 and 11.4% HPV35/39/51/56/59/66/68 (in this age group, these low-oncogenicity HPV types are no longer targeted by the screening program in Sweden). The decline of HPV16 and 18 prevalences are in agreement with modelling predictions of the effect of a 60% quadrivalent vaccine coverage. The prevalence of the "other" HPV types appears to not have been significantly affected by quadrivalent HPV vaccination. Modelling also predicts that a population-based nonavalent HPV vaccination campaign reaching at least 65% coverage will (on top of the previous 60% coverage of quadrivalent vaccine) result in an extinction of the 7 major oncogenic HPV types.

Conclusions: Conclusion: Assessing whether a campaign with concomitant HPV vaccination and HPV screening of young women is followed by elimination of HPV and cervical cancer could be helpful for design of strategies for accelerated cervical cancer elimination.

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#4928

REDUCED HPV PREVALENCE IN THE SECOND ROUND OF HPV SCREENING IN NORWAY

10 - HPV screening

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Background/Objectives: The Norwegian human papillomavirus (HPV) screening pilot with quinquennial screening interval was initiated in 2015 and replaced primary cytology screening with triennial screening interval. Women who tested HPV negative in the first round have now been invited for their second round. The objective of the study was to present performance indicators from the second round.

Methods: Real world data from women aged 34 to 69 years participating in the Norwegian cervical cancer screening programme (CervicalScreen Norway) is included in the study. The women are divided into three different cohorts: Cohort 1 consists of women with a second round of HPV screening, i.e. a negative HPV-test in 2015 and a new HPV screening test five years thereafter (13 966 women). In cohort 2, women who participated in HPV screening for the first time in 2020 are included, i.e. women with a screening test with a normal cytology result in 2017 and a primary HPV screening test three years thereafter (19 723 women). Women in cohort 3 overlap with women in cohort 1, but only screening results from the first round of HPV screening in 2015 are used (27 374 women). HPV-positive women were referred to a gynecologist at baseline if their cytology triage test showed high-grade abnormalities, low-grade abnormalities and HPV16/HPV18 positive or after a retest (early recall) at 12 or 24 months if they had persistent HPV infection (genotype independent). Histology results reported within nine months after the screening test or retest indicating referral to gynecologist, are included in the analyses.

Results: A reduced HPV positivity rate was observed in the second round of HPV screening, 3.6% for cohort 1 compared to 5.6% for cohort 2 and 6.7% for cohort 3. A decreased proportion of HPV16/HPV18 was observed in cohort 1 (18%), as compared to cohort 2 (23%) and cohort 3 (28%). The recommendation based on the screening test results showed 30% reduced baseline referral to gynecologist among the women with a HPV-positive test in cohort 1 (17%) compared to cohort 3 (25%). Preliminary histology data indicates a reduced morbidity in the second round of HPV screening. Updated histology results will be presented.

Conclusions: These data show a reduced HPV prevalence and decreased baseline referral to gynecologist in the second round of HPV screening.

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#4930

THE 2022 GLOBAL HPV DNA TYPING AND HPV SCREENING PROFICIENCY STUDIES

09 - HPV testing

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Background/Objectives: The International HPV Reference Center supports quality and order in HPV research and diagnostics. Notably, the center assigns HPV type numbers to novel HPV types, maintains a reference clone repository, and issues international proficiency panels for HPV genotyping and screening. In 2022, we issued two different proficiency panels: The HPV DNA genotyping panel assesses the proficiency of the different HPV typing assays as used in different laboratories. The HPV DNA screening panel assesses the sensitivity and specificity of the various HPV screening assays, as used in different laboratories.

Methods: Participating laboratories were asked to perform HPV testing using one or more of their usual assays on coded samples composed of purified whole genomic plasmids of sixteen HPV types (HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68a and 68b) in a background of human cellular DNA. Proficient genotyping requires detection in both single and multiple infections of 50 International Units of HPV 16 and HPV 18 DNA/ 5ul and 500 genome equivalents in 5 ul for the other types, with no false positive results. The screening study has the same requirements for HPV 16 and HPV 18. HPV 31, 33, 45, 52 and 58 are also include as single infections, whereas HPV types rarely found in cancers are included only as pools.

Results: The 2022 genotyping proficiency study was subscribed to by 73 different laboratories worldwide. The screening study had 92 panels distributed, particularly to laboratories from Latin America, Europe, and Asia. Both public health laboratories, research laboratories and diagnostic test manufacturers are participating.

Conclusions: A continuing global proficiency program will promote reliable laboratory services both for genotyping in HPV vaccine research and monitoring as well as for HPV-based cervical screening.

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#4457

DIAGNOSIS OF CERVICAL CANCER IN REGION SKÅNE, SWEDEN 2017-2020 AFTER THE IMPLEMENTATION OF PRIMARY HPV SCREENING: A QUALITY ASSURANCE AUDIT

10 - HPV screening

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Background/Objectives: Primary HPV screening to detect cervical cancer was implemented in Region Skåne 2017 for women aged 30-70. The aim of this study was to investigate the screening history of women diagnosed with cervical cancer to evaluate the efficacy of the screening programme.

Methods: We performed a quality assurance audit. The data was collected from the National Cervical Cancer Prevention Registry, Region Skåne Labmedicin database and Melior Journal system.

Results: We identified all 249 women diagnosed with cervical cancer in Region Skåne in 2017-2020. Out of these, 34 (13.7%) had a screening history over at least two screening rounds before diagnosis. There were 26 (10.4%) women diagnosed with cervical cancer in between screening intervals, i.e. interval cancer. The most common main explanation for development of cervical cancer was non-participation in the screening programme, 144 (57.8%), followed by 45 (18.1%) women above screening age. HPV was expressed in 95% of the cervical tumours. The screening programme detected 38.6% of the patients, 60.6% were diagnosed through symptoms and 0.80% were incidental findings.

Conclusions: The most powerful tool in the secondary prevention of cervical cancer is attendance to the screening programme and prolongation with HPV screening amongst elderly women.

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#4843

Validation of an HR-HPV proficiency panel by the Belgian National Reference Centre for HPV: concept and pilot projects.

23 - Diagnostic procedures / management

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Background/Objectives: To guarantee high quality standards in a diagnostic routine setting, it is mandatory and insightful for laboratories to participate in EQC-schemes. In the fast-growing field of HPV diagnostics, new laboratories start participating in screening due to shift towards primary screening, combined with a tendency towards extension of genotyping, a strong need for a broadened HPV EQC panel is rising. To this end, the Belgian National Reference Centre (NRC) for HPV has developed an EQA-concept, fulfilling the current needs, and tested it in two pilot schemes with all accredited Belgian HPV-testing laboratories. The aim of these pilot projects was to standardize and define minimum criteria for samples to be included in an in-house developed EQA-scheme. Furthermore, confirmation of feasibility to produce and validate such EQA scheme, including timely distribution, was a study endpoint.

Methods: This non-plasmid based EQA-scheme was developed from anonymized leftover cervical LBC samples, and after obtaining informed consent. Hereto, strong positive samples, as determined by the quantitative Riatol qPCR full genotyping assay, were selected to have coverage of all hrHPV types. Interpretation of results was done using an AI-based algorithm, ensuring objective genotype calling. These samples were diluted and combined to obtain a final volume sufficient to provide all accredited Belgian HPV testing laboratories an aliquot for further processing. The panel was extensively validated for presence of HR-HPV genotypes at the level of repeatability, reproducibility, robustness, and uniformity of aliquot preparation before sending to the participating laboratories. Extended sample evaluation was done on 3 different HPV assays, including the WHO IARC assay considered as gold standard. Only samples with 100% concordant results between the different assays were selected. Stability was confirmed weekly for 5 weeks. To simulate robustness, transport to Sciensano and back was organized prior to testing. A penalization scheme at different levels, i.e. clinical, genotyping, and analytical level, was prepared and used for objective interpretation of results. Distribution of the panel and result analysis was facilitated by the Quality of Laboratories service (Sciensano).

Results: Out of 20 samples who fulfill the robustness criteria, 12 samples were selected hereby generating a well-defined and balanced EQC panel. The final panel consisted of 2 negative samples and 10 samples comprising at least 1 HPV type. Special attention was given to HPV 16/18, also including samples having low viral load, but the majority of samples were positive for other HPV types or contained multiple HPV genotypes.

Conclusions: It can be concluded that in two consecutive pilot projects, the Belgian NRC has been able to produce a robust EQA-panel for hrHPV genotyping. This feasibility project has made a first attempt to define guidelines how to validate EQA-samples and has hereby set criteria to be fulfilled by samples to be part of an EQC scheme.

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#4995

SCREENING AND VACCINATION: RESULTS ON NUMBER OF VACCINE DOSES FROM THE ITALIAN STUDY EVALUATING BEST STRATEGIES ON HOW TO SCREEN VACCINATED WOMEN

10 - HPV screening

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Background/Objectives: The first women invited for HPV vaccination when 16 years old in Italy in 2007/08 reached the age for cervical screening (25 years) in 2017. Preliminary results were previously reported (Carozzi et al Eurogin 2021). We now consider, on an accrued population, the effect impact of the number of vaccine doses on type-specific HPV infection, detection rate and positive predictive value (PPV)

Methods: Women born in 1993-1996 and invited for routine screening in the Florence, Turin and Savona organised screening programmes in 2018-2021 were eligible after informed consent. They were tested for high-risk HPV by Hybrid Capture 2 or Cobas and genotyped by Anyplex. Positives were triaged by cytology and if ASCUS+ referred to colposcopy. Infection prevalence analysis considered infections, not women. CIN2+ cases were hierarchically attributed to the pool of HPV16 and 18 or to that of HPV31,33 and 45 or that of other types and used for PPV computation with infected women having attended colposcopy attributed in the same way as denominator. The study was approved by Ethical Committees

Results: Of 12,761 enrolled women with valid genotyping data, 4421 had no vaccination, 139 one dose and 8201 ≥2 doses. Comparing women vaccinated with ≥2 doses to the unvaccinated the relative infection prevalence (RIP) was 0.02 (95%CI 0.01-0.05) and 0.09 (0.04-0.21) for HPV16 and 18 respectively, 0.30 (0.23-0.39), 0.77 (0.55-1.17) and 0.46 (0.31-0.66) for HPV31,33 and 45 respectively and 1.03 (0.94-1.12) for the pool of all other genotypes. Among women who just had one dose of vaccine no infection by HPV16 or 18 was detected (p=0.0022 for HPV16 1 dose vs no vaccination). However, no other significant prevalence reduction vs. no vaccination was observed. When comparing 1 to ≥2 doses RIP was 4.49 (2.12-9.50), 0.73 (0.10-5.20) and 1.18 (0.16-8.48) for HPV31, 33 and 45 respectively. When comparing ≥2 doses to the unvaccinated the relative PPV for CIN2+ (RPPV) was not significantly different from 1 for the pools of hpv16/18 (1.32;0.49-3.65), HPV31/33/45 (0.97;0.47-3.56) and all other high-risk types (1.78; 0.89-3.56) but borderline for the pool of all HPV infections (0.71, 0.51-1.01). However with a single dose the PPV for the pool of 31,33,45 was significantly increased both vs. no. vaccine (3.04;1.21-8.21) and 2-dose vaccination (3.15;1.22-7.55). The same happened for the pool of all infections.

Conclusions: Vaccination with ≥2 doses caused a strong decrease of the infections by the types most progressive to high-grade lesions, resulting in an average reduction of PPV in these women despite substantial stability within type. Vaccination with a single dose show good protection against the directly targeted types but data suggests that cross protection vs. hpv31/33/45 needs increased immuno-stimulation by further doses. The increased PPV for CIN2+ was unexpected

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#4984

NEXT GENERATION SEQUENCING (NGS) AND COBAS HPV TEST TO ANALYSIS OF HIGH-RISK HPV TYPES IN EUROPEAN AND LATIN WOMEN: PRELIMINARY RESULTS FROM THE ELEVATE STUDY

14 - Genotyping

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Background/Objectives: The main etiological factor of cervical cancer and its precursor lesions is a persistent human papillomavirus (HPV) infection. This virus can be classified into several levels: genus, species, type, subtype, and variants, which can be divided into lineages and sub-strains according to the percentage of genetic similarity. This study aims to identify hr-HPV types in women in Ecuador, Brazil, Portugal, and Belgium with different cytological results.

Methods: The hr-HPV genotyping was performed using Next Generation Sequencing (NGS) (Ampliseq manually and Ion Torrent S5) for the E6/E7 genes, with a workflow developed in the QIAGEN CLC Genomics Workbench 21 platform, in which the alignment was made against the 14 hr-HPV. The Cobas® 4800 HPV Test is used as the gold standard method.

Results: Up to now, the Cobas® 4800 HPV Test was performed in 892 samples: 245 Brazilian, 255 Ecuadorian, 220 Belgian and 177 Portuguese. The positive is 42% and the majority samples is positive to HPV others followed by HPV 16. In relation to NGS, to date 753 samples have been sequenced: 195 Brazilian, 124 Ecuadorian, 199 Belgian, and 118 Portuguese. These samples correspond to 254 high-grade lesions, 204 low-grade lesions, and 297 normal samples. The overall positivity rate is 47%. These samples correspond to 254 high-grade lesions, 204 low-grade lesions, and 297 normal samples, with the positivity of 49%, 31%, and 20% respectively. In 25% of these positive samples, multiple HPV were found: 17% with 2 hr-HPV, 7% with 3 hr-HPV, 1% with hr-HPV and 0,3% with 5 hr-HPV. The most present HPV types were HPV 31 (12%), 16 (10%), 56 and 58 (9% each), and HPV 66 (14%), 16 (13%), 31 and 59 (12%), and HPV 59 (16%), 31 (13%), 16 and 52 (12% each), respectively in high-grade lesions, low-grade lesions and normal samples. In Belgium, most frequent hr-HPV types found overall are 31 and 66 (16% each), 56 (11%) and in high-grade lesions are HPV 31 (16%), 66 and 56 (12% each). In Brazilian samples, overall, HPV 16 (16%), 59 (15%) and 31 (12%) were most detected; HPV 16 (17%), 31, 35, and 56 (11% each) were most frequently in the high-grade lesions. In Ecuador, HPV 16 (28%), 59 (14%) and 52 (10%) are the types most frequent overall and in high-grade lesions (35%, 10% and 10%). In the Portuguese samples, HPV 51 (16%), 16 and 52 (14% each) were most frequent, with HPV 16 (33%), 66 (20%) and 45 (13%) most commonly found in high-grade lesions.

Conclusions: Identification of HPV types present in cervical lesions is important in order to monitor the impact of vaccination and plan further vaccination and screening strategies, considering the different vaccines used in the countries.

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#4936

VALUE OF A CATCH-UP HPV TEST IN WOMEN AGED 65 AND ABOVE: A POPULATION-BASED NON-RANDOMIZED INTERVENTION STUDY

40 - Public health

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Background/Objectives: In several countries, high-risk human papillomavirus (HPV) test has replaced cytology as the primary cervical cancer screening test due to superior sensitivity, but in most countries women over 65 years have never had a HPV test. We evaluated the effectiveness of a catch-up high-risk human papillomavirus (HPV) cervical cancer screening test among 65-69-year-old women with no previous record of HPV-based screening.

Methods: This population-basednon-randomized intervention study included Danish women aged 65-69with no record of cervical cancer screening in the previous ≥ 5.5 years and no HPV-exit test at age 60-64.Eligible women residing in the Central Denmark Region were invited for a catch-up HPV test either by attending clinician-based sampling or requesting a vaginal self-sampling kit (intervention group). Women residing in the remaining four Danish regions received standard care which was the opportunity to have a cervical cytology collected for whatever reason (reference group). Main outcome measures were screening uptake and detection ofcervical intraepithelial neoplasia (CIN) grade two or worse (CIN2+) per 1,000 women eligible for the screening offer with 95% confidence intervals (CIs).

Results: The study population consisted of 11,192 and 33,387 eligible women in the intervention and reference groups, respectively. In the intervention group, 6,965 women (62.2%) were screened, while 743 (2.2%) women had a record of a cervical cytology in the reference group. The CIN2+ detection was significantly higher in the intervention group (3.9, 95% CI: 2.9 to 5.3, n=44/11,192) as compared to the reference group (0.3, 95% CI: 0.2 to 0.6, n=11/33,387).

Conclusions: The intervention was associated with high screening uptake and resulted in 13-fold higher CIN2+ detection but longer follow-up is necessary to observe if the intervention translates into fewer cervical cancers and deaths in the screened women. Decisions on whether women aged 65 and above should be offered a catch-up HPV test may depend on the available resources and attitudes to cervical cancer risk in each country.

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#5097

Cervical cancer screening by visual inspection and HPV testing in Eswatini

10 - HPV screening

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Background/Objectives: Cervical cancer remains a significant public health problem, with 604,127 new cases and 341,831 deaths occurring annually worldwide. Eswatini (formerly Swaziland) has the highest incidence of cervical cancer, where approximately 6.5% of women develop cervical cancer before 75 years of age, and 35% of women aged 15-49 years are affected by the human immuno-deficiency virus (HIV). In 2009, visual inspection with acetic acid (VIA) followed by cryotherapy (VIA-and-cryotherapy), was introduced into the Eswatini cervical cancer prevention programme. Therefore, the study aim was to establish cervical cancer screening using visual inspection and HPV testing in Eswatini.

Methods: : We present screening results of 654 women attending VIA-and-cryotherapy who participated in a sexually transmitted infections prevalence study, at which samples for HPV DNA testing and liquid-based cytology (LBC) were also collected. VIA positives (VIA+) ineligible for cryotherapy, suspected cancers and women with high-grade squamous intraepithelial or worse lesions (HSIL+) on LBC were referred for diagnosis and treatment. Women with negative VIA who were HPV positive (HPV+) and those VIA+ treated with cryotherapy were recalled for another VIA one-year later.

Results: The positivity rates of VIA, HPV, atypical squamous cells of undetermined significance or worse cytology abnormalities (LBC ASCUS+) and low-grade squamous intraepithelial or worse lesions (LBC LSIL+) were 9.7%, 42.6%, 13.2% and 5.3%, respectively. HPV testing detected 29 of 31 LSIL+ (93.6%, 95%CI: 78.6-99.2) while VIA only detected 11 (35.6%, 95%CI: 19.2-54.6). The HIV prevalence was 43% (95%CI: 39.2-46.9). HIV positives were at increased risk of being VIA+ (age-adjusted odds ratio: 2.5, 95%CI: 1.5-4.3), HPV+ (3.7, 2.6-5.3) and having LSIL+ (16.3, 4.9-54.8). The ineligibility rates for cryotherapy were 38% (24 of 63 VIA+), and 46% among HIV positives (18 of 39 VIA+).

Conclusions: testing was substantially more sensitive than VIA, thus, HPV followed by ablative treatment may be more effective. However, the high ineligibility for cryotherapy highlights the need for improving the assessment of eligibility, particularly in populations with high HIV prevalence.

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