EUROGIN 2021 ABSTRACTS

MAIN CONGRESS PROGRAM

WS01 - Cervical Cancer Screening Organization Around the World

#2428

38 - Public health

CERVICAL CANCER SCREENING IN FLANDERS (BELGIUM)

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Background/Objectives: Before 2013, screening was largely opportunistic. In June 2013, an organized screening program was set up in the Flemish Region. The program is financed by the Flemish government. A call-recall system has been developed, whereby only women are invited who are due for screening. Women recently screened are therefore not invited. The screening program uses a centralized invitation procedure; all invitation letters are sent out by the Centre for Cancer Detection. The organisation and monitoring the quality of the screening program is done through an extensive collaboration with the Belgian Cancer registry, which is done in accordance with the General Data Protection Regulation.

Methods: The database of the Belgian Cancer Registry (BCR) consists of the cancer database and a central cyto-histo pathology registry (CHP) with all results of cervical samples delivered by laboratories. This CHP includes cytology, HPV results as well as all histological results, regardless of the diagnosis. The data bases are supplemented with reimbursement data of medical acts relevant for cervical pathology.

Results: In 2019 6.2% of the target population was covered by exclusion, due to removal of the cervix or an invasive tumour in the past. The total coverage was 64.8%. The coverage of the youngest age group (25-29y) declined with 4% since 2013. Women in poverty participate less as measured with three proxy indicators: being entitled to higher reimbursement, not having a paid job, and a low level of work intensity of household level. Furthermore, uptake was less among immigrants, especially among women from Eastern Europe origin, and among women with a disability. After a tumour is diagnosed, the stage distribution differs according to the screening profile of the women. For screened women, 71.6% is stage I. For unscreened women, more tumours are seen in a more advanced stage and only 40% in stage I. Between 2015-2018 the follow-up rate (FUP) of abnormal screening smears fluctuates around 80%, but varies strongly depending on the diagnosis and the corresponding HPV result. To improve the FUP rate, a fail-safe system was set up in 2018. Both GMD-GP, the GP who manages the central medical record, and the doctor who took the sample received a letter in their secured electronic mailbox. After 1 year, the fail-safe system was evaluated and showed that 54 % of the women had a FUP.

Conclusions: Specific efforts are needed to achieve equity in the program. The FUP needs to be, improved, so that more women with an abnormal screening result will receive adequate follow-up.

#2471

9 - HPV screening

Organization of screening in Italy

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Background/Objectives: In Italy screening program for cervical cancer is actived from 1996 at National level in agreement with Regions . In 2001 the Ministry of Health established the National Screening Observatory, which has the task of monitoring the progress of screening throughout the country and Screening has also been included in the LEA that is the primary level of care.The target population, women 25-64 year old , are actively invited by letter and women with abnormal test are followed free of Charge. Every year an annual survey is elaborated by the National Screening Observatory in collaboration with the scientific societies of the sector, in particular with Gisci (Italian Group for cervical cancer screening).

Methods: After the publication of the major results of NTCC (a big study on HPV as primary screening conducted in Italy) in 2012 we published a Health tecnology assesment report on hpv that support the introduction the HPV test as primary test starting not before 30-35 years of age. So in 2013 Ministry of Health recommends HPV screening in women from 30-35 years .The target age of the creening is confirmed 25-64 years: HPV test is introduced in women from 30-34 years to 64 every 5 years while In youger women , Pap test continues to be the screening test every 3 year. In all age group HPV testing is introduced in the follow-up of women treated for CIN2 lesions e in women with abnormal pap test but negative at assessment (colposcopy).In 2015 the National Prevention Plan set as objective for cervical cancer screening to complete the transition from Pap to HPV within 2019 in all Italy.

Results: A first National HPV screening Survey was conducted in 2014 as part of the annual survey of Cervical Cancer Screening by organized programmes. A complete HPV survey is available 2 years after invitation because the complete results are available when 1 year recall results are completed (HPV positive and PAP triage negative at enrolment). So In 2020 we have overall results from women invited in 2018. In 2020 all Italian regions had activated the HPV program but some only on certain areas and in 2021 Covid clearly slowed coverage in the missing areas .

Conclusions: As required by the Italian and European LLGG, the transition to HPV has also provided a strong reorganization of laboratory activities. with a centralization of HPV tests and triage pap tests in a few laboratories per region.In Tuscany we have only one regional laboratory for cancer prevention that performs all the HPV tests in the region (about 120,000 per year).In Piedmont we have two screening laboratories, in Emilia Romagna 3, in other regions (especially in the south the centralization has been less strong. All laboratories use HPV tests validated for screening and a External quality assurance program for HPV e Pa p Test was implemented.

HN01 - Epidemiology and Screening

#2285

29 - HPV and oropharynx / Head and neck cancer

COST-EFFECTIVENESS OF OPSCC ELIMINATION

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Background/Objectives: HPV vaccination for girls was launched to prevent cervical cancer, but is expected to protect also against HPV associated OPSCCs and other HPV cancers. While providing herd protection for boys, the girls-only vaccination programs with moderate coverage still do not eliminate the crucial HPV types, or consequently, HPV associated OPSCCs, of which males have higher incidence. Finland set up an expert group to evaluate whether also boys should be included into the HPV vaccination program.

Methods: HPV related disease burden, including OPSCC, was estimated from nationwide health registers. A transmission model with the Finnish contact structure and associated disease models, calibrated to data from pre-vaccination era were used to project the disease burden with time for each HPV vaccination strategy: no vaccination, girls-only, and sex-neutral. Corresponding incremental cost-effectiveness ratios (ICER) with 3% discount rate were determined.

Results: The sex-neutral HPV vaccination with a moderate 70 % coverage was predicted to practically eliminate HPV-associated cancers in a long run. The predicted ICER for sex-neutral vs. girls-only HPV vaccination with 70% coverage was 4,000-23,000 EUR per QALY gained with European tender-based vaccine prices (15-40 EUR per dose).

Conclusions: Extending HPV vaccination from girls to boys is likely a cost-effective intervention, which has potential to eliminate HPV-associated OPSCCs, among other benefits. Consequently, boys were included into the HPV vaccination program in Finland in 2020.

HN02 - Management and Surveillance

#2455

29 - HPV and oropharynx / Head and neck cancer

Biomarker-based surveillance in HPV-associated OSCC

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Background/Objectives: The Incidence of HPV-associated oropharyngeal cancer (OSCC) is rising. The prognosis of this tumor type is better than the "traditional" type of head and neck squamous cell cancer caused by smoking and alcohol. But although the rate of recurrent disease or second primaries is lower the optimal surveillance strategy is still a challenge since recurrences do not typically occur in the first 2 years posttreatment but later and and can be observed in atypical sites.

Methods: There are no consensus guidelines on the frequency and modality of routine posttreatment imaging and no specific recommendations for HPV-associated disease. According to the literature, there is a questionable survival benefit for the use of routine FDG-PET scans especially if a 3 months FDG-PET is negative. Therefore, the question arises whether a blood-based surveillance test could have the potential to facilitate early detection of cancer recurrence. This has recently been demonstrated for bladder, breast and colorectal cancer using personalized circulating tumor DNA assays. In OSCC possible blood-based biomarker are antibodies against HPV-Oncoproteins, circulating Tumor HPV DNA, cell-free DNA (cf DNA) and circulating tumor cells (CTCs).

Results: Although antibodies against HPV-oncoproteins are reliable diagnostic markers, their use for posttreatment surveillance have constraints due to their long biological half-life leading to a slow-acting biomarker, potentially hampering the timely diagnosis of tumor recurrence. A very promising marker is the circulating Tumor HPV DNA. According to a study by Chera et al (2020) two consecutively abnormal ctHPVDNA tests had a NPV 100%, PPV 94%, sensitivity 100%, and specificity 99% to identify patients at highest risk for relapse. Disease recurrence was predominantly asymptomatic and could not be identified at clinical examination and ctHPV DNA levels responded to salvage therapy.

Conclusions: In conclusion a future algorithm for tumor surveillance could be based on pretreatment risk assessment by TNM, HPV-status of the tumor and the risk factor smoking and posttreatment surveillance consisting of a combination of a 3 months posttreatment FDG-PET-CT and if negative no further imaging but clinical and blood-based surveillance tests.

References: Chera BS, et al. Plasma Circulating Tumor HPV DNA for the Surveillance of Cancer Recurrence in HPV-Associated Oropharyngeal Cancer. J Clin Oncol 38:1050-1058. 2020.

HN04 - Molecular and Immunologic Considerations

#2454

29 - HPV and oropharynx / Head and neck cancer

Role of biomarkers in HPV-OPC treatment

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Background/Objectives: Incidences of oropharyngeal squamous cell carcinoma (OPSCC) are rising, which is attributable to a rising fraction of human papillomavirus (HPV)-related OPSCC. With 5-year overall survival rates of up to 80% in HPV-related OPSCC patients and high rates of side effects accompanying standard treatment, therapeutic deintensification is approaching. However, valid biomarkers for proper risk stratification of these patients are urgently needed to enable personalized therapy concepts while remaining favorable outcome.

Methods: Recent literature was reviewed for potential biomarkers that might play a role for risk stratification of HPV-related OPSCC patients.

Results: Multiple clinical and molecular biomarkers have been identified to this point. Still p16- and HPV-status remain the most important and valid predictors in OPSCC. Besides location of the OPSCC, further clinical factors for risk stratification are T-stage, extranodal extension and smoking status. Focusing on molecular biomarkers, integration status, viral load, methylations status, oxidative stress signatures, specific mutations as PIK3CA and NOTCH besides immunocharacteristics have been identified to have an impact on survival. New technological advances as whole-exome/genome sequencing or deep-learning algorithm will open up new possibilities.

Conclusions: Constantly growing incidence of HPV-related OPSCC require further investigation and understanding of the unique features of this disease. Multiple potential biomarkers have been identified in HPV-related OPSCC either treated with standard treatment or deescalated therapy approaches. Future studies will shed more light on the validity and their role in targeted treatment settings.

SS02 - HPV Vaccines Special Session

#2394

5 - HPV prophylactic vaccines

EMERGING DATA FROM THE POST-LICENSURE PROGRAM FOR THE 9-VALENT (9vHPV) AND QUADRIVALENT (QHPV) HUMAN PAPILLOMAVIRUS VACCINES

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Background/Objectives: The quadrivalent human papillomavirus (qHPV; HPV6/11/16/18) and 9-valent human papillomavirus (9vHPV; HPV 6/11/16/18/31/33/45/52/58) vaccines were initially licensed in 2006 and 2014, respectively, and are widely used and recommended for the prevention of cancers, precancers, and genital warts associated with the HPV types targeted by the respective vaccines. Licensure of these vaccines was based on demonstration of efficacy, immunogenicity, and acceptable tolerability in Phase 3 clinical trials of 3-5 years' duration. The post-licensure qHPV and 9vHPV vaccine programs include long-term follow-up (LTFU) extensions of clinical trials to evaluate the durability of vaccine effectiveness through 10-14 years post-vaccination across male and female clinical trial participants 9-45 years of age. In addition, data on the real-world impact and effectiveness of the qHPV vaccine against infection and disease have emerged following implementation of vaccination in the 15 years post-licensure. Finally, postmarketing safety data have been collected and analyzed since licensure for both vaccines.

Methods: N/A

Results: N/A

Conclusions: Results from LTFU extensions of clinical trials and real-world evidence studies support the long-lasting benefits of qHPV and 9vHPV vaccination for prevention of infection and disease related to vaccine HPV types. The real-world impact and effectiveness of qHPV vaccine and post-marketing safety experience with both vaccines have been generally consistent with observations from the clinical trial programs. Data from the qHPV and 9vHPV vaccine post-licensure program continue to confirm the favorable benefit-risk assessment established in clinical studies and support the use of these vaccines in broad immunization programs.

#2346

5 - HPV prophylactic vaccines

HPV vaccination coverage rates in 53 WHO European countries

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Background/Objectives: Success of National immunization program (NIP) in preventing vaccine-preventable diseases depends on several factors one of which includes vaccine coverage rates (VCR). Globally, the approach to measuring, reporting and monitoring VCR is heterogenous across different countries. The objective of the study was to describe the publicly available VCR data for HPV vaccination (HPVv) NIP in WHO Europe (WHO/ER) geographical region.

Methods: A targeted literature review of WHO database and country specific websites (e.g. ministry of health, public health authorities) was conducted between August 2018-September 2019 across WHO/ER countries (n=53). Data was retrieved on VCR (monitored and targeted) as reported including the target timeframe, population of interest and dosing schedule, when available. When monitored and targeted VCR were available for a country, the difference (monitored - targeted VCR) was calculated.

Results: Of the 53 countries in WHO/ER, 38 (72%) had an HPVv NIP. Of those 38, 29 (76%) had a monitored HPVv VCR reported for girls' primary cohort and 28 (74%) did not have a defined VCR target. VCR targets ranged from 60%-95%. Only one country reported VCR that exceeded its target (Portugal, VCR >85%). Of the 9 countries with VCR less than their target, the difference between the target and the monitored VCR ranged from 6%-71%. The lowest monitored VCR was reported in Bulgaria (4%), while the highest VCR was reported in Portugal (90%-94%). Lack of common definition of VCR limits the ability to directly compare VCRs across countries.

Conclusions: In WHO/ER, most countries with NIPs did not establish a VCR target, and a substantial number of countries do not have published national VCR. Establishing a target and monitoring progress towards achieving it may help countries improve protection of populations against HPV diseases.

#2300

5 - HPV prophylactic vaccines

LONG-TERM FOLLOW-UP (LTFU) STUDIES EVALUATING EFFECTIVENESS AND IMMUNOGENICITY OF THE QUADRIVALENT (QHPV) AND 9-VALENT (9VHPV) HUMAN PAPILLOMAVIRUS (HPV) VACCINES IN FEMALE CLINICAL TRIAL PARTICIPANTS

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Background/Objectives: Pivotal efficacy and immunogenicity trials of qHPV and 9vHPV vaccines (3-5 years [yrs] duration) were extended to provide ≥10 yrs LTFU.

Methods: Efficacy studies of qHPV and 9vHPV vaccines in women aged 16-26 yrs were extended as registry-based LTFU studies conducted in Nordic countries to evaluate qHPV (NCT00092534) and 9vHPV (NCT02653118) vaccine effectiveness against cervical disease over 14 yrs. Effectiveness was estimated by comparing observed vaccine HPV type-related disease incidence rates with expected rates from an unvaccinated population with similar risk level. Immunogenicity studies of the qHPV (N=614; NCT00092547) and 9vHPV (N=971; NCT00943722) vaccines in girls aged 9-15 yrs were extended to assess effectiveness against cervical and external genital persistent infection and disease over 10 yrs. The efficacy study of qHPV vaccine in women aged 24-45 yrs (NCT00090220) was extended (N=685) to assess effectiveness against cervical and external genital disease over 10 yrs. A 2-dose qHPV vaccine immunogenicity (NCT00501137) was followed in girls aged 9-13 yrs over 10 yrs. Primary analyses were performed in per-protocol populations (i.e., those uninfected at baseline).

Results: At 14 yrs post-vaccination in 16- to 26-yr-old women, there were no new cases of HPV16/18-related CIN2 or worse in qHPV vaccine recipients (n=2121) who contributed 24099.0 person-yrs of follow-up during the entire study. Vaccine effectiveness was 100% (95% CI: 94.7-100%) versus an age-/risk-matched unvaccinated population. At an 8-yr interim analysis, there were no new cases of HPV16/18/31/33/45/52/58-related CIN2 or worse in 9vHPV vaccine recipients (n=1448) during 4084.2 person-yrs of follow-up since start of the LTFU period; vaccine effectiveness was 100% (95% CI: 79.4-100%). In adolescent qHPV vaccine recipients, there were no cases of HPV6/11/16/18-related disease (maximum follow-up post-dose 3: 10.7 yrs; median: 10.0), and incidence rates of HPV6/11/16/18-related persistent infection remained within ranges observed in vaccinated cohorts of the qHPV and 9vHPV vaccine efficacy trials. Similar results were observed at an interim analysis of the ongoing 9vHPV vaccine LTFU study in girls (maximum follow-up post-dose 3: 8.2 yrs; median: 7.6). No new cases of HPV6/11/16/18-related CIN or genital warts were observed in 24- to 45-yr-old women during LTFU (maximum follow-up post-dose 3: 10.1 yrs; median: 8.7). Across studies, antibody responses persisted during LTFU.

Conclusions: Over 10-14 yrs, the qHPV and 9vHPV vaccines provided sustained protection from infection and disease related to vaccine HPV types across studies in girls and women aged 9-45 yrs.

#2303

5 - HPV prophylactic vaccines

LONG-TERM EFFECTIVENESS OF QUADRIVALENT (QHPV) AND 9-VALENT (9VHPV) HUMAN PAPILLOMAVIRUS (HPV) VACCINE IN MALE CLINICAL TRIAL PARTICIPANTS

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Background/Objectives: In a 3-year placebo-controlled trial, the qHPV vaccine demonstrated efficacy against HPV6/11/16/18-related anogenital disease in young men 16-26 years of age. In immunobridging trials, the efficacy of the qHPV and 9vHPV vaccine has been extrapolated to boys 9-15 years of age. These clinical trials were extended to provide ≥10 years follow-up for effectiveness post-vaccination in males 9-26 years of age.

Methods: The qHPV vaccine base study in young men (NCT00090285) was extended for 10 years total follow-up. During the base study, men aged 16-26 years were randomized 1:1 to receive 3 doses of qHPV vaccine or placebo. In the long-term follow-up (LTFU), participants (N=936) were assessed annually for HPV6/11/16/18-related external genital lesions (EGL), and men having sex with men (MSM) were also assessed for HPV6/11/16/18-related anal intraepithelial neoplasia (AIN) or anal cancer. Similarly, effectiveness against genital infection and EGL through 10 years of total follow-up was assessed in boys 9-15 years of age who received qHPV vaccine (N=565) or 9vHPV vaccine (N=301) in LTFU extensions of 3-year immunogenicity base studies (NCT00092547; NCT00943722). Primary analyses were performed in per-protocol populations.

Results: There were no new cases of HPV6/11/16/18-related EGL or HPV6/11/16/18-related high-grade AIN during LTFU among young men followed for qHPV vaccine effectiveness for up to 11.5 years (median: 9.5 years) post-dose 3. Among boys who received qHPV vaccine, there were no cases of HPV6/11/16/18-related EGL for up to 10.6 years (median: 9.9 years) post-dose 3. Similarly, there were no cases of HPV6/11/16/18/31/33/45/52/58-related EGL in boys who received 9vHPV vaccine for up to 8.1 years (median: 7.6 years) post-dose 3 at an interim analysis of the ongoing 9vHPV vaccine trial. In boys who received the qHPV or 9vHPV vaccine, incidence rates of HPV type-related external persistent infection (60 and 37 per 10,000 person-years, respectively) remained within ranges previously observed in the qHPV vaccine cohort of the qHPV vaccine efficacy study in men 16-26 years of age (59 per 10,000 person-years).

Conclusions: The qHPV vaccine provides durable protection from vaccine type-related anogenital disease and persistent infection through at least 10 years post-vaccination with the qHPV vaccine in males aged 9-26 years. Durable protection was also observed through at least 8 years post-vaccination with the 9vHPV vaccine in an ongoing study.

#2269

38 - Public health

DATA SYSTEMS UTILIZED TO ASSESS THE IMPACT OF HPV VACCINATION IN HIGH-INCOME COUNTRIES: A SCOPING REVIEW

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Background/Objectives: In 2019, the WHO launched plans to achieve the ambitious goal of eliminating cervical cancer as a public health problem globally. To support this goal, data systems need to be in place to monitor vaccine delivery, as well as infection and disease outcomes. The objective of this review was to identify and summarize the characteristics of existing data systems that monitor HPV vaccination outcomes within a set of high-income countries.

Methods: To ensure comprehensive identification of data systems, targeted searches of government and non-peer reviewed data sources including websites, repositories and reports, were supplemented by a systematic literature review of peer-reviewed publications for the select countries. All publications providing relevant information on data systems were included. Data systems reporting on vaccine delivery, vaccine coverage rate, HPV infection and disease outcomes were recorded, along with key characteristics of that data system. Data extracted included but were not limited to; the type of system, type of data recorded, frequency of data recorded, and population reported on. The presence and potential for registry linkage to provide robust information were additionally noted. The USA, Canada, Australia and countries within Europe including Sweden, France, Italy, and Scotland were identified for particular focus from scoping searches. These countries were chosen due to their wide range of established systems, thereby allowing the review to highlight different approaches to surveillance.

Results: Data systems identified in the review which monitored vaccine coverage included national immunization registries, electronic health records and claims databases. Infection and disease outcomes were further monitored by population-based registries, annual reports and self-report surveys. These methods of monitoring outcomes primarily focused on cervical screening and HPV-related cancer outcomes, with limited systems identified recording HPV infection and early onset HPV-related disease outcomes. The countries included highlight different examples of initiatives and therefore monitoring, with organized screening and vaccination versus opportunistic initiatives, and national versus regional surveillance for disease outcomes.

Conclusions: Overall, this summarization supports the design and development of future monitoring and evaluation systems, in settings where immunization programs may be at an earlier developmental stage, for example in low- and middle-income countries.

#2221

38 - Public health

REAL-WORLD IMPACT AND EFFECTIVENESS OF THE QUADRIVALENT HPV VACCINE: STUDY DESIGNS AND DATA SOURCES

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Background/Objectives: Vaccine impact and vaccine effectiveness (VE) studies are used to demonstrate real-world benefit of vaccination. As there is a delay between human papillomavirus (HPV) exposure and its many preventable outcomes, including cancer, real-world studies rely heavily on existing data sources and non-experimental study designs.

Methods: A systematic literature review was conducted to identify studies reporting on the impact and VE of the quadrivalent HPV (4vHPV) vaccine, with focus on data sources and associated study methods used. An evidence base of studies reporting on multiple disease endpoints, including HPV genital infections, anal/oral infections and lesions, cervical lesions, anogenital warts and recurrent respiratory papillomatosis was collected from March 2007 to March 2020.

Results: Among the 8,754 publications screened, 167 publications were identified describing 100 vaccine impact and 96 VE studies. Most publications utilized a cross-sectional study design (129/196, 66%), with either a single study or repeated cross-sectional studies. This design was used to investigate 71% of impact studies (71/100) and 60% of VE studies (58/96), and typically measured prevalence of HPV infection or cervical lesions at different time points (Table 1). Cohort study design was the second most commonly used methodology: they were typically conducted to evaluate impact (29/100, 29%) or VE (32/96, 33%) of HPV vaccination against AGW or cervical lesions. Six case-control studies were also identified. These were all VE studies, mostly investigating cervical lesions and of small sample sizes. Outcome data sources included electronic health records, claims databases, cancer screening registries and self-report surveys. Surveys were used most frequently for both impact (34/100, 34%) and VE studies (52/96, 54%), especially when analyzing HPV infections. Cervical screening, AGW and cancer registries were also frequent (impact 30/100, 30%; VE 26/96, 30%). Regarding vaccination status, impact studies primarily utilized vaccination coverage data at the national level, whilst VE studies often relied on self-reported vaccination status. Multivariate modelling and propensity score weighting were frequently used to mitigate for potential confounders such as sexual activity.

Conclusions: A large variety of data sources and study designs are being utilized globally to assess impact and VE of 4vHPV in real-world settings. Our collation and summary of these different methods provides a useful resource to support the design of additional real-world observational studies. Further, we highlight multiple options for evaluating impact and effectiveness, even in resource-limited settings.

Table 1

#2197

38 - Public health

REAL-WORLD IMPACT AND EFFECTIVENESS OF THE QUADRIVALENT HPV VACCINE: AN UPDATED SYSTEMATIC LITERATURE REVIEW

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Background/Objectives: Determining benefit of HPV vaccination in real world settings is challenging due to setting heterogeneity and need for long-term follow-up to assess impact on cancer, a key outcome. The impact and effectiveness of the quadrivalent HPV (4vHPV) vaccine ten years post licensing (2006-2015) was previously summarized in a systematic literature review (SLR) of 61 studies from 9 countries1, which demonstrated notable decreases in vaccine-type HPV infection and related diseases. Since then, continued vaccine implementation has led to availability of data with longer follow-up and program expansion has increased focus on disease endpoints beyond cervical cancer. Therefore, an updated summary is timely to guide vaccination initiatives worldwide.

Methods: A 4vHPV vaccine real world impact SLR (03/2016 to 03/2020) was performed to assess vaccine benefit using previously assessed endpoints (vaccine-type HPV genital infections, anogenital warts and cervical abnormalities) as well as new endpoints (recurrent respiratory papillomatosis, vaccine-type HPV oral/anal infections and oral/anal lesions). Studies were identified from peer-reviewed literature according to pre-defined search terms and selection criteria, with rigorous SLR protocols in place.

Results: Although covering half the time as the prior SLR1, the current SLR identified twice as many studies (N=122) and a 156% increase in countries reporting HPV vaccine impact across all endpoints (N=23). The current SLR identified substantial and statistically significant decreases in prevalence of HPV-type infection (up to 92%) and anogenital warts (up to 82%) among females of vaccine-targeted age groups. The level of decrease varied by cohort age, coverage rate, whether vaccine program included catchup and time since vaccination. There was also evidence of herd protection and cross-protection in men and women, and indication of vaccine benefit among males with gender-neutral vaccination. Vaccine effectiveness in preventing late-stage cervical lesions was well demonstrated, with up to 73% reduction in cervical intraepithelial neoplasia 3+ in vaccine-targeted females, with effectiveness varying according to doses received and age at vaccination. Fewer studies (16) reported on new endpoints; however, statistically significant decreased disease outcomes were shown for oral and anal infection, anal high-grade intraepithelial neoplasia, and juvenile onset RRP.

Conclusions: These data support elimination of cervical cancer and other HPV-related diseases as an achievable goal, especially in countries with high, sustained vaccine coverage and highlight the importance of 4vHPV vaccine as a key component in realizing that goal.

References: [1Garland SM, Kjaer SK, Munoz N, et al. Impact and Effectiveness of the Quadrivalent Human Papillomavirus Vaccine: A Systematic Review of 10 Years of Real-world Experience. Clin Infect Dis 2016; 63(4): 519-27.]

#2248

5 - HPV prophylactic vaccines

SAFETY OF 4-VALENT HUMAN PAPILLOMAVIRUS VACCINE AMONG MALES IN THE UNITED STATES

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Background/Objectives: The 4-valent human papillomavirus (HPV) vaccine (4vHPV vaccine), GARDASIL® was licensed in the US for females in 2006 and for males in 2009. The objective was to report general safety results from an observational self-controlled risk interval study of 4vHPV vaccine in males.

Methods: This study used a US health claims database. Males vaccinated with 4vHPV vaccine between 2009 and 2016 were followed for occurrence of any clinical outcome associated with emergency department (ED) visit or a hospitalization within a 60-day risk period after each administration and a subsequent 60-day self-comparison period. Outcomes were identified by diagnosis codes mapped into categories developed by the Healthcare Cost Utilization Project (HCUP). Within HCUP category, events in the risk and self-comparison periods were compared using relative rates (RR) and 95% confidence intervals (CI). Analyses were conducted for all vaccine doses combined, first dose only, and incident outcomes (those without a similar outcome in the prior year).

Results: Among 114,035 males who initiated 4vHPV vaccine (receiving 202,737 doses), there were 5 HCUP categories with significantly elevated RRs in the combined dose analysis: ear conditions (RR 1.28, 95% CI 1.03-1.59); otitis media (RR 1.65, 95% CI 1.09-2.54); cellulitis and abscess of arm (RR 2.17, 95% CI 1.06-4.72); intracranial injury (RR 1.23, 95% CI 1.01-1.50); and concussion (RR 1.29, 95% CI 1.05-1.59).

Conclusions: The study results are consistent with the known safety profile of 4vHPV vaccination and no new safety concern was identified. The association of vaccination with certain outcomes could be due to the seasonality of 4vHPV vaccination in adolescent males.

#2232

5 - HPV prophylactic vaccines

9-VALENT HUMAN PAPILLOMAVIRUS VACCINE SAFE IN ROUTINE USE: OBSERVATIONAL STUDY IN MORE THAN 140,000 INDIVIDUALS

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Background/Objectives: Nine-valent human papillomavirus (HPV) vaccine (9vHPV vaccine, Gardasil®9) was licensed in the United States in Dec-2014. Using a self-controlled risk interval design, we conducted a post-licensure cohort study within Kaiser Permanente in Northern California (KPNC) to assess the safety of 9vHPV following routine administration.

Methods: We included KPNC female and male members 9-years or older who received 9vHPV as their first dose of HPV vaccine between Oct-2015 and Sep-2017. We followed vaccinated individuals for all emergency visits and hospitalizations using diagnosis codes in the electronic health record. Codes were grouped into meaningful health outcome (HO) categories using the Healthcare Cost and Utilization Project (HCUP) hierarchical classification of ICD-10 codes. Rates of HO within risk intervals (days 1-60 or 0-14) following vaccination and during later self-comparison intervals were compared using conditional logistic regression, following all 9vHPV vaccine doses combined, and by dose. We investigated statistically significant findings by assessing post-vaccination timing and through medical record review. We evaluated and reviewed the medical records for all day 0 allergic reaction and syncope events, and all deaths during the study. An independent Safety Review Committee reviewed potential safety signals.

Results: We studied 140,628 9vHPV-vaccinated individuals, including 69,027 (49%) who received 2 doses and 29,901 (21%) 3 doses, totaling 239,556 doses. Eight HCUP categories were significantly increased in at least one analysis (Table). Upon review, most findings were previously known or preceded vaccination, or were better explained by other medical history. Some day 0 allergic reactions and syncope were potentially related to vaccination. None of the 20 deaths were considered related to 9vHPV. Table. Health outcome (HO) categories with statistically significant elevations in at least one analysis comparing risk and self-comparison intervals. HO Categories ORs (95% CI) Diabetes mellitus 1.66 (1.01, 2.74) Delirium NE (1.11, NE) Nervous system disorders+2 1.33 (1.02, 1.72) Digestive disorders+4 1.21 (1.03, 1.41) Male genital disease 1.60 (1.04, 2.46) Skin disorders+1 1.88 (1.00, 3.53) Congenital anomalies, nervous system 5.01 (1.10, 22.83) Symptoms, ill-defined+1 1.36 (1.13, 1.64) +n indicates number of elevated HCUP subcategories within each HCUP category, for a total of 16 elevated categories. NE: not estimable.

Conclusions: This large study of individuals who received only 9vHPV vaccine did not identify any new safety events related to 9vHPV administration and provides reassuring evidence of the favorable safety profile of the 9vHPV vaccine.

#2352

5 - HPV prophylactic vaccines

POSTMARKETING SAFETY EXPERIENCE WITH THE 9-VALENT HUMAN PAPILLOMAVIRUS VACCINE THROUGH DECEMBER 2019

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Background/Objectives: The 9-valent human papillomavirus (9vHPV) vaccine (HPV 6/11/16/18/31/33/45/52/58) is licensed for the prevention of cancers, precancers, and genital warts associated with the HPV types included in the vaccine. Postmarketing safety data have been collected since licensure.

Methods: The manufacturer's global pharmacovigilance database was queried for reports of adverse events (AEs) following vaccination, from licensure (10 DEC 2014) through 31 DEC 2019. Postmarketing reports of serious and nonserious AEs, including fatal outcomes and AEs of special interest, temporally associated with 9vHPV vaccination were reviewed. AEs of special interest including autoimmune diseases and chronic fatigue syndrome/post-viral fatigue syndrome (CFS/PVFS) were specifically reviewed to characterize any potential causal associations between vaccine exposure and these rare AEs. Reported events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Clinicians systematically reviewed medical information and reports to estimate reporting rates per million doses distributed, and to evaluate the AEs for potential causal association with vaccine exposure.

Results: Of >75 million 9vHPV vaccine doses distributed in more than 80 countries during the reporting period, there were 19,802 reports of AEs (263 reports per million doses distributed); these reports represent 52,702 events. Most reports were nonserious (17,912 reports; 90.0%) and related to female vaccine recipients (11,033 reports; 55.7%). Excluding medication error AEs, the 10 most common AEs reported were (in descending order) dizziness, syncope, headache, injection-site pain, pyrexia, nausea, pain in extremity, injection-site swelling, fatigue, and pain. Forty-four medically confirmed deaths were reported, with no clustering of diagnosis, age, geographic locations, or time to death. Case reviews of reports involving AEs of special interest (7 autoimmune diseases and CFS/PVFS) found confounding factors, implausible time to onset of symptoms, and/or limited clinical data precluding assessment in most reports. Thus, a causal relationship between the 9vHPV vaccine and the autoimmune diseases of interest or CFS/PVFS was not supported by these reports.

Conclusions: Findings were consistent with the established safety profile for the 9vHPV vaccine previously demonstrated in clinical trials. The majority of the most frequently reported postmarketing AEs were nonserious; all vaccine-related AEs were consistent with those described in the current product labels.

MSS02 - Comparing Immune Responses Induced by Different HPV Vaccines and HPV Vaccine Doses

#2450

19 - Serology

Sensitivity of Neutralizing HPV Antibody Response to Between and Within Type Variation

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Background/Objectives: Natural variants of Human Papillomavirus (HPV) have been classified into lineages and sublineages based upon their whole genome sequence. Variants exhibit both geographical bias in their distribution and differential disease risk and efforts are underway to understand the evolution of HPV variants from their prehistoric origins. The impact of HPV variant diversity on protein function and the potential consequences for vaccine immunity are unclear.

Methods: We investigated the susceptibility of 37 representative pseudovirus variants of HPV16, HPV18, HPV31, HPV33, HPV45, HPV52 and HPV58 to neutralization by bivalent, quadrivalent and nonavalent vaccine sera and monoclonal antibodies (MAbs).

Results: Neutralizing antibodies recognized most variants similarly. For each genotype, however, there was at least one lineage or sublineage variant that displayed a significantly reduced neutralization sensitivity to vaccine sera and/or MAbs, though these differences tended to be of a low magnitude. For genotypes HPV33, HPV52 and HPV58, one or more variants exhibited consistent and markedly reduced sensitivity to vaccine sera and MAbs.

Conclusions: For most genotypes, these data suggest that HPV vaccine antibodies recognize global variants similarly. However, these empirical observations provide support for the capsid proteins of some lineage variants of HPV33, HPV52 and HPV58 being antigenically distinct within their respective genotypes. The implications for vaccine effectiveness are uncertain.

MSS05 - Methylation Markers

#2474

17 - Methylation

HOST CELL DNA METHYLATION MARKERS FOR CANCER RISK STRATIFICATION OF HIGH-GRADE ANAL INTRAEPITHELIAL NEOPLASIA

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Background/Objectives: Human papillomavirus-induced anal cancer incidence is increasing worldwide. HIV-positive (HIV+) men-who-have-sex-with-men (MSM) have the highest incidence rates, but other (HIV-negative) risk groups are also at substantial risk of developing anal cancer. Precancerous lesions, called high-grade anal intraepithelial neoplasia (HGAIN; AIN2-3), are highly prevalent in risk groups. Yet, only a minority will eventually progress to cancer. Screening and treatment of HGAIN to prevent cancer in high risk groups is difficult, burdensome and under debate. Since the risk of progression cannot be established, current screening options result in substantial over-referral and overtreatment. Therefore risk stratification of HGAIN using biomarkers is needed.

Methods: We evaluated host cell DNA methylation markers for detection of HGAIN and anal cancer in a cross-sectional series of 148 anal cancer, AIN3, AIN2, AIN1 and normal control tissue samples of HIV+ men using quantitative methylation-specific-PCR. The best performing markers were validated in a large, independent cross-sectional series of 345 HIV+ samples and also evaluated in a cross-sectional series of 176 samples of HIV-negative women and men. Accuracy for detection of AIN3 and cancer (AIN3+) was determined by univariable and multivariable logistic regression analysis, followed by leave-one-out-cross-validation. The association with cancer progression was assessed in a longitudinal series of ten anal cancer cases with preceding HGAIN at similar anatomic locations.

Results: In all series of anal biopsies tested methylation marker levels increased with increasing severity of disease ($p<0.05$). A high resemblance was found between all patient groups. Histopathologically similar HGAIN revealed a heterogeneous methylation pattern, a subset resembling cancer. In HIV+ MSM a three-marker panel (ASCL1, SST, ZNF582) was most accurate (AUC=0.89) in distinguishing AIN3 and cancer from controls, not missing cancers. AIN3+ detection using these markers in HIV-negative women and men was comparable (AUC=0.85). In the longitudinal series, all HGAIN preceding cancer displayed high methylation levels similar to cancers.

Conclusions: We identified and validated methylation markers for the detection of anal (pre-)cancer in HIV+ MSM. Accurate AIN3+ detection was confirmed in HIV-negative patients. High methylation levels were associated with progression to cancer. Therefore, these methylation markers provide a promising cancer risk stratification tool for all risk groups of anal cancer. Methylation testing can identify HGAIN in need of treatment and prevent overtreatment of HGAIN with a low cancer risk.

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SS05 - VALidation of HUman papillomavirus assays and collection DEvices for HPV testing on Self-samples and urine samples (VALHUDES)

#2311

10 - Self-sampling

ATTITUDES AND PREFERENCES OF WOMEN REGARDING THE USE OF SELF-SAMPLING METHODS: RESULTS OF THE VALHUDES QUESTIONNAIRE

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Background/Objectives: Women who are under-screened or never-screened are at high risk for cervical cancer (CC). Endeavours to increase screening-participation in hard-to-reach women may reduce this risk substantially. Self-collection of a vaginal specimen has been shown to increase participation among under-screened populations. Clinical accuracy of HPV testing on first-void (i.e. initial stream) urine is being investigated in the VALHUDES trial. The current study assesses attitudes and experiences regarding self-sampling (vaginal specimen or urine) or collection by a clinician among women enrolled in VALHUDES.

Methods: Questionnaires from 515 women (age 25 - 64 years [N=502]; <25 [N=10], age ≥65 [N=3], enrolled between December 2017 - January 2020) referred to colposcopy because of previous cervical abnormalities and recruited within the framework of VALHUDES (NCT03064087) were analysed. Participants completed the questionnaire before and after carrying out self-collected first-void urine (using the Colli-Pee) and vaginal samples (using diverse devices) for HPV testing, and then a gynaecologist collected a cervical cell specimen.

Results: Of the 515 participants, nearly all women agreed with the statement that self-sampling is a good solution to reach under-screened women (93%). Nevertheless, our results showed that women have still hesitancy about self-sampling as 44% of them found, before executing self-sampling, that a clinician-collected cervical sample is better than a self-collected sample. After self-sampling, the majority of women (>95%) agreed with the clarity of the device instructions, the ease of collection, and were confident that they had executed the procedure correctly, for both urine and vaginal collection. Sixteen of participating women experienced vaginal sampling as unpleasant versus 10% indicated this for urine collection. For their next screening round, women would prefer self-sampling (57%, urine and vaginal self-samples combined) over a sample taken by a clinician (41%, gynaecologist or general practitioner). Among women preferring self-sampling, 53% would choose for urine collection, 38% for vaginal self-collection and 9% did not make a favourite choice. Bivariate analysis indicated that preferences for collection methods were not influenced by age.

Conclusions: Our results indicate that both urine and vaginal self-samples are well accepted by women, with a preference for urine sampling. Even, if women are confident in their ability to carry out self-sampling, some of them still prefer sample taken by a clinician.

SS06 - Immunology - Resistance Mechanisms to Immunotherapy

#2235

7 - Immunotherapy - Immuno-oncology - New treatments

DNA-BASED IMMUNOTHERAPHY FOR TREATMENT OF HPV-16 AND/OR 18 (HPV16/18) ASSOCIATED VULVAR HSIL: PHASE 2 OPEN LABEL TRIAL EFFICACY AND SAFETY RESULTS

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Background/Objectives: Management of vulvar high-grade squamous intraepithelial lesions (HSIL) remains challenging. Surgical treatments are disfiguring and at 3 years post-treatment have approximately a 30% lesion recurrence rate, and HPV infection presence of up to 45% [1]. This presentation [2] reports efficacy and safety data for VGX-3100 treatment from our Phase 2 proof-of-concept study of VGXâ€"3100, a DNA-based HPV16/18-specific immunotherapy, in women with HPV16/18-positive vulvar HSIL. Spontaneous resolution of VIN within a 12 month period is considered to be a rare occurrence (<2%) [3].

Methods: Women with tissue-confirmed HPV16/18-related vulvar HSIL received four (4) doses, one dose each at 0, 1, 3, and 6 months, of an investigational DNA-based immunotherapy, VGX-3100, intramuscularly with electroporation (EP), either alone (n=25) or with topical imiquimod (n=8) thrice weekly for 20 weeks. Efficacy endpoints included regression of HSIL, virologic clearance of HPV16/18, and lesion size reduction.

Results: 80% of the women in the VGX-3100 group had VIN3. Full demographics will be presented. Among the 20 women in the VGX-3100 only group who completed their efficacy assessment at 6 months following treatment, 3 (15.0%) resolved their vulvar HSIL (Table 1) and had no HPV16/18 detectable in the healed area. 12 of 19 women (63%) with evaluable lesion measurement results had clinically significant (i.e., greater than 25%) reduction in lesion area. There have been no related SAEs, no treatment discontinuations from AEs, and no cases of progression to vulvar carcinoma on the trial. The impact upon HPV-16 and HPV-18 multizonal infection will also be reported.

Conclusions: Results from this trial support that this DNA-based immunotherapy has a potential therapeutic effect on HPV16/18â€"associated vulvar HSIL. Given the high medical need and morbidities of surgery, the ability to reduce the burden of disease and optimize the management of vulvar HSIL with immunotherapy would represent a significant advancement.

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Table 1. Efficacy at 6 months after treatment, VGX-3100 Group

#2306

7 - Immunotherapy - Immuno-oncology - New treatments

AN ORGANOTYPIC IN VITRO MODEL OF HPV-ASSOCIATED PRECANCER FACILITATING PRECLINICAL DRUG TESTING

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Background/Objectives: Despite considerable knowledge about the molecular biology of HPV-induced carcinogenesis, no causal, targeted treatment options for HPV-related cancers or their precursor lesions are currently available. The development of effective yet tissue-sparing new treatment options and HPV tumor models that realistically reflect the in vivo treatment situation are urgently needed. We aimed to establish durable organotypic epithelial raft cultures (OTCs) resembling HPV-induced precancerous lesions.

Methods: HPV-transformed cells derived from cervical cancer cell lines were cultivated in conjunction with normal human keratinocytes. The epithelium was supported by a dermal equivalent comprising viable human fibroblasts, embedded in a collagen-free scaffold-based matrix. To demonstrate suitability of our model for preclinical drug application studies, we treated the OTCs with different compounds commonly used in the context of HPV-associated disease. After an initial culture period of 2 weeks, the drugs were either applied locally onto the air-exposed surface or into the growth medium. OTCs were repeatedly treated and observed over the course of up to 4 weeks, and subsequently harvested and processed as formalin-fixed paraffin-embedded specimens. Tissue sections were subjected to hematoxylin and eosin as well as immunofluorescence staining procedures to assess the tissue architecture and biological treatment consequences, such as proliferative activity and apoptosis.

Results: Three-dimensional OTC models of cervical precancerous lesions using HPV-16 and HPV-18-transformed cervical cancer cell lines were successfully created and optimized. Suitability of the developed models for the simulation of both systemic as well as topical treatment approaches could be demonstrated. The model allowed monitoring treatment effects in a three-dimensional context with differentiated consideration of the targeted HPV-transformed cells and surrounding normal epithelium for several weeks. Notably, if left untreated, the cells in the OTCs remained viable and proliferatively active for the whole observation period, which is of considerable importance for studying long-term treatment approaches.

Conclusions: The established model can serve as a valuable tool in analyzing major treatment endpoints, such as effectivenes on target cells and potential side effects on normal epithelium, and facilitate treatment schedule optimization in a preclinical setting.

#2524

4 - Immunology

Complete response of vulvar high-grade squamous intraepithelial lesions to different forms of immunotherapy depends on a pre-existing coordinated inflammatory microenvironmen

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Background/Objectives: Immunotherapy of vulvar high-grade squamous intraepithelial lesion (vHSIL) is investigated as an alternative for surgery, because of high comorbidity and risk of recurrence. Limited evidence exists on the role and composition of the immune microenvironment in current immunotherapeutic approaches for vHSIL.

Methods: The vHSIL of 29 patients biopsied before treatment with imiquimod were analyzed by two multiplex seven-color immunofluorescence panels to investigate the pre-existing T cell and myeloid cell composition in relation to treatment response. The samples were scanned with the Vectra multispectral imaging system. Cells were automatically phenotyped and counted with inForm advanced image analysis software. Cell counts and composition were compared to that of vHSIL patients before therapeutic HPV peptide vaccination (n=29) and to healthy vulva (n=27).

Results: Our data show that the immune microenvironment of complete responders (CR) to imiquimod resembled the coordinated infiltration with type 1 CD4+ and CD8+ T cells and CD14+ inflammatory myeloid cells also found in healthy vulva. However, more CD8+ T cells and FoxP3+ regulatory T cells were present in CR. The lesions of partial responders (PR) lacked such a coordinated response and displayed an impaired influx of CD14+ inflammatory myeloid cells. Importantly, complete responses after imiquimod or therapeutic vaccination both showed the same dependency on a pre-existing coordinated type 1 T cell and CD14+ myeloid cell infiltration.

Conclusions: In conclusion, a good clinical outcome after two different forms of immunotherapy for vHSIL is associated with the presence of a primary inflammatory process resulting in the coordinated influx of several types of immune cells which is then futher amplified. This could potentially be used as a predictive biomarker for repsonse of vHSIL to immunotherapy, and provides a rational foundation for future immunotherapy design in these patients.