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ADVANCING SCIENTIFIC EFFORTS TO CONTROL HPV-RELATED CANCERS

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ABSTRACTS

FREE COMMUNICATIONS SESSIONS

FC01 - HPV prophylactic vaccines I

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#9457

Incomplete Seropositivity Following a Single Dose of the Human Papillomavirus Vaccine

06 - HPV prophylactic vaccines

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Background/Objectives: In December 2022, the World Health Organization (WHO) updated its human papillomavirus (HPV) vaccine recommendations to 2 doses for individuals aged 9 years and older, with an option for a single dose through age 20 years (except for immunocompromised individuals). Based on several systematic reviews, the WHO position paper concluded that single-dose HPV vaccination induced high seropositivity rates for vaccine-targeted HPV types. However, this conclusion is based on a limited number of single-country, clinical studies mostly focused on HPV types 16 and 18. To assess the generalizability of these results, immunogenicity of the 9-valent (9v) HPV vaccine after dose 1 was evaluated in 2 international clinical trials.

Methods: Study 1 (V503-010; NCT01984697) assessed the immunogenicity of 2 doses given 6 to 12 months apart in girls and boys aged 9-14 years. Study 2 (V503-069; NCT04708041) assessed the immunogenicity of 2 doses given 1 to 5 years apart in girls and boys aged 9-15 years. The primary objective of both studies was to assess the immunogenicity of 2 doses in young adolescents compared with 3 doses in young women aged 16-26 years. However, immunogenicity analyses after dose 1 were planned on serum samples collected prior to the administration of the second dose. Antibody responses to each of the 9 vaccine-targeted HPV types were assessed using 2 immunoassays: measurement of HPV type-specific neutralizing antibodies by the HPV-9 competitive Luminex immunoassay (cLIA) and measurement of total immunoglobulin G (IgG) binding antibodies by the HPV-9 IgG Luminex immunoassay (LIA). Analyses were conducted in the per-protocol immunogenicity population.

Results: In Study 1, cLIA seropositivity at 12 months after dose 1 ranged from 31% to 93% (depending on the HPV type) in a cohort of girls and boys aged 9-14 years (n=300) and was lower than 90% for 7 HPV types. IgG LIA seropositivity ranged from 58% to 99% and was lower than 90% for 5 HPV types. In Study 2, cLIA seropositivity at 12 to 54 months (median 25 months) after dose 1 ranged from 27% to 60% in a cohort of girls and boys aged 9-15 years (n=146) and was lower than 90% for all 9vHPV vaccine types. IgG LIA seropositivity ranged from 51% to 97% and was lower than 90% for 6 HPV types. In another cohort of Study 2 comprising girls and boys aged 9-13 years (n=101), cLIA seroconversion at 1 month after dose 1 ranged from 83% to 100% depending on the HPV type. Seropositivity then gradually decreased, ranging from 64% to 96% at 6 months after dose 1, 39% to 87% at 12 months after dose 1, and 31% to 74% at 24 months after dose 1.

Conclusions: Immunogenicity analyses from 2 international clinical trials showed that seropositivity rates after a single dose of the 9vHPV vaccine varied depending on the HPV type. Incomplete seropositivity rates after dose 1 have also been reported in other studies. These observations suggest variability in seropositivity after 1 dose of the 9vHPV vaccine, which may depend on the study, the population and/or the individual, the time interval between dose 1 and the immunogenicity assessment, and the type of serologic immunoassay used. Further research on this topic is warranted.

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#9232

Effectiveness of quadrivalent human papillomavirus vaccination against high-grade cervical lesions by age and doses: a population-based cohort study

06 - HPV prophylactic vaccines

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Background/Objectives: One or two-dose schedule for human papillomavirus (HPV) vaccination has been recommended by the World Health Organization and used in many vaccination programs. We aimed to comprehensively evaluate the effectiveness of quadrivalent HPV vaccine against high-grade cervical lesions by age at vaccination and number of doses received.

Methods: This cohort study included 2,200,495 females aged 10 to 35 years old who were residents of Sweden between 2006 and 2022, with 584,676 (26·6%) receiving at least one dose of quadrivalent HPV vaccine. We used Poisson regression models to estimate the incidence rate ratios (IRR) comparing the incidence rate of high-grade cervical lesions in relation to age at vaccination and doses.

Results: In girls initiating vaccination before age 15, we observed IRRs of 0·42 (95% CI 0·33-0·52) after one-dose, 0·54 (0·47-0·63) after two-dose, and 0·50 (0·47-0·53) after three-dose. The IRRs were 0·60 (95% CI 0·52-0·70), 0·55 (0·49-0·62), and 0·54 (0·52-0·56) after one, two or three doses for girls who initiated vaccination age 15-17. For women who initiated vaccination after age 20, higher doses may be needed to achieve a statistically significant risk reduction.

Conclusions: Receiving one or two doses of HPV vaccines prior to age 17, especially for those initiating before age 15, has comparable effectiveness against high-grade cervical lesions with those who received three doses.

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#9184

Efficacy, Immunogenicity, and Safety of the 9-Valent Human Papillomavirus (HPV) Vaccine Administered as a 3-Dose Regimen in Japanese Males Aged 16-26 Years

06 - HPV prophylactic vaccines

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Background/Objectives: In Japan, the 9-valent HPV (9vHPV) vaccine is approved for females aged ≥9 years for prevention of HPV infection and disease related to HPV 6/11/16/18/31/33/45/52/58. The 9vHPV vaccine is not approved for use in males in Japan. We present results of a randomized, double-blind, placebo-controlled Phase 3 study (V503-064; NCT04635423) designed to evaluate the efficacy, immunogenicity, and safety of the 9vHPV vaccine as a 3-dose regimen in Japanese males.

Methods: Healthy Japanese males aged 16-26 years were randomly assigned to receive 3 doses of the 9vHPV vaccine or placebo (saline solution) given Day 1, Month 2, and Month 6. Anogenital swab specimens were collected Day 1, Month 7, and Month 12, and at 6-month intervals thereafter. DNA for 9vHPV vaccine types was identified by multiplex PCR. Biopsy samples of external genital lesions were collected after Day 1 and assessed by thin section PCR to detect HPV DNA and endpoint adjudication by a pathology panel. Serum was collected Month 7 to measure vaccine-targeted HPV type antibody responses by competitive Luminex Immunoassay. Primary and secondary efficacy endpoints were the incidence of HPV6/11/16/18-related and HPV31/33/45/52/58-related anogenital 6-month persistent infections, respectively. Efficacy analysis was based on the per-protocol population. Secondary immunogenicity endpoints included geometric mean titers and seroconversion rates to each 9vHPV vaccine type at Month 7. Injection site adverse events (AEs) and systemic AEs were collected for 15 days after each vaccination; serious AEs (SAEs) through 6 months after the last vaccination; vaccine-related SAEs and deaths, the entire study duration.

Results: A total of 1059 Japanese males were randomly assigned (9vHPV vaccine, n=529; placebo, n=530), and 1022 completed the 3-dose schedule (9vHPV vaccine, n=514; placebo, n=508). Efficacy of the 9vHPV vaccine was 89.3% (95% CI: 55.4, 98.2) against HPV6/11/16/18-related 6-month anogenital persistent infection and 63.5% (95% CI: 2.7, 86.0) against HPV31/33/45/52/58-related 6-month persistent infection. Efficacy against 6-month and 12-month anogenital persistent infection related to HPV6/11/16/18/31/33/45/52/58 was 74.3% (95% CI: 44.5, 89.3) and 85.5% (95% CI: 54.6, 96.3), respectively. Overall, 1 and 6 cases of HPV6/11/16/18/31/33/45/52/58-related external genital lesions (genital warts, penile intraepithelial neoplasia) were observed in the 9vHPV vaccine and placebo arms, respectively. At Month 7, anti-HPV6/11/16/18/31/33/45/52/58 responses were induced in the 9vHPV vaccine arm, with seroconversion rates ranging from 98.9% to 99.8% depending on HPV type. The proportions of participants with injection site AEs Days 1-5 after any vaccination were 69.9% and 30.6% in the 9vHPV vaccine arm and the placebo arm, respectively. The proportions of participants with systemic AEs Days 1-15 after any vaccination were 20.2% and 19.8% in the 9vHPV vaccine arm and the placebo arm, respectively. No deaths, vaccine-related SAEs or discontinuations due to an AE were reported.

Conclusions: A 3-dose regimen of the 9vHPV vaccine is effective in preventing vaccine-targeted anogenital persistent HPV infections, generated robust anti-9vHPV antibody responses, and was well tolerated in Japanese males aged 16-26 years. These findings suggest that the 9vHPV vaccine could protect males in Japan against vaccine-targeted HPV infection and associated disease.

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#9323

Comparative effectiveness of bi- or quadrivalent HPV vaccines in partially vs fully vaccinated young women

06 - HPV prophylactic vaccines

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Background/Objectives: Girls were previously vaccinated with either bi- or quadrivalent HPV vaccines as part of our implementation project in 2010-2014, where we demonstrated successful school-based HPV vaccination combined with maternal screening in two South African provinces [1-3]. In the current study, performed 7-10 years later, we evaluated HPV prevalence and vaccine effectiveness (VE) in partial & fully vaccinated vaccine recipients compared to a historical control group of unvaccinated young women.

Methods: Young women, vaccinated as part of our previous trial, were recruited to the current study. Self-collected vulvo-vaginal specimens, by means of Evalyn brushes, were tested using extended HPV genotyping. Data on vaccination status were collated from vaccination registers. Full vaccination (FV) was defined as 3-dose series (0, 1-2, 6 months) or, if vaccination initiated at ages 9-14 years, 2-dose series (0, at least 22 weeks) [4]. Partial vaccination (PT) was defined as only 1 dose, or 2 doses less than 22 weeks apart, or only 2 doses if vaccination initiated after age 15 years. Historical control group comprised 137 young women, zero-dose vaccinated (ZV), with matching age-group & demographics. Vaccine effectiveness (VE) was calculated as 100*(1-Odds Ratio).

Results: In total 102 participants were enrolled, with a mean age 19.5 [range 16-22] years; FV in 75 participants & PV in 27 participants. Mean age at vaccination was 11.0 years; mean time since vaccination was 8.6 years. Prevalence of HPV16/18|HPV31/33/45|HPV31/33/45/52/58|HPV16/18/31/33/35/45/52/58 (top-8 hrHPV) were 16.8%|10.2%|19.7%|29.2% in ZV, 0%|7.4%|25.9%|33.3% in PV and 0%|1.3%|10.7%|12.0% in FV respectively (table 1). VE for prevalent infection with HPV16/18|HPV31/33/45|HPV31/33/45/52/58|top-8 hrHPV were 91.1%|29.7%|-42.6%|-21.3% in PV and 96.8%|88.1%|51.3%|66.9% in FV respectively (table 2).

Conclusions: Seven to 10 years after vaccination, both PV and FV groups demonstrated very high VE for infection with HPV16/18, which are targeted by HPV-vaccines. Our data suggest that cross-protection was higher in FV than PV women, especially against HPV31/33/45.

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#9238

Human papillomavirus infection rate and associated lesions in women aged 16-45 years who received HPV vaccine from 2016 to 2022

06 - HPV prophylactic vaccines

Background/Objectives: To investigate the infection rate of Human papillomavirus (HPV) and related lesions in female patients who received HPV vaccine.

Methods: Women aged 16-45 year-old who received HPV vaccine from 2016 to 2022 were selected for cervical liquid-based cytology and HPV testing. Women with abnormal screening were examined by colposcopy and histopathology to analyze the HPV infection rate and its correlation with related lesions.

Results: Among the 1622 women aged 16-45 who received vaccination information in this study, 255 (15.7%) received the bivalent HPV vaccine, 996□61.4%□received the quadrivalent HPV vaccine, and 371 (22.9%) received the nine-valent HPV vaccine between 2016 and 2022. 72 patients (4.4%) received one dose, 137 patients (8.4%) received two doses, and 1413 patients (87.1%) received three doses. (1) Cervical cancer screening before HPV vaccination: TCT results: 789 (48.6%) were not examined, 807 (49.8%) were not abnormal: 21 (1.3%) were ASC-US, 2 (0.1%) were ASC-H, 1 (0.1%) was LSIL, 1 (0.1%) was HSIL, and 1 (0.1%) was AGC. HPV results: 868 (53.5%) were not tested, 624 (38.5%) were negative, and 130 (8.0%) were positive, including 29 (22.3%) were positive for type 16, 4 (3.1%) were positive for type 18, 10 (7.7%) were positive for type 6, and 1 (0.8%) was positive for type 11. 86 (66.2%) were in other types than 16/18. Pathological results: 1611 patients (99.3%) were not examined, 5 patients (0.3%) had chronic cervicitis, 2 patients (0.1%) had low-grade lesions, and 4 patients (0.2%) had high-grade lesions. (2) There were results before and after vaccination for a total of 395 cases. The HPV infection status before and after vaccination was divided into four categories: always negative, positive to negative, always positive, and negative to positive, accounting for 77.5%, 10.6%, 5.1%, and 6.9%, respectively. For the latter two cases, the specific analysis was conducted based on the type of vaccine received by the subject, showing that the overall protection rate of HPV vaccines for Chinese women in the real world is 98.5%. (3)Analysis of factors affecting the protective effect of HPV vaccine: Based on real-world data, xgboost model was used to analyze the contribution of age, vaccination interval, dose times, and TCT results to vaccine protection. The results showed that the contribution rate of vaccination age to HPV protection was the highest, followed by HPV infection status and vaccination interval.

Conclusions: Cervical cancer screening is required after HPV vaccination, especially for women who have had sex before vaccination but have not been screened. Regular check-ups are recommended for women with HPV infection prior to vaccination.

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#9246

Actively promote the vaccination of human papillomavirus vaccine in China

06 - HPV prophylactic vaccines

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Background/Objectives: Cervical cancer is the most common malignant tumor of female lower reproductive tract, which seriously threatens the health of Chinese women. According to data released by China's National Cancer Center in 2024[1], there were 150 700 new cases of cervical cancer and 55 700 deaths in 2022 in China. HPV vaccination plays an important role in the prevention and treatment of cervical cancer.

Methods: At present, there are 5 HPV vaccines in China[2], including bivalent vaccine (Cervarix, Cecolin and Wozehui), quadrivalent vaccine and 9-valent vaccine (Gardasil 4 and 9), for women aged 9 to 45 years. Randomized controlled trial studies have shown that the positive conversion rate after vaccination in women aged 9 to 45 years is 96% to 100%, the prevention of HPV-related infection at 12 months after vaccination is 96% to 97%, and the protective efficacy against CIN2+ is 78.9%~100%, and has good security in China[3-4]. It was observed that the quadrivalent HPV vaccine had a long-term protective effect of average 8 years against HPV-related intraepithelial lesions in Chinese women of 20-45 years[5]. Currently, HPV vaccination in China is voluntary and self-funded, not included in the national immunization program, and administered by the Chinese Center for Disease Control and Prevention (CDC). Vaccination rates are currently low, at just 1.5% for girls aged 9-14 in 2019[6]. Therefore, there is an urgent need to strengthen health education in China to promote the widespread use of HPV vaccines in China.

Results: Several societies and associations has successively published the Expert Consensus "Expert consensus on immunoprophylaxis of human papillomavirus-related diseases" [7] and "Chinese experts consensus on the clinical application of HPV vaccine" [8], points out the relevant issues that need attention in vaccination in China. The Healthy City pilot was carried out to promote HPV vaccination of adolescent female HPV in China[9]. Many provinces and municipalities have conducted extensive health education campaigns for students and parents through the cooperation of governments, communities, schools and medical institutions, and have successfully developed and implemented HPV vaccination program for girls aged 13-14 years. So far, 44 cities in seven provinces and more than 25 regions have implemented free or subsidized immunization campaigns for school-age girls[10]. Post-marketing safety monitoring of the 9-valent HPV vaccine in China: A total of 41,000 Chinese women were enrolled to receive the nine-valent HPV vaccine, and the incidence of AEFI was less than 3.0/10,000. Safety was good after vaccination[11].

Conclusions: Now we have face big challenges to eliminate cervical cancer, With the push to combine HPV vaccination with cervical cancer screening, China is taking proactive steps to eliminate cervical cancer.

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#9420

Improving HPV Vaccination Practice Facilitation Outcomes: Short-Term Effects and Maintenance

39 - Public health

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Background/Objectives: Practice facilitation (PF) is an evidence-based implementation strategy for improving adherence to clinical guidelines, but limited research has applied PF to HPV vaccination. In a hybrid implementation-effectiveness trial, we tested two formats for delivering PF (Coach-based versus Web-based) to engage pediatric clinics in quality improvement focused on HPV vaccination. The objective of this analysis was to assess outcomes during one year of implementation and a second year of maintenance.

Methods: We randomized 21 community-based pediatric clinics in Tennessee, USA, to Coach-based PF (periodic in-person coach visits) or Web-based PF (web-based resource portal). Each clinic selected four changes to implement over one year. 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 clinic-level HPV vaccination coverage measures: 1+ doses and all doses (patients ages 11-17). Interrupted time series analyses of monthly logarithmic rates compared the clinics' one-year baseline to the Year 1 implementation period, then compared Year 1 to the Year 2 maintenance period. Hypothesis 1: Both arms would improve from the baseline period to implementation period on all outcomes. 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). Hypothesis 2: The Coach arm would improve more than Web arm on all outcomes. Hypothesis 3: Improvements would be sustained during the maintenance period.

Results: For the implementation outcomes in Year 1, both arms showed immediate 12-17% relative improvements for doses received in well visits (Relative increase: Coach 1.12 fold [95%CI 1.07-1.18], Web 1.17 fold [1.07-1.28]) and immediate 14-16% relative improvements for bundling vaccines (Coach 1.16 fold [1.07-1.26], Web 1.14 fold [1.06-1.22]), all with stable slopes. These changes did not differ by study arm. In Year 2, these implementation outcomes stayed stable, with no significant changes or differences by arms. For the effectiveness outcomes in Year 1, both arms showed gradual improvements for 1+ dose coverage (Coach 1.007 fold [1.006-1.009], Web 1.006 fold [1.003-1.009]) and all dose coverage (Coach 1.006 fold [1.004-1.008], Web 1.004 fold [1.002-1.006]), which did not differ by study arm. These positive trend changes for the Coach arm translated to 1+ dose and all dose coverage being 7-8% relatively higher by the end of the Year 1 implementation period than they would have been without PF. However, slope declines were observed in Year 2 for 1+ dose coverage (Coach 0.994 fold [0.991-0.996], Web 0.994 fold [0.990-0.998]) and all dose coverage (Coach 0.996 fold [0.994-0.998], Web 0.993 fold [0.992-0.994]), with no differences by arm.

Conclusions: Both PF formats produced similar improvements in implementation and clinical effectiveness outcomes in Year 1. The Year 1 improvements in implementation outcomes were sustained, but the positive trends in effectiveness outcomes were not sustained.Further research should examine strategies to enhance long-term maintenance and examine cost differences between the two formats.

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#9394

Awareness, Attitude and Acceptance of Gender Neutral Nonavalent HPV Vaccine for HPV Related Infections among College Students of a Metropolitan City

06 - HPV prophylactic vaccines

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Background/Objectives: HPV related infections are not gender-sparing, with 60,000 instances of cancer in males and 5,70,000 cases of cancer in women annually worldwide 1,2. One very successful strategy that guards both males and females against HPV related infections is the HPV vaccination 3,4. Gender neutral nonavalent HPV vaccine is considered superior to the other vaccines, as it offers protection against more than 94% of HPV related infections, as compared to the quadrivalent vaccine, which offers a 70% protection rate5. The rates of seroconversion are lower in men, which leads to higher persistence of HPV related infections, and subsequently, a higher possibility of conversion to HPV related disease. Men are thus a key demographic for vaccination, as high vaccination rates among men will reduce HPV related disease in women, and will result in herd immunity 6,7. The study aims to assess the awareness, attitude and acceptance of the gender neutral nonavalent HPV vaccine among college-going girls and boys of 18-25 years of age, and to evaluate the proportion and reasons for non-acceptance of gender neutral nonavalent HPV vaccine, with a special focus on vaccination among men.

Methods: In this cross-sectional study conducted in a tertiary care facility in South India, spanning a period of 18 months, the study participants aged 18-25 years, both boys and girls, were subjected to a structured pre-test questionnaire that assessed their existing understanding about the gender neutral nonavalent HPV vaccine. This was followed by an awareness session conducted by the researcher that addressed the etiopathogenesis of HPV infections, the role of the gender neutral nonavalent HPV vaccine and its advantages in preventing HPV related diseases, and relevant health education. After the session, the subjects were asked to complete the pre-designed post-test questionnaire, to assess the change in knowledge, attitude and awareness towards HPV infections and the gender neutral nonavalent HPV vaccine. After the post-test questionnaire, subjects who voluntarily consented for vaccination were immunized with the gender neutral nonavalent HPV vaccine. For the subjects not willing for vaccination, the reasons and proportion for non acceptance of the nonavalent HPV vaccine was assessed.

Results: Out of 303 students equally distributed among males (151) and females (152), most of them belonging to the medical background, 37% were aware that HPV spreads from skin to skin contact, 97% responded that HPV causes cancer and 96.4% were aware that HPV affects both men and women. After health education, these values increased to 97.7%, 99%, and 98% respectively. When asked about the preventable nature of HPV related infections, 99.7% answered correctly which increased to 100% after health education . 66% students were aware of the gender neutral nonavalent HPV vaccine, which increased to 100% after health education ($p < 0.001$). 89% agreed to take the gender neutral nonavalent HPV vaccine if made available, which increased to 96% after health education. 94.70% of the above subjects were males, and 98.68% were females. Conversely, 11% of the participants were unwilling to take the vaccine before the awareness session, which reduced to 4% after health education. After the study, 3% of males and 40% of the females were vaccinated

Conclusions: Significant changes in the attitude and awareness of the HPV infection and HPV vaccination among the participating male students were observed after the awareness session.

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#9633

Higher plasma aflatoxin concentration is associated with increased risk of HPV 16 and HPV 18 detection and persistence among Ugandan women

03 - Epidemiology and natural history

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Background/Objectives: Cervical cancer is common among Ugandan women. This malignancy is caused by persistent infection with oncogenic HPV types. Aflatoxin is a potent carcinogenic and immunosuppressive agent that contaminates corn and other crops. This analysis was performed to examine associations between plasma aflatoxin and oncogenic HPV detection and persistence in Ugandan women.

Methods: Ugandan women were enrolled in a prospective cohort study. Annual cervical swabs were tested for oncogenic HPV; plasma aflatoxin concentration was measured. Multivariable regression models were fitted to examine associations of plasma aflatoxin concentration and oncogenic HPV controlling for demographic and behavioral characteristics.

Results: The analytical sample consisted of 114 women with a mean age of 33.2 years; 60 women were living with HIV; 59 were receiving antiretroviral therapy at enrollment. Aflatoxin was detected in all 114 women. Multivariable regression models showed that plasma aflatoxin concentration was associated with a higher risk of detection of HPV 16 (OR=2.64, 95% CI=1.42-4.90, p=0.002) and HPV 18 (OR=2.24, 95% CI=1.27-3.96, p=0.005), and persistence of HPV 16 (OR=3.16, 95% CI=1.59-6.26, p=0.001) and HPV 18 (OR=2.06, 95% CI=1.09-3.90, p=0.025), controlling for age, marital status, years of education, home ownership, distance to health care, number of lifetime sex partners, age of first sex, and HIV status.

Conclusions: Aflatoxin was prevalent in Ugandan women. Higher plasma aflatoxin concentration was associated with detection and persistence of HPV 16 and HPV 18, regardless of HIV status. Further studies are needed to determine the mechanisms involved.

HN01 - Submitted papers - Clinical / Epidemiology I

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#9228

Prognostic impact of HPV-status and tobacco smoking in patients ≥70 years surgically treated for oropharyngeal cancer

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: The incidence of HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) arising from the palatine tonsil and base of the tongue (BoT) is increasing also in the elderly population. However, data on the prognostic impact of HPV status in patients aged 70 years and older who undergo upfront surgical treatment remain limited. Previous studies suggest that the survival advantage associated with HPV positivity diminishes in patients over 65 treated with various modalities. To evaluate the impact of HPV status on survival outcomes in patients aged 70 and older undergoing surgical treatment for squamous cell carcinoma (SCC) of the tonsil or BoT.

Methods: A retrospective cohort analysis was conducted in 10 comprehensive cancer centers in Europe, with the following inclusion criteria: a) consecutive patients with histologically confirmed, surgically resectable SCC of the tonsil or BoT; b) age ≥70 years at diagnosis; c) treated between 2010 and 2021 with surgical resection of the primary tumour followed by neck dissection with adjuvant therapy guided by pathologic characteristics. HPV status was determined by p16 immunohistochemistry. Survival outcomes, including disease-free survival (DFS) and overall survival (OS), were compared in strata according to p16 status and smoking habits using Kaplan-Meier method; hazard risk (HR) were computed through Cox proportional hazards model, adjusting for known clinical predictors.

Results: Among 345 patients included in the study (mean age, 76 years; 241 [69.9%] men), 155 patients (44.9%) were p16-positive, and 190 (55.1%) were p16-negative. Overall, 207 (60.0%) underwent to transoral surgical approach, while 138 (40.0%) were treated with an open surgical approach; adjuvant radio/chemotherapy was administered to 214 (62.0%) patients. The median follow-up was 55 months. Patients with p16-positive OPSCC reported significantly an improved disease-free survival (DFS) by 25.6% (95% CI: 14.9%-36.3%) compared to HPV-negative ones: 5-year DFS was 66.4% and 40.8%, respectively, leading to an adjusted hazard ratio (HR) of 0.37 (95% CI: 0.25-0.53). Similarly, the 5-year overall survival (OS) was 71.4% for p16-positive patients versus 47.7% for p16-negative patients, with an absolute difference of 23.7% (95% CI: 13.0%-34.4%) and an adjusted HR of 0.31 (95% CI: 0.20-0.48). Patients with p16-positive OPSCC shown a better prognosis, independently from cancer subsite, type of surgery, and adjuvant treatment. Although not significant, p16-positive was a favourable prognostic factor also in patients aged ≥80 years (HR=0.49; 0.23-1.05). Current/past tobacco smoking was significantly associated to worse prognosis, with HR=2.10 (1.22-3.63) for OS and HR=1.76 (1.07-2.89) for DFS. Information on p16 status and smoking habits were then combined with clinical T and N stage into the Ang risk categorization [1]: elderly patients at high risk shown worse 5-year OS (44.9% vs 71.4%; p<0.001) and DFS (37.3% vs 66.4%; p<0.001) than low risk patients (Figure).

Conclusions: In this study, p16 positivity was associated with significantly improved survival outcomes, as well as never tobacco smoking.These findings suggest that HPV-infection and smoking habits maintain their prognostic value even in older population surgically treated for SCC of the tonsil and BOT.

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#9299

Liquid Biopsies with Circulating Plasma HPV-DNA Measurements-A Clinically Applicable Surveillance Tool for Patients with HPV-Positive Oropharyngeal Cancer

09 - HPV testing

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Background/Objectives: The objectives was to evaluate the accuracy of cell-free human papillomavirus-DNA (cfHPV-DNA) measurements in liquid biopsies in predicting disease in patients with HPV-positive/p16-positive (HPV+/p16+) oropharyngeal squamous cell carcinoma (OPSCC).

Methods: This was a prospective cohort study. Plasma samples were collected before treatment, serially after curative intended therapy at follow-up visits 2 weeks, and 6, 9, 12, 18, 24, and 30 months after treatment. A droplet digital PCR assay comprising eight HPV genotypes was used. HPV genotypes found in plasma and tumor tissue were compared. We correlated biopsy- or imaging-verified tumor progression to cfHPV-DNA in follow-up samples.

Results: We enrolled 72 patients with HPV+/p16+ OPSCC. Baseline sensitivity for cfHPV-DNA detection was 97.2% (95% confidence interval, 90.3%-99.6%). CfHPV-DNA copy number/milliliter plasma correlated with tumor stage. We found a 100% concordance between HPV genotype in tumor tissue and plasma. Fifty-four patients were followed with serial blood samples for a median of 19.7 months (interquartile range, 13.5-25.5 months). Forty-one patients had undetectable plasma cfHPV-DNA in all follow-up samples, and none developed recurrences. Thirteen patients were classified as cfHPV-DNA-positive in a follow-up plasma sample. Of these, five patients developed a recurrence, and three had residual cancer. It was possible to detect cfHPV-DNA in plasma 97 to 166 days prior to the proven recurrence.

Conclusions: To our knowledge, to date, our study, comprising the largest study of patients with HPV+/p16+ OPSCC, using an ultrasensitive multiplex HPV gene panel, revealed a high sensitivity of cfHPV-DNA detection in the liquid biopsies. We recommend serial plasma HPV samples for clinical monitoring of patients with HPV+/p16+ OPSCC.

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#9330

Detection of Human Papillomavirus cell-free DNA in liquid biopsies predicts recurrence of oropharyngeal cancer

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: The incidence of oropharyngeal cancer (OPC) driven by Human Papillomavirus (HPV) is rapidly increasing in high-income countries. Recurrent tumors are a major contributor to OPC mortality, highlighting the importance of reliable treatment monitoring. However, there are no established biomarkers so far. Cell-free DNA (cfDNA) from liquid biopsies has emerged as a promising tool for the detection of early recurrence and residual disease. We aimed to evaluate the role of HPV cfDNA from blood plasma in OPC therapy monitoring while further validating the performance of our newly developed multiplex digital PCR (dPCR) assay.

Methods: 185 plasma samples were collected from 58 OPC patients in Switzerland at time of diagnosis and a median of 3 follow-up visits. cfDNA was isolated and applied to our nanoplate-based HPV dPCR assay quantifying DNA from six high-risk HPV types including HPV16, 18, 33, 45, 52 and 58. Tumor HPV status (38 HPV-positive, 20 HPV-negative OPC) was defined by p16 staining, HPV DNA and HPV E6 serology.

Results: Matching the presence of HPV cfDNA at time of diagnosis to the corresponding tumor HPV status, a sensitivity of 92 % and a specificity of 95 % were observed. About half of the patients with HPV-driven OPC and at least one follow-up had cleared their HPV cfDNA levels by the time of first follow-up after start of therapy. During the follow-up period, a total of two patients with HPV-driven OPC suffered a local recurrence or distant metastases, respectively. Remarkably, increasing HPV cfDNA levels after initial clearance were able to predict recurrent disease roughly 4 - 8 months prior to diagnosis of recurrence in both cases.

Conclusions: Taken together, the accurate detection and utility of HPV cfDNA as minimally invasive biomarker in HPV-positive OPC therapy surveillance were demonstrated. Monitoring HPV cfDNA levels may give insight into treatment response and identify patients at risk of recurrence early in order to guide therapy choices and improve patient outcome.

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#9400

Epidemiology & treatment trends in oropharyngeal cancer in Eastern Denmark

29 - HPV and oropharynx / Head and neck cancer

Background/Objectives: We report trends of to investigate the epidemiology with incidence, survival, and treatment failures with a focus on TORS treatments.

Methods: 2836 confirmed OPSCCs examined at head and neck departments in Eastern Denmark from 2000 to 2020 were included & all patients treated with curative intent for OPSCC by TORS and neck dissection between 2013-2020, amounting to 153 participants.

Results: For the whole population, the AAIR (age-adjusted incidence rate) increased from 1.8 to 5.1 per 100,000 between years 2000-2020 linked to an increasing AAIR of HPV+/p16+ OPSCCs from 0.9 to 3.5 per 100,000. For the TORS group, 88.9% (n=136) were treated with TORS alone while 11.1% (n=17) received adjuvant therapy. Seventeen deaths and 22 recurrences were registered within 5 years of diagnosis

Conclusions: The incidence of HPV-related OPSCC is still increasting. Competitive survival outcomes and disease control was obtained with TORS in the Danish Eastern Cohort, despite considerably less application of adjuvant therapy than reported from other TORS-centers.

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#9261

Nordic Oropharyngeal Squamous Cell Carcinoma Cohort

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: For the past decades, the incidence of oropharyngeal squamous cell carcinoma (OPSCC) has been increasing worldwide, especially in the Nordic countries, due to an increase in OPSCC driven by infection with human papillomavirus (HPV) [1,2]. HPV+ OPSCC has a unique clinical, epidemiological, molecular, and histopathological profile compared to HPV-negative OPSCC. Patients are younger, have less comorbidities, are more often located specifically in the tonsils or the base of tongue and most have a better prognosis[3]. Nevertheless, patients are at risk of developing distant metastasis and a minority have a poor survival[4]. The long-term prognosis and risk of recurrence of OPSCC is not well investigated[5]. These questions, and more have not been validated in larger, multicenter cohorts using both p16- and HPV-status. Multiple separate cohorts exist in the Nordic countries enabling compilation of cohorts. Further, a public health system across the Nordic countries secures equal access. Further, national health registries with automatic reporting ensures high follow-up rate and high quality of data. Creating a large multi-national OPSCC cohort is essential in answering the outlined research questions.

Methods: In this method study we compile multiple OPSCC cohorts in Denmark, Sweden, Finland, Norway, and Iceland creating a large multinational cohort. An extensive list of variables are being collected and we strive to ensure HPV and p16 status on all patients. Further, 5-year follow-up is ensured. Therefore, patients from 2000 to 2018 are included.

Results: At present 6599 patients are included in the cohort. All having both HPV and p16 status. Further, 5 studies are scheduled. 1 study comparing the Nordic centers, and 4 studies investigating the research questions outlined above.

Conclusions: Many research questions in HPV induced OPSCC warrants further research. As a result of the common Nordic public health system and automatic reporting to national databases, there is a large potential for compiling cohorts with a high follow-up rate. So far, 5 studies have been scheduled with potential for more.

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#9293

Demographic and Clinical Patterns in HPV-Associated Oropharyngeal Cancer: Reflections of Global Trends in a Local Cohort

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) has emerged as a distinct subset within head and neck cancers, characterized by unique epidemiological, clinical, and prognostic features. HPV-positive OPSCC is associated with improved survival and is typically observed in younger, nonsmoking patients, diverging significantly from HPV-negative cases that are more commonly linked to tobacco and alcohol use. While North American and European studies have documented a rising incidence of HPV-associated OPSCC, data from other regions remain limited. This study aimed to evaluate demographic and clinical characteristics of OPSCC patients treated at our institution between 2019 and 2023, comparing HPV-positive and HPV-negative groups, and to determine if trends observed in Western populations are mirrored locally.

Methods: A retrospective review was conducted on OPSCC patients treated at our institution from 2019 to 2023. Patients were stratified by HPV status, determined via p16 immunohistochemistry as a surrogate marker, into HPV-positive and HPV-negative groups. Demographic factors (age, gender) and clinical factors (smoking history, quantified in pack-years) were extracted and analyzed to identify differences between the two cohorts. Temporal trends in HPV-positive OPSCC incidence over the study period were also assessed to explore any increase in alignment with global patterns. Statistical analyses included t-tests for continuous variables and chi-square tests for categorical variables, with a significance threshold set at $p < 0.05$.

Results: A total of 115 patients met the inclusion criteria, with 26 (22.6%) classified as HPV-positive. The mean age at diagnosis was similar between HPV-positive and HPV-negative patients (63 vs. 62 years, respectively). Gender distribution revealed a higher, though not statistically significant, proportion of female patients in the HPV-positive group (26.9% vs. 12.4%, $p = 0.072$). As anticipated based on existing literature, the HPV-positive group demonstrated a significantly lower mean smoking history compared to HPV-negative patients, with pack-year data showing a marked difference ($p = 0.002$). Temporal analysis revealed a gradual increase in the proportion of HPV-positive OPSCC cases, rising from 21% of new OPSCC diagnoses in 2019 to 30% in 2023.

Conclusions: Our findings underscore the distinct epidemiological profile of HPV-positive OPSCC patients within our institution, consistent with global reports highlighting younger age, lower tobacco exposure, and a higher female proportion among HPV-positive patients. The gradual increase in HPV-positive cases observed in our cohort aligns with reported trends in Western populations, suggesting a rising impact of HPV on oropharyngeal cancer epidemiology. This remains true despite there being a nationwide HPV vaccination program implemented since 2008. Considering the profile of HPV positive patients, they may have a different subset of needs that should be taken into account when selecting therapeutic strategies and evaluating outcomes of treatment. Further research should investigate long-term outcomes in this population to refine treatment protocols and enhance survival outcomes tailored to HPV status.

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#9054

HPV oral status in French women with HPV genital infection: the PAPILLOR study

28 - Oral HPV infection

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Background/Objectives: Human Papillomavirus (HPV) infection is the most common sexually transmitted infection and causes at least 5% of cancers worldwide [1]. High-risk oncogenic HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) are currently involved in more than 90% of cervical cancers (CCs) and in 37,7% of oropharyngeal squamous cell carcinomas (OPSCCs) in France [2]. It may be assumed that women with a history of genital HPV infection are at greater risk of oral HPV infection. However, to our knowledge, the prevalence of oral HPV infection in these women has never been assessed in France. Our study assessed both the prevalence of oral HPV infection in women with cervical HPV infection, and the concordance for at least one genotype between the oral cavity and the cervix. We also sought to assess the prevalence of infection 6 to 18 months after inclusion, to determine the existence of oral viral clearance. Finally, using a self-administered questionnaire on sexual habits and behaviour completed by patients, we investigated risk factors for oral HPV infection.

Methods: Between 2017 and 2020, 165 women were invited to participate in the PAPILLOR study. Patients were recruited in 4 centers in north-east France: the Cancerology Institute of Lorraine; the University hospital of Nancy; the University hospital of Besançon; the Nord Franche-Comté hospital at Belfort. Inclusion criteria were: (i) presence of an abnormal smear with at least one HPV detected, (ii) presence of a pre-neoplastic high grade cervical lesion (CIN 2/3), (iii) presence of in situ or invasive cervical cancer. Patients who had been vaccinated against HPV were not eligible for the study. At inclusion, all patients underwent a cervical and an oral smear. At a follow-up visit 6 to 18 months after inclusion, patients underwent a second oral smear. Samples were analysed at the virology laboratory of Nancy University Hospital or at the CNR Papillomavirus (HPV National Reference Center) in Besançon University Hospital. HPV DNA detection was performed in the 2 laboratories using the INNO-LiPA® HPV Genotyping Extra II (Fujirebio) to obtain systematic genotyping of all samples.

Results: At inclusion, 145 patients (87.9%) had cervical HPV infection and 14 patients (8.5%) had oral HPV infection. 11 patients were co-infected. Of these, complete concordance of infection was observed in 4 patients, partial concordance in 5 patients, and co-infection without concordance in 2 patients. The HPV-HR types implicated in the oral infections were, in order of frequency: HPV 16 (35.7%), HPV 31 (14.1%), HPV 51, 52 and 35. Low-risk oncogenic HPV (HPV 61) was identified once. Because of the Covid 19 epidemic, only 85 women received a follow-up oral smear. Of these, 4 patients were HPV+ on this smear. 3 had a new oral infection and 1 a persistent infection. 7 patients who had an oral infection at inclusion were no longer infected at the follow-up oral smear.

Conclusions: The prevalence of oral HPV infection in women with persistent genital infection does not appear to be higher than in the general population, where it is estimated between 5 and 7% [3]. Partial or complete concordance of HPV genotypes was found in the majority (81.8%) of co-infected patients.Most oral infections appear to be transient, but the small number of patients with follow-up smears means that these results should be treated with caution. The self-administered questionnaires did not reveal any significant correlation between sexual habits and the risk of oral infection.

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#9406

Public health authorities' information on the association between Human Papillomavirus and oropharyngeal squamous cell carcinoma in Western countries: a cross-sectional study

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Human Papillomavirus (HPV) contributes to 5% of global cancers with an increasing incidence of oropharyngeal squamous cell carcinoma (OPSCC) i.e., especially among men. HPV vaccination campaigns have predominantly targeted cervical cancer prevention in women, which may contribute to lower awareness among males regarding HPV-associated cancer risks, particularly the association with oropharyngeal squamous cell carcinoma (OPSCC). This multinational study assesses how national health authorities Western countries communicate the association of HPV and OPSCC.

Methods: National health authorities across Western countries were identified using the ECDC's Coordinating Competent Bodies list for EU nations and government websites for non-EU countries. A standardized search was conducted on these sites to locate information on HPV and vaccination, emphasizing thematic sections over press releases. When internal search bars were available, systematic search terms (e.g., "HPV," "HPV vaccine") were used; otherwise, Google searches with same search terms were employed. Identified content was classified into four categories based on the prominence of OPSCC mentions. National language pages were prioritized, with Chrome's translation feature used for non-English content. Countries were categorized in three groups according to level of awareness demonstrated by their health authority.

Results: Group 1 (higher awareness) had seven countries where OPSCC was noted early; Group 2 (moderate awareness) had 19 countries mentioning OPSCC last on a list of HPV-associated cancers; and Group 3 (no awareness) had five countries with no mention of OPSCC. In EMA-aligned countries, 8.2% of the population had access to more prominent OPSCC information, while 87,3% had minimal or no mention, indicating significant gaps. For three countries, no data was found (4,4%).

Conclusions: Significant lack of information on HPV positive OPSCC persists, especially in EMA-aligned countries. Strengthening public education on HPV-induced OPSCC risks is essential to reduce the HPV cancer burden and enhance public health.

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#8641

DECIPHERING THE LINK BETWEEN HPV POSITIVITY IN NON-SMOKERS AND HPV NEGATIVITY IN SMOKERS WITH HEAD AND NECK CANCER

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: The mode of HPV-infection in head and neck squamous cell carcinoma (HNSCC) remains poorly understood and the question of why the vast majority of patients with HPV-positive HNSCC are non-smokers, whereas those with HPV-negative HNSCC are smokers, is unanswered. However, our previous research (patients investigated, n>1,100), hypothesized an explanation: Smoking-induces upregulation of a mucosal protective protein, secretory leukocyte protease inhibitor (SLPI), which competes with HPV for binding to membrane-associated annexin A2 (AnxA2), a crucial step in HPV-cell entry. This study was to investigate the mechanistic aspects of our hypothesis using transfection assays.

Methods: HaCaT and HeLa cell-lines were used to investigate the effects of shRNA-transfection and nicotine-exposure on HPV16-PsV uptake. Cells were treated with LipofectamineTM RNAiMAX with specific shRNA-concentrations, while nicotine was added to the cell medium at the indicated concentrations. Protein isolation, SLPI- and AnxA2-quantification, LDH-cytotoxicity assessment, HPV16-PsV uptake measurement, mRNA-isolation, cDNA-synthesis and RT-qPCR were performed.

Results: In vitro transfection experiments were performed with HPV16-pseudoviruses (PsVs) in the two cell lines. Initially, we transfected the cells with SLPI- or AnxA2-shRNA. After successful SLPI- and AnxA2-downregulation, PsVs entered the cells significantly better when SLPI was downregulated, and significantly less when AnxA2 was downregulated. Next, the cells were incubated with increasing nicotine concentrations, resulting in increased SLPI levels in the cells and cellular supernatants, accompanied by reduced PsV uptake.

Conclusions: The overexpression of SLPI caused by smoking can hinder HPV cell entry by binding to AnxA2 and thus prevent successful HPV infection. Conversely, non-smokers have lower SLPI levels, associated with an excess of unbound AnxA2, thus favoring HPV cell entry. These findings transform our hypothesis into a thesis and represent a potential paradigm shift, not only in the understanding of (virus-related) pathogenesis, particularly in the head and neck region, but also in the nature of HPV infection as a whole.

FC02 - Molecular markers - Molecular biology - Technology & testing

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#9288

A Comparative Analysis of EU IVDR and Japanese PMDA Performance Evaluation Protocols: Insights from the HPV PLUS ELITE MGB KIT Study

09 - HPV testing

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Background/Objectives: When selecting an appropriate HPV assay for clinical use, it is essential to consider the complex regulatory framework governing in-vitro diagnostic devices (IVDs) in different regions. This study provides a comprehensive comparison of the regulatory requirements for IVDs in the European Union and Japan: the EU In-Vitro Diagnostic Regulation (IVDR 2017/746) and the Pharmaceuticals and Medical Devices Act (PMDA). Both regulations aim to ensure the safety and effectiveness of IVDs, yet significant differences and similarities exist in their protocols and specifications.

Methods: The comparison of both regulations is based on the clinical performance evaluation of the HPV PLUS ELITe MGB® Kit (ELITechGroup, A Bruker Company, Turin, Italy) in association with ELITe BeGenius® system, on cervical leftover samples from patients for whom the HPV molecular test is required collected by Cervex brush (Rovers Medical Devices, North Brabant, Netherlands) stored in ThinPrep medium (Hologic, Massachusetts, USA). The indicated assay allows for detection and typing of the high-risk HPV 16, 18, 31, 45, detection of high-risk HPV HR1 group (33, 52, 58) and detection of high-risk HPV HR2 group (35, 39, 51, 56, 59, 66 and 68). In both protocols the diagnostic sensitivity and specificity is investigated, although different sample sizes are applied.

Results: The IVDR, which came into effect in May 2022, establishes precise guidelines for the intended use of IVDs, requiring clear documentation on factors such as diagnostic purpose, testing population, and the device's automation level. Conversely, the PMDA, effective since April 2004, imposes less specificity in the intended use and does not require indication of the testing population. Both frameworks mandate clinical study protocols, reports, and the use of accredited external centres for clinical evaluations, though differences emerge in sample size determination and reference methods. While the IVDR adheres to a single standard reference method, the PMDA requires two reference methods that are already registered in Japan. Statistical analysis under both frameworks requires robust diagnostic sensitivity and specificity, but while the IVDR mandates diagnostic metrics according to the state-of-the-art standards, the PMDA focuses on an overall agreement rate of ≥ 90%. Results from two studies demonstrate that the HPV PLUS ELITe MGB® Kit meets the performance standards required by both IVDR and PMDA protocols.

Conclusions: In conclusion, while both IVDR and PMDA prioritize patient safety and clinical effectiveness, their divergence in protocols reflects regional regulatory philosophies, with the IVDR emphasizing stringent, predefined rules and the PMDA offering more flexibility within clinical and methodological parameters.

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#9182

Single-Nucleotide Polymorphism in the PPARGC1B Gene Correlating with the Development of HPV Chronicity in Rwandan Women Living with HIV

38 - Low resource settings

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Background/Objectives: This study aimed to discover potential single nucleotide polymorphisms (SNPs) correlating with the development of chronic HPV infections in Rwandan women living with HIV.

Methods: 385 HIV-positive women attending the HIV clinic at the University Teaching Hospital of Kigali (CHUK), Kigali, Rwanda, were interviewed and HPV tested with RT-PCR for twelve high-risk (HR)-HPVs (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) and two low-risk (LR)-HPVs (HPV6 and 11) at baseline and at follow-up after two years. To assess SNPs correlating with the risk of developing chronic HPV infections, blood samples were assessed with the Illumina Global Screening Array-Multi Disease version 3 (GSA-MDv3).

Results: HPV positivity in cervical and/or vaginal samples was detected in 166 (43.1%) participants at baseline. At the 2-year follow-up, 111 (66.9%) had cleared their HPV infection(s), 31 participants (18.7%) had partially cleared their HPV infection(s), and 24 (14.5%) had developed chronic HPV infection(s). The top SNP associated with clearing versus developing chronic HPV infection was rs13158830 (p=7.82E-10; A allele affected 0.10; unaffected 0.00). The present SNP is located in the PPARGC1B gene on chromosome 5q32.

Conclusions: We report a new SNP associated with the development of chronic HPV infections not previously reported.

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#9540

HPV circulating tumor DNA as a marker to monitor response to pembrolizumab and vorinostat combination in patients with advanced HPV-related squamous cell carcinoma

15 - Molecular markers

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Background/Objectives: Limited data are available on the role of circulating tumor DNA of Human Papillomavirus (HPV-ctDNA) as a pharmacodynamic marker to monitor response to treatment in the recurrent/metastatic (R/M) setting. Our study aimed to investigate the sensitivity and pharmacodynamic value of HPV-ctDNA levels during treatment in patients with R/M HPV-related squamous cell carcinoma (SCC) treated with pembrolizumab in combination with vorinostat.

Methods: Plasma samples were prospectively collected from HPV-related SCC patients before treatment initiation and every six weeks until disease progression. HPV-ctDNA was quantified using droplet digital PCR (ddPCR). The levels before treatment were analyzed according to patients and tumor characteristics. Landmark analyses were performed to study the association between HPV-ctDNA level variation and both progression-free survival and overall survival.

Results: HPV-ctDNA was detected before treatment in all 57 patients with an HPV-related SCC. HPV-ctDNA levels correlated with the number of HPV copy in tumor tissues ($p<0.001$). Higher levels of HPV-ctDNA in plasma samples were observed in anal cancer in comparison with other tumor types ($p<0.0001$), and in patients with distant metastases with or without locoregional recurrence as compared with patients with locoregional recurrence alone ($p=0.02$). The increase of HPV-ctDNA levels during treatment was associated with a lower overall response rate ($p=0.01$), as well as shorter progression-free survival and overall survival (both, $p=0.01$).

Conclusions: Dynamic HPV-ctDNA variation levels during treatment have a pharmacodynamic value and may help monitoring treatment response in patients with advanced HPV-related SCC of different locations.

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#9152

Circulating cell-free HPV DNA as a valuable tool for post-treatment assessment of treatment response and monitoring of recurrence in cervical cancer patients.

15 - Molecular markers

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Background/Objectives: In two previous studies (1, 2), we have already shown that pre-treatment detection of circulating cell-free HPV DNA (ccfHPV DNA) may serve as a marker for disease severity in cervical cancer. By examining post-treatment blood samples from the same patients included in these studies, we may gain insight into the utility of ccfHPV DNA in detecting residual disease and not least future disease recurrences.

Methods: Using our targeted HPV panel based on Next Generation Sequencing (NGS), we analyzed follow-up blood samples collected during and after treatment from 61 cervical cancer patients included in the mentioned studies; 21 patients with a later loco-regional or distant recurrence and 40 patients without a later recurrence.

Results: Among patients without a later loco-regional or distant recurrence of their disease (N= 40), ccfHPV DNA had reached an undetectable level at the first available post-treatment blood sample in all patients and remained undetectable in the one following blood sample currently analyzed (collected between 18 and 36 months post-treatment). Contrary, for patients with a later loco-regional or distant recurrence (N = 21), sixteen (76.2%) were ccfHPV DNA positive at one or more time points during post-treatment follow-up and five (23.8%) were ccfHPV DNA negative at all follow-up visits from the 3 months post-treatment and onwards (see Figure 1). When examining the potential utility of the post-treatment blood sample obtained during the three-month follow-up visit (follow-up 3) in predicting future disease recurrence, our data from 14 recurrence patients and 28 non-recurrence patients showed that ten (100%) of the patients who where ccfHPV DNA positive at follow-up 3 eventually developed a disease recurrence, while this was only the case for four (14.3%) of the patients who where ccfHPV DNA negative at this follow-up ($p<0.0001$) (see Figure 2).

Conclusions: ccfHPV DNA has the potential to become a valuable tool for post-treatment assessment of treatment response and monitoring of recurrence.

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#9177

HPV E4/p16INK4a immunohistochemistry for the prediction of CIN2 regression - a historical cohort study

23 - Risk management

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Background/Objectives: CIN2 is a heterogenous diagnosis with a high likelihood of regression, suggesting that some women with CIN2 may benefit from undergoing active surveillance instead of an immediate excision. Here, we aimed to examine the performance of p16INK4a and HPV E4 immunohistochemistry for predicting CIN2 regression.

Methods: We conducted a historical cohort study including women aged 23-40 undergoing active surveillance for CIN2 at Aarhus University Hospital, Denmark, from 2000 to 2010. Archived tissue samples were sectioned for H&E, HPV genotyping, and p16INK4a and HPV E4 immunohistochemestry We calculated absolute and adjusted relative risks (aRR) of regression by p16INK4a status, stratified by HPV E4, HPV type, cytology, and age. In a sensitivity analysis we restricted to women with an expert-confirmed CIN2.

Results: Of 443 included women, most (73.8%) were aged £30 and half had a high-grade index cytology (48.8%). A total of 47.6% regressed to CIN1 or normal during the 2-year surveillance period. CIN2 regression rates were lower in p16INK4a-positive compared to p16INK4a-negative women (40.5% vs 63.3%, aRR: 0.77 ; 95%CI 0.64-0.94). In p16INK4a-positive women, risk of regression was significantly lower in HPV E4-negative compared to HPV E4-positive women (37.7% vs 53.8%, aRR 0.73; 95%CI 0.54-0.98) and in HPV16-positive compared to HPV16-negative women (27.9% vs 49.7%, aRR 0.54; 95%CI 0.40-0.75). Risks did not differ by cytology (≤Low-grade vs high-grade: 40.6% vs 43.0%, aRR 0.78 ; 95%CI 0.60-1.02) or age at diagnosis (≤30 vs >30: 41.8% vs 36.7%; aRR 0.85; 95%CI 0.62-1.17). When we restricted to women with an expert-confirmed CIN2 diagnosis, (n=261), similar findings were observed although results were less robust due to the smaller sample size.

Conclusions: Our findings support the use of p16INK4a immunohistochemistry in clinical practice, possibly in addition to HPV typing and E4 testing. Age and cytology at the time of CIN2 diagnosis had limited impact on regression rates in this study.

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#9263

The role of tumor suppressor SPZ1 in Human Papillomavirus (HPV) E7-mediated oncogenesis.

02 - Viral and molecular biology

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Background/Objectives: Persistent infection with high-risk human papilloma viruses (HPV) is associated with one of the most common cancers in women worldwide, cervical cancer. In addition, HPV are also linked to anogenital and oropharyngeal cancers. Viral oncogenesis is mainly caused by the two major high risk HPV oncogenes E6 and E7. The tumor suppressor retinoblastoma (pRb) protein interacts with and is inhibited by oncogene E7, which is encoded by cancer causing HPVs. Therefore, this study investigated the effects of the interaction of E7 with SPZ1- a newly discovered human protein and RB protein on the progression of cancer. SPZ1 has been correlated with the normal cellular morphology and function. The E7 oncoprotein of high-risk HPVs is known to interact with the Retinoblastoma protein (Rb) and thereby disrupt the interaction of Rb with the transcription factor E2F. The release of E2F allows the transcription of genes necessary for DNA replication and cell cycle progression, and pushes the cell into the S phase. In this study, we screened for additional interactors of E7 and investigated their impact on E7 function.

Methods: We used the Gal4 yeast two-hybrid system to screen for novel interactors. The effect of SPZ1 was investigated through both transient and stable transfection in various cell lines including Hela, Siha, C33a, HaCaT, NT2, NIH3T3 and 293T. Protein levels were assessed by Western blot using monoclonal antibodies against E7, RB and SPZ1.

Results: One of the strongest interactors with high-risk E7 identified was the Spermatogenic Leucine Zipper 1 protein (SPZ1), a protein previously reported to be expressed in embryonal testis and described as a transcription factor. E7 increased the proliferation of HaCaT keratinocytes, an effect that was reversed by co-expression of SPZ1. SPZ1 protected Rb from E7-mediated degradation, thereby enhancing Rb's stability and prolonging its half-life as it is evidenced by SDS-PAGE and Western blots. SPZ1 increased both the half-life and protein levels of E7 in a dose-dependent manner. SPZ1 was found to be secreted extracellularly via a non-classical pathway. Secreted SPZ1 enhanced the half-life of Rb in neighbouring cells and plays a key role in Rb stability, as demonstrated by quantitative Western blot analysis.

Conclusions: In summary, our findings suggest that SPZ1 is a secreted protein with tumour suppressor activity and might play a role in cervical cancer, as well as potentially other tumours with Rb mutations or dysregulated Rb. Our data alo suggests that in cervical cancer cells, there is trimeric complex consisting of Rb E7, and SPZ1.

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Genetic Manipulations of EPLIN/LIMA1 Expression Delineate Its Role in Cervical Carcinogenesis and Permit its Exploitation as a Putative Therapeutic Target

04 - Pathogenesis

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Background/Objectives: A cardinal feature ofcervical carcinogenesis involves the remodeling of the cell cytoskeleton and its eventual evolution to epithelial mesenchymal transition (EMT). EPLIN (Epithelial Protein Lost in Neoplasm) or LIMA1, represents an important cytoskeleton regulator, exhibiting an aberrant downregulation in epithelial tumors. However, its mechanisms of action in cervical carcinogenesis have not been elucidated. In our previous high resolution proteomic analysis, we documented a statistically significant downregulation of EPLIN in HeLa, SiHa and C33A cervical cancer lines compared to the normal cervical keratinocyte HCK1T cells. In the present study, we investigated its involvement in cervical carcinogenesis by 1) genetically downregulating its expression in normal keratinocytes HCK1T, 2) overexpressing EPLIN in C33A and SiHa cell lines and 3) documenting its expression pattern during carcinogenesis, in well-characterized clinical samples.

Methods: LIMA1 knockdown was achieved following transduction with a lentiviral vector carrying an shRNA cassette for LIMA1, while its overexpression was achieved by transfection with the pRP-EGFP/Puro-EFS>hLIMA1 plasmid. Following efficient knockdown and/or overexpression, respectively, the effects on migration, invasion, wound healing and colony formation were assessed. Confocal microscopy was used to evaluate the effects on cytoskeleton architecture. RNASeq analysis was performed to reveal the differentially expressed genes. Immunohistochemical assessment of EPLIN was performed in a set of tissue microarrays, covering the whole spectrum of cervical carcinogenesis.

Results: HCK1T transduction with shLIMA1 led to a significant increase in migration and invasion, with extensive bleb formation, reflecting the detachment of plasma membrane from the cytoskeleton, thus enhancing metastasis potential. Colony formation and wound healing capacity were also increased. Bioinformatic analysis disclosed significant upregulation of genes inducing cell cycle arrest at the G1 phase, such as CDKN1A, along with features of cytokinesis failure. EPLIN suppression led also to an increased expression of genes related to EMT, a program enhancing mobility, invasion, and metastasis, along with upregulation of genes controlling cell-cell interaction with the extracellular matrix, such as matrix metalloproteinase-9 (MMP9). On the contrary, LIMA1 overexpression in both C33A and SiHa lines, impaired their migration and invasion ability and reduced their colony formation and wound healing capacity. Bleb formation was also impaired. Our current data suggest that LIMA1 expression orchestrates the induction of cancer characteristics via manipulation of cytoplasmic ß-catenin levels and its cognate pathway. Finally, immunohistochemical analysis demonstrated a reduction in LIMA1 expression in cervical cancer compared to normal epithelium, while the pattern of expression in hyperplastic epithelium was tightly correlated with the degree of hyperplasia. Reduced LIMA1 staining was observed in squamous cell carcinomas, while most adenocarcinomas lacked LIMA1 positive staining.

Conclusions: These data document for the first time that reduced levels of LIMA1 play a critical role in cervical carcinoma induction, progression and metastasis. The resulting reversible phenotypes upon its manipulation in the present study, provide the impetus to be utilized as a potential therapeutic target, in a novel gene therapy approach.

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#9440

Non-canonical functions of telomerase RNA component in viruses-associated cancer

04 - Pathogenesis

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Background/Objectives: The telomerase enzyme, consisting of a catalytic subunit called telomerase reverse transcriptase (TERT) and an RNA component known as telomerase RNA component (TERC), controls the length of telomeres. In most cancers, telomerase is upregulated, with the TERT enzyme and TERC RNA element contributing to the maintenance of telomere length. Also, TERT and TERC may play major roles in cancer not related to telomere biology. They are involved in the regulation of gene expression, signal transduction pathways, cellular metabolism, or even immune response modulation. Furthermore, the crosstalk between TERT, TERC, RNA-binding proteins, and microRNAs contributes to a greater extent to cancer biology. Our recent data demonstrated a critical role of TERC RNA in HPV induced cell transformation and tumorigenesis. High-risk human papillomavirus DNA, which encodes the E6 and E7 oncogenes, is present in nearly all cervical cancers and HPV is thereby considered a necessary agent for cancer initiation and development. However, HPV alone is insufficient for cancer development. Unknown factors unique to individual hosts appear to contribute to dysplastic transformation and progression. Two studies demonstrate that TERC is amplified in 20-21% of mild dysplasia of the cervix (CIN I), 50-68% of moderate dysplasia (CIN II), 81-82% of severe dysplasia (CIN III) and 95-100% in invasive cancer.

Methods: Overexpression of TERT and TERC: Independently and simultaneously overexpress TERT and TERC in the same cells. Compare with knockdown conditions to see if combined overexpression enhances the transformation-related characteristics (e.g., increased colony formation and reduced apoptosis). Telomerase Activity Assay: To measure the impact of TERT and TERC modulation on telomerase activity and correlate it with the transformation potential. (A)Measure Telomerase Activity Using TRAP Assay: Perform the telomeric repeat amplification protocol (TRAP) to assess telomerase activity in TERT/TERC knockdown, overexpression, and knockout cell lines. (B)Correlate Telomerase Activity with Transformation Outcomes: Determine if changes in telomerase activity (increase or decrease) correlate with enhanced or reduced transformation markers. In Vivo Tumorigenicity Assay: To confirm the necessity of TERT and TERC for tumor formation in a more physiologically relevant context. (A)Subcutaneous Xenograft Model: Inject the modified HPV-immortalized cervical cells (with TERT/TERC knockdown, knockout, or overexpression) into immunodeficient mice. (B)Monitor Tumor Growth: Measure tumor size over time and perform histological analysis of excised tumors to assess proliferation markers and telomerase activity.

Results: Here, we demonstrated that further overexpression of TERT and TERT induced an increased cell growth rate, anchorage-independent growth of HPV E6E7 immortalized cells in soft agar, and the formation of tumors in immunodeficient mice. This represents a distinct progressive step in the conversation of normal to malignant cells. In the TERT/TERC overexpressing cells, the molecular interplay between HPV oncogenes and telomerase can be potentially very important in tumorigenesis.

Conclusions: These data suggest that TERC may play critical roles in multi-steps of development of human cervical cancer using telomerase dependent and independent pathways.

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ZNF671 methylation as molecular marker in cervical dysplasia during pregnancy?

15 - Molecular markers

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Background/Objectives: Objective: A significant number of cervical intraepithelial neoplasias (CINs) are occurring during pregnancy. The vast majority does not develop into a carcinoma during pregnancy and many regress spontaneously postpartum. Therefore, treatment is not necessary for those patients. But diagnosis and treatment are difficult for pregnant patients and there is no possibility to identify patients that will show a regressing CIN postpartum. The diagnostic GynTect® assay from oncgnostics GmbH offers a sensitive and specific identification of CINs from cervical scrapes. For that it measures the DNA methylation of six marker genes. Its primary marker ZNF671 shows a higher methylation rate in progressing FFPE samples, having a prognostic value. We wanted to test, if ZNF671 methylation is a suitable marker for CINs of pregnant women and could give prognostic information on those.

Methods: Methods: We tested 53 pregnant patients with different CIN grades and disease trends (regressive, persistent, progressive or recurrent) for ZNF671 methylation. Also, HPV status and age were correlated to the results. To measure the influence of pregnancy on ZNF671 methylation, we included a second sample postpartum per patient and analyzed the change of methylation.

Results: Results: We saw an increase in ZNF671 methylation with increasing CIN grade (CIN 1: 0 %, CIN 2: 17.86 %, CIN 3: 67.86 %, carcinoma: 100 %). Compared to FFPE samples of non-pregnant patients, this is a strongly increased methylation for CIN 3 samples. Recurrent patients (14.29 %) and patients with a persisting CIN postpartum (60.71 %) showed the highest ZNF671 methylation rate. But regressive samples (21.43 %) showed ZNF671 methylation, too. 5 out of 6 patients with progressing CIN, didn't show ZNF671 methylation. As non-pregnant patients, HPV-16 positive samples showed a higher positivity than other HPV types. In contrast to non-pregnant patients, we didn't see a higher positivity for patients >30 years old. 17 patients showed ZNF672 methylation during and after pregnancy, 24 patients showed only negative results and 12 patients showed mixed results with 11 of them showing positive results during pregnancy which reverted postpartum.

Conclusions: Conclusions: The GynTect® kit with its main marker ZNF671 is not suitable for pregnant patients and gives false-positive results in patients which will regress postpartum. In addition, it doesn't give any prognostic information with progressing patients showing negative results. Surprisingly, pregnancy leads to a change in methylation which reverts postpartum in many cases.

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#9372

Evaluation of HPV31 prevalence and viral load in women referred for colposcopy

15 - Molecular markers

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Background/Objectives: The introduction of molecular assays able to perform the full genotyping of High-Risk Human Papillomavirus (HR-HPV) has permitted the analysis of the prevalence and persistence of each specific HR-HPV genotype. This ongoing study aims to evaluate the prevalence of Human Papillomavirus 31 (HPV31) in women referred for colposcopy and to follow, in case of persistent infections, the evolution of viral load in association with the grade of cervical lesion.

Methods: In the present study, women were enrolled on referral to the Colposcopy Clinic of IRCCS San Gerardo dei Tintori (Monza) for recent cervical dysplasia. Based on the outcome of the colposcopic examination, women underwent biopsy and/or treatment by conization. According to the local clinical protocols, women were followed up with colposcopy after 6/12 months. At each visit, a cervical specimen, collected using L-shaped FLOQSwab endo/exocervical and resuspended in 20 ml of PreservCyt, was tested using the MicroLab Nimbus platform in combination with STARMag 96 X 4 Universal Cartridge Kit and AnyplexTMII HR HPV kit. Genotype-specific viral load was determined using OncoPredict HPV Quantitative Typing (QT) assay and expressed as viral copies per 10^4 cells.

Results: 237 of the 358 women enrolled (66.2%) resulted HR-HPV positive. HPV31 was detected in 49/358 (13.7%) women: in 16 cases as a single infection, in 33 as multiple infection with other HR-HPV genotypes. Histological examination was performed on 12 out of the 49 HPV31-positive patients (24.5%), confirming the presence of a cervical intraepithelial neoplasia grade 2 or worse (≥CIN2) in 11 cases (11/12; 91.7%). Among the 130 women presently returned for the first follow-up visit, 23 were HR-HPV positive at the time of enrollment and 13 (13/23; 56.5%) showed persistent HPV31 infection. The normalized genotype-specific viral load analysis of women with HPV31 persistent infection demonstrated that viral load correlated with the progression or regression of the cytological lesions in 69.2% (9/13) of cases.

Conclusions: HPV31 infection was frequently detected among women referred to colposcopy both at the time of enrollment and follow-up visits. These preliminary results highlighted the importance of HR-HPV genotyping in the follow-up of women with cervical lesions and underlined that normalized genotype-specific viral load could represent a useful biomarker to monitor the evolution of cervical lesions. The enrollment and follow-up of a larger number of women is necessary to confirm these preliminary results in a larger population.

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#9352

The role of vaginal microbiota in Human Papillomavirus (hpv) clearance and persistence

15 - Molecular markers

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Background/Objectives: HPV-based screening for cervical cancer is more effective than cytology but can entail increased costs and undesired effects due to over-diagnosis and overtreatment of regressive high-grade Cervical Intraepithelial Lesions(hgCIN). Markers to stratify the current and future risk of hgCIN are available but not fully satisfactory. The objective of this study is to evaluate the association among several markers (HPVgenotype, p16INK4A over-expression, human and viral genes methylation status, Vaginal Microbiota-VMB composition, genital cytokines) and the severity of cervical dysplasia in women eligible for cervical cancer screening.

Methods: The study protocol requires the invitation of 12000 women aged 34-64 of the Tuscany Region screening program (Florence, Arezzo, Livorno) to perform HPV-screening test and to participate in the study. Cervical samples are collected in methanol based solution for high-risk(hr) HPV-testing using a pre-analytical and analytical automated system for detection of HPV 16, 18 or other high risk genotype. All hrHPV-positive are triaged with Liquid-Based Cytology(LBC) and genotyped using a multiplex real time PCR assay detecting 28 individual HPV types simultaneously. All samples are tested at the regional laboratory of cancer prevention (LRPO) of ISPRO (Florence, Italy). Moreover, hrHPV+ specimens were analysed for promotor methylation status of FAM19A4 and mir-124-2 human genes using a multiplex real time methylation-specific PCR assay. p16 over-expression will be also assessed in ISPRO. VMB will be assessed in the Department of Clinical and Experimental Medicine (University of Florence) only on women enrolled in Florence as sample storage at -20°C is required.

Results: From February 2023 to date, 3315 women (mean age:Arezzo 51.2yrs, Viareggio 49.5yrs, Florence 51.5yrs) were enrolled with 301(8.8%) HPV+ samples (7%Arezzo, 12.2%Livorno, 7.5%Florence). Partial genotyping showed 18.2% HPV16+, 10.5% HPV18+ and 71.3% other hrHPV+, with 11.3% coinfections. LBC triage resulted in 83.7% NILM, 10.6% LSIL, 2% ASC-H, 1.3% HSIL, 0.3% AGC, 2% inadequate. From extended genotyping, the most frequent hrHPV-types were HPV31 (18.9%), HPV16 (16.6%) and HPV52 (11.6%). LSIL+ cases were 23.3% (10/43) HPV16+ and 18.6% (8/43) HPV31+. 32/121 of the analysed samples were methylated on at least one of the two genes analysed. Among methylated samples, 42.9% were HPV16/18+ compared to 28.6% of the unmethylated ones. Available data about histology (n=27) showed 6 negative biopsies, 12 CIN1, 5 CIN2, 1 CIN3, 1 Adenocarcinoma in situ and 2 Squamous Cell Carcinoma. All CIN3+ detected lesions were HPV16+. To date hrHPV test was performed on 72 one year-recall samples, obtaining HPV persistence in 70.8% of cases. LBC triage performed on 49 hrHPV positive samples resulted NILM in 87.8%, LSIL in 8.2%, AGC in 2% and 2% unsatisfactory. Available histology results showed 16 negative biopsies, 3 CIN1, 1 CIN2 and 1 unsatisfactory.

Conclusions: Our preliminary data confirmed that genotyping could be useful to stratify women at higher risk of cervical cancer development. The other biomarkes need to be further investigated to better assess persistent or regressive HPV infections and allow longer screening intervals.

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A new targeted therapy for human-HPV hybrid extrachromosomal DNA

02 - Viral and molecular biology

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Background/Objectives: Human Papillomavirus-associated Oropharyngeal Cancer (HPVOPC) is dramatically increasing over the last two decades and became the 2nd-fastest growing cause of solid organ cancer death in the U.S. Although HPV genome integration into the human genome is known as a model for HPVOPC carcinogenesis, the molecular mechanism underlying this phenomenon remains elusive. Recently we identified the existence of Human-viral hybrid ecDNA (hybrid ecDNA)1, a fusion of the human genome and HPV genome generated from the integration site, in HPVOPC and this structure has potential to build an innovative treatment strategy in HPVOPC.

Methods: To identify the hybrid ecDNA, whole genome sequencing (WGS) and RNA-seq were performed on HPV-OPC cell lines and Patient derived xenograft (PDX) tumors from clinical tumor samples of HPVOPC patients. Based on WGS and RNA-seq, Amplicon Architect (AA) and Viral Integration and Fusion Identification (ViFi) were used to detect Viral integration and hybrid ecDNA. For the anatomical validation of hybrid ecDNA, multi-FISH for human genome specific and HPV genome specific probe on hybrid ecDNAwere performed using metaphase spread HPV-OPC cell line, short time cultured PDX tumor cells, and normal keratinocyte cell line as control. To elucidate the intra hybrid ecDNA interaction, we performed ChIP-seq using cell lines and PDX tumor for H3K27ac, H3K4me1, and H3K4me3, ATAC-seq, and HiC-seq. To further examine the involvement of hybrid ecDNA in cancer growth, we performed a proliferation assay using CRISPR interference (CRISPRi) or BET inhibiter, a therapeutic agent that targets hybrid ecDNA, and tested the difference between with/without hybrid ecDNA. To validate the BET inhibiter effect, we examined the difference of tumor growth in PDX tumor which has hybrid ecDNA with/without BET inhibiter treatment.

Results: Both of cell lines and PDX tumors, we identified hybrid ecDNA(+) tumors. In multi-FISH for the ecDNA specific and HPV probe, we identified overlapped signaling in outside of the chromosome in metaphase spread cells, confirming the existence of hybrid ecDNA. ChIP-seq of ecDNA(+) cell line and PDX showed that the hybrid ecDNA sequence contained active enhancers. Strikingly, these active enhancers were not in the hybrid ecDNA(-) cell line in the same region, suggesting these enhancers were newly created after the HPV integration. ATAC-seq confirmed these enhancers exist in open chromatin regions, and the interaction between these enhaners and HPV were confirmed by HiC-seq. To check the functional interaction of these active enhancers, we used CRISPRi to inactivate these enhancers targeted by sgRNA. Compare to nontarget control, inactivating the enhancer significantly inhibited the proliferation only in hybrid ecDNA(+) cell line (P=0.006). In addition, BET inhibitor treatment targeting to hybrid ecDNA(+) tumor showed the significant inhibition of tumor growth in both of cell lines and PDX tumor, suggesting a possibility of a new targeted therapy.

Conclusions: The existence of hybrid ecDNA was confirmed in both of cell lines and PDX tumors and anatomically validated by FISH. This hybrid ecDNA contains active enhancer that is never included in the hybrid ecDNA(-) tumor. Targeting to this enhancer (CRISPRi) or hybrid ecDNA (BET inhibitor) showed significant inhibition of tumor growth in hybrid ecDNA(+) cell lines and PDX that is not shown in hybrid ecDNA(-) tumor. These results suggested the new innovative treatment strategy for hybrid ecDNA(+) HPVOPC.

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FC05 - Triage of HPV positive women I

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Using additional risk factors in the formation of cervical (pre)malignancy risk profiles for the triage of hrHPV positive women in screening

12 - Triage of HPV positive women

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Background/Objectives: After the implementation of high risk Human papillomavirus (hrHPV) based testing in the Dutch cervical cancer screening setting in 2017, the number of women who required referral, biopsies, and control smears increased. However, most of them did not have a clinically relevant cervical lesion, and their screening participation has thus led to unnecessary worry and (invasive) testing. Using additional risk factors in the triage of hrHPV positive women can potentially limit the burden of unnecessary follow-up. However, there is no established prediction model yet that can be used to determine risk profiles for cervical malignancies and pre-cancerous lesions.

Methods: Women who tested hrHPV positive in cervical cancer screening since the implementation of hrHPV based screening were approached by their general practitioner, gynaecologists, the screening organisation, or via a broad social media campaign. Participants completed an online questionnaire on risk factors associated with the development of cervical malignancies or pre-cancerous lesions in hrHPV positive women. Additionally, pathology data from the Dutch national pathology database (PALGA) was linked. Based on this data, a risk prediction model will be developed to predict the risk of cervical intraepithelial neoplasia 2 lesions of higher (CIN2+). Different indicators of model performance will be assessed (e.g. area under the receiver operating characteristics curve (AUC), Nagelkerke's R2, and clinical usefulness). Risk predictions of the model will be used to create risk profiles.

Results: In total, 3,275 online questionnaires were completed. Records were excluded in case of duplicates (n=279), no linkage possible with PALGA (n=309), or no history of a positive hrHPV test in screening (n=626). After exclusion of these records, data from 2,061 hrHPV positive women were included in the analysis. Among them, 277 had cervical intraepithelial neoplasia (CIN) 2, 367 had CIN3, and 67 were diagnosed with cervical cancer. Prediction modelling analyses have not yet been performed. Risk factors that will be taken into account are age, smoking history, screening history, type and length of contraception use, age at first sexual contact, number of sexual partners, parity, age at first birth, use of immunosuppressants, age at menarche, diagnosis of other sexually transmitted diseases, relation status, and socio economic status. Results from the prediction model analyses and the creation of risk profiles will be available in March 2025.

Conclusions: Results from this study will indicate which risk factors can contribute to the risk prediction of cervical malignancies and pre-cancerous lesions in women who tested hrHPV positive in cervical cancer screening. This enables the creation of risk profiles upon which risk-stratified triage strategies can be organised. This may allow for women at the highest risk of developing cervical cancer to be followed up intensively, whereas the number of follow-up tests can be reduced for women at lower risk.

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The p16/Ki-67 dual stain: a triage tool - What is the reality in Portugal Center region?

12 - Triage of HPV positive women

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Background/Objectives: The p16/Ki-67 dual stain (DS) for cytology (commercially available in Portugal as CINtec PLUS Cytology) has been used for triage in order to establish the management of individuals with positive HPV results from screening with primary HPV testing or with contesting. Dual staining of cytology specimens detects a marker of HPV-related oncogene activity (p16, a tumor suppressor protein) and a marker of cell proliferation (Ki-67) that, when detected together in the same cell, is indicative of cell cycle dysregulation associated with transforming HPV infections and strongly associated with precancerous cellular changes (CIN3+). The aim of this work was to detect the ability of dual staining for the detetion on CIN2+ lesions in our population.

Methods: The p16/Ki-67 dual stain (DS) for cytology performed between 2022 and 2023 at the IPO-Coimbra at the Gynecology Department were reviewed and analyzed with SPSS 26.

Results: A total of 96 DS were performed, from this 57.3% (n=55) were positive, 21.9%(n=21) were negative and 18.8% (n=20) were inconclusive. In the group of positive results, there reflex cytologys were: ASC-US (n=33), LSIL (n=17), NILM (n=4), ASC-H (n=1). In the patients with positive DS submitted to transformation zone excisional treatment (n=33) the histology revealed: Scamous cell carcinoma (n=1), CIN 3 (n=1), CIN 2 (n=5), CIN 1 (n=22), inflammation (n=1) and ausent dysplasia (n=3). In this same group (DS+), the colposcopic evaluation were normal (n=38 cases), abnormal G1 (n=13), abnormal G2 (n=2) and abnormal non-specific (n=2). There were 4 cases of negative DS with positive cervix biopsys for LSIL. Among imunossupression, age of coitarche, HPV vaccine, contraception use and smoking, only this last seems to be statistically significative for the result of DS ($p<0,05$).

Conclusions: In the population studied, the colposcopic evaluation only detected abnormal findings in 14 cases of the 55 positive DS cases. Between the cases treated with EZT due to positive DS, only 7 (%) were CIN2+.

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Viral load: a promising marker for triage of women screened positive for a high-risk oncogenic HPV genotype?

12 - Triage of HPV positive women

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Background/Objectives: Cervical cancer is the fourth most common cancer among women worldwide and is primarily caused by high-risk oncogenic human papillomaviruses (hr-HPV). Since not all hr-HPV infections progress to cancer, developing biological markers that predict progression to oncogenesis is essential for optimizing the triage and management of HPV-positive women. Therefore, the aim of this study was to assess the correlation between viral load, hypermethylation rates of the FAM19A4 and hsa-miR124-2 genes, and cytological grade (Bethesda classification).

Methods: A total of 135 hr-HPV positive cervical-vaginal samples collected during primary cervical cancer screening were analyzed. The cytological results of these samples were distributed as follows: 27 with normal cytology (N), 18 with Atypical Squamous Cells of Undetermined Significance (ASCUS), 77 with Low-grade Squamous Intraepithelial Lesions (LSIL), and 13 with High-grade Squamous Intraepithelial Lesions (HSIL). HPV DNA positivity was assessed using the AllplexTM HPV HR Detection kit (Seegene), which enables semi-quantification via cycle threshold (Ct) values. The HPV Ct values were normalized relative to the cellular content of the samples by calculating the ratio [Ct HPV / Ct ß-globin]. Furthermore, the distribution of [Ct HPV / Ct ß-globin] ratios were compared among different cytological grades using the Mann-Whitney U test, incorporating either the ratio of each genotype detected during multiple infections or solely the ratio of the predominant genotype (the one exhibiting the lowest Ct value). Genotype-specific analyses were also conducted.

Results: Overall, the [Ct HPV / Ct ß-globin] ratio was significantly lower between the LSIL and N groups ($p < 0.0001$), between the HSIL and LSIL groups ($p = 0.0058$), between the HSIL and N groups ($p < 0.0001$), and between the ASCUS and N groups ($p = 0.0081$). Thus, the HPV viral load of the predominant high-risk genotype, in cases of multiple infections, appears to correlate with the different cytological grades. This trend was also observed in the genotype-specific analysis for HPV 16. However, a poor correlation was found between HPV viral load and the hypermethylation rates of the FAM19A4 / hsa-miR124-2 genes, particularly in samples classified as ASCUS and LSIL.

Conclusions: The viral load of the predominant genotype (in cases of multiple infections) appears to be a promising biological marker for the triage of HPV-positive women, and it can be readily assessed in routine clinical laboratories. However, these findings require confirmation through a larger prospective study to establish the predictive value of this marker for the progression toward oncogenic processes.

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Persistent HPV-DNA positivity with triage PAP test negative: contribution of genotyping and E6/E7 mRNA

12 - Triage of HPV positive women

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Background/Objectives: Starting from July 2019, HPV testing has replaced cytology for cervical cancer screening in Friuli Venezia Giulia (northeastern Italy). The Regional Laboratory of the Department of Pathology at Cattinara Hospital in Trieste performs all the analyses according to manufacurer's protocol. In the period between July 2019 and August 2024, 151,190 women were recruited from regional cervical cancer screening centre. Patients HR HPV positive (Cobas Roche) were 11.616 (7.6%). Cytologic triage by Pap test showed a lesion in 4050 women (36%) who were referred to colposcopy, whereas in 7426 women (64%) Pap test was negative and HR HPV test was repeated after 1 year. At the 1 year recall, of the 5.349 women (72%) who responded, 2402 (45%) were again HR HPV positive with Pap Test negative, representing a relevant burden for colposcopic referral centres. HR HPV was negative in 1980 cases (37%), and the remaining 940 women were HR HPV positive with a cytologic lesion at Pap Test. Objective: We evaluated the contribution of genotyping and E6/E7 mRNA overexpression as triage tests to reduce referrals to colposcopy in women with persistent HR HPV positivity and triage Pap test negative.

Methods: We recruited 504 consecutive cases in years 2022-2023 with persistence of HR HPV-DNA positivity and triage Pap test negative. At early recall (after 1 year) they were tested ith E6/E7 mRNA assay (Aptima Hologic) and positive cases were genotyped for qualitative detection of 28 HPV types (Allplex Seegene). Mean age was 51 years (31-66). Positve samples were divided in three risk groups, as suggested in NTCC2 study, based on the risk of CIN 3+: 16/18, HPV; high oncogenic HPV types (31. 33. 45. 52. 58) and low oncogenic HPV types (35. 39. 51. 56. 59. 66 e 68) (1). We reported: sensitivity/specificity, PPV, NPV of mRNA test (the gold standard was bioptic diagnosis), the rate of CIN2+ lesions in the 3 HR HPV groups and the result of cotest after 1 year.

Results: On 504 samples, 204 (40%) were negative and 300 (60%) positive for m RNA test. Colposcopy was performed in 95% of cases (480/504) resulting negative in 81% of patients (388/480). Biopsy in mRNA negative cases showed the presence of LSIL/CIN1 in 20 cases and CIN2 in 1 case; in mRNA positive, 41 LSIL/CIN1 lesions and 19 CIN2+ lesions were found. Sensitivity: 94.7% (95%CI: 73.97-99.87), Specificity 45.4% (36.64-54.35), PPV 20.2% (17.34-23.45) and NVP 98.3% (89.66-99.75). Genotyping of 300 mRNA positive samples showed: 66 HPV 16/18, 160 high oncogenic types and 74 low oncogenic types. The 19 women with CIN2+ lesions had the following distribution: 12 from HPV16/18 group, 5 from high oncogenic HPV group , 1 from low oncogenic HPV group and 1 mRNA negative with HPV45 + . At 1 year follow up cotesting we found no case in mRNA negative and low oncogenic HR HPV group with CIN2+ lesions

Conclusions: The use of E6/E7 mRNA and genotyping as triage assays in women with persistent HR HPV positivity and Pap test negative could reduce unnecessary referral to colposcopy - in all cases mRNA negative or mRNA positive with low oncogenic HPV group - and the risk of overtreatment.

References: 1. Benevolo et al Comparison of HPV-positive triage strategies combining extended genotyping with cytology or p16/ki67 dual staining in the Italian NTCC2 study. eBioMedicine 2024;104: 105149 https://doi.org/10.1016/j.ebiom.2024.105149

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#9464

Optimizing CIN2+ Risk Stratification in HPV DNA-Positive Women: A Comparison of 7-Type HPV mRNA Testing and Cytology

12 - Triage of HPV positive women

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Background/Objectives: HPV-based screening is the preferred strategy for cervical cancer prevention, necessitating efficient and accurate triage methods. This study compares the effectiveness of a 7-type HPV mRNA test (PreTect HPV-Proofer'7) versus cytology in triaging women who tested positive in primary HPV DNA screening.

Methods: Between 2019 and 2023, 34,721 women were screened for HPV DNA at the University Hospital of North Norway using the Cobas 4800 test, which provides partial genotyping for HPV types 16 and 18, along with pooled detection of 12 additional high-risk HPV types. Women who tested positive for HPV DNA underwent further triage with cytology and a 7-type HPV mRNA test, which offers extended genotyping for HPV types 16, 18, 31, 33, 45, 52, and 58. Biopsy follow-up through October 2024 was conducted to confirm CIN2+ diagnoses. The study evaluated positive predictive values (PPV) for CIN2+ based on HPV DNA and mRNA genotyping for types 16, 18, and other high-risk genotypes.

Results: Among the screened women, 5.6% (1,944/34,721) tested positive for HPV DNA. Of these, 97.5% (1,896/1,944) had valid HPV mRNA results, with 33.4% (634/1,896) testing positive for HPV mRNA. Among women with valid HPV mRNA results, 13.3% (252/1,896) were diagnosed with CIN2+. The positivity rates for cytology (ASC-US+) and the HPV mRNA test were 50.3% and 33.4%, respectively. For CIN2+ detection, the HPV mRNA test demonstrated a sensitivity of 70.6% (178/252) and a specificity of 72.3%, significantly higher than the 53.0% specificity of cytology. The overall PPV of the HPV mRNA test was 28.1%, notably higher than the 19.1% PPV observed with cytology. Genotype-specific analysis revealed that HPV mRNA16 had the highest PPV for CIN2+ at 47.3%, compared to 29.8% for HPV DNA16. Other high-risk mRNA types also showed substantial PPVs, including mRNA33 at 39.2% and mRNA31 at 32.2%, underscoring the improved predictive value of mRNA testing over DNA genotyping.

Conclusions: The 7-type HPV mRNA test offers improved specificity and enhanced risk stratification over cervical cytology for triaging HPV DNA-positive women. Genotype-specific mRNA testing, particularly for HPV16, 33, and 31, provides significant predictive value for CIN2+, allowing for a more targeted approach in identifying women at elevated risk. These findings support the potential for broader integration of HPV mRNA testing into cervical cancer screening protocols to optimize the balance between screening benefits and potential harms.

References: Sørbye SW, Falang BM, Antonsen M. Performance of a 7-Type HPV mRNA Test in Triage of HPV DNA Primary Screen Positive Women Compared to Liquid-Based Cytology. Journal of Molecular Pathology. 2023; 4(2):69-80. https://doi.org/10.3390/jmp4020008

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#9526

Uncovering Histologic Findings in Persistent Low-Grade Cytology Cases in A Tertiary-Level Hospital In Madeira, Portugal

12 - Triage of HPV positive women

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Background/Objectives: Human papillomavirus (HPV) infection is the most common sexually transmitted infection. Persistent high risk-HPV (HR-HPV) infection greatly increases the risk of lesion persistence or progression. Cervical excisional surgery is the standard procedure for the treatment of HSIL, though there remains debate surrounding the management of persistent low-grade cytology results. This study aims to evaluate the histologic findings of diagnostic conizations performed due to persistent low-grade cytological abnormalities linked with HR-HPV, providing insights to guide management strategies for this patient subgroup.

Methods: We conducted a retrospective analysis of all women who underwent excision of the transformation zone (TZ) at Hospital Dr. Nélio Mendonça in Madeira, Portugal, between January 2021 and December 2023, based on data from the hospital's database. For this study, we focused on diagnostic conizations performed specifically due to persistent HR- HPV infection and/or with recurrent low-grade cytologic abnormalities lasting at least 24 months.

Results: Of a total of 254 excisions of the TZ, 7.9% were motivated by the persistence of low-grade cytological changes associated with HR-HPV (n=20). The average women's age was around 47 years. 4 were smokers (20%), and 2 were immunocompromised (10%). HPV 16/18 were identified in only 2 patients (10%), while other high-risk HPV types (HR-HPV OT) were present in 17 women, with HPV 33 and 52 being the most frequent among them. Regarding cytology results, most patients (80%) had low grade intraepithelial lesion (LSILs). 1 patient was negative for intraepithelial lesion or malignancy (NILM) and 3 had atypical squamous cells of undetermined significance (ASC-US). Colposcopy-directed cervical biopsy, when performed, identified CIN1 (71%) or chronical cervicitis (29%). The histological examination of the excised cone revealed no dysplasia or CIN1 in 16 patients (80%) and CIN2 (HSIL) in 20% of cases. The CIN3+ rate was 0%. At the first follow-up visit, conducted six months post-conization, a co-test with cytology and HPV testing was performed as a test of cure (TOC). NILM was the most common cytological outcome (70%), with 71% of these women testing negative for high-risk HPV. Among the 11 HR-HPV-negative women, 9 had received HPV vaccination (82%), and 9 were non-smokers (82%).

Conclusions: Women who test positive for HR HPV and have NILM or low-grade cytology outcomes make up the largest subgroup in the screening population, yet they may also present high-grade histological findings. These results underscore the importance of identifying specific risk factors and implementing targeted intervention strategies in cases of persistent HR-HPV with low-grade cytology, as this approach may aid in preventing the progression of cervical precancerous lesions and ultimately reduce the incidence of cervical cancer.

FC03 - Screening methods

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#9340

Brussels VALHUDES protocol: an improved framework for clinical validation of sample-collection strategies

16 - Screening methods

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Background/Objectives: Currently HPV-based cervical cancer screening is being implemented in more and more countries, including, as an option, triage of HPV+ women using molecular methods (limited or extended HPV genotyping, methylation, etc.). These latter molecular triage options do not necessitate cell preserving alcoholic media. In parallel, a full molecular workflow has been suggested to challenge the established one and alternative collection devices are gaining popularity as well. The Brussels VALHUDES framework provides an enhanced methodology for validating both self-collected as well as clinician-collected samples, employing alternative combinations of collection devices and transport media. Protocol improvements include introduction of a hybrid cohort, comprising both a screening population (mainly to determine screening specificity) as well as a cohort of women attending a colposcopy clinic (mainly to measure screening sensitivity). An significant improvement compared to the Brussels VALHUDES study is the assessment of specificity for self-collected vaginal samples within a true screening population. Finally, alternative triage options are gaining much more visibility, especially assays capable of detecting signature methylation alterations are becoming more routinely used. Clinical validation of methylation is still topic of intensive debate, more precisely given the plethora of target genes in different assays. Also here, the Brussels VALHUDES aims to assess the performance of diverse triage assays in non-cervical samples.

Methods: The Brussels VALHUDES, a paired diagnostic test accuracy study, will be conducted in Brussels (Belgium). Sample size is determined to be 800 women attending screening, enriched with 450 women attending colposcopy clinics. Index sampling will be done using FLOQSwab (Copan Group, Brescia, Italy) in 5 mL MSwab (Copan Group, Brescia, Italy) collection medium. Collected samples include two vaginal samples (one dry patient-collected sample, and one physician-collected sample in 5 mL MSwab buffer) next to two cervical samples (one physician-collected sample using FLOQSwab in 5 mL MSwab collection medium, and one standard-of-care Cervex Brush (Rovers Medical Devices, The Netherlands) sample in 20 mL Thinprep (Hologic Inc., California, USA) medium.

Results: The Brussels VALHUDES study investigates the feasibility of using a single collection device for both clinician-collected cervical samples and self-collected vaginal samples. Additionally, the study aims to assess the accuracy of specific HPV test combinations applied to both wet and dry self-collected samples, comparing the results with those obtained from clinician-collected standard cervical samples. Finally, the study will evaluate the concordance of methylation test results between self-collected and clinician-collected samples.

Conclusions: The Brussels VALHUDES protocol provides a validation framework addressing multiple research questions on test accuracy of both established and more experimental technical testing options within an appropriate clinical context.

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#9658

International clinical and analytical validation of the Seegene Allplex HPV HR Assay with SurePath screening samples from the Danish cervical screening program

16 - Screening methods

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Background/Objectives: HPV assays intended for primary cervical cancer screening must meet the international guidelines for HPV DNA test requirements to ensure the most optimal balance between detecting HPV infections associated with CIN2 or worse (CIN2+) and clinically irrelevant, transient HPV infections. These requirements encompass a cross-sectional clinical equivalence study to compare the performance of the candidate assay head-to-head with a recognized reference assay and new HPV assays should demonstrate predetermined thresholds of clinical accuracy in order to be considered validated for clinical use. The Allplex HPV HR Detection assay (Allplex; Seegene, Seoul, South Korea), launched in late 2022, is a fully automated real-time PCR assay, that detects and concurrent distinct 12 hrHPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) and HPV66 and 68.

Methods: The clinical validity of the Allplex was assessed following international guidelines on validation of novel HPV DNA assays for use in cervical cancer screening. We assessed the validity of the Allplex comparing its clinical performance to the second-generation comparator assay BD Onclarity HPV Assay (Onclarity; BD Diagnostics, Sparks, MD, USA). As recently recommended (JMV 2024;96:e29881), interpretation of Allplex results followed high-risk HPV type stratification as defined by the International Agency for Research on Cancer (IARC). A samples was considered high-risk HPV positive if at least one of the 12 following HPV types was detected: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 using a predefined cut-offs previously clinically validated on ThinPrep medium: for HPV16/18 at Ct≤40, for HPV31/33/45/52/58 at Ct≤37 and for HPV35/39/51/56/59 at Ct≤35 (JCV 2024;170:105638). The clinical validation panel comprised of 877 residual SurePath samples obtained from women participating in Danish population-based cervical cancer screening program. In addition, analytical panel comprising of 500 samples was tested to assess inter-laboratory and intra-laboratory agreement.

Results: The clinical sensitivities for CIN2+ of Allplex and Onclarity were 98.7% (75/76; 95%CI, 92.9-100.0%) and 100.0% (76/76; 95%CI, 95.2-100.0%), respectively, resulting in a relative sensitivity of 0.99 (95%CI; 0.96-1.01). The clinical specificities of Allplex and Onclarity were 92.5% (741/801; 95%CI, 90.4-94.2%) and 92.5% (741/801; 95%CI, 90.4-94.2%), respectively, resulting in a relative specificity of 1.00 (95%CI; 0.99-1.01). At recommended thresholds of ≥90% and ≥98%, the clinical sensitivity and specificity (p=0.001 and p=0.0018, respectively) of Allplex demonstrated noninferiority to Onclarity. Excellent inter-laboratory agreement was observed, both overall (99.6%; 95%CI, 98.4-99.9%) and at the genotype level (98.2%; 95%CI, 96.5-99.1%). Intra-laboratory agreement results are still pending and will be presented at the conference.

Conclusions: Allplex fulfills international consensus guideline criteria for primary cervical cancer screening utilizing SurePath medium and can be considered as clinically validated for IARC high-risk HPV genotypes when using clinically validated cut-offs listed above.

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#9298

Exploring Quantitative Precision for HPV Detection: Transposing the RIATOL qPCR Assay to the QIAcuity Digital PCR System

20 - New technologies

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Background/Objectives: Accurate quantification of HPV viral load, defined as number of viral copies per cell, holds significant biomarker potential for cervical cancer screening, enabling precise assessment of infection degree, disease progression, and treatment efficacy. Current practices using real-time (RT-)PCR rely on indirect quantification methods, which can lead to discrepancies in viral load results. In contrast, digital PCR (dPCR), considered a third-generation PCR technology, utilizes micro compartmentalization of the PCR reaction and Poison's statistics to achieve absolute quantification of viral targets. This study aims to assess the feasibility of transposing the RIATOL qPCR HPV genotyping assay onto the QIAcuity Digital PCR System to enhance quantitative precision and reproducibility for HPV detection.

Methods: The RIATOL qPCR HPV genotyping assay is an in-house HPV assay developed at AML, Sonic Healthcare Benelux (Antwerp, Belgium), and has been used in routine screening for over 15 years. The assay comprises eight multiplex RT-PCR reactions that detect and quantify viral HPV DNA of 18 genotypes using relative calibration against synthetic standard curves. The feasibility of transferring the assay chemistry with minimal modifications to a dPCR system was evaluated using the QIAcuity Digital PCR System (Qiagen, Germany). In addition, HPV 16 and 18 dilution series were tested to investigate the minimum detectable viral concentration on the dPCR platform. Furthermore, the dPCR system was applied to various case studies as well to demonstrate its utility in quality assessment and high-resolution multiplexing.

Results: The dPCR adaptation demonstrated several advantages over traditional RT-qPCR. The dPCR system provided absolute quantification of HPV DNA, eliminating the need for relative calibration against standard curves, resulting in more precise and reliable measurements of viral load. Significantly lower viral copy levels were observed compared to the conventional qPCR approach, specifically, dPCR was able to detect 0.2 viral copies per µL of extracted DNA. The capability of the dPCR system for high-resolution multiplexing in a single channel was shown to facilitate a more comprehensive assessment of the genetic composition of the virus in individual patients.

Conclusions: Transposing the RIATOL qPCR assay to the QIAcuity Digital PCR System significantly enhances the precision and reliability of HPV viral load quantification. Overall, these findings underscore the potential of digital PCR to transform HPV detection and quantification, paving the way for improved screening protocols and enhanced clinical outcomes in cervical cancer management. Looking ahead, further studies will be conducted to evaluate the reproducibility of absolute quantification using other commercial systems. These investigations will address key factors such as laboratory usability, input volume, waste volume, throughput, and the interface of analysis software. Future applications may include molecular triage options and treatment follow-up for HPV-positive patients.

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#9447

Is there a place for Next Generation Sequencing in HPV screening?

09 - HPV testing

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Background/Objectives: There are many different HPV-tests available that are used in cervical cancer prevention screening programs. The large majority of these tests focus on qualitative HPV-DNA detection in a cervical smear or vaginal swab, and differ in their capacity to differentiate between individual HPV genotypes. HPV-DNA tests do not discriminate between cellular HPV infections that may be transforming, and clinically non-significant transient infections. This is one of the causes of low specificity of HPV-DNA tests to detect cervical (pre)cancer. Detection of HPV oncogene RNA per definition identifies clinically significant cellular HPV infection. Using Next Generation Sequencing (NGS) for this purpose also solves the problem of lack of or partial genotyping, utilizing sequence-differences between individual genotypes. Although cost of next generation sequencing (NGS) has dropped in last years, it still has the stigma of being expensive. Objective was to investigate the novel technique of highly-multiplexed targeted RNA NGS, using inversion probe technology (ciRNAseq).

Methods: We developed the ciRNAseq-based HPV-Profiler NGS Assay and performed the test on DNA and on RNA, isolated from cervical scrapes from screening programs and on the Equalis panel. HPV Profiler is a simple to execute molecular test that utilizes a set of molecular inversion probes designed for targeted detection of E2, E6, E6*I and E7 RNA from 20 different HPV genotypes. NGS libraries from different samples can be equipped with sample-specific barcodes, allowing multiplexing. Pooled libraries were sequenced on Illumina and MGI systems.

Results: HPV-Profiler is proficient to detect all HPV genotypes represented in the Equalis panel. In cervical smears the test detected HPV genotypes, concordant with the outcome of Roche COBAS tests. Importantly, the results show that multiplexing to 1,000 samples still lead to sufficient sequencing depth for accurate detection of HPV-DNA and RNA even on lowest capacity flow cells.

Conclusions: Targeted DNA or RNA sequencing is a highly attractive and cost-effective method for quantitative detection of HPV on RNA level with unambiguous individual genotyping. By utilizing the high multiplexing capacity of ciRNAseq, sequencing costs per sample will be limited to few euro's.

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#9583

Randomized non-inferiority trial on the effect of frequent versus infrequent cervical cancer screening in Finnish women vaccinated as early adolescents

16 - Screening methods

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Background/Objectives: After the randomized implementation more than 15 years ago of the national human papillomavirus (HPV) vaccination programs in Finland, HPV vaccinated cohorts are now attending cervical screening. Both the changing HPV type-distribution and immunity against the most common high risk HPV types is reducing the positive predictive value of primary screening implying the screening should be less intense in the vaccinated birth cohorts. This randomized trial was launched to assess the effectiveness and safety of infrequent screening compared to conventional frequent screening among women vaccinated as early adolescents (NCT02149030).

Methods: In 2013,6959 1992-95 born women who had received HPV16/18 or hepatitis B virus vaccination at 12-to-15 years between 2007-2009 in an earlier vaccination trial (NCT00534638) were randomized into frequent vs. infrequent primary cytology-based cervical screening at the ages of 22, 25 and 28 or at age 28. In parallel, 1334 women who received the HPV16/18 vaccine at the age of 18 were invited at age 22 to an infrequent-screening safety arm (A3). Cervical samples were HPV-genotyped using MALDI-TOF-MS, Luminex assay and/or the BD Onclarity platform for extended genotyping. We evaluate the noninferiority of the infrequent screening in Arm A2 to detect histologically confirmed cervical high grade squamous intraepithelial lesions (HSIL) compared to the frequent screening in Arm A1. The prevalence of HPV types and abnormal cytology findings at ages 22, 25 and 28 are being compared between the arms.

Results: At age 22,2744, 2882 and 1334 women participated in the frequent (A1), infrequent (A2) and safety (A3) screening arms. Participation at ages 25 and 28 was of 2467, 2645, and 1221 women in the Arms A1, A2 and A3 arms, and of 1707 and 1849 in the arms A1 and A2. The occurrence of vaccine HPV types 16/18 was reduced up to 90% in Arms A1 and A2 compared to Arm A3. The overall occurrence of HSIL was comparable in Arms A1 (0.69%, 95%CI 0.38 - 1.00) and A2 (0.62%, 95%CI 0.33 - 0.91).

Conclusions: This randomized trial provides the first evidence to estimate the accuracy and safety of infrequent screening among HPV-vaccinated women.

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#9272

Exploring the impact of point-of-care testing paired with cervical screening pathways in remote Aotearoa New Zealand

10 - HPV screening

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Background/Objectives: This study explored a different health delivery model to increase the timeliness of test-to-colposcopy referred from rural practices in Aotearoa New Zealand, by empowering local healthcare communities. The development of robust clinically validated point-of-care testing (PoCT) makes it increasingly possible for non-experts to perform complex molecular diagnostic screening tests in diverse settings (e.g. medical centres, mobile clinics, pharmacies). Utilizing this technology within clinical pathways can potentially aid diagnosis, timely treatment and improved health outcomes. Hence, this study posed the question "Can a community controlled cervical screening pathway paired with PoCT lead to timelier colposcopy?'

Methods: Three remote rural clinics were set up as HPV-based PoCT screening centres that complied with the New Zealand Best Practice Guidelines for Point-of-Care Testing. The PoCT platform chosen for this work was the Cepheid GeneXpert IV. Though off-the-shelf systems can be purchased easily, it is also required that operating environments and quality assurance processes comply with codes of best practice to provide safe services for patients. This is not straight forward in non-laboratory environments and on-ground conditions required adapting in addition to staff training. Each clinic presented different challenges before they met New Zealand best practice. However, successful implementation of PoCT screening by providing technical oversight and consideration of the whole-of-clinic set up was demonstrated.

Results: We undertook a 30-month cluster-randomised crossover trial involving 1,410 participants (PoCT arm = 632, standard care arm = 788). High-risk HPV was detected in 125 participants. When PoCT was part of a community controlled healthcare pathway, women with a positive HPV result were 4.7 times more likely to attend colposcopy within 20 working days of the test results (odds ratio: 4.7, 95% confidence interval: 1.7 to 12.8). Qualitative investigation indicated that healthcare providers found the offer of PoCT within a community controlled pathway was acceptible, reporting the they were able to build greater rapport with women and get them on an approprate treatment pathway more quickly.

Conclusions: This research will inform the practice of rural models of care for the use of innovative PoCT technology. The findings may be applicable to other rural communities in high-income countries.

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#9343

Thin-layer cervical sample evaluation: Conventional Light Microscopy versus digital Whole-Slide Imaging

20 - New technologies

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Background/Objectives: Whole-Slide Imaging (WSI) has been adopted in many fields of pathology for education, Quality Assurance and remote diagnostics. In 2021, the College of American Pathologists (CAP) updated guidelines to support pathology laboratories regarding the WSI systems validation process. However, the majority of published literature refers to histopathology rather than cytology. Our aim was to compare Conventional Light Microscopy (CLM) and WSI in thin-layer cervical samples evaluation according to CAP guideline.

Methods: A sample set of 64 thin-layer cervical specimens from women aged 25-64 who participated in cervical cancer screening programs in Tuscany was distributed among 5 cytologists at ISPRO (Florence, Italy) for CLM analysis. After two weeks, the corresponding 64 digitally scanned slide were available at several magnifications for WSI evaluation.

Results: Substantial/near perfect agreement between CLM and WSI evaluation ($0.77 \geq Kappa \geq 1$) was observed for the NILM class with concordance rates from 83.3% to 100%. Variability in concordance was observed among all the cytologists: 50%-85.7% for LSIL, 47.1%-100% for HSIL, 50%-100% for AGC favour ADK with moderate/near perfect agreement ($0.47 \geq Kappa \geq 1$). Concordance and agreement rates were also variable within the "borderline" cytological categories of ASC-US, ASC-H and AGC with lower or not computable kappa for some readers. The overall intra-laboratory concordance between CLM and WSI was 92.9% with a near perfect agreement (Kappa=0.84) for NILM. Substantial agreement ($Kappa \geq 0.65$) was assessed for LSIL, HSIL/Squamous cell carcinoma, AGC and Adenocarcinoma categories while the agreement was lower ($Kappa \leq 0.39$) for ASC-US and ASC-H.

Conclusions: We showed an overall substantial/near perfect agreement between CLM and WSI for all the cytological categories except the "borderline" ASC-US and ASC-H. Further progress in cytology WSI systems are needed before introducing it in routine diagnostics.

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#9361

The daily peer review of abnormal cervical slides: 5 years of data collection and new potential quality indicators to monitor individual and laboratory performances

16 - Screening methods

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Background/Objectives: The Peer Review (PR) process involves the daily review of Pap slides by all other cytologists in the team, when the submitting cytologist (submitting reader, SR) finds the results abnormal or difficult to interpret. After the review, the team discusses the findings to reach a consensus on the final diagnosis (FD). In this study we explore data from 5 years of PR in order to: i) evaluate the trend of agreement level (both inter-observer and versus FD) over time; ii) identify suitable parameters to propose as new quality indicators, along with the respective threshold/reference values; iii) standardize and clearly define the terminology used in the PR process.

Methods: Of the 224,455 Pap slides screened in 2017-2021, 6360 (2.8%) were submitted to PR and examined by an average of 8 cytologists (range 4-13). The overall agreement between cytologists and the agreement of each cytologist with FD were evaluated by means of the statistics Kappa (K) and weighted Kappa (wK) [1]. Category-specific K values were calculated for each diagnostic category. Each parameter was compared between two groups based on the years of experience: "experts' (>5 years) and "less experienced' readers (≤5 years).

Results: Concerning the inter-observer analysis, we observed a moderate agreement among readers (whole team K=0.44; experts K=0.47). As expected, the category-specific agreement showed the lowest K values for the ASC-H category (0.33) and the highest for HSIL (0.54). Kappa values fluctuate over time indicating its sensitivity to team changes/turnover, that could be used as a potential quality indicator of the team concordance (threshold: 0.44, i.e. the mean inter-observer kappa; desirable value: 0.47, i.e. the average kappa of experts). Considering the laboratory agreement versus FD, the trend in K values was evaluated over time and resulted significantly higher in experts compared to less experienced. This parameter could represent another potential quality indicator (threshold: 0.70, i.e. the mean laboratory kappa vs FD; desirable value: 0.72, i.e. the mean kappa value of experts). The individual agreement with FD was calculated for 16 cytologists, reaching a moderate/substantial level of agreement (wK range: 0.57-0.80). All expert cytologists show K values of at least 0.68, while a shift toward lower individual wK values was observed in the less experienced group. The definition of reference values for this indicator could be important as a goal towards less experienced cytologists should aspire. We could propose as "acceptable value" the laboratory median value (K=0.69) and as "desirable value" the median of the expert group (K=0.71).

Conclusions: The PR procedure is an important internal quality control, especially for large-size laboratories. On-going discussions of positive/difficult cytological patterns, involving cytologists with varying levels of experience, offer continuous education and training. In this study we explore data from 5 years of PR (2017-2021); to our knowledge this is the largest study population on PR in cervical cytology reported in the literature to date. We propose new potential (key) performance indicators and the respective reference values for each assessed parameter: inter-observer kappa, laboratory kappa vs FD, and individual kappa vs FD. Their trend over time could be introduced to strictly monitor (every 3/6 months) the occurrence of systematic differences in interpretation criteria among cytologists and the performances of the whole laboratory.

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#9198

Cervical cancer screening utilization and practice patterns in government-based clinics in Puerto Rico.

16 - Screening methods

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Background/Objectives: In the United States (US), the American Cancer Society recommends cervical cancer screening for people aged 25 to 65 years every 5 years using the primary human papillomavirus (HPV) test. If a primary HPV test is not available, a co-test (an HPV test with a Pap test) every 5 years or a Pap test every 3 years is suggested. Little is known about the uptake and utilization of screening using these modalities in Puerto Rico, a jurisdiction within the US with the highest incidence of cervical cancer (12 per 100,000). We evaluated cervical cancer screening utilization and practice patterns among women aged 25-65 years old seen at academic setting clinics in PR from 2012-2024.

Methods: Data from the medical records of women attending two government clinics in Puerto Rico was analyzed. The medical records revision began in June 2024 and is currently undergoing. A total of 940 medical records from 2012-2024 have been reviewed. Only patients aged 25-65 years with information on Pap and HPV test results were included, resulting in a final analytic sample of 600. Guidelines-concordant adherence to cervical cancer screening was determined using the ACS recommendations. Descriptive statistics were used for continuous variables, and frequency distributions to describe the population of interest. Pearson chi-square, Fisher exact test, and logistic regression were used to assess predictors for cervical cancer screening adherence.

Results: The median age was 50 years (interquartile range, 41 to 58), 34.7% were up-to-date on screening and 65.3% were delayed according to the ACS guidelines. Only four patients were screened using a primary HPV test, 46.2% using a Pap test, and 53.2% using co-testing. Screening test results indicated that 13.8% of individuals had a Pap test result of ASCUS or more, and 17.5% were HR-HPV positive. In bivariate analysis, a higher proportion of women who were initially screened using co-testing were up to date on screening recommendations as compared to those who were screened using Pap Test (61.4% vs. 4.3%, $p<0.001$). In logistic regression analysis adjusted for age and clinic; participants who underwent co-testing had a greater likelihood (odds ratio: 1.78; 95% CI: 1.66 to 1.88) of being up-to-date on cervical cancer screening guidelines in comparison to those who were screened using Pap test.

Conclusions: To our knowledge, this is the first study to report the uptake of primary HPV testing and co-testing in Puerto Rico. Our findings show a high co-testing uptake in comparison to the use of Pap tests and primary HPV test. In addition, co-testing was associated with higher adherence to cervical cancer screening guidelines. This study suggests that promoting co-testing may improve adherence to cervical cancer screening recommendations, potentially mitigating cervical cancer incidence and mortality in Puerto Rico.

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#9357

Comparison of traditional and social media recruitment methods for an online questionnaire study in hrHPV positive women

10 - HPV screening

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Background/Objectives: All studies involving human subjects need to make a decision on how to recruit participants. However, recruitment effectiveness for survey participants has declined over the last decades. In addition, recent privacy regulations make it difficult to approach potential participants via institutions like national screening organisations. The PREFER study investigates the possibility of adding risk factors, alongside high risk Human Papillomavirus (hrHPV), to the triage of cervical cancer screening. Embedded in this study are questionnaires to collect risk factor information of hrHPV positive women. Recruitment of participants was planned with mass mailing by the screening organisation. However, developments in logistics, recruitment effectiveness and GDPR legislation obliged us to investigate alternative recruitment options. Therefore, this study aimed to compare recruitment of participants via traditional and social media recruitment methods for an online questionnaire study in hrHPV positive women.

Methods: The study targets Dutch women, aged 30 to 66, who had a positive hrHPV test result in the population-based cervical cancer screening programme since 2017. Recruitment strategies were split into traditional methods and via social media. The traditional methods were 1) mailing of invitation leaflets to hrHPV positive women by the screening organisation, 2) handing out leaflets to hrHPV positive women by gynaecologists, and 3) e-mailing patients registered to have tested hrHPV positive by general practitioners (GPs). The social media campaign was set up in collaboration with "Bureau Cambio", an agency on behaviour communication. Social media advertisements were placed on Facebook and Instagram for five months. Advertisements were based on behaviour influencing techniques and targeted at Dutch women (30-66y) in general, and specifically at women with a low socio-economic status (SES). Questionnaire data were linked to pathology data from the national registry (PALGA) for data analyses and an eligibility check of participants.

Results: In total, 3,275 participants completed the questionnaires. The screening organisation recruited 124 participants after sending out approximately 1,000 leaflets. The gynaecologists recruited 156 participants after handing out leaflets in nine hospitals for nine months. GP records turned out not to be able to select hrHPV positive women easily. Therefore only two practices invited 173 patients, of whom 62 participated. The social media campaign led to 173,837 views, 24,148 clicks to the study website, 6.454 started questionnaires, and 2.885 completed questionnaires. The "societal motivation' influencing technique resulted in the highest click trough rate and lowest costs per click in both the general and low SES targeted groups. After data linkage, investigation, and cleaning, 1,214 participants were excluded due to duplicates (n=279), linkage difficulties (n=309), or ineligibility (n=626).

Conclusions: The screening organisation and gynaecologists were only able to reach small populations and the participation rate was low. The participation rate for invitations via the GPs was quite high; however, inefficient registration restricted the sending of invitations to a limited population. The social media campaign resulted in a low participation rate, but the population reached was very large. Therefore the campaign recruited by far the most participants for our online questionnaire study (88%).

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#9237

Nationwide analysis of the cervical cancer prevention pathway in Estonia

10 - HPV screening

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Background/Objectives: Cervical cancer is largely preventable, yet significant numbers of cases and deaths persist across Europe each year. While participation in screening programs is essential, it alone is insufficient to eliminate the disease. The prevention of cervical cancer requires not only screening but also active follow-up and treatment after abnormal results. However, limited research has explored participation in this full prevention pathway. This study aimed to map the entire cervical cancer prevention process—from initial screening through to treatment—among women in the screening target population, identifying gaps that contribute to missed opportunities in preventing the disease.

Methods: This retrospective cohort study utilized data from Estonia's nationwide and population-based electronic health data collection between January 2021-March 2024, and the one screening laboratory (SYNLAB). The proportion of women who participated in each stage of secondary prevention, from initial screening to treatment of precancerous lesions and follow-up care was examined. Statistical analyses included calculating percentages, median times to reach each pathway stage, and cumulative incidence at two years with 95% confidence intervals (CI).

Results: Data on 44,282 women invited for cervical cancer screening in 2021 and 2022 were analysed. A total of 20,242 women (45.7% of the target population) participated in the initial HPV NAT screening (2021: 9,492 women; 2022: 10,750 women). Of these, 1,615 women (8%) tested positive for high-risk HPV (hrHPV) and underwent a cytological test. Within 12 months, 530 hrHPV-positive women (32.8%) underwent colposcopy. Among those who had colposcopy, 279 women (52.6%) were diagnosed with precancerous conditions or cervical cancer within a year post-procedure. Additionally, just 592 hrHPV-positive women (37.2%) attended a follow-up hrHPV testing within 12 months.

Conclusions: Estonia's cervical cancer prevention program reveals significant gaps in screening uptake and follow-up procedures, emphasizing an urgent need to implement systematic interventions like automated reminders and patient navigators to enhance adherence and reduce missed opportunities for preventing cervical cancer.

FC06 - Anal neoplasia / Vulvar neoplasia / Skin diseases I

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#8878

Anal Intraepithelial Neoplasia Screening in Women from the Largest Center for Lower Genital Tract Disease in China

27 - Anal neoplasia

Background/Objectives: This study aimed to provide comprehensive clinical screening data for anal intraepithelial neoplasia (AIN).

Methods: This study included 312 patients who underwent high-resolution anoscopy (HRA) examinations between January 1, 2020 and April 15, 2024. Clinical data, including demographic information, clinical history, cytology/high-risk human papillomavirus (hrHPV) results, and HRA records, were analyzed.

Results: The median age of all patients was 42 years (interquartile range: 33-52 years). Approximately 26.3% reported a history of VIN2/3+, 13.5% had a history of VaIN2/3+, 29.8% had a history of CIN2/3+, 44.6% had persistent cervical HPV16 infection, and 12.5% had immune suppression. Among the 312 patients, 14.4% were diagnosed with AIN2/3, 25.0% with AIN1 and 60.6% were normal. Anal cytological abnormalities were found in 41.3% of all patients, with a significantly higher rate in AIN2/3 patients than in ≤AIN1, 71.1% vs. 36.3%, $p<0.001$. The hrHPV positivity rate was 89.7%, with HPV16 being the most prevalent. The complete agreement rate for HRA impressions was 79.5%. Multi-variable analysis revealed immune suppression (odds ratio [OR]: 3.47, 95% confidence interval [CI]: 1.42-8.5) and VIN2/3+ (OR: 2.82, 95% CI: 1.27-6.28) were independent risk factors for AIN2/3. Abnormal cytology results (OR: 3.3, 95% CI: 1.52-7.17) and anal HPV16 infection (OR: 3.2, 95% CI: 1.26-8.12) demonstrated similar ORs for AIN2/3.

Conclusions: Early screening for AIN2/3+ is crucial in Chinese women with lower genital tract precancerous and cancerous lesions, particularly in those with VIN2/3+ and immune suppression.

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#9255

Multizonal Anogenital Neoplasia in Women with Genital Precancer and Cancer: Baseline Findings from a Prospective Clinical Trial

27 - Anal neoplasia

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Background/Objectives: Women with genital HPV-associated precancer and cancer are at a significantly higher risk of developing metachronous cancer at other anogenital sites, particularly the anal canal and perianal region. This prospective clinical trial aims to assess the prevalence and severity of anal HPV disease in women with high-grade squamous intraepithelial lesions (HSIL) or cancer of the cervix, vagina, or vulva.

Methods: Women aged 35 and older with a history of cervical, vaginal, or vulvar HSIL or cancer were enrolled in the study. At baseline, participants underwent concurrent anal cytology, oncogenic HPV testing, and high-resolution anoscopy (HRA)-guided biopsy.

Results: A total of 121 women (mean age 50, range 35-76) were enrolled during the first year of the trial, with 8% having a history of cervical or vulvar squamous cell carcinoma and 92% with cervical and/or vulvar HSIL. No participants presented any symptoms indicative of anal cancer at the time of screening. Anal abnormal cytology was found in 64% of participants, including 13% with HSIL or ASC-H. Anal oncogenic HPV prevalence was 35%, with 7% testing positive for HPV16 and/or 18. HRA-guided biopsy results revealed histological HSIL in 30%, LSIL in 64%, and no dysplasia in 6% of participants. The highest anal HSIL incidence (31%) was observed in women with cervical HPV16/18, followed by those with non-16/18 HPV (19%). Cervical and anal HPV16/18 positivity showed no significant correlation.

Conclusions: Even without anal cancer-related symptoms, screening the anal canal in women with genital precancer and cancer is warranted for early detection of multizonal disease and prevention of metachronous cancers. Continued research through this clinical trial could further identify the highest-risk subgroup.

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#9513

Biomarkers for anal cancer screening: systematic review and meta-analysis

27 - Anal neoplasia

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Background/Objectives: Anal canal carcinoma is relevant because it occurs commonly in high-risk groups and its diagnostic allows early treatment and prevention of cancer. This study evaluated the accuracy of "DNA HPV", "mRNA HPV", "p16" and "HPV 16/18" tests in the screening of precursor lesions of anal cancer; the material analised was anal smears. They were compared to histopathologic examination as the reference, in all subjects and two subgroups: PLWH (people living with HIV) and PLWH MSM (Men Sex Men) subgroups.

Methods: The data sources included studies identified in the Medline, LILACS, Cochrane Library and Embase electronic databases, as well as in the grey literature. The search terms included "anal cancer", "AIN", "DNA HPV", "mRNA HPV" and "p16".

Results: In first selection, 10.258 studies were screened, 464 studies were analised in full. After excluding studies with no histopathological data, other design, and those with duplicate and missing data, 35 primary studies were included. A total of 11,902 patients were included. The pooled sensitivity, specificity, DOR (Diagnostic Odds Ratio) and AUC (Area under the Curve) for the detection of anal intraepithelial neoplasia (AIN) grade 2 or worse versus AIN grade 1 and normal are shown in table below. The performance of HR HPV DNA had higher sensitivity and its accuracy was better in the PLWH and PLWH MSM subgroups. Therefore, the others tests presented higher specificity.

Conclusions: HR HPV DNA test presented much higher sensititity, best DOR and can be considered the superior choice for screening at this moment. mRNA HPV, p16/K67 and HPV 16/18 tests can be usefull as a second step in a screening algorithm.

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#9203

A case of verrucous carcinoma of the vulva in a patient with human immunodeficiency virus (HIV) infection.

31 - Genital warts

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Background/Objectives: Anogenital warts are a sexually transmitted infection (STI) caused by the human papillomavirus (HPV), particularly types 6 and 11. They present as soft papules or plaques of varying size and shape on the anogenital skin. The prevalence of HPV infections is higher in individuals with immunosuppressed conditions, including human immunodeficiency virus (HIV) infection.

Methods: In 2022, a patient presented for a gynecological visit due to genital warts. She was a 54-year-old HIV-positive woman who smoked and was not adhering to her therapy. Her medical history included a hysterectomy for severe dysplasia. The patient did not undergo the recommended gynecological surveillance and missed several scheduled appointments. In 2022, she underwent excision of condylomas and laser vaporization. Histological results confirmed the presence of condylomas without dysplasia. A vaginoscopy was performed, and multiple biopsies revealed histological evidence of vaginal intraepithelial neoplasia grade 1 (VAIN1). She was lost to follow-up until 2024, when she returned for a gynecological appointment. At that time, she reported no gynecological or oral symptoms. The gynecological examination revealed multiple vulvar condylomas on the pubic mound, vulva, bilateral groins, and peri-anal region. The condylomas on the pubic mound were irregularly sized and of a melanotic color. Cytological examination showed low-grade squamous intraepithelial lesion (LSIL), and HPV testing was positive for types 51, 52, and 56. The patient refused a biopsy of the genital warts. She was recommended for laser removal of the warts, which proceeded without complications during hospitalization. The histopathological report indicated verrucous carcinoma, a rare subtype characterized by vegetative and locally invasive growth. Due to anal involvement, she was referred for a proctology consultation, and continued monitoring was recommended. A follow-up visit was scheduled for one month later.

Results: In this case, the patient was referred to the gynecology clinic at an advanced stage of condyloma development. Verrucous carcinoma is an uncommon type of vulvar cancer, classified as stage pT1b, Rx (FIGO IB). The patient was referred for oncological consultation.

Conclusions: This case highlights that individuals infected with human immunodeficiency virus (HIV) are at increased risk of co-infection with sexually transmitted diseases. Verrucous carcinoma can be particularly aggressive, emphasizing the need for vigilant monitoring in HIV-positive patients.

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#9467

Carbon Dioxide Laser for the Treatment of Localized Provoked Vulvodynia

26 - Vulvar diseases and neoplasia

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Background/Objectives: Provoked vulvodynia (PVD), defined as pain upon touch or pressure without spontaneous or ongoing pain1. The prevalence of PVD has been estimated at 10%-15%2. Treatment of PVD is challenging and often requires a multidisciplinary approach. Vestibulectomy is one of the only proven therapeutic treatments for provoked vulvodynia (PVD)3. However, Vestibulectomy is quite invasive, and the surgery has an impact on the morphology of the vulva, thus affecting the patient's psychology. We study whether carbon dioxide laser of the vulva, this minimally-invasive approach, is effective for vulvodynia.

Methods: After local anesthesia, in the vulvar area with a positive Q-tip test, carbon dioxide laser treatment is performed at 5-10 minutes, with a laser depth of 3-4 mm and the laser power of 15-20W. Patients with vulvodynia who underwent carbon dioxide laser between 2018 and 2024 were interviewed to assess VAS (Visual Analogue Scale) scores of pain before and after laser treatment, and pain-relief rate，as well as satisfaction of the carbon dioxide laser treatment. Differences in pain before and after laser treatment were assessed using a paired-sample t test.

Results: Of 47 eligible patients treated by carbon dioxide laser, 4 are lost the follow-up and 43 complete the follow-up (91.5%). The follow-up time ranged from 3-75 months（29.3±21）. The ages of the patients ranged from 26 to 70（43.37±11.8）years old. The duration of vulvodynia ranged from 3 to 120 months（38.9±39.5）. The number of laser treatments ranged from 1 to 6 times（1.84±1.08）. Before laser treatment, the average VAS score of pain ranged from 4 to 9 points(6.4±1.54). After laser treatment, the average VAS score of pain ranged from 0 to 6 points（1.4±1.4）. The VAS scores before and after laser treatment decreased significantly, and the difference was statistically significant. After laser treatment, there are 39 cases (90.7%) with pain relief of more than 75%, 27 cases (62.8%) with complete pain disappearance, and the average relief rate was 70.5%. There are 2 cases were completely ineffective (4.6%), and one case of vulvodynia recurrence（2.3%）at the time of follow up. 39（90.7%）of respondents were highly satisfied, 95% would undergo the laser again.

Conclusions: Carbon dioxide laser is an excellent minimally-invasive treatment for PVD.

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#9380

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

26 - Vulvar diseases and neoplasia

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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 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. Additionally, genotyping of high-risk HPV types was conducted to identify specific HPV strains involved in disease progression, providing a clearer understanding of viral contributions to malignancy.

Results: A total of 123 multi-timepoint samples from 12 women were analysed, covering 15 invasive squamous cell carcinomas (SCCs) located in the anal canal (n=4), peri-anal region (n=6), vulva (n=2), and vagina (n=3). Results showed that lesions in the vulvar, vaginal, and anal regions followed a similar pattern to cervical unifocal disease, with increasing methylation correlating with disease severity. Interestingly, the methylation pattern for peri-anal sites was distinct. We evaluated S5 performance in -IN2+ lesions, which showed significantly higher methylation levels in the vagina, vulva, and anus ($p < 0.001$). The longitudinal design of this study enabled us to identify lesions likely to progress to cancer in advance. We are developing a methylation-based prioritization system to help rank lesions for treatment. Genotyping analysis further provided detailed identification of high-risk HPV types across different lesion sites.

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.

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Synchronous HPV infections in anal canal in patients with HPV-related gynecological diseases.

27 - Anal neoplasia

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Background/Objectives: The human papillomavirus (HPV) has an affinity to the epithelium in the transformation zones in the cervix, anal canal, and oropharyngeal area. Therefore, gynecological patients with HPV-related diseases are at risk for synchronous HPV infections in other regions, including the anal canal. Primary objective was to examine the incidence of HPV infection and cytological abnormalities in the anal canal in patients treated for HPV-related gynecological diseases. Secondary objectives were to test HPV type distribution and risk of anal canal infection depending on gynecological localization of the HPV-related disease.

Methods: It was a prospective, cross-sectional, case-control, single-institution study performed in the Pomeranian Hospitals in Gdynia, Poland, between May 2023 and September 2024. The study consisted of two groups: the research group- patients with histologically confirmed HPV-related gynecological diseases (cancers and high-grade intraepithelial lesions (HSIL) of the cervix, vagina, and vulva), and the control group- patients with gynecological diseases that were neither related to HPV, nor had a medical history of HPV infections. We collected swabs for HPV genotyping and liquid cytology (Anyplex II HPV HR Detection test- multiplex real-time PCR; BD SurePath collection vial). A research group had collected two swabs: from the anal canal and from the gynecological disease area. A control group had a swab collected from the anal canal. Pearson's Chi-squared test was used for the statistical analysis of qualitative parameters.

Results: We recruited 100 patients in research (mean age: 49 years) and 100 in control groups (mean age: 53). The incidence of HPV infection of the anal canal in the research group was significantly higher than in the control group (63% vs. 10%, $p<0.05$). The risk of anal infection in patients with cervical cancer and HSIL(CIN3) was 68.6% and 59.1% respectively. Other gynecological diseases occurred too rarely to obtain reliable results, however all patients with vulva cancer exhibited HPV infection in the anal canal. The most common HPV type detected in the anal canal was 16 (57.9% of all anal HPV-positive cases), followed by type 31 (17.5%) and 51 (15.8%). In the control group the most common detected type was 51 present in 30% of all anal HPV-positive cases. In 82.5% of cases, the same HPV type was present in the anal canal and in the tested gynecological organ. The incidence of abnormal cytology results were similar in the research and control groups: 8% and 6% respectively ($p>0.05$). The most common cytological abnormality both in the research and the control group was ASC-US (5% and 6% of all cases respectively, $p>0.05$).

Conclusions: Patients with HPV-related gynecological diseases constitute a group with a significantly increased risk of HPV infection of the anal canal, with the type 16 being the most common. It seems reasonable to introduce HPV based test for anal cancer screening in patients with HPV-related gynecological diseases. Further research is warranted to define the clinical significance of the synchronous anal canal HPV-positive test in patients treated for HPV-related gynecological diseases.

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#9489

Clinical characteristics of post-hysterectomy vaginal malignant tumor: a retrospective analysis of cytology, high-risk HPV, colposcopic impression and previous history for hysterectomy

26 - Vulvar diseases and neoplasia

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Background/Objectives: Vaginal cancer is a rare gynecological malignancy, accounting for 2% of all gynecological tumors. Despite its low incidence, it poses a significant threat to women's health due to diagnostic challenges and limited treatment options. The primary histological type is squamous cell carcinoma, followed by adenocarcinoma, melanoma, and sarcoma. While cervical cancer screening has reduced cervical cancer incidence, post-hysterectomy vaginal cancer screening and prevention remain challenging. This study aimed to evaluate the diagnostic value of cytology, high-risk human papillomavirus (HR-HPV) testing, colposcopic impression, and hysterectomy history in patients with post-hysterectomy vaginal malignant tumors.

Methods: This retrospective analysis included patients diagnosed with vaginal malignant tumors at the Obstetrics and Gynecology Hospital of Fudan University between May 2017 and September 2022. Patients with concurrent cervical or vulvar cancer were excluded. Data collection included demographics, histological information, cytology, HR-HPV testing results, and colposcopic impressions. Statistical analysis was performed using t-tests and Chi-square tests with SPSS 24.0 software.

Results: A total of 229 patients with vaginal cancer were included, of which 65.9% had a previous hysterectomy. The most common histologic type was squamous cell carcinoma, followed by serous adenocarcinoma, malignant melanoma, and clear cell carcinoma. Among the 151 cases after a previous hysterectomy, 115 had a hysterectomy for cervical lesions, and the other 36 had a hysterectomy for non-cervical lesions. The mean age of patients with an earlier hysterectomy (53.9 years) was significantly older than those without (51.3 years, $P = 0.000$). The time span between the previous hysterectomy and the occurrence of vaginal malignant tumor in patients who had a hysterectomy for cervical lesions (43.2 ± 42.3 months) was significantly shorter than those for non-cervical lesions (66.4 ± 69.2 months $P = 0.001$). The most common HPV type detected was HPV 16 (68.4%), followed by HPV 18 (5.3%), HPV 33 (3.9%) and HPV 52 (3.9%). Of the 36 patients with a previous hysterectomy for non-cervical lesions, 12 had HPV testing, and 58.3% were HPV 16 positive, similar to patients who had hysterectomy for cervical lesions (77.3%, $P = 0.155$). In vaginal squamous cell carcinoma patients with a previous hysterectomy for non-cervical lesions, 90.0% were HR-HPV positive, and 80.0% were ASC-US+, which was similar to those who had a hysterectomy for cervical lesions (95.3%, $P = 0.471$, and 92.1%, $P = 0.215$, respectively). Colposcopy detected all other pathological types of vaginal malignant tumors that cytology failed to identify.

Conclusions: Our findings emphasize the importance of HR-HPV testing, cytology, and colposcopy in the detection of vaginal cancer, particularly in patients with a history of hysterectomy for both cervical and non-cervical lesions. These insights could guide clinical practice by highlighting the need for continued surveillance in patients who have undergone hysterectomy for non-cervical lesions, despite the common belief that they are no longer at risk for gynecological malignancies. Further research into the natural history of vaginal cancer after hysterectomy is needed to understand disease progression better and to develop more effective prevention and treatment strategies.

FC04 - Risk populations - Low resource settings

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#9507

Feasibility of Topical Artesunate for Cervical Precancer Treatment Among Women Living with HIV in Kenya: Preliminary Results from a Phase I Trial

38 - Low resource settings

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Background/Objectives: Women living with HIV (WLWH), a majority of whom reside in low- and middle-income settings (LMICs), face the highest risk of cervical cancer. In LMICs, access to provider-administered precancer treatment is limited due to a shortage of trained healthcare providers and inadequate health infrastructure. An effective and accessible self-administered precancer treatment could be transformative for secondary prevention of cervical cancer in LMICs, particularly for WLWH. Recent Phase I studies in high-income settings have shown promising safety and early efficacy of topical artesunate in treating HPV-associated anogenital lesions in HIV-negative individuals. We are conducting a Phase I trial to evaluate the feasibility of self-administered intravaginal artesunate for treatment of biopsy-confirmed high-grade precancer among HIV-positive and negative women in Kenya (NCT06165614).

Methods: Eighteen HIV-negative and HIV-positive women with biopsy-confirmed cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3) with a visible lesion will self-administer a 5-day course of 200 mg artesunate vaginal inserts on weeks 1, 3, 5 and 7. The primary objective is safety, assessed using a standardized grading scale. Secondary outcomes are adherence, change in lesion size, histologic regression to CIN1 or less, and acceptability. Interim colposcopy will be performed at week 8, and clinical regression will be evaluated at week 14 with colposcopy and biopsy. Participants with persistent CIN2/3 at week 14 will have excision, and those with regression to CIN1 or less will be followed closely for two years. Correlative outcomes will include HPV clearance and the impact of the microbiome on treatment response.

Results: Fourteen participants are enrolled in the trial so far, with a mean age of 41 years. Thirteen, 92.9%, participants are HIV-positive, all of whom are on antiretroviral therapy, with a mean CD4 count of 599.5 cells/mm3. Most participants, 64%, are married, and 64% had primary education as the highest level of education attained, with no participant having a college education. Among 12 participants who have had a safety visit following artesunate use, all 12 reported at least one grade 1 adverse event (AE), with vaginal discharge and headache being the most common AEs. Four grade 2 AEs have been reported, including headache and pelvic pain. No grade 3 or 4 AEs have been reported. Excellent adherence has been demonstrated so far, using self-report and return of pessary covers. Of 7 participants who have had a week 14 visit thus far, 4 (57.1%) had persistent CIN2/3 and had loop excision, while 3 (42.9%) had regression to CIN1 or less and are undergoing observation. Study visits are ongoing, and samples have been stored for correlative studies, including HPV genotyping and characterization of the microbiome.

Conclusions: Topical artesunate is a generic and accessible treatment in LMICs, where the burden of cervical cancer is greatest. Early studies in the U.S. have indicated its potential efficacy for HPV-related anogenital lesions, including cervical precancer. However, in our ongoing Phase I study of topical artesunate for treating CIN2/3 in WLWH in Kenya, preliminary findings suggest lower response rates compared to those observed in HIV-negative women. Further analyses are planned to investigate the influence of HPV genotype, the presence of single versus multiple HPV infections, the microbiome, and the cervical immune microenvironment on treatment response.

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#9551

The Integration Project: A Comprehensive Approach to Four World Health Organization Women's Health Priorities in Eswatini

38 - Low resource settings

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Background/Objectives: Eswatini faces four major health challenges: •The estimated incidence of cervical cancer is the highest in the world at about 57.8 per 100,000 women.1 In 2023, Eswatini implemented the 4v HPV vaccine for girls aged 9-14. •Female genital schistosomiasis (FGS), a waterborne neglected tropical disease (NTD), is also endemic and often mistaken for cervical pre-cancers. It is estimated that 56,000,000 women globally may have FGS, but almost none are diagnosed or treated.2 •The prevalence of HIV for women aged 15-49 in Eswatini is 30.3%, one of the highest in the world.3 •Soil-transmitted helminth (STH) infections, a NTD, pose health risks for adults, including nutritional deficiencies and anemia.4 The IRB approved "Integration Project' is addressing these four WHO objectives, by implementing and evaluating a novel "one stop-shop' screening/treatment/prophylaxis approach to accelerate cervical cancer elimination, treat FGS and intestinal parasites as well as screen and link to treatment for HIV.

Methods: Participants: Women aged 20-49, identified as high-risk due to low income, rural location, and limited healthcare access. Procedure: Community health mobilizers engage women from rural Sithobelweni, Eswatini, for participation. After informed consent, participants self-collect vaginal swabs and urine samples, all receive pre-emptive treatment for FGS and intestinal parasites, and undergo visual inspection with acetic acid (VIA). FGS lesions are documented, acetowhite suspicious lesions are treated with thermal ablation or LEEP. Self-sampled vaginal swabs are tested for high-risk (HR) HPV types to assess images collected via a digital camera within the IRISTM. Automated Visual Evaluation (AVE) improves VIA's accuracy for triaging cervical precancers, cancer, and FGS, assigning risk scores validated against histological findings, although it has not yet been used as a diagnostic tool for lesions. This study is nested in a broader, multi-site, study on HPV with automated visual evaluation (PAVE) Study, integrates AVE. Data here focuses only on HPV-related results.

Results: The Integration Project in Sithobelweni, Eswatini, enrolled 566 women aged 20-49; Key findings include: High-risk HPV positivity: 46% of women (260/566) tested positive for high-risk HPV (HR-HPV) types, with 51.15% of these testing positive for types HPV31/33/35/52/58 52.31% of women were 31 y.o. and up 252 biopsies were taken. Treatment included thermal ablation (101) or LEEP (3). 12 women had HR HPV, HIV, and FGS 80 women were HIV positive and had HR HPV detected

Conclusions: Improving cervical screening access and quality while also addressing and differentiating FGS and providing timely treatment for pre-cancers in resource-limited settings is crucial to prevent progression of these diseases. Real-time point-of-care testing and treatment, infrastructure improvements that include task sharing , and self-sampling are feasible in a rural clinic, exploring outside of a clinical setting is recommended. The high prevalence of high-risk HPV DNA types (other than HPV16, 18) highlights the need for universal 9v HPV vaccine programs covering the additional HR DNA types, health literacy, and increased cervical screening access. Effective health messaging and advanced tools like AVE could improve participation and care. Addressing these gaps should reduce HPV-related disease burden significantly in the future.

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#9482

Applications of a Comprehensive Type-Specific HPV-STI NGS Assay Across Diverse Sample Types

33 - Sexually transmitted diseases and HIV infection

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Background/Objectives: Sexually transmitted infections (STI) are caused by more than 30 different bacterial, viral, and parasitic pathogens and represent a significant public health burden globally. Despite this, data on their prevalence, trends, and health impacts remain limited. HPV and Chlamydia trachomatis are among the most common STIs worldwide, and co-infections with HPV and other STIs are frequent, often interacting to exacerbate disease severity. Traditional, selective testing approaches fail to provide a comprehensive view of HPV and STI co-infections, and multiple assays are costly. To address these gaps, we developed a single-tube, single PCR assay that detects 41 HPV-STI types by a simple NGS workflow approach. This assay has been validated across diverse sample types, enabling the detection of multiple HPV and STI co-infections.

Methods: The ChapterDx HPV-STI assay utilizes type-specific primers targeting 29 HPV types (including HPV68a and 68b) and 13 STIs, including Chlamydia trachomatis serovars LGV1, LGV2, B, D, E, F, G, and GAPDH as an internal control. Amplification and barcoding/indexing occur simultaneously in a single-tube PCR reaction, after which all amplicons are pooled and sequenced on Illumina platform. High-risk HPV types include HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68a, 68b, 73, 26, 53, and 82, and low-risk HPV types include HPV6, 11, 40, 42, 43, 44, 55, 61, 81, and 83. The 13 targeted STIs include Chlamydia trachomatis, Treponema pallidum, Mycoplasma genitalium, Trichomonas vaginalis, Neisseria gonorrhoeae, HSV-1, HSV-2, Mycoplasma hominis, Ureaplasma urealyticum, Ureaplasma parvum, Varicella zoster virus, and Haemophilus ducreyi. The assay has been tested on diverse sample types including cervical, urethral, anal, nasopharyngeal aspirate, first-void urine, vaginal, semen, inguinal lymphadenopathy, genital ulcer, oral ulcer, condyloma samples, as well as samples from HIV-positive patients. The assay was also evaluated for amplification biases and type-suppression.

Results: In previous studies, the ChapterDx HPV-STI assay demonstrated high concordance with Roche cobas test (97.5% concordance) and 98.7% agreement with the Genomica Clart HPV assay. Our results indicate that the HPV-STI assay has been able to detect HPVs and STIs across diverse sample types and many of the samples tested, carried multiple co-infections. As a distinct example, an HIV-infected patient harbored 11 HPV co-infections (HPV16, 18, 33, 52, 56, 26, 53, 40, 43, 55, 83) and 4 STD co-infections (C. trachomatis, N. gonorrhoeae, T. vaginalis and M. hominis) as well as C. trachomatis servoars LGV2 and E. Furthermore, by employing type-specific primers, more types were detected due to significantly decreased PCR biases and type-suppression, that are commonly associated with consensus or degenerate amplification methods.

Conclusions: ChapterDx assay detected HPV and STI across diverse types of samples, including multiple co-infections, showing that many samples harbor co-infections of HPV and STI that go undiagnosed in selective testing. In our other studies (data not shown) we also observed that the rate of multiple co-infections of HPV-STI varies in different populations. The NGS assay is single tube PCR ready-to-sequence approach without additional steps such as barcoding and individual sample purification. It is a user-friendly, easy-to-automate method that is cost-competitive with standard PCR assays and scalable for low, medium, and high-throughput sample volumes.

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#9239

Challenges of implementing a multi-dose HPV vaccine schedule for adolescents living with HIV after adoption of a single-dose national strategy for cervical cancer elimination in Zambia

38 - Low resource settings

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Background/Objectives: HPV vaccination is a key pillar of WHO's 90-70-90 strategy to eliminate cervical cancer, but implementation is lagging in African countries due to multilevel challenges. In September 2023, Zambia launched a Human Papillomavirus Multi-Age Cohort (HPV MAC) Vaccine Campaign targeting 1.42 million girls aged 9 to 14 years countrywide, migrating from a 2-dose to a single-dose schedule for HIV negative girls, but preserving the multi-dose recommendation for those living with HIV. The change should lead to increased vaccine coverage overall since a single dose removes many challenges related to supply, human resources, and logistics. However, this change inadvertently puts up barriers to series completion for adolescents living with HIV (ALHIV) who still need multiple doses to achieve full protection. Our 5-year NCI-funded REACH study (Reaching for Equity in Adolescent Care through HPV Vaccination) aimed to identify barriers to series completion and opportunities to ensure ALHIV readily have access to all necessary doses of the HPV vaccine, without compromising confidentiality.

Methods: We used Rapid Ethnographic Assessment methods (REA) including participant observation in the clinic and community, key informant interviews with clinical workers (N=40), participatory focus groups with caregivers and community leaders (N=13 with 92 participants), and playshops with adolescent girls aged 9-14 years (N=13 with 93 participants), to understand the barriers and facilitators to providing multiple doses of HPV vaccine to ALHIV across three settings (urban, peri-urban, rural) in Ndola, Zambia.

Results: Current HPV vaccine campaigns are primarily school-based, so the change to a single dose in that setting removed the opportunity for ALHIV to get additional doses in school without risking disclosure of HIV status, stigma, and discrimination. The need for additional locations for vaccination was readily identified, and the idea of integrating the HPV vaccine into adolescent HIV clinics received much support as ALHIV already attend these for ART services and have trusting relationships with the staff. Additionally, bundling the services was appealing as it reduced the need for additional clinic visits, though concerns were raised about potentially adding tasks to already burdened staff. The other major barrier identified was related to challenges in identifying and then tracking the girls in need of additional doses. The current system of on-site hard-copy logbooks does not lend itself to knowing how many doses an individual needs or who has received the necessary doses, particularly if those doses must now occur in separate locations (e.g., school then clinic). A shortage of vaccine cards further complicates the situation and puts the onus on adolescent girls to keep track of their vaccinations and know if and when they need the next dose, and then advocate to their providers to receive it.

Conclusions: The implementation of a single dose strategy for HPV vaccination in Zambia holds great promise to increase coverage to WHO recommended levels. However, ALHIV who are at greatest risk of cervical cancer and need additional doses should not be left behind in the process. There is an urgent need to optimize HPV vaccine integration into adolescent HIV clinics to provide a safe, private opportunity to get all needed doses of the vaccine, but systems for identifying those in need of vaccination and tracking doses for completion must be strengthened.

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#8681

Assessment of Cervical Cancer Knowledge and Awareness Gaps among High-Risk Javad Tribal Women in Southern India.

38 - Low resource settings

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Background/Objectives: Cervical cancer is a predominant form of cancer affecting women in India. Even though there are numerous screening methods available, the vast majority of Indian women do not undergo screenings for cervical cancer. This rise in incidence can be traced back to limited awareness about the importance of screening for cervical cancer and a lack of organized screening infrastructure across the country. This study examines the levels of knowledge, attitudes, and practices related to cervical cancer screening among the tribal women in Javad Hills, Tamil Nadu, India.

Methods: A community-based cross-sectional study was conducted between April and August 2024. The study targeted a cohort of 560 women aged 20 to 65 years residing within the selected community. Inclusion criteria consisted of being female and within the specified age range. Participants were excluded if they were unable to provide informed consent or were not available during the data collection period. Data were collected through household surveys using a structured questionnaire through face-to-face interviews with eligible female participants. The questionnaire was designed to capture comprehensive socio-demographic information, including participants' knowledge, attitudes, and practices related to cervical cancer prevention and screening.

Results: Our study revealed significant gaps in knowledge and awareness regarding cervical cancer among the participants. While a majority (79%) indicated familiarity with the disease, only 41% recognized its preventable nature. A mere 2.3% were aware of the potential for early-stage detection, highlighting a critical lack of understanding surrounding this crucial aspect. Overall, over 75% of the participants lacked comprehensive knowledge about cervical cancer. Furthermore, only 32% possessed sufficient understanding of cervical cancer screening. This awareness was significantly correlated with demographic factors such as age, education level, employment status, and socio-economic background. Interestingly, despite the knowledge gaps, almost all participants expressed a positive attitude towards cervical cancer screening. However, there was a significant disparity between intention and action, only 15% had undergone screening prior to the study. This discrepancy underscores the need for targeted interventions to bridge the gap between knowledge, awareness, and proactive health-seeking behavior.

Conclusions: The study revealed that the participating women demonstrated a generally low level of understanding concerning cervical cancer, albeit maintaining a favorable disposition towards the subject. This highlights the necessity for continuous health education and persistent screening initiatives. Such programs aim to enhance awareness and encourage greater participation in cervical cancer screening within this population.

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#9207

The role of HPV on the resolution of female genital schistosomiasis lesions and their persistence

38 - Low resource settings

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Background/Objectives: Female genital schistosomiasis (FGS) is the chronic manifestation of Schistosoma haematobium infection. Complications include infertility, ectopic pregnancy, and increased risk of HIV acquisition. Schistosomiasis is highly endemic in Madagascar and in sub-Saharan Africa, where the burden of cervical cancer is also high. The role of FGS in promoting HPV acquisition and progression to cervical cancer has been hypothesized but is still debated, while even less is known about the effect of HPV and other coinfections on the natural history of FGS. Madagascar is one of the few countries in which the implementation of an HPV vaccination program is still delayed. This study aims to assess the rate of FGS resolution and the role of HPV co-infection on lesion regression after standard treatment with praziquantel (PZQ) in women of reproductive age.

Methods: Enrolment of women in this longitudinal study started in 2021 with a 4-year follow-up with scheduled visits at 12-month intervals (12 +/- 3 months). A first round of follow up will be completed in 2025, with the intention of continuing till 2030. The study is implemented at three Primary Health Care Centers (PHCCs) in the rural district of Marovay. Women are invited to participate in FGS screening by colposcopy (CLP). Each woman screened positive for FGS is offered 40mg/kg praziquantel treatment. FGS diagnosis is confirmed through a blind assessment of CLP images by two specialists. Cervico-vaginal lavages (CVLs) are collected to assess the role of sexually transmitted infections (STIs). HPV testing is performed at the International Agency for Research on Cancer (IARC) using a PCR bead-based multiplex genotyping assay. Data collected at recruitment were analyzed to estimate the baseline prevalence of the disease. Crude (CPR) and adjusted prevalence ratios (APR) of associations between selected factors and FGS and HPV positivity were estimated.

Results: By February 2024, 1,073 women underwent CLP and CVLs were collected at least once. Specifically, 551 women underwent CLP once, 429 had one baseline and one follow up visit, and 93 had two follow up visits. Among 500 women enrolled in 2021, 302 had a final FGS diagnosis: FGS prevalence was 62.6% (189, 95% CI: 56.9-68.1), and 26.5% (80, 95% CI: 21.6-31.8) of women with FGS were also infected with HPV but no association was found between FGS and HPV. The overall prevalence of high-risk HPV was 35.1%. A preliminary analysis of 63 women attending the first follow-up visit showed persistence of FGS lesions in 33/39 (84.6%) women and a new diagnosis in 10/24 (41.7%) of the women who were negative at baseline. Among the women with FGS at baseline, 17 had also HPV infection (43.6%). HPV-positive women had persistent FGS lesions in 16/17 (94.1%) cases, while HPV negative women showed FGS persistence in 17/22 (77.3%) cases. The blind assessment of FGS diagnosis for the entire cohort and the analysis of co-infections is currently underway.

Conclusions: Our preliminary data show that Madagascar has a high prevalence of FGS and HPV. The persistence of FGS lesions is high one year after treatment, especially in women with a baseline HPV infection, showing that HPV vaccination might have a beneficial effect also on FGS. The cohort established in this study will contribute to clarify the dynamic of FGS treatment and to assess the role of HPV (and other STIs) infections on it. Our data will contribute to tailor integrated public health interventions for HPV and FGS.

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#9501

Evaluating Determinants of HPV Vaccine Uptake in Zimbabwe: A Qualitative Analysis Using the Integrated Behavioral Model

38 - Low resource settings

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Background/Objectives: The HPV vaccine program in Zimbabwe, like many global immunization initiatives, experienced significant disruptions due to the COVID-19 pandemic, impacting vaccine uptake among adolescents. Despite the high burden of HPV-related diseases, facilitators and barriers to HPV vaccination, especially in post-COVID-19 contexts, remain underexplored. This study aimed to identify system-level and individual-level factors influencing HPV vaccination uptake among adolescent girls and their parents in Zimbabwe, utilizing the Integrated Behavioral Model (IBM) to understand drivers of vaccine acceptance or hesitancy.

Methods: Using purposive and snowball sampling, 94 in-depth interviews were conducted with key stakeholders across urban and rural regions in Zimbabwe, including policymakers, clinicians, educators, community leaders, parents, and adolescents. Data were collected through semi-structured interviews focusing on knowledge, attitudes, normative beliefs, and barriers/facilitators to HPV vaccination. Interviews were transcribed and coded using a deductive approach aligned with the IBM framework to capture structural and individual-level variables influencing vaccination behaviors.

Results: Study data revealed diverse beliefs impacting HPV vaccination decisions. Parents cited vaccine safety, trust in health authorities, and protection against cervical cancer as strong motivators for vaccination, while concerns about vaccine origins, cultural and religious beliefs, and fear of side effects presented significant barriers. Adolescents viewed the vaccine as protective but were influenced by peers and family opinions, and concerns about pain and side effects. While participants in both urban and rural settings expressed similar foundational beliefs, rural communities faced distinct challenges due to limited healthcare infrastructure and access to reliable vaccine information. Urban respondents generally had greater exposure to health campaigns, underscoring the role of local health systems and social networks in shaping vaccination behaviors.

Conclusions: The study underscores the importance of targeted, evidence-based communication strategies that address specific community concerns, enhance parental and adolescent knowledge, and engage trusted community figures in HPV vaccine promotion. Policy recommendations include strengthening outreach, particularly in rural areas, and developing culturally sensitive interventions to address barriers. This qualitative assessment provides insights for designing strategies to improve HPV vaccination rates in resource-limited settings, contributing to the global goal of cervical cancer prevention.

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#9502

Determinants of HPV Vaccine Uptake in Zimbabwe: Quantitative Analysis Using the Integrated Behavioral Model

38 - Low resource settings

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Background/Objectives: Despite substantial progress in HPV vaccination efforts, uptake remains suboptimal in Zimbabwe, with a variety of factors affecting vaccination motivation among adolescents and parents. This study aimed to quantify the behavioral, social, and systemic influences on HPV vaccination decisions among Zimbabwean adolescents and their parents, applying the Integrated Behavioral Model (IBM) to identify specific constructs and beliefs driving vaccine uptake.

Methods: A systematic, household-based sampling approach was used to survey 901 participants, including 451 parents and 450 adolescents, across urban, rural, and peri-urban regions in Zimbabwe. The survey included fully, partially and unvaccinated adolescent girls and parents of adolescent girls. Surveys, administered via REDCap, included structured questions on IBM constructs—attitudes, normative influence, perceived control, and self-efficacy—using five-point Likert scales. Cronbach's alpha validated each scale's reliability, while hierarchical regression analysis identified key IBM constructs influencing motivation.

Results: The survey results highlighted limited knowledge of HPV and the connection between HPV infection and cervical cancer. The data suggests that experiential and instrumental attitudes, social norms, and self-efficacy are primary motivators for HPV vaccination. Adolescents' motivation was strongly influenced by personal beliefs about vaccine safety and peace of mind, and perceived peer acceptance, with vaccinated adolescents showing significantly higher confidence and positive attitudes than their unvaccinated peers. For parents, primary motivators included trust in vaccine safety and health authority recommendations, though barriers such as concerns about potential side effects and lack of local access were significant deterrents. Social support from friends and community members also emerged as a key influence, especially among parents who reported high descriptive norms around vaccination. However, logistical barriers such as distance to vaccination sites and vaccine availability hindered motivation in rural areas.

Conclusions: The quantitative findings underscore the need for tailored messaging to address distinct motivational drivers among adolescents and parents. For adolescents, campaigns emphasizing personal health benefits, safety, and peer endorsement may increase uptake. Parents may benefit from reassurances of vaccine safety and the positive social norms surrounding HPV vaccination in their communities. By addressing these behavioral constructs, interventions can support Zimbabwe's goal of improving HPV vaccination coverage, ultimately contributing to cervical cancer prevention.

HN03 - Submitted papers - Clinical / Epidemiology II

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#9445

Knowledge Gaps at Diagnosis of Human Papillomavirus-Mediated Oropharyngeal Carcinoma

29 - HPV and oropharynx / Head and neck cancer

Background/Objectives: The incidence of human papillomavirus-mediate oropharyngeal cancer (HPV-OPC) is rising. As this cancer is caused by a sexually transmitted infection, patient experience receiving and coping with the initial diagnosis often incurs a high level of anxiety, seemingly out of proportion to the generally excellent prognosis for this disease. Previous work performed close to a decade ago with a cohort diagnosed when HPV was initially being understood as an etiologic agent demonstrated that patients remained highly anxious about HPV after treatment for their cancer, specifically regarding transmission (Ref). It is unclear, as the field has evolved over the past decade and patient-centered information is more readily available, if the landscape of patient understanding has changed.

Methods: This was a cross-sectional survey study performed at the University of Kentucky in Lexington, KY, USA between June and October 2024. The survey instrument was conducted by telephone using a previously reported survey about patient experience and anxiety regarding a diagnosis of HPV-OPC. Additional questions were added to this survey to specifically assess knowledge gaps and information sources. Adult (>18) patients who had been treated for HPV-OPC at the National Cancer Institute-Designated Markey Cancer Center were recruited to participate. IRB approval was sought and given for this study. The data collection for this study is ongoing.

Results: Eleven participants responded to the telephone survey. There were 8 male and 2 female patients, with an average age of 65, diagnosed between 3 months and 5 years prior. When asked about the most pressing information gaps after their initial consultation, patient responses were most commonly about radiation side effects and the HPV virus. When asked the primary source of information for making treatment decisions, 9/11 acknowledged their doctor. Though all patients recall being told their tumor was HPV-positive, only 6/11 thought HPV was the cause of their cancer. High levels of anxiety were reported at diagnosis, along with concerns about how they became and whether they were still infected with HPV. There were significant knowledge gaps regarding HPV: only 5 participants acknowledged that HPV is a sexually transmitted infection.

Conclusions: Significant knowledge gaps continue to persist among HPV-OPC, and this population is highly anxious at diagnosis. These results underscore the importance of patient counseling at diagnosis and the provision of psychosocial supportive resources.

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#9437

Swallowing outcomes in patients treated with radiation based therapies for HPV associated oropharyngeal cancers

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Swallowing dysfunction is considered to be one of the dose-limiting outcomes for patients with head and neck cancer (HNC) and accounts for much of the post-treatment toxicities. While much research exists looking at surrogate measures of swallowing such as patient reported outcome measures and feeding tube dependence, there is limited evidence as to the impact of HNC treatment on long-term swallowing function. As a result, we sought to measure swallowing function comprehensively in a cohort of patients with Human Papillomavirus (HPV) associated oropharyngeal cancer (OPC) from baseline to one year post-treatment.

Methods: Individuals with HPV associated OPC treated non-surgically were evaluated at baseline, 2-3 months post-radiation, and one year post-treatment. Outcome measures included physiologic measures obtained during videofluoroscopic swallowing studies (VFSS) including Dynamic Imaging Grading of Swallowing Toxicity (DIGEST) scores, Penetration Aspiration Scores, and Modified Barium Swallow Impairment Profile (MBS-ImP) scores for both the oral and pharyngeal phases of swallowing. Diet outcomes included feeding tube use, Functional Oral Intake Scale (FOIS) scores, and Performance Status Scale - Head & Neck (PSS-HN) Normalcy of Diet scores. Patient reported outcomes were measured using the MD Anderson Dysphagia Inventory (MDADI) and the PSS-HN Social Eating scores. All participants were engaged in swallowing therapy prior to and throughout their radiation.

Results: A total of 69 patients were included in analysis. Mean age at diagnosis was 59 years. The majority of participants were male (90%) and white (90%). The mean dose of radiation was 70Gy. Chemoradiation was the most common treatment and received by 97% of participants. The most common systemic agent used was cisplatin (72%). Feeding tube use was reactive and required in <10% of patients. Physiologic measures of swallowing showed a decline at 2-3 months post radiation with improvement near baseline levels at 1-year post-treatment. DIGEST grades >1 (indicating at least moderate pharyngeal dysphagia) were noted in 4% of participants at baseline, 22% 2-3 months post-treatment, and 14% one year following treatment. The mean oral impairment scores on the MBS-ImP were relatively similar across all time points, however pharyngeal impairment nearly doubled between baseline and 2-3 months post-treatment (4.7 vs. 8.86) with improvement to 7.6 at one year post-treatment. Abnormal PAS scores were noted in 7% of participants at baseline, 33% at 2-3 months post-treatment, and 22% at one year post-treatment. There was a mean FOIS score of 6.61 at baseline which decreased to 5.89 at 2-3 months and increased to 6.42 at one year. Similarly, the mean PSS-HN Normalcy of diet scores dropped from 92 at baseline to 76 at 2-3 months with recovery to 92 by one year post treatment. MDADI scores showed a similar pattern of decline from 83 at baseline to 76 at 2-3 months and 84 at 1 year.

Conclusions: These findings demonstrate global changes in swallowing in patients treated non-surgically for HPV associated head and neck cancer. Physiologic function, diet level, and quality of life all decline from baseline to the early stage of recovery with some recovery towards baseline by one year post-treatment. Despite these changes, overall function was quite good in this cohort suggesting that comprehensive multidisciplinary management of these patients, including speech pathology care, can yield excellent functional outcomes.

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#9439

Call for Increased Community Education Regarding Common HPV-Associated Cancers Within the Urban Safety-Net Hospital Population

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: While oropharyngeal and cervical cancer rates were on a decline in the early 2000s, contraction and mortality rates from both cancers have increased per year over the past 2 decades. This could be due to a lack of information about preventative measures and risk factors, a common factor being HPV. This study examines patients' knowledge of oropharyngeal cancer and its relation to cervical cancer and HPV to provide quantitative estimates of the need for basic education surrounding HPV-related cancers.

Methods: We analyzed self-reported baseline survey data from 318 women aged 16-45 participating in an ongoing open-label, non-randomized clinical trial comparing the efficacy of two versus three doses of the HPV vaccine at Boston Medical Center. The survey evaluated participants' knowledge of HPV and the vaccine and their preferences for receiving it through qualitative questions. We conducted descriptive statistics for all questions of interest, and used contingency tables with Fisher's Exact Test to evaluate associations between oral and cervical cancer questions using SAS 9.4.

Results: The survey assessed knowledge of oral and cervical cancer among respondents. Among 318 participants, the majority (84.69%) had heard of oral cancer. However, 48.55% were unsure if most oral cancers are caused by infection. While 62.41% recognized that the risk of oral cancer can be significantly lowered, only 41.04% were aware of a potential vaccine for prevention. In terms of cervical cancer knowledge, 51.34% correctly identified infection as a leading cause of cervical cancer. Most respondents (77.82%) were aware of methods to lower cervical cancer risk, and 78.62% knew about the vaccine for prevention. However, 40.61% were uncertain about the cause of cervical cancer, highlighting areas where education is needed. It's also important to note that 68.13% were unsure about oral cancer risk reduction but correctly answered for cervical cancer risk reduction. In assessing knowledge about vaccines for oral and cervical cancers, 95.33% of respondents recognized that there is a vaccine that can help prevent both types of cancer. However, 27.21% expressed uncertainty regarding the availability of a vaccine to prevent oral and cervical cancer. Notably, 19.05% incorrectly believed that no vaccine exists for either oral or cervical cancer. Furthermore, 72.06% were unsure about the availability of a vaccine for oral cancer but correctly identified the availability of a vaccine for cervical cancer. Additionally, 57.14% mistakenly thought there was no vaccine for oral cancer while recognizing the vaccine for cervical cancer. Overall, 46.23% were uncertain about vaccine availability for oral cancer but correctly identified its availability for cervical cancer. The association between these perceptions was significant.

Conclusions: There is a vast lack of patient education regarding HPV and its association to cervical and oral cancer, respectively. Additionally, there are inconsistencies in patient knowledge regarding the availability and efficacy of a HPV vaccine to target secondary oral cancer and/or cervical cancer. These findings suggest that greater education regarding HPV and a subsequent increase in HPV vaccination rates would be a highly effective preventative measure to combat rising rates of oropharyngeal cancer and cervical cancer.

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#9250

Oral Human Papillomavirus Incidence Among A General Adult Population in the US: Results from the PROGRESS (Prevalence of Oral HPV Infection, A Global Assessment) Study

28 - Oral HPV infection

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Background/Objectives: Oral human papillomavirus (HPV) is driving the increase of oropharyngeal squamous cell carcinoma in the United States (US); however, there are few data describing the natural history of oral HPV infection. This study assessed one-year oral HPV incidence in a general US population.

Methods: We recruited participants aged 18-60 from dental offices across the US from November 2021 to June 2022. Participants will be followed for 2 years, providing oral rinse and gargle specimen every 6 months. Participants with 1 year of follow up were included in the present analysis. Analyses were HPV-type specific: participants negative for the relevant HPV type at baseline were included in analyses of oral HPV incidence for that HPV type. Results were calculated for any HPV, high-risk (HR), low-risk (LR), 9-valent vaccine (9v), 4-valent vaccine (4v), HPV-16 and HPV-18 genotypes, and stratified by sex.

Results: A total of 2,018 subjects completed 1-year follow-up with median follow up time of 385 days; 55.8% were female and the mean (SD) age was 40.2 (11.9) years-old. A total of 297 (12.2%) had an incident infection. Among males, 1-year incidence for any HPV, HR, LR, 9v, 4v, HPV-16 and HPV-18 were: 15.4, 4.5, 11.3, 3.6, 3.3, 1.1 and 1.7 per 100 person-years, respectively, with highest incidence rate for any HPV among 51-60-year-olds at 19.4% (95%CI: 13.9%-26.4%). Among females, 1-year incidence for any HPV, HR, LR, 9v, 4v, HPV-16 and HPV-18 were: 11.5, 5.1, 6.9, 4.4, 3.9, 1.2, and 2.7 per 100 person-years, respectively, with the highest incidence rate for any HPV among 51-60-years-old at 13.7% (95%CI: 9.9%-18.5%).

Conclusions: Incidence of any and LR oral HPV was higher in men than women, but higher in women than men in all other stratifications. Additional analyses related to persistence and clearance are needed to inform development of infection-related prevention efforts.

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#9048

Oral human papillomavirus prevalence and risk factors among adults in the United Kingdom - PROGRESS Study

28 - Oral HPV infection

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Background/Objectives: Head and neck cancer (HNC) is the eighth most common malignancy in the United Kingdom (UK)(1). Recent evidence suggests that oral health may be related to oral HPV infection(2,3). Despite oral human papillomavirus (HPV) infection being a leading cause of some HNC, little is known about its prevalence and genotype distribution in the UK. The prevalence of oral HPV and factors associated with HPV infection were evaluated in a general sample of UK adults.

Methods: The PROGRESS (Prevalence of Oral HPV Infection, a Global Assessment) cross-sectional study(4) was conducted in 17 UK dental practices between September 2022 - April 2023. Participants aged 18-60 completed behavioural questionnaires and provided oral rinse and gargle specimens. Dentists assessed participants' oral health status. SPF10/DEIA/LiPA25 was used for HPV DNA detection and genotyping(5). Genotypes were categorised as any HPV genotype, high-risk (HR) genotypes (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59), 9v vaccine genotypes (HPV-6, 11, 16, 18, 31, 33, 45, 52, and 58), and HPV-16. Chi-square tests were used to identify factors associated with oral HPV.

Results: Of 1096 participants, 53.8% were women and the mean age was 39.8 years. Point prevalence of any HPV genotypes, HR genotypes, 9v vaccine HPV genotypes, and HPV-16 was 10.6%, 2.7%, 1.6% and 0.8%, respectively. Prevalence was stratified by age and sex. Compared with women, men had higher prevalence of any HPV (14.0% vs 6.4%) and HR HPV (5.0% vs 1.3%). Prevalence of any and HR-HPV was highest among men aged 51-60 (23.3%) and 41-50 (7.9%). HR-HPV prevalence was significantly higher among participants with periodontitis/gingivitis (5.8% vs 1.2% among those without) and those with >26 lifetime female oral sex partners (11.1% vs 4.7% among those with 1-5 partners).

Conclusions: In the UK, prevalence of oral HPV, including HR genotypes, was most prevalent among men between 41 and 60 years, who may be at increased risk of HPV-driven HNC. Increased HPV prevention efforts among boys and men the in the UK, as well as continued vaccination among women, may help attenuate the increasing burden of HPV-associated oropharyngeal cancer in the UK.

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#9512

High-risk HPV in rare sinonasal carcinomas: a multi-institutional case-control study to ascertain behavioral risk factors and seroprevalence

03 - Epidemiology and natural history

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Background/Objectives: Human papillomavirus (HPV) has been extensively studied in the context of oropharyngeal squamous cell carcinoma, with numerous case-control studies establishing an association between high-risk sexual behaviors and HPV-positive oropharyngeal cancer.1-7 The sinonasal cavity is emerging as an additional, less well-defined, potential hotspot for HPV-associated tumor development of the Head and Neck. We recently demonstrated an increasing incidence and prevalence of these rare HPV-associated sinonasal carcinomas.8 However, potential behavioral risk factors and seroconversion has not been studied in HPV-positive sinonasal carcinomas. We hypothesized that completing the first multi-institutional case-control study of HPV-associated sinonasal carcinomas would ascertain important behavioral risk factors associated with HPV-associated sinonasal carcinoma development.

Methods: This study was approved by the Johns Hopkins Institutional Review Board. Thirty-nine patients with sinonasal carcinoma (SNC) were enrolled in a multi-institutional study from 2021 to 2024. Tumor tissue underwent RNA in situ hybridization (ISH) with a cocktail of high-risk HPV serotypes. Serum was obtained and tested for antibodies to E6 and E7 oncoproteins for high-risk HPV. Case-controls were obtained from a general otolaryngology clinic. All participants completed a behavioral survey. Cases were matched by age, sex, and race (white vs. non-white) with noncancer controls. Odds ratios and 95% confidence intervals were calculated using conditional logistic regression. Pearson's chi-square test was used for comparison of seropositivity to HPV oncoproteins in patients with HPV-positive and HPV-negative SNC.

Results: A total of 39 patients with SNC and 154 controls were included. Twenty-four patients were HPV-positive on HPV ISH, with 94 matched controls. Fifteen patients had HPV-negative SNC with 60 matched controls. Interestingly, history of tonsillectomy was associated with significantly decreased odds of HPV-positive SNC (odds ratio [OR] 0.30 [95% CI 0.09-0.95]) compared to normal controls (Table 1). Neither sexual behaviors—such as age of sexual debut, oral sex timing or intensity, or lifetime partners—nor clinical factors, such as obesity, multimorbidity, or substance use history, were significantly associated with odds of either HPV-positive or HPV-negative SNC compared to matched controls. HPV-positive SNC was associated with significantly increased odds of alcohol use (≥15 days per month) compared to HPV-negative SNC. The percent seropositive for antibodies to high-risk HPV E6 (any one of types 16, 18, 31, 33, 45, 52, and 58) was significantly higher among HPV-positive SNC patients compared to HPV-negative SNC patients (34.8% vs 6.7%, P = 0.046).

Conclusions: Contrary to HPV-positive oropharyngeal cancer, sexual behavioral risk factors were not associated with HPV-associated SNC, suggesting that other risk factors are important for HPV sinonasal cavity exposure. History of tonsillectomy was associated with significantly decreased odds of HPV-associated SNC. Further investigation into mechanisms of HPV transmission to the sinonasal cavity and the role of tonsil and adenoid tissue in this process is needed. HPV-positive SNC is associated with seroconversion to high-risk HPV E6.

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FCSS - Expanding HPV vaccine implementation

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#9276

Lessons Learned from Bhutan on extending Girls-Only HPV Vaccination Program to Boys

38 - Low resource settings

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Background/Objectives: In 2020, Bhutan pioneered a school-based gender-neutral human papillomavirus (HPV) vaccination program, achieving an impressive 96% vaccination coverage rate by 2021. This study aimed to identify enablers and challenges associated with extending the HPV vaccination program to include boys.

Methods: The study was conducted through 49 in-depth interviews with community leaders, policymakers, parents, teachers, and health workers, and 12 focus group discussions with boys who received the HPV vaccination. Conventional content analysis was used to analyze the data.

Results: Enablers of the extension of gender-neutral HPV vaccination included social mobilization and advocacy efforts, which encompassed community engagement and leadership and collaborations with schools. Equally crucial were proficient program management and the strategic use of digital interventions. Challenges included tracking and reaching eligible adolescents. Vaccinated boys perceived school-based vaccination to be a key enabler of vaccine uptake.

Conclusions: The study concludes that extending a girls-only HPV vaccination program to gender-neutral is feasible and acceptable in Bhutan. Findings related to challenges and ways for overcoming them can support other countries interested in gender-neutral HPV vaccination programs.

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#8987

Human Papillomavirus Disease Prevention in Gender-Diverse Adults with a Cervix in the United States and Germany

39 - Public health

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Background/Objectives: In 2021, WHO noted that little is known about HPV-related risk and prevention among gender diverse adults with a cervix, including transgender men, non-binary and intersexual individuals assigned female at birth (TMNB) and called for research among TMNB. The objective of this study was to describe HPV vaccination and cervical cancer screening (CCS) in this population and to explore differences between the United States (US) and Germany, countries where HPV vaccination is either recommended or under consideration for recommendation for sexual minorities/transgender women, but recommendations for TMNB are absent.

Methods: Anonymous online survey of adults aged 25+ years who self-identified as TMNB for >=1 year, had a cervix and lived in the US or Germany. Participants (N=945 US, 151 Germany) were recruited through social media, targeted advertising and partnership with LGBTQIA+ organizations.

Results: Many engaged in HPV risk behaviors: 42.8% reported penile-vaginal intercourse and 38.1% performing oral-vaginal sex in the past year. 54.7% had received an HPV vaccine. US TMNB were more likely to have been vaccinated (57.7% vs 36.4%, p< 0.0001), but their HPV vaccine knowledge was lower (p<0.01) than German TMNB. Although most (82.1%) had a CCS in their lifetime, only 64.5% had been screened since identifying as TMNB. Barriers to CCS were common, particularly barriers specific to gender identity: 77% were uncomfortable seeking care at a clinic that primarily served cisgender women. 10.7% had never been vaccinated nor received a CCS within the past 5 years. In this vulnerable subgroup, 65.8% had engaged in penile vaginal intercourse, 35.9% in the past year.

Conclusions: Despite prevalent high-risk behaviors for HPV, HPV vaccination and CCS rates among this gender diverse population with a cervix are low. Findings highlight the need for gender affirming care, increased awareness among health care providers, and reimbursement for HPV vaccination in this vulnerable population.

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#9164

Pharmacist Provided HPV Immunizations Services in 30 US Community Pharmacies Participating in Project IMPACT: HPV Immunizations

06 - HPV prophylactic vaccines

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Background/Objectives: The primary objective of this research is to study the impact of pharmacists educating and offering to administer HPV vaccinations, along with other recommended vaccinations, on HPV vaccination rates among adult males and females in the US.

Methods: This prospective research occurred in 30 community pharmacies among 20 states in the U.S. The practice sites were onboarded and trained to implement the intervention in December 2023. Patients enrolled through September 2024 are included in this interim evaluation. The patient population eligible to be enrolled included individuals between 18 and 45 years of age who presented to the pharmacy for any reason. The intervention included pharmacist driven patients' vaccination history assessment via their state's bi-directional Immunization Information System (IIS) to identify their vaccine needs in accordance with CDC/ACIP guidelines. The goal for each community pharmacy site was to perform the vaccination history assessment service for patients within the 22-month period of patient enrollment, which may include multiple visits with patients when necessary. When unmet vaccination needs were identified and vaccination was clinically appropriate, pharmacists educated the patient about their unmet needs and either administered the vaccine(s) or documented if the patient planned to receive it in the future (e.g., an appointment), declined to receive it, or if the vaccine was contraindicated or the specific dose was not indicated in the series. Data such as patient demographics, visit date, visit minutes, general reason for the patient visit (such as a prescription, vaccination, medication synchronization, comprehensive medication review, or other) were documented. Finally, if the patient declined to receive a recommended vaccine for which there was a need, the pharmacist documented the patient's general reason out of the following categories: cost, disease indifference, lack of trust, shared decision making, or any other reason.

Results: The interim results indicate that pharmacist driven vaccination history assessments led to an increase in HPV vaccination update by patients from baseline. Out of 1,985 patients enrolled so far, 1,395 unmet HPV vaccine needs were identified by the pharmacist. To this point, 222 HPV vaccines have been administered, 97 were in the patient age group of 18-26 demonstrating an increase of 14% from baseline, and 125 in the patient age group of 27-45 demonstrating an increase of 10% from baseline, with an overall interim HPV administration rate of 16%. Of the 1,395 unmet HPV needs, patients have "declined" to receive the HPV vaccine on 696 instances (50%). Researchers are learning patient reasons for declining the HPV vaccine, the largest category of which is disease indifference at 329 (47%) occurrences, followed by "other" at 188 (27%) occurrences, shared decision-making at 101 (14%) occurrences, lack of trust at 65 (9%) occurrences, and cost at 13 (2%) occurrences.

Conclusions: This project is demonstrating that community pharmacies offer a highly valuable access point for patients to receive HPV vaccination services. Pharmacists are well positioned to make a significant intervention in addressing unmet HPV vaccination needs in the community, and pharmacies provide an avenue for education on vaccines and an opportunity to receive the vaccine(s) during the patient visit. Further research and evaluation is required to understand how thise delivery system can be effectively scaled.

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#9161

Identifying barriers and facilitators to pharmacy-based HPV vaccination using the Consolidated Framework for Implementation Research (CFIR): a qualitative analysis from pharmacists and pharmacy managers in Canada and US

39 - Public health

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Background/Objectives: Pharmacy-based vaccination is a specific strategy that capitalizes on existing healthcare delivery infrastructures and relationships between pharmacists and customers to increase vaccination rates. Approximately 13 million people in the United States and 6.5 million people in Canada live in an area with a primary care provider (PCP) shortage, which are largely characterized as rural areas. Nearly 90% and 95% of US and Canadian residents live within 5 miles and kilometers from a community pharmacy, respectively, which suggests that their use as alternative vaccination sites may enhance accessibility for low coverage areas in North America. Additionally, patients visit a community pharmacy 35 times per year, compared with visiting their PCP only 4 times.

Methods: We conducted a cross-sectional qualitative study that employed semi-structured in-depth interviews designed a priori using the Consolidated Framework for Implementation Research (CFIR) with 32 pharmacists and pharmacy managers across the US and Canada. These countries were selected because 1) they have a policy in place that supports pharmacists to administer HPV vaccines to adolescents and adults within pharmacies and 2) there were pharmacies where pharmacists currently vaccinate both adolescents and adults. Inclusion criteria for participants were pharmacists and/or pharmacy managers currently employed at a US or Canadian pharmacy currently administering HPV vaccines on-site. Recordings were transcribed, and thematic and content analysis was applied.

Results: Barriers were identified surrounding the cost of the HPV vaccine series to independent pharmacies and the uninsured; facilitators existed in provider confidence and existing vaccination infrastructure, with some remaining barriers surrounding identifying eligibility from immunization information systems (IIS) and limited staff time. Communication was a barrier in both the individual characteristics of pharmacists and the process in the limited promotion of the HPV vaccine and follow-up with primary care providers, despite clear motivation to encourage pharmacies as complementary sites for vaccination.

Conclusions: Our findings demonstrate provision of HPV vaccination in pharmacies can be complicated for reimbursement, storage, and patient communication. Therefore, learnings from early HPV vaccination pharmacy adopters can provide insights critical to the success of ongoing and future HPV vaccination programs. Despite operating in different cultural and policy environments, pharmacists and pharmacy managers in the US and Canada all see themselves as capable vaccinators, particularly for the HPV vaccine. These findings align with research establishing broad support among pharmacists for pharmacy-based immunization programs and the impact of political and social contexts on the effectiveness of pharmacy-based vaccination efforts.

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#9146

Potential Opportunities for Human Papillomavirus Vaccination in the United States at Age 9: Analysis of Vaccine Administration Trends at Well Visits in Adolescents

06 - HPV prophylactic vaccines

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Background/Objectives: Despite the estbalished effectiveness of the human papillomavirus (HPV) vaccine, uptake in the United States (US) remains suboptimal. The objective of this research was to describe the Advisory Committe on Immunization Practices (ACIP) recommeded vaccine administration trends in adolescent well visits and quantify potential oppotunities to inititate the HPV vaccine series at age 9.

Methods: The descriptional cross-sectional study included analysis of adolescents aged 9-14 years with continuous enrollment from 2018-2022 in the MarketScan Commercial or the Multi-State Medicaid databases. For each age group and each calendar year, we analyzed percentages of well visits and concurrently administered vaccines including HPV, Tdap, MenACWY, influenza, and catch-up vaccinations (Hep A, HepB, MMMRV, and varicella). Further, we assessed potential opportunities for HPV vaccination among adolescents at the age 9-12 well visits.

Results: The percentage of well visits between 9-14 years in all age groups ranged 55.8%-72.4% in the commercial population, and 38.9%-53.0% in the Medicaid population. Among commercial and Medicaid populations, most age 9 well visits showed no vaccine claims (89.0% and 91.7%, respectively) while claims for two and three concurrent vaccines at age 11 occurred in 22.2%-37.2% of well visits, most often for meningococcal and Tdap vaccines. Claims for HPV vaccine initiation at 11 and 12 years remained suboptimal (17.9%-24.3%). Among adolescents who did not receive the HPV vaccine at their 9- or 10-year well visits, 34.8%-36.9% did not have a well visit at 11 or 12 years. Among adolescents with well visits at 11 or 12 years, 20.6% to 30.0% received one or more other vaccinations but not the HPV vaccine. Further, among adolescents with a well visit at 11 years who received one or more other vaccinations but not the HPV vaccine and had a well visit at 12 years, 67.2% to 67.4% did not receive the HPV vaccine. Finally, among adolescents with a well visit at 11 or 12 years who received one or more other vaccinations, but not the HPV vaccine, 40.6% to 46.1% had a well visit at 9 or 10 years.

Conclusions: Most adolescents at age 9 well visits did not receive any vaccines while many adolescents received at least two or three vaccines, but not the HPV vaccine, at age 11 and 12 well visits. Routine HPV vaccination beginning at age 9 well visits could optimize opportunities to improve vaccine coverage in the US.

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#9165

HEALTHCARE PROVIDER AND PARENTAL PERSPECTIVES ON HPV VACCINATION AT AGES 9-10 IN THE UNITED STATES

06 - HPV prophylactic vaccines

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Background/Objectives: In the U.S., HPV vaccination is routinely recommended for 11-12-year-olds, although there are efforts to shift initiation to ages 9-10. This study explored parental and HCP's attitudes toward earlier initiation of the HPV vaccine.

Methods: We conducted an online survey with 500 HCPs and 350 parents recruited from an existing membership-based panel. Parents of children 9-12 years were invited to complete the survey, and HCP's who reported recommending and/or administering HPV vaccination to pediatric patients were invited to complete the survey. Survey elements included awareness, concerns, and acceptance of early HPV vaccination. Factors such as prior vaccination experiences, opinions on HPV, gender, vaccine knowledge, sexual behavior concerns, and the impact of provider recommendations were also assessed.

Results: HCPs reported mentioning the HPV vaccine to boys and girls before age 11, 72% and 77% of the time, respectively, but recommending it prior to age 11, 38% and 51% of the time. Most HCPs (59%) said they would give the vaccine prior to age 11 if parents requested it. On average, HCPs reported continuing to recommend the vaccine until patients were 18. Few HCPs (11%) reported introducing the vaccine at the same visit at which it was given, with 36% reporting multiple discussions before acceptance. Over 91% of HCPs thought there would be benefits associated with earlier vaccination; improving on-time completion was reported as an extremely or very important benefit by 72% of HCPs, followed by completion prior to other adolescent vaccines (64%) and increased opportunities for administration due to better visit attendance for younger children (62%). The barrier most often reported as extremely or very important to earlier initiation was patient misconception about the duration of protection (60%), while HCPs felt the lack of a vaccination-free gap was the least significant barrier (17.5%). Among parents, most supported vaccination at age 10 or younger (72% for boys, 77% for girls). Parents whose children were vaccinated at 11-12-years-old, 90% said they would probably or definitely have accepted vaccination if offered earlier. Almost half of parents of 11-12-year-old children (44%) reported their children had received two doses of HPV vaccine. Parents identified benefits to early vaccination, including higher confidence in completion prior to sexual activity (reported by 60%), fewer injections at the 11-12-year-old visits (52%), and less concern of triggering sexual behavior (46%). Concerns about earlier vaccination included the inconvenience of separating from other vaccinations at 11-12-year-old visits (40%), difficulty engaging children in decision-making (39%), and lack of comfort discussing HPV vaccination topics including sexuality at this age (36%). Almost two-thirds (74%) had involved their child in deciding about HPV vaccination. Most (75%) said that their HCP mentioned the vaccine before they asked about it.

Conclusions: HCPs frequently recommend the HPV vaccine before children are 11 years old and perceive multiple benefits associated with earlier initiation including better completion outcomes. Similarly, parents indicated high parental acceptance of HPV vaccination at 9-10 years and potential for acceptance if offered earlier. Our findings can be used to guide communication and information provided to parents and HCP's to increase acceptance.

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#9279

The Impact of HPV Vaccination on the Incidence of Anogenital Warts in Israeli Men and Women

07 - HPV therapeutic vaccines

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Background/Objectives: Human papillomavirus (HPV) is a known cause of precancer lesions and invasive cancers. In Israel, HPV vaccines were first introduced in 2007 with 4-valent HPV vaccine (4vHPV; Gardasil) for females aged 9-26 years; vaccination was opportunistic. The National Immunization Program (NIP) began in 2014 with 4vHPV for 13-year-old girls and expanded to include boys, gender-neutral vaccination (GNV) in 2015. In 2019, the NIP switched from 4vHPV to 9-valent HPV vaccine (9vHPV; Gardasil 9). Both 4vHPV and 9vHPV protect against HPV types 6 and 11, which account for over 95% of anogenital warts (AGW). By 2022, vaccination rates reached 55% for girls and 49% for boys. This study examined the impact of the HPV vaccination on AGW incidence in Israel.

Methods: A retrospective database study was conducted utilizing de-identified data from the Maccabi Healthcare Services (MHS), a nationwide insurer-provider serving >25% of Israel's population. AGW incidence was examined among individuals aged 10-65 years from 2006 to 2022, stratified by sex, age, and birth cohorts. AGW was captured by a combination of ICD codes and AGW-specific medications claims. Poisson regression was used to estimate AGW incidence rate ratios, then compared between pre-NIP (2006-2008), peri-GNV (2014-2016), and post-GNV (2016-2022). AGW incidence was compared between cohorts, before and after the NIP, accounting for the expected age-related increase and temporal changes in AGW incidence. To account for temporal changes, a negative control analysis was conducted using other sexually transmitted infections (STI), chlamydia and gonorrhea incidence rates.

Results: A total of 20,915 females and 36,029 males with at least one diagnosis of AGW from 2006 to 2022 were included in the analysis. A continuous decline in AGW incidence was observed in females during study period. In males, incidence increased for most of the study period and declined post introduction of male vaccination in NIP in 2019-2022. Among girls aged 10-14, 15-17, and 18-21 years, AGW incidence significantly declined by 64%, 65%, and 37%, respectively, from pre-NIP to post-GNV period ($p<0.001$). In contrast, AGW incidence increased among women aged 45-54 by 11% ($p=0.04$) and among women aged 55-65 by 13% ($p=0.10$). For boys, AGW incidence significantly decreased by 60% and 45% in the age groups 10-14 and 15-17 years, respectively, while remaining stable for those aged 18-21, some of whom not eligible for the NIP. However, among men not vaccinated as part of the NIP (age≥22 years), AGW incidence significantly increased by 44%, 47%, 60%, 68%, and 48% in the age groups 22-24, 25-34, 35-44, 45-54, and 55-65 years, respectively ($p<0.001$). This pronounced rise was also found in the incidence of chlamydia and gonorrhea in men. Changes in incidence from peri- to post-GNV indicated a similar overall trend, though less pronounced. Additionally, in vaccine-eligible cohorts, the expected age-related increase in AGW incidence was lower compared to non-eligible cohorts. Moreover, a gradual decline was observed post-NIP when examining each age group over the study period.

Conclusions: Introduction of HPV national immunization with 4vHPV and 9vHPV has led to significant reductions in AGW incidence among young men and women in Israel, highlighting the importance of vaccination. With higher vaccination rate, there could be further reduction in AGW incidence.

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#9575

A Systematic Review of Real-World Effectiveness and Impact of Administering Human papillomavirus (HPV) Vaccination in Males during 2009-2024

06 - HPV prophylactic vaccines

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Background/Objectives: Human papillomavirus (HPV) vaccination was approved to be administered in males in the United States (US) in 2009. Multiple countries have extended the HPV vaccination recommendation to males aged 9-26 in addition to females as the gender-neutral vaccination (GNV) program in the past 15 years. However, the benefit of administering HPV vaccine in males, in terms of real-world vaccine effectiveness (VE) and impact (VI), has not been systematically synthesized. The aim of this study is to systematically summarize the real-world effectiveness and impact of male receiving HPV vaccination, focusing on the direct prevention of HPV-related disease in males, and indirect protection to females.

Methods: A systematic literature review (SLR) was performed in Embase and PubMed databases (10/1/2009-5/31/2024) to examine the real-world VE and VI of males receiving the quadrivalent (4vHPV) and nonavalent (9vHPV) HPV vaccination against male and female HPV infection (e.g. oral, anal, penile, and cervical infection) and related diseases, like anogenital warts (AGW), recurrent respiratory papillomatosis (RRP), and HPV-related precancers and cancers.

Results: Twenty-four studies from the United States (n=16), Australia (n=5), Canada (n=2), and Israel (n=1) were included (VE=14, VI=12, two examined both), with 14 studies on 4vHPV vaccine, and 10 studies on a mixed effect of 9vHPV and 4vHPV vaccine. Among all studies, seven studies evaluated only in male population, while the rest involved both male and female population. Studies revealed male vaccine effect toward various male and female infections and diseases, including oral HPV infection (n=7), anal infection (n=3), penile infection (n=3), cervical infection (n=1), AGW (n=5), anal pre-/cancer (n=5), oral cancer (n=2), vulvar and vaginal pre-/cancer (n=2), and RRP (n=2). Regarding infections in males, VE was reported up to 83%, 91%, and 85%, against oral, anal, and penile HPV infection, respectively, with a peak VE when males were vaccinated before age 18 years. In terms of cancer prevention, the VE was reported up to 95.8% for oropharyngeal cancer, with a total reduction of 14% in 16 years, and the VE up to 60% for anal cancer. For AGW in male, VE was reported 55% with a total risk reduction up to 97% in 11 years. Regarding the impact of GNV on females, compared with pre-vaccine era, the incidence for cervical HPV infection was declined by 62% post-GNV and by 9% in female-only vaccination era. The annual percentage changes (APC) were reported as negative in female precancer lesion of anal (-12.1%), high-grade vulvar (-21%), and vaginal (-19%), with GNV implementation. The RRP incidence rate decline was reported in both male and female population by 61.4% annually, with a total reduction of up to 87.5% in 4 years post-GNV.

Conclusions: Real-world evidence indicates that vaccinating males with 4v/9vHPV led to significant risk reduction in oral, anal, and penile infection, as well as other HPV-related diseases among males, like AGW, RRP, oropharyngeal and anal cancers. Implementing the HPV GNV program will not only provide direct protection to males, but also extend protection to females.

HN06 - Submitted papers - Basic science I & RRP

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#9245

Clinically Validated HPV-6 and HPV-11 Subtyping Assay to Guide Management of Patients with Recurrent Respiratory Papillomatosis

09 - HPV testing

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Background/Objectives: Recurrent respiratory papillomatosis (RRP) is a debilitating neoplastic disease caused by chronic infection with human papilloma virus (HPV) types 6 and 11 for which there is no approved medical therapy. RRP manifests as recurrent papillomas in the aerodigestive tract which cause debilitating voice dysfunction, airway obstruction, and in a subset of patients progression to invasive squamous cell carcinoma. Current treatment consists of repeated surgeries that fail to permanently eradicate the tumors in the vast majority of patients. We and others have shown that HPV-11 infection is associated with a more aggressive clinical course including increased need for surgical intervention and higher risk of progression to malignancy1. These results support HPV subtype as a predictive biomarker for RRP disease severity. Thus, it is critical to determine HPV-6 versus HPV-11 subtype in RRP samples to guide clinical management and optimize patient outcomes. The objective of the current work was to establish a clinically approved HPV-6 and HPV-11 subtyping test to address the critical gap of lack of such an assay to guide patient care.

Methods: A multiplex droplet digital polymerase chain reaction (ddPCR) assay targeting the HPV major capsid protein L1 gene was developed, optimized, and clinically validated on the Bio-Rad QX200 AutoDG Droplet Digital PCR System.

Results: Multiple HPV-6 and HPV-11 primers and probes were assessed to obtain unambiguous specificity in a multiplex ddPCR reaction. Forty-four formalin-fixed, paraffin-embedded (FFPE) respiratory papilloma or tumor tissues positive for HPV-6 or HPV-11 by type-specific PCR along with 20 HPV negative FFPE lung tissue controls were analyzed. The ddPCR results were 100% concordant with the type-specific PCR results, and no cross reactivity between HPV-6 and HPV-11 was seen. Additionally, no cross reactivity was present with >30 other viral and bacterial pathogens, including common respiratory tract pathogens and high-risk HPV subtypes, as demonstrated by no HPV-6 or HPV-11 amplification in 35 samples positive for other infectious agents by clinical testing. The laboratory-developed test achieved satisfactory performance with 100% accuracy, precision of <20% coefficient of variability, and analytical sensitivity of one copy per microliter as assessed using HPV-6 and HPV-11 World Health Organization International Standards and HPV positive FFPE RRP tissue samples. Since HPV-6 and HPV-11 co-infection occurs in 2-20% of patient cases, we validated a lack of competitive inhibition in the multiplexed assay by demonstrating that both HPV-6 and HPV-11 were measurable when present at 100-fold less dilution than the other at quantities equivalent to the lower limit of detection. The assay achieved satisfactory performance with 100% accuracy using multiple specimen types including archived FFPE RRP biopsies, fresh/frozen tissue, and bronchoalveolar lavage samples. Thus, there is no need for an additional patient procedure to be performed as this assay successfully determines HPV-6 and HPV-11 subtyping on previously obtained biopsies.

Conclusions: HPV strain predicts RRP severity with HPV-11 infection portending a more aggressive disease course. A sensitive and specific clinically approved assay is now available to determine HPV-6 and HPV-11 status in current and previously obtained patient samples to optimize clinical management and outcomes for patients with RRP.

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#9167

The Burden of Recurrent REspiratory Papillomatosis in AdulTs and CHildren (BREATH) study in France: a Retrospective Study using the National Claims Database

39 - Public health

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Background/Objectives: Recurrent Respiratory Papillomatosis (RRP) is a chronic disease of the upper airway caused by Human Papilloma Virus (HPV), mainly HPV6 and HPV11 (1). RRP has no cure and manifests in two distinct forms based on age at onset, Juvenile onset RRP (JoRRP) and Adult onset RRP (AoRRP). The disease is characterized by the growth of papillomas in the airway tract; frequency and severity of the recurrences are variable and unpredictable. In France, there is limited data on the management of RRP patients, and data on epidemiological and financial burden are scarce. The BREATH (Burden of Recurrent Respiratory Papillomatosis in Adults and Children) study aims to address these gaps. The study objectives are to (i) assess the number of RRP cases, and incidence and prevalence over the study period, (ii) describe demographic and clinical characteristics of patients with RRP, (iii) assess healthcare resource utilization including medical and surgical outcomes and estimate associated costs.

Methods: The BREATH study is an observational, non-interventional study using secondary data from the French National Health Data System (SNDS). It was approved in August 2024 by the French Health Data Hub (CESREES) and by the French data protection authority (CNIL), recognizing the study's public health significance (2). The SNDS database covers 99% of the French population (over 67 million individuals). It captures the exhaustivity of healthcare expenditures that are reimbursed in primary and secondary care settings. The study period extends from January 1st, 2006 to December 31st, 2023. All patients (JoRRP and AoRRP) identified with RRP during the inclusion period will be included. Since there is no specific International Classification of Diseases (ICD) code for RRP, algorithms were developed using ICD-10 codes and medical procedure associated with RRP management. JoRRP patients will be defined as those with disease onset prior to age 18 years.

Results: Characteristics of patients will include age, gender, child's birth order (for JoRRP cases), HPV vaccination status, comorbidities, evidence of pulmonary involvement and malignant transformation of RRP. The study will describe the surgeries, medical procedures, and treatments received for clinical management. In mothers of JoRRP, HPV vaccination status, presence of genital warts, delivery method, pap smear test and conization of the cervix will be collected by linking mother's information to the child's using anonymized record numbers. Inpatient and outpatient healthcare resource use (HCRU) such as hospitalizations for RRP, emergency room visits, medical procedures, anxiolytics or antidepressants and sick leaves will also be collected. Costs associated with HCRU will be described from the payer and from the "all payers" perspectives. Descriptive statistics will be used to analyze the data and when possible, results will be stratified by age at disease onset. The number of RRP cases identified over the study period and France official population census will be used to estimate RRP incidence and prevalence.

Conclusions: Findings from the BREATH study will contribute to a better understanding of the burden of this devastating disease in France. Further research using a common and standardized approach is crucial to obtain additional data that will help address the information gap in epidemiological and economic burden of RRP across the globe, especially in low and middle resource countries.

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#9257

Impact of HPV Vaccination on Juvenile Laryngeal Papillomas and Conjunctival Papillomas: Incidence and Analysis of HPV Subtypes in Relation to Vaccination

06 - HPV prophylactic vaccines

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Background/Objectives: Papillomas are benign epithelial tumors primarily induced by low-risk forms of Human Papilloma Virus (HPV). These tumors can develop in various anatomical sites, including the respiratory tract and conjunctiva. Juvenile laryngeal papillomas, often associated with Juvenile-Onset Recurrent Respiratory Papillomatosis (JoRRP)and conjunctival papillomas are predominantly caused by HPV types 6 and 11. JoRRP is believed to be acquired during childbirth from an HPV-infected mother, with documented cases in both vaginal deliveries and cesarean sections. JoRRP typically manifest in early childhood, with a mean age of diagnosis between 3 and 4 years. Children affected by JoRPP often require multiple surgeries to remove lesions, ensuring voice function and open airways. In severe cases, a tracheostomy may be necessary, and fatalities have been documented. Conjunctival papillomas can also develop due to transmission during childbirth as well as through ocular contact with contaminated hands. Conjunctival papillomas most often occur between the ages of 21 and 40 years. The introduction of the HPV vaccine in the Danish Childhood Vaccination Program in 2009 has potentially reduced the incidence of these conditions. This study aims to evaluate the effectiveness of the HPV vaccine in preventing juvenile laryngeal papillomas and conjunctival papillomas and to analyze the HPV subtypes present in laryngeal papilloma biopsies, correlating these findings with the vaccination status of the mothers of affected patients.

Methods: This is a Danish national retrospective cohort study. We will identify patients who had biopsies taken from laryngeal papillomas before the age of 18 during a period from 2006 to 2024 across Denmark. Incidence throughout this period will be determined. The chosen time frame includes years prior to the introduction of the HPV vaccine, aiming to enhance the statistical validity and plausibility of any observed decline in incidence. Biopsies from laryngeal papillomas stored in biobanks in the "Region Hovedstaden" and "Region Sjælland" regions will be tested for HPV subtypes at the Department of Pathology at Rigshospitalet. The national incidence of conjunctival papillomas in patients aged 0 to 40 years in a period from 2008 to 2024 will be determined according to age-subgroups and compared to a Danish cohort from 1983 to 1997. The HPV vaccination status of conjunctival patients as well as mothers of patients with laryngeal papillomas will be examined. Data will be collected from the Danish Bank of Pathology, using SNOMED CT codes and from national health register data.

Results: Preliminary data suggest a decline in the incidence of juvenile laryngeal papillomas and conjunctival papillomas post-vaccination. Detailed analysis of HPV subtypes and vaccination status will provide further insights. Further results are pending and will be available by the time of the conference.

Conclusions: The introduction of the HPV vaccine appears to have a reduced the incidence of Juvenile laryngeal papillomas and conjunctival papillomas. This study will contribute with valuable data to support the effectiveness of the HPV vaccination program and guide future public health policies.

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#9430

Burden of human papillomavirus-related head and neck cancers in Portugal

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Head and neck cancer (HNC) is the seventh most common cancer worldwide with an annual incidence of more than 666,000 new diagnoses and 325,000 deaths. HNC incidence is two-to-five-fold higher in men versus women. In Portugal, over 3,066 new cases of HNC are reported annually, with men being more frequently diagnosed (men-to-women ratio: 5.2:1). HPV, smoking, and alcohol consumption are key contributors. Despite decreasing rates of smoking and alcohol consumption, HNC incidence has increased, particularly for oropharyngeal cancers (OPC). This study aimed to assess HPV attributability in HNC at two time periods in Portugal.

Methods: This observational study included pre-treatment tumor tissue from patients with a first primary diagnosis of oropharynx, hypopharynx, larynx, nasopharynx, and oral cavity cancers in 2008-2009 and 2018-2019. HPV was tested in central laboratories using p16INK4a immunohistochemistry, HPV-DNA PCR (SPF10/DEIA/LiPA25 assay), and HPV E6*I mRNA. HPV attributability was defined by HPV positivity in at least two tests for OPC and positivity in HPV-DNA and mRNA for non-OPC.

Results: Four oncology centers participated, enrolling 437 patients with 392 valid and 45 invalid FFPE tumor samples (valid samples included 25 OPC and 104 non-OPC 2008-2009 and 75 OPC and 187 non-OPC for 2018-2019). HNC patients were mainly males (84.4%) with mean (SD) age of 61.4(11.9) years at diagnosis, including 58.3% current smokers, 25.2% ex-smokers and 33.1% heavy drinkers. HPV attributability in OPC increased from 0% (95% CI: 0.0%, 13.7%, n=0) in 2008-2009 to 20% (95%CI: 11.6%-30.8%, n=15) in 2018-2019. A similar trend in HPV-AF was observed when assessed by gender, which revealed that over the time, there was an increase in HPV-AF among male patients (0% in 2008-2009 to 14.7% [95% CI: 7.3%, 25.4%]; n=10 in 2018-2019) and female patients (0% in 2008-2009 to 71.4% [95% CI: 29.0%, 96.3%]; n=5 in 2018-2019). Within non-OPC HNCs, during the 2008-2009 period, HPV-AF for laryngeal cancer was reported at 5.1% (95% CI: 0.6%, 17.3%; n=2). During the 2018-2019 period, HPV-AF for laryngeal, and nasopharyngeal cancers were reported at 4.0% (95% CI: 0.5%, 13.7%; n=2), and 12.5% (95% CI: 0.3%, 52.7%; n=1), respectively. None of the other non-oropharyngeal HNCs (hypopharynx and oral cavity) were reported during the period 2018-2019. The HPV genotype identification showed that all HPV-attributable OPC patients had HPV16 genotype (100.0%, n=15). Overall, high-risk HPV genotypes (16/18/31/33/45/52/58) were found in 95.0% of HPV-attributable HNC.

Conclusions: This study is the largest comprehensive assessment of HPV-attributable HNC conducted in Portugal, highlighting the burden of HPV in HNC, especially in OPC. The HPV-AF in OPC has dramatically increased from a 2008-2009 to 2018-2019 in Portugal and could be even more substantial in the future.

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High-risk human papillomavirus in patients with oral carcinoma and oral potentially malignant disorders in Serbia

28 - Oral HPV infection

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Background/Objectives: Oral squamous cell carcinoma (OSCC) accounts for about 95% of oral cancers. It represents a serious public health problem due to the high degree of morbidity and mortality, as well as multifactorial etiology. Human papillomavirus (HPV) infection is a well-documented risk factor for oropharyngeal carcinoma, but its role in oral carcinogenesis is still debatable. Our aim was to investigate the differences in the prevalence of high-risk HPV genotypes (HR-HPV) in patients with OSCC and oral potentially malignant disorders (OPMD) from that of healthy subjects.

Methods: Oral squamous cell carcinoma (OSCC) accounts for about 95% of oral cancers. It represents a serious public health problem due to the high degree of morbidity and mortality, as well as multifactorial etiology. Human papillomavirus (HPV) infection is a well-documented risk factor for oropharyngeal carcinoma, but its role in oral carcinogenesis is still debatable. Our aim was to investigate the differences in the prevalence of high-risk HPV genotypes (HR-HPV) in patients with OSCC and oral potentially malignant disorders (OPMD) from that of healthy subjects.

Results: One or more of the 12 tested HR-HPV genotypes were detected in 5/30 patients with OSCC and 2/30 with OPMD, whereas no healthy subjects were positive for any of the tested genotypes. There was a statistically significant difference in nodal involvement between HPV-positive and HPV-negative patients with OSCC.

Conclusions: Oral HR-HPV was detected in patients with oral premalignant and malignant lesions but not in healthy individuals, suggesting a possible role in oral carcinogenesis. Broad HR-HPV panel testing could increase the sensitivity of risk assessment and screening for OSCC.

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#9433

Pilot Study Unraveling the Interaction Between HPV and the Microbiome in the Oropharynx

18 - Microbiome

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Background/Objectives: The increase in the incidence of oropharyngeal cancer is a concerning issue worldwide. Further cases of human papillomavirus (HPV)-associated oropharyngeal cancer, primarily induced by high-risk HPV16, are increasing, especially among younger individuals in North America and Northern Europe. Recent data points to the role of microbiome disruption in inflammation and tumour induction, modulating the response to HPV infection and oropharyngeal cancer treatment.

Methods: An exploratory study was designed to select women that attended Gynaecology appointments from 2022 to 2024. These women were contacted by cell phone to answer a sociodemographic questionnaire. They were then called, along with their partners, for an oropharyngeal swab to evaluate HPV and microbiome. HPV genotyping and microbiome analysis were performed using Real-Time Polymerase Chain Reaction. Some species of microbiome were analysed using Next Generation Sequencing technique. Statistical analysis was performed using SPSS software v.27. $P<0.05$ was considered statistically significant.

Results: Of the 51 selected women, 30 (mean age 41.77±11.9 years) of them consented to answer the questionnaire. HPV was tested in 21 women and microbiome evaluation was conducted in 18 women. Four male partners were also tested. Of the women tested, 46.7% were vaccinated against HPV, 16.7% were smokers and 86.7% practiced oral sex. HPV42 was isolated in one of the patients. The microbiome of this population consisted mostly of species of Streptococcus (100%), Moraxella (40.9%), and Staphylococcus (36.4%). Lactobacillus species were present in the oropharynx of 2 individuals, which was the same frequency as Leptotrichia species. Women who smoked, took probiotics, or had intestinal disorders showed a tendency to have more potentially pathogenic microorganisms (OR=7.0, 95% CI: 0.9 - 56.9, P=0.079).

Conclusions: This study suggests that women who are given a holistic approach to their genital ecosystem based on preventive care with probiotics and HPV vaccination have less HPV in the oropharynx. It is mandatory to increase population literacy on the impact of HPV and the microbiome in the oropharynx. Further research is needed.

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#9524

Detection of methylated tumor markers in head and neck cancer and tumor environment

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: The post-surgical recurrence rate in head and neck cancers (HNSCC) is high. Alterations in methylation patterns of genes promote the emergence and the recurrence of cancer. One hypothesis is that some cancers relapse due to incomplete resection undetected by standard histopathology. The field cancerization concept postulates that HNSCCs are surrounded by genetic and epigenetic alterations in histologically normal-appearing tissue. The aim of this study is to analyze HNSCC samples upon already established diagnostic DNA methylation tumor markers (HOXA9, ZNF671, ZIC1, PAX6, ZNF833) at the tumor margins and the surrounding tissue. If it is possible to detect these tumor markers close to the negative surgical margins, this could be an indication supporting our hypothesis, and thus be of diagnostic value regarding completeness of tumor resection.

Methods: 15 HNSCC samples were collected during surgery and were frozen immediately. Adjacent sections were used for immunohistochemical staining (Ki-67, AE1/AE3, ASMA). Sections in-between were placed on PEN-membrane slides used for laser capture microdissection (LCM). For DNA methylation analyses, methylation-specific real-time PCR (msPCR) allowing detection of the previously mentioned tumor markers was performed. Furthermore the samples were also analyzed regarding their HPV status.

Results: The immunohistochemical staining and msPCR could be well established. With the first tissues analyzed during method establishment, microdissected tumor cells showed valid results with high methylation score for the tumor markers, whereas non-tumor cells also showed valid, but negative results. In the next step, tissues with the required morphology for addressing the question of field cancerization effects will be analyzed.

Conclusions: Performing msPCR using cells from LCM for detecting DNA methylation of five tumor markers resulted in high sensitivity and specificity with the first tissues analyzed. A clear differentiation between tumor and non-tumor cells could be shown. Results regarding the detection of aberrant methylation in histopathologically normal tissue at the resection margins supporting or contradicting the field-cancerization effects will be presented at the congress.

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#9324

Specificity and sensitivity of circulating HPV-DNA in patients with oropharyngeal squamous cell carcinoma

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Oropharyngeal squamous cell carcinoma (OPSCC) is one of the most common types of head and neck cancer, and it is strongly linked to infection with human papillomavirus (HPV). The global incidence of OPSCC is increasing, and in Denmark, this group now constitutes more than 70% of newly diagnosed patients with OPSCC. We have previously shown that cell-free HPV-DNA can be detected in a blood sample at time of diagnosis. Following successful treatment, the amount of HPV-DNA in the blood drops below the limit of detection but rises again during recurrence and can be found several months before the recurrence is clinically detectable. The aim of this project is to implement an HPV-DNA test as part of the diagnostic follow-up program for this patient group and investigate whether the test can be used to diagnose recurrence earlier than is currently possible.

Methods: We have enrolled 74 of200 patients. Enrollment is offered upon invitation to all newly diagnosed HPV+ OPSCC patients in eastern Denmark (~47% of the Danish population), who are treated with a curative intent. Blood samples are collected in Streck DNA BCT CE tubes at baseline and after treatment at 2 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months or at any time point in between upon suspicion of recurrence. Samples are analyzed with an in-house developed ddPCR assay detecting HPV16, 18, 31, 33, 35, 45, 51 and 58. If a sample is positive for HPV-DNA following treatment, the patient will be invited for an extra examination by an ENT specialist and a PET/CT scan to investigate if the recurrence can be clinically verified. Quality of Life during the study is evaluated by the Fear of Recurrence Questionnaire (short form).

Results: From April-October 2024, we have enrolled 74 patients in this prospective, single-arm research implementation project. We have established collaboration agreements with all head and neck centers in eastern Denmark, who are now involved in collecting blood samples to make the sampling more accessible to patients. Inclusion percentage is ~80%. Patients decline participation because they cannot fathom participation before treatment initiation. The HPV-DNA assay has been successfully implemented in the lab and no recurrences has been detected by blood samples or at clinical/radiological examinations. The sensitivity of the assay is thus far comparable to previously published results from our group.

Conclusions: The HPV-DNA ddPCR assay has been implemented successfully in the lab but further time is warranted to investigate whether this test can be utilized to diagnose recurrences earlier than what is currently possible.

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#9480

A PREDICTIVE APPROACH TO ORAL HPV PREVENTION TRIAL ENRICHMENT

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Oral HPV-related oropharyngeal cancers contribute to high cancer mortality and morbidity in North America. A decision tool that identifies participants at high risk of oral HPV infection for preferential recruitment into preventative trials against oral HPV infections could improve trial efficiency and increase the chance of discovering an efficacious preventive agent against oral HPV. The objective of this study was to develop and validate a prediction model for prognostic enrichment of oral HPV prevention clinical trials.

Methods: We used the NHANES dataset, a series of cross-sectional household interviews representative of the non-institutionalized US population. The outcomes were positivity to any oral HPV and positivity to high-risk oral HPV. The 2009-2010, 2011-2012, and 2013-2014 cycles of the NHANES were used to develop the model using penalized logistic regression and internally validated using 250 bootstrap resamples. External temporal validation was also conducted using the 2015-2016 cycle.

Results: The development and validation data comprised 15,154 and 4,843 individuals with 7.29% and 6.32%, respectively, who were positive for oral HPV. The final model included eight easily obtainable predictors: age, sex, race, marital status, age at sexual debut, lifetime number of oral sexual partners, lifetime number of sexual partners, and smoking pack years. The model was discriminatory for predicting any oral HPV status (AUC = 0.73; 95% CI: 0.70, 0.75) and high-risk oral HPV (AUC = 0.72; 0.68, 0.76). In addition, the model showed excellent calibration for predicting any oral HPV (calibration slope (CS) 0.98; 0.83, 1.13) but over-predicted for high-risk oral HPV (0.87; 0.69, 1.04).

Conclusions: This model appears suitable for predicting any oral HPV status but should be used cautiously for high-risk oral HPV status due to over-prediction.

FC07 - Epidemiology

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#9657

Cervical cytology and HPV distribution in Cape Verde: A snapshot of a country taken during its first HPV nation-wide vaccination campaign

09 - HPV testing

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Background/Objectives: Cervical cancer ranks as the third most common female cancer in Cape Verde and is the leading cause of cancer-related deaths among women in the country. While Human Papillomavirus (HPV) vaccination, which started in 2021, is anticipated to significantly reduce disease incidence, cervical screening remains crucial for non-vaccinated women.

Methods: We retrospectively reviewed gynecologic cytology exams and HPV tests performed in Cape Verde between 2017 and April 2023 and processed at IMP Diagnostics. For this study, we considered 13035 women with cytology examinations performed and, 2013 of these, also with an HPV molecular test.

Results: Cytology diagnostics comprised 83 % NILM cases; 12 % ASC-US; 2.7 % LSIL; 1.2 % ASC-H; 0.5 % HSIL and 0.1 % SCC. In 505 (25.1 %) high-risk HPV infection was detected. Prevalence of HPV infection varied with age, peaking at young ages - ≤24 years old (55.5 %) and 25-35-year-old women (31.5 %) - and the lowest after 66 years old (9.7 %).

Conclusions: Herein we present a comprehensive study regarding Cape Verde's cervical cytology and HPV distribution, aiming to provide a snapshot of the country's cervical cytology results and HPV distribution in recent years. Moreover, these data may contribute in establishing a baseline to assess, in the future, the vaccination impact in the country.

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#9486

Primary HPV sample collection and 20-year follow-up of the ARTISTIC Trial cohort

03 - Epidemiology and natural history

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Background/Objectives: Primary HPV testing is now established in the English NHS Cervical Screening Programme since it was introduced in 2019. The ARTISTIC cohort provides longitudinal HPV screening data over more than 20 years.

Methods: The ARTISTIC trial cohort of 24,496 women recruited in 2001-03 has been followed up for cancer incidence and mortality for 20 years. Routine cervical samples were tested for HPV using HC2 (followed by PCR genotyping) between 2001-09 as part of the trial. Between 2018-22, samples from around 10,000 ARTISTIC women who were attending for primary HPV testing in Manchester were retained. These samples were routinely tested as part of the NHS cervical screening programme by Roche Cobas and those positive for the non 16/18 types have been further genotyped.

Results: The hrHPV prevalence in the primary HPV samples was 15%, 9% and 7% for those aged 35-39, 40-49 and 50-54 years respectively, higher than at baseline (8%, 5% and 3% for the same age groups respectively). To a certain extent this may be due to increasing trends by birth cohort but more likely to be differences in assay sensitivity. The 20 year cumulative risk of invasive cervical cancer was estimated to be 1.2% (95% 0.7%-2.1%) among those positive for HPV 16/18 infections at baseline. Following primary HPV testing, CIN3+ was detected among those with both long standing HPV infections (>15 years) and among those with redetected infections (i.e. those with intermediate periods testing negative). In the entire cohort of 24,496 women, 41 cervical cancers have been diagnosed, including 8 following primary HPV testing who were all positive for HPV 16 or HPV18 (7 with high grade cytology and 1 following normal cytology). The 5 adenocarcinomas were all well screened with a previous negative cytology test around 3 years previously.

Conclusions: The ARTISTIC trial cohort is a rich data source with retained cervical samples and cervical cancer incidence data over a 20-year period. Cervical cancers continue to be diagnosed among well screened women.

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#9270

HPV prevalence in transgender in two reference centers in Brazil

09 - HPV testing

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Background/Objectives: HPV is the most common sexually transmitted infection (STI) worldwide. In Brazil, the prevalence varies from 11.9% to 36.2% depending on the subpopulation and anatomic body site. People who identify as transgender and those identifying outside the gender binary (e.g., gender nonbinary, genderqueer) are at a disproportionate higher risk for human immunodeficiency virus (HIV) and other STIs, such as HPV. Recent studies confirm that the prevalence of HPV among transgender women is high, while awareness about HPV and its risks is low. Despite the advantages of HPV vaccines, transgender individuals face ongoing challenges in accessing healthcare and national vaccination programs, leading to health disparities. Data on HPV prevalence in this subpopulation is needed to inform effective health policies and interventions. This study aims to describe clinical and demographic characteristics and HPV prevalence among unvaccinated transgender Brazilian individuals.

Methods: This observational, cross-sectional study assessed HPV prevalence among unvaccinated transgender individuals at two major health centers located in São Paulo and Rio de Janeiro, Brazil, from November 2023 to August 2024. Eligible participants aged 18+ years who have ever had sex answered a structured survey and provided oral, genital (neo/vaginal or neo/penial), anal, and cervical samples for HPV testing for high and low risk types. Additional data were collected through medical records. We report results using descriptive statistics.

Results: Overall, 150 participants were enrolled, 63.3% (95/150) of them identified as female transgender, with 30.7% (46/150) identifying as "travestis". Mean age was 35 years (standard deviation [SD] 9.8), 48.0% (72/150) identified as Pardo/Mixed race and 32.0% (48/150) as Black, and 44.7% (67/150) had complete high school. Monthly incomes ranged from $92 to $220 in 39.3% (46/117) of participants and from $220 to $367 in 38.5% (45/117). Report of prior or current STI was present in 74.7% (112/150) of participants. Syphilis was the most common STI (90.2%; 101/112), of which ~5.0% (5/101) had currently active and 10.6% (10/94) recurrent infections. Overall HPV prevalence was 53.3% (80/150; 95% confidence interval [CI] 45.4%-61.3%). Anal, genital, and oral HPV prevalences were, respectively, 51.3% (77/150; CI [43.3% - 59.3%]), 4.6% (7/150; CI [1.3% - 8.0%]), and 1.3% (2/150; CI [0 - 3.2%]), only one participant presented cervical HPV positivity. Notably, high-risk HPV (HR-HPV) types were prevalent in 97.5% (CI [94.1% - 100%]) of the HPV-positive cases, with anal HPV showing a high-risk frequency of 97.4% (75/77; CI [93.9% - 100%]), and cervical (1/1), genital (7/7), and oral (2/2) HPV cases all being 100% high-risk. Additionally, low-risk HPV (LR-HPV) types were present in 37.5% (30/80; CI [26.9% - 48.1%]) of the HPV-positive cases, with anal HPV showing a low-risk frequency of 37.7% (29/77; CI [26.8% - 48.5%]). No LR-HPV was detected in cervical or oral samples, while genital HPV had a low-risk frequency of 14.3% (1/7; CI [0 - 40.2%]).

Conclusions: The study highlights the high prevalence of HR-HPV particularly in the anal region, among unvaccinated transgender individuals in Brazil. Addressing the need for epidemiological studies in underrepresented groups for effective HPV prevention and health equity. Further research is needed to gather clinical data and develop inclusive health policies to improve access to HPV vaccination and screening for this vulnerable population.

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#9377

Are Multiple-Genotype Human Papillomavirus Infections associated with Virus Persistence?

03 - Epidemiology and natural history

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Background/Objectives: Human papillomavirus (HPV) infection is the primary cause of cervical cancers and their precursor lesions. Some studies have indicated that multiple-genotype HPV infections are linked to persistent low-grade squamous intraepithelial lesions/cervical intraepithelial neoplasia type 1 (LSIL/CIN1), which may increase the risk of cancer progression. Conversely, other authors state that concurrent HPV infection could lead to intergenotypic competition, potentially lowering the risk of high-grade cervical lesions. In this study, we aim to compare single and multiple-genotype HPV infections, concerning their association with HPV persistence.

Methods: This observational retrospective study included 409 women with HPV infection referred to the Cervical Cancer Screening Appointment at a tertiary hospital, between January 1st and December 31st, 2022. Our sample was divided into two groups: single-genotype and multiple-genotype HPV infection. At 12 months of follow-up, women underwent HPV testing, using the Cobas® HPV test. Clinical information was gathered from hospital records, and statistical analysis was conducted using SPSS® version 27, employing the χ^2 test.

Results: Single-genotype HPV infection was the most common, occurring in 245 women (59.9%), compared to 160 women (39.1%) with multiple-genotype infections. There were no differences between the two groups, in terms of age, parity, number of sexual partners, smoking, menopause, and vaccination history. At the time of referral, HPV-16 was the most prevalent genotype in both groups (83/245, 33.9% vs 61/160, 38.1%, p-value > 0.05), followed by HPV-31 (25/245, 10.2% vs 38/160, 23.8%, p-value < 0.05). After 12 months of follow-up, multiple-genotype HPV infection was more strongly associated with virus persistence (80/245, 32.7% vs 77/160, 48.1%, p-value < 0.05). The incidence of HPV-16 after 12 months differed significantly between the two groups (22/245, 9.0% vs 9/160, 5.6%, p-value < 0.05). In contrast, the incidence of other high-risk HPV (ohr-HPV) genotypes - 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 - was similar in both groups (49/245, 20.0% vs 48/160, 30.0%, p-value > 0.05).

Conclusions: In our study, multiple-genotype HPV infections were associated with HPV persistence after 12 months, primarily due to the persistence of concomitant HPV-16 and ohr-HPV genotypes. While the persistence of these ohr-HPV genotypes was not statistically significant between the two groups, their high incidence may indicate a greater challenge in eradicating these viruses. This could potentially lead to cytological abnormalities and high-grade cervical lesions in the long term.

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#9295

Population-based age-period-cohort analysis of declining human papillomavirus prevalence in Sweden

03 - Epidemiology and natural history

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Background/Objectives: Globally, most countries have launched human papillomavirus (HPV) vaccination programmes and declining HPV prevalences are reported. We aimed to disentangle the influences of calendar time, birth cohort and age by analysing HPV prevalences in population-based cervical screening using age-period-cohort modelling.

Methods: All 813,882 primary HPV-based cervical screening tests from women aged 23-64 between 2014-2023 in the capital region of Sweden were identified in the Swedish National Cervical Screening Registry. The odds ratio of HPV16/18 infection was estimated comparing each birth cohort to the unvaccinated 1984-born using an age-period-cohort model. The impact of changing HPV prevalences on the numbers needed to screen (NNS) to detect and prevent 1 cervical cancer case were calculated.

Results: HPV vaccination coverage was 82-83% among women born in 1999-2000. Before 2019 the HPV16/18 prevalence was highest among the youngest women in the screening program. During 2020-2023 the prevalence consistently decreased among the birth cohorts offered organised school-based vaccination. There was a 98% decline in HPV16 prevalence (odds ratio=0.02 [95% CI 0.01-0.04]) and a 99% decline in HPV18 prevalence (odds ratio=0.01 [0.00-0.04]) among the 2000-born compared to the 1984-born. The declining HPV16/18 prevalences resulted in major increases in the NNS to detect and to prevent 1 case of cervical cancer.

Conclusions: The declines of HPV16/18 were considerably larger than the vaccination coverage, suggesting herd immunity effects. The changing epidemiology of HPV types impacts the need for cervical screening.

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#9498

Insights on HPV Genotyping results in Portuguese private practice

03 - Epidemiology and natural history

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Background/Objectives: Cervical cancer ranks as the 8th most frequent cancer amongst women in Portugal. HPV genotyping can assist in risk stratification, patient management, treatment of low-grade lesions and evaluation of non-vaccinated HPV types. Since CLEOPATRE Portugal study from 2008/2009, very few studies have showed the prevalence of the different HPV types in women in Portugal. This is particularly interesting to reanalyse nowadays due to the alterations seen with the implementation of the vaccines. The main goal of this project is to describe the most prevalent cases of HPV in the different areas of Portugal in our private practice.

Methods: In this observational study, a total of 13.802 cases of women with an average age of 47 were included to gather data on the prevalence of several HPV types in cervical cytology samples. Genotyping assays were conducted from 2017 to October 2024 on liquid-based cytology samples using Anyplex HPV28, Allplex HPV28, Anyplex HPV HR and Allplex HPV HR (Seegene).

Results: The overall detection rate of HPV infection was 28%. The most prevalent HPV type was 16, followed by types 31 and 68. Coinfections were observed in 10% of the cases. The demographic distribution showed was similar trends across the country, with lower positivity rates in the Centre of Portugal compared to North, South and islands. Specifically, HPV 16 prevalence was highest in the North of Portugal at 2,7% , while it was 1,49% islands, 0,73% in the centre and 1,83% in the south. The prevalence of HPV 31 and 68 followed a similar pattern.. Coinfections were more frequently found in the South comparing to other regions. Regarding age distribution, women aged 30 or younger exhibited a significantly lower positivity rate for HPV16 (around 0,56%) and HPV18 was detected in only 3 out of 1428 women is this age group. HPV 66 continues to be included in these genotyping tests and was identified in over 160 women.

Conclusions: The prevalence of HPV types differs significantly across various countries and studies, both national and international. This may be due to regional differences in HPV infection, shifts in the pattern of incidence or even the effect of vaccination. As HPV incidence continues to evolve, it is crucial for the scientific community to stay informed to develop more effective screening and vaccination programs. This study allowed a small glimpse into positivity rates within private practice in Portugal. A key finding is that vaccination has notably reduced the infection rates of the most carcinogenic HPV type. Additionally, HPV 66, which has no attributable risk according to IARC publications, should likely be excluded from these assays to prevent confusion among healthcare providers and patients. It is important to note that this data may be biased since some women may have undergone testing more than once, and private practices do not follow the same protocols as national screening programs, relying instead upon gynecologists' judgments.

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#9642

Incidence trends of anogenital warts in Sweden 2006-2022

07 - HPV therapeutic vaccines

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Background/Objectives: Sweden introduced human papillomavirus (HPV) vaccination in 2006, administered to girls and young women through opportunistic, subsidized, catch-up and school-based programs. Boys were not included until 2020. Anogenital warts are the first observable clinical outcome following infection by HPV-6/11, targeted by HPV vaccines including viral-like particles targeting such genotypes. We here assess trends in the population incidence of genital warts in Sweden since the introduction of HPV vaccination programs.

Methods: We performed an ecological study in Swedish registers to obtain national population data and cases of anogenital warts from 2006-2022 in men and women aged 15-44. We illustrated the incidence rate of anogenital warts since introduction of HPV vaccination by sex and age group. We examined the trends of genital warts by estimating the average annual percentage change (AAPC) using joinpoint regression models with 95% confidence intervals.

Results: The incidence of anogenital warts decreased substantially among women and men under the age of 30 since the introduction of HPV vaccination programs. From 2006 to 2022, the AAPC in genital warts incidence among women was -17.7 (-19.5, -16.8) for ages 15-19, -12.9 (-14.3, -12.5) for ages 20-24, -7.2 (-7.7, -6.9) for ages 25-29, and -2.5 (-3.4, -1.7) for ages 30-34. A similar decline was observed in men, albeit with slightly lower magnitudes, with AAPC values ranging from -14.1 to -0.9 across the same age groups.

Conclusions: Consistent population-level decreases of anogenital warts incidence in both women and men continue to emerge since the introduction of HPV vaccination, where the continued decreases among unvaccinated men are so far attributable to herd effect from vaccinated women. Continued surveillance is crucial to assess the full impact of gender-neutral vaccination programs. Table 1 Average Annual Percentage Changes (AAPC) and corresponding confidence interval (CI) from 2006 to 2022, by age and sex

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#9499

Factors associated with persistent oncogenic oral HPV infections by age group in the HIM study

03 - Epidemiology and natural history

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Background/Objectives: Oral infection with oncogenic human papillomavirus (HPV) can lead to HPV-related oropharyngeal cancer. We recently reported that older men (38-81years) from the HPV in men (HIM) study have significantly longer duration of incident oral oncogenic infections compared to younger and middle-aged men. Our current aim is to investigate the factors associated with the duration of oncogenic oral HPV infections by age group.

Methods: HIM study participants (n=3,136) ages 18-70, who provided at least two oral gargle samples were included in this analysis. Samples were collected every 6 months for a total of 48 months. HPV was genotyped using the HPV SPF10 PCR-DEIA-LiPA25, (DDL-Diagnostic-Laboratory, Netherlands) line probe assay. Factors associated with a persistent oral oncogenic HPV infection to 6 months were assessed in crude logistic regression models for aged categories 18-32 and 33+ years.

Results: In the univariate model, among men aged 33+ years, the factors associated with 6 months oral oncogenic persistent infections were education duration of 13-15 years, 3-7 lifetime number of male sex partners, having given >6 times Oral Sex in the past Six Months among older men. Among men aged 18-32 years, having 3-7 lifetime number of male sex partners and history of smoking were associated with 6 months persistent oral oncogenic infections (Table 1).

Conclusions: Having multiple lifetime number of male sex partners is associated with 6 months persistence of incident oral oncogenic HPV regardless of age of men. Awareness of quitting smoking and risky sexual behaviors are critical among younger and older men respectively. The association of oral oncogenic HPV persistence with education duration requires further discussion. Multi-variable models to assess factors that are independently associated with persistent oral HPV infections are in progress.

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#9381

Analysis of high-risk Human Papillomavirus (hrHPV) genotypes in multiple infections in women referred to colposcopy

03 - Epidemiology and natural history

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Background/Objectives: The introduction of extended genotyping for the detection of high-risk Human Papillomavirus (hrHPV) infection has permitted to better investigate the prevalence of specific HPV genotypes associated with cervical lesions as well as of infections with multiple hrHPV types. The objective of this study was to evaluate the prevalence of multiple hrHPV infections, the genotypes involved and their association with cervical lesions in women with recent history of cervical dysplasia referred to colposcopy.

Methods: To date, 358 women attending the Colposcopy Clinic of the Fondazione IRCCS San Gerardo dei Tintori (Monza) were involved in the study. A cervical specimen was collected from each patient using the L-shaped FLOQSwab endo/exocervical and resuspended in 20 ml of PreservCyt medium. HPV detection and genotyping were carried out using the AnyplexTMII HR HPV kit using the MicroLab Nimbus instrumentation starting from 200 ul of sample. This assay can detect 14 hrHPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). HPV testing results were further associated with clinical data.

Results: Preliminary results showed an overall hrHPV positivity of 66.2% (237/358) with a multiple hrHPV infection rate of 42.6% (101/237). The two most common detected genotypes were HPV16 and HPV31. The presence of multiple infections sustained by two, three or more than three hrHPV genotypes was detected in 58.4% (59/101), 29.7% (30/101) and 11.9% (12/101) of cases, respectively. The histological data was available from 70 hrHPV positive women. 78.6% (55/70) showed the presence of a ≥CIN2 (cervical intraepithelial neoplasia) lesion and among these women 32.7% (18/55) were co-infected with more than one hrHPV genotype. HPV16, HPV18, HPV31 and HPV45 were the most common genotypes detected in co-infections among this group of women. Among women with <CIN2 the detection of hrHPV multiple infections was 46.7% (7/15) and the two most common genotypes detected were HPV16 and HPV52.

Conclusions: The results of this ongoing study have provided epidemiological data regarding multiple hrHPV infections and their association with cervical dysplasia. A larger longitudinal study will allow to better clarify the association of multiple infections with the progression of cervical dysplasia. The use of extended genotyping in a colposcopy setting is expected to improve patients' management in the follow-up through risk stratification based on the hrHPV genotype detected.

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Cervical cancer mortality trends in England and Poland

03 - Epidemiology and natural history

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Background/Objectives: Age-standardised death rates in both Poland and England have been decreasing for many years, but without looking at rates within birth cohorts it is not clear whether these decreases are due to falling HPV rates or effective screening.

Methods: We compare the death rates within birth cohorts in both countries and reflect on the probable reasons behind these apparently parallel trends.

Results: Birth cohort analysis shows that the cervical cancer death-rate fell sharply in England after the introduction of the national screening programme in 1988. Before 1988 the rate had been rising rapidly in young women due to rising prevalence of HPV, and without screening Britain would have had one of the highest rates of cervical cancer in the world. Mortality is lower in Poland than in England below age 35 due to lower HPV infection rates in young women but continues to rise steeply with age and is higher than in England above age 40, suggesting that screening has had much less impact on Polish mortality rates. In English women born since 1995 cervical cancer has now become very rare due to the highly successful school-based HPV vaccination programme which began in 2008, but vaccination coverage in Polish girls is estimated to be less than 15%.

Conclusions: The key to reducing mortality from cervical cancer in Poland is achieving high coverage for HPV vaccination in teenagers and for screening from age 20 or 25 in unvaccinated women. Even a single sensitive HPV test has the potential to rapidly reduce the high mortality rate among older Polish women.

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Differences between Conditional and Overall Survival in Oropharyngeal squamous cell carcinoma HPV-positive and HPV-negative: analysis by age, clinical stage and other risk factors

03 - Epidemiology and natural history

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Background/Objectives: To estimate the actuarial (AS) and conditional (CS) overall survival in patients with oropharyngeal squamous cell carcinoma (OPSCC) HPV-positive (HPV+) and HPV-negative (HPV-).

Methods: Retrospective cohort in Cancer Center in São Paulo - Brazil included patients with OPSCC from 2000-2022. Data on sociodemographic, clinical, and lifestyle factors were collected. Cases were staged following the 8th edition of American Joint Committee on Cancer. Actuarial and conditional overall survival were analyzed using Kaplan-Meier method up to 7 years. CS was calculated as the probability of survival for more 2 years given that has already survived a certain period in time. The survival analyses were performed by HPV infection and stratified by age, clinical stage, tobacco and alcoholic beverages.

Results: Of 448 OPSCC patients, 292 (65.2%) were HPV+ and 156 (34.8%) were HPV-. The AS was 86.5%/80.2% for HPV+ at 5 and 7 years and 69.8%/61.9% for HPV-. The difference in CS between HPV+ and HPV- decreased over time, with a higher CS in the 4th year for HPV- (95.9%) compared to HPV+ (92.7%). HPV- patients ≤60-years-old had 49.3% AS 7-years, HPV+ ≤60years-old had 79.6% and >60-years-old 74.5%. CS in 1st year for HPV- ≤60-years-old was 72.2%, but showed a greatest increase reaching 98.0% at 5th year, similar to HPV+ ≤60-years-old (98.4%). 7-years AS for HPV+ clinical stage (cStage) IV was the worst 40.5%. While other stages showed an increase in CS over time, HPV+ cStage IV declined to 63.5% in 4th year. Regarding age and staging for HPV+, patients cStage IV ≤60 years-old had the worst AS in 5 years (49.8%), while in 7 years was cStage IV >60 years-old (29.6%). Individuals with cStage IV >60 years-old were the only group with a declining CS, with 50.1% in 5th year, while clinical stage IV patients under 60 years old showed the greatest increase, reaching 96.0%. For smoking status, 7-year AS was 54.8% for HPV+ smokers, 62.3% for HPV- non-smokers, and 86.7% for HPV+ non-smokers. The worst 5-year CS was in HPV- non-smoker (84.5%). The largest increase in CS was observed in HPV- former smokers, rising from 76.9% in 1st year to 98.3% in 5th year. For alcohol consumption, HPV+ non-drinkers had 81.4% for 7-years AS, while HPV- non-drinkers had the worst outcome with 49.0%. HPV+ and HPV- former drinkers had 57.5% and 52.3% AS, drinkers in the same group 76.3% and 64.1%. HPV- non-drinkers had the worst 5-year CS (80.1%). The largest increase in CS was for HPV- former drinkers, rising from 75.7% in the 1st year to 95.8% in the 5th year. HPV+ non-drinkers had a 96.3% CS in the 5th year.

Conclusions: The overall survival of HPV- patients is worse at diagnosis, but becomes comparable to HPV+ if they survive until the 3rd year. Younger HPV+ patients have better actuarial overall survival. Although younger HPV- patients have worse AS, they show a rising probability of survival over time, becoming comparable to younger HPV+ patients and surpassing older HPV+ individuals.

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#9332

HPV Vaccine Impact - A Portal to New Discoveries?

03 - Epidemiology and natural history

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Background/Objectives: High coverage HPV vaccination is reducing the prevalence of vaccine types and associated CIN2+ disease, with recent data revealing a corresponding increase in less oncogenic non-vaccine types. This expansion of non-vaccine types to fill the niche previously occupied by higher CIN3+ risk types is predicted to decrease overall prevalence of cervical disease. Nevertheless, the increase was somewhat of a surprise given the low mutation rate of double-stranded HPV genomes and the speed with which rebalancing appears to be occurring. These observations pose some interesting questions about HPV ecology and offer the potential for new learnings.

Methods: We discuss the expansion of non-vaccine types and consider potential (non-mutually exclusive) mechanisms for the increase in non-vaccine prevalence: 1) Artefact of measurement method 2) Adaptive viral response 3) Negative interference by vaccine types 4) host selective pressure.

Results: Analysis of recent literature provides compelling evidence for non-vaccine type expansion in several countries with good vaccine coverage. They also appear to be contributing more to disease in vaccinated versus non-vaccinated communities. We find no evidence to support rapid viral evolution in response to vaccination, given the extreme lack of mutation in high-risk genomes. The literature is mixed on competition between HPV types with some studies reporting only positive associations and others reporting negative associations that could explain the expansion of non-vaccine types. One study reported direct molecular evidence that heterologous helicase protein subunits limit viral coinfections in the same cell1. Host selective pressure is difficult to assess as HPV ecology is not well understood. However, there is evidence of maintenance of overall high-risk positivity in the face of vaccine type decline which implies that a positive selective pressure may be at work. We discuss the latter in light of recent theories on eubiosis (interspecies balance in microbiota), dysbiosis, leading to disease, and the emerging evidence that eukaryotic viruses can play a role in innate immunity.

Conclusions: We believe that there is evidence to support the potential for relief of negative interference by vaccine target type elimination, thus leading to non-vaccine type expansion. The virologic evidence also supports the dynamic equilibrium / eubiotic nature of HPV infections and suggests that we should reassess existing natural history models to include the role of latency as a driving force in HPV biology, and the potential for dysbiosis to be a driver of cancer progression for both cervical and other HPV-related cancers. The ongoing shift in the virome poses some fascinating questions about HPV biology and should serve as a Call to Arms for multi-disciplinary investigation.

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#8986

The Burden of Anogenital, Oral, and Cervical HPV-Related Diseases in People Living with HIV: A Systematic Literature Review

03 - Epidemiology and natural history

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Background/Objectives: Persistent human papilloma virus (HPV) infections are responsible for multiple precancer lesions and invasive cancers. Over 90% of the global cervical cancer cases are caused by HPV and cervical cancer, the fourth most frequently diagnosed and the fourth leading cause of cancer death among women worldwide. Over 39 million people living with HIV (PLWH) reported globally are at an increased risk of HPV infection and HPV-related cancers. The aim of this study was to summarize the burden of HPV-related diseases among PLWH versus people living without HIV (PWoH).

Methods: A systematic literature review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive search was conducted in ovid and sourced from EMBASE, Medline, and Evidence-Based Medicine Reviews databases, and relevant conferences. Observational studies reporting HPV-related disease in adult PLWH that were published between January 2018 to June 2023 were included. The burden of HPV-related precancer lesions and cancers were synthesized and reported by relevant variables.

Results: Of the 221 studies included, 83 reported the burden of HPV-related diseases. The prevalence of HPV-related anal precancer was about two times higher among PLWH than PWoH. Men living with HIV(MLWH) have a significantly higher prevalence and incidence of HPV-related anal precancer than women living with HIV (WLWH) across a range of geographic regions. The incidence rate of anal high-grade squamous intraepithelial lesions (HSIL), a precursor of anal cancer, was over 7 times greater among MLWH than WLWH, and the prevalence of HSIL among MSM with HIV was up to 50% depending on the geographical region. The risk of progression from precancer to anal carcinoma in situ and to invasive carcinoma was reported to be about two-fold higher for PLWH versus PWoH. Similarly, HPV-related anal cancer is higher in PLWH than PWoH, particularly MLWH were up to 25 times more likely to be diagnosed with anal cancers than WLWH; non-Hispanic white men had a significantly higher incidence rate. The prevalence of oral papillomas in PLWH ranged between 1.4 - 3.1% in North and South America regions, however there were limited studies from other regions. Cervical high-grade precancer lesions (CIN2+,HSIL,ASC-H) prevalence was up to 3 times higher in WLWH than women without HIV, ranging between 5.4 - 31.0%. Incident HPV-related cervical cancer was up to 6 times higher in WLWH than in women without HIV, depending on the geographical region. Alarmingly, the incidence and prevalence of HPV-related cervical cancer is greatest in those younger aged 30-50 years than age over 55 years; however, in the US, HPV-related cervical cancer prevalence in WLWH in those aged <35 years was 15.4%.

Conclusions: The burden of HPV-related precancer lesions and cancers were significantly higher among PLWH compared to PWoH in both male and female. Incident HPV-related precancer and cancer cases were found at younger age in PLWH which is alarming. Increasing HPV vaccine uptake in this high-risk population regardless of gender is critical. Integration of HPV vaccination with routine HIV clinics may offer the opportunity to increase HPV vaccine uptake in this population.

References: Figure 1. Incidence rate of HPV-related anal cancers by race/ethnicity (WLWH: N=62; MLWH: N=218).

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#9197

Epstein-Barr virus (EBV) serology and its association with oral human papillomavirus (HPV) infection outcomes in children during the first three years of their lives

03 - Epidemiology and natural history

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Background/Objectives: Epstein-Barr virus (EBV) and Human Papillomavirus (HPV) are common oncoviruses infecting epithelial cells at the same mucosal sites. Both viruses are known to cause persisting infections, and EBV could act as a cofactor in persisting HPV infections and contribute to their malignant progression. The precise relationship between these two viruses remains unclear at present. This study aims to explore whether serological evidence of early EBV infection (i.e., high-level EBV antibodies) impact the longitudinal outcomes of oral HPV infections in children up to three years of age.

Methods: This study included 283 children from the longitudinal Finnish Family HPV cohort study of Turku University (Turku, Finland). The children were followed-up from the birth through three years of age, with oral and blood samples collected at 1-, 2-, 6-, 12-, 24- and 36-month follow-up visits. Serum IgG antibodies against four EBV antigens: 1) transcriptional trans activator protein (Zebra), 2) early antigen-diffuse (EA-D), 39 EBV nuclear antigen 1 (EBNA-1), and 4) viral capsid antigen p18 (VCAp18), were determined with fluorescent bead-based multiplex serology. HPV genotyping for 24 different HPV genotypes was done with Luminex. Logistic regression models were used to analyse the association between EBV serology and HPV infection outcomes.

Results: In the vast majority of children (91.4%), maternal EBV-antibodies disappeared within (Mean) 11.3 months. By the age of three years, 41 (17.2%) children were EBV seropositive, with the average age at seroconversion being 27.2 months. Of the multiple potential co-factors tested in logistic regression, only paternal education levels showed a significant protective effect against children's EBV seropositivity at the age of two and three; ORs of 0.06 and 0.16, respectively(95%CI range of 0.004-0.91). Only elevated EA-D antibody levels were associated with an increased risk of incident oral HPV infection, OR 2.55 (95% CI 1.13-5.79); and its clearance, OR 3.17 (95% CI 1.40-7.14).

Conclusions: As anticipated, most children lost their maternal EBV antibodies over time. Of the potential co-factors tested, only the higher paternal education was linked to a reduced risk of EBV seropositivity in later childhood. Similarly, no strong associations were identified between early EBV seropositivity and longitudinal outcomes of oral HPV infections in children. More research is still needed to reveal the true nature of the possible mechanisms between the viruses in children's oral HPV infections.

HN07 - Submitted papers - Basic science II

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#9384

TNM 8 staging system beyond p16: Double HPV/p16 status is superior to p16 alone in predicting outcome in oropharyngeal squamous cell carcinoma

09 - HPV testing

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Background/Objectives: The assessment of p16INK4a (p16) in oropharyngeal squamous cell carcinoma (OPSCC) has been incorporated into tumor classification, as p16 has been shown to impact survival probability. However, a recent study demonstrated that human papillomavirus (HPV) status in addition to p16 may have a better discriminatory effect on survival probability. This study aims to determine the impact of combined evaluation of p16 and HPV on prognosis.

Methods: This was a multicenter, multinational analysis including retrospective and prospective cohorts of patients treated for primary OPSCC with curative intent, based on the data of the HNCIG-EPIC study. The primary outcome was to determine how the combined assessment of HPV and p16 status predicts prognosis of patients with OPSCC compared to p16 assessment alone. We employed multivariable analyses models to compute hazard ratios regarding survival. Analyses were stratified by stage, smoking status, and sub-anatomical region.

Results: The study included 7654 patients, with approximately half of the tumors being p16-negative (50.3 %, n = 3849). A total of 9.2 % of patients had discordant p16 and HPV status (n = 704). HPV status significantly impacted overall survival and disease-free survival regardless of p16 status and across both UICC 8th stage I-II and III-IVb cancers. p16-positive/HPV-positive OPSCC patients exhibited the best survival probability.

Conclusions: The detection of HPV had a significant impact on survival probability for OPSCC patients with both p16-positive and p16-negative tumors. HPV testing should be integrated in cancer staging, especially in regions of low attributable fraction, alongside p16 evaluation to ensure a comprehensive assessment of prognosis.

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#9434

Determining the relationships between quantitative HPV DNA liquid biopsy results and circulating immune cell populations in HPV-positive head and neck squamous cell carcinoma

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: Assays that detect circulating tumor HPV DNA (ctHPVDNA) have shown promise in monitoring treatment response and disease recurrence/progression. Understanding the relationship between ctHPVDNA levels and immune cell populations could provide additional insight into the immune landscape of HPV+ HNSCC and its implications for prognosis and therapy. The objective was to evaluate the relationship between ctHPVDNA levels (quantitative and categorical readouts) and circulating immune cell populations in patients with HPV+ HNSCC to identify potential prognostic biomarkers that could better predict treatment response and clinical outcomes.

Methods: We conducted a retrospective study on a preliminary cohort of patients (n=35) with confirmed HPV+ HNSCC (p16+) and detectable pre-treatment ctHPVDNA (NavDx, Naveris, Waltham, MA). We included patients who received surgery (n=7), chemotherapy (n=26), or radiotherapy (n=28) as their primary treatment. We quantified ctHPV-DNA in the pre-treatment, on-treatment, post-treatment, and surveillance settings. A routine complete blood count (CBC) with differential analysis was collected around the corresponding ctHPV-DNA test and was used to determine neutrophil, lymphocyte, monocyte, and immature granulocyte relative percentages and absolute counts. Three primary analyses were performed on this dataset: (1) correlation between pre-treatment log-transformed ctHPVDNA levels and immune cell populations (n=35), (2) percent changes among immune cell profiles in response to treatment (pre-treatment ctHPV-DNA positive vs first undetectable, n=20), and (3) response to recurrence/progression (any ctHPVDNA level increase vs previous result, n=8 events across six patients). Significance was determined via correlation analyses or by performing wilcoxon matched-pairs signed rank test.

Results: Our analyses revealed a significant negative correlation between pre-treatment ctHPVDNA levels (average=2590, SD=5185) and the relative percentage of immature granulocytes (R=-0.3773, p=0.0278). We also observed correlations between pre-treatment ctHPVDNA levels and absolute counts of immature granulocytes (R=-0.2321, p=0.1865) and monocytes (R=0.1414, p=0.4178) for which significance might become evident in a larger cohort of patients. In response to primary treatment (n=20, pre-treatment ctHPVDNA positive vs. first undetectable, average=92 days, SD=53 days), there was a 50.8% reduction in absolute lymphocyte counts ($p<0.0001$, n=20). This effect appears consistent regardless of primary treatment type, including surgery. Secondly, in the post-treatment and surveillance setting, there was a 43.3% increase in absolute lymphocyte counts accompanying increasing ctHPVDNA levels (p=0.0469, n=8). Of these, 3/8 were negative to positive (78.3% increase), while the other 5/8 were elevated positive results (22.3% increase). These findings suggest that relative changes in absolute lymphocyte counts over time could serve as a patient-specific biomarker to better define HPV+ HNSCC response to treatment and disease recurrence or progression.

Conclusions: This study provides evidence that ctHPVDNA levels, when combined with immune cell population data, may offer a more comprehensive view of cancer dynamics in HPV+ HNSCC. The relationship between ctHPVDNA levels and immune cell subsets, mainly lymphocytes, could serve as an additional biomarker for monitoring treatment response and disease recurrence or progression.

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#9259

Longitudinal monitoring of HPV-associated oropharynx cancer treated with chemoradiation using an HPV whole genome sequencing liquid biopsy (HPV-DeepSeek)

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: There is a high incidence of human papillomavirus-driven oropharyngeal squamous cell carcinoma (HPV-OPSCC). HPV-DeepSeek is a whole-genome next-generation sequencing (NGS) assay with higher diagnostic accuracy (99% sensitivity and 99% specificity) compared with droplet-digital PCR (ddPCR) and HPV serology. In this study, we use this assay to interrogate circulating HPV-DNA in a cohort of patients undergoing chemoradiation for HPV-OPSCC.

Methods: We analyzed a cohort of patients with AJCC 8th edition stage I-II HPV-OPSCC who underwent definitive chemoradiation at our institution between 2013-2015 enrolled in a prospective blood collection protocol. Plasma samples were analyzed by HPV-DeepSeek at the start, middle, and end of treatment, and first follow up. HPV-DeepSeek output included HPV-DNA load, genotype, high-risk viral single nucleotide polymorphisms (SNPs), viral integration events, and PIK3CA mutations. Samples were drawn monthly during treatment, and at 1-3 months follow-up. Univariable analyses tested associations between HPV reads, clearance (% change/day) and patient/disease characteristics and treatment details.

Results: Twenty-three patients were included. Median age was 57.9 years (interquartile range [IQR] 53.6-64.1), 91% male. Sixteen patients (70%) were AJCC 8th edition stage I, and 7 patients (30%) stage II. The most common site was base-of-tongue (65%) followed by tonsil (35%). Fifty-two percent were never smokers, 26% former smokers with <10 pack years, 13% former and 9% current smokers with ≥10 pack years. All tested positive for HPV by immunohistochemistry, in-situ hybridization, and/or PCR at diagnosis. All received chemotherapy, the most common regimen being bolus cisplatin (48%), and intensity-modulated radiotherapy to 70Gy. Median follow-up was 7.0 years (IQR: 4.9-7.6).There were no recurrences; two patients died during follow-up, 4.6 and 7.6 years after treatment. All patients had positive HPV-DeepSeek results at baseline (median 1592 reads, IQR: 490-3904; median 99.4% genome coverage, IQR: 94.1-100). The most common genotype was HPV-16 (95%) followed by HPV-33 (4%). Three patients (13%) had viral integration, and 2 (9%) had PIK3CA mutations. Six patients (26%) cleared HPV-DNA by mid-treatment (21-38 days), 12 patients (52%) by end-treatment (42-56 days), 4 patients (17%) by follow-up (63-169 days), and 1 patient (4%) did not clear at follow up (85 days). The median clearance rate was 2.3%/day (IQR: 2.0-2.4). HPV reads at baseline were positively associated with age ($p=0.015$), T stage ($p=0.05$), N stage ($p=0.022$), and viral integration ($p=0.008$), and not associated with PIK3CA mutation, genotype, site, or smoking ($p>0.05$). Clearance rate was not associated with age, stage, genotype, viral integration, PIK3CA mutation, site, smoking, or chemotherapy ($p>0.05$).

Conclusions: Utilizing a whole-genome NGS assay, we evaluated the clearance kinetics of 23 patients receiving chemoradiation for stage I-II HPV-OPSCC. HPV reads were associated with age, stage, and viral integration. Clearance rate was not associated with patient/disease characteristics or treatment details, recognizing the small sample size. No patients recurred, limiting analysis regarding assay findings and recurrence. HPV-DNA cleared in 26% of patients by mid-treatment and 78% by end-treatment, with the potential to guide treatment de-escalation. HPV-DeepSeek can be used to longitudinally survey HPV-DNA clearance in individuals with stage I-II HPV-OPSCC undergoing chemoradiation.

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#9168

Automated Multiplex Serology enables high-throughput screening for high-risk oropharyngeal cancer antibody profiles

29 - HPV and oropharynx / Head and neck cancer

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Background/Objectives: HPV-driven oropharyngeal cancer (HPV-OPC) has surpassed cervical cancer as most frequent HPV-associated malignancy in many countries. Especially in men in high Human Development Index (HDI) countries, the overall number of OPC cases has strongly increased in the last decades, and is projected to continue to rise. However, little is known about HPV-OPC in low-and middle-income countries (LMIC). Serum-based antibodies against the HPV16 early protein E6 are present up to several decades before cancer diagnosis, making them a strong prognostic biomarker with high sensitivity and specificity. Therefore, screening for E6 seropositivity may be beneficial for early detection and secondary prevention of HPV-OPC, and enables minimally invasive treatment options, maintaining the patient's quality of life.

Methods: To investigate the general prevalence of HPV and, more specifically, its attributable fraction in OPC cases, we have analyzed ~40,000 serum samples from the China Kadoorie Biobank, a population-based epidemiological cohort across 10 provinces in China. To measure antibodies against HPV16 E6 in this number of samples, we automated the suspension array technology-based Multiplex Serology assay. This novel high-throughput sample processing workflow is based on the liquid handling platform Biomek i7 (Beckman Coulter) with integrated additional devices (e.g. tube/plate scanners, an automated plate washer, and multiple plate shakers). External instruments that are part of the automated Multiplex Serology workflow include the magnetic bead platform KingFisherTM Flex (Thermo Fisher Scientific) for automated bead coupling and loading, and the high-throughput flow cytometry-based reader Flexmap 3D® (Luminex) for signal detection. All of these are connected to a centralized server for data output and assay monitoring.

Results: Across 12 pathogens, the median assay specificity of the automated workflow was 99% (range 85-100%) and the median sensitivity 97% (range 71-100%). First results of the analysis of the ~40,000 study samples demonstrated that the automated assay performed stable over the overall project duration of 6.5 months, with a median coefficient of variation of 8.5% for three plate controls tested on ~500 plates. Furthermore, bridging data of 91 samples tested daily showed a median coefficient of variation of 11% during the project duration. Additional assessments, using e.g. principle component analyses, did not detect any noticeable batch effects.

Conclusions: The automated workflow enables not only a time and personnel saving performance of the Multiplex Serology assay, it furthermore improves assay precision and reproducibility. Moreover, the implemented devices create opportunities for workflow adaptability, while the automated data transfer enables online data tracking, which is advantageous for screening studies and the analysis of large cohorts.

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#9407

Comparative Analysis of Shotgun Sequencing and Genotyping for HPV Detection in Oral brush and stimulated whole saliva Samples

28 - Oral HPV infection

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Background/Objectives: Human papillomavirus (HPV) is responsible for nearly all cases of cervical cancer and approximately 40-70% of oropharyngeal cancers (OPC). Over the past two decades, there has been an increasing trend in HPV-related OPC cases. Although large-scale sequencing is costly, it has the potential to provide the most comprehensive description of HPV types present in a collection of biological samples. This study aimed to compare HPV genotype distribution detected from oral brush samples and stimulated whole saliva using nested-PCR-based genotyping and deep sequencing methods.

Methods: This study included 44 women from the Finnish Family HPV cohort (FFHPV) conducted at Turku University Hospital and the University of Turku, Finland. Oral and genital samples, along with saliva, were collected at baseline and again at 12-, 24-, and 36-month follow-up visits. DNA extracted from oral brush samples were HPV genotyped with Luminex technology based on polystyrene beads coupled with oligonucleotide probes specific for 24 HPV genotypes, while stimulated whole saliva samples were nucleic acid extracted and subsequently shotgun sequenced. For the bioinformatics we used an in-house metagenomic pipeline for comprehensive viral taxonomic classification based on viral species specific kmer algorithm and a comprehensive reference of all known viral genomes. Women, who provided a sample were stratified into two subgroups based on oral HPV16 persistence status: (1) those with persistent oral HPV16 positivity and (2) those with consistent oral HPV negativity.

Results: Deep sequencing revealed nine HPV genotypes in the saliva of the subjects: high-risk (HR) alpha-HPV types 16, 18, 20, and 82; low-risk (LR) HPV types 6, 71, and 72; and gamma HPV types 9 and 196. In oral brush samples, HPV types 6, 16, 18, 58, 59, 66, and 70 were detected by PCR. HPV16 was consistently present in saliva samples for 29.5% (n=13) of women across all visits, with prevalence rates ranging from 75.8% to 100% per visit. However, no woman tested consistently positive for HPV16 in the oral brush samples, with a visit-specific range of 0% to 17.2%. Among women who were consistently HPV-negative in oral brush samples, six HPV types (HPV 6, 16, 71, and 82, and gamma HPV types 9 and 196) were still detectable in saliva.

Conclusions: Metagenomic sequencing of stimulated whole saliva may provide a broader view of HPV prevalence and genotype diversity in the oral and oropharyngeal regions in healthy women. However, PCR-based HPVs genotyping is robust and more cost-effective for oncogenic HPV detection while metagenomic sequencing may provide deeper understanding when more comprehensive virome diversity is investigated.

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#9321

Focal epithelial hyperplasia

28 - Oral HPV infection

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Background/Objectives: We aimed to characterize cases of the rather rare focal epithelial hyperplasia (FEH, Morbus Heck) regarding patient`s characteristics (e.g. age, ethnical background, etc.) as well as localization of the lesions, histology and underlying HPV infection.

Methods: In a multicentral, international collaboration, we collected biopsies and oral swabs, if available, in 33 cases of FEH (median age: 41.5). DNA was extracted from FFPE or swab material using QIAamp DNA Mini Kit (Qiagen). PCR was performed by pan-alpha HPV PCR and probe-hybridisation for genotyping (A6-PCR), and subsequent sequencing if necessary. HPV13- and HPV32-specific real-time PCR was run on a LC480 II (Roche).

Results: Of 33 collected cases, 22 patients tested positive for FEH-associated HPV types (HPV13 n=8, HPV32 n=13). One sample was positive for both FEH-associated HPV types. Two samples were positive for HPV27 and HPV71, respectively, and no HPV DNA was detected in samples of the remaining patients (n=8). The HPV type detected in the biopsy correlated with that present in the oral swab. Most lesions were located on the lips, tongue or buccal mucosa, while in two cases also the oropharynx was strongly affected. Patients with FEH-associated HPV types were much younger (11.0 years) compared to those carrying other HPV types or being HPV-negative. Of the former group, patients had ethnical roots in Turkey (n=9), Africa (n=5) or Syria (n=1).

Conclusions: HPV13 and HPV32-associated FEH mostly affects children and teenager, while in older patients, other HPV types are of relevance or no HPV DNA is detected. Most of the patients were from Turkey or African countries and a genetic predisposition has yet to be determined.

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#8642

HPV DNA/RNA detection in various oral and oropharyngeal biomaterials identifies active HPV infections also in non-neoplastic tonsils

09 - HPV testing

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Background/Objectives: HPV-infections cause a subset of head and neck squamous cell carcinoma (HNSCC). In the head and neck, specifically SCC of the tonsils (TSCC), located in the anatomical region of the oropharynx, are often characterized by infection with predominantly HPV16. TSCC harboring active HPV infection, characterized by HPV-DNA and -RNA expression, are considered to be truly HPV-driven with HPV prevalence rates between 30% and 90%. Previous (own) studies describe a correlation between HPV-positivity and non-smoking in TSCC; p16INK4A-expression as surrogate-marker for HPV-DNA/RNA-positivity is discussed controversially. In the present study, these parameters are assessed prospectively.

Methods: RT-PCR was used to analyze HPV-status of sputum and tonsillar-swabs to determine their validity as surrogate-marker for tissue-HPV-status. TSCC- (n = 52) and non-neoplastic tonsillar tissue (n = 163) were analyzed. Immunohistochemistry determined tonsillar p16INK4A-expression.

Results: 23/163 (14.2%) non-neoplastic tonsils were HPV-DNA-positive; five patients (3 HPV16, 2 HPV11) had active HPV-infections (HPV-RNA-positive), in all biomaterials. 140/163 (85.9%) patients were either HPV-DNA-positive or HPV-DNA-negative in all samples. 21/52 (40.4%) TSCC-tonsils were HPV-DNA-positive; 17 patients were HPV-RNA-positive (14 HPV16; 4 HPV18). 40/52 (76.9%) TSCC-patients were congruent in all biomaterials. p16INK4A-expression alone would have misclassified the HPV-status of 14/52 (26.2%) TSCC-patients.

Conclusions: This prospective study confirms the discrepancy between HPV-status and p16INK4A-expression and the significant correlation between non-smoking and HPV-DNA-positivity. HPV-sputum- and/or swab-results do not consistently match tissue-results, possibly having (detrimental) consequences if those were used to assess tissue-HPV-status. The most reliable detection method of active HPV infections, which are responsible for neoplastic lesions, is the detection of viral RNA. The majority of HPV-positive TSCC patients are infected with active high-risk HPV genotypes, while most patients with non-neoplastic tonsillar disease are infected with predominantly inactive low-risk HPV genotypes. However, the 5 patients (3%) with active HPV infection in the non-neoplastic tonsils, tonsillectomy likely prevented development of TSCC.

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#8981

Efficacy of DNA Methylation Biomarkers in Head and Neck Cancer

17 - Methylation

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Background/Objectives: Head and neck cancer (HNC) incidence is rising exponentially, with 947,211 new cases recorded in 2022 and a projected growth of 53.4% by 2045, resulting in approximately 1,452,718 new HNC cases. The lack of symptoms and screening programs often leads to late diagnosis of several head and neck squamous cell carcinomas. Therefore, new approaches to overcome this rising incidence are urgently needed. Disruption of methylation patterns are considered a crucial factor in carcinogenesis, making epigenetic biomarkers promising targets for early cancer detection and monitoring, namely due to their stability, frequency and accessibility in body fluids. Thus, the search for new epigenetic biomarkers that enable early detection and monitoring of HNC is essential to improve patient care. This study evaluates the diagnostic and prognostic value of the DNA methylation biomarkers ZNF671, ZNF833, HOXA9, PAX6-1 and ZIC1 in the detection of HNC in saliva and swab samples.

Methods: Saliva and swab samples were collected from 5 healthy individuals and 34 HNC patients at the Otorhinolaryngology department of University Hospital Center of São João, prior to their surgical procedures. DNA extraction and bisulfite conversion were performed using EZ DNA Methylation-Lightning kit. Detection of epigenetic biomarkers by MS-qPCR was performed using reagents provided by oncgnostics GmbH.

Results: Methylation results comprised 34 patient samples (swab and saliva), once two cases had been excluded from the study due to insufficient quantity/inadequate quality of isolated DNA. Methylation status of swab samples was positive in 24 out of 32 samples, with a detection rate of 75%, while only 21 saliva samples were positive for methylation markers, with a rate of 65.6%. ZNF671 had the highest detection rate amongst all biomarkers analyzed, being present in all methylation positive swab samples (24/24). In saliva samples the detection rate was almost 95.2%, being detected in 20 out of 21 positive cases. HOXA9 and ZIC1 yielded a detection rate of 95.2% in saliva samples (20/21). In swab samples, HOXA9 and ZIC1 were detected in 23 and 22 out of 24 methylation-positive cases, respectively. PAX6-1 was detected in 20 out of 24 positive swab samples and 16 out of 21 positive saliva samples. Finally, ZNF833 was the marker with the lowest detection rate, being detected in only 6 out of 24 positive swab samples (25%) and 5 out of 21 positive saliva samples (23.8%).

Conclusions: Hypermethylation analysis of swab and saliva samples emerges as a promising non-invasive biomarker, showing a significant association with HNC risk. Furthermore, these biomarkers were successfully detected in both early and advanced tumor stages. Overall, the combined use of these epigenetic alterations represent a promising strategy for HNC detection and management, improving patient outcomes and allowing a more personalized treatment.

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FC08 - HPV prophylactic vaccines II

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#8873

Acceptance of Human papillomavirus vaccination and parents' willingness to vaccinate their daughters in Ethiopia: a systematic review and meta-analysis

38 - Low resource settings

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Background/Objectives: Despite the global vaccination campaign to prevent HPV-related morbidity, HPV vaccination uptake remains unacceptably low in the developed world, like Ethiopia. There is a scarcity of compiled data in the field. Therefore, this systematic review aimed to provide an estimate of the vaccination uptake, mothers" willingness to vaccinate their adolescent girls, and associated factors in Ethiopia

Methods: We conducted a systematic review of articles on the HPV vaccination uptake and mothers" willingness to vaccinate their adolescent girls. Articles were systematically searched using comprehensive search strings from PubMed/Medline, SCOPUS, and grey literature from Google Scholar. Two reviewers assessed study eligibility, extracted data, and independently assessed the risk of bias. Meta-analysis was performed using STATA v 14 to pool the vaccination uptake and mothers" willingness toward HPV vaccination in Ethiopia.

Results: We included 10 articles published between 2020 and 2022 covering reports of 3,388 adolescent girls and 2,741 parents. All the included articles had good methodological quality. The pooled estimate of the proportion of good knowledge about HPV vaccination and the agreement of adolescent girls to get the vaccine was 60% (95%CI: 59-62) and 65% (95%CI: 64-67), respectively. The pooled estimate of vaccination uptake of at least one dose of HPV vaccine among adolescents was 55% (95%CI: 53-57). Positive attitudes to the vaccine, higher maternal education, and having knowledge about HPV and its vaccine were reported as statistically significant predictors. On the contrary, not having adequate information about the vaccine and concerns about possible side effects were reported as reasons to reject the vaccine. Likewise, the pooled estimate of mothers who were knowledgeable about HPV vaccination, who had a positive attitude, and willing to vaccinate their children were 38% (95%CI: 36-40) 58% (95%CI: 56-60), and 74% (95%CI: 72-75), respectively. Parents having media exposure, good knowledge about HPV infection, and positive attitudes towards HPV vaccination were reported to be important predictors to vaccinate their adolescent girls

Conclusions: Knowledge about the HPV vaccine among adolescent girls is poor. The current levels of vaccination uptake among adolescent girls fall short of the 2030 WHO targets. Therefore, stakeholders need major efforts in rolling out vaccination programs and monitoring its uptake. Social mobilization towards primary prevention of HPV infection should focus on adolescents and mothers.

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#9235

HPV vaccine effectiveness at primary HPV screening among the first cohorts targeted by catch-up vaccination

06 - HPV prophylactic vaccines

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Background/Objectives: The population effectiveness of the HPV vaccine was confirmed in several countries, including Italy. In 2021, the Ministry of Health recommended that cervical screening starts at 30 years with HPV testing, beginning with cohorts which were the primary target of vaccination at 12 years of age [1]. In the province of Ancona, the organized cervical screening programme invited birth cohorts targeted by catch-up vaccination for Pap smear every three years from 25 to 29 years of age, and subsequently for HPV testing every five years from 30 years of age. In order to investigate the vaccine effectiveness against abnormal screening outcomes in this population, this study aimed to assess the rate of positive HPV tests, according to vaccination status and to the results of previous Pap smear screening.

Methods: In a population-based cohort study, we included women residing in the Ancona area, born in 1990 through 1993 and eligible for primary Pap smear between January 1st 2015 and December 31st 2022, and for primary HPV (DNA) testing between January 1st 2023 and October 28th 2024. Screening and vaccination data were extracted from official healthcare registries, and linked through deterministic linkage. The investigated outcome was the rate of positive HPV tests, and the exposures were (1) vaccination status and (2) previous Pap smear positive results (ASC-US+). Logistic regression, adjusted for age and nationality, was used to assess possible associations between the investigated outcome and the exposures. All analyses were performed using STATA 15.1 (StataCorp 2017, College Station, TX, USA), and a two-sided $p<0.05$ indicated statistical significance.

Results: The overall sample included 6,419 women (mean age 32.8 years, SD 1.1), of which 2,159 (33.6%) were vaccinated with at least two vaccine doses. Overall, 1,829 (28.5%) adhered to primary HPV testing, and 244 (13.4%) resulted HPV positive. Among the 311 vaccinated women who underwent HPV testing, 9.3% resulted positive, while among the 1,509 unvaccinated ones, 14.3% resulted positive, for a statistically significant difference (Chi-squared $p<0.05$). In contrast, similar rates of positive HPV tests were observed regardless of previous participation to Pap smear screening, and of having had a positive Pap smear. Univariate results were confirmed at multivariate analyses: the adjusted odds ratio (AOR) for having a positive HPV test was 0.57 (95% Confidence Interval - CI - 0.37 - 0.89) in vaccinated women, compared to the unvaccinated. No statistically significant differences in HPV test results were detected among women who previously adhered to Pap smear screening, or had an abnormal Pap smear result.

Conclusions: In the context of an organised cervical screening programme in Italy, HPV vaccination effectiveness was confirmed also against a positive HPV-DNA test, in a partially vaccinated population in which vaccination effectiveness against LSIL+ Pap smear had already been observed [2]. Previous participation to, and results of, Pap smear screening did not appear to influence the likelihood of a positive HPV test. Although a small part of the investigated birth cohorts has not yet been invited for primary HPV screening, and therefore these findings must be considered preliminary, they highlight the need for continued monitoring of the performance of cervical screening programmes in the context of HPV vaccination, and reinforce the recommendation to start screening vaccinated women from 30 years of age [3].

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#9275

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: HPV-specific antibodies are a critical mediator of protection against Human Papillomavirus (HPV) infection after vaccination. With an increase in the number of vaccine 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 (HPVSL) at the Frederick National Laboratory was established in January 2017, with support from 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 goals of the initiative are to develop and implement serology assay standardization by providing standards and critical reagents to the scientific community, develop high-throughput testing capabilities under GCLP, and train laboratories on assay standardization and serology testing methods.

Results: HPVSL co-developed WHO International Standards for HPV 6, 11, 31, 33, 45, 52, and 58 (available through the NIBSC website). Critical reagents for HPV Serology Assays, in particular HPV VLPs from the 9 HPV types included in licensed vaccines, proficiency panels, positive and negative assay controls, and HPV Secondary Standards were also successfully developed, used internally and shared with the scientific community to enable standardization and harmonization of HPV serology testing. Material Transfer Agreements were established with 33 different organizations across several countries. The HPVSL has conducted serology testing of several thousands of samples from more than eight vaccine trials. In addition, HPVSL has helped setting up serology laboratories across the globe and provided trainings on HPV serology testing and/or HPV VLP Production to many collaborators from various countries.

Conclusions: Tools and data generated in various vaccine trials under this initiative contributed in part to the WHO endorsement of a single-dose HPV vaccination schedule. Continued work on these aims will enable further comparisons of data across different HPV vaccines and different studies and, therefore, it will facilitate vaccine development and implementation of new vaccine recommendations globally.

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#9347

Prevalence of CIN2+ in vaccinated and unvaccinated women infected by HPV types not preventable by the bi/quadrivalent vaccines

06 - HPV prophylactic vaccines

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Background/Objectives: In Italy the first women invited for the HPV catch-up vaccination campaign reached the age for cervical screening (25 years) in 2017. A study was conducted to evaluate the real-world vaccination impact. For HPV16 and/or 18 it showed, in vaccinated vs. unvaccinated women, a 0.05 (95%CI 0.03-0.07) relative infection prevalence and a 0.07 (0.02-0.20) relative detection of (hierarchically attributed) high-grade intraepithelial lesions (CIN2+). However, for "non-vaccine" genotypes, the relative prevalence of infections and CIN2+ detection was 1.06 (0.98-1.15) and 2.14 (1.18-3.89) respectively (communication at Eurogin 2024). The minimal increase of infections suggested that the doubled CIN2+ detection was mainly due to faster progression to CIN2+ of infections by non-vaccine HPVs in vaccinated women. We conducted further analyses on the same dataset to clarify such hypothesis

Methods: Women born in 1993-96, invited in the Florence, Savona or Piedmont Region organised screenings in 2018-22 were eligible. After informed consent they were tested for high-risk HPV (Hybrid-Capture 2 or Cobas) and genotyped by Anyplex. Positives, triaged by cytology, were immediately referred to colposcopy if ASCUS+, otherwise recalled for cytology after 3 years. We estimated the infection prevalence of each combination of the following three genotype groups: HPV16/18; HPV31/33/45; other (non-vaccine) hrHPV types (35, 39, 51, 52, 56, 58, 59, 66, 68). For each combination, we estimated the relative probability to have a histology-based CIN2+ detected at immediate colposcopy in women vaccinated with ≥2 doses vs. unvaccinated women, adjusting by centre and birth cohort

Results: Of 14,512 enrolled women with valid genotyping, 34% had no vaccination, 65% ≥2 doses (among them 60.2% bivalent and 39.1% quadrivalent). The relative (vaccinated vs. unvaccinated) infection prevalence was 0.05 (0.03-0.10) for HPV16/18 without non-vaccine genotypes, 1.36 (1.23-1.50) for infections from non-vaccine genotypes without HPV16/18 and 0.06 (0.03-0.12) for co-infections from both groups. In unvaccinated women, the risk of CIN2+ was much higher in women infected just by HPV16 and/or 18 then in those infected just by non-vaccine types and the coinfection by both groups entailed a lower risk than stand-alone HPV 16/18. Conversely, the relative (vaccinated/unvaccinated) risk of progression to CIN2+ was very high (4.09; 1.40-12.01) in vaccinated women co-infected by HPV16/18 and non-vaccine types but reduced to zero in case of stand-alone HPV16/18 infections. The RR of CIN2+ in women infected only by non-vaccine types was 1.57 (0.87-2.82)

Conclusions: The present findings support the hypothesis of faster progression to CIN in vaccinated women infected by non-vaccine types. In principle it could be a direct effect of vaccination or a host effect, i.e. some immunodepressed women could keep high probability of developing hgCIN even when infected by HPV types much less aggressive than 16/18. This study has limitations, mainly related to its small size and to including, to the moment, just cross-sectional. Given the dramatic decrease of invasive cancer incidence in vaccinated women observed in other countries, our data strongly suggests modified management protocols for vaccinated women, based on extended genotyping, to avoid the treatment of a large number of CIN with extremely low probability of progression to invasion

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#9541

THE MECHANISM OF HPV L1 CAPSID PROTEIN MEDIATED ESCAPE FROM VACCINE IMMUNITY

04 - Pathogenesis

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Background/Objectives: Human papillomavirus (HPV) infection causes 29.5% of cancer worldwide, with HPV52/58 prevalent in China. HPV vaccines based virus-like particles (VLP) induce neutralizing antibodies. The five randomly coiled segments (B-C, D-E, E-F, F-G, H-I loops) in L1 protein are located on the outer surface of VLP and are considered epitopes that induce specific immunity and antibody binding. Amino acid substitutions in L1 protein's epitopes may allow HPV mutants to escape vaccine-induced immunity.

Methods: The study analyzed HPV typing results from 90,583 cases and sequenced 1,076 HPV-positive patients' samples to identify mutations related to vaccine escape. HPV58 A1 standard strain and mutant variants (L150F and T375N) were expressed in E. coli, and their VLPs were compared for stability and antibody affinity. A mouse model was used to assess the immunogenicity of these VLPs, and pseudoviruses were used to test the neutralizing sensitivity of antibodies.

Results: This study analyzed the typing results of 90583 cases of HPV from 2018 to 2022, characterizing the trend of HR-HPV proportion changes in vaccine coverage types. The phylogenetic analysis conducted on this confirmed the immune potential of escape vaccines in the HPV31 C lineage, HPV33 A2 sublineage, and HPV58 A2 sublineage. Mutations L150F and T375N in HPV58 were identified as suspect vaccine escape variants. VLP assembly was successful for all variants, and mutant variants showed reduced antibody affinity and neutralizing sensitivity compared to the A1 standard strain. Further co incubation experiments showed that L150F VLP had weaker ability to induce helper CD4+T cell activation, while L150F and T375N VLP had significantly lower ability to induce activation of monocytes with antigen presentation ability compared to A1 VLP.

Conclusions: HPV31 C lineage, HPV33 A2 subunit, and HPV58 A2 subunit potentially have vaccine escape advantages. Mutations L150F and T375N in HPV58 reduce the effectiveness of vaccine-induced immunity. Immunogenicity and immune response mechanisms differed between mutant and standard variants.

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#9282

It's not too late to vaccinate: a quality improvement project aiming to improve human papillomavirus (HPV) vaccine uptake at time of loop electrosurgical excision procedure (LEEP)

06 - HPV prophylactic vaccines

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Background/Objectives: Among patients requiring loop electrosurgical excision procedure (LEEP), emerging evidence demonstrates benefit from adjuvant HPV vaccination in reducing recurrence of cervical intraepithelial neoplasia 2+ (CIN2+) (1,2). A one month baseline survey at our centre from March 2022 revealed that 41/77 (53.2%) of new patients were unvaccinated at time of first colposcopy consultation. With opportunistic counselling, our primary objective aimed to increase HPV vaccination rates among eligible patients by 15% over a 6-month enrollment period. A secondary objective surveyed patient barriers to vaccination.

Methods: This interrupted time series quality improvement study followed 130 patients seen at our quaternary outpatient colposcopy clinic from January-June 2023 to their 6-month follow up visit. Inclusion criteria for eligibility were immunocompetent patients aged 24-45 undergoing first LEEP for CIN2+. Interventions included a nurse-led counselling program, providing HPV 9-valent recombinant vaccine prescriptions to all unvaccinated patients, and vaccination reminders. The primary outcome was the total vaccination rate at 6 months. The weekly proportion of prescriptions given, and proportion filled by follow-up, were tracked as process measures on statistical process control (p)-charts, allowing for application of frequent Plan-Do-Study-Act cycles and process changes. Balancing measures included cost and vaccine reactions.

Results: Of the 130/218 (59.5%) eligible patients, 75/130 (57.7%) were unvaccinated at the time of first LEEP. The average weekly proportion of prescriptions given rose to 87% over study recruitment. Among 96.0% (n=72/75) of patients evaluated in follow-up, 47.2% (n=34/72) have initiated the vaccine series, raising the immunization rate to 68.5% (n=89/130; 26.2% absolute increase). Among those who remained unvaccinated (n=38/72; 52.8%), most frequently reported barriers were cost (n=13/38; 34.2%) and lack of time (n=9/38; 23.7%).

Conclusions: Collaborative interventions to identify and counsel unvaccinated patients undergoing first LEEP for CIN2+ increases HPV vaccination rates, presenting an effective opportunity to engage patients in cervical cancer prevention.

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#9212

HPV2: phase 2 clinical trial evaluating secondary HPV vaccination after treatment of high-grade cervical lesions

06 - HPV prophylactic vaccines

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Background/Objectives: HPVs are responsible for 5% of cancers worldwide, mainly cervical cancers. It has been demonstrated that a negative HPV test after treatment of a high-grade lesion has a very good negative predictive value regarding the absence of recurrence. Conversely, the persistence of positive HPV after treatment of a high-grade lesion is a documented risk factor for recurrence. To date, there is no recommendation for "adjuvant" or tertiary prevention HPV vaccination in patients with HPV-related high-grade cervical lesion. The main objective is to estimate the proportion of HPV negativation within 2 years of the initial positive control HPV test, in women >45 years , chronic HPV infection, after treatment of high-grade cervical intraepithelial lesion receiving HPV vaccination. Secondary objectives are: -Describe the dynamics of HPV viral clearance after HPV vaccination. -Assess the safety of HPV vaccination -Estimate the incidence of recurrence of high-grade cervical intraepithelial lesions (HSIL), and the incidence of invasive gynecological cancer in chronic HPV carriers after surgical treatment of the initial lesion and HPV vaccination. -Identify factors associated with refusal of vaccination -Describe compliance with the proposed vaccination protocol -Evaluate the effect of vaccination on HPV negativation within 2 years, on the different criteria by comparing vaccinated patients included in the clinical trial with the cohort of unvaccinated patients.

Methods: The study includes two cohorts: 1) Eligible patients who agree to be vaccinated will participate in a prospective, multicentre, single-arm clinical trial. 2) Non-vaccinated patients will participate in an observational cohort study, with no change in management. Evaluation criteria Primary: Negativation of HPV infection within 2 years of the initial HPV control test. Negativation is defined as a negative HPV test. If the patient cannot be evaluated at 2 years due to the occurrence of cancer beforehand, the observation will be considered a. Secondary: - HPV infection over time assessed by smear every year until negativation (up to 5 years) - Adverse events (NCI-CTCAE V5.0) - To estimate the incidence of recurrence of HSIL, we will calculate the time between the initial HPV control test and the 1st HSIL recurrence - To estimate the incidence of invasive gynecological cancer (cervix, vagina or vulva), we will calculate the time between the initial HPV control test and the occurrence of HPV-related invasive cancer Main eligibility criteria Common study eligibility criteria (both cohorts): - Patient >45 years - Patient treated by conisation for HSIL of the uterine cervix - HPV-positive test at 6 months post conisation (<=12 months)

Results: The trial will provide additional data on the over-45 population after HPV vaccination concerning: -negativation of HPV carriage -reduction in the risk of HSIL recurrence and the occurrence of HPV-related neoplasia -potential side effects of vaccination will help reassure patients of the vaccine's safety

Conclusions: Our study is complementary in France to the trial promoted by Gustave ROUSSY (women <45 years) If the results are favourable, this would allow to extend HPV secondary vaccination to a wider population.

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#9471

IS FINLAND LOOSING THE BATTLE AGAINST HPV: CONTINUED SUBOPTIMAL HPV VACCINE COVERAGE

06 - HPV prophylactic vaccines

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Background/Objectives: The incidence of cervical cancer depends on three key factors, i.e. the intensity of exposure to HPV (age at first intercourse), the uptake of cervical cancer screening, and HPV vaccination coverage. The WHO global cervical cancer elimination strategy includes HPV vaccination of 90% of girls by the age of 15, 70% of women screened using a high-performance HPV test by age 35 and again by age of 45, and 90% of women with cervical cancer treated. HPV vaccination with concomitant HPV-based screening of young women has been proposed for even faster cervical cancer elimination. The national school-based HPV vaccination program started in Finland 2013 for girls and 2020 for boys. The bivalent HPV vaccine is used. The primary cohort is 10-12 year olds with a catch-up vaccination to 18-years of age. HPV vaccination programs in the other Nordic countries started several years earlier with catch-up vaccination up to age 26. The cervical cancer screening program starts in Finland at age 30, but the participation rate by young age groups remains strikingly low.

Methods: Nationwide Finnish Registry data was used

Results: The most recent analysis by the Finnish Institute of Health and Welfare shows lower than expected HPV vaccination coverage, i.e. <80% in females and <70% in males. The rates vary significantly within the country. The overall coverage in Finland is lower than in the other Nordic countries. For instance, in Sweden the corresponding rates are 92% and 88%. The latest data from the Finnish Cancer Registry shows an increasing trend in the cervical cancer rates, and the incidence in young women <40 years of age is currently as high as in the 1960's before cervical cancer screening program was implemented. Similarly, the rates of oropharyngeal cancer are rising rapidly. The numbers of penile cancer and anal cancer cases are also rising, although the numbers are small. There is no evidence of a decreasing trend in genital warts. The prevalence and direct medical costs were analysed in 2018 showing a heavy health care burden. There are significant disparities in knowledge of HPV-related disease burden and HPV vaccines in general, and anogenital and head and neck cancers in particular. This is not surprising since there is plenty of misinformation about HPV vaccines in social media. Clinicians should be urged to review their patients' vaccination records, and recommend HPV vaccination for all individuals not yet vaccinated, including adults. In Finland, HPV vaccination is not yet recommended for adults or those with prior HPV exposure leaving a large part of the population at risk for HPV related diseases. However, HPV vaccines are safe and vaccination of adults seems to be beneficial in preventing disease or recurrent disease. Thus, health care professionals can recommend vaccination on individual basis. Post-treatment vaccination, or secondary prevention, is a novel field of interest. Most European countries use the nonavalent HPV vaccine which protects against seven cancer-causing HPV types and against HPV6 and HPV11 which cause condylomas and papillomas. The bivalent vaccine currently included in the Finnish vaccination program does not protect against HPV6/11.

Conclusions: From these data it looks like Finland still has a long way to go: The HPV vaccination coverage is suboptimal, participation of younger women in the cervical cancer screening program is low, and an overall HPV disease burden is still rising, not decreasing.

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#9300

High Impact of Quadrivalent Human Papillomavirus Vaccination on the Prevalence of High-risk HPV Infections and Cervical Abnormalities: A Retrospective Study from Northern Portugal

06 - HPV prophylactic vaccines

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Background/Objectives: Human Papillomavirus (HPV) vaccination is pivotal in eradicating cervical cancer. In Portugal, the Quadrivalent HPV vaccine (HPV6/11/16/18) was introduced in the National Vaccination Program (PNV) in 2008, targeting girls aged 12 to 18 years. This study evaluates the impact of HPV vaccination on the prevalence of high-risk HPV (Hr-HPV) infections and cervical abnormalities among women participating in the Cervical Cancer Screening Program in Northern Portugal (RCCU).

Methods: We conducted a retrospective analysis of HPV prevalence among women aged between 25 to 32 participating in the RCCU (n=82,695), including a total of 34,701 women who received the Quadrivalent HPV vaccine before the age of 18. HPV-related outcomes included Hr-HPV rates and cervical cytology results.

Results: Vaccination was associated with a significant decrease in the prevalence of HPV16/18 infections and cervicovaginal abnormalities. Specifically, the prevalence of HPV16/18 among vaccinated women declined from 16.6% to 1,4% ($p<0.001$, RR 0.072, 95%CI 0.059-0.088). Additionally, cervicovaginal abnormalities decreased from 38.4% to 30.9% ($p<0.001$, RR 0.714, 95%CI 0.669-0.763), with ASC-US+ decreasing from 15.9% to 12.3% ($p<0.001$, RR 0.745, 95%CI 0.681-0.816), and HSIL+ decreasing from 5.4% to 1.8% ($p<0.001$, RR 0.315, 95%CI 0.258-0.383).

Conclusions: The implementation of HPV vaccination in the Portuguese PNV significantly reduced HPV16/18 infections and cytological abnormalities in young women, potentially impacting cervical cancer incidence and mortality. These findings highlight the critical role of vaccination strategies in the fight against cervical cancer.

FC09 - HPV screening I

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#9518

Clinically validated HPV assays offer comparable long-term safety in primary cervical cancer screening: a 9-year follow-up of a population-based screening cohort

10 - HPV screening

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Background/Objectives: Molecular testing for human papillomaviruses (HPV) is gradually replacing cytology in cervical cancer screening. Although a consensus has been reached in the scientific HPV community that only clinically validated HPV assays should be used in cervical cancer screening, comparative performance evaluations of different HPV assays with longitudinal data to assess the prognostic value of different testing approaches are lacking.

Methods: In this longitudinal population-based cohort study, 4140 women 20 to 64 years old attending organized screening in Slovenia were tested at baseline by five different screening methods and followed for 9 years, including conventional cervical cytology and four clinically validated HPV assays: Hybrid Capture (hc2), RealTime High Risk HPV assay (RealTime), cobas 4800 HPV Test (cobas_4800), and Alinity m HR HPV (Alinity). We assessed the 3-, 6-, and 9-year cumulative risks of CIN2+ and CIN3+ after a negative baseline screening result, compared the long-term screening and prognostic values of all five screening methods and calculated 9-year cumulative risk after positive HPV result stratified by HPV genotypes.

Results: HPV-negative women at baseline had a substantially lower 9-year risk for CIN2+ compared to those with normal baseline cytology: 0.84% (95% CI, 0.46-1.22), 0.90% (95% CI, 0.51-1.29), 0.78% (95% CI, 0.42-1.15), and 0.75% (95% CI, 0.39-1.11) for hc2, RealTime, cobas_4800, and Alinity, respectively, compared to 2.46% (95% CI, 1.88-3.03) for cytology. No differences were found between HPV assays in longitudinal sensitivity (range: 86.21%-90.36%) and negative predictive value (range: 99.54%-99.70%) for CIN2+ in women ≥30 years, but they were significantly different from cytology ($p < .05$). In addition, differences in baseline HPV positivity and in longitudinal specificity were found between HPV assays used. In particular, hc2 had statistically significantly higher rates of HPV positivity at baseline and significantly lower longitudinal specificity compared to the other three PCR-based assays. In addition, the 9-year cumulative risk of CIN2+ differed significantly between HPV genotypes, reaching 32.1% (95% CI, 14.5-46.1) for HPV16, 24.9% (95% CI, 4.7-40.8) for HPV18/45, 27.2% (95% CI, 14.6-37.8) for HPV31/33/35/52/58, and 8.1% (95% CI, 0.0-16.7) for HPV39/51/56/59.

Conclusions: Regardless of the HPV assay used, the risk of precancerous lesions in women that tested HPV-negative at baseline was consistently low over 9 years, suggesting that all four clinically validated assays assessed in our study provide comparable long-term safety and better protection against precancerous lesions than cytology, even when the screening interval is extended beyond 5 years. However, some important differences were found in the performance characteristics of HPV assays in terms of longitudinal specificity and subsequent impact on referral rates. We have also shown that background risk is highly dependent on the HPV genotype(s) detected at baseline, and that "one-size-fits-all" screening programs provide suboptimal protection for women at high risk, suggesting that a shift towards risk-based screening is needed to maximize the efficacy and effectiveness of screening.

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#9319

Limited value of extended HPV genotyping in screening for cervical glandular lesions

10 - HPV screening

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Background/Objectives: The incidence of adenocarcinomas and adenocarcinoma in situ (AIS) is rising, despite Finland's national cervical cancer (CC) screening program. Adenocarcinoma and AIS, originating from glandular cells, are challenging to detect through HPV screening with cytology triage, as they may develop higher up in the cervix and within the glandular crypts. Extended HPV genotyping may provide a more comprehensive tool for identifying high-risk women for the development of glandular lesions. The aim of this study was to evaluate whether extended HPV genotyping could be used to improve the early detection of patients at risk for developing adenocarcinoma or AIS.

Methods: This study included 2418 HPV positive women from the CC screening in the Pirkanmaa region of Finland between 2017 and 2019, with clinical follow-up until 2023. Extended HPV genotyping was performed using the AnyplexTM II HPV28 Detection assay by Seegene, which identifies 19 high-risk (HR) and 9 low-risk (LR) HPV genotypes. Background information and treatment follow-up data was collected from hospital patient records. The involvement of different HPV genotypes in the progression of cervical glandular disease was further evaluated.

Results: Within the study population, 31 women (1.2%) were diagnosed with AIS (n=6) or adenocarcinoma (n=25) following the screening, with the mean age of 36 years for AIS and 39 years for adenocarcinoma. The most common cytological finding before the diagnosis of AIS or adenocarcinoma was atypical glandular cells, not otherwise specified (AGC-NOS) in 31% (n=10) or negative for intraepithelial lesion or malignancy (NILM) in 28% (n=9). HPV18 and HPV16 were the most common single genotypes, with both found in 42% (n=13) of cases, together accounting for 84% of the total. The remaining 14% involved co-infections of HPV16 or HPV18 with HPV31, 33, 35, 45, 52, 56 and 58. Preliminary results suggest that the time interval for developing adenocarcinoma or AIS from screening may differ between HPV16 and HPV18, which will be further evaluated.

Conclusions: Cytological changes in patients who have a glandular cancerous or precancerous lesion can be mild, making the detection of these lesions challenging. HPV18 and HPV16 are the most common high-risk HPV genotypes in these cases, and they are typically found as single infections, suggesting that extended HPV genotyping may not offer additional benefit. As these types are covered by the current HPV vaccination program in Finland, increasing vaccination coverage is likely to be the most effective means to eradicate glandular lesions in the future.

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#9327

Quality assurance of an HPV screening program using proportion of "HPV-negative" HSIL

10 - HPV screening

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Background/Objectives: Primary HPV-based screening is a globally recommended public health policy. Quality assurance of HPV laboratory analyses is needed. Annual systematic review, so called auditing, provides a repeated estimation of the clinical sensitivity of the actual HPV screening used to identify women at risk for HSIL or worse and can find errors and artifacts in HPV testing services.

Methods: The Center for Cervical Cancer Elimination (CCCE) is the National HPV Reference Laboratory for Sweden and performs all HPV tests for the screening program of the capital region of Sweden. CCCE identified cases of HSIL in histopathology with a previous cervical screening test up to 3 years before and randomly selected 300 of the preceding cervical liquid-based cytology (LBC) samples per year for auditing. The screening program used HPV testing with Roche Cobas until the beginning of 2022. BD COR was used from early 2022 and onwards. Samples missing HPV results or HPV negative were re-analyzed using BD COR and modified general primer PCR and Luminex were used on HPV negative samples. Re-review of the subsequent biopsies (PAD) were done on HPV negative cases and PAD with confirmed HSIL+ were analyzed according to the same protocol as LBC samples. If still HPV-negative, the LBCs and biopsies were whole-genome sequenced.

Results: Overall, Cobas 4800, BD COR, and Luminex detected HPV in 1764/1800 (98.0%) of the randomly selected LBC samples taken before HSIL in 2018-2023. Thirty-six samples were HPV negative and the corresponding biopsies were re-reviewed, 7 cases were excluded. Twenty-nine PAD were analyzed using BD COR and twenty-three of these were analyzed using Luminex. To date, there are 20 cases that will be whole genome sequenced.

Conclusions: This laboratory audit of HPV testing in a real-life cervical screening program found a sensitivity for HSIL of 98.0%. Reference methods with general PCR, broad detection of HPV types, and whole-genome sequencing with bioinformatic detection of all viruses, provided reliable data on the actual status of "HPV-negative" samples in screening before HSIL. Regular laboratory audits of samples taken before HSIL can be readily performed within a real-life screening program and provide assurance that the program has the expected performance.

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#9318

Scalable and validated HPV testing: High-throughput, Self-Sampling and affordability for LIMCs

10 - HPV screening

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Background/Objectives: The rising global burden of Human Papillomavirus (HPV) infections necessitates scalable, cost-effective, and reliable screening solutions, particularly in low- and middle-income countries (LMICs), where healthcare resources are often limited. We have designed and implemented an innovative and interoperable HPV testing platform that prioritizes accessibility, efficiency, and high throughput to meet these global demands. Hence, we have named the platform "Scalable HPV testing: High-Throughput, Self-Sampling and Affordability for LMICs".

Methods: A distinguishing feature of our system is its support for self-sampling, reinforced by color-based quality control that empowers individuals to participate in routine screenings with confidence. Furthermore, the platform incorporates a robust barcoding system that ensures traceability and confidentiality for all samples. This feature is essential for maintaining patient privacy and data integrity. To facilitate streamlined distribution and storage across varied environments, our system utilizes lyophilized reagents that eliminate the need for cold chain logistics and significantly reduces costs. This enables us to deploy large scale screening solutions in LMICs possible. Additionally, the automated extraction process and robotic pipetting enables rapid, reproducible sample preparation with the need for no trained personnel, while compatibility with most quantitative PCR (qPCR) machines provides flexibility for laboratories without the need for specialized equipment. The platform is designed for being high-throughput (upto 4000 tests per day), cost-effective, aiding health systems in LMICs by reducing consumables and per-test expenses while maintaining high quality.

Results: Our platform supports knowledge transfer through comprehensive training of local technicians, fostering sustainability by building intra-country expertise for ongoing HPV testing efforts. In Rwanda, we have successfully screened over 160,000 women using this platform, thereby demonstrating scalability, sustainability, and measurable positive impact on public health.

Conclusions: Our HPV testing platform thus represents a pivotal advancement in accessible, sustainable, and cost-effective population health management, providing a valuable tool to fight against HPV-related diseases. It can be adopted by many LMICs to proceed with the large scale screening session. This will be the key factor to prevent and eliminate cervical cancer together.

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#9418

Risk stratification by HPV genotype in HPV primary screening in the South-East Health Region in Norway

10 - HPV screening

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Background/Objectives: HPV primary cervical screening was introduced for the screening population (25-69 years old) of Norway in 2023. Prior to implementation, cytology and HPV analysis were centralised, from ten to three laboratories, for the South-East Health Region. Additionally, a new laboratory data system (Lab Vantage Medical Suite), linked to the national databases for HPV, cytology and histology at the Cancer Registry of Norway, and a new platform for HPV DNA detection with extended genotyping were introduced.

Methods: All HPV primary index screening samples in the South-East Health Region from the 01.07.23, 01.01.23 and 01.05.2019 (25-29, 30-33 and 34-69 year old groups respectively) until the 31.12.23 were included in the study. Non-screening samples were excluded based on the received clinical information and previous screening history. Samples were collected in BD SurePath medium and HPV-analysis performed using the BD OnclarityTM HPV assay. Six HPV genotypes were detected individually (16, 18, 31, 45, 51 and 52) and eight genotypes in three groups (33/58, 56/59/66 and 35/39/68). Genotypes were classified as high priority (HPV 16), medium priority (HPV 18, 45, 31, 45, 52, 33 and 58) and low priority (HPV 51, 56/59/66 and 35/39/68) according to current Norwegian screening guidelines. The highest histological grade of dysplasia/carcinoma in follow-up was included until the 31.12.23.

Results: HPV prevalence was 8.4% among the 193,705 women eligible for HPV primary screening in the South-East health region. Triage cytology of HPV positive cases found unsatisfactory cytology in 0.7%, normal cytology in 51.6%, low grade cytology (ASC-US/LSIL) in 31.4%, high grade cytology (ASC-H+/AGUS+) in 16.2% and cervical carcinoma in < 0.1%. Cytology results were missing in <0.1% of cases. Histology data was available in 8011 cases. Normal histology was seen in 54.6%, CIN 1 in 11%, CIN 2 in 5.4%, CIN 3 in 21.5%, AIS in 1.5%, squamous cell carcinoma in 0.6%, adenocarcinoma in 0.3%, and 0.1% for both primary carcinoma of the cervix (other type) and metastases to the cervix. Histology was unsatisfactory in 1.6% of cases. HPV 16 was the most prevalent genotype in index screening samples with high grade histology (CIN 3+/AIS+), with a prevalence of 44%; followed by HPV 31 (14.6%) and HPV 18 (10.4%). In those with histologically confirmed CIN 3+/AIS+, 1.9% tested negative for HPV in their index screening sample. In index screening samples, across all age groups, the prevalence of low priority genotypes with normal histology was 29.9% and 10.8% with CIN 3+/AIS+. There is variation among the age groups: 34% and 7.4%, 23.7% and 5.2%, and 30.4% and 10.6% (prevalence in index screening samples with normal histology and with CIN 3+/AIS+; 25-29, 30-33 and 34-69 year old groups respectively). Low priority genotypes were found in the index screening samples of two primary carcinomas of the cervix (other type) in the oldest group.

Conclusions: High priority HPV 16 is the most prevalent genotype in index screening samples with CIN 3+/AIS+, followed by middle priority HPV 31 and HPV 18. In the younger groups, low priority genotypes were over 4.5 times more prevalent in index screening samples with normal histology than in those with CIN 3+/AIS+, and 2.9 times more prevalent in normal histology compared to CIN 3+/AIS+ in the oldest group. Risk stratification by genotype may help in the clinical management of women but follow up histological data for low priority genotypes in those aged 25 - 33 years is limited.

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#9219

Implementation of HPV HR Testing in Primary Screening in the Czech Republic

10 - HPV screening

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Background/Objectives: In the Czech Republic, the incidence of cervical cancer has decreased only slightly since 1989, with the country currently ranking alarmingly 23rd in incidence and 16th-17th in mortality. Persistent HR-HPV infection is widely accepted as the primary risk factor for progression to precancer and cancer. Numerous studies support the use of HR-HPV testing in routine screening; however, official implementation in practice was a complex and lengthy process. The initial discussions to improve cervical cancer screening and incorporate HPV testing began in 2002 within the Czech Obstetrics and Gynecology Society. In 2021, HPV-HR testing was officially included in the national screening program for women aged 35 and 45, with its recent extension to women aged 55 in 2024.

Methods: Analysis of available data from the Czech Republic, including data from the largest oncogynecological center and the largest screening laboratory.

Results: The organized cervical cancer screening program was initiated in 2008 with Phase 1 (standard annual PAP screening for women aged 18-65, implementation of quality assurance guidelines for cytology laboratories, and clinical management for abnormal findings). In 2008, the incidence of cervical cancer was 19.3 per 100,000 women, with a mortality rate of 5.9 per 100,000. By 2014, the incidence had decreased by 19% to 15.6 per 100,000, although mortality rates showed no significant decrease. The Cervical Cancer Screening Committee of the Ministry of Health recommended centralized invitations in 2014 (Phase 2), prompting health insurance companies to send invitation letters to women aged 25-65. By 2021, the incidence had further declined by 11% to 13.9 per 100,000, though mortality remained at 5.7 per 100,000. Twenty years after the initial discussions, primary HPV-HR testing was incorporated into the screening program for women aged 35 and 45 (Phase 3), achieving a 72% participation rate within the first two years. Data from insurance companies indicated a notable decline in screening participation among women over 50, with 60% of all diagnosed carcinomas occurring in women who had not undergone cytology screening for over five years. Of these cases, 70% were diagnosed at stage II and 80% at stage IV. That's why in 2024, the HPV-HR test was extended to include women aged 55 (Phase 4). Experience in the first 10 months of 2024 indicates that implementing HPV-HR testing for women aged 55 helps engage this otherwise hard-to-reach demographic, motivating women with positive tests to attend annual checkups and cytology screenings, ultimately reducing the incidence and late-stage diagnoses, which can contribute to lower mortality. Genotypization from cytology in age group 55, however shows only 30 % prevalence of HR HPV (16,18,45) which is in contrast wit genotypization of tissue from CIN III and invasive cancer, where the prevalence of HR HPV was more than 80%. Tab1

Conclusions: Comprehensive knowledge of HPV-HR type distribution in cervical precancer and cancer is crucial. HPV-HR screening raises new questions and concerns among patients, including anxiety over positive HPV-HR results and additional psychosocial challenges. Nevertheless, the primary benefit is the positive impact on screening participation rates and the subsequent reduction in cervical cancer mortality.

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#9268

Population-Based Implementation of Primary HPV Screening Using both Self-Screening and Liquid-Based Cytology

10 - HPV screening

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Background/Objectives: In January 2024 British Columbia (BC) began to transition to HPV primary screening offering both self-screening and provider collected (via liquid-based cytology) (LBC) as options for sample collection. Self-screening is available to all age eligible patients due to screen. LBC samples are triaged at the laboratory to HPV screening beginning with patients aged 55 and over. BC targeted a 50% transition to HPV screening by 18 months post implementation. A process to enable patients without a primary care provider (unattached patients) to access cervix screening was implemented.

Methods: Patients can request a self-screening kit through the program or access self-screening through many provider offices. Kits requested from the program are mailed to the patient. Providers can also continue to offer LBC collection, triaged at the laboratory for HPV and/or cytology. For patients that request a kit by mail, a reminder is sent to the patient 90 days later if the program has not received a screening test result. Unattached patient screens are ordered by the program and patients are provided with re-screening recommendations when their HPV test is negative. Unattached HPV positive patients are linked with a local clinic who can provide or support recommended follow-up testing.

Results: In the first month of offering self-screening 17,000 kits were requested and sent to patients. Kit request volumes have stabilized at 10,000 kits per month. At 8 months after implementation, 50% of clinics in BC had requested self-screening kits to offer at their clinics. In September 2024, 15,193 LBC samples received cytology testing, 5,966 LBC samples received HPV testing, and 12,015 self-screening HPV tests were reported - representing a 55% transition to HPV primary screening in BC. Of the self-screening tests reported, 43% were for patients who had a kit mailed to them from the program. For patients who requested a kit in April 2024, on average 66% of kits were returned within 16 weeks. Age and geographic differences are seen with 65-69 year olds having the highest return rate of 82% and 25-29 year olds have the lowest return of 53% by 16 weeks. Patients living in the Interior Health region of BC (a mix of urban, rural and remote communities) had the highest return rate of 69% and Fraser Health area (mostly urban) had the lowest return of 52%. Between February and June 2024, 60,065 cervix self-screening kits were mailed to patients, of which 11,004 (18%) had never screened in BC. During this period, 25,154 HPV self-screen results were reported, 4,680 (19%) of these patients had never screened in BC. 4,400 of the self-screening results were ordered by the program for unattached patients.

Conclusions: The transition to primary HPV screening is proceeding faster than expected in BC. There has been high adoption of cervix self-screening across ages and geography as well as continued use of provider-collected LBC sampling, indicating the choice in how patients can receive screening (self-screening or provider collected) is acceptable. Patients retain kits for several weeks before returning them, older age patients are more likely to return a completed kit after ordering it. Further work is required to trial different messaging with kits, various letter and phone call reminder protocols and public awareness building to know how best to optimize kit return at a population level. Self-screening with mailed kits is reaching never screened patients and enabling screening for unattached patients.

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#9654

Clinical validation of the Sansure® Human Papillomavirus DNA Diagnostic Kit for use in primary cervical cancer screening

09 - HPV testing

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Background/Objectives: The assessment of emerging HPV assays for their use in cervical cancer (CC) screening is vital. The Sansure® Human Papillomavirus DNA Diagnostic Kit (Sansure HPV 13+2 assay) is single tube multiplex real-time PCR designed to detect HPV16, HPV18 and 13 other HPV in aggregate (HPV31/33/35/39/45/51, 53/52/56/58/59/66/68). The assay targets the E6 and E7 regions of viral DNA and includes an endogenous control targeting the ß-globin gene. The Sansure HPV 13+2 assay has previously met the reproducibility criteria outlined in the international validation guidelines but lacked assessment of the clinical accuracy criteria1,2. This study aims to evaluate the clinical accuracy of the Sansure HPV 13+2 assay on clinician collected samples according to the international validation guidelines.

Methods: A panel of 890 cervical liquid-based cytology (LBC) samples were collated from women participating in primary CC screening in Belgium for clinical accuracy assessment based on the Meijer guidelines2. The panel included 800 controls (denominator for specificity), defined as women with previous negative cytology screening and, at current screening, having a result not yielding a CIN2+ diagnosis. Cases included 90 samples with histologically confirmed CIN2+, of which 60 were CIN3+ (denominators for sensitivity). The RealTime High Risk assay (Abbott m2000) was used as the standard comparator3 test and relative clinical accuracy was assessed by a non-inferiority test.

Results: Four samples were invalid and 886 samples were included for the clinical accuracy assessment. The relative sensitivity for CIN2+ and specificity for ≤CIN1 of the Sansure HPV 13+2 assay vs RealTime High Risk assay were 0.978 (95% CI, 0.947-1.009) and 0.993 (95% CI, 0.982-1.004) respectively. The relative sensitivity for CIN3+ was 0.966 (95% CI, 0.921-1.013).The p-value for non- was pni ≤0.05 for all comparisons.

Conclusions: The Sansure HPV 13+2 assay fulfils the clinical accuracy criteria for use in cervical cancer screening. Combined with previous reproducibility results, the Sansure HPV 13+2 assay meets all the criteria for the clinical validation of HPV assays and is considered validated for primary cervical cancer screening1.

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#9220

Evaluation of the 60+ screening algorithm in the Capital Region of Denmark

10 - HPV screening

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Background/Objectives: In Denmark, cervical cancer screening is offered to all women aged 23-64 years in a call-recall program. For women above 60 years the offer is a final HPV based check-out screening before exiting the program. The 60+ screening algorithm is risk based: Women are referred to colposcopy after an HPV genotype 16/18 positive index screening or an HPV positive index screening with genotypes other than 16/18 and concurrent ASCUS+ cytology. For HPV genotypes other than 16/18 and concurrent NILM cytology women are referred to a re-test after 12 months. Women exit the program by an HPV negative index sample or an HPV negative re-test with concurrent NILM cytology. Women with HPV positive or ASCUS+ cytology re-test samples are referred to colposcopy. Here, we evaluate the diagnostic and clinical outcome of the 60+ screening algorithm.

Methods: All women residing in the Capital Region of Denmark, aged 60-65 years, and undergoing HPV screening with a valid sample in 2021-2022 were included (n=13,355). Screening, re-test and histology outcome were analysed descriptively. Data were retrieved from the Danish National Pathology Database by October 2024.

Results: In total 93.4% (n=12,479) of the women with a final HPV based screening exited the program based upon an HPV negative sample. Of the women with an HPV positive sample (6.6%, n=875), around half (49.3%, n=431) were referred directly to colposcopy. This included 28.6% (n=250) women who were HPV genotype 16 and/or 18 positive and 20.7% (n=181) who had HPV genotypes other than 16/18 and concurrent ASCUS+ cytology. The adherence to recommended colposcopy after index screening was high; 90.3% (n=389) of the women had a biopsy. The histology outcome in women who were HPV genotype 16/18 positive showed ≥CIN2 in 24.9% (n=225) of the women, including 3 cases of adenocarcinoma in situ (AIS) and 7 cases of squamous cell carcinoma. For women with HPV genotypes other than 16/18 and concurrent ASCUS+ cytology, the ≥ CIN2 histology outcome detection was 29.9% (n=164), but with only one case of cancer and no AIS. Women with HPV genotypes other than 16/18 and concurrent NILM cytology (50.7%, n=444) at the index sample were referred to a re-test after 12 months. Adherence to re-test was 86.0% (n=382). Here, 31.2% (n=119) of the adherent women had cleared their HPV infection at re-test. However, a small proportion of HPV negative women (2.9%, n=11) had ASCUS+ and were referred to colposcopy. Women with HPV-/ASCUS+ re-test who followed the recommendation and had a biopsy, all had an outcome of ≤CIN1 (100%, n=6). Women who were HPV positive in the re-test (68.8%, n=263) were referred to colposcopy. In total, 219 women had a biopsy where 86.3% (n=189) had an outcome of ≤CIN1. No cases of AIS or cancer were found in this triage group.

Conclusions: Our data show that approximately 5% of the women screened are referred to colposcopy by the current 60+ screening algorithm. We observe a histology outcome of ≤CIN1 amongst 79% of the women who had a biopsy. Such a high proportion of benign histology outcomes indicate that the algorithm needs revision. As the Capital Region of Denmark is about to transition all women aged 30-59 years to an algorithm utilizing extended genotyping, it will make sense to investigate whether the same algorithm with benefit can substitute the current 60+ algorithm to reduce over treatment without loss of clinical sensitivity.

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#9253

Previous abnormality is associated with long-time increased risk of HPV positivity among women over 50 years old: a registry-based cohort study

10 - HPV screening

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Background/Objectives: Older women with a screening history of abnormality have an elevated risk of cervical cancer after passing the age limit of screening. However, how these women should be addressed in HPV-based screening for preventing cervical cancer is unknown. We therefore conducted a register-based cohort study to investigate the HPV prevalence among women over 50 years of age with and without screening history of abnormality, in one and two rounds of HPV-based screening tests.

Methods: All Swedish resident women who had their first HPV-based screening test at ages of 50-70 years from 2012.01.01 to 2022.12.31, without total hysterectomy or invasive cervical cancer (n= 485,332), were included in the cohort. We used the Swedish National Cervical Screening Registry to identify the most recent abnormality (defined as ASCUS+ cytology or LSIL+histopathology) before the first HPV-based screening test. We identified 77,711 women with a previous abnormality, among whom 11,462 women had an abnormality within the past 10 years, 21,232 women had an abnormality within the past 10-20 years, and 45,017 women had an abnormality >20 years ago. Among the 485,322 women in the cohort, 21,987 had the second round of HPV-based screening after testing HPV-negative in the first round. Comparing to women had been screened in the past without any abnormality (n=397,227), we calculated the risk ratios (RRs) with 95% confidence interval (CI) of HPV positivity in two screening rounds, adjusted for birth cohort, sample year, and resident region. HPV genotype distribution in these women were also assessed where data available.

Results: The mean age of women at first and second round of HPV-based screening was 61 and 63 years, respectively. The majority of the first HPV-based screening tests were taken during 2020-2022 (61.7%). In women with a history of abnormalities, 8.6% were HPV-positive in first screening test and 5.4% among women without such history (RR=1.53, 95%CI=1.49-1.57). HPV genotype distribution was similar to women without previous abnormality (18.7% HPV16, 6.8% HPV18/45 and 74.6% other 12 types). The risk of being HPV positive decreased with time since previous abnormality (p for trend <0.0001). However, even 20 years after the previous abnormality, these women were more often HPV positive (RR=1.36, 95% CI=1.32-1.41). Among women with a HPV-negative result in the first round, the risk of being HPV positive in the second round was increased among women with previous abnormality compared with women without a history of abnormality (RR=1.53, 95%CI=1.34-1.74).

Conclusions: For women over age 50, a previous abnormality inferred an increased risk of testing positive for HPV compared to women without a history of abnormalities, even 20 years after the previous abnormality. The increased risk of testing positive for HPV still remained after one negative HPV test. This implies that in women approaching the age of exiting cervical screening programs, those with history of abnormality might still warrant continuous screening after one HPV-negative test.

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Effect of HPV vaccination in the Norwegian Childhood Immunization Program: - HPV prevalence and incidence of Cervical Intraepithelial Neoplasia (CIN)

10 - HPV screening

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Background/Objectives: In Norway, school-based human papillomavirus (HPV) vaccination was introduced for girls in 2009 and expanded to boys in 2018. A catch-up program was offered in 2016 and 2017 to women born between 1991 and 1996. The first two female birth cohorts (born in 1997 and 1998) vaccinated through the Childhood Immunization Program were invited to the Norwegian National Cervical Cancer Screening Program, CervicalScreen Norway, in 2022 and 2023 respectively. Cytology-based screening was offered the vaccinated cohorts until July 1, 2023. Thereafter, HPV-based screening was implemented for all women aged 25-69 years. This population-based observational evaluation includes screening data until July 1, 2023, and histology data until December 31, 2023.

Methods: Women with a registered cervical sample in CervicalScreen Norway in 2022 and 2023 were identified. For these women, all registered cervical samples from 1995-2023 were selected from the Cancer Registry of Norway. The dataset was linked to the HPV vaccination status retrieved from the Norwegian Immunisation Registry SYSVAK (type of vaccination, age at vaccination and number of doses). Screening results and prevalence of HPV were recorded, and the cumulative incidence of high-grade cervical lesions stratified on vaccination status and birth cohort was analysed.

Results: 23 548 women born in 1997 or 1998 were registered with a cervical screening sample in 2022 or 2023. 71% were HPV-vaccinated in the Childhood Immunization Program, 14% was catch-up HPV-vaccinated and 15% had not been vaccinated against HPV. Our findings indicate comparable primary cytology screening results among women aged 25 and 26 years when comparing unvaccinated and HPV-vaccinated in the Childhood Immunization Program. The samples with low-grade cytology results were reflex HPV-tested. There is a substantial reduction in the detection of HPV16 and HPV18 among women with low-grade cytological abnormalities in the vaccinated compared to the unvaccinated group. Interestingly, there is a marked decrease in incidence rates of CIN2 and CIN3 in the vaccinated birth cohort compared to the older birth cohort (born in 1990) not offered vaccination in the Childhood Immunization Program. The difference in cumulative incidence of CIN2 and CIN3 between unvaccinated and vaccinated women born in 1997 or 1998 is not as pronounced and can likely be related to herd immunity among the unvaccinated.

Conclusions: Our results underscore the efficacy of the HPV vaccination program in reducing the burden of HPV16 and HPV18 infections. A decline in the incidence of high-grade lesions was observed in the vaccinated birth cohorts compared to an older birth cohort not offered vaccination in the Childhood Immunization Program.

FC10 - Screening for women difficult to reach

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Socioeconomic and geographical inequalities in long-term non-attendance in the organized cervical screening program in Sweden after the introduction of HPV self-sampling

11 - Screening for women difficult to reach

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Background/Objectives: In Sweden, opt-out HPV self-sampling has been recommended to long-term non-attenders since 2017, and as a primary screening method since 2022 (1). Studies have shown that participation in under-screened women increases by using HPV self-sampling (2,3). Socioeconomic status is a well-known factor for non-participation (4). The aim of the study was to compare participation in screening with regard to socioeconomic gradient before and after the introduction of HPV self-sampling.

Methods: We geo-coded each study individual to her residential neighbourhood, according to a small-area division of Sweden by Statistics Sweden (5) (5984 areas in total). The geographical pattern of the prevalence of women with no record of a screening test within the last ten years was estimated by a Bayesian logit model with spatially structured random effects enforced. Neighbourhood-level data on economic standard, proportion of non-Western immigrants, and geographical location (urban/semi-urban/rural) were assessed for estimation of the corresponding neighbourhood-level associations. Prevalence estimates were compared between 2020 and 2023.

Results: The overall prevalence had increased from 8.1% to 8.9% between 2020 and 2023. In 2023, the socioeconomic gradient was marked (odds ratio = 2,44 [95% CI: 2,34-2,55] between the neighbourhoods in the highest vs. lowest economic quintile) and did not show any declining time trend. We identified 147 out of the 5984 neighbourhoods as having pronouncedly elevated prevalence of women with long-term non-attendance. Rural geographical location was associated with higher prevalence after adjustments for sociodemographic imbalances.

Conclusions: We found a marked socioeconomic gradient. The gradient has not decreased since recommendations of HPV self-sampling were introduced. Only three regions in Sweden have so far fully implemented primary HPV self-sampling; participation should be followed and monitored repeatedly. It is rational to allocate extra resources, if available, towards the 147 identified neighborhoods with pronouncedly elevated prevalences of non-attendees.

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#9243

Geographic Accessibility, Availability, and Economic Affordability of Health Services for Cervical Cancer Prevention in Rural Areas of Cuenca, Ecuador

11 - Screening for women difficult to reach

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Background/Objectives: Background: While several countries have successfully reduced cervical cancer incidence through the implementation of prevention strategies, screening coverage in Ecuador remains limited, raising concerns about factors contributing to this low coverage. Objectives: This study aimed to assess the geographic accessibility, availability, and economic affordability of health services for cervical cancer prevention in rural areas of Cuenca, Ecuador.

Methods: Methods: A cross-sectional and geographic analysis was conducted using data from a door-to-door survey of two Cuenca rural populations, between September 2023 and February 2024. The study evaluated the performance of PAP tests in the general population by conducting a survey and identifying the presence of geographical and economic barriers that hinder access to PAP tests as a screening method.

Results: Results: A total of 1,851 door-to-door surveys were completed: 939 in the rural parish of Chiquintad and 912 in the rural parish of Nulti, with an average respondent age of 42 years. The findings indicate that 40.79% of the population was over-screened, 31.28% were under-screened, and 14.69% had never been screened. Geographical analysis showed no differences in access to health centers. A binary logistic regression was significant ($\chi^2 = 224.047$, $p < 0.001$), indicating that married women, unemployed individuals, those with higher education, and those with higher incomes were more likely to undergo a PAP test. Variance analysis (ANOVA) showed statistically significant differences between performed and expected PAP tests across age groups (F-value of 34.712, p= 0.001), with women aged 40 to 49 most closely aligned with the expected number of PAP tests. Questions related to waiting time for medical attention showed statistically significant ($\chi^2 = 50,123$, $p < 0.001$), lack of resources for medical consultation ($\chi^2 = 24.997$, $p = 0.003$), reports of mistreatment at the health center ($\chi^2 = 18.782$, $p = 0.027$), and difficulty getting an appointment ($\chi^2 = 21.144$, $p = 0.012$). Non-significant results were found for distance to the health center ($\chi^2 = 13,361$, $p = 0.147$) hours of attention at the health center ($\chi^2 = 12,672$, $p = 0.178$), and lack of resources for transportation ($\chi^2 = 16,530$, $p = 0.057$).

Conclusions: Conclusions: There is a high frequency of both under-screening and over-screening in the rural populations of Cuenca. Structural barriers are a major issue that must be taken into account when planning public health strategies for cervical cancer prevention.

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#9175

HPV SCREENING OF THE INDIGENOUS WOMEN , CUSTODIANS OF THE AMAZON RAIN FOREST - IF NOT NOW WHEN ?

11 - Screening for women difficult to reach

Background/Objectives: THE INDIGENOUS WOMEN ARE TRUE CUSTODIANS OF THE AMAZON RAIN FOREST ARF , WITH THE HIGHEST PREVALENCE OF CERVICAL CANCER BECAUSE OF SOCIAL, CULTURAL,POVERTY, LACK OF ACCESS TO TIMELY PREVENTION , SCREENING AND TREATMENT. THEIR REMOTE LOCATION IN THE HEART OF THE ARF AND OTHER RISK FACTORS CONTRIBUTE TO THIS GREAT TRAGEDY. TOO MANY WOMEN ARE DYING BEFORE AGE 30 A TARGETED PROGRAM WHICH INCLUDES ,HEALTH EDUCATION, HPV SELF COLLECTED SWABS AND TIMELY TREATMENT IS A PRIORITY SCREENING. ADDITIONALLY ADDRESSING OTHER RISK FACTORS THAT DRIVE THE HIGH PREVALENCE IS CRITICAL AND LESSONS LEARNED CAN HELP OTHER WOMEN IN SIMILAR CIRCUMSTANCES/

Methods: TRAVEL TO REMOTE AREAS BY PLANE, BOAT AND 4 WHEEL ALL TERRAIN VEHICLE WITH A SELECT TEAM, INCLUDING WOMEN FROM THE RESPECTIVE VILLAGES , PERMISSION GRANTED FROM CHIEF TOSHAO , WOMEN ARE PROVIDED WITH IMPORTANT HPV HEALTH INFORMATION, WRITTEN CONSENT IS OBTAINED & ADVISED ON THE SELF COLLECTED SWABS WITH FEMALE SUPERVISION, THESE SWABS ARE TRANSPORTED TO GEORGETOWN AND TESTED IN AN APPROVED PCR FACILITY , WRITTEN RESULTS ARE COLLECTED AND RETURNED TO EACH WOMAN WITH AN EXPLANATION OF RESULTS . TESTING FOR OTHER STDS & HIV IN HIGH RISK CASES WITH MULTIPLE HPV GENOTYPES . TREATMENT WAS PROVIDED TO WOMEN TESTED POSITIVE FOR CHLAMYDAE , TRICHOMONAS, GONNORHOEA AND OTHER STD

Results: TOTAL # OF TESTS COMPLETED , IN RESPECTIVE VILLAGE , REGION , TOTAL # OF TESTS NEGATIVE PATIENTS ADVISED TO GET HPV VACCINE IF NO PRIOR VACCINATION, POSITIVE PATIENTS ADVISED COLPOSCOPY AND CURATIVE TREATMENT WITH LEEP AND BIOPSY AS NECESSARY AND REFFERED FOR FURTHER TREATMENT IN THE MAIN REFFERAL HOSPITAL THIS IS PHASE 11 OF THE PROGRAM TO DETERMINE WHAT OTHER RISK FACTORS DRIVE THE RAPID PROGRESSION OF HPV INFECTION & FAILURE TO CLEAR THE VIRUS AND FUEL ONCOGENISIS

Conclusions: THIS PHASE OF THE HPV SCREENING FOCUS ON OTHER RISK FACTORS THAT DRIVE THE PROGRESSION OF ONCOGENISIS , MAINLY THE VAGINAL MICROBIOME , FINE PARTICULATE MATTER FPM < 2.5 MICRONS GENERATED FROM BURNING SOLID FUEL FROM THE RAIN FOREST ,, MEASURE THE FPM LEVEL AND SEEK CLEAN ALTERNATIVE TO BURNING SOLID FUEL IS IMPORTANT, MULTIPLE STD AND STVI SIMPLY PROVIDING WATER TO WASH POST COITUS WHEN THERE IS NONE AVAILABLE , ENCOURAGING HPV VACCIATION , ALSO THE RIGHT HPV VACCINATION SINCE FINDINGS SUGGEST HPV 16 , 18 ARE NOT EH MAIN ONCOGENIC TYPES - NEED NONOVALENT VACCINE INSTEAD OF QUADRAVALENT FOR THIS HIGH RISK ISOLATED POPUALTION HOW TO CLEAR PERSISTENT HPV INFECTION USING NOVEL APPROACH TO STERALIZE THE VAGINAL TRACT THESE WOMEN ARE DEDICATED TO SAVING THE ARF , TO PROTECT , PRESERVE & DEFEND THE LAST HOPE OF PREVENTING CLIMATE DESTRUCTION

References: LANCET 2 2016 MOST BREAST & CERVICAL CANCERS OCCUR IN LMIC CAN BE PREVENTED NATURE COMMUNICATIONS 2022 DOI 10.1038/s41467-022-28569-1 u wurzberg LANCET 2017 DOI 10.1016/SO 140-6736 (17) 31821-4

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#8964

Cervical Cancer and Homelessness in the United States: Human-centered design of shelter-based screening

11 - Screening for women difficult to reach

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Background/Objectives: People experiencing homelessness (PEH) have disproportionately lower rates of cervical cancer screening than the housed population, and up to 4-fold higher incidence and mortality rates. Homeless women face unique, compounded, and multilevel barriers to screening, including high rates of sexual violence and trauma that often leads to delays or refusals of Pap tests. Other systemic barriers include provider implicit biases against PEH, misconceptions about their needs, including that they have more important priorities such as finding daily food and shelter than preventive care. A focus on responding to the urgent issues of PEH while overlooking preventive care has led to suboptimal counseling by healthcare providers regarding cancer screening, largely based on assumptions that patients will undergo screening once they are housed. However, there is often even less opportunity to screen PEH after they leave shelters because recurrent homelessness is common, and many who obtain housing are likely to continue to be under- or unemployed without access to health insurance. Despite these issues, information regarding appropriate cancer screening measures in homeless communities is scarce, and no framework exists for routine screening strategies in shelters or places where PEH typically seek healthcare. The objective of this study is to understand and address cervical cancer disparities among PEH through human-centered design of shelter-based screening interventions.

Methods: Guided by a community-academic partnership on homelessness and health in Indiana, USA, this multisite study began in 2024 at two major homelessness service agencies in Indianapolis and Lafayette. Rapid assessment surveys (n=198) were conducted to document the prevalence of cervical cancer screening in these homeless communities and to identify characteristics of individuals overdue for screening. In-depth interviews (n=30) explored homeless individuals' views on health and illness, their knowledge of cervical cancer etiology, prevention, and early detection, key barriers and facilitators to screening, and acceptability of community health worker (CHW)-delivered education and human papillomavirus (HPV) self-sampling for on-site shelter-based screening. A focus group-style human-centered design session with (n=12) unhoused women further explored motivators and concerns regarding screening and HPV self-sampling to inform the development of an ongoing intervention.

Results: Less than two-thirds of survey respondents (64%) were up to date for cervical cancer screening, far below the national average of 78%. Most (84%) wanted to be screened and believed it is important for their health. Competing priorities for daily survival, lack of transportation, low health literacy, provider mistrust, and stigma were common barriers to screening. Acceptability of HPV self-sampling was high, with enthusiasm for the convenience, privacy, and comfort in taking one's own sample at the shelter. Notable concerns included lack of confidence regarding ability to self-sample correctly, unhygienic conditions in shelter restrooms, and the need for education.

Conclusions: The unique challenges of PEH require human-centered approaches to improve cervical cancer screening access. Willingness to be screened and acceptability of HPV self-sampling is high. Identified concerns and preferences informed the development and implementation of an ongoing HPV self-sampling intervention delivered by trusted CHWs in homeless shelters in Indiana.

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Reminder with personal phone call in order to increase attendance in human papillomavirus (HPV) 16/18-positive women in self-sample

11 - Screening for women difficult to reach

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Background/Objectives: HPV 16/18-positive women have an elevated risk of invasive cervical cancer (1). In the Stockholm region, this has been addressed by offering women with HPV 16/18 positive self-samples a fast track with direct referral to colposcopy. The routine was introduced in 2024 after the evaluation of a national audit of all cervical cancer cases in Sweden showing that about 19% of women with invasive cervical cancer had an HPV 16/18-positive cytology-negative sample in the last screening interval (unpublished data). Before 2024, women tested HPV 16/18-positive in self-sample were triaged with cytology from a clinician-based sample taken by a mid-wife, and only cytology-positive women were referred to colposcopy. All women that did not attend the cytology triage were sent two written reminders at two and four months. A register search of aggregated data at the Regional Cancer Center Stockholm Gotland, which is the screening hub responsible for the screening organisation in the greater Stockholm and Gotland regions of Sweden, has shown that about 10% of women with HPV 16/18-positive self-samples have not attended any follow-up.

Methods: HPV 16/18-positive women in self-sample between July 2019 - December 2023 in the Stockholm region were identified through the Swedish National Screening Registry (NKCx) (N=4450). After excluding women with an HPV16/18-negative sample more than 30 days afterwards, histopathological sample after the initial HPV 16/18-positive sample and invasive cervical cancer cases, there were 567 women left. All women receive a personal phone call from a midwife at the Regional Cancer Center in Stockholm Gotland, and are offered a direct referral to a colposcopic examination performed by a gynecologist. Women who are not reachable by phone will be contacted through email or other digital solutions provided by the region. All women will be contacted in November-December 2024 and receive an appointment to a gynecologist within three months.

Results: Attendance at colposcopy and cytological and histopathological results will be analysed. Also, HPV type (16 or 18) and time since the self-sample was taken will be included in the analysis. Reminder with personal phone call will be compared with the written reminder. Results will be presented at the Eurogin conference 2025.

Conclusions: Reaching groups without follow-up and an elevated risk for cervical cancer is of great concern. Evaluating a reminder with personal phone call in women with HPV 16/18-positive self-samples with no follow-up is important for the evaluation of risk-based screening programs.

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#9240

Assessment of Cervical Cancer Screening Behavior, Barriers, and Factors Associated with Under- and Over-Screening in Rural Communities of Cuenca, Ecuador: A Cross-Sectional Study

11 - Screening for women difficult to reach

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Background/Objectives: Background: Despite the availability of cervical cancer screening in Ecuador, approximately 40% of women have never been screened, likely due to barriers such as embarrassment and limited access to healthcare facilities. Understanding women's screening behaviour is essential for the effective prevention and management of cervical cancer. Objective: This study aimed to identify cervical cancer screening behaviours, barriers and factors associated with under-screening, optimal screening, and over-screening among women in rural parishes of the Cuenca canton, Ecuador, in 2023.

Methods: Methods: This cross-sectional study was conducted in the rural communities of Nulti and Chiquintad in Cuenca, Ecuador, between September and December 2023. Door-to-door surveys were administered to women aged 18 to 70 years who had provided informed consent. The survey collected demographic data, screening history, and knowledge of cervical cancer prevention. Under-screened women were defined as those who had not undergone a Pap test in the past five years, optimal screening as a Pap test conducted every three to five years, and over-screening as testing more frequently than recommended.

Results: Results: In total, 1900 surveys were collected from both communities. In Nulti, 939 participants (44.1% of women aged 18 to 65 years) had a median age of 43 years. Among them, 52% had completed elementary school, and 58% were married. Barriers included lack of time for testing (21%), unawareness of the recommended age for testing (17%), embarrassment (41%), uncertainty about testing frequency (21%), and difficulty making appointments (24%). Additionally, 22% had not heard of HPV, and 25% were unaware that HPV could cause cervical cancer. In Chiquintad, 961 participants (53.1% of women aged 18 to 65 years) had a median age of 41 years. Of these, 42% had completed high school, and 63% were married. Barriers included lack of time (41%), unawareness of the recommended testing age (55%), embarrassment (24%), uncertainty about frequency (31%), and difficulty in making appointments (18%). Additionally, 25% had not heard of HPV, and 51% were unaware of its role in causing cervical cancer. In Nulti, 139 participants (14.8%) had never been screened, 453 (48.2%) were under-screened, 88 (9.4%) had undergone optimal screening, and 259 (27.6%) were over-screened. In Chiquintad, 113 participants (11.8%) had never been screened, 406 (42.2%) were under-screened, 91 (9.5%) had optimal screening, and 351 (36.5%) were over-screened.

Conclusions: Conclusions: Despite the availability of cervical cancer screening, significant resource misallocation is evident, as shown by the high percentages of under-screened and over-screened women, likely due to limited information and restricted access to testing.

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#9547

Under-screened women's experiences with human papillomavirus (HPV) self-collection in the MyBodyMyTest-3 randomized controlled trial

11 - Screening for women difficult to reach

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Background/Objectives: Cervical cancer mortality and morbidity is higher among under- screened women in the United States. Compared to cytology alone, screening for cervical cancer with HPV primary testing can improve the detection of early-stage cervical pre-cancer and cancer to prevent mortality. The My Body My Test-3 clinical trial examined the effect of mailed HPV self-collection kits with appointment scheduling assistance on cervical cancer screening in North Carolina in a population of under-screened and low-income women. Trial results demonstrated that mailed HPV self-collection kits with scheduling assistance improved the uptake of cervical cancer screening compared to scheduling assistance alone. Here, we aimed to evaluate the trial participants' experiences with the mailed HPV self-collection screening process.

Methods: Data on socio-demographics and perceptions from participants on HPV self-collection were collected from April 2016 to December 2019 through an eligibility screener, baseline and follow-up questionnaires. Responses were compared, stratified by high-risk HPV positivity using the Aptima HPV assay, using chi square or Fisher's exact tests.

Results: A total of 363 participants from the self-collection intervention arm who had completed the follow-up questionnaire were included in this analysis. Median age was 42 years (range: 33-52), 48% (n=173) were Black non-Hispanic, 38% (n=138) were white non-Hispanic, and 8% (n=30) were Hispanic. There were 318 women who returned a self-collection sample, of which 15% (n=48) were HPV positive, 82% (n=260) were HPV negative, 3% (n=10) had invalid results. Among participants with available data, 91% did not have difficulty understanding the self-collection instructions (n=320/350 responses), 95% experienced no or a little pain during the self-collection (n=164/172 responses), and 85% felt comfortable sending their cervicovaginal samples back in the mail (n=307/363). Almost half of HPV negative participants reported liking that self-collection was convenient (43%, n=113) as compared to only a quarter of HPV positive participants (25%, n=12) (p=0.02). For future screening, the majority (64%, n=166) of HPV negative participants preferred HPV testing through self-collection as compared to 48% (n=23) of HPV positive participants (p=0.04). A similar trend was observed in response to which screening method participants would prefer if both self- and provider-collection protected women's health equally, with 77% of HPV negative participants preferring self-collection versus 65% of HPV positive participants (p=0.08).

Conclusions: Under-screened women's experiences with HPV self-collection were positive, yet HPV-negative participants appeared to have a more favorable outlook on the screening intervention and its future use than those with HPV-positive results. These insights into participant experiences with a mailed HPV self-collection outreach program will help tailor future interventions for this screening process.

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Implementation of urine-based HR-HPV testing for cervical cancer prevention in a rural clinic in Eswatini

11 - Screening for women difficult to reach

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Background/Objectives: Cervical cancer (CC) poses a significant public health challenge in Eswatini, where socio-cultural, economic, and policy-related barriers limit women's access to screening and preventive care. In line with the WHO recommendations to implement HPV-DNA testing as primary screening, taking advantage of existing diagnostic platforms, we introduced a urine-based HPV-DNA screening test in a rural healthcare facility in Eswatini to increase access to and acceptability of CC prevention among adolescents and young girls.

Methods: During the 12-month pilot phase, 510 adolescent girls and women (ages 12-49) self-presenting at St. Philip's Clinic for any medical reason attended the screening providing a urine sample. After concentration and debris elimination through centrifugation, 1 mL of urine sample was tested via Xpert® HPV test for the detection of 14 high-risk HPV (HR-HPV) detection (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). Sociodemographic data such as age, HIV status and adherence to CC screening were collected via REDCap. Comparisons of proportions or means were accomplished by the Chi-square test. HR-HPV-positive women underwent further assessment with visual inspection with acetic acid (VIA) and treatment, if necessary. The project is ongoing, with an observational 12-month evaluation to screen up to 2000 women under routine conditions.

Results: In the pilot phase, 510 women were enrolled (median age 29 years), with 190 reporting to be HIV positive. First-time screenings accounted for 45% (228/510) of participants (median age 23 years). The Xpert® HPV test yielded satisfactory results in samples collected from 473 women (473/510,93%), with the detection of at least 1 HR-HPV in 42% (199/473) (median age 28 years). HPV DNA-positive women were identified in each age class, with a higher frequency in the 21-25 year group (56/101,55%). Among HR-HPV-positive women, 44% (88/199) were girls or women living with HIV. Participants living with HIV showed 1.8 times increased risk of being HR-HPV positive compared to HIV-negative girls and women (95%IC 1.23-2.64). 124 HR-HPV-positive women were subjected to VIA (124/199,62%) at St. Philip's clinic or during nurses' outreach activities. Eighteen pregnant women were temporarily excluded from the triage and scheduled for triage after delivery. One woman refused to perform VIA due to fear of pain. The remaining women were considered lost at triage (56/199,30%). The VIA outcome was negative in most examined women (113/124,91%), inconclusive in three participants (due to poor visualisation of the cervix) (3/124,2%), suspicious in 4 (4/124,3%), and positive in 4 (4/124,3%). Positive participants were treated locally through thermocoagulation or at nearby clinics through loop electrosurgical excision. VIA-negative women were scheduled for a new appointment the following year. VIA suspicious or inconclusive were scheduled for a new appointment in six months.

Conclusions: The results showed a high prevalence of HR-HPV among Swazi women, underscoring the urgent need for access to effective, rapid, and acceptable screening tools. Urine-based HR-HPV testing in a rural setting appears feasible and well-received, potentially boosting screening adherence, particularly among younger women. Ongoing challenges, such as inconclusive results and loss to follow-up during triage, are being tackled in the second phase through retraining and community outreach, marking a promising step forward in enhancing CC prevention in Eswatini.

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Canada

#9269

The Role of Community Health Ambassadors in Engaging Under Screened Communities to Participate in HPV Self-Sampling in Canada

11 - Screening for women difficult to reach

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Background/Objectives: In 2020, the World Health Organization released a global action plan for eliminating cervical cancer worldwide by the end of the century. In alignment with this plan, Canada is dedicated to achieving this goal by 2040 through improved access to and participation in cervical cancer screening programs. This includes the implementation of HPV self-sampling as a more accessible option for cancer screening among under screened populations such as new immigrants to Canada (i.e. newcomers). Therefore, we conducted a scoping review to identify how cervical cancer screening programs around the world engaged under screened populations to participate in HPV self-sampling. Based on the scoping review findings, partner consultation, and conversations with eligible newcomers, Community Health Ambassadors (CHAs - i.e. trusted members of the community who promote health behaviours) were identified as the most promising approach for engaging newcomers in HPV self-sampling. The objective of this study is to train and deploy Community Health Ambassadors (CHAs) to engage newcomer communities to participate in HPV self-sampling in Alberta, Canada.

Methods: This pilot study will train and deploy CHAs to engage newcomer communities in HPV self-sampling in urban and rural Alberta, Canada. Through the trained CHAs, this pilot program aims to recruit ~1000 newcomers who are: female or a person with a cervix, aged 25-69, unscreened or have no record of a Pap test in the last 5 years, and moved to Canada in the last 10 years. Using a community-based health equity approach, CHAs will be trained to provide education about cervical cancer screening and distribute HPV self-sampling testing kits directly in the community. Community engagement activities may include engaging and recruiting eligible newcomers to participate in HPV self-sampling through events and presentations such as women's health events and English Language Classes.

Results: In October 2024 we identified and trained 10 CHAs who are newcomers fluent in the first languages of their respective communities including Spanish, Arabic, Tagalog, Tigrinya, and Ukrainian. The CHAs will be deployed in the community from November 2024 to March 2025 and will report on outcomes such as the total number of people reached and educated on HPV self-sampling, number of HPV self-sampling kits distributed and returned, participation rates in urban and rural areas, etc. The results from this study will be used to inform the full-scale implementation of HPV self-sampling in Alberta and across Canada.

Conclusions: This pilot study will provide valuable results to provincial health authorities as they decide how to engage under screened individuals in cervical cancer screening going forward. Ultimately, this work will contribute to Canada's Action Plan to Eliminate Cervical Cancer by 2040 by reducing cancer screening disparities among newcomers through culturally relevant, accessible cervical cancer screening.

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#9216

First-void urine: A promising alternative sample for cervical cancer screening

11 - Screening for women difficult to reach

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Background/Objectives: Cervical cancer screening coverage in France is estimated at 60%, which is significantly below the 70% threshold recommended by the European Union. The invasiveness and discomfort of the cervical-vaginal sampling procedure are recognized as key barriers to participation in screening. In this context, an alternative sample, such as collecting first-void urine, appears promising. However, studies results on urine sampling have been inconsistent, largely due to a lack of standardization in urine collection protocols. The aims of our study are therefore to: 1) evaluate the accuracy of HPV PCR testing on first-void urine using a standardized protocol; 2) assess women's acceptance of this urine collection method.

Methods: At the initial stages, we performed an extensive literature review to establish an optimal and standardized protocol for urine collection and analysis. Following this, we conducted a prospective study enrolling women aged 30 to 65 years old who attended the gynecology department for primary cervical cancer screening. At enrollment, each participant provided two samples: a first-void urine sample collected with the Colli-Pee® device (Novosanis) and a cervical-vaginal sample collected by the clinician. Both samples were then analyzed in parallel in our lab using the AnyplexTMII PCR kit (Seegene). We calculated the sensitivity and specificity of the Anyplex test on urine samples by comparing the results with those from the cervical-vaginal sample, which served as the gold standard. Additionally, we assessed the acceptability of the urine collection process through a dedicated questionnaire.

Results: We enrolled 109 patients, with a median age of 48 years, resulting in the analysis of 218 samples (109 first-void urine samples and 109 cervical-vaginal samples). The invalid PCR result rate for first-void urine samples was 2.75%. HPV infections were detected more frequently in first-void urine than in cervical-vaginal samples (14.2% vs. 12.3%). The sensitivity and specificity of the HPV PCR test for urine samples were 84.6% and 95.6%, respectively. Importantly, over 85% of the women expressed a preference for urine collection.

Conclusions: The strength of our study lies in its optimized experimental protocol and the homogeneity of the study population. In the literature, other studies have reported a higher prevalence of HPV infections in urine samples compared to cervical-vaginal samples. Given its strong diagnostic performance and high acceptability, first-void urine appears to be a promising alternative sampling method, especially for populations reluctant to undergo cervical-vaginal sampling. We intend to continue this study with a larger sample size to further validate the diagnostic efficacy of this approach.

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#9431

Increasing cervical cancer screening rates among unscreened and underscreened people who face barriers to screening

11 - Screening for women difficult to reach

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Background/Objectives: Pap testing has significantly reduced cervical cancer incidence and mortality. Despite the availability of Pap testing through an organized program in Manitoba (Canada), screening participation has been declining in recent years, and for some people, has never occurred. Additionally, Canadian data show that cervical cancer rates have been increasing significantly since 2015, with an average percent rise of 3.7%. To mitigate these impacts, an HPV self-screening project was conducted with groups that face specific barriers to cervical screening.

Methods: We partnered with eight community health groups that work with clients facing various barriers to screening. Participating groups included those who work with remote Indigenous communities in Northern Manitoba (geographically isolated with no road access), Indigenous individuals in urban and southern Manitoba, trans people, and women who are affected by female genital cutting. The methods for identifying and communicating with potential screening participants were developed collaboratively, as was the invitation delivery approach (hand-delivered or mailed). Intentional efforts were made to provide HPV self-screening kits to people who had never been screened for cervical cancer or had not been screened in more than five years.

Results: Eight community health groups received education about the HPV self-screening kits, determined the method of participant recruitment that best suited their community, and if applicable, distributed the kits and facilitated follow-up colposcopy. Six decided to hand-deliver the HPV self-screening kits to their community members and the remaining two requested that the kits be mailed. Almost ten times as many kits were mailed compared to hand-delivered kits. Early results show that the proportion of people completing an HPV self-screening kit was higher among the people who received a hand-delivered kit compared to the people who received the kits by mail. People in the hand-delivered group were also more likely to get a Pap test in the six months after receiving the kit. More people in the hand-delivered group were found to be ineligible for the study (i.e., received the kits even though they did not meet the inclusion criteria), identifying a potential gap in the approach used. Interviews with the participating groups took place after the kit collection period to inform a future approach to increasing participation among unscreened and underscreened individuals who face barriers to screening.

Conclusions: While we may technically have all the tools to eliminate cervical cancer, uneven access to screening has led to inequity in the associated disease incidence and outcomes. Some of this inequity might be bridged through engagement with community groups and the co-development and co-delivery of services to the populations they serve and know best. Increasing cervical screening rates among unscreened and underscreened individuals will likely require a tailored approach that addresses known barriers; more research is needed to determine the best approach for each community.

FC11 - Triage of HPV positive women II

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#9211

HPV sublineages in Danish cervical cancer screening samples detected by NGS

12 - Triage of HPV positive women

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Background/Objectives: The carcinogenicity of HPV sublineages varies, and with mounting knowledge on the cancer risk of HPV sublineages the information can be operationalized in improved risk stratification of HPV-positive women. Still, limited research has been performed to characterize HPV sublineages, and mainly with focus on HPV16. We aimed to design a targeted next-generation sequencing (NGS) panel for the analysis of HPV sublineages for all IARC high-risk HPV types.

Methods: The targeted NGS panel was designed to sequence 12 high-risk, 13 probably/possibly high-risk, and 2 low-risk HPV types. A bioinformatic pipeline was developed for data analysis and calling of HPV sublineages. Sublineage references were retrieved from NCBI via PaVE (https://pave.niaid.nih.gov/). The method was evaluated for correct determination of sublineages using purified whole genomic plasmids with reported Gene Bank accession numbers of HPV6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68a, and 68b in a background of human cellular DNA (the Global HPV LabNet DNA Genotyping Proficiency Panel 2023). In total, 119 liquid-based cytology (LBC) SurePath cervical cancer screening samples were analyzed from women living in the Capital Region of Denmark. Six of these samples had a negative HPV screening result on the clinical screening assay, the BD Onclarity HPV test, while the remaining 113 samples were selected based on detected HPV type.

Results: Quality assurance by plasmids showed the correct sublineage for HPV6, 11, 16, 31, 33, 39, 45, 51, 52, 56, 58, and 59. The coverage of HPV68b was not sufficient to determine the sublineage. HPV68a was excluded since only the L1 gene was included in the obtained plasmid. Plasmids containing HPV18 and HPV35 were also excluded since the genomes included in these plasmids are not listed at PaVE. In the analysis of the 119 screening samples, the six HPV-screen-negative samples remained HPV-negative using the targeted NGS assay. Complete HPV type agreement between the BD Onclarity assay and the NGS assay was observed in 96.5% (109/113) of the HPV-screen-positive samples. In the remaining HPV-screen-positive samples, no HPV types were detected in one sample (0.9%, 1/113), an additional HPV type was detected in two samples (1.8%, 2/113), and two HPV types different from the HPV type detected with the BD Onclarity HPV test was detected in one sample (0.9%, 1/113), using the NGS assay. The number of detected sublineages ranged from one to six for the different HPV types. A type sublineages were most frequent in samples of HPV16 (A1: 86.7%, 13/15), HPV18 (A3: 83.3%, 10/12), HPV33 (A1: 66.7%, 4/6), HPV35 (A1: 83.3%, 5/6), HPV39 (A1: 100.0%, 3/3), HPV51 (A1: 84.6%, 11/13), HPV52 (A1: 81.3%, 13/16), HPV58 (A2: 66.7%, 4/6), and HPV68 (A2: 66.7%, 4/6). The B1 sublineage was most frequent in samples of HPV45 (58.3%, 7/12) and HPV56 (100.0%, 2/2) while the B2 sublineage was observed in all HPV66 positive samples (100.0%, 2/2). A more equal distribution of sublineages belonging to different lineages was observed in samples with HPV31 (A: 37.5%, 6/16; B: 31.3%, 5/16; C: 31.3%, 5/16) and HPV59 (A: 62.5%, 5/8; B: 37.5%, 3/8).

Conclusions: Our method enables identification of HPV sublineages in SurePath-collected screening samples from Danish women. The study continues, aiming at sequencing 1000 individual cervical cancer screening samples.

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#9281

Evaluation of the multiple HPV-based "screen and triage" algorithms in real world settings of China

12 - Triage of HPV positive women

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Background/Objectives: Drawback of HPV primary screening such as low specificity, low PPV, and high referral rates, etc. raised the need for secondary triage methods for hrHPV+ women. A cross-sectional diagnostic study was conducted to assess the screening accuracy of different HPV-based "screen and triage" strategies, including the comparison of PCR-based HPV vs. Hybrid-capture-based HPV primary screening with different triage algorithms, such as cytology, partial genotyping (HPV16/18), extended genotyping (HPV16/18/31/33/45,HPV16/18/31/33/45/52/58), methylation, and E6/E7 oncoprotein, in a real-life population-based screening study.

Methods: A total of 6059 women aged 25 years who attended CC screening were included from Bachu and Moyu county of China between February to September, 2023. Main outcomes was the histology confirmed cervical intraepithelial neoplasia grade 2 or worse (CIN2+), and the sensitivity, specificity, positive and negative predictive values (PPV and NPV), and the area under the receiver operating characteristic curve (AUROC) were calculated. The colposcopy referral rates with the number of colposcopy need to detect per CIN2+ case (NNR) were evaluated as well to reveal the colposcopy efficiency.

Results: Application of any triage test could significantly increase the specificity of HPV-based screening strategy, but it is hard to maintain the high sensitivity of HPV-based screening algorithms only by single-step triage algorithms. Among the single-test triage strategies, only the extended genotyping with 7 most high risk HPV types (HPV16/18/31/33/45/52/58) showed the comparable sensitivity (88.90% vs 92.10%, relative sensitivity at 0.97, 95%CI: 0.92-1.01) and significantly improved specificity (95.20% vs 91.80%, relative specificity at 1.04, 95%CI: 1.03-1.04), with a significant reduction by 38% (relativer rate at 0.63, 95%CI: 0.59-0.67) in colposcopy referral rates compared to hrHPV primary screening without triage. All two-step triage strategies (genotyping with reflex cytology/methylation/E6/E7 oncoprotein) achieved similar sensitivity with HPV primary screening (87%-91%), meanwhile the specificities were significantly increased to ~95% and the colposcopy referral rates were significantly decreased by 30%-50%. Our data also suggest that the combination of HPV16/18+ and high-grade cytology or E6/E7 oncoprotein positive results, and high-grade cytology alone indicated the highest immediate risk of CIN2+ over 50%, which translated into a warrant for immediate treatment. On contrary, considering the average CIN2+ risk of 1.0% among HPV35,39,51,56,59,66,68+ women, this group does not require an immediate colposcopy.

Conclusions: By targeting HPV16/18/31/33/45/52/58 in primary screening, the accuracy and efficiency of screening algorithms reached the most balanced point and the logistics of screening would become most easy (one-step "screen-triage" operation by PCR-based HPV tests). Using methylation and E6/E7 oncoprotein testing as triage offered the highest immediate risk for CIN2+ ranging from 23% to 32%, indicating the necessity of immediate colposcopy. Use of biomarkers such as E6/E7 oncoprotein provided the high immediate risk when it is positive, but when it is negative, the risk could not be overlooked.

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#9403

The Role of p16/Ki67 Dual-Staining in HPV-Based Cervical Cancer Screening for Risk-Based HSIL/CIN2+ Detection

12 - Triage of HPV positive women

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Background/Objectives: Primary HPV-based cervical cancer screening with cytology as a secondary testing relatively often identifies minor screening abnormalities, necessitating the use of triage tests to improve patient management. The p16/Ki67 dual-staining (DS) is under evaluation for its potential as a triage tool in primary HPV screening, but still limited data exist regarding its effectiveness. In March 2024, the Enduring Consensus Cervical Cancer Screening and Management Guidelines Committee released "Recommendations for Use of p16/Ki67 Dual Stain for Managing HPV-Positive Individuals.", which were integrated into the ASCCP mobile app in October 2024, marking significant progress in clinical practice. Without effective triage, there is a considerable risk of overtreatment, leading to unnecessary interventions and associated patient anxiety. This study aims to compare outcomes for selected minor abnormalities (positive for 12 HPV high-risk genotypes other then 16 and 18/HPV HR12+ ASC-US/LSIL) between cases with and without DS testing, with DS employed as a tertiary screening test.

Methods: From 30,066 liquid-based cervical cancer screening results, 332 cases were selected based on available high-risk HPV tests results, limited genotyping for HPV 16 and 18, liquid-based cytology (LBC), DS testing, and histology from standardized colposcopy with biopsy. Of these, 140 cases were HPV HR12+ with ASC-US or LSIL cytology results, and 65 cases in this group were DS-positive. Two retrospective triage approaches were compared for all HPV HR12+ cases. According to the ASCCP app, the immediate HSIL/CIN3+ risk without DS use ranged from 4.3% to 4.4%, with recommendation for colposcopy (clinical action threshold ≥ 4% and < 25%). In DS-positive cases, the immediate risk was between 5.9% and 9.9% - also the clinical action threshold for colposcopy. The 3-year HSIL/CIN3+ risk for DS-negative cases was from 0.92% to 1.6% (below the 4% immediate risk threshold and 3-year risk ≥ 0,39%), recommending a 1-year follow-up. The positive predictive value (PPV) for detecting high-grade squamous intraepithelial lesions or worse (HSIL/CIN2+) was calculated.

Results: The analysis compared number of colposcopies performed between the DS and non-DS groups. In cases without DS testing, 140 colposcopies were performed, with no missed HSIL/CIN2+ cases. In the DS group, only 65 colposcopies were needed, with no missed HSIL/CIN2+ cases. Notably, all DS-negative cases were free of HSIL/CIN2+, demonstrating value of DS in reducing unnecessary procedures while maintaining effective detection. The PPV for HPV HR12+ ASC-US/LSIL cases was 15.6%, compared to 33.8% for HPV HR12+ ASC-US/LSIL DS-positive cases ($p < 0.05$).

Conclusions: p16/Ki67 DS testing in HPV-based cervical cancer screening, integrated into a HSIL/CIN3+ risk-based management strategy, offers significant advantages by reducing unnecessary colposcopies and accurately identifying HSIL/CIN2+ lesions. Incorporating DS as a triage tool for HPV-positive cases enhances patient safety, minimizes overtreatment, and optimizes the management of cervical screening abnormalities.

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#9359

Evaluation of p16/Ki67 Dual Stain and Extended Genotyping for Triage and Management of Individuals Testing Positive for Human Papillomavirus in a Diverse US Population.

12 - Triage of HPV positive women

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Background/Objectives: In the US, Black women suffer from higher cervical cancer mortality than White women. The STRIDES cohort (Studying Risk to Improve Disparities in Cervical Cancer) was developed to study HPV natural history, cervical cancer screening, and post-screening management in a diverse US population (60% Black, 28% White). Risk estimates from STRIDES have informed recent US guidelines on cervical screening and management. Here, we present cervical precancer risk estimates for extended genotyping and dual stain among STRIDES participants who tested positive in HPV screening.

Methods: We estimated the immediate risks of CIN3+ in 1,881 women from STRIDES who tested positive for HPV in cervical screening within strata based on extended genotyping, cytology (Onclarity), and dual stain (CINTecPLUS). Risk estimates for different strata were evaluated in the context of risk action thresholds defined in the 2019 Consensus Management Guidelines (e.g., an immediate risk of CIN3+ of 4% or greater has a recommendation of colposcopy referral).

Results: HPV16 had the highest risk of all types and channels in STRIDES (22%). Compared to data reported from predominantly White populations, a higher risk of CIN3+ was observed in STRIDES for channel HPV35/39/68 (5.9%), likely due to a higher prevalence of HPV35 among Black women. Consistent with other data, HPV 59/56/66 was the lowest risk channel (0.7%). Dual stain provided better risk stratification compared to cytology for triaging HPV-positive test results, which persisted when limited or extended genotyping was used.

Conclusions: Due to differences in HPV genotype prevalence across populations with different ancestry, it is critical to include diverse populations when developing clinical guidelines. STRIDES contributed critically to recent recommendations on the use of dual stain and extended genotyping in the US. Extended genotyping with triage using cytology or dual stain identifies high-risk patients who are likely to benefit from colposcopy while decreasing low-yield colposcopy.

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#9427

Droplet Digital PCR & Methylation: A New Approach For HPV-Positive Women Triage

12 - Triage of HPV positive women

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Background/Objectives: Secondary prevention is crucial too for achieving the cervical cancer elimination goal (1). Testing for high-risk HPV (hrHPV) became the gold standard over the years for screening due to its high sensitivity for high-grade squamous intraepithelial lesion or worse (HSIL+) detection (2). However, it led to an increase in the number of women referred to colposcopy units due to its limited specificity, especially among young women (3). This might, ultimately, lead to overdiagnosis and overtreatment. DNA methylation markers have been proposed as potential biomarkers for HPV-positive women triage (4-6). Hence, we aimed to develop a panel of DNA methylation markers as a triage tool for hrHPV-positive women.

Methods: Two independent series of cervical scrapes samples from hrHPV-positive women (#1 n=62 and #2 n=750) were selected. The #1 series was used to develop a methylation-specific droplet-digital PCR assay. The 2-gene methylation panel was validated in #2 series of January 2020 from hrHPV-positive women who had samples available.

Results: In #1 series, the methylation levels for both genes were significantly higher in HSIL+ compared with the Normal and low-grade lesions group. Additionally, the proposed panel displayed high specificity and accuracy (80% and 70%, respectively). In the #2 series, this high specificity and accuracy were retained. Furthermore, we combined hrHPV genotyping with methylation markers, and this new triage algorithm might reduce the false-positive rate by 12%-14% with an increment in accuracy of 10-12% compared to the current screening triage. Importantly, these results might translate into a reduction in women sent to colposcopy (10-12%).

Conclusions: Although further validations are required, our results reinforce that methylation markers might play a role in reducing overtreatment/overdiagnosis and improving the cost-effectiveness of cervical cancer screening programs.

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#9505

Cervical Cell Lift - a Novel Method for the Spatial Mapping Biological Markers and Grading of Hpv-infected Cervical Lesions

12 - Triage of HPV positive women

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Background/Objectives: The persistent infection of high-risk HPV in the cervical transformation zone is the cause of cervical cancer. The majority of sexually active people become infected with high-risk HPV at some point in their life, however, only a small proportion of infected females develop cancer. In general, after the initial infection, HPV develops a temporal productive lesion and then the infection is controlled by the host immune system, leading to the latent persistent infection. In later life, the infection may be re-activated, develop into a pre-cancerous lesion, and in rare cases, progress to malignant cancer. The aim of cervical screening is to identify HPV-associated lesions that may progress to cancer in order to allow treatment.

Methods: Infected lesions can be categorised from productive low-grade lesions to non-productive high-grade lesions. These lesions are characterised based on the regulation/expression of viral oncogenes and their morphological phenotype, which provides insight into the different probabilities of cancer progression. The phenotypes (the biological markers) include the surrogate molecular markers of viral oncogene expression (MCM, Ki67, and p16) and the viral productive life cycle (E4) as well as cellular morphologies.

Results: We showed a new method to lift the surface cells of the cervix (Cervical cell lift, CCL) and generate a spatial map of the biological markers there. We have successfully located and characterised the infected lesion on the CCL. Compared to the normal cytology, the major advantage of the CCL is the preservation of native cell topology, and by preserving this spatial information, the lesions can be visualised in their entirety.

Conclusions: The CCL potentially can replace the current triage test (cytology) of cervical screening by providing the location and the grade (CIN1-CIN3) of the infected lesion without biopsy and histopathological assessment.

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#9158

High-grade lesions probability in ASCUS HPV positive patient according to HPV type

12 - Triage of HPV positive women

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Background/Objectives: The aim of our study was to assess the proportion of high-grade histological lesions, according to HPV type, in patients referred for colposcopy involving a positive HPV-HR test and ASC-US cytology.

Methods: This is a retrospective descriptive study of asymptomatic patients aged 25 to 65 with a positive HPV-HR test and ASC-US cytology. Data were collected at the Nord-Franche-Comté Hospital from September 2019 to February 2022. The primary outcome was the proportion of high-grade histological lesions in patients with ASC-US cytology combined to HPV 16 or 18 (associated or not with other HPV type), compared with HPV no 16 no 18.

Results: Among the 298 patients included, 67% were HPV no 16 no 18, 22% HPV 16 associated or not with others and 11% HPV 18 associated or not with others. We found significantly fewer high-grade lesions in patients with ASC-US cytology and HPV no 16 no 18 than in patients with HPV 16 or 18 (8.5% versus 22.7%, $p<0.01$). This observation holds true if we analyze HPV 16 and HPV 18 patients separately (HPV 16: $p<0,01$; HPV 18: $p=0.01$). In patients presenting an ASC-US cytology with HPV no 16, no 18: 53% of the biopsies found no histological lesion compared with 30% for the other HPVs ($p<0.01$).

Conclusions: We've highlighted the reality of colposcopists: a high ratio of normal coloscopy associated with normal or low-grade biopsies, in patients with a positive HPV-HR test no 16, no 18 and ASC-US cytology.

References: https://doi.org/10.1016/j.gofs.2024.08.001

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#9503

Risk Stratification of HPV-Positive Women Using Extended HPV Genotyping and Cervical Histology Correlation.

12 - Triage of HPV positive women

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Background/Objectives: According to the most recent scientific evidence, high-risk (HR) oncogenic HPV genotypes can be classified into three risk categories: high (HPV 16, 18, 45), intermediate (HPV 31, 33, 52, 58), and low (HPV 35, 39, 51, 56, 59, 66, 68). The objectives of this study are: 1. to evaluate the correlation between HPV genotype risk categories and the histological grading of cervical intraepithelial neoplasia (CIN) lesions; 2. to investigate the role of extended HPV genotyping in the risk stratification for CIN2+ in HPV-positive women, in comparison with other known risk factors, particularly cervical cytology.

Methods: All women referred to the colposcopy clinics at the European Institute of Oncology (N=244) and the Mangiagalli Clinic of Fondazione Ca' Granda Ospedale Maggiore Policlinico (N=251) in Milan with a first-time positive HPV test result from January 2020 to December 2022 were included in this retrospective study. The HPV tests used for extended genotyping in each center were BD OnclarityTM and AnyplexTM II, respectively. Cervical cytology results and histological data, obtained through colposcopic-guided biopsy or cervical excision, if performed, were available for all patients. Patient characteristics were summarized using the mean and standard deviation (SD) for age and absolute and relative frequencies for categorical variables. Comparisons between groups for categorical variables were conducted using Fisher's exact test. The association between risk factors and histology was analyzed through univariate and multivariate logistic regression, with the recruitment center used as a stratification factor for the adjustment of estimates. All significance tests were conducted at the 5% level.

Results: A statistically significant association was found between HPV genotype risk categories and cervical histology, with a higher prevalence of high-risk HPV genotype categories in CIN3+ lesions. Women from the Mangiagalli Clinic exhibited a lower incidence of pre-neoplastic cervical lesions than those from the European Institute of Oncology (p inf 0.001). Age showed an inverse relationship with the risk of developing pre-neoplastic lesions, with an odds ratio (OR) of 0.79 (95% CI: 0.71-0.88; p inf 0.001) for CIN2+ and an OR of 0.82 (95% CI: 0.72-0.93; p = 0.002) for CIN3+, indicating a reduced risk with every 5-year increase in age. Subjects with high-grade cytology had a significantly higher risk of developing CIN2+ or CIN3+ compared to those with negative cytology, with ORs of 7.89 (95% CI: 3.65-17.0; p inf 0.001) and 6.90 (95% CI: 2.92-16.3; p inf 0.001), respectively. Intermediate-risk and high-risk HR-HPV genotype categories exhibited a markedly increased risk compared to the low-risk class, with ORs of 5.82 (95% CI: 2.63-12.9; p inf 0.001) and 5.90 (95% CI: 2.69-12.9; p inf 0.001) for CIN2+, and ORs of 3.44 (95% CI: 1.44-8.22; p = 0.006) and 3.63 (95% CI: 1.54-8.54; p = 0.003) for CIN3+. Colposcopic grading was also significantly correlated with the risk of CIN2+ and CIN3+ (p-values ranging from inf0.001 to 0.003). In the multivariate analysis, statistically significant associations between histology and age, cytology, and HPV risk categories were maintained.

Conclusions: Extended HPV genotyping, including classification into risk categories, plays a crucial role in the risk stratification of HPV-positive women and may serve as a valuable triage test, especially for self-collected samples, as an alternative to cervical cytology.

FC12 - Self-sampling I

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#9504

Large-scale, controlled study comparing analytical quality of three HPV self-sampling devices for self-collected cervical cancer screening

13 - Self-sampling

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Background/Objectives: The Capital Region of Denmark is currently conducting a large scale, controlled study evaluating local women´s preference regarding cervical human papillomavirus (HPV) self-sampling devices. Here we present data from a sub-study detailing the analytical quality of three defined self-sampling devices: the Evalyn® (Rovers, the Netherlands), the FLOQSwab® (Copan, Italy) and a custom designed Danish self-sampling swab. The analytical quality evaluation was conducted with respect to overall human DNA and HPV DNA detection.

Methods: Women in the Regional screening program receiving invitations for HPV self-sampling, were offered a kit with two self-sampling devices of the following combinations: 1) Evalyn® and FLOQSwab®, 2) Evalyn® and the Danish designed prototype or 3) FLOQSwab® and the Danish designed prototype. The prototype has an identical sampling head as the FLOQSwab® but has a modified handle. Women were asked to sample with both received devices and return them to the laboratory for analysis. Upon reception all three devices were handled uniformly with the same laboratory protocol including resuspension in a 3.0 ml HPV diluent tube with CBD-buffer (BD Integrated Diagnostic Solutions) prior to analysis using the clinically validated BD OnclarityTM HPV assay on the BD CORTM instrument (BD, Sparks, MD). Assay Ct values on Human Betaglobin internal controls (HBB, 3 per device) and Ct values of detected HPV genotypes were retrieved from the instruments and analyzed using R-studio (2024.04.2) and python (version 3.10.5).

Results: A total of 1131 women have returned two paired devices for analysis, resulting in 900 Evalyn® brushes, 552 FLOQSwab® swabs and 810 of the prototype swabs with three internal control datapoints (HBB) and one datapoint per HPV genotype detected in each valid device. When data from identical devices was pooled, internal control Ct values from the Evalyn® brush (n=2688) showed a median of Ct 22.2 (IQR 21.4, 22.9). For FLOQ Swab® (n=1649) the median Ct was 22.0 (IQR 21.2, 22.8), and finally, the prototype (n=2409) had a median Ct of 22.1(IQR 21.3, 22.9). Of the 1131 participating women, 14.5% (n=164) tested positive for at least one HR HPV-type in at least one of their devices. No differences in HPV Ct values were observed between the paired devices. Pairwise analysis of clinical concordance shows that Evalyn® and FLOQ® has an overall concordance of 98% (n=334), Evalyn® and the prototype 96 % (n= 527) and FLOQ® versus prototype was 98% (n=220). Effect of time from self-reported sampling date to analysis was assessed using HBB Ct values. All samples were received within 50 days after the woman's self-reported sampling date. Independent of device and time since sampling date, HBB Ct values remained stable for at least 30 days; intervals beyond 30 days contained too few datapoints to be conclusive.

Conclusions: Independent of device the analytical quality was uniform with respect to detection of HBB and HPV. No significant degradation of the diagnostic samples was observed on any device for at least 30 days after women's´ self-reported sampling date. These results emphasizes that these defined self-sample devices are analytically similar and therefore are interchangeable with respect to the analytical quality.

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#9309

Look twice before you leap? - Is HPV self-sampling a safe choice as last cervical screening sample before program exit?

13 - Self-sampling

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Background/Objectives: Pending an HPV negative screening test at age 60-64 years, the negative predictive value of HPV tests allows for safe discharge from the cervical cancer screening program for women; a so-called exit test. As part of the HPV self-sampling initiative in the Capital Region of Denmark, non-attenders in the screening age group of 60-64 years are offered an HPV self-sample as an alternative to the clinician collected sample. This to facilitate a last round of participation before screening program exit by age. The use of HPV self-samples as exit test is new but the safety is deemed high given the non-inferior ability of HPV self-samples to detect cervical intraepithelial neoplasia grade 2 or worse (≥CIN2) compared to clinician collected samples. Lacking local, national and international experiences with use of HPV self-samples for exit testing, the Capital Region of Denmark cervical cancer screening program decided to require women with an HPV negative self-sample to conduct an additional HPV self-sample after 12 months as a safety measure before exit from the program. Here, we evaluate whether two consecutive HPV negative self-samples are needed before a woman can safely exit the screening program.

Methods: Summary statistics of data retrieved from the Danish National Pathology Database (Patobank) for a cohort of women in the age 60-64 years in the year 2023, were used to describe the algorithm trajectory with a double self-sample in the exit phase. A total of 1363 women were identified as offered HPV self-sampling as a check-out test (Evalyn Brush, Rovers, Oss, Netherlands). Women were automatically mailed a 2nd HPV self-sampling kit 12 months after the first HPV negative self-sample. Upon reception in laboratory, self-samples were diluted in a 3 ml BD OnclarityTM HPV Self Collection Diluent Tube and tested using BD OnclarityTM HPV test (both BD Integrated Diagnostic Systems, Sparks, MD).

Results: Of the 1363 women offered an HPV self-sample as exit test, 884 (64.9%) returned a 2nd self-collected sample. One sample was found to be invalid. Of the 883 returned samples, 32 (3.6%) tested positive for HPV. Overall, 23 of these had undergone clinical follow-up with a clinician collected cervical sample at time of data retrieval. The clinician collected follow-up tests showed i) 20 women had no HPV upon sampling of the cervix, ii) one woman with HPV genotype 16 and normal cytology, iii) one woman with genotypes 16/52 and ASCUS, and lastly iv) one woman with genotype 18 and normal cytology. None of the three HPV positive women had a screening history of cells with suspected malignity. However, common to all three women was that they had missed one or more screening rounds prior to the exit phase.

Conclusions: Offering a double self-sample before exit from the cervical cancer screening program was initiated as a safety measure to secure against false negative self-collected samples. However, the initial statistics suggest that a single self-collected sample can act as an exit HPV test without loss of negative predictive power. This increases the cost-effectiveness of the exit screening strategy while at the same time, improving the path to cancer prevention by increasing participation at the last round before exit.

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#9485

Clinical validation of a three-marker methylation panel to detect CIN3+ in the Dutch population-based screening programme

13 - Self-sampling

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Background/Objectives: Self-sampling is a promising screening method for cervical cancer. However, cytology cannot be performed on self-sampling material after a high-risk human papilloma virus (hrHPV)-positive result. In our recent discovery study, we identified a three marker panel (LHX8, EPB41L3 and ANKRD18CP) with high sensitivity and specificity for CIN3+. Here, we performed the clinical validation of this three-marker panel on a hrHPV-positive self-samples obtained through the Dutch population-based screening programme (PBS).

Methods: LHX8, EPB41L3 and ANKRD18CP were analysed using quantitative methylation-specific PCR (QMSP) on DNA from a consecutive cohort of hrHPV-positive self-samples (n=2482: 408 women with CIN3 and cancer (CIN3+) and 2074 women with CIN2 or less (<CIN3)). Diagnostic performance was determined by area under the curve (AUC) of receiver operating characteristics (ROC) analysis. Scenario analysis was performed on a virtual population of 100,000 hrHPV-positive women who used the self-sampling device comparing our methylation triage test in versus cytology triage testing, considering that 10-20% will visit their general practitioner for cytology, regarding referral rate (for colposcopy), and number of detected CIN3 and cancer cases.

Results: The three marker panel showed an AUC of 0.82 with a 75% sensitivity and 78% specificity to detect CIN3+, and 96% (22/23) cancers were detected. Scenario analysis revealed that referral rates (29.4% vs 31.2%) and detection of CIN3 (72% vs 68-77%) were similar between methylation analysis and cytology, but interestingly more cancer cases (864 vs 770) were detected with our methylation panel.

Conclusions: DNA methylation analysis using the three-marker panel LHX8, EPB41L3 and ANKRD18CP shows good performance to detect CIN3+ and therefore is feasible to be implemented as triage test after a positive hrHPV-result on self-sampling material. The implementation of DNA methylation as molecular triage test on the same DNA used for hrHPV-testing, would not only make the GP visit unnecessary but also result in quicker decision-making regarding referrals and shorter uncertain waiting times.

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#9373

The current state of DNA methylation biomarkers in self-collected liquid biopsies for the early detection of cervical cancer: A literature review

13 - Self-sampling

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Background/Objectives: Cervical cancer (CC) is a preventable and treatable disease, yet it remains a significant cause of mortality, particularly in lower- and middle-income countries (LMICs). A primary factor contributing to high CC rates in LMICs is the limited uptake of screening due to cultural and systemic barriers. Recently, self-sampling has emerged as a promising strategy to increase screening accessibility and participation, particularly among underserved populations. Alongside self-sampling, DNA methylation has been proposed as a novel biomarker for triaging self-collected samples that test positive for high-risk human papillomavirus (HPV) types.

Methods: This study involved a literature review of research published from 2019 to 2024 that assessed the efficacy of DNA methylation markers for detecting cervical intraepithelial neoplasia (CIN) in self-collected cervicovaginal swabs or urine samples. We examined studies that focused on the performance of DNA methylation markers in detecting CIN, specifically in samples collected through self-sampling methods

Results: Our review highlighted promising results for the combined use of self-sampling and DNA methylation as a triage method. Findings from the selected studies suggest that DNA methylation markers, when used in conjunction with self-sampling, can perform comparably to traditional cytology in detecting CIN. Additionally, this approach has the potential to improve CC screening uptake and reduce loss to follow-up, particularly in LMICs where barriers to conventional screening are more prevalent.

Conclusions: The combined use of self-sampling and DNA methylation markers holds significant promise for enhancing CC screening and early detection, especially in LMICs. However, further research is necessary to identify the most effective DNA methylation tests. Future studies should aim to evaluate the utility of these biomarkers within large, diverse

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#9183

Stability of HPV after exposure to 3- and 5-day extreme temperature shipping conditions on novel self-collection device

13 - Self-sampling

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Background/Objectives: A vaginal self-collect device utilizing a novel sampling substrate (polyurethane (PU) foam) and collection device was developed by Teal Health ("Teal Wand') as an alternative to the current validated self-collection devices. This study assessed the analytical shipping stability of the Teal Wand under specified extreme shipping conditions.

Methods: The sampling component of the Teal Wand was inoculated with 2 and 10 times the limit of detection at the clinical threshold for HPV16 and HPV18 positive cultured cell lines with clinical vaginal matrix obtained from residual self-collect samples in mSwab media and eluted into a Hologic Thinprep vial (20 mL PreservCyt). HPV detection and cycle threshold values (ct) on the Roche cobas HPV test were assessed following cycled simulated summer (22 to 40°C) and simulated winter (-10 to +18°C) 3- and 5-day shipping cycles, representing an extreme case of standard shipping. Detection of HPV and ct differences between conditioned and unconditioned controls were assessed.

Results: All samples generated expected results (100% agreement) for HPV16 HPV18, and cellularity (beta-globin) controls under winter and summer 3-day and 5-day cycled extreme temperature profiles. HPV-negative clinical vaginal matrix (CVM) was also conditioned on the Teal Sponge as a control. The differences in ct values from non-conditioned controls (control) were all inf1 ct, which met the acceptance criteria of a inf3ct difference from baseline. Using the students t-test, none of the samples exposed to shipping conditions showed statistically significant increases (indicating a drop in sensitivity) in HPV ct values.

Conclusions: The Teal Wand, which utilizes a novel PU foam substrate, shows robust stability under simulated summer and winter shipping conditions for retrieval of HPV without collection media ("dry"). The Teal Wand offers a novel approach to self-collection devices and is suitable for dry collection and transport under shipping conditions commonly encountered in the postal service - a critical component to safe, effective at-home sample collection and processing.

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#9042

Differential release of female genital secretions components and HPV DNA by veil, swabs, non-woven tissue and vaginal tampon

13 - Self-sampling

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Background/Objectives: The Vitroveil® (VITROSA, Granada, Spain) self-sampling device enables in Spanish women to obtain higher prevalence of molecular detection of any high risk (HR)-HPV than clinician collected samples by cervical scraping (30.6% versus 24.3%; P<0.0001) (1). Using the same veil medical device, Nodjikouambaye et al. reported in African women that the rates of any HPV DNA and HR-HPV DNA positivity were significantly higher (1.67- and 1.57- fold, respectively; P<0.0001) when using veil-based collected genital secretions than clinician-collected cervical secretions by swab (2).

Methods: The in vitro capabilities of the veil (Vaginal Veil Collector V-Veil Up UP2TM device, V-Veil-Up Production SRL, Pitesti, Romania) to uptake and further release the various components (e.g. total proteins and nucleic acids) of female genital secretions, were evaluated by comparison to those of flocked swab (FLOQSwabs®, Copan, USA), commercially available absorbent non-woven tissue, non-absorbent plastic film, and commercial vaginal tampon. An artificial medium was created with PBS completed by serum and nucleic acids extracts, including episomal HPV-16 DNA, in order to reach the composition of normal female genital secretions. Ten serial two-fold dilutions of the pool in PBS were further carried out. For the collection step, 400 µl of each dilution were applied for exactly 5 min on the external surfaces of the veil, flocked swab, vaginal tampon, non-woven tissue and plastic film, as well as within the pocket of the veil, and then kept frozen immediately at -20°C. For the elution step, the frozen impregnated devices and controls were eluted in 3 ml of PBS at room temperature, then vortexed during 2 min, and aliquoted in 1.5 ml tube. The release of total proteins and that of total nucleic acids were finally measured by spectrophotometry. HPV-16 DNA was quantified using Multiplex Real Time Human Papillomavirus Genotyping Real Time PCR Kit (Bioperfectus Technologies, Taizhou, China).

Results: The release of genital components from the pocket of the veil, the external surface of the veil, flocked swab, vaginal tampon, non-woven tissue and plastic film, are shown in figure 1. The values obtained with the non-absorbent plastic film was considered as background noise. The mean quantities of proteins release for the veil were 1,21-fold, 1,82-fold, 2,88-fold and 12,90-fold higher, respectively, than for the swab, the absorbent non-woven tissue, the vaginal tampon and the plastic film. The quantity of nucleic acids release and HPV-16 DNA in mean for the veil was 1,29-fold, 1,91-fold, 11,63-fold and 30,23-fold higher, respectively, than for the swab, the absorbent non-woven tissue, the vaginal tampon and the plastic film. The release of total proteins and that of total nucleic acids were maximal for the veil at physiological concentrations.

Conclusions: The veil retains and releases the different biochemical components as well as HPV-16 DNA of female genital secretions better than do swab and absorbent non-woven tissue, and much better than vaginal tampon. It is likely that the special tissue of the veil allows high saturation level, with ad hoc release of genital components, including microbial genomes. In contrast, the vaginal tampon behaves like a sponge and retained the various components of female genital secretions. We do believe that these in vitro findings could contribute to explain why the veil allows to obtain higher rates of oncogenic HR-HPV molecular detection than permitted by swab or tampon.

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#9256

At-home HPV self-collect device for cervical screening

13 - Self-sampling

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Background/Objectives: Under-screening for cervical cancer is a worldwide challenge with persistent universal barriers which can be overcome with safe, reliable at-home collection. The self-collect (SC) device is designed for at-home use and features a novel sponge collection substrate and a profile similar to an applicator tampon. The collection device is designed for dry collection and storage, with no liquid media, to be stored and shipped for up to 7 days. The SC device underwent method comparison study, safety, ease-of-use, and patient preferences.

Methods: 609 participants between ages 25-65 years with a cervix were recruited from 16 US clinical sites, representing diverse US demographics across race, income, education, and geographies. 599 had paired SC and clinician-collected (CC) cervical/vaginal samples for testing on an HPV test FDA-approved for primary HPV screening (Roche cobas). The dry sample was eluted into preservative at the lab and tested per protocol, requiring minimal pre-analytical changes to the HPV test procedures. Usability and preference surveys were completed at the initial visit and participants completed safety follow-up for 2 weeks.

Results: In a representative US population (age, race/ethnicity, education, income), the positive percent agreement (PPA) for detection of HPV was 95%for SC samples compared to the matched clinician-collected sample from the same participant. The clinical sensitivity for detection of high-grade dysplasia (n=48) was 96%, equivalent to the clinician collected sample (RelSe of 1.00). Usability was rated at 93% Easy/Very Easy to use with only 0.5% rating it Difficult. 94% of participants reported they would choose SC if they knew the results were accurate. These results held across demographic groups representative of the US population. Category SELF-CERV study 2022 US Census Data ATHENA trial White 58.5% 75.5% 83.4% Black or African American 25.5% 13.6% 13.7% Asian 3.9% 6.3% 1.6% American Indian/Alaska Native 0.7% 1.3% 0.6% Native Hawaiian or Pacific Islander 0.5% 0.3% 0.2% Hispanic or Latino 19.5% 19.1% 18.0%

Conclusions: The SC device shows equivalent clinical sensitivity and PPA for detection of hrHPV to clinician collect in a dry sample stored up to 7 days. The design shows high usability across diverse demographics. The SC device is a clinically validated, preferred alternative for at-home SC currently undergoing expedited FDA review after receiving a Breakthrough device designation. It is expected to be the first FDA-approved at-home SC device for cervical screening.

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#9506

Easy, simple and safe: large-scale preference study on Danish women's preferences in HPV self-sampling devices

13 - Self-sampling

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Background/Objectives: HPV self-sampling is increasingly deployed as a supplement or alternative to clinician collected samples for cervical cancer screening. However, women's opinion on different self-sampling devices is largely undocumented. This large-scale preference study, including regular screening attenders and screening non-attenders, evaluate women's preference for self-sampling and perceptions on three defined HPV self-sampling devices: the Evalyn brush (Rovers, the Netherlands), the FLOQSwab (Copan, Italy) and a custom designed Danish self-sampling swab. We asked women to answer a questionnaire on perceptions of safety, ease-of-use, discomfort of HPV self-sampling with the different devices.

Methods: The study included respondents from three HPV self-sampling activities in the Capital Region of Denmark: 1) women receiving an up-front offer of HPV self-sampling (n=1048) 2) women receiving a 2nd reminder letter to participate in the screening program after an unanswered invitation (n=2010) and 3) women who have been unscreened for more than 4 years (23-49 years old) or 6 years (50-64 years old) (n=2225). Inclusion period conducted April 2024 to November 2024. Women received a kit with two self-sampling devices in the following preference group combinations: a) Evalyn and FLOQSwab, b) Evalyn and the Danish designed prototype or c) FLOQSwab and the Danish designed prototype. Kits were assigned randomly. The women were asked to sample with both devices and fill in a questionnaire of 8 questions rating the devices and experience. Participation was free-of-change and undertaken as a quality development study in the Capital Region of Denmark. Informed consent was obtained by electronic acceptance of participation.

Results: In total 5283 women were presented with the invitation to participate in the study while registering for a regular HPV self-sampling kit. Of all invited, 40% (n=2105) accepted participation in the study. By sub-group, 23.9% (n=503) came from the regular screening invitation group, 39.8% (n=838) from 2nd reminder group and 36.3% (n=764) from the screening non-attenders group. Of these, 53.9% (n=1134) returned a questionnaire. Aggregated data shows that Evalyn was evaluated more positively than FLOQSwab and new prototype regarding the ease-of-use (p=<0.001;p=0.017) and women's perception of certainty that the tests were performed correctly (p=<0.001;p=<0.001). The prototype was evaluated more positively than FLOQSwab regarding the ease-of-use (p=<0.001), less discomfort (p=0.026) and women's perception of certainty that the tests were performed correctly (p=<0.001). Overall, 87% (n=969) expressed a preference for self-sampling at their next screening over clinician collected sampling, with 93.5% (n=428) preferring self-sampling amongst regular screened, 83% (n=239) amongst women receiving 2nd reminder, and 83% (n=302) amongst screening non-attenders.

Conclusions: Women reported the self-sampling devices easy to use and the self-sampling was, in most cases, reported to cause no or slight discomfort. Most women did not worry about performing the self-sampling themselves nor felt uncertainty about whether the test was done correctly. Overall, the women rated the Evalyn more positively when given the option and evaluated the prototype more positively than the FLOQSwab. The study is intended to guide and inform future choice of HPV self-sampling brush to be used in cervical screening programs.

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#9172

Evaluation of a population based mailed and opportunistic in-clinic HPV-self sampling in a large US health system

13 - Self-sampling

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Background/Objectives: Despite strong evidence that direct mailing of HPV-kits increases cervical cancer screening rates, HPV self-sampling mail programs have been slow to be adopted in the United States.1,2 Furthermore, little is known about using HPV self-sample kits in clinic in addition to direct mailing. We performed a mixed methods evaluation of a combined population-based mailed and opportunistic in-clinic HPV self-sampling cervical cancer screening program implemented in a large health care system in Washington state.

Methods: The HPV self-sampling program began in July of 2023. It uses electronic health records to identify individuals aged 30-64 with a cervix, at average risk, and due for cervical cancer screening and directly mails HPV self-sampling kits (Cobas) or opportunistically offers kits at clinic visits or mailed at telehealth visits. Positive tests are managed using texts, secure email, and mail, with nurse telephone outreach for HPV 16/18 if colposcopy is not completed within 3 months. The learning health system team and organization leaders worked together to evaluate the program. Quantitative assessments included HPV self-sampling completion rates from September 1, 2023 to August 31, 2024 comparing population-based direct mail to opportunistic clinic-ordered testing, and positive testing and follow-up rates. Qualitative assessments included interviews with 14 clinic medical directors. The interview guide included open-ended questions on program acceptability and usability, and implementation facilitators and barriers. Site visits were conducted at three primary care clinics, one obstetrics/gynecology practice, and the laboratory. Qualitative data were analyzed using a Rapid Group Analysis Process.3

Results: During the evaluation period, 12628 HPV self-samples were directly mailed to patients and 3603 were ordered in clinic with 34.9% (4412) and 82.2% (2960) completed respectively. Positive HPV results were 8.0% by mail and 10.3% by clinic, with 1.6% HPV 16/18 and 7.5% HPV other overall. Follow-up completion rates were 62.7% colposcopy for 16/18 and 66.8%, for in-clinic pap for other. Interviews and site visits revealed enthusiasm for the program, noting time saving, high patient acceptance, and increased access for many patients who might not otherwise screen or those with male clinicians who preferred pelvic exams to be performed by female clinicians. Most clinicians were unaware of or underestimated HPV self-sampling accuracy. Clinics varied in their workflow processes and use of opportunistic screening. Laboratory concerns included receiving home specimens without a date, no recent orders, and moldy specimens, which prevented them from processing the test and wanted patient materials with clear instructions on adding collection date. The single obstetrics/gynecology practice perceived no increase in work due to added colposcopies, but one nurse midwife was concerned that high-risk individuals might be receiving average-risk HPV self-sampling kits.

Conclusions: In our context where both options were available, clinic ordered HPV self-sampling had higher completion rates, while direct mail resulted in more people being screened over one year. Opportunistic screening at a visit has the advantage of trusted clinicians' recommendation and patient questions being answered. Population based direct-mail had the potential to reach more people, including those without clinic visits. Both programs are complementary to each other.

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#9530

Barriers to cervical screening and the potential for self-sampling methods to improve screening uptake in people from ethnically diverse backgrounds living in the UK: the Alternative CErvical Screening (ACES) Diversity study

13 - Self-sampling

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Background/Objectives: People from ethnically diverse backgrounds are less likely to attend cervical screening in the UK. Self-sampling may overcome some of the barriers experienced. This study aimed to understand these barriers and explore the potential for vaginal and urine self-sampling to improve cervical screening uptake among people from ethnically diverse backgrounds in the UK.

Methods: A cross-sectional survey was co-created with community groups in Greater Manchester, UK and distributed through community partners and social media using online and paper surveys, targeted to maximise recruitment from ethnically diverse groups. The survey was available in 10 languages. People over 18 years and invited for cervical screening were eligible. Data were collated via the Qualtrics platform and analysed using descriptive statistics.

Results: A total of 629 completed surveys were analysed, 450 (71.5%) participants from African (n=91, 20%), Chinese (n=69, 15.2%), Indian (n=69 ,15.2%), Pakistani (n=49, 10.8%), Mixed (n=52, 11.6%), Caribbean (n=21, 4.6%), Eastern European (n=19, 4.2%), Arabic (n=11, 2.4%), or from other ethnically diverse backgrounds (n=69, 15.3%) and 173 were White British. Emotional barriers, including worry about discomfort/pain (n=165, 36.7%) and lack of female practitioners (n=133, 29.6%) were the primary barriers to routine cervical screening reported by participants from ethnically diverse backgrounds. By contrast, practical barriers, including difficulty finding a good time for screening, were the most frequent barriers reported by White British participants (n=75, 43.3%). Participants invited to screening who reported their preference for future screening, 157/343 (45.8%) preferred self-sampling, especially poor attenders, across all ethnic groups. More ethnically diverse participants felt confident about taking a urine self-sample than a vaginal self-sample for future cervical screening (375/450; 82.2% vs 271/450; 59.8%).

Conclusions: People from ethnically diverse backgrounds in the UK face specific barriers to cervical screening. Self-sampling may be an acceptable alternative to these populations, with urine self-sampling having the broadest appeal.

FC13 - Methylation I

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#9369

"DNA Methylation Markers for Triage in High-Risk HPV Screening: Identifying and Addressing Research Gaps"

17 - Methylation

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Background/Objectives: High-risk human papillomavirus (hrHPV) screening is critical for early detection of cervical cancer, but it often leads to over-referral for invasive follow-up procedures. DNA methylation biomarkers have emerged as potential tools to refine triage and improve risk stratification in hrHPV-positive women, reducing unnecessary interventions. However, key research gaps remain, limiting the implementation of DNA methylation in routine clinical settings. This review outlines the current state of DNA methylation as a triage tool for hrHPV-positive women, emphasizing unmet needs and future research directions.

Methods: Analysis if the following missing Gaps and Key Areas for Further Research: Standardization of Methylation Marker Panels: Current studies use different panels of methylation markers, making it difficult to compare outcomes directly. Developing standardized panels with well-defined cut-off points for hrHPV-positive women is crucial for widespread clinical application. Longitudinal Data on Disease Progression: Most studies provide cross-sectional data, but prospective data on how methylation markers correlate with the progression of cervical dysplasia over time would strengthen their use in risk stratification. Comparison with Existing Triage Methods: It's essential to evaluate how DNA methylation biomarkers perform relative to other triage methods, such as cytology and HPV genotyping. This comparison can clarify whether methylation markers add significant value to current screening algorithms. Optimizing Sample Collection and Processing Techniques: Variations in sample collection methods (e.g., self-collected vs. clinician-collected samples) and laboratory processing can impact methylation results. Standardized protocols are needed to reduce variability and increase reliability. Understanding the Biological Role of Methylation Changes: Research should continue exploring the underlying biology of DNA methylation changes in hrHPV infections and their role in carcinogenesis. This could lead to better-targeted methylation markers specific to high-risk disease pathways.

Results: DNA methylation markers demonstrated high specificity (up to 90%) for CIN2+ lesions, outperforming traditional cytology in triaging hrHPV-positive women. Studies using MSP and pyrosequencing showed consistent methylation patterns in high-grade lesions, while high-throughput bisulfite sequencing provided a scalable approach suitable for large populations. Methylation testing was effectively performed on residual samples, simplifying integration into clinical workflows without additional patient visits or procedures.

Conclusions: The implementation of DNA methylation as a triage tool in hrHPV-positive screening protocols has the potential to reduce unnecessary colposcopies and streamline cervical cancer prevention. However, barriers such as cost, standardization of testing protocols, and the need for population-specific validation studies remain. Future work should focus on large-scale validation, cost-effectiveness analysis, and development of automated workflows to facilitate broader clinical adoption. Integrating methylation biomarkers into existing HPV testing algorithms could transform cervical cancer screening, improving outcomes and resource utilization in healthcare settings.

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#9355

Type-specific and overlapping DNA methylation markers for female gynaecological cancers and HPV-associated cancers

17 - Methylation

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Background/Objectives: DNA methylation has gained great interest as biomarker for the detection and follow-up of oncological disease. It is a known universal and early event in carcinogenesis. For cervical cancer specifically, it is of interest due to its applicability to self-samples, offering a fully molecular approach for screening. Yet, it is important to ensure that the methylation markers are cancer-type specific and thus lead to correct clinical follow-up. Therefore, we have analysed the methylation patterns of the most common female gynaecological cancers and compared the signatures of two HPV-associated cancers to identify type-specific and overlapping markers.

Methods: The Gene Expression Omnibus (GEO) was searched for public DNA methylation data from Illumina methylation arrays (450K and EPIC) for cervical cancer (CC), ovarian cancer (OC), endometrial cancer (EC) and anal cancer (AC). To ensure compatibility of the data, only datasets containing raw IDATs were included. The data of 17 datasets was combined (GSE134772, GSE136791, GSE143752, GSE146552, GSE169622, GSE178610, GSE186835, GSE186858, GSE211686, GSE226823, GSE65820, GSE67116, GSE71523, GSE81224, GSE90060, GSE99511 and GSE68339). In total we included data from 292 CC samples, 98 normal cervix, 182 EC, 34 normal endometrium, 407 OC, 15 normal ovarium, 121 AC and 9 normal anus. We compared cancer vs. normal DNA methylation patterns for each cancer type to identify significantly ($p<0.05$) differentially methylated probes (DMPs) and perform gene set enrichment analysis (GSEA). This was done using an in-house developed bio-informatic pipeline starting from the ChAMP package.

Results: A total of 292,351, 233,587, 185,904 and 29,567 DMPs were detected for CC, EC, OC and AC resp. Of those, 12,766 were common between the four cancer types and 52,933 were specific for the female gynaecological cancers (CC, OC and EC). In addition, 5,126 DMPs are shared only between CC and AC, suggesting the possibility of an HPV-associated signature. CC had the most type-specific DMPs (133,813), followed by EC (69,037), OC (44,159) and AC (1,372). Next, we stratified on hyper- or hypomethylation status and filtered on delta-beta of resp. inf0.16 and sup-0.16. This resulted in resp. 3,836 and 1,251 DMPs found in all types. Type-specific hypermethylated DMPs were 15,602 for CC, 9,533 for OC, 9,670 for EC, and 370 for AC. Moreover, type-specific hypomethylated DMPs were 8,446 for CC, 20,003 for OC, 8,562 for EC and 693 for AC. The overlapping signature for the female gynaecological cancers included 2,420 hypermethylated DMPs and 5,111 hypomethylated DMPs. Furthermore, the HPV-associated cancers shared 5,260 hypermethylated and 595 hypomethylated DMPs. GSEA resulted in one significantly enriched overlapping KEGG pathway and one overlapping Reactome pathway for all the types, resp. "Olfactory transduction' and "Expression and translocation of olfactory receptors'. CC and AC shared all their KEGG and Reactome pathways, two and seven resp. Lastly, we identified two overlapping Gene Ontology (GO) categories between all types, 70 shared categories between CC and AC, and type-specific GO categories.

Conclusions: In conclusion, we identified type-specific DMPs for CC, OC, EC and AC. We also found overlapping patterns for female gynaecological cancers and detected common markers between HPV-associated CC and AC. These could serve as starting point for clinically relevant biomarkers, ensuring correct clinical management and allowing appropriate treatment approaches.

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#9429

Methylation of promoters of the genes ASTN1, DLX1, ITGA4, RXFP3, SOX17 and ZNF671 in patients conized by CIN 2/3 and its relationship with the histological results of the conization specimen

17 - Methylation

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Background/Objectives: The detection of a hypermethylation pattern in the promoters of ASTN1, DLX1, ITGA4, RXFP3, SOX17 and ZNF671 through a specific PCR represents a promising diagnostic tool in patients with cervical lesions caused by HPV. We have studied in a group of patients older than 25 years with HSIL/CIN2+ cervical lesions who are going to undergo cervical conization the relationship between the detection of the hypermethylation pattern and the anatomopathological results of the specimen.

Methods: A prospective, observational, non-randomised, multicentre, study has been carried out involving 136 participants who attended the cervical pathology and colposcopy units of four hospitals in Madrid (Spain). The recruitment period was from July 2020 to January 2022. The sample for methylation test was taken by cervical brushing prior to conisation, and preserved for study in Thinprep medium. The results are collected in an encrypted and "online' database, with restricted access to collaborating researchers. The pathologists and collaborating researchers were unaware of the result of the methylation test. Statistical analysis was performed with IBM SPSS Statistics v.29.0.

Results: In two patients the result was invalid and in one case the sample was not received, so we have considered 133 for analysis. Mean age: 38 years (no statistically significant differences between groups -positive and negative for methylation-). We didn´t find differences between groups: HPV vaccination was 33% and smoking rate 39% (no statistically significant difference between groups). The results of the histological study of the conisation specimen were as follows: Methylation + group: 0% normal, 3% CIN I 92.4% CIN 2/3, 4.6% cancer. Methylation negative group: 18% normal, 12% CIN I, 70% CIN 2/3, 0% cancer. These differences were statistically significant. Regarding the the margins of the conization piece: Methylation +: 68% free margins, 32% affected margins. Methylation negative: 91% free margins, 9% affected margins. These differences were statistically significant. Methylation was present in 78% of patients with cones with affected borders. If methylation is positive, margin involvement is three times higher (9% vs. 32%). The involvement of resection margins has been described as a risk factor for lesional persistence. In fact, in the follow-up up to 2 years after conisation 8 patients underwent reconisation, and all these patients initially were methylation-positive. While 0% of the methylation-negative patients required a reconisation, 12.5% of the methylation-positive group required a reconisation. These differences were statistically significant.

Conclusions: Prior detection of a hypermethylation pattern in patients conised for CIN2+ is statistically significantly associated with a higher rate of detection of CIN2+ and cancer in the conisation specimen and a higher likelihood of involvement of the specimen margins, which is a risk factor for persistence of cervical lesion and HPV infection after conisation. Detection of a pattern of hypermethylation in patients with CIN2+ cervical lesions to be treated by cervical conisation could help identify the group of patients at highest risk of needing reconisation in the first 2 years of follow-up.

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#9189

HPV genes methylation as a possible prognostic biomarker in women with cytological diagnosis of low-grade lesion

17 - Methylation

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Background/Objectives: Cervical cancer ranks fourth among the most common cancers in women and is the leading cause of death from gynaecological malignancies worldwide. The main risk factor for cervical cancer is human papilloma virus (HPV) infection. The lesions presented by HPV-positive women often tend to regress spontaneously and only a small percentage of them have a persistent infection leading to a high-grade lesion; however, most of them undergo unnecessary, invasive and expensive treatment. There is a need to investigate new triage biomarkers that can provide predictive information on the evolution of the lesion from precancerous to invasive cancer before the patient undergoes invasive procedures. In the present study, we evaluated viral genome methylation in the L1 I, L1 II and L2 regions in women with low-grade squamous intraepithelial lesion (LSIL) as a marker of progression and cancer.

Methods: Methylation levels in the three regions were measured by pyrosequencing in DNA obtained from cervical cell samples of 116 women recruited as part of a cervical cancer screening programme conducted from March 2010 to January 2014 in Turin. Of these, 60 women had a single HPV infection and 56 had multiple HPV infections. The HPV types included in the analysis were those belonging to the IARC group I, also called high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59).

Results: The results show an association between increased viral DNA methylation and a more severe lesion (CIN2+). The association was observed in the L2 region in a first analysis including all HPV types [OR 3.13 (95%CI 1.28-7.65), p-value 0.0122]. The second analysis, limited to HPV 16, 31, 51 and 58, showed an association with the L2 region [OR 3.12 (95%CI 1.17-8.35), p-value 0.0236] and L1 I [OR 8.14 (95%CI 2.57-25.71), p-value 0.0004].

Conclusions: These results suggest that methylation of HPV L1 I and L2 genes could act as an epigenetic marker to discriminate whether a woman is at risk of incurring high-grade lesions (CIN2+). Therefore, epigenetic modifications have the potential to be used as a powerful new biomarker to assess the prognosis and treatment of HPV-infected women.

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#9190

DNA methylation and genetic variants as features in a machine learning methodology for CIN3 progression in hr-HPV positive women

17 - Methylation

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Background/Objectives: High risk human papillomavirus (hr-HPV) is the main cause for cervical cancer with more than 95% of cases being related to an infection [1]. Despite the development of an HPV vaccine, cervical cancer remains the 4th most common cancer among women globally, with its prevalence and fatality rate especially elevated in low- and middle-income countries (LMICs) [2]. Current prevention strategy in the UK is based on regular screening tests for hr-HPV infection and further cytology triages for the hr-HPV positive cases. However, cytology lacks the accuracy to be a definitive test for the detection of cervical intraepithelial neoplasias (CIN) leading to a more invasive histological biopsy for definitive diagnosis. DNA methylation [3] and genomic variation profiling [4] have been found to identify prospective biomarkers that can help in the early detection of CIN3 progression. In addition, multi-omic integration in machine learning methodologies has shown potential to outperform single omic approaches for classification purposes in cancer studies [5].

Methods: DNA was isolated from cervical tissue samples of hr-HPV infected women with no CIN enrolled in the ARTISTIC cohort [6] and was sent for reduced representation bisulfite sequencing (RRBS) and whole exome sequencing (WES). Each participant was monitored for a period of up to 6 years, during which histology testing was conducted to determine the incidence of CIN3.

Results: A machine learning CIN3 classifier was previously developed based solely on DNA methylation. This classifier was constructed using 31 differential methylated positions (DMPs) and exhibited 93.3% sensitivity and 94.4% specificity. The WES results will provide new features to the model either as individual additions or by means of a polygenic risk score from the most important variants.

Conclusions: The addition of somatic variants to the classifier will potentially strengthen its accuracy and offer important insights on the genetic mechanism behind the disease progression. Due to the longitudinal nature of our study, this classifier can prove to be an indispensable tool for the very early diagnosis of CIN3 even when no abnormal cells are present yet in the cervix. This is especially crucial in LMICs, where inadequate access to HPV vaccines and healthcare services persists, as it can open avenues for new targeted prevention and treatment strategies.

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#9193

Clinical utility of Digital PCR (dPCR) platform for DNA methylation detection (S5 classifier) to improve triage of hrHPV positive women attending cervical cancer screening programme.

17 - Methylation

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Background/Objectives: The implementation of HPV testing as a primary screen has become the norm worldwide and started in 2019 in UK. Even thou HPV testing is very sensitive but the lack of specificity suggests that other appropriate triage strategy for hrHPV positive women will be essential for future cervical screening community.In UK, the evalution of HPV implementation in UK result in a 4.9% increase of colposcopy which could further increase the tension in NHS system. Furthermore, the decrease in cervical cancer screening programme attendance is becoming concerning and new methods such as self-sampling are very attractive but with a downside of the inability to perform cytology test on this samples.Hence the need for a new molecular triage method allowing to use self-samples with a good accuracy could help the reduction of colposcopy referral. We propose to triage hrHPV+ women who self-collected their sample using DNA methylation markers. S5 DNA methylation classifier combines the host gene EPB41L3 with markers in the late regions of HPV16, 18, 31 and 33 genomes. In a screening population, the S5 classifier gave a triage sensitivity of 84% (69-95%), specificity of 65% (60-70%) and AUC of 0.78 on HPV-positive women. This was significantly better than cytology or HPV16/18 genotyping triage. Currently, the gold standard for measuring methylation levels has been utilising pyrosequencing technique. However, due to its technical limitation pyrosequencing such as long processing time, and lower sensitivity therefore is not amenable to clinical setting and hence the need for another platform. Digital PCR is a third-generation PCR which utilized the partition technique that allows for precise detection and absolute quantification of both the nucleic acid target sequences.

Methods: By using dPCR for measuring the methylation level of the S5 classifier in a cervical cancer referral population (n=207) and compare to methylation level of the S5 classfier obtain from the current gold standard pyrosequencing.

Results: High concordance in the methylation level between dPCR and pyrosequencer for the S5 classifier with (Pearson R2=0.824) for EPB41L3 and (Pearson R2=0.7-0.9) for the hr-HPV type 16, 18, 31, 33. Apart from that high level of concordance was observed for the final S5 score with (Pearson R2=0.923). Next, there was no significant difference in AUC of digtalPCR and pyrosequencing for Cancer (0.983 vs 0.984), CIN3+ (0.812 vs 0.816), CIN2+ (0.772 vs 0.78). FInally, my study also showed that different thresholds for S5 score is needed to be set for the digital PCR for achieving the same specificity and sensitivity in pyrosequencing.

Conclusions: Taken together the results and advantages of dPCR such as increased sensitivity, cost-effectiveness, and easy workflow, suggest that the dPCR would have a superior clinical utility, especially in the context of cervical cancer screening.

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#9157

Improving risk stratification in cervical cancer screening using DNA Methylation: evidence from a 12-year matched case-control study

17 - Methylation

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Background/Objectives: HPV-based screening is highly sensitive for detecting high-risk (hr)HPV infections, but it lacks specificity for serious high-grade cervical precancer or cancer. As a result, there is a need for a triage method that can accurately stratify the risk of present and future cervical disease among HPV-positive women. One promising approach is the use of DNA methylation markers. This is based on the evidence that DNA methylation of host cell genes correlates with increased severity of cervical lesions. In this retrospective cohort study, we mimic a real-world setting by utilising residual cervical screening biobank samples with long follow-up time and known outcome of cervical disease, to evaluate the performance of DNA methylation analysis as a triage method for HPV positive. We also compare the performance of DNA methylation with hrHPV genotyping and cytology, in a screening setting.

Methods: Residual liquid-based cytology (LBC) cervical cancer screening samples were collected in Norway between 2007 and 2013 and HPV prevalence was determined by the Luminex method (Dillner et al., 2018). For this study, only samples positive for at least one of the 14 hrHPV types (16,18,31,33,35,39,45,51,52,56,58,59,66,68) were included. The excess LBC samples which have been processed and stored in our biobank were analysed by GynTect® DNA methylation assay (Oncgnostics, Jena Germany). The outcome of cervical disease was known through linkage with health registries, and samples were categorised based on the worst diagnosis recorded during the follow-up time (up to 12 years). HPV-positive participants who only had normal cytology/histology result recorded in the cervical cancer screening programme were compared to HPV-positive participants who developed cervical intraepithelial neoplasia (CIN) grade 2 or worse (CIN2+) either when the LBC sample was donated to study, or during the follow-up time. To ensure that the results are comparable, participants that developed CIN2+ lesions were matched on age and HPV type to participants that did not develop CIN2+ lesion. For the CIN2+ samples, concordance between HPV types found in the LBC screening sample and in the cervical lesion developed during follow-up time was examined and only samples with at least one concordant HPV type were included. Cumulative incidence rates of CIN2+ were analyzed with Kaplan-Meier curves for methylation-negative and positive groups, different cytology groups (normal, ASC-US/LSIL, ASC-H/HSIL), and hrHPV, and these groups were compared.

Results: We selected 186 participants with a normal cytology/histology and 187 participants that progressed to CIN2+. In total, 99.7% of samples provided a valid GynTect DNA methylation result, and of these, 57 samples returned a methylation positive result. The percentage of methylation positive samples increased with lesion grade, up to 100% for cancer (n=5). DNA methylation was found to be more informative in predicting CIN2+ than hrHPV genotyping and was comparable to cytology. However, for the five cancer cases, DNA methylation was able to detect all cases (two of which were diagnosed up to 8 years after the LBC sample was donated). In comparison, the cytology of the same LBC samples returned either a normal or an unsatisfactory diagnosis.

Conclusions: These results indicate that the GynTect® DNA methylation assay can improve specificity for detection of CIN2+ in HPV-based screening, which can contribute to reduced overdiagnosis and overtreatment.

References: Dillner J, et al. Vaccine 2018;36(26)

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#8870

Validation of a methylation index in an independent cohort, using an Epigenome-Wide Association Study (EWAS)

17 - Methylation

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Background/Objectives: Current cervical screening practices remain limited, as most still rely on cytology to triage high-risk Human papillomavirus (HPV) positive patients for colposcopy. DNA methylation markers and signatures have shown potential for diagnosis of Cervical Intraepithelial Neoplasia (CIN) grade 3 or worse, including as triage tests. WID-CIN is a methylation test comprising 5000 Cytosine-phosphate-guanine sites. We aimed to assess and validate the WID-CIN index in an epigenome-wide association study (EWAS) in an independent cohort.

Methods: 247 women were recruited between 2014-2020 (N=119 benign, N=74 CIN3/CGIN (cervical glandular intraepithelial neoplasia) and N=54 cancer). DNA was extracted from Liquid Based Cytology samples, and subjected to EPIC Illumina 850k array after bisulfite conversion. The WID-CIN index was applied using the methylation data for our cohort and applied to case-control status, and correlated with clinical variables.

Results: All 247 samples met quality control thresholds. The WID-CIN index in our cohort generated an Area Under the Curve (AUC) of 0.92 in all samples, and AUC of 0.89 when hrHPV negative samples were excluded. The WID-CIN index was independent of age, hormonal contraception status, BMI, comorbidities, and smoking status.

Conclusions: Methylation markers, panels and signatures offer promise for use in cervical screening algorithms, including as triage tests. We have validated a methylation signature index that offers a high accuracy for detection of CIN3 or worse in our independent cohort.

References: Barrett, J.E., Sundström, K., Jones, A. et al. The WID-CIN test identifies women with, and at risk of, cervical intraepithelial neoplasia grade 3 and invasive cervical cancer. Genome Med 14, 116 (2022). https://doi.org/10.1186/s13073-022-01116-9

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#9236

Non-invasive Diagnosis of Vulvar Dysplasia using Methylation Markers

17 - Methylation

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Background/Objectives: Diagnostic screenings for vulvar intraepithelial neoplasia (VIN) are limited, and it is difficult to identify disease prognosis. A panel of six methylation markers showed promising results for identification of cervical intraepithelial neoplasia with a 100% positivity of cervical carcinoma. The panel measures ASTN1, DLX1, ITGA4, RXFP3, SOX17, ZNF671 and the two positive controls ACHE, and IDS-M. Due to the similarities in the carcinogenesis of the cervix and vulva, this study aimed to apply the panel to vulvar FFPE tissue and to explore the potential for non-invasive vulvar dysplasia diagnostics using vulvar smears.

Methods: In total, 121 vulvar FFPE samples and 238 fresh vulvar cell smears with different VIN grades, HPV status, and with or without Lichen sclerosus/ruber were tested with the GynTect® panel. Additionally, we included dysplasia-free vulvar cell smears from patients with high-grade cervical dysplasia and measured the expression of DNA methyltransferases in the FFPE samples.

Results: The markers demonstrated high specificity in vulvar smears, with sole 5.41% of dysplasia-free smears testing positive. Yet, 75.00% of vulvar carcinoma smears appear positive in the methylation panel, similar to VIN III smears with 77.78%. In FFPE samples, dysplasia-free samples from the tumor microenvironment of high-grade vulvar neoplasia showed 37.50% positivity. The positivity rates for VIN I, VIN II, VIN III, and carcinoma samples were 84.62%, 64.71%, 79.41%, and 87.80%, respectively. DNMT3a expression was the highest in VIN I samples, while DNMT1 was only expressed in VIN III and carcinoma samples. Lichen sclerosis and ruber showed a high false positive rate of 45.45% for dysplasia-free and 54.54% for smears with dVIN. High-grade cervical dysplasia seemed to influence the results of the vulvar smears. Although the vulvar smears were dysplasia-free, they showed an increased positivity in the methylation kit of 26.19 %. In contrast, the HPV status had no impact on the panels positivity.

Conclusions: The diagnostic panel of six methylation markers is suitable for vulvar neoplasia samples and shows a high sensitivity. However, for comparable specificity, the thresholds and scores of the panel should be adapted. The score for cervical samples is highly dependent on the positivity of the ZNF671 gene, while in vulvar samples, it is not as convincing as other markers. Patients with lichenoid diseases show a high rate of positivity in the methylation panel, independent of the dysplasia status. Therefore, the panel should not be used for lichen patients. In addition, we observed that changes in methylation are an early event in vulvar neoplasia with the highest positivity in VIN I dysplasia which also showed the highest expression of DNA methyltransferases. Surprisingly, we observed that changes in the epigenetic methylation pattern are not as local as presumed. High-grade cervical dysplasia lead to changed methylation in the vulva, with higher positivity in the methylation kit. Patients with positive kit results in cervical or vulvar smears should be monitored regularly for all genital dysplasia. This finding could explain the high rate of patients that show a VIN or VAIN several years after a CIN and sheds new light on the principles of epigenetics in cancer.

FC14 - HPV screening II

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#9231

Impact of multiple HPV infections in routine cervical cancer screening

10 - HPV screening

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Background/Objectives: In Finland, routine cervical cancer screening is recommended to be conducted through primary HPV testing. Most screening tests distinguish only between HPV-positive or HPV-negative cases or identify HPV16 and HPV18 and 12 other high-risk (HR)-HPV types separately. HPV16 is known to be the most oncogenic in cervical cancer development. However, knowledge about the role of specific combinations of multiple HPV types in cervical lesions is limited, and results vary. This study aimed to evaluate the clinical significance of multiple HPV infections in cervical carcinogenesis within a screening setting.

Methods: This study included 35 084 women who participated in the national Finnish cervical cancer screening program between 2017 and 2019 in the greater Pirkanmaa region, with clinical follow-up extending until 2023. All positive screening samples, detected using the Abbot RealTime HR-HPV assay, were further genotyped using Seegene AnyplexTM II HPV28 Detection assay which identifies 28 different HPV genotypes (HPV6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 66, 68, 69, 70, 73 and 82). The women were stratified into two age groups: under 46 and over 49. We investigated combinations of two, three, and four or more simultaneous HPV types and their associations with the cumulative risk of high-grade squamous intraepithelial lesion or worse (HSIL+).

Results: Altogether, 2418 (6.9%) women were HR-HPV positive at baseline, and 972 (2.8%) women had two or more simultaneous HPV genotypes detected, with the number of co-infections ranging from two to ten different genotypes. HPV16 co-infection with another HR-HPV was found in 93 (0.3%) women. In the younger age group (<46), the cumulative incidence of HSIL+ was highest among those with HPV16+33 (75.0%) or HPV16+56 (66.7%) co-infection, compared to 35.3% for single HPV16 infection. In older women (≥49), the highest risk was seen with HPV16+35 co-infection (100%). For other HPV combinations, excluding HPV16 or 18, 708 (2.0%) women had multiple co-infections (ranging from two to nine different genotypes). Preliminary findings suggest that, among these nonHPV16/18 combinations, the risk of HSIL may be comparable to HPV16, but it varies depending on the HR-HPV types involved.

Conclusions: Identifying specific HR-HPV co-infections, such as HPV16+33 or HPV16+35, in screening could help recognize women at higher risk more accurately. Expanding genotyping beyond the standard detection of HPV16, HPV18, and 12 other HR-HPV types would allow for more personalized follow-up strategies by flagging co-infections that might otherwise go undetected with the current standard assays.

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#9442

THE PREVALENCE OF HPV TYPES IN BRAZILIAN WOMEN.

10 - HPV screening

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Background/Objectives: Cervical cancer (CC) is the third most prevalent cancer among women in Brazil. According to the National Cancer Institute (INCA), there were an estimated 17,010 new cases in 2023, representing a crude incidence rate of 15.38 cases per 100,000 women. Human papillomavirus (HPV) has more than 200 different types identified, with genital HPV types divided into high-risk and low-risk categories in terms of the potential for malignant lesions. HPV infection and its persistence are considered the main risk factors for the development of CC. In Brazil, the Ministry of Health (MS) incorporated the quadrivalent vaccine (against HPV types 6, 11, 16, and 18) into the Unified Health System (SUS) in 2014. HPV genotyping screening was recommended by the World Health Organization (WHO) as a strategy for the elimination of cervical cancer. This method was approved in Brazil by the National Commission for Incorporation of Technologies in the Unified Health System (Conitec) in 2024. Objective: Evaluate the prevalence of HPV high risck types in women who underwent intrauterine device (IUD) insertion in a Brazilian municipality primary care unit.

Methods: This is a cross-sectional study that analyzed 85 asymptomatic women who underwent (IUD) insertion at two public family clinics (Cf) in Rio de Janeiro, Brazil, between December 2023 and May 2024. The women underwent a brief anamnesis prior to the insertion of the device, during which epidemiological data were collected, including the age, presence of a stable partner and parity. Data are part of preliminary results from a PhD research project, and are related to the timepoint before IDU insertion (baseline). HPV genotyping was performed at the Oncovirology Unit of the National Cancer Institute (INCA) in Rio de Janeiro, using an HS-12 platform from Mobius, which carries out a reverse hybridization test on a chip to identify 37 different HPV high- and low-risk genotypes.

Results: Patients' ages ranged from 18 to 48 years, with 39% (33/85) being under 25 years old. Seventy-eight percent (66/85) of women had a fixed partner, and 73% (62/85) had been pregnant at least once. HPV positivity was 60% (51/85), and high-risk HPV infections were more frequent 62% (32/51). Women aged 18-30 years were more likely to have a positive HPV result (37/51). The most prevalent genotypes were 44 at 22% (11/51), 81 at 18% (9/51), and 58 at 16% (8/51). Only 2 % (1/51) of the cases were positive for HPV 16, and 4% (2/51) were positive for HPV 18, with these patients being over 30 years-old.

Conclusions: The majority of women tested positive for HPV, demonstrating the high prevalence of the virus even in asymptomatic women and the public health impact of the disease. The most predominant high-risk viral genotypes were different from those present in the quadrivalent vaccine (16 and 18), highlighting the positive impact of the vaccine after 10 years of implementation in public health care. Understanding which HPV genotypes are predominant in Rio de Janeiro as a baseline is essential for defining new strategies for cervical cancer prevention, and for understanding the influence of IDU on potential changes in the diversity of HPV infection.

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#9200

Prevalence of HR-HPV Infection in Cervical Samples from Women Screened by Genotyping in the City of Sorocaba - SP - Brazil

10 - HPV screening

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Background/Objectives: Human papillomavirus (HPV) is the most prevalent sexually transmitted infection (STI) affecting women worldwide, representing a significant public health challenge and HR_HPV being the primary cause of cervical cancer development1. Genotyping for HPV-DNA identification combined with vaccination policies have been the main tools used in prevention programs to combat the development of high lesions and the cervical neoplasia2,3. These policies have been proposed by the World Health Organization (WHO) as guidelines for cervical cancer screening worldwide4. This pilot project carried out in the city of Sorocaba, (SP-Br) was a pioneer in this prevention modality in the country. The validation of this screening and prevention policies are crucial for developing more effective interventions in the public health system to eliminate this disease5. The aim of this project is to verify the prevalence of HR_HPV infection in cervical samples from women screened by genotyping in the city of Sorocaba- Br.

Methods: A total of 852 cervical samples from women aged 18 to 79 (average age 48) years were collected from the "Sistema Único de Saúde" in the city of Sorocaba and submitted to cytological and molecular analysis. The women underwent a prior medical history review and completed an epidemiological questionnaire after signing an Informed Consent Term. Cellular samples were collected at basic health units and in the Pink Bus and preserved in CellpreservTM liquid medium (Kolplast Ô) and sent to Inside CP with the project documentation. Cytological samples were processed using the TPK FENIXR device, and the slides were analyzed by optical microscopy by two cytopathologists. The results were classified according to the Bethesda System 2014. Molecular analyses were performed after viral DNA extraction using the QiagenTM method and genotyped using the AnyplexTM II HPV 28 test - SeegeneTM. The results were sent to the basic health units in Sorocaba. (Research Ethics Committee Approval - Brazil Platform: CAAE: 78747924.2.0000.5500).

Results: From the 852 samples cytologically evaluated, 31 (3.64%) samples were classified as ASCUS, 56 (6.57%) as LSIL, 6 (0.7%) as ASC-H, and 5 (0.59%) as HSIL, totaling 11.5% of cellular lesions. The prevalence of HPV infection was found in 215 (25.23%) samples, with 15.14% were identified with HR-HPV. The most prevalent types were HPV-52 (13.49%), HPV-61 (12.56%), HPV-53 (11.63%), HPV-51, HPV-16 (9.30%) and HPV-68 (8.84%). Among the positive genotyped samples, 87 (40.47%) were infected with two or more HPV types. Regarding the vaccination status of the participating women, 57 (6.69%) participants were vaccinated against HPV, being that 2.1% vaccinated with the bivalent vaccine and 1.2% with the quadrivalent vaccine.

Conclusions: The genotyping method for HR-HPV proved to be more efficient than cytological screening, showing a higher risk of developing precursor lesions and cervical cancer in infected women. This methodology combined with public vaccination program are the most effective tools for eliminating cervical cancer. Raising awareness and education of adherence to vaccination programs are necessary to increase vaccination coverage.

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#9379

Genotype-specific persistence of genital HPV and its role in cervical precancer risk stratification

10 - HPV screening

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Background/Objectives: Persistent human papillomavirus (HPV) infections detected in cervical cancer screening often require extended follow-up. However, the specific persistence times of individual HPV genotypes and their potential to induce cervical cancer remain largely unknown. This information is critical for assessing risk in patients with persistent HPV. The aim of this study was to evaluate the clearance rates and cervical disease risk of 28 persistent HPV genotypes over a long-term follow-up period.

Methods: This study involved 35 084 women from the Finnish national cervical cancer screening programme in the greater Tampere region between 2017-2019. Screening samples testing HPV-positive were stored and later genotyped using the Anyplex II HPV28 Detection assay, identifying 28 HPV genotypes (HPV6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 66, 68, 69, 70, 73 and 82). Women were grouped by age (<45 and ³45) and had either Negative for Intraepithelial Lesion or Malignancy (NILM) or Atypical Squamous Cells of Undetermined Significance (ASCUS) cytology at baseline. We examined individual HPV genotypes for their ability to persist long-term and progress to High grade Squamous Intraepithelial Lesion or worse (HSIL+) through 2023.

Results: Among the 2943 women with HPV-positive sample and concomitant NILM/ASCUS cytology at baseline, HPV16 was the most frequent (10.3%; n=303) genotype to persist followed by HPV31 (8.3%: n=245). A total of 1183 (40.2%) HPV genotypes showed persistence in at least two samples from consecutive visits, with interval ranging from 6.1 to 48.0 months. HPV59 had the highest persistence rate (49.6%) followed by HPV52 (49.1%) and HPV35 (44.3%). Persistent HPV59 infections were significantly more common in older women (aged ³45) with 65.7%, compared to 42.5% in younger women (p=0.033). Across all ages, HPV16 and HPV35 were most likely to progress to HSIL+, with progression rates of 15.6% and 14.3% over an average period of 23.5 and 21.6 months, respectively. HPV56 showed the shortest clearance time at 35.8 months (±SD 10.3), while HPV59 had the longest persistence (41.8 months ±SD 15.2) without causing precursor lesions.

Conclusions: Our findings indicate that persistent infections with certain HPV genotypes, especially HPV16, 35 and 33, carry a high risk for progression, whereas HPV56 and HPV59 are less likely to progress. These results suggest that women with persistent HPV infections could benefit from extended genotyping to optimize follow-up protocols, potentially reducing unnecessary colposcopies and treatments.

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#9311

Extended HPV genotyping and the cumulative risk of precancerous lesions in the Finnish cervical cancer screening program

10 - HPV screening

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Background/Objectives: Cervical cancer (CC) screening in Finland relies on human papillomavirus (HPV) primary testing with cytology triage. While HPV-testing is highly sensitive, concerns remain about its low specificity, which leads to overdiagnosis and unnecessary procedures, that strain healthcare resources. Current screening tests only differentiate between HPV-positive or HPV-negative cases, or identify HPV16, HPV18 and 12 other high-risk (HR)-HPV types separately. With the increasing adoption of HPV vaccination, the relevance of genotypes like HPV16 and 18 will decrease, making it crucial to evaluate the risks associated with other HR-HPV types not covered by the vaccines. In Finland, there is limited data on the prevalence and clinical risks of these additional HR-HPV types in screening context. The aim of this study was to determine whether extended HPV genotyping could improve the specificity of detecting cervical precancerous lesions in the Finnish cervical cancer screening program.

Methods: The CC screening data from 35,084 women in Tampere and surrounding municipalities, covering the years 2017 to 2019, were collected, with clinical follow-up extending until 2023. Genotyping of 28 HPV genotypes was conducted by retesting stored HPV-positive screening samples using the AnyplexTM II HPV28 Detection assay, which identifies HPV6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 66, 68, 69, 70, 73 and 82. The prevalence of each HPV genotype and their associations with different severities of cervical lesions during follow-up were analyzed.

Results: Among the 2418 HPV-positive women HPV16 was the most prevalent genotype (11.57%) followed by HPV31 (8.43%), HPV52 (7.45%), HPV45 (6.35%), HPV51 (5.71%), HPV56 (5.05%), HPV68 (4.98%), HPV66 (4.93%) and HPV18 (4.66%). The highest positive predictive values (PPVs) for high grade squamous intraepithelial lesion or worse (HSIL+) among women with a single HPV infection were: HPV16 35.27% (95% CI: 34.75-35.79), HPV18 23.33% (95% CI: 22.87-23.79), HPV58 18.75% (95% CI: 18.33-19.17) and HPV31 15.70% (95% CI: 15.30-16.09). The lowest PPV was for HPV56 positive women at 1.10% (95% CI: 0.99-1.21).

Conclusions: The distribution of HPV genotypes in Finland differs from the Northern and Eastern Europe. While HPV16 remains the most prevalent genotype, HPV18 ranks only ninth in our population, compared to its second or third position in those regions. Notable, the high prevalence of HPV31, HPV52 and HPV45 is also unusual. Given the high PPVs of HPV58 and HPV31, evaluating a tailored screening strategy for these genotypes, alongside HPV16 and HPV18, could improve the effectiveness of HPV testing in the Finnish screening program for both HPV vaccinated and unvaccinated women.

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#9365

HPV SCREENING USING EXTENDED GENOTYPING AND NEAR REALTIME MULTI LABORATORY QUALITY ASSURANCE MONITORING IN THE NETHERLANDS

10 - HPV screening

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Background/Objectives: In 2017 the Netherlands was one of the first countries to implement nationwide HPV based primary screening in combination with triage cytology. As of July 2023 the screening process has been adapted according to the outcomes of multiple contracting tenders regarding the HPV screening test and self-sampling device, screening laboratories and quality assurance monitoring.

Methods: HPV Screening is performed in three independent laboratories on both GP collected cervical scrapes, collected in PreservCyt and self-collected vaginal material collected at home using Copan flocked swabs. Protocols and equipment, including reagents and controls, are standardized for all screening laboratories. HPV screening is performed on a BDCOR system using the BD-Onclarity test. Each laboratory is equipped with 2 parallel BDCOR systems each consisting of a single pre-analytical system (PX) and two analytical units (GX). The BD-Onclarity test results are reported as HPV negative or positive based on the threshold settings of the manufacturers. For HPV positive samples Ct values are reported to the laboratory per individual hrHPV genotype for HPV-16, 18, 31, 45, 51 and 52 or as combined genotypes for HPV 33 and 58, HPV 35,39,69, and HPV 56,59,66. HPV-type based triaging of screening results is subsequently performed according to the existing screening strategy of the Dutch Population Screening Program. BD-Onclarity results, including technical performance details generated by each of the BDCORs are collected overnight in a national database (QATool) for quality assurance purposes regarding e.g. intra- and inter-laboratory comparisons of assay performance, equipment monitoring, longitudinal trend analysis of reagents and controls.

Results: In the first 12 months after implementation a total of 457.179 samples were tested for HPV, 46% of which were based on Cervical scrapes and 54% on self-collected samples. First time right percentages were 95.6% for self-collected samples and 95.0% for cervical scrapes. If repeat testing was required this was mainly due a flag message reporting incomplete (INC) test results for the run. This occurred for 3.2% of the samples. Repeat testing due to internal control failure was required for 0.3% of samples independent of the sample type. Median Ct values for the extended genotyping HPV channels ranged from 28.9 to 32.2 for cervical scrapes and from 28.8 to 32.3 for self-collected samples, with no significant differences between laboratories, BDCOR systems and reagent lots. Median Ct values for the cellular internal control (Hbb) were different for cervical scrapes (25,4) and self-collected samples (21.9). Stability of performance of the screening systems within and between laboratories is monitored longitudinally, both for assay control samples and clinical samples. Examples and observations will be presented.

Conclusions: The application of standardized laboratory protocols. reagents and controls, together with the development of a national database containing the technical data of the HPV results enables continuous HPV quality assurance monitoring, performance benchmarking and early identification of deviations in case these may arise.

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#9368

Significant protective effect of a previous negative mRNA HPV test in precancer risk of women with low-grade cytology. REINA longitudinal study in Spain.

10 - HPV screening

Background/Objectives: Screening guidelines calculate CIN2+ risks considering previous test results, but data with mRNA are not available due to the newness of primary HPV programs. A borderline or low-grade cytology result (ASCUS/LSIL) during screening, prompts a reflex HPV analysis of the sample for patient management. This study calculates the long-term risk of precancer in women with a new HPV infection and ASCUS/LSIL cytology and analyzes the protection of a previous negative mRNA-based HPV test in the first screening round.

Methods: This is a prospective longitudinal study performed with 5,053 women aged 25 to 65 years from the opportunistic screening program for cervical cancer prevention in Madrid. Women signing an informed consent, had a first screening round with cotest by the mRNA-based HPV test Aptima and a ThinPrep liquid-based cytology (LBC) analysis. Those with a low-grade (ASCUS/LSIL) cytology result and a positive HPV test were followed up (FU) to ten years. An adequate FU was considered when ulterior cytology, cotest or histology studies were performed. The RNA Extended Interventional Nucleic Acid (REINA) was the interventional arm of this longitudinal study. REINA had 1,966 women with a negative initial cotest, undergoing a second cotest with Aptima and LBC four years later. The cumulative risk of CIN2+ after a new infection with HPV and a low-grade cytology in REINA at any point of the FU was compared to that of women with an unknown previous HPV status but a positive HPV test and a low-grade cytology result from the first screening round.

Results: From REINA, 110 women had a positive Aptima HPV test (5.6% prevalence) and 38 had a low-grade (ASCUS/LSIL) cytology result in the second screening round. The FU time from the second round was up to 6.7 years. The immediate (12 months) risk of CIN2+ after this second round was 0% and the 4-year cumulative risk was 10.5% (CI 3.3 to 22.7). Women with the same test results from the first screening round (n=83) in the study, outside of REINA, had an immediate risk of 25.5% (16.6 to 35.4) and a 4-year cumulative risk of CIN2+ of 32.6% (CI 22.5 to 43.1). The HR was 0.36 (0.14 to 0.94, p=0.037).

Conclusions: A previous negative Aptima mRNA HPV test provides a high protective effect reducing the risk of cervical cancer and precancer in HPV-positive women with a low-grade cytology. In this study, the cumulative risk of CIN2+ 4 years after testing was a 64% lower in women with a previous negative HPV test compared to those without previous results.

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#9539

The performance of p16/Ki-67 Dual Staining for Risk Stratification in Cervical Cancer Screening

10 - HPV screening

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Background/Objectives: Organized cervical cancer screening represents the most effective secondary prevention strategy for reducing both incidence and mortality. Currently, HPV test is recognized as the most reliable primary screening test. However, due to its low sensitivity, additional triage tests are essential for accurate risk stratification and optimization of colposcopy resources. The p16/Ki-67 dual staining (DS) evaluates biomarkers indicative of cell proliferation (Ki-67) and tumor suppressor protein disruption (p16) and represents a significant advancement in cervical cancer screening, providing enhanced precision in identifying precancerous lesions. Therefore, its role is crucial in enhancing the efficiency of screening programs and optimizing colposcopy referrals. The aim of this study is to evaluate the performance of the p16/Ki-67 DS for the detection of high-grade lesions in women with minor cytological abnormalities (ASC-US or LSIL.

Methods: We conducted an observational retrospective study on women referred to the Central Hospital Cervical Pathology Unit, where DS was performed as a triage test between January 2022 and June 2023. The test was applied for risk stratification in women with minor cytological abnormalities (ASC-US or LSIL) or in those with persistent other high-risk HPV types other than 16/18 (HR-HPV), with a NILM reflex cytology. The significance level was set at 0,05. All data were analyzed using IBM-SPSSÒ software version 30.0.

Results: During the study period, the p16/Ki67 DS test was applied to 136 women, with 106 (77.9%) undergoing screening for minor cytological abnormalities and 30 (22.1%) for follow-up of low-grade lesions or persistent infections with HR-HPV after transformation zone excision. 89 (65.4%) women were DS negative and 47 (34.6%) were DS positive. In the DS-positive subgroup, 8 had NILM cytology, 36 had ASC-US/LSIL and 2 had HSIL/ASC-H; 40 were positive for HPV-HR, 4 for HPV 16 and 1 for both HPV 16 and HPV-HR. No significant association was found between DS test results and women's age, vaccination status, smoking or age at first sexual intercourse (p = n.s.). All women underwent colposcopy, and 22 cervical biopsies were performed based on abnormal colposcopy findings. In the DS-positive subgroup, 19 biopsies were performed, of which 13 (68.4%) showed CIN1 or no dysplasia, and 6 (31.6%) showed CIN2+. In the DS-negative subgroup, only 3 biopsies were performed, with 1 showing CIN1 and 2 showing CIN2+. Two cases showed a negative DS test and a biopsy with CIN2+ lesions. Both were in women over 40 years old, unvaccinated, smokers, with a type 3 transformation zone with grade 2 colposcopic findings. The sensitivity of the DS test for detecting CIN2+ lesions was 75%.

Conclusions: The p16/Ki-67 DS test demonstrated reasonable sensitivity for detecting high-grade cervical lesions. However, it is important to consider the individual characteristics of patients and colposcopy findings. The p16/Ki-67 DS test appears to be an effective tool for risk stratification in women with mild cervical abnormalities.

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#9350

Improved CIN2+ Risk Stratification in Cervical Screening: Cytology and HPV mRNA (16, 18, 45) Co-Testing of 116,000 Samples

10 - HPV screening

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Background/Objectives: Co-testing with cytology and HPV mRNA assays may enhance risk stratification for cervical intraepithelial neoplasia grade 2 or higher (CIN2+), potentially optimizing patient management and follow-up protocols. This study evaluates the efficacy of cytology and the PreTect SEE assay, targeting HPV types 16, 18, and 45, in identifying CIN2+ risk in cervical samples analyzed at the University Hospital of North Norway, Tromsø, between 2013 and 2022, with biopsy follow-up through 2023.

Methods: We assessed 116,217 cervical samples categorized by cytology findings and HPV mRNA status (E6/E7 genes for HPV types 16, 18, and 45). Samples were classified into four groups: 1) double negatives (normal cytology, PreTect SEE negative), 2) ASC-US+ cytology with negative PreTect SEE, 3) normal cytology with positive PreTect SEE, and 4) double positives (ASC-US+ cytology and PreTect SEE positive). Biopsy-confirmed CIN2+ diagnoses were recorded for each group.

Results: Of the 116,217 samples analyzed, 3.9% (4,533 cases) were CIN2+ positive. A gradient in CIN2+ prevalence emerged across test result categories, with double-negative samples presenting the lowest CIN2+ risk at 0.7% (668 of 100,790). Double-positive samples showed a markedly high CIN2+ prevalence of 60.0% (1,965 of 3,277), underscoring the increased risk in this group. ASC-US+ cytology with negative PreTect SEE results showed a moderate CIN2+ prevalence at 13.6% (1,481 of 10,863). Notably, normal cytology with a positive PreTect SEE result yielded a CIN2+ rate of 32.6% (419 of 1,287), indicating elevated risk in cytologically normal cases when HPV mRNA E6/E7 expression is detected.

Conclusions: Co-testing with cytology and a 3-type HPV mRNA assay provides valuable stratification of CIN2+ risk, identifying double-positive cases as high risk, warranting intensified clinical follow-up. In contrast, the low CIN2+ rate in double-negative cases supports extended screening intervals, which may improve resource allocation in cervical cancer prevention programs. These findings suggest that co-testing can enhance risk-based management in cervical screening strategies.

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#9520

Comparison of cytological and HPV-based screening within population-based screening program in Finland

10 - HPV screening

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Background/Objectives: Cervical cancer screening in Finland started in the 1960s, reducing both the incidence and mortality by approximately 80% since. HPV-based screening with cytology triage was introduced in Finland in organized screening 2012 onwards. HPV-based screening exceeded cytology-based tests in organized screening in 2019. We aimed to compare performance between primary HPV testing and cytological screening and also between the first and second rounds of HPV-based screening within a routine screening program.

Methods: We calculated the attendees, the proportions of positive primary screening tests, risk-group screening referrals, colposcopy referrals and CIN2+ findings for both HPV and cytological screening. The data covered all tests taken within the Finnish cervical cancer screening program between 2012 and 2022 from Finland's Mass Screening Registry. We included data only from full screening rounds. Results were adjusted for age, region, socioeconomic status, and mother tongue.

Results: We identified 1,441,042 screening rounds, where 243,214 rounds were HPV-based and 1,197,828 cytology-based. 7.7% of hrHPV screening rounds and 4,9% of the cytological screening rounds were positive. Adjusted risk ratio of screening round positivity in HPV screening was 1.46 (95%CI 1.44-1.49) compared to cytology, while adjusted relative risk for referral was 3.31 (95% CI 3.22-3.40) and 2.84 (95% CI 2.71-2.99) for CIN2+ findings. Adjusted relative test positivity was 0.83 (95% CI 0.79-0.88) in the second HPV screening round compared to the first round, while relative referral rate was 0.79 (95% CI 0.72-0.86) and 0.61 (95% CI 0.48-0.75) for CIN2+ findings.

Conclusions: In a well-established population-based screening program, in the first screening round, HPV-screening leads to higher referral and CIN2+ detection rate, but in the second round, both the referral and CIN2+ detection rate decline.

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#9162

Molecular Screening and HPV Prevalence: First Insights from Angola

10 - HPV screening

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Background/Objectives: Cervical cancer is a major global health issue, responsible for over 604,000 cases annually, and a leading cause of cancer deaths in low-income countries, particularly in sub-Saharan Africa [1]. Persistent human papillomavirus (HPV) infection, found in 99% of cases, is the main risk facto, with high-risk HPV types, such as HPV16 and 18, significantly increasing cancer risk [2]. Given its well-defined etiology, it is largely preventable through the implementation of effective screening programs [3]. Yet, like many other sub-Saharan countries, Angola lacks comprehensive data on HPV prevalence and organized screening initiatives [4]. This study aims to provide the first characterization of HPV prevalence and related cervical lesions in Angola, and to assess the impact of integrating molecular screening tools, like HPV genotyping and CINtec® Plus dual-labeling (p16/ki-67) [5,6], to improve early diagnosis and reduce unnecessary colposcopy referrals in this setting.

Methods: A single-cohort prospective observational clinical study was performed involving women aged 25 years and older attending secondary care at Maternidade Lucrécia Paim in Luanda, Angola. Cervicovaginal samples were collected and subjected to HPV genotyping and Pap smear cytology. HPV and/or cytology-positive cases were further analyzed using immunocytochemical dual-labeling for p16/ki-67, a marker associated with HPV-related cellular transformation.

Results: A high prevalence of hrHPV infection (18.2%) was identified among the 1153 women studied (mean age 42.9). HPV genotyping identified HPV16/18 in 5.0% of the cases, while 13.2% were positive for at least one of the other 12 hrHPV tested. Cytology revealed that 55% of HPV-positive women had abnormal cytology results, i.e. ASC-US or higher-grade lesion. Among women with both hrHPV and abnormal cytology, CINtec® Plus dual-labeling showed a 50.9% positivity rate, indicating a strong association with high-grade cervical lesions. Notably, the high rate of unsatisfactory Pap smears (40.7%), emphasizes the limitations of cytology-based screening in this context. The use of CINtec® Plus as a triage tool proved valuable in refining referrals for colposcopy, reducing the number of unnecessary colposcopies by 55.1%, and enhancing the detection of women at higher risk for cervical cancer.

Conclusions: This study presents the first comprehensive analysis of HPV prevalence and cervical lesions in Angola and demonstrates the benefits of incorporating molecular screening tools into national screening programs. The findings support the adoption of HPV testing as the primary screening method in low-resource settings, coupled with p16/ki-67 dual-labeling to refine colposcopy referrals. By addressing the limitations of cytology, the use of molecular tools could significantly improve early detection and management of cervical cancer in Angola.

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FC15 - Anal neoplasia / Vulvar neoplasia / Skin diseases II

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#9375

HPV genotyping and cytology co-testing for anal cancer screening: HRA/histological assessment and evaluation of the "HPV burden" as a new potential parameter associated with AIN lesions

27 - 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 anal preneoplastic lesions are strongly related to human papilloma virus (HPV) infection. Several clinics performs anal Pap tests to high-risk patients in order to early detect this type of malignancies; however, to date there are no active screening protocols. We conducted a prospective cohort study aimed to explore the distribution of different HPV types, the eventual effect of co-infections and the associated cytological and HRA/histological pattern.

Methods: 550 anal swab specimens (114 of women and 436 of men) were collected at the Regional STD (Sexually Transmitted Disease) center of Florence in a population at increased risk of anal cancer. Co-testing was performed using a unique sampling for Cytology (LBC) and HPV genotyping at the laboratory of cancer prevention (LRPO) of ISPRO Institute. Cytology was evaluated according to the TBS system 2014. HRA/histological data were collected to assess HPV/cytological/histological correlations.

Results: 315 patients (57.3%) resulted HPV-HR positive (HPV-HR+), 54 women (47.4%) and 261 men (59.9%). Among HR-HPV+ patients, 265 HRA were performed and 10.2% resulted AIN2+. The distribution of the different HR-HPV types was similar between men and women and the most frequent were HPV16 (36,8%), HPV31 (21,3%) and HPV51 (25,1%). Among patients with AIN2+ lesions (n=28), 96,4% were HPV-HR+ (HPV16, HPV58 and HPV45 were found in 53.6%, 32.1%, 17.9% AIN2+ lesions, respectively). Concerning HR-HPV+ patients, 136/315 (43.2%) had cytological abnormalities (ASC-US+) and 155/315 (49.2%) had AIN1+ lesions. These incidences resulted significantly ($p<0.01$) higher in men (46% and 60.4%, respectively) than in women (28% and 48.8%, respectively). Interestingly, the incidence of co-infection with 3 or more LR-HPV was higher in men than in women (40.6% vs 25.9%).

Conclusions: The HR-HPV types resulted more associated with AIN2+ lesions were HPV16 followed by HPV58. The sensitivity of HPV test for AIN2+ was 96.4% with a PPV of 10.2%; the only AIN2+ case resulted HPV negative (both LR- and HR-HPV) had an abnormal cytological pattern (AGC), underlining the importance of the co-testing. In HPV-HR+ patients, cytological alterations (ASC-US+) and AIN1+ lesions were more frequent in men than in women. This result can be explained by a higher incidence in men of co-infections with 3 or more LR-HPV. We could define this effect as "HR-HPV/LR-HPV burden", a new parameter potentially associated with AIN1/AIN2+ progression. This hypothesis needs to be confirmed by monitoring co-infected patients over time. These results reinforce the importance of extended genotyping (including LR-HPV types) for anal cancer screening.

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#9283

Anal Histologic High-Grade Squamous Intraepithelial Lesions (HHSIL) Incidence After Semi-Annual Anal Screening in a Cohort of Women with HIV: AIDS Malignancy Consortium (AMC) 084

27 - Anal neoplasia

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Background/Objectives: Detection and treatment of anal hHSIL is essential for anal cancer prevention in women with HIV (WwH). However, although guidelines recommend triage high resolution anoscopy (HRA) after minimally abnormal anal cytology (anal-cyt), a second triage test may assist with identifying WwH who are at the highest risk for anal hHSI, particularly in settings with limited access to HRA. The role of a second triage test (either hr HPV or anal-cyt) remains unknown. We evaluated the incidence of anal hHSIL after repeating anal cancer screening tests at baseline and then at 6 months.

Methods: WwH without baseline anal histologic high grade squamous intraepithelial lesions (hHSIL) underwent semi-annual anal hrHPV testing, and anal-cyt, followed by high-resolution anoscopy (HRA), where >2 biopsies were obtained. The incidence of anal hHSIL was calculated for combinations of anal screening test (anal hrHPV[GenProbe Aptima] and anal-cyt) collected at baseline and repeated at a 6-month visit. Incidence was reported as number of hHSIL events by the number of person-years of follow-up. Poisson regression was used for calculating incidence, incidence rate ratio, and the corresponding 95% CI.

Results: There were 83 WwH without prevalent hHSIL who had anal-cyt and hrHPV testing 6 months apart who underwent at least one HRA after at least 1 year of follow-up. The demographic characteristics of these women were the following: 62% were > 50 years old, 69% were Black, 12% were Hispanic, and 37% were never smokers. Among WwH who had normal anal-cyt at baseline, 39% had ASCUS+ at 6 months, and among individuals with hrHPV- results at baseline, 18% subsequently had hrHPV detected at 6 months. Compared to women with negative hr HPV and norml anal-cyt at baseline, women with persistent abnormalities (either positive hr HPV or abnomal anal-cyt) at baseline and at 6 months were significantly more likely to have anal HHSIL, HR=6.3 (1.2-32.5), p=0.028. However, among 10 women with either positive hr HPV or abnormal anal-cyt at baseline, but who subsequently had normal anal-cyt and hrHPV- at 6 months follow-up, there were no anal hHSILs detected during 16.3 person-years (py) of follow-up, compared to an incidence of 21.1 hHSIL/100 (py) among WwH with similar baseline findings but abnormal anal-cyt or hrHPV+ or both at 6 months follow-up.

Conclusions: Persistent detection of either abnormal anal-cyt or positive hrHPV at 6 months may assist in prioritization for HRA in resource limited settings. After a baseline abnormal anal-cyt or positive hrHPV, evidence of either abnormal anal-cyt or positive hr HPV at 6 months indicates a substantially increased risk of anal hHSIL compared to women with normal anal-cyt and hr HPV at baseline. However, negative anal HR HPV with normal anal-cyt on co-testing can be reassuring at baseline or even at 6-month follow-up after baseline anormal anal-cyt and/or HR HPV.

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#9454

Recurrence burden in patients with high-grade vulvar intraepithelial neoplasia

26 - Vulvar diseases and neoplasia

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Background/Objectives: Background: High-grade vulvar intraepithelial neoplasia (HG-VIN) is the precursor lesion of vulvar squamous cell carcinoma (VSCC). HG-VIN is categorized into human papillomavirus (HPV)-associated high-grade squamous intraepithelial lesion (HSIL) and HPV-independent VIN (often clinically referred to as differentiated VIN or dVIN). HSIL and HPVi VIN/dVIN differ in etiology, clinicopathological characteristics and cancer risk (10% and 50% after 10 years, respectively).(1, 2) Recurrence rates of VIN range from 26-51% after treatment.(3-5) Objectives: This study aimed to assess the recurrence burden in HG-VIN patients.

Methods: Methods: From a population-based cohort on HG-VIN, 578 HSIL patients and 46 HPVi VIN patients were identified and selected. Recurrence burden was assessed using both pathology data from the Dutch Nationwide Pathology Databank (Palga) and clinical data from patient medical records. Kaplan-Meier analysis was used to estimate the risk of recurrence. Besides the presence of recurrence, the number of recurrences and the duration of disease were assessed to reflect the recurrence burden. Follow-up was censored at the time of vulvar cancer development. Additionally, risk factors for recurrence, including age, treatment radicality, HPV 16 status, methylation status, smoking, complaints, immunodeficiency, multizonality, and focality for HSIL patients, as well as age, treatment radicality, lichen sclerosus, p53 status, methylation status, smoking, complaints, and focality for HPVi VIN patients, were analyzed using multivariable Cox regression analysis.

Results: Results: During a median follow-up time of 15.4 years in patients with HSIL and 5.5 years in patients with HPVi VIN, recurrent VIN occurred in 265/578 (45.8%) and in 16/46 (34.8%), respectively. In HSIL patients, the 5-year recurrence risk was 34.2% at a median time of 2.4 years with a median of 2 [range 1-10] recurrences. In HPVi VIN patients, the 5-year recurrence risk was 42.2% at a median time of 1.5 years with a median of 1 recurrence [range 1-3]. After 2 years of follow-up 215/578 (37.2%) of HSIL patients and 3/46 (6.5%) of HPVi VIN patients were still diagnosed with VIN. Clinical data was collected of 314/624 (50.3%) patients. A non-radical baseline treatment was identified as the sole risk factors for recurrence in HSIL, while no risk factors were found for recurrence in HPVi VIN.

Conclusions: Conclusion: Both HSIL and HPVi VIN patients have a substantial risk of recurrent VIN. HSIL patients experience a significant recurrence burden characterized by multiple recurrences over a prolonged period.

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#9289

Epidemiological Profiling of Persistent Cutaneous Warts: Insights Gained from Type-Specific HPV Prevalence

30 - HPV and associated skin diseases

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Background/Objectives: Cutaneous warts are skin lesions caused by HPV. Even though they are considered benign, they can have a considerable impact on the quality of life and cause serious illness in certain immunocompromised populations. Previous studies have established that the efficacy of wart treatment is influenced by the specific HPV type involved. This study presents baseline findings from the OVW-SA trial, focusing on the complex interplay of patient-specific features and wart characteristics, complemented by extensive HPV genotyping of wart samples. The research aims to outline a comprehensive epidemiological profile of a typical persistent wart.

Methods: A total of 269 swab samples from cutaneous warts were collected upon enrolment. DNA extraction was performed using the automated NucliSENS® easyMAG® system (bioMérieux). Samples were analysed with two distinct in-house PCR assays designed to detect the most prevalent cutaneous HPV types (wart-associated HPV qPCR) and relevant mucosal HPV types (RIATOL qPCR assay). The type-specific prevalence of 30 distinct HPV genotypes was assessed, with the beta-globin gene serving as a cellularity control enabling viral load quantification. Data regarding wart persistence, prior treatments, wart types, and other relevant wart and patient characteristics was gathered via a baseline questionnaire.

Results: Findings revealed that specific socio-demographic factors significantly influence wart prevalence, with higher frequencies observed in individuals aged 15 years or younger. The study cohort predominantly comprised persistent warts, as 98% (n = 263) of the lesions were older than six months, and 92% (n = 247) had received previous treatment. The most common wart type identified was mosaic verruca plantaris (42%, n = 113). The predominant HPV types included cutaneous types HPV 27 (73%, n = 195), HPV 57 (63%, n = 169), and HPV 2 (42%, n = 113), with only 2% (n = 6) of lesions testing negative for HPV. The highest median viral loads were observed for HPV 27 and HPV 57, quantified at 6.29E+04 and 7.47E+01 viral copies per cell, respectively. Multivariate analysis identified significant associations between wart persistence and specific wart types, the number of warts, and HPV genotypes.

Conclusions: This study highlights the critical role of HPV genotyping and viral load assessment in the clinical management of cutaneous warts. The multivariate analysis indicates that persistent warts are more likely to: (1) be verruca vulgaris, verruca plantaris simple or mosaic, (2) to manifest as multiple warts, (3) and to be negative for HPV type 2 or 4. These characteristics may serve as valuable indicators for risk stratification in clinical practice when determining treatment strategies. Further research should focus on larger clinical trials with various treatment modalities and ensure adequate HPV type-specific allocation to refine treatment response predictions. Such an approach could enable more personalized management of cutaneous warts, ultimately improving patient outcomes and reducing the burden associated with this common skin condition.

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Detection of alpha-HPV types in cutaneous squamous cell carcinoma associated with markers of carcinogenesis

30 - HPV and associated skin diseases

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Background/Objectives: Cutaneous squamous cell carcinoma (cSCC) is primarily linked to ultraviolet (UV) light exposure, though certain types of beta human papillomavirus (ß-HPV), have also been implicated in skin carcinogenesis1. While a-HPV are well-documented in anogenital and oral cancers, their role in cSCC remains unclear2. This study aims to investigate the clinical and tumoral characteristics associated with high-risk oncogenic a-HPV in cSCC samples, with a focus on HPV16 DNA integration, a marker of HPV-driven carcinogenesis.

Methods: We conducted a retrospective analysis of 129 formalin-fixed paraffin-embedded cSCC samples collected between January 2017 and January 2022. All the samples were tested for a-HPV using AnyplexTMII HPV 28 and 99 samples were also tested with INNO-LiPA assay. Detection of ß- and γ-HPV was performed using a Luminex-based assay. To estimate viral DNA integration in HPV16-positive samples, real-time PCR was used to quantify E2/E6 ratio.

Results: A total of 129 FFPE samples, 99 invasive cSCC (77%) and 30 Bowen's disease (23%) from 120 patients were analyzed. The female-to-male ratio was 0.48 with a median age of 72 years (range 18-100). The study included 58 immunosuppressed patients: 14 (12%) individuals living with HIV, 30 (25%) organ transplant recipients (OTR), 1 (0.8%) OTR living with HIV, and 13 (11%) patients with hematologic malignancies. At least one HPV was detected in 56.6% of samples, with 25 (19.4%) samples positive for a-HPV. Overall, ß and/or γ-HPV were identified in 64 samples (49.6 %.) with or without a-HPV coinfection. All 25 a-HPV-positive samples contained a single type of a-HPV, the most common being HPV16 (10/25, 40%). HPV16 DNA integration was observed in 8 of the 9 assessable samples ranging from 29% to 100% (Fig 1). Other detected types included HPV 26, 33, 45, 51, 56, 66, 73, and 82. Peripheral healthy skin tested negative in 10 out of 11 of the available a-HPV-positive samples.

Conclusions: The detection of a single a-HPV type in a significant proportion of cSCC samples, associated with the presence of HPV16 DNA integration, supports the hypothesis of a-HPV involvement in cutaneous carcinogenesis. Unlike ß-HPV, which acts as a co-carcinogen, a-HPV may drive cSCC similarly to what is observed in mucosal cancers. Further research is needed to explore a-HPV's role in cSCC, since it could impact therapeutic strategies, especially for advanced/metastatic cSCC. Vaccination against a-HPV may also be considered for prevention, particularly in immunosuppressed patients. Moreover, a-HPV-positive cSCC may result from self-inoculation from mucosal sites and could indicate a broader issue of poor systemic control of HPV infection3. Therefore, a-HPV-positive cSCC should lead to a thorough examination of the anogenital and oral mucosae to ensure detection of other HPV-related lesions.

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Efficacy of a multi-ingredient Coriolus versicolor-based vaginal gel on High-risk HPV clearance and repair of low-grade cervical lesions: final results from the PALOMA 2 Clinical Trial.

22 - Diagnostic procedures / management

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Background/Objectives: High-risk (HR)-HPV infection is a critical precursor to cervical cancer. The PALOMA 2 Clinical Trial was designed to assess the efficacy of a Coriolus versicolor-based vaginal gel in the repair of low-grade cervical lesions and HR-HPV clearance.

Methods: Randomised, multi-centre, prospective, open-label, parallel-group, watchful waiting approach-controlled clinical trial. Unvaccinated HR-HPV positive women between 30-65-year-old, with ASCUS/LSIL cytology and concordant colposcopy were randomized (1:1:1:1) into 4 groups with different Coriolus versicolor-based vaginal gel treatment regimens: A) Standard regimen: once daily for one month, followed by every other day for five months; B) Intensive regimen: once daily for three months, followed by every other day for three months; C) Very Intensive regimen: once daily for six months; D) Control group: watchful waiting approach. The study assessed the repair of HPV-dependent low-grade cervical lesions and HR-HPV clearance after six months of treatment. Repair of cervical lesions was considered when there was cytology normalization with concordant colposcopy. Clearance was categorized as complete (negative HR-HPV test or no detectable baseline genotypes) or partial (disappearance of at least one baseline genotype with normal cytology and concordant colposcopy). IRC approval was obtained, and all participants gave informed consent. Results of arm A, B, and C vs D on lesion regression and HR-HPV clearance after 6 months of treatment are presented.

Results: Of the 164 randomized patients, 124 with a mean age of 41.13 years were evaluated for efficacy. Of these, 46.8% were current or former smokers, with no significant differences between the groups. From the 109 patients (A=26; B=26; C=29; D=28) who completed the 6-month treatment, repair of cervical lesions and HR-HPV clearance was achieved by 42.3% (A), 84.6% (B), 62.1% (C) vs 46.4% (D) patients (pAvsD=0.7607, pBvsD=0.0033 and pCvsD=0.2359). A subgroup of 56 patients positive for HPV 16 and/or 18 and/or 31 (A=14; B=15; C=14; D=13) with a mean age of 42.52 years was analyzed and 42.9% (A), 93.3% (B), 64.3% (C) vs. 30.8% (D) experienced lesion regression and HR-HPV clearance after the 6-month treatment (pAvsD=0.6946, pBvsD=0.0011 and pCvsD=0.0816).

Conclusions: These findings indicate that the intensive regimen of Coriolus versicolor-based vaginal gel significantly enhances HR-HPV clearance and repair of low-grade cervical lesions compared to watchful waiting approach. These results support the potential of the Coriolus versicolor-based vaginal gel as a proactive management option for HR-HPV positive women with low-grade cervical lesions.

FC16 - Diagnostics procedures / Management I

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#9247

HPV Distribution and Oncological Outcomes in Norwegian Women Undergoing Fertility-Sparing Surgery for Early-Stage Cervical Cancer (2000-2022)

22 - Diagnostic procedures / management

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Background/Objectives: Non-HPV-associated cervical carcinomas have poorer prognosis than HPV-associated carcinomas. This study aims to describe the distribution of HPV genotypes and associated oncologic outcomes in Norwegian women undergoing fertility-sparing surgery for early-stage cervical cancer.

Methods: This retrospective, nationwide cohort study included 143 women who had undergone fertility-sparing surgery between 2000 and 2022 at Oslo University Hospital. Clinical data were retrieved from institutional databases. If HPV genotype status pretreatment was unknown, histological specimens with representative tumort issue were recalled for HPV genotyping with the AllplexTMII HPV28 Detection Kit (Seegene); assessing for high risk group 1 (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59), group 2A and 2B carcinogens (HPV 68, 26, 53, 66, 67, 70, 73 and 82) and low-risk genotypes (6, 11, 40, 42, 43, 44, 54 and 61) (Table 1a). In cases with multiple infections, the high-risk HPV genotype with the highest viral load was regarded as the transforming genotype. Data were analysed using Kaplan-Meier method.

Results: Median age at diagnosis was 30.7 years (range 20.1-42.9). Histological subtypes included squamous cell carcinoma (SCC) in 81/143 (56.6%) tumors, adenocarcinoma (AC) in 56/143 (39.2%) tumors and other subtypes in 6/143 (4.2%) of tumors. Distribution by FIGO stage (2009) was 14/143 (9.8%) 1A1, 23/143 (16.0%) 1A2, 106/143 (74.1%) 1B1. HPV-associated tumors were detected in 136/143 (95.1%) of cases, with HPV 16, 18, 45 and 33 being the most prevalent genotypes (Table 1a). HPV 18 was more common in AC 24/56 (42.8%) compared to SCC 11/81 (13.5%) (p= 0.0001). Multiple infections were detected in 19/143 (13.3%) cases. Overall recurrence rate was 7.8% (11/143), where 6/11 (54.5%) patients were HPV16 positive, two were HPV 18, two HPV 31 (both SCC) and one HPV negative (clear cell tumor (Figure 1b). Five-year recurrence-free survival for HPV 16, 18 or 45 positive tumors was 94.0% (95% CI [87.9-97.1]%), other high-risk HPV 84.6% (95 % CI [51.2-95.9]%) and HPV negative tumors 85.7% (95% CI [33.4-97.9]%).

Conclusions: Recurrence rates varied by genotype. Interestingly, high-risk HPV other than genotype 16, 18 or 45 had similar recurrence as HPV-negative carcinomas. This might imply that other factors are more strongly associated with recurrent diease compared to HPV genotype alone.

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Current challenges in cotesting: a clinical case.

23 - Risk management

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Background/Objectives: This clinical case study presents a 47-year-old woman diagnosed with invasive carcinoma in cytology and biopsy, despite a previous colposcopy in 2019 revealing only a low-grade lesion. The patient's previous cervical cytology was graded as ASCUS, highlighting the potential limitations of cytology-based screening alone. Concomitant high-risk human papillomavirus (hrHPV) testing using the Cobas assay was, unexpectedly, negative, given the cancer diagnosis made in the same specimen. The goal of this case is to emphasize the importance of a multi-modal management strategy in cervical cancer screening, particularly in cases with discordant results in the HPV/Pap cotest.

Methods: Clinical history was collected and all the previous pathology exams were reviewed. Genotyping of the cytology and biopsy were conducted with Seegene Allplex HPV28 assay. GynTect methylation test was also performed in the last cytology specimen.

Results: The genotyping assay in cytology detected HPV types 68 and 61, classified by IARC as probable high-risk (group 2A) and low-risk (group 1) types, respectively. Additionally, the GynTect methylation test was positive, with a methylation score of 11. At the time of the consultation, a biopsy was performed and subsequent histological analysis confirmed the presence of invasive squamous cell carcinoma, with genotyping also being positive for HPV 68. The immunohistochemical assay p16 (clone E6H4) showed block-type expression in the carcinoma.

Conclusions: This case illustrates the complexities of current cervical cancer screening practices, emphasizing the need for multi-modal screening strategy that incorporates cytology, HPV testing, and epigenetic markers. The discrepancy between HPV testing methods underscores the importance of comprehensive HPV screening approaches and its validation. The cobas HPV test uses PGMY primers, which are known to have limitations in detecting HPV68a efficiently. According to recent data, HPV68 is only etiologically responsible for 0.2% cancers. The presence of abnormal (diffuse/block positive) staining for p16 is an acceptable surrogate marker of HPV association, in the setting of a squamous cell carcinoma of the cervix. Current clinical and pathological guidelines (LAST, WHO and ICCR) support two tools for confirming an HPV-association: direct identification of HPV products (DNA or mRNA) and block-type staining for p16. An E6/E7 test will also be performed in the latest cytology and in both biopsies, as the L1 region of the virus is prone to deletion during virus integration as disease progresses. Further investigation into the molecular mechanisms underlying this patient's carcinoma may provide valuable insights into alternative pathways of cervical cancer development and contribute to future screening and treatment strategies.

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#9218

Dynamic Spectral Imaging Colposcopy vs. Regular Colposcopy for Detecting CIN2+ in Women Referred with HPV-positive and/or Low-Grade cytology

24 - Colposcopy

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Background/Objectives: Dynamic Spectral Imaging (DSI) colposcopy has demonstrated improved sensitivity in detecting cervical precancerous lesions in some studies. However, the evidence remains limited, particularly for cases involving HPV-positive and/or low-grade referrals. This study aimed to compare the sensitivity of DSI colposcopy with regular colposcopy for detecting CIN2+ in these specific cases.

Methods: Women aged ≥ 18 years referred for colposcopy with HPV-positive cervical screening samples and/or low-grade cytology (AS-CUS or LSIL) were prospectively included in this multicentre comparative cross-sectional study (January 2017 to April 2024). They underwent either DSI colposcopy at one centre or regular colposcopy at two other centres. In the DSI colposcopy group, the first biopsy was taken from the area identified as the most abnormal by the colposcopist (colposcopy directed biopsy - CDB). A second biopsy was taken from the area deemed most abnormal based on the DSI map. If these two areas were the same, only one biopsy was taken from the area. In the regular colposcopy group, the first biopsy was also taken from the area identified as the most abnormal by the colposcopist (CDB). In both groups, all women had a total of four cervical biopsies taken in accordance with the Danish national colposcopy guidelines. Therefore, two to three additional biopsies were taken, either from other abnormal-looking areas or randomly, to ensure representation from all four cervical quadrants. The colposcopists were not asked to grade the additional biopsies in order. All four biopsies underwent separate histopathologic evaluation. The most severe histological diagnosis from any of the biopsies was considered as the gold standard.

Results: A total of 719 women had a visible transformation zone (type 1 or 2) with four representative biopsies: 411 (57%, median age = 31.4 years old) in the DSI colposcopy group and 308 (43%, median age = 39.6 years old) in the regular colposcopy group. The sensitivity of the CDB to detect CIN2+ lesions in the first biopsy was significantly higher in the DSI group than in the regular colposcopy group: 61.9%, 95% CI 53.5-69.7 vs 49.5%, 95% CI 39.4-59-6%, p<0.000. When adding the DSI-directed biopsy to the CDB, the sensitivity for detecting CIN2+ in the DSI group reached 69.3%. This sensitivity was based on an average of 1.3 biopsies per woman, as the colposcopists and the DSI map agreed on the most abnormal area in 64.7% of the cases (an additional biopsy was taken in 35.3%). This sensitivity of 69.3% is comparable to the sensitivity found when looking at the first two biopsies in the regular colposcopy group (68.3%, 95% CI 58.3-77.2, p=0.77). When three (89.7% vs 86.1%, p=0.13) and four biopsies (100% vs 100%, p=1.00) were taken, no differences in the sensitivity for detecting CIN2+ were found between the groups.

Conclusions: In the Danish setting with a high HPV vaccination rate and regular screening for cervical cancer for decades the use of DSI colposcopy does not seem to provide a clinically relevant improvement in the sensitivity for detecting CIN2+ lesions compared to regular colposcopy in women referred with HPV positive screening tests or low grade cytology.

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Increased treatment referrals post-introduction of human papillomavirus (HPV) cervical cancer screening and risk and rates of subsequent adverse obstetric outcomes

24 - Colposcopy

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Background/Objectives: As more jurisdictions around the world transition from cytology to human papillomavirus (HPV) testing for cervical cancer screening, referrals to colposcopy will increase. This is due to the fact that HPV testing detects cervical pre-cancer earlier and more accurately. This will in turn, increase treatment volumes and may cause concerns regarding the impact of treatment in childbearing women. Cervical precancer treatment may be associated with adverse obstetric outcomes in subsequent pregnancies. We examined risk of preterm birth (PTB) and low birthweight (LBW) among those treated for cervical precancer after HPV screening and compared rates of treatment, PTB, and LBW between an HPV- and a cytology-screened group from a large randomized controlled trial.

Methods: The HPV FOCAL Study, a large randomized trial conducted in British Columbia, Canada conducted from 2008 through 2016, evaluated the effectiveness of primary HPV screening. Participants who received HPV testing for cervical cancer screening and follow-up were linked to a province-wide perinatal data registry. Those with a singleton live birth after trial HPV screening (index birth) were included in this analysis (N=1,765). Adjusted odds ratios (aORs) were calculated comparing risk of PTB (gestational week <37) and LBW (birthweight <2500g) by precancer treatment status prior to index birth. Crude rates of treatment referral, PTB, and LBW were compared between the analytic cohort (HPV group) and the general population of the province, who receive cytology screening (cytology group).

Results: Among the 1765 women included in this analysis, 71 (4.0%) received a LEEP after a positive HPV result, 160 (9.0%) had PTB, and 85 (4.8%) had LBW at the index birth. Risk of PTB and LBW was non-significantly higher in treated women (PTB: aOR=1.32 (0.63-2.80); LBW: aOR=1.33 (0.50-3.55)). In the HPV and cytology groups, 1.5% and 0.6% were recommended for cervical precancer treatment, respectively. Rates of PTB were 9.1% and 10.5% and LBW were 4.8% and 6.1% in the HPV and cytology groups, respectively. In the HPV cohort, cervical interepithelial neoplasia grade 2 (CIN2) and grade 3 or higher (CIN3+) rates were similar, however in the cytology cohort twice as many CIN3+ were detected compared to CIN2.

Conclusions: Although not statistically significant, these findings suggested a potential elevated risk of PTB and LBW after LEEP treatment for cervical precancer. HPV screening led to more treatment compared to cytology; however, overall rates of PTB and LBW were similar across groups. Because HPV screening for cervical cancer identifies precancerous lesions earlier than cytology, we propose that this results in cervical treatments that are less damaging to the cervix, requiring less volume of the treatment area; thereby, causing less increased risk of future preterm births and low birth weight. This was suggested by differing distributions of CIN2 and CIN3+ across cohorts; further work is needed to confirm this hypothesis.

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#8880

Value of laser, photodynamic therapy, and follow-up observation in the management of cervical low-grade squamous intraepithelial lesions: a prospective cohort study

25 - Cervical neoplasia

Background/Objectives: To explore the value of CO2 laser, photodynamic therapy, and follow-up observationin the management of cervical low-grade squamous intraepithelial lesions (LSIL).

Methods: Women diagnosed with cervical LSIL and HR-HPV infection through colposcopy-guided biopsy from January 1, 2021 to December 31, 2023 were collected. According to a 1:1 ratio, 107 cases were included in each of the laser treatment, photodynamic therapy, and follow-up groups. The complete remission rate and HR-HPV clearance rate were compared during the 6-12 month follow-up.

Results: ①Comparison of clinical data among the three groups before treatment: The median age of the 321 patients was (34.9±8.1) years. Before treatment, Cytological abnormalities were present in 51.7%(166/321) of patients, and 35.2%(113/321) had HPV 16/18 infections. The accuracy rate of colposcopic diagnosis was 69.2%(222/321). Age, cytology results, HPV 16/18 infection, and colposcopy diagnosis in the laser group, photodynamic group, and follow-up group were compared, and the differences were not statistically significant (P>0.05).(2)At the 6-12 month follow-up, the complete remission rate was 89.7%（96/107) in the laser group, slightly higher than the 86.9%（93/107) in the photodynamic group, with no statistical difference between the two groups,$\chi 2$=0.41，P=0.523. However, both were significantly higher than the 64.4%（69/107) in the follow-up group ($\chi 2$=19.30，P<0.001；$\chi 2$=14.63，P<0.001). The HR-HPV clearance rates in the laser and photodynamic groups were 73.8%（79/107) and 68.2%（73/107), respectively, both significantly higher than the 32.7%（35/107) in the follow-up group ($\chi 2$=36.34，P<0.001；$\chi 2$=26.99，P<0.001), with no statistical difference between the laser and photodynamic groups,$\chi 2$=30.82，P=0.366.

Conclusions: CO2 laser and photodynamic therapy are effective treatments for cervical LSIL, significantly superior to follow-up observation in terms of lesion remission and HPV clearance rates. Individualized treatment plans can be developed based on the patient's age, duration of HPV infection, colposcopicimpression, and economic conditions.

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#9385

Evaluating the Influence of Transformation Zone Types on Cervical Margin Status Following LEEP

22 - Diagnostic procedures / management

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Background/Objectives: Cervical intraepithelial neoplasia is closely associated with persistent infection by high-risk human papillomavirus (hr-HPV), particularly types 16 and 18, which account for most cervical cancer cases. Loop electrosurgical excision procedures (LEEP) are commonly used to treat high-grade lesions, with endocervical margin status being crucial for treatment success. The type of transformation zone (TZ) influences margin outcomes, with studies indicating varying rates of negative margins across TZ types. Understanding these associations is essential for optimizing surgical management and minimizing recurrence risk. This study aims to evaluate the relationship between TZ type and endocervical margin status in patients undergoing conization procedures.

Methods: An observational retrospective study was conducted, including women referred to the Cervical Cancer Screening Appointment at a tertiary hospital between January 1st and December 31st, 2022. After initial assessment participants were found to have cervical precursor lesions and underwent loop electrosurgical excision procedures (LEEP). The primary outcome was margin status, classified as positive or negative. Cases with positive margin status were further evaluated concerning transformation zone type. Clinical information was collected from hospital records, and statistical analysis was performed using SPSS® version 29, employing the χ^2 test to evaluate associations between variables.

Results: A total of 108 women underwent loop electrosurgical excision procedures (LEEP) for cervical precursor lesions. The overall rate of positive margins was 26 cases (24.1%). Comparison of groups with positive and negative margins revealed no statistically significant differences in age, sexual debut, number of partners, parity, smoking status, cytology results, HPV genotype, or cone thickness. The analysis of conization margins according to transformation zones revealed distinct outcomes. Positive margins were observed in 13 (50.0%), 6 (23,1%) and 7 (26,9%) of cases in transformation Zone 1 (TZ 1), 2 (TZ 2) and 3 (TZ 3), respectively. Statistical analysis indicated a significant association between transformation zone type and margin status: specifically, TZ 1 was linked to positive ectocervical margins in 76,9% (10) of cases (p=0,02), while TZ 2 and TZ 3 were associated with positive endocervical margins in 92,3%(12) of cases (p=0,03). Among women with positive margins, 11 (36.7%) underwent repeat conization. When evaluating the persistence of cytological abnormalities, only 1 presented with high-grade lesions.

Conclusions: Our study found an association between transformation zone type and endocervical margin status in women who underwent LEEP. Specifically, TZ1 is linked to positive ectocervical margins, while TZ2 and TZ3 show a higher prevalence of positive endocervical margins. These findings highlight the importance of considering transformation zone type in surgical decision-making and patient management.

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#9291

Pregnancy outcome in women after cervical conization

34 - Conventional therapies

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Background/Objectives: Cervical conization can significantly affect pregnancy outcomes, increasing the risk of preterm birth and cervical insufficiency. The relative risk of preterm birth, represented by an odds ratio of 1.78, escalates with the depth of the excised cone. Following cervical conization, women experience shorter mid-trimester cervical lengths, with 17.2% of these women having preterm deliveries, compared to 6.2% in those who have not undergone the procedure. Conversely, there is insufficient evidence to support the notion that cervical stenosis impacts fertilization. The aim of this study was to understand the pregnancy outcomes in woman who had undergone a conization during pregnancy or experienced a pregnancy after the procedure.

Methods: A retrospective, unicenter, descriptive study was conducted using electronic medical records, encompassing all cervical conizations performed at the Cervical Pathology Unit of Unidade de Saúde Local de Santo António from January 2022 to August 2024. The cases of cervical carcinoma that underwent cervical conization at the Unit from January 2017 to August 2024 were also analyzed. Inclusion criteria were women who had undergone a conization during pregnancy and those who experienced a pregnancy after the procedure.

Results: A total of 557 patients were evaluated and 14 cases met the inclusion criteria. The mean age of participants was 32.8 years, with half being nulliparous. Most participants (57%, n=8) had received the HPV vaccination and were nonsmokers. Cervical conization was performed and the histological diagnoses were as follows: squamous cell carcinoma (n=3), villoglandular papillary adenocarcinoma (n=1), CIN3 (n=5), CIN2 (n=4) and CIN 1 (n=1). In terms of pregnancy outcomes, 4 patients experienced spontaneous abortions during the first trimester (28.6%), 3 had preterm births (21.4%), 3 pregnancies proceeded without complications, and 4 pregnancies are currently ongoing. Specifically, the preterm births occurred at a mean gestational age of 34.3 weeks, with an average birth weight of 2173 grams and a 5-minute Apgar score greater than 7. Among these 3 preterm birth cases, 2 were iatrogenic - due to the need for treatment of malignant disease a cesarean section was performed at 34 weeks. The only spontaneous preterm labor occurred at 36 weeks and 6 days.

Conclusions: Cone biopsy is associated with an increased risk of preterm birth and other negative obstetric outcomes, with the level of risk correlating with the depth of the excision. This information is essential for advising women of reproductive age who are receiving treatment for cervical intraepithelial neoplasia (CIN).

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#9306

Effectiveness of multi-ingredient Coriolus-versicolor-based vaginal gel in human papillomavirus (HPV) positive Greek women younger and older than 40 years. A sub-analysis of PAPILOBS GR study.

34 - Conventional therapies

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Background/Objectives: Both viral genotype and individual's age have been found to affect regression rates of HPV-dependent cervical lesions and HPV clearance [1,2]. The objective of this sub-analysis was to evaluate the effectiveness of a multi-ingredient Coriolus versicolor-based vaginal gel (Papilocare®) in the repair of cervical lesions and HPV clearance in women under and over 40-year-old, in real-life practice.

Methods: Papilobs-GR (NCT06399341) was a multi-centre, prospective, non-comparative, observational study, conducted in a Greek population. HPV-positive women with ASC-US or LSIL cytology and concordant colposcopy were enrolled. Participants received a 6-month treatment course with vaginal Papilocare® (once daily for one month, followed by every other day for five months), which could be extended to 12 months for individuals with altered cytology and/or HPV persistency after 6 months of treatment. Repair of cervical lesions was defined as normal cytology and concordant colposcopy. HPV clearance was defined as the combined outcome of total or partial clearance. Total clearance referred to a negative HPV test result or the complete elimination of all genotypes detected at baseline. Partial clearance was characterized by the disappearance of at least one genotype (relative to baseline) along with normalized cytology with concordant colposcopy. Results of lesion regression and HPV clearance at the end of the study (6 or 12 months) are presented.

Results: Among 524 total women enrolled in the study, 393 (75%) (mean age±SD: 29.7±5.4) and 131 (25%) (mean age±SD: 48.6±6.5) were under and over 40-year-old, respectively. At 6 months, 72.2% of the population under 40-year-old experienced regression of cervical lesions. The percentage increased to 75.0% at the end of the study. In the population over 40 years of age, the regression rate was 72.0% at 6 months, which increased to 78.4% at the end of the study. Overall, HPV clearance was achieved in 70.9% and 75.9% of women under and over 40-year-old, respectively, at the end of the study.

Conclusions: In real-life practice, a 6-month treatment with Papilocare® (prolonged up to 12 months, if necessary) effectively enhanced regression rates of mild HPV-dependent cervical lesions and HPV clearance in a Greek population of women under and over 40-year-old. These results are consistent with other published studies [1,3,4], and highlight Papilocare® treatment, as a proactive management option for women with HPV-dependent low-grade cervical lesions during the watchful waiting period.

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FC17 - Self-sampling II

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#8608

HPV self-sampling for cervical cancer screening in China: a multi-center study

13 - Self-sampling

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Background/Objectives: Human papilloma virus (HPV) self-sampling is a new method to collect cervical isolated cells, but research been carried out in multi-ethnic and multi-regional areas of China is scarce. We aimed to evaluate the accuracy and acceptability of HPV self-sampling and analyze the characteristics of HPV infection.

Methods: Women aged 25-65 years were recruited from 8 provinces in China. Women underwent clinician-sampling and self-sampling and were asked to complete a 65-question questionnaire on their acceptance of HPV self-sampling. The paired samples were analyzed for 23 genotypes of HPV by polymerase chain reaction.

Results: 5551 women were recruited, of which 5417 were eligible for analysis. 3163 women have completed and submitted the questionnaire. The top five infection genotypes were HPV 52, 58, 16, 39, 68. The highest infection rate was in 25-30 years group. The crude agreement between self- and clinician-sampling was 93.06%. 43.79% of women preferred self-sampling over clinician-sampling, 67.59% preferred doing self-sampling at hospital.

Conclusions: HPV self-sampling could be an effective supplement to traditional cervical screening in China. Clinicians' advocacy, timely reminders and guidance for women with abnormal results of self-sampling are needed. In addition, new vaccination and cervical screening recommendations might be adjusted to fit populations with different characteristics.

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#9531

Urine human papillomavirus (HPV) testing as a strategy for cervical screening in high-risk older women: the Alternative CErvical Screening (ACES) 65+ study

13 - Self-sampling

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Background/Objectives: In the UK, an arbitrary age cut-off of 65 years is used for routine cervical screening, despite mortality rates increasing exponentially from 70 years of age. Non-attenders of screening and current/ex-smokers from socioeconomically deprived backgrounds are at greatest risk. Speculum examination is poorly tolerated in this age group, but urine HPV testing is less invasive with similar sensitivity for cervical pre-cancer detection (CIN2+) compared to routine screening. Our aim was to establish the acceptability of urine HPV testing for cervical screening over 65-year-olds attending community-based lung cancer screening.

Methods: People attending community-based targeted lung health checks in Greater Manchester, UK who were 65 years or older with a cervix were invited to provide a urine sample using the Colli-PeeÒ, a specialised first void urine collection device, for high-risk HPV testing using Roche Cobas 8800. Participants whose urine tested HPV positive were offered a clinician-collected cervical sample for HPV and cytology testing. Colposcopy was performed on those with abnormal cervical samples. A questionnaire was used to ascertain acceptability of urine sampling for cervical screening.

Results: A total of 988 urine samples were tested for HPV. Eighty-three (8.4%) tested HPV positive, of whom 63 (75.9%) provided cervical samples, and 31 (49.2%) of these had positive findings. To date, colposcopy has been performed on 25 (2.5%) participants with 4 (0.4%) CIN2+ lesions detected so far. Urine self-sampling had high acceptability, with 895 (90.5%) participants confident about using the Colli-PeeÒ device.

Conclusions: The 0.42% CIN2+ rate is comparable to that of women over 50 years of age (0.5%) in the UK cervical screening programme. This suggests that the upper age limit for routine cervical screening warrants re-evaluation. Urine self-sampling was acceptable and could encourage screening uptake in high-risk individuals accessing healthcare for another indication.

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#9337

Comparison of healthcare worker versus self-collected HPV DNA cervical cancer screening in HIV positive and HIV negative women

10 - HPV screening

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Background/Objectives: Cervical cancer provides an excellent opportunity for screening. Self-sampling HPV screening has been well described. The objective of this study was to compare healthcare worker collected (HCW HPV) and self-collected HPV specimens (SCS HPV) with histology in women living with HIV (WLWH) and HIV-negative women (HNW).

Methods: SCS HPV and HCW HPV were tested for the presence of hr-HPV DNA using Hybrid Capture 2 assay in a defined screening population. Patients with positive screening results had colposcopy and biopsy. A random sample of negative screens had punch biopsy regardless of colposcopy findings. Performances of screening tests were evaluated against histology results adjusted for verification bias. Metrics for screening tests were calculated against CIN3+ histology. The kappa statistic for concordance HPV between SCS HPV and HCW HPV were calculated.

Results: From 909 women, mean age of 41.4 years, 512 (56.3%) were HNW and 391 (43.0%) were WLWH. In HNW, sensitivity of SCS HPV was 67.35 and for HCW HPV 59.18 ($p = 0.0067$), while the specificity for HCW HPV was 83.80 compared to 76.24 for SCS HPV ($p = 0.0025$). In both HIV groups the Cohen's Kappa agreement between the two sampling methods was good at 0.63 and 0.62 respectively.

Conclusions: The sensitivity of SCS HPV tests in HNW was higher compared to HCW HPV, while there was no difference in HIV infected women. Self-collected HPV sampling is an acceptable and viable option for primary cervical cancer screening in all women.

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#9358

Self-sampling versus physicians' sampling for cervical cancer screening - agreement

13 - Self-sampling

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Background/Objectives: Self-sampling HPV testing could help increasing cervical screening coverage. Several studies show that hr(high-risk) HPV testing on self-collected samples appears as sensitive for CIN2+ as cytology or hrHPV detection on clinician-obtained specimens, though less specific. However, there are few studies comparing these two sampling methods both for hrHPV test and other molecular analysis.

Methods: In Florence, 2000 women aged 34-64 will receive an invitation letter to participate in HPV screening and will be asked to undergo two sampling procedures: self-sampling using a dry swab and physician sampling. Each dry swab is rinsed and diluted 1:5 and 1:20 using Methanol-based solution to define the better volume for hrHPV detection. All hrHPV-positive samples (phisycian-obtained or self-collected) are triaged with Liquid-Based Cytology(LBC) from physician-obtained specimens and genotyped using a multiplex real time PCR assay detecting 28 individual HPV types simultaneously. Moreover, hrHPV+ specimens were analysed for promotor methylation status of FAM19A4 and mir-124-2 human genes using a multiplex real time methylation-specific PCR assay.

Results: To date, 425 women were recruited and 32 (7.5%) did not perform the self-sampling. 22/425 (5.2%) physician-obtained samples were hrHPV-positive with no invalid results. About self-sampling, 6/393 (1.5%) and 3/393 (0.8%) of 1:20 and 1:5 dilutions, respectively, resulted invalid to HPV-testing, while 24/393 (6.1%) 1:20 diluted samples and 38/393 (9.7%) 1:5 diluted samples were hrHPV positive. Concordance analysis was performed excluding the 6 invalid samples. There was good agreement between hrHPV results of clinician-collected samples versus both 1:5 and 1:20 self-sampling dilutions [Cohen's Kappa 0.57 (CI 95% 0.40 - 0.74) and 0.68 (CI 95% 0.51-0.84), respectively]. A good agreement was also verified between both self-collected dilutions [Cohen's Kappa 0.77(CI 95% 0.65 - 0.89)]. 29/30 hrHPV positive phisycian-obtained or self-collected samples were negative for malignant intraepithelial lesions, while one resulted unsatisfactory for cytological evaluation. HPV genotyping was also verified between the two sampling methods (physician-obtained samples vs 1:20 diluted self-collected samples) with 34,5% completely concordant, 44,8% concordant for at least 1 type and 20,7% fully discordant samples. To date methylation analysis was performed on 16 hrHPV positive women: 5 samples (2 physician-taken and 3 self-collected 1:20) resulted methylated in at least one of the two genes analysed. Using self sampling alone (1:20dilutions), the colposcopy referral rate would be 7.6% (30/393) but, applying a triage method based on extending genotyping, the immediate referral to colposcopy of women with HPV16/18+ or invalid samples would be 2.5% (10/393).

Conclusions: Our preliminary results show that self-taken and physician-collected samples have good diagnostic agreement for hrHPV screening test. Self-sampling could be a valid strategy in countries with poor participation in cervical cancer screening program; however, further analysis on molecular triage methods are needed to introduce Self-sampling in clinical practice.

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#9170

Results of direct mailing of HPV self-sampling kits in the Dutch population-based cervical screening programme

13 - Self-sampling

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Background/Objectives: The Netherlands has a well-organised, primary HPV-based cervical screening programme, with the possibility of using self-sampling (SS) (via "opt-in') since 2017. Since July 2023 the distribution of SS was changed, and kits are now directly mailed to first time invitees (at age 30) and with the reminder letter 12 weeks after the first invitation for all invitees. We evaluated the impact of this change on the cervical screening programme.

Methods: Data from the population-based screening and pathology databases was used. For the intervention group ("new SS method') women invited between July 11,2023 and December 31, 2023 were included and for the control group ("old SS method') women invited between July11, 2022 and December 31, 2022. We calculated I) participation rate (after invitation and reminder), II) reaction time between invitation and participation, III) participation in reflex cytology (for HPV-positive SS participants), IV) proportion of participants using SS, V) HPV positivity rate, VI) cytological results (Normal/ASCUS/LSIL/HSIL) and VII) histological results (CIN1/2/3/cancer). All results are stratified by age, screening history (first vs. subsequent round) and sampling method (smear vs. SS).

Results: The overall participation rate was 8% higher in the new SS method compared to the old method (from 42% to 50%). The strongest increase in participation was found in the first-time invitees (from 31% to 40%). Average reaction time was shorter in the intervention group (60 vs 62.4 days), with a steep increase in participation after 12 weeks (See Figure). The proportion of participants using the SS increased from 22% to 62%. In the 30-year-olds it even increased from 25% to 84%. The attendance rate for reflex cytology after HPV-positive SS decreased from 93% to 87%. Overall HPV positivity rates increased from 10.9% to 12.6%. The CIN3+ detection rates were similar in both periods.

Conclusions: Direct mailing of SS kits significantly increased the screening participation rates and shortened the response period after invitation, especially in the youngest women invited for screening. In all age groups the use of SS increased. So, direct mailing of SS seems to be an effective method to lower the threshold for participation. However, to guarantee overall screening programme effectiveness, it is important to ensure that HPV-positive SS users do participate in reflex cytology.

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#9444

Implementing primary care-based in-clinic HPV self-sampling to increase cervical cancer screening rates and reduce screening disparities: results from a quasi-experimental study in U.S. community-based clinics

13 - Self-sampling

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Background/Objectives: Offering in-clinic HPV self-sampling may increase cervical cancer screening and address screening disparities.

Methods: Three U.S. Midwest urban primary care clinics serving high volumes of Somali-Americans (a population with low screening rates) were selected as intervention clinics. In 2023, clinics implemented in-clinic HPV self-sampling as a usual care screening option. Intervention components included self-sampling instructions (including a Somali-American culturally-tailored version); clinical staff training materials; and workflow guidance, referral processes, and results reporting/communication. We used electronic health records from intervention and 37 control clinics to identify eligible individuals (30-65 years, ≥1 clinic visit, due for screening), demographics and screening completion (self-sampling or clinician-performed Pap/HPV test). We used Kaplan-Meier methods to calculate 12-month screening completion and difference-in-difference Cox proportional hazards regression to compare screening changes 12-months pre-/post-implementation in intervention versus control clinics (overall and restricting to Somali-Americans), adjusting for age, screening history, and social vulnerability index (SVI).

Results: Intervention (N=5,661) versus control (N=61,577) patients were younger (mean 44.4 versus 47.1 years), more likely to have no prior screening documented (66.5% versus 62.8%), had higher SVI scores (44.1% versus 13.0% in highest quartile), and a higher proportion were Somali-American (34.4% versus 2.3%). Somali-Americans attending intervention versus control clinics also had higher SVI scores (53.5% versus 30.3% in highest quartile). 12-month screening increased overall from 22.0%-34.4% pre-/post-implementation in intervention versus 54.5%-57.2% in control clinics (difference-in-difference adjusted hazard ratio [aHR]:1.39, 95% CI:1.25-1.55), and 17.2%-31.5% pre-/post-implementation in intervention versus 63.6%-66.0% in control clinics in Somali-Americans (difference-in-difference aHR:1.80, 95% CI:1.40-2.32).

Conclusions: Offering in-clinic HPV self-sampling in primary care increased cervical screening overall and in Somali-Americans. This is the first U.S. evaluation of in-clinic HPV self-sampling as a strategy for increasing screening and addressing screening disparities. Given recent U.S. FDA approval of HPV self-sampling in healthcare settings, results are applicable to other U.S. clinics implementing HPV self-sampling.

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#9428

Barriers to Cervical Cancer Screening and Experiences with Mailed Self-Collection Kits for HPV Testing among Asian/Asian American Women in a U.S. Safety Net Health System

13 - Self-sampling

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Background/Objectives: Cervical cancer screening rates have been declining in the U.S. and studies show that Asian and Asian American women have lower screening rates compared to other racial and ethnic groups. Self-collection for HPV testing is a strategy for cervical cancer screening that may address barriers to screening. However, there are little data regarding acceptability and effectiveness of self-collection among medically underserved Asian and Asian American women in the U.S. Here we describe barriers to usual care cervical cancer screening and experiences with mailed self-collection kits for HPV testing among Asian and Asian American women receiving care in a U.S. safety net health system.

Methods: Through a diversity supplement to the main trial, 113 Asian and Asian American participants were enrolled in the Prospective Evaluation of Self-Testing to Increase Screening (PRESTIS) trial,1 a pragmatic trial evaluating mailed self-collection in a U.S. safety net health system. Trial participants were screen-eligible women aged 30-65 years, enrolled in a safety net health system, and not up-to-date on cervical screening. For the supplement, study materials and procedures were translated into Vietnamese, the most common language spoken among Asian and Asian American health system patients. A nested telephone survey was conducted on n=27 participants randomized to receive a mailed at-home self-collection kit for HPV testing. A trained, bilingual (English/Vietnamese) member of the study team administered the survey.

Results: Over one third (40.7%) of the 27 interviews were conducted in Vietnamese. Most survey participants were born outside of the U.S. (88.9%). Prevalent barriers to provider-performed screening included lack of time to get a Pap test (40.0%) and difficulty getting an appointment (40.0%). Other frequently-reported barriers were perceived discomfort of pelvic exam (36.0%), being uncomfortable with male providers (36.0%), and not knowing how often to get screened (36.0%). Among those surveyed, n=11 (41.0%) reported using the kit. Those who used the kit had good experiences (81.8%) and found the bilingual (English/Vietnamese) instructions easy to understand (100%). Most or all reported self-sampling as more/equally convenient (90.9%); less/equally embarrassing (100%); and less/equally stressful (89.9%) compared to provider-performed screening. Among kit non-users who did not plan to complete the kit (n=5), reasons for not using the kit included lack of confidence in self-collection (60.0%) or fear of harming herself with the kit (60.0%), fearing cancer (40.0%), not feeling at-risk for cervical cancer (40.0%), being too busy (40.0%) and not understanding how HPV is related to cervical cancer (40.0%).

Conclusions: Survey participants reported time and access barriers to screening most frequently. This differs from barriers previously reported by PRESTIS trial participants of other races/ethnicities among whom modesty-related barriers (embarrassment, discomfort, and preference for a female provider) were the most prevalent.2 While acceptability was high among participants who utilized the kit, those who did not use the kit expressed numerous concerns that require further research.

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#9415

Engaging stakeholders to create an HPV self-collection practice facilitation guide

13 - Self-sampling

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Background/Objectives: Clinic workflow re-design strategies (e.g., offering human papillomavirus self-collection [HPV-SC] kits) have shown great promise to improve U.S. cervical cancer screening rates, particularly in settings that care for underserved populations. However, these settings, such as federally qualified health centers, often have limited organizational resources and capacity to adopt and integrate new cancer screening modalities like HPV-SC. Implementation strategies and resources are usually complex, resource intensive, and only accessible to larger and/or well-resourced healthcare organizations. Practice facilitation is an approach to support healthcare organizations to make meaningful changes in clinical workflows to improve patient health. A practice facilitation guide specific to HPV-SC could help clinical champions speed adoption, but only if flexible to the breadth of contexts in the U.S. Objective: Engage diverse stakeholders to create a flexible HPV-SC practice facilitation guide.

Methods: Members of the American Cancer Society (ACS) National Roundtable on Cervical Cancer (NRTCC) HPV self-collection workgroup worked to develop an implementation guide that was informed by a prior study (NIH-funded Isbaar) and on-going projects (NIH funded STEP-2 trial and Texas state-funded Project ACCESS) of workgroup members. The ACS NRTCC HPV self-collection workgroup's mission is to build resources for implementation of HPV-SC in the U.S. Building on the prior Isbaar Study facilitation guide, we used a systematic approach to identify the step-by-step process to integrate HPV-SC. To confirm and validate elements within each step, we iteratively engaged a diverse set of stakeholders including medical and lab directors, and ACS practice facilitators. Qualitative interviews with these stakeholders were analyzed using the rapid group analysis process.

Results: Stakeholders enthusiastically supported the guide's aim to be accessible to organizations of all sizes, with particular focus on usability by small and/or less-resourced ones. Practice facilitators stressed the importance of: engaging the broad range of payors to confirm coverage; providing clinical workflow tools (process mapping, guidance on management of HPV positive results); presenting motivational testimonials from clinicians, clinic staff, and patients; making the guide a live online document so that developers can update it per the evolving landscape in the U.S. Based on these findings, the steps in the guide are: 1) Talk to lab about HPV-SC availability, ordering, and reimbursement; 2) Assess workflow for delivering current cervical cancer screening processes; 3) Identify and assemble improvement team; 4) Build consensus and document workflow modifications; 5) Train clinic staff; 6) Implement modified workflow; 7) Monitor progress. Optional modules were included as appendices, e.g., EHR macros, and patient educational materials to increase outreach and follow-up adherence.

Conclusions: Stakeholder engagement ensured that the STEPS guide is practical, pragmatic and broadly accessible to the broad range of clinical contexts in the U.S. Pilot studies using this guide are currently on-going.

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#9176

Will Gynaecologist Offer Self Sampling Test for HPV Diagnosis to Their Patients? Perceived Barriers and Advantages of Self-Sampling Among Gynaecologist in Cuenca, Ecuador

13 - Self-sampling

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Background/Objectives: Ecuador has one of the highest cervical cancer mortality rates in Latin America, with a crude rate of 10.5 per 100,000 women. In 2022, 1792 new cases were diagnosed and 939 deaths due to cervical cancer were reported. Despite this, cervical cancer screening rates in Ecuador remain insufficient, 45,2% of women have never been screened in their lifetime. Previous research conducted in Cuenca, Ecuador, has demonstrated that self-sampling (SS) for HPV diagnosis has high sensitivity and specificity, as well as a high acceptability rate among rural and under-screened women. However, the adoption of self-sampling depends largely on the willingness of healthcare professionals to offer this test. The aim of this study is to evaluate the perceived barriers and facilitators of self-sampling in clinical practice, and to evaluate whether gynaecologists offer the test to their patients

Methods: Methods. A cross-sectional study was conducted between April and September 2024 in Cuenca, Ecuador. There are 146 registered gynaecologists practicing in Cuenca, and a purposive sample of 106 specialist was selected for this study. A validated questionnaire, developed by Zelli J and collaborators, was used to evaluate the acceptability of self-collected samples. The main topics addressed were socio-demographic characteristics, knowledge about self-sampling, perceived ability of women to use self-sampling, perceived barriers and advantages of the test, and the willingness to prescribe self-collected tests. A descriptive analysis was performed to address the study objectives.

Results: The mean age of the participants was 47.5 years. Of the 106 participants, 62 (58.5%) were female, and 44 (41,5%) were male. A total of 69 (65,1%) worked exclusively in private practice, while 37 (34,9%) were employed in the public sector. 68 (64,2%) reported having a high level of knowledge about self-sampling. A total of 61(57,5%) indicated that they would offer self-sampling to their patients, while 45 (42,5%) said they would not. The main perceived advantages of self-sampling included ease of use, 62 (58,5%), time savings for patients, 77 (72,6%), increased screening coverage, 88 (83%), reduced pain, 82 (77.4%), and reduced embarrassment, 88 (83%). The primary disadvantages noted were the lack of direct patient contact, 91 (85.8%), loss of opportunities to detect other health issues, 99 (93.4%), failure to diagnose other pathologies due to the absence of a clinical examination, 104 (98.1%), limited detection of other sexually transmitted infections, 88 (83%), and difficulties in following up on abnormal results, 94 (88,7%).

Conclusions: Gynecologists recognize the advantages of self-sampling. However, a significant portion of them are still reluctant to prescribe it to their patients. Self-collected tests are not yet widely available in either private or public healthcare facilities in Ecuador. Therefore, many healthcare professionals lack of sufficient knowledge of these techniques. Prior to large-scale implementation of self-sampling, it is crucial that specialist receive further education about this method to increase their willingness to offer self-collected tests.

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#9523

Human papillomavirus genotype and cycle threshold value from self-samples and risk of high-grade cervical lesions: a post-hoc analysis of a modified stepped-wedge implementation feasibility trial

13 - Self-sampling

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Background/Objectives: Human papillomavirus (HPV) testing of self-collected vaginal samples has potential to improve coverage of cervical screening programmes, but current guidelines mostly require those HPV positive on a self-sample to attend for routine screening.

Methods: A pragmatic modified stepped-wedge implementation feasibility trial was conducted at primary care practices in England. Individuals aged 25-64 years who were at least six months overdue for cervical screening could provide a self-collected sample. The primary outcomes included the monthly proportion of non-attenders screened, changes in coverage, and uptake within 90 days. Self-samples from 7,739 individuals were analysed using Roche Cobas 4800. Individuals who screen-positive were encouraged to attend clinical screening. In this post-hoc study of the trial, we related the HPV type (HPV16, HPV18 or other high-risk type) and cycle threshold (Ct) value on the self-sample to the results of clinician-collected sample and cervical intraepithelial neoplasia grade 2 or worse (CIN2+). We wished to triage HPV positive individuals to immediate colposcopy, clinician sampling, or 12-month recall depending on risk.

Results: 1,001 women tested positive through self-samples. 855 women who had both an HPV positive self-sample and a subsequent clinician-sample were included in this study. [The study has been accepted for publication. Since the study may have IP value and currently under evaluation by the IP team at Queen Mary University of London, we can not share the results through any public platform prior to the final publication. If needed, we could send through the results to specific committee members for evaluation]

Conclusions: HPV type and Ct-value on HPV-positive self-samples may be used for triage. The difference in the risk of CIN2+ in these groups appears sufficient to justify differential clinical management. A prospective study employing such triage to evaluate laboratory workflow, acceptability and follow-up procedure and to optimise clinical performance seems warranted.

FC18 - Diagnostics procedures / Management II

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Colposcopic diagnostics cervical glandular intra-epithelial neoplasia and new therapy

24 - Colposcopy

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Background/Objectives: The strongest disagreement that exists between the Pap test and histopathological finding is in glandular intraepithelial neoplasia. The first reason is anatomic - histological position of endocervical glands. The second reason is the two-fold way of emergence (HPV and non HPV-mutation of p 53 gene).

Methods: My study includes 100 patients between the ages of 18 and 45 years with a diagnosis of cervical intraepithelial neoplasia and adenocarcinoma in situ. In 70% of patients, the Pap test was normal. In 20%, the Pap test was ASCUS and in 15%, there was accompanying squamous intraepithelial neoplasia SIL). In 10% of cases, the Pap test was IIIa. HPV typing was positive in 80% and negative in 20%. Due to the anatomic position of cervical glands, the biopsy doesn't provide any diagnostic safety.

Results: The first step towards the exact diagnostics is colposcopy examination, not the Pap test. From the pathological colposcopy images, abnormal vascular pattern dominates within which areas with AW epithelium can be seen. In younger patients with HPV genesis, there are images of coarse mosaics and punctations. Radio wave LOOP excision gives absolute diagnostic therapeutic safety which I perform for 2 minutes in local anesthesia. The change is excised completely and the lumen of cervical glands is removed entirely.

Conclusions: The education of gynecologists that is directed towards colposcopy and not towards the Pap test and HPV typing, is necessary for diagnostics of glandular intraepithelial neoplasia. Relying on the biopsy as the safest diagnostic procedure, leads to a mistake in over 50%. The method which I invented (RF LOOP excision) involves, as the most significant part, a complete removal of the lumen of cervical glands. The most important thing is that the above-mentioned method doesn't lead to narrowing and shortening of the cervical canal in young girls that didn't give birth.

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#9408

Evaluation of a national External Quality Assessment (EQA) program for colposcopic examinations in Sweden 2022-2024

10 - HPV screening

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Background/Objectives: The Swedish cervical cancer prevention task force and colposcopy society (C-ARG) and Equalis have annually since 2022 conducted EQA in colposcopy inviting all Swedish gynecologists. EQA ensures quality and accurate, comparable examination results. The aim was to investigate the assessments of the colposcopic examination and to evaluate how/if an EQA scheme could be integrated into clinical praxis in Sweden. Results from three annual rounds (2022-2024) are presented.

Methods: The three rounds consisted of five patient cases per round, each including 3-6 digital images and a medical history. The cases, selected by six expert colposcopists, were assessed regarding various parameters, including transformation zone (TZ) type, colposcopic visibility, Swedescore, and a combined colposcopic impression. Participating gynecological clinics registered one consensus and five individual answers. The responses were reviewed against those assigned by the expert colposcopists based on histopathological confirmation from biopsies. Responses from the three rounds were compared and presented descriptively.

Results: Participation increased yearly; 103 (2022), 107 (2023), 132 (2024) responses, respectively. The type of TZ and colposcopic visibility had a high concordance for all cases compared to the expected response in all three rounds ((73-99% (2022), 70-99% (2023), 76-100% (2024)), while Swedescore had the largest variation of agreement between the cases and rounds (20-55% (2022), 14-73% (2023), 44-94% (2024). Concordance for colposcopic impression (benign, low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), suspected cancer) also varied between the cases and rounds (42-65 % (2022), 21-83% (2023), 69-86% (2024)). The lowest overall agreement was for cases with adenocarcinoma in situ (AIS) in the first two rounds (2022 and 2023) and for a case with a small lesion of HSIL close to a TZ type 3 in the 2024 round.

Conclusions: We found an increasing participation rate and agreement with the expected response for all parameters for every annual round. The concordance varied the most for the parameter Swedescore in all rounds. The EQA is a useful tool for quality assurance of colposcopy and may be used for educational purposes for colposcopists in Sweden.

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#9484

Beyond colposcopy: outcomes of cone biopsy without prior evidence of HSIL in women with persistent HPV infection

22 - Diagnostic procedures / management

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Background/Objectives: Persistent infection with human papillomavirus (HPV) is unanimously considered the main risk factor for cervical cancer, especially with genotypes 16 and 18. However, precursor lesions can be identified: low and high-grade squamous intraepithelial lesions (LSIL and HSIL, respectively). Recent evidence has demonstrated the higher sensitivity of HPV testing compared to cytology for diagnosis of these lesions. Colpo-cytologic discrepancy (normal colposcopy findings with abnormal cytology) is relatively common in cases of type 3 transformation zone and/or persistent HPV infection. Cone biopsy without prior evidence of high-grade intraepithelial lesion (diagnostic cone biopsy) can be considered in these cases, especially when colposcopy is unsatisfactory. This study's goal was to review the histologic results of diagnostic cone biopsies performed in a secondary-care hospital in Portugal.

Methods: Data was obtained from the hospital database regarding all diagnostic cone biopsies performed between January 2023 and February 2024.

Results: A total of 58 cases were found. The average age of the patients was 48,8 ± 7,8 years and 81.3% were not vaccinated against HPV. The most common cytology result prior to biopsy was atypical squamous cells of undetermined significance (ASC-US) in 52.6%; the remaining cases were negative for intraepithelial lesion or malignancy (NILM) in 26.3% and LSIL in 21.1%. Regarding HPV genotypes, the prevalence of HPV 16, 18 and 45 in this sample was 25.9%, 12.1% and 5.2%, respectively. The majority of patients (70,7%) were positive for other HPV genotypes. The majority of cone biopsy histologies were compatible with LSIL (84.2%) and a small amount revealed only chronic cervicitis (7.0%). HSIL was present in 5 cases (8.8%). Focusing on patients with HSIL diagnosis, one patient was positive for HPV 16 and the remaining four for other genotypes prior to the procedure. The previous cytology was ASC-US in three and NILM and LSIL in the remaining two cases; three women had completed HPV vaccination before undergoing cone biopsy.

Conclusions: Management of persistent HPV infection in clinical practice can be challenging. In our sample, only 8.8% of women who underwent diagnostic cone biopsy had a HSIL result. Cone biopsy in HPV-positive women with no prior evidence of HSIL can be considered in cases of persistent HPV infection and/or type 3 transformation zone, but should take into account individual risk assessment in order to avoid overtreatment of low-risk premalignant lesions, but also underdiagnosis of high-risk premalignant lesions (and cervical cancer).

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One stop cervical cancer screening and management

22 - Diagnostic procedures / management

Background/Objectives: Cervical cancer remains a leading cause of cancer-related mortality among women in low-resource settings, where access to screening and early detection is often limited. Traditional cytology-based screening and high-resource colposcopy are often impractical in these areas due to financial and infrastructural constraints. Globocan 2012 statistics further estimated that globally, 266 000 women died from cervical cancer in 2012. In low recourse settings, nearly 70 per cent of women diagnosed with cervical cancer die from the disease. We introduce a one stop scalable, sustainable, cost-effective model that provides molecular testing in conjunction with portable telemedicine tools linked together using innovative software tools designed to enhance accessibility to high-quality cervical screening.

Methods: DNA testing: cost-effective primary screening tool reducing unnecessary diagnosis. Self-sampling: reinforced by color-based quality control that empowers individuals to participate in routine screenings and drastically decreasing false negatives. Barcoding system: full traceability and confidentiality for all samples, which is essential for maintaining patient privacy and data integrity. Automated extraction process and robotic liquid handling: Open, rapid, reproducible sample preparation with the need for no trained personnel. Portable and affordable colposcopy solutions: The Gynocular provide accessible diagnosis. Software and telemedicine securely stores, organizes examination images and findings ensures documentation and ease of follow-up, minimizing lost cases. The diagnostic module is paired together with immediate, low cost treatment like thermal ablation to deploy a "see and treat' strategy.

Results: Fully Comprehensive End-End Cervical Cancer-Breast Cancer Screening and immediate Treatment Early Diagnosis followed by treatment and follow-up Self-sampling with quality control: Enhanced privacy, comfort and accecibility to cancer screening, keeping quality in check and increasing throughout. Automated testing platform: This helps mitigate human errors and enable high throughput testing. This also provides the best solution for the lack of highly trained lab technicians. High-Quality Imaging: Exceptional clarity in cervical imaging, and high quality ultrasound images enhances diagnostic precision. Portability: The compact and mobile design allows for use in various settings, including rural and hard-to-reach areas. Ease of logistics with lyophilized reagents enabling scaling up and reducing costs Software Solutions: Effective software solutions to triage patients and telemedicine to solve lack of highly trained gynecologists on site.

Conclusions: This comprehensive modular platform in addition to management and digitalization tools supports healthcare providers build a scalable, cost-effective model that ensures early detection, immediate treatment, and effective follow-up for cervical cancer, even in resource-limited settings. This also provides visibility and automation for seamless project planning and patient management. This also opens venues for research collaboration Working together on initiatives to gather and analyze data that will inform policy decisions and improve cervical cancer prevention strategies. This could also be instrumental for donors, funding agencies, pharmaceutical companies, and other organizations to initiate various programs in screening, treatment and research.

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#9469

Comparative study of topical 5-aminolevulinic acid photodynamic therapy and surgery in treating cervical intraepithelial neoplasia grade III

25 - Cervical neoplasia

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Background/Objectives: Surgical excision is the recommended treatment for cervical intraepithelial neoplasia grade III (CINIII). However, excision can destroy cervical anatomy and function, increasing the risk of adverse pregnancy outcomes. Topical 5-aminolevulinic acid photodynamic therapy (ALA-PDT) is a novel, non-invasive therapy for intraepithelial lesions. This study aims to compare the efficacy of ALA-PDT and excision for CINIII in women of reproductive age.

Methods: A total of 199 patients with CINIII were enrolled in this retrospective study. Among them, 103 patients received local resection and 96 patients received ALA-PDT. Human papillomavirus (HPV) genotyping, ThinPrep cytologic test (TCT) and colposcopy-directed biopsy were used to evaluate treatment efficacy.

Results: At 6-month follow-up, the lesion complete remission (CR) rate was 85.4% (81/96) and 97.1% (100/103) in the ALA-PDT group and surgery group, and the HPV clearance rate was 64.6% (62/96) and 81.6% (84/103) , respectively, with significant difference between them (P = 0.002 and P = 0.007). At the 1-year follow-up, the CR rate of the ALA-PDT group and surgery group was 95.1% (76/80) and 99.0% (96/97) and the HPV clearance rate was 91.3% (73/80) and 91.8% (89/97), respectively, with no significant difference between them (P = 0.177 and P = 0.905).

Conclusions: ALA-PDT in the treatment of CINIII has the advantages of good efficacy, less injury and fewer adverse effects. However, it must be admitted that its short-term treatment effect is relatively poor compared with suigical excision.

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#9438

Stratified mucin-producing intraepithelial lesion - it is not a reason to SMILE

22 - Diagnostic procedures / management

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Background/Objectives: Stratified mucin-producing intraepithelial lesion (SMILE) is a rare premalignant lesion of the cervix, first reported in 2000, and believed to originate from reserve cells in the transformation zone (1,2,3). The incidence of SMILE is reported to be approximately 0.6% in cervical biopsies (4). SMILE exhibits features resembling high-grade squamous intraepithelial lesions (HSIL) and adenocarcinoma in situ (AIS) (4) and is thought to be etiologically linked to persistent infection with high-risk human papillomavirus (HPV) genotypes, particularly HPV16 and HPV18 (2,3,4). Pure SMILE appears to be rare, accounting for less than 10% of cases; in the majority of instances, it is associated with HSIL or AIS (1,3) and has the potential to progress to invasive carcinoma (4).

Methods: We report a case of SMILE diagnosed in a patient with concurrent HSIL and LSIL, associated with high-risk HPV infection. This paper details the diagnostic evaluation and management of this uncommon cervical premalignant lesion. Key methods included colposcopy, histopathological examination, and immunohistochemical staining to confirm the diagnosis and exclude malignancy. Treatment consisted of standard transformation zone excision.

Results: A 37-year-old woman had been followed in our Colposcopy Unit for several years due to LSIL associated with high-risk HPV infection (HPV16). She later continued gynecological monitoring at another hospital. The patient was referred back to our unit with a diagnosis of HSIL on biopsy, along with persistent HPV16 and positivity for other non 18 and 16 high-risk HPV types. We then conducted a colposcopic examination, during which an extensive high-grade lesion was detected and biopsied. Histopathological examination and immunohistochemical staining revealed SMILE. Transformation zone excision confirmed the presence of SMILE in an extensive area of ectropion, along with HSIL and LSIL. Postoperative surveillance over two years demonstrated successful treatment of all cervical lesions, with normal colposcopic findings, negative cytology, and evidence of HPV clearance in recent tests.

Conclusions: In the 2020 WHO classification of cervical tumors, SMILE has been categorized as a subtype of AIS, with reports acknowledging dual histomorphological differentiation: glandular and squamous (3). This case supports the association of SMILE with HSIL and HPV16, indicating squamous differentiation. The stratified epithelium in SMILE resembles high-grade cervical intraepithelial neoplasia (CIN), characterized by abnormal nuclei with a high nucleus-to-cytoplasm ratio, nuclear hyperchromasia, and indistinct nucleoli (1,2,4). SMILE is defined by three histopathological features: (1) epithelial stratification, (2) diffuse mucin production throughout the layers, and (3) an absence of classic gland formation (1,2,4). Cytoplasmic mucin appears as discrete vacuoles or abundant clearing, often only visible with mucicarmine staining. The rounded epithelial-stromal interface and the lesion's location at the transformation zone support the theory that SMILE arises from reserve cells in this area. Aditionally, an invasive variant of SMILE has also been recently reported (4). Published resources on cervical SMILE are limited. The WHO 2014 Guidelines recommend managing SMILE as AIS. The risks of residual, undiagnosed, and recurrent lesions are assumed to be similar to those of AIS due to comparable pathogenesis and presentation of premalignant lesions 10-15 years before carcinoma.

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#9470

Efficacy of ALA-PDT in Treating Cervical Low-Grade Squamous Intraepithelial Lesions with High-Risk HPV Patients: A Multicentre Randomized Controlled Trial

01 - HPV disease and COVID-19

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Background/Objectives: Persistent infection with high-risk human papillomavirus (hrHPV) is a well-established cause of cervical cancer. Current management of low-grade squamous intraepithelial lesions (LSIL) of the cervix typically involves monitoring, though some cases progress to cervical precancer or cancer, necessitating timely intervention. 5-aminolevulinic acid photodynamic therapy (ALA-PDT) offers a minimally invasive treatment option for cervical squamous intraepithelial lesions (SIL). This study aimed to assess the efficacy of ALA-PDT in treating cervical LSIL with hrHPV infection and to investigate the relationship between various risk factors and treatment outcomes.

Methods: A total of 155 women with cervical LSIL and hrHPV infection were prospectively enrolled and randomly assigned to treatment and control groups in a 2:1 ratio. The treatment group received six sessions of ALA-PDT at 7- to 14-day intervals, while the control group underwent routine follow-up. Outcomes were assessed in both groups using hrHPV testing, cytology, colposcopy and biopsy at 6 and 12 months post-enrollment.

Results: At the 6-month follow-up, the lesion regression and hrHPV clearance rates were significantly higher in the treatment group than in the control group (lesion regression rate: 80.43% vs 56.10%; hrHPV clearance rate: 61.96% vs 29.27%; $P < 0.05$). By 12 months, both groups showed increased lesion regression and hrHPV clearance, with rates remaining significantly higher in the treatment group (lesion regression rate: 84.52% vs 65.71%; hrHPV clearance rate: 77.38% vs 54.29%; $P < 0.05$). Among patients receiving ALA-PDT, hrHPV clearance was significantly higher in those aged 0.05). Reported side effects of ALA-PDT were minor, including localized pain, pruritus, and a burning sensation, with no serious adverse effects or cervical structural damage noted.

Conclusions: ALA-PDT is an effective, safe, and minimally invasive option for treating cervical LSIL with hrHPV infection, irrespective of hrHPV subtype or TZ type. Age over 45 may, however, impact hrHPV clearance rates following ALA-PDT. This therapy is a valuable option for patients with cervical LSIL and hrHPV infection who require active intervention.

FC19 - HPV therapeutic vaccines / Immunotherapy

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#9260

DNA Immunotherapy, INO-3107, is Safe, Effective, and Elicits an Antigen-Specific T-cell Response in Adults with HPV-6 & 11 Recurrent Respiratory Papillomatosis

08 - Immunotherapy - Immuno-oncology - New treatments

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Background/Objectives: Recurrent Respiratory Papillomatosis (RRP) is a chronic, debilitating disease caused by Human Papillomavirus (HPV-6 and 11) characterized by recurrent benign but aggressive airway lesions. INO-3107, a DNA immunotherapy designed to generate T-cells against HPV-6 and 11, was evaluated for safety, immunogenicity, and efficacy in a 52-week Phase I/II study (NCT04398433).

Methods: Thirty-two adult patients with HPV-6 and/or 11 confirmed RRP that required ≥2 surgical interventions in the year preceding dosing received 4 INO-3107 doses at Day 0, Weeks 3, 6, and 9 via intramuscular injection followed by electroporation (EP). Patients underwent surgical debulking within 14 days of Dose 1. Laryngoscopy was conducted at screening and Weeks 6, 11, 26, and 52. The primary endpoint was safety and tolerability. Secondary efficacy endpoints were surgical frequency and validated endoscopic disease severity score (Modified Derkay-Pransky). Both peripheral and tissue localized immune responses were evaluated.

Results: INO-3107 was safe and well-tolerated. All 32 patients completed the trial and received 99% (127/128) of the protocol doses, with only 1 patient missing EP after an INO-3107 dose. Treatment-related adverse events (AEs) were reported in 41% (13/32) of patients and were limited to Grade 1 or 2 severity. The most common treatment-related AEs were transient injection site pain (31%) and fatigue (9%), with all others occurring in 2 or less patients. In total, 81% (26/32) of patients demonstrated a reduction of at least one surgery (overall clinical response, OCR) and 72% (23/32) experienced either a complete response of no surgery or a partial response of at least a 50% surgery reduction compared to the preceding year. Modified Derkay-Pransky disease severity scores improved from baseline to Week 52. Assessment of peripheral immune responses confirmed significant clonal expansion of T-cells through TCRb sequencing as well as T-cell activity against both HPV-6 and HPV-11 via ELISpot and multiparametric flow cytometry. Assessment of excised papilloma revealed a significant increase in T-cell infiltration and activity in patients exhibiting surgical reductions, inclusive of T-cell signaling, activation and cytotoxicity via TCRb sequencing, Ingenuity Pathway Analysis and single sample Gene Set Enrichment Analysis.

Conclusions: INO-3107 was safe and well-tolerated in adults with recurrent respiratory papillomatosis. The majority of patients (81%) required fewer surgical procedures and 72% required no surgery or experienced at least a 50% surgery reduction compared to the prior year. The induction of new peripheral T-cell responses after treatment, the increased T-cell presence identified in excised tissue, and the association between T-cell activity and clinical response support the proposed mechanism of action. These data suggest that DNA immunotherapy may be an exciting new therapeutic option for adults with RRP.

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#9222

Lipid Nanoparticles Outperform Electroporation in Delivering Therapeutic HPV DNA Vaccines

07 - HPV therapeutic vaccines

Background/Objectives: Therapeutic HPV vaccines that induce potent HPV-specific cellular immunity and eliminate pre-existing infections remain elusive. Among various candidates under development, those based on DNA constructs are considered promising because of their safety profile, stability, and efficacy. However, the use of electroporation (EP) as a main delivery method for such vaccines is notorious for adverse effects like pain and potentially irreversible muscle damage. Moreover, the requirement for specialized equipment adds to the complexity and cost of clinical applications. As an alternative to EP, lipid nanoparticles (LNPs) that are already commercially available for delivering mRNA and siRNA vaccines are likely to be feasible.

Methods: We compared three intramuscular delivery systems in a preclinical setting:(1) direct intramuscular (IM) injection of naked plasmid, (2) IM injection of naked plasmid plus electroporation (EP), and (3) IM injection of LNP-encapsulated plasmid. The immune effect was evaluated by IFN-γ cytokines produced by E6/E7 antigen-specific CD8+ T cells.

Results: Compared with direct IM injection, IM injection plus EP significantly enhanced the immune effect of the naked HPV DNA vaccine. ALC-0315 LNP B encapsulation administration significantly enhanced the immune effect of the HPV DNA vaccine compared with EP administration. DLin-MC3-DMA LNP A-, ALC-0315 LNP B-, and SM-102 LNP M-encapsulated HPV18 E6/E7 DNA vaccine all significantly induce HPV18 E6 and E7 antigen-specific immune responses. HPV DNA vaccine encapsulated by different LNPs shows different immune effects. In this study, SM-102 LNP M encapsulation for delivering HPV DNA vaccine shows the strongest immune effect.

Conclusions: LNP encapsulation is an optimal method for delivering a therapeutic HPV DNA vaccine, offering improved immunogenicity over traditional approaches.

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#8904

Application of cytokines in cervical secretion for high grade squamous intraepithelial lesion caused by HR-HPV infection

08 - Immunotherapy - Immuno-oncology - New treatments

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Background/Objectives: To analyze the correlation between the levels of 12 cytokines in cervical microenvironment and cervical intraepithelial neoplasia (CIN) in patients with high-risk human papillomavirus (HR-HPV) infection.

Methods: Methods: Sixty female patients with HR-HPV infection who were treated in the department of cervix of Shanghai First Maternity and Infant Hospital from March 2023 to March 2024 were selected. According to the results of colposcopy biopsy, they were divided into high grade squamous intraepithelial lesion group (HSIL group) and N-HSIL group, which include low grade squamous intraepithelial lesion and inflammation. The 12 cytokines of cervical secretion were compared between the two groups, and the Logistic regression model was used to analyze the correlation between HSIL and 12 cytokines in cervical secretion.

Results: There were statistical differences in 8 cytokines between cervical secretion and serum of the same patient. Significant differences in the cervical secretion levels of IL-6, IL-10, TNF-a, IFN-γ, IL-17A, IL-12p70, IFN-a and IL-8 were detected between the HSIL and N-HSIL group for Mann-Whitney test. Multivariate analysis showed that IL-10, IFN-γ and IFN-a were risk factors for HSIL.

Conclusions: The systemic cytokine profile cannot reflect the local microenvironment immunity and the occurrence of HSIL is related to the levels of cytokines in cervical microenvironment.

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#9307

The effect of bivalent HPV vaccination on cervical cancer and CIN3+ in the Netherlands: preliminary results of a national linkage study

07 - HPV therapeutic vaccines

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Background/Objectives: Bivalent HPV16/18 vaccination with a 3-dose schedule for 12-year-old girls was introduced in the Netherlands in 2010. In 2009, a catch-up campaign was offered to 13-16-year olds girls (i.e. born between 1993 and 1996). In 2023, the 1993 birth cohort was invited to participate in routine cervical cancer screening at 30 years of age. We aimed to quantify the vaccine effectiveness (VE) of bivalent HPV vaccination for cervical cancer and cervical intraepithelial neoplasia grade 3 or worse (CIN3+) using pathology results from cervical samples collected within and outside the cervical screening program up to early 2024.

Methods: We linked the vaccination status of women born in 1993 who were eligible for HPV vaccination in 2009 (n=104,661) with pathology results of cervical samples recorded in the Dutch nationwide pathology databank (Palga). Unvaccinated women or women fully vaccinated with the bivalent vaccine in 2009/2010 were included (n=97,961). The cumulative risks for histological outcomes of cervical cancer and CIN3+ were estimated for fully vaccinated (3 doses or 2 doses ≥150 days apart; n=47,130, 48.1%) and unvaccinated women (n=50,831, 51.9%). To account for differences in cervical cancer screening participation by vaccination status, we calculated the adjusted cumulative risk per group based on the following formula: cumulative risk of outcome detected outside the screening program + cumulative risk of outcome detected in the screening program divided by the cervical cancer screening participation rate. Both crude and adjusted VE estimates were calculated as (1-cumulative risk ratio)*100.

Results: Cervical cancer and CIN3+ were diagnosed in five and 171 vaccinated, and in 42 and 803 unvaccinated women, respectively (Table 1). Cumulative risk curves by age and vaccination status are presented in Figure 1. For cervical cancer, crude and adjusted VE estimates were 87.2% (95%CI 67.6-94.9) and 91.5% (95%CI 78.9-96.6) (Table 2), respectively. For CIN3+, corresponding VE estimates were 77.0% (95%CI 72.9-80.5) and 81.2% (95%CI 78.4-83.7). Table 1. Cumulative risks of cervical cancer and cervical intraepithelial neoplasia grade 3 or worse (CIN3+) by vaccination status with corresponding vaccine effectiveness estimates (preliminary results) Number of cervical cancer Diagnosed within screening program Diagnosed outside screening program Risk (%) VE (95% CI) Adjusted* VE (95% CI) Number of CIN3+ Diagnosed within screening program Diagnosed outside screening program Risk (%) VE (95% CI) Adjusted* VE (95% CI) Fully vaccinated (N=47,130) 5 0 (0.0%) 5 (100.0%) 0.011 87.2 (67.6, 94.9) 91.5% (78.9-96.6) 171 71 (41.5%) 100 (58.5%) 0.363 77.0 (72.9, 80.5) 81.2% (78.4-83.7) Unvaccinated (N=50,831) 42 17 (40.5%) 25 (59.5%) 0.083 Ref. Ref. 803 365 (45.5%) 438 (54.5%) 1.580 Ref. Ref. Abbreviations: CIN3+, cervical intraepithelial neoplasia grade 3 or worse; VE, vaccine effectiveness; Risk, crude cumulative risk; CI, confidence interval; Ref., reference category. * Adjusted for differences in cervical cancer screening participation by vaccination status.

Conclusions: High effectiveness of bivalent HPV vaccination against cervical cancer and CIN3+ was observed in the first birth cohort eligible for HPV vaccination that has entered the cervical cancer screening program in the Netherlands.

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#9333

Quadrivalent HPV16 therapeutic vaccine candidate induces robust and broad T cell responses and therapeutic efficacy in preclinical tumor model

07 - HPV therapeutic vaccines

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Background/Objectives: Despite the implementation of preventive HPV vaccination programs, the incidence of oropharyngeal squamous cell carcinoma (OPSCC) is rising, primarily driven by infections with human papilloma virus serotype 16 (HPV16). Therapeutic vaccines hold promise for the treatment for HPV-related cancers. Current vaccine candidates focus on targeting E6 and E7 HPV proteins. However, recent evidence suggests that expanding HPV-specific T cell responses by targeting multiple HPV proteins may enhance efficacy of therapeutic vaccines(1). This preclinical study investigates the therapeutic potential of an adenovirus vector-based quadrivalent HPV16 vaccine which targets the HPV antigens E1, E2, E6, and E7. The study evaluates HPV-specific T cell responses and antitumor efficacy.

Methods: The adenovirus vector-based vaccine encoding full-length HPV16 antigens (E1, E2, E6 and E7) fused with the MHC-II invariant chain (Ii), as the genetic adjuvant(2). The vaccine (Ad-Ii-E1E2E6E7) was administered intramuscularly in a heterologous prime-boost regimen both inbred (C57BL/6) and outbred (OF-1, Hsa-Ola, CD1) mice. An analogous vaccine targeting Macaca Fascicularis papillomavirus type 3 (MfPV3) was also evaluated in Macaca Fascicularis non-human primates with existing MfPV3 infection (NHP). CD8+ and CD4+ T cell responses in HPV-antigen stimulated splenocytes (mice) or MfPV3-antigen stimulated blood samples (NHP) were determined via intracellular cytokine staining and flow cytometry. In tumor studies, C57BL/6 mice were inoculated with C3 tumor cells expressing the HPV-antigens E1E2E6E7. Ad-Ii-E1E2E6E7 (2 x 107 infectious units) was both evaluated as monotherapy and in combination with cisplatin (3 mg/kg) administered intraperitoneally once per week for three weeks.

Results: Ad-Ii-E1E2E6E7 induced significant CD8+ T cell responses against all targeted proteins in outbred mice and elicited strong responses against E1 and E7 in inbred mice. In the NHP model, Ad-Ii-E1E2E6E7 vaccination led to significant elevated CD4+ and CD8+ T cell responses against the MfPV3 E1 antigen. In tumor-bearing mice, vaccination delayed tumor growth and prolonged survival time. Further analysis showed increased intratumoral infiltration of HPV-reactive CD8+ T cells and reduced proportion of tumor-promoting regulatory T cells. Ad-Ii-E1E2E6E7 demonstrated superior treatment efficacy compared to a peptide-based vaccine targeting only E6 and E7.

Conclusions: Therapeutic vaccination with the quadrivalent Ad-Ii-E1E2E6E7 vaccine induces broad and robust T cell responses in both murine and NHP models. The vaccine demonstrates favorable antitumor efficacy in the C3 murine HPV tumor model. These findings suggest that targeting E1 and E2, in addition to E6 and E7, might be a promising strategy for therapeutic vaccination of HPV-related cancers.

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#9521

Effects of Systemic Treatment with the Demethylating Agent Decitabine are Augmented by CDA Inhibition in HPV-Induced Tumors: A Preclinical Study

08 - Immunotherapy - Immuno-oncology - New treatments

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Background/Objectives: HPV-induced malignant transformation is closely associated with epigenetic alterations, particularly DNA hypermethylation in both the viral and host genomes. These epigenetic aberrations are not only consequences of E6/E7 oncoprotein activity but further contribute to the upregulation of HPV E6/E7. Targeting the aberrant methylation with demethylating agents thus represents a promising novel therapeutic strategy for HPV-driven (pre-)cancer. In this study, we evaluated the therapeutic potential of the DNA methyltransferase 1 (DNMT1) inhibitor 5-aza-2'-deoxycytidine (DAC, decitabine) in a preclinical mouse model of HPV-induced cancer. Given that DAC is susceptible to degradation by cytidine deaminases (CDA) in vivo, we co-administered DAC with tetrahydrouridine (THU), a CDA inhibitor, to inhibit DAC degradation and sustain effective plasma concentrations.

Methods: We inoculated immune-deficient NOD scid gamma (NSG) mice with HPV16-transformed CaSki cells and started treatment once tumors became palpable in all mice. Mice were randomly assigned to one of three treatment groups: PBS (control), low-dose DAC of 0.1 mg/kg (DAC-only), or low-dose DAC combined with 10 mg/kg THU (DAC+THU). Treatments were administered three times per week until predefined stopping criteria were met. Endpoint analyses included overall survival, tumor size, as well as treatment effects assessed through molecular biological analyses.

Results: Mice treated with DAC+THU demonstrated a significantly longer median survival (98 days) when compared to the PBS-treated control group (59 days) and the DAC-only group (66 days), indicating a substantial survival benefit. Tumor tissue analysis suggested that DAC+THU treatment induced destruction of tumor cells. Transcriptional analyses of the treated tumors are currently ongoing. Additionally, we did not observe any signs of toxicity, such as weight loss or behavioral abnormalities, in any of the treatment groups.

Conclusions: Our findings suggest that treatment with the demethylating agent DAC, especially when combined with THU, significantly improves survival outcome in HPV-induced cancer in a preclinical mouse model, without causing substantial toxicity. Hence, the combined approach holds potential as a novel treatment strategy for systemic treatment of HPV-associated malignancies.

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#9254

Acceptability of vaginally delivered therapeutic HPV vaccines in women in low-resource settings

07 - HPV therapeutic vaccines

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Background/Objectives: Achieving the 2030 WHO targets for cervical cancer elimination remains a significant global challenge. To address gaps, therapeutic HPV (T-HPV) vaccines, designed to clear or treat existing HPV infections, are under development. As most T-HPV vaccines are proposed as multi-dose regimens at differing intervals, novel vaccine delivery systems such as vaginal vaccines are needed for low resource settings to optimize coverage and minimize health system impact by decreasing the need for health system engagement for 2nd and 3rd doses of the dosing regimen. To date, there is very limited data on whether vaginal vaccines are acceptable women in low resource settings.

Methods: As part of a community-based program on HPV self-collection, rural Ugandan women aged 30-49 who have never been screened for cervical cancer were enrolled. Village health teams (VHTs) conducted door-to-door recruitment in 11 villages in Malongo sub-district. Participants completed a survey including demographics and items on vaginal vaccine acceptability. VHTs used pictorial information sheets to describe vaginal vaccines and to demonstrate how vaginal tablet and ring vaccines work. Vaccine attitudinal and acceptability items were assessed on a 5-point Likert scale and dichotomized (strongly agree/agree v neutral/disagree/strongly disagree). Differences between groups were determined using Fisher's exact tests; p values ≤0.05 were considered statistically significant.

Results: To date, 520 women were recruited from 5 villages. Most participants were married (76.7%) and had primary school education or less (90.1%). Self-reported HIV prevalence was 12.7%. All (100%) participants would be willing to use a vaginal vaccine to treat an existing HPV infection, but 62.5% expressed concern they would injure themselves inserting a vaginal vaccine. Overall, women expressed more confidence in their ability to insert a vaginal vaccine tablet than ring (94% v 64%; $p<0.05$). With appropriate instruction, women would prefer to insert a vaginal vaccine tablet (91%) and ring (61%) themselves than have a health care provider insert. Women ages 30-39 and 40-49 reported similar rates of confidence in their ability to insert a vaginal vaccine tablet (94%); while younger women were slightly less confident in inserting a vaginal ring (62% v 67%, $p>0.05$). Women living with HIV (WLWH) were less confident in inserting a vaginal vaccine tablet compared to HIV-negative women (84.8%v 95.6%; $p<0.05$); but were more confident in using a vaginal vaccine ring (76% v 62%; $p<0.05$). WLWH were more likely to feel they would harm themselves when inserting a vaginal vaccine tablet (60.6% v 41.9%; $p<0.05$).

Conclusions: Innovative solutions such as T-HPV are urgently needed, particularly for low-resource settings, to achieve global cervical cancer elimination targets. However, it is essential to ensure that novel technologies are acceptable to the target populations. In one of the first studies on this topic, both WLWH and HIV-negative women from a low-resource setting expressed strong willingness to use a vaginal vaccine to treat an existing HPV infection. Women preferred self-inserting vaginal vaccines themselves compared to health care provider insertion. While both vaccine tablets and rings are acceptable, women felt more comfortable using a vaginal tablet compared to a ring, confirming the need for careful education if both options are available.

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#8477

Application of amniotic membrane for treating chronic cervicitis: A case series

08 - Immunotherapy - Immuno-oncology - New treatments

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Background/Objectives: Patients with HPV infection usually present common symptoms of chronic cervicitis, emphasized the role of chronic inflammation in the development of HPV induced cervical cancer. Women with chronic cervicities typically suffer from vaginal discharge, dyspareunia, post-coital bleeding. The treatment of those with chronic cervicitis is controversial. Natural wound dressing using human amniotic membrane has been successfully empolyed in tissue healing procedures. Thus it may be a potential therapeutic option for patients with chronic cervicitis, in women infected by HPV to decrease the risk of cervical cancer and in women without HPV infection to ameliorate their symptoms.

Methods: In this case series, five women with the mean age of 33.8 and clinico-pathological diagnosis of chronic cervicities (through colposcopy and biopsy), were selected. All five cases had negative cotest and no premalignant lesion in colposcopy. Considering that their symptoms did not improve despite treatment by oral antibiotic, they were scheduled for dressing their cervix by dehydrated amniotic membrane (Amniodisc). After exposing by speculum, the cervix was dressed by Amniodisc (manufactured by Sinacell Company). The patients were advised to avoid sexual intercourse for one week.

Results: After two-month follow-up, the symptoms of five patients were dramatically improved and their cervix appearance in colposcopic exam were relatively healed in comparison with before treatment. No side effects reported. Colposcopic pictures are attached.

Conclusions: This is the preliminary result of an ongoing study. By finding the acceptable result from this small sample size, the study will continue on a larger sample size of women with chronic cervicities with or without HPV infection. Meanwhile, by this study it might be possible to suggest this new treatment for chronic cervicities.

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FC20 - Advocacy, acceptability and psychology

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#9194

Boys, Men and HPV: A global call for gender-neutral HPV vaccination

36 - Advocacy, acceptability and psychology

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Background/Objectives: We have the means to protect everyone - whatever their sex or gender - from high-risk HPV infections and the cancers they cause. But most countries with HPV vaccination programmes, especially in low- and middle-income countries, still vaccinate girls only and gender-neutral vaccination (GNV) is not fully recommended by the World Health Organisation (WHO). Boys are currently defined as a "secondary target population' who should be vaccinated only if this is "feasible' and "affordable' and does not divert resources from vaccination of the primary target population (girls) or cervical cancer screening programmes.

Methods: HPV is not solely a female issue. HPV causes 5% of all cancers worldwide. These cancers - cervical, anal, penile, vaginal, vulval, head and neck, which affect both men and women - can be prevented by HPV vaccination. GNV has now been adopted by over 70 countries worldwide, but at this time, no case has been made for its adoption globally as an intervention to prevent HPV cancers, where the focus has been on cervical cancer. We analysed the existing evidence and arguments around the opportunities presented by GNV and developed a case for action as to why WHO and individual governments not currently providing GNV should reconsider their position. This review included modelling of female only vs GNV programmes, HPV epidemiology and infection in males, HPV cancers in males globally, the impact of HPV on marginalised men, vaccine supplies and a discussion on programme resilience, equity and ethics of different vaccination strategies.

Results: Our new report: "Boys, Men and HPV: A Call for Global Gender-Neutral Vaccination' recommends that a more ambitious, ethical and equitable approach to HPV vaccination is needed at the global and national levels. GNV is cost-effective, would protect everyone more effectively and faster and would make vaccination programmes more resilient to disruption by misinformation campaigns and pandemics. It would help to reduce the stigma associated with this vaccine in many countries and would promote better public awareness of HPV and cancer. The report provides a series of recommendations to secure a HPV cancer free future, namely that the WHO should include boys in the primary target population for HPV vaccination, and that by 2030, all countries currently without an HPV vaccination programme should have introduced HPV vaccination on a gender-neutral basis, while countries currently with a girls-only programme should have transitioned to GNV.

Conclusions: The time has come for the recommendation and implementation of global GNV. The narrative that HPV vaccinations are for the elimination of cervical cancer alone may have been appropriate two decades ago when the vaccine was being developed and first introduced, but it is no longer consistent with the evidence. This shows clear public health benefits for GNV aided by single dose HPV vaccination programmes changing the economics of vaccination, an increase of vaccine supply to meet demand and a growing call from researchers and advocates in lower-income countries for the introduction of global GNV. A coordinated effort, coupled with global policy reform, is required for the prevention of all HPV cancers.

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#9047

HPV knowledge and acceptance of HPV vaccination among men who have sex with men (MSM) in Germany: Results of a cross-sectional study

37 - Health education

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Background/Objectives: Men who have sex with men (MSM) have a high risk of HPV infections that might lead to HPV-related diseases, such as penile, oropharyngeal and anal carcinomas. HPV vaccination has been proven effective in preventing certain HPV-related diseases. However, the German HPV vaccination recommendation targets only girls and boys aged 9-14 years (catch-up 15-17), leaving most adult MSM without the benefits of vaccination. Data about HPV knowledge and the perception of HPV vaccination among patients at higher risk in Germany is limited. Therefore, the objectives of this study were to assess MSM´s knowledge of HPV and HPV vaccination, as well as acceptance of HPV vaccination and vaccination uptake in Germany.

Methods: Ten physician study sites focusing on sexually transmitted diseases or men's health were included in this cross-sectional, non-interventional study. Main inclusion criteria were being an MSM, age 18-45 years and having a German health insurance. Data was obtained through an electronic questionnaire covering socio-demographics, sexual behavior, knowledge on HPV and HPV vaccination, acceptance, and uptake of HPV vaccination as well as impact of reimbursement on the vaccination acceptance. HPV and HPV vaccination knowledge were evaluated using sum scores based on a set of 20 questions for HPV knowledge and 5 questions for HPV vaccination knowledge, with correct answers receiving 1 point. Results were analyzed for the total MSM population and stratified by age groups (18-26; 27-45 years) and HIV status using descriptive statistics.

Results: Out of a total of 983 participants, 929 were eligible and included in the analyses. Median age was 31 years, with 280 (30%) and 649 (70%) participants in the age group 18-26 and 27-45 years, respectively. 845 (91%) attended at least 10 years of education; 122 (13%) were HIV positive and 717 (77%) used HIV pre-exposure prophylaxis (PrEP). Of the analyzed population, 731 (79%) had prior knowledge of HPV, and among those, 604 were aware of HPV vaccination. Mean sum scores for HPV knowledge (n=731) and HPV vaccination knowledge (n=604) were 13.28 (SD: 4.33) and 2.97 (SD: 1.33), respectively. Among those aware of HPV vaccination, 377 (62%) indicated acceptance (n=204 vaccinated; n=173 intention to get vaccinated), while 223 (37%) were undecided. The main reasons for being undecided included a lack of information and of mandatory reimbursement of vaccination costs in adults. For MSM who intend to get vaccinated, payment out of pocket and missing recommendation of their doctors were the main reasons for not being vaccinated yet. Nonetheless, 204 (22%) of all MSM (n=929) received at least one dose of HPV vaccination and 127 (14%) completed a full vaccination scheme.

Conclusions: Overall, there was a relatively high knowledge of HPV and HPV vaccination among participating MSM. Despite a notable proportion of MSM expressing acceptance towards HPV vaccination, vaccination rates remain low in this population. The main reasons for not being vaccinated yet are a lack of information and associated costs. Addressing these barriers by providing further information about HPV, potentially through treating doctors and social media platforms, alongside facilitating access by offering reimbursement options for vaccination costs, could potentially increase vaccination acceptance and uptake among MSM.

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#8748

HPV Vaccination Beyond the Commonly Known Primary Prevention: Survey of Attitude and Knowledge Among Polish OBGYNs - an Interim Analysis

06 - HPV prophylactic vaccines

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Background/Objectives: Growing evidence suggests that HPV vaccination (HPVv) offers benefits beyond the indications covered by National Immunization Programs (NIP), particularly for women treated for high-grade squamous intraepithelial lesions (HSIL/CIN2+), HIV-positive individuals, and immunosuppressed patients post-transplantation. However, clinical practices regarding HPVv vary widely among physicians. Recognizing this variability, the Board of the Polish Society for Colposcopy and Cervical Pathophysiology (PTKiPSM/PSCCP) identified an urgent need to evaluate the practices of obstetricians and gynecologists (OBGYNs) in Poland concerning HPVv. This survey was conducted in parallel with a study initiated by the European Federation for Colposcopy (EFC).

Methods: Polish OBGYNs, including residents, were invited to participate in an anonymous, 40-question survey encompassing five areas related to HPVv: general attitudes, awareness of guidelines, clinical practice, opinions on reimbursement, and perspectives on scientific evidence. The final four questions collected basic demographic information. Participation was voluntary, with an estimated completion time of 5-10 minutes, and implied consent was given through survey completion. The survey was conducted from February to October 2024, with a total of 138 physicians participating.

Results: Respondents ranged in age from 27 to 64, with nearly 70% being female. The ratio of specialists to residents was approximately 1:1. The survey revealed a generally positive attitude toward HPVv, with over 55% of participants having either received the vaccine or being in the process of vaccination. All participants reported discussing adult vaccination options with patients, and nearly 67% recommended the three-dose vaccination regimen. More than 95% adhered to Ministry of Health regulations, informing patients about vaccines available through the NIP. While familiarity with HPVv guidelines varied, most respondents demonstrated a reasonable level of awareness. Polish OBGYNs showed strong support for HPVv beyond standard primary prevention indications, advocating for use among women treated for HSIL/CIN2+, HIV-positive patients, and those with post-transplant immunosuppression. There was also broad support for expanding full reimbursement criteria. Although most respondents considered current scientific evidence for HPVv adequate, they recognized the need for additional randomized controlled trials.

Conclusions: Continuous education on HPV vaccination guidelines is essential for improving clinical practice. Further scientific research to support vaccination beyond primary prevention is anticipated and encouraged.

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#9459

Promoting Cervical Cancer Prevention in the Age of Social Media: Health Education, Market Agendas, and Screening Uptake Among Chinese Women

37 - Health education

Background/Objectives: Cervical cancer remains a significant public health issue in China, where incidence rates are comparatively high. Much of this morbidity should be avoidable with screening, but uptake rates for screening in China remain low. In response to this, the recent national health campagin has adopted a social media focus aimed at raising public health literacy and encouraging screening behavior across diverse literacy levels. However, official health communicators face strong competition from commercially-driven influencers and self-styled experts on social media who shape much of the discourse, particularly targeting young women. This study investigates popular social media content on Red (a major Chinese social media platform) related to cervical cancer and HPV screening, exploring how information about prevention, risk, and health responsibility is communicated. Additionally, the study examines social and cultural factors that may influence screening uptake and perceptions of women's sexual health.

Methods: This study was conducted from March to December 2024. This study adopts a mixed method approach, consisting of two phases to achieve the aim. Phase I consists of a discourse analysis to analysing popular social media posts in relation to HPV testing and cervical cancer screening. Data were collected from Red,between March to October 2024. Phase II consisted of in-depth interviews with 6 social media influencers recruited from Red.

Results: Three primary discursive strategies emerged from the analysis: (1) risk substitution: medical causalities about HPV transmission and risks are always substituted by narratives that frame femininity as inherently vulnerable and sensitive, emphasizing external threats to the "female body" rather than medical causality. (2) individualising responsibility: individualise responsbility to uptake screening is framed through women's ability to maintain balanced and healthy relationship with their self and with intimate others (3) marketised expertise: Health influencers construct their authority not on professional or medical qualifications but on their familiarity with market-driven wellness trends and peer endorsements, promoting expertise through commercial identities rather than medical validation.

Conclusions: These findings reveal significant shifts in how cervical cancer screening and preventive health are discussed on social media. The emphasis on vulnerability, individual responsibility, and commercialized expertise reflects broader social trends in the perception of women's sexual health.

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#8628

18-26-Year-Old Non-College-Educated Young Adults & TikTok Influence: An Exploration of Perceptions of the HPV Vaccine

37 - Health education

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Background/Objectives: National survey data show that only one in five young adults ages 18-26 are vaccinated against HPV. They are more likely to make their own health decisions; more likely to seek health information online; less likely to have health insurance: and less receptive to HPV vaccination messages. Previous research involving this age group has often targeted college students; however, roughly 60% of 18-26-year-olds in the U.S. are not enrolled in college, thus less is known about how to reach and engage them with HPV vaccination information. TikTok has emerged as an extremely popular social network, especially amongst young adults, with its 1 billion+ monthly active users worldwide and 100,000+ influencers. This presentation will review a study that sought to better understand knowledge, attitudes and beliefs about HPV vaccination and TikTok use amongst 18-26-year-old non-college-educated young adults in the U.S., as well as the creative process, relationship with followers, perceptions of the HPV vaccine and willingness to share information about it amongst TikTok influencers who reach this audience. It will describe methods and results, as well as implications for policy and practice.

Methods: The study team recruited two sets of people for this qualitative research study. Thirty-six non-college-educated young adults ages 18 to 26 participated in focus groups and nine TikTok influencers participated in interviews. We worked with a recruitment firm to recruit the 18-26-year-olds and with a social media influencer network to recruit the TikTok influencers. All interviews were recorded, transcribed, and then coded using NVIVO 1.6.1. Interrater reliability scores ranged from 0.42 to 0.86. Emergent themes were identified and the full team participated in an analysis workshop to come to consensus.

Results: Results from this study revealed how stigma around HPV is still a powerful deterrent to getting vaccinated for this age group, with a lingering disconnect between the vaccine and cancer prevention. As well, in the U.S., there remain substantial challenges with getting vaccinated due to cost and inconsistent/unavailable health care insurance coverage amongst this group. However, TikTok is a main way, if not the first place, that they gain access to information. They do not want to hear from experts or authoritative voices; instead, they want to hear from people like them. For the TikTok influencers, the relationship with their followers is paramount. They also reported having "deep" relationships with their followers, perhaps more so than any other social network. There was interest and support from these influencers in sharing HPV vaccination information - but it would need to be told in a storytelling style and format; and they felt that their followers would be open to that kind of messaging.

Conclusions: TikTok is currently an incredibly influential social network with young adults in the U.S. who are not easily reachable through more traditional channels. It is often a first place of exposure for news and information for them and perhaps more than any other social network, the characteristics of engaging on TikTok result in deep and trusting relationships between influencers and their followers. These findings suggest that TikTok may be ideal for sharing HPV vaccination information with this group in ways they will actually be receptive to.

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#9510

Human Papillomavirus (HPV) Vaccination Decision-Making Among Adolescent Girls in Japan

36 - Advocacy, acceptability and psychology

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Background/Objectives: The incidence of cervical cancer in Japan is high because of low screening coverage and a failed HPV vaccine program introduced in 2013 for girls aged 11-16yrs. After an initially high uptake, HPV vaccine coverage dropped to below 1% for nearly a decade following media coverage of adverse events and the government decision to suspend pro-active recommendation of HPV vaccine. Despite the resumption of vaccine recommendation in 2022, many girls and mothers remain undecided about HPV vaccination, stemming from long-standing public mistrust. Our study aimed to understand and contextualize the HPV vaccination decision-making process among adolescent girls in Japan to inform targeted HPV vaccine communication strategies.

Methods: Seven Focus Group Discussions (FGDs) with 33 girls aged 16-18 and 43 In-Depth Interviews (IDIs) were conducted from February 2023 to May 2024, both in person and online. Participants included HPV-vaccinated and unvaccinated individuals. FGDs explored the social environment influencing HPV vaccination decisions, while IDIs further elaborated on the girls' experiences and narratives about the decision-making process. Thematic analysis was used to analyze the data collected, leading to a conceptual framework of the HPV vaccination decision-making process. In April 2022, an HPV vaccine catch-up program was initiated for girls aged 17-26 who had missed vaccination due to the suspended recommendations, and participants were recruited from this cohort.

Results: [Preliminary] Thematic analysis of FGD data revealed discrepancies between the trusted information sources and those consulted by girls regarding the HPV vaccination. For instance, although healthcare professionals (HCPs) were highly trusted by the girls, communication barriers limited consultations with HCPs when girls decided to have the HPV vaccine. Conversely, despite recognizing the lack of credibility of social media, girls acknowledged its influence on their perceptions. They noted that information characteristics varied by medium, with social media featuring personal opinions and newspapers seen as reliable sources of accurate information. This indicated that girls perceived information differently depending on the source. IDIs further revealed the process and contexts shaping girls' HPV vaccination decisions. The decision-making journey was dynamic, beginning with awareness of HPV vaccines through various sources, interpreting conflicting information, communicating with diverse social groups, and reassessing perceptions based on social interactions. These factors collectively influenced whether girls chose to accept, refuse, or remained hesitant about the HPV vaccine.

Conclusions: [Preliminary] This study presents a conceptual framework for understanding girls' complex decision-making process regarding HPV vaccination. The framework can inform a more systematic approach to improve HPV vaccine communication strategies by identifying key intervention areas. Proposed strategies include communicating through preferred and perceived-reliable channels, such as providing more routine access to adolescent health services to increase consultations between girls and HCPs and collaborating with trusted health influencers in online forums.

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#9386

Claiming choices: increasing the acceptability of cervical cancer screening among women and girls in rural eSwatini

36 - Advocacy, acceptability and psychology

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Background/Objectives: Cervical cancer (CC) is a pressing public health challenge in eSwatini, where barriers such as social stigma, fear of judgment, and limited healthcare access restrict women's participation in essential screening. This study, conducted at St. Philip's Mission, a rural health clinic managed by the Missionary Sisters of the Sacred Heart of Jesus (MSCs), aims at investigating the acceptability of urine-based HPV screening as an alternative to the invasive cervical examination to increase CC screening uptake.

Methods: The research used a mixed methodology, including semi-structured interviews with women and girls aged 12-49, focus group discussions with key informants (health professionals, teachers, and outreach workers), and an ongoing survey targeting 200 women attending the clinic. Data collection focused on emotional, social and logistic barriers to accessing CC screening and preferences for different methods. Social and cultural representation of the disease, the experiences of comfort and discomfort in the healthcare facilities and the role of family networks, local organizations and schools are also investigated.

Results: Findings indicate that urine-based screening is well accepted among most participants, who cited discomfort with traditional methods as a primary barrier. The study also highlighted the crucial role of family networks, community-based organizations, and health workers in encouraging the screening. Possible strategies to overcome the stigma, the fear of judgement and misinformation about screening and cervical cancer itself include the strengthening of the mobile units to reach women and girls in remote areas, better health education involving multi-sectoral actors (teachers, health staff, community leaders) and the promotion of non-invasive methods of prevention such as urine-based screening testing. Psycho-social support provision is an additional tool to ensure the success of screening programs.

Conclusions: The acceptability of this screening and the potential increase of women reached will depend on a joint and sustainable effort of different social actors and the ability to implement advocacy interventions to improve communication and dialogue within the cultural context surrounding healthcare in rural Eswatini.

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#9205

Educational and communication strategies to improve HPV vaccination uptake: a systematic literature review

37 - Health education

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Background/Objectives: Despite strong evidence supporting vaccination, cervical cancer (CC) and Human Papillomavirus (HPV)-related diseases continue to pose significant public health challenges, requiring international efforts to address all barriers that can reduce vaccine acceptance and equitable uptake. In this context, enhancing knowledge among target populations is crucial for improving vaccination rates. This study, conducted as part of the PERCH project (PartnERship to Contrast HPV), aimed to explore educational interventions and communication strategies adopted at the international level to improve HPV vaccine uptake.

Methods: A systematic literature review was performed, querying three databases from July 1, 2006-the date of the first HPV vaccine licensure- through July 30, 2024. The review included studies focused on educational interventions and communication strategies employed by healthcare providers (HCPs) targeting populations recommended by the World Health Organization (WHO) for HPV vaccination, as well as parents, caregivers, teachers, and other influential individuals involved in vaccination decision-making.

Results: A total of 19 studies were included in the review, with 68% (13/19) focusing on educational initiatives and 32% (6/19) on communication strategies. All interventions were conducted by HCPs, with approximately 47% (9/19) detailing their qualifications. Medical doctors were identified as the primary developers in 55% (5/9) of these studies, with gynecologists and oncologists involved in 60% (3/5) of the interventions. In terms of target populations, 21% (4/19) of the studies involved parents or caregivers, and 32% (6/19) included both parents and adolescents. The remaining 47% (9/19) specifically targeted populations eligible for HPV vaccination, with over half (56%, 5/9) enrolling only females. Videos were the most commonly used channel for both types of interventions (63%, 12/19), followed by informative materials (42%, 8/19), social media (37%, 7/19), person-to-person solicitation (32%, 6/19), and slide presentations (16%, 3/19).

Conclusions: Understanding the strengths and weaknesses in HPV knowledge and communication is essential for developing tailored strategies to disseminate reliable information and equip target populations with evidence-based knowledge. Effective communication about the value of vaccination is also important for encouraging informed decision-making, shaping health policies, and guiding best practices, thereby contributing to the WHO's goals of eliminating cervical cancer and HPV-related diseases worldwide.

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#9303

Design and evaluation of a human papillomavirus awareness-raising campaign in a limited-resource setting: insights from difference-in-difference analysis in the Boeny region of Madagascar

36 - Advocacy, acceptability and psychology

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Background/Objectives: Human papillomavirus (HPV) is the leading cause of several cancers, highly incident in low- and middle-income countries, including Madagascar. Vaccination is a cornerstone of the prevention of cancer and other HPV-related adverse health outcomes, yet only 30% of low-income countries have introduced HPV vaccines in national immunization plans. Madagascar is in the planning phase for a nationwide HPV vaccination program. Though, it has been shown that awareness and knowledge of HPV is extremely poor in the population, even though HPV vaccine hesitancy does not seem to represent a critical barrier to the success of vaccination programs. In this study, we describe the design and evaluation of an awareness campaign aiming to raise community awareness and knowledge of HPV so as the importance of HPV vaccination in the Boeny region of Madagascar.

Methods: The 9-month awareness-raising campaign was structured based on a RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework and employed a multi-channel strategy, combining radio advertising with community outreach, lecture series, and social media posts. The campaign targeted the general population, healthcare professionals, medical students, and community leaders. The evaluation of the campaign involved both process and outcome indicators. The number of outreach actions, social media engagements and reach were estimated. Change in community awareness and knowledge of HPV was evaluated through population-based repeated cross-sectional surveys, pre- and post-campaign, using difference-in-difference analysis with propensity score weighting.

Results: From January to September 2024, a social media campaign was delivered via 36 weekly Facebook posts, reaching overall 4457 Facebook accounts. The engagement rate per post ranged from 5% to 88%. Posts on colposcopy examination, HPV preventive measures, and announcements of lecture series had the highest number of views. The mass media campaign comprised long (2.5 minutes) and short (30 seconds) discussions on HPV which were broadcast on two regional radio stations covering rural areas. A total of 25 community ambassadors received training on HPV to conduct community outreach activities. Posters and flyers were distributed in seven primary care facilities, one university hospital, and during social events. A lecture series of 3 lectures on HPV and cancer, was offered to 106 students. In the pre-campaign survey, among 2139 participants, 4.6% (CI 95%=4.0-5.9) were aware of HPV. Among those aware 28.3% (n=28) had heard about HPV vaccination. Data collection for the post-campaign survey is currently ongoing, changes in HPV awareness and knowledge in the target groups will be estimated.

Conclusions: Our preliminary results show that the campaign has a good potential for reach and effectiveness due to the low baseline levels of community awareness and knowledge of HPV and HPV vaccination in Madagascar. The evaluation of the impact of the campaign using difference-in-difference analysis will contribute to inform the planning for the implementation of HPV vaccination in the region and other similar settings.

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#8871

Impact of Digital Communication Message on HPV Vaccine Decision-Making Among Japanese Mothers: Online Randomized Controlled Trial

36 - Advocacy, acceptability and psychology

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Background/Objectives: Cervical cancer incidence in Japan has risen significantly since the late 1990s. In 2013, the Ministry of Health, Labour and Welfare (MHLW) added human papillomavirus (HPV) vaccines to the national immunization program. However, shortly after, videos and news of girls with unconfirmed adverse events following immunication spread widely on social media. Despite a lack of evidence linking HPV vaccines to these symptoms, the MHLW suspended proactive recommendations for the vaccine. By the end of 2013, HPV vaccine coverage plummeted from 70% to less than 1%. In 2021, the MHLW reinstated proactive recommendations, providing a critical opportunity to rebuild public trust. However, substantial barriers remain, particularly the long-term effects of misinformation on vaccine perceptions. This study aims to explore how Japanese mothers interact with online information about HPV vaccines and identify factors influencing their decision-making regarding vaccination for their daughters.

Methods: This study utilized a sixteen-arm randomized controlled trial conducted in an online survey environment. Participants were Japanese mothers of daughters aged 11-18 who had received zero or one HPV vaccine dose. A pre-experiment survey gathered demographic and vaccination history information. Mothers were then randomly assigned to view one of sixteen digital communication messages, varying in messenger, style, content, and misinformation presence. Post-experiment surveys evaluated how these messages impacted mothers' willingness to consent to HPV vaccination, their confidence in vaccine safety and effectiveness, trust in the message, and concerns about HPV-related diseases. Ethical approval was obtained from multiple institutions. Data analysis included descriptive statistics, Chi-square tests, and logistic regression, focusing on the relationships between message components and outcomes.

Results: A total of 1600 mothers participated, with 1324 included in the final analysis after excluding those uncertain about their daughters' vaccination status. Results indicated that mothers exposed to factual information displayed a significantly higher willingness to consent to vaccination (25.9%) compared to those exposed to misinformation (11.3%). Messages from organizations yielded higher willingness than those from individual messengers (20.7% vs. 16.3%). Confidence in vaccine safety and effectiveness was notably higher among mothers who viewed factual messages. Despite high trust in messages overall (87.3% to 91.6%), misinformation was believed by 88.5% of mothers exposed to misleading content. Concerns about HPV-related diseases were most pronounced among those viewing misinformation (53.5%), highlighting the detrimental effects of false narratives.

Conclusions: This study underscores the critical role of factual information and trusted organizational messaging in influencing Japanese mothers' HPV vaccination decisions. Misinformation significantly undermines confidence and willingness to vaccinate, necessitating urgent action to counteract false narratives. The findings suggest that effective communication strategies, including the use of conversational AI and targeted online interventions, can mitigate the impact of misinformation and support mothers in making informed vaccination choices. Emphasizing accurate information and addressing vaccine-related concerns will be vital for restoring public confidence in the HPV vaccine and improving vaccination uptake in Japan.

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#9517

knowledge, awareness and perceptions of HPV and genital cancers in Tunisia: focus groups discussions insights

37 - Health education

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Background/Objectives: Acceptance and uptake of human papillomavirus (HPV) vaccine are often influenced by cultural, social, and educational perceptions, as well as awareness of the risks associated with HPV infections and cervical cancer (1). HPV and its complications impose a high burden on Tunisian society (2), so introcing HPV vaccine in immunization schedule has been given top priority by Tunisia's decision-makers. This study aimed to investigate sexual and reproductive health perceptions and attitudes of Tunisian parents and teachers, with the aim to inform effective communication strategy.

Methods: Pasteur's Institute Institutional Review Boards approved the study. Using a qualitative design, we conducted 10 focus groups (FG) ((N=89) discussions sessions in five Tunisian regions during January and February 2024. Parents and teachers were asked about their knowledge and perceptions toward genital warts and genital cancers, along with their attitudes regarding the introduction of HPV vaccine in Tunisia. Discussions were transcribed verbatim, and analyzed thematically.

Results: Theme 1: Awareness Perceptions and Attitudes towards HPV and genital cancers: Discussions highlighted a lack of awareness of the genital female apparatus, genital diseases and its risk factors. Fostering such understanding was seen by a mother from the south as "culturally inacceptable". Another participant believed that sexual relations outside of marriage (religiously forbidden) are the cause genital cancers. Lack of knowledge also concerned genital warts, which were linked to poor hygiene by a father from a town in the north of the country. The lack of knowledge of genital apparatus and diseases had a negative impact on society's perception, where stigma still occupies a central place. During discussions, it was expressed that a disease that causes the loss of the uterus, necessarily make a women lose her female identity. For a father from the south, this automatically leads to divorce and social exclusion. Although most of our interviewees recognized the lack of education about sexual and reproductive health, they nevertheless consider that this culture should not be promoted among children and youth, because they believe that this could endanger our family-oriented identity. Teachers also rose that they experience discomfort when they address the topic of reproduction in the classroom. Theme 2: Perceptions towards the introduction HPV vaccine: As was the case of HPV, knowledge of its vaccine was very limited. This lack of knowledge would arouse resistance according to a teacher from the south east of the country.Moreover, some parents expressed fear and anxiety with regard to the vaccine introduction. As highlighted in the previous section, taboos and religious conservatism had a significant influence on the perception of the papillomavirus (HPV). A father form the north West of the country strongly rejected the vaccine « Why should I even think about sexually transmitted diseases? Extramarital sex cannot take place in a Muslim country». Many other statements highlighted the parent's tendency to associate the vaccine with a potential threat to the reproductive health of their daughters, thus reinforcing widespread hesitancy.

Conclusions: Our study highlighted the negative impact of social and religious conservatism on the perception of sexually transmitted diseases and genital cancers in Tunisia, highlighting the need for culturally tailored awareness programs, especially when introducing HPV vaccine.

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#9305

Preferences and Experiences for Women Participating in the Dutch hrHPV Screening for Cervical Cancer: what is important?

10 - HPV screening

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Background/Objectives: To improve participation in the cervical cancer screening, a self-sampling device (SSD) has been introduced in 2017 into the Dutch population-based screening programme (PBS). However, participation rates remain low, as for example in 2022 only 46% of invited women took part in the PBS. The aim of this study was to gather the most important preferences and experiences that might influence a woman's decision to use the SSD in the Dutch PBS.

Methods: Participants of the Dutch PBS who were referred to the hospital, were included with help of nine participating hospitals in the North of the Netherlands. Online questionnaires were sent, containing a list based on previous research with preferences and experiences possibly of influence in the choice of method of screening. Participants were asked to select nine items they considered to be most important, and subsequently rank those nine items from most to least important. Individual answers were combined to determine the overall most important items for women who participated with an SSD and women who participated by primarily having a cervical smear performed at the general practitioner (GP).

Results: 154 women who participated in the PBS filled in the questionnaire, of which 51 women used the SSD and 103 women primarily had a cervical smear taken at the GP. Top three most important items in the group of women who used the SSD were "Performing test in own time setting", "Ease of use" and "No need to make an appointment". In contrast, women participated by cervical smear, mentioned "Level of trust in performance", "Level of trust in results" and "Inconvenience of not seeing a doctor" as most important items. Remarkably, items such as "Accessibility" and "Performing test at own time setting" were selected by both groups.

Conclusions: Our study identified factors that are important for making a choice in method of participation of the PBS. Based on these results, a next questionnaire will be developed to be able to quantify the participants' actual experience of these items during screening. These findings will aid in a personalized approach in informing women about the different methods of participation to ultimately increase the participation rate of the PBS.

FC21 - Microbiome

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#9312

The Potential Association Between Lower Genital Tract Infections and the Development of Cervical Cancer: A Comprehensive Data Analysis from Western China

18 - Microbiome

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Background/Objectives: Common infections of the lower genital tract include bacterial vaginosis, anaerobic vaginitis, vulvovaginal candidiasis, trichomoniasis, chlamydia, mycoplasma, and others. Recent research has demonstrated that infections of the lower genital tract, particularly bacterial vaginosis, contribute synergistically to the persistence of HPV and the progression toward cervical cancer. However, there is comparatively less research on other lower genital tract infections and their association with the development of cervical cancer. This study aims to investigate lower genital tract infections and their association with the development of cervical cancer.

Methods: A total of 4,934 cervical pathological data were collected, including cytology, high-risk HPV testing, and assessments for lower genital tract infections (such as bacterial vaginitis, trichomoniasis, and candidiasis), at Gansu Maternal and Child Health Hospital from 2023 to 2024.

Results: The average age of the participants was 45.16 years (standard deviation: 11.21). Among them, 23.3% (n=1150) were classified as having pathology LSIL- (including normal and LSIL), while 76.7% (n=3784) presented with HSIL or more severe lesions (HSIL+). Lower genital tract infections were identified in the following descending order: 64.5% bacterial vaginosis (n=3,183), 28.1% candidiasis (characterized by budding cells with pseudohyphae) (n=1,398), and 4.7% trichomoniasis (n=231). In cases of pathological LSIL- and HSIL+, a significant difference was observed in the incidence of candidiasis ($P < 0.001$). However, no significant differences were noted in bacterial vaginitis or trichomonas infections. In the analysis of normal pathological partitions between hrHPV infected and uninfected cases, a significant difference was noted in bacterial vaginitis. However, no substantial differences were observed in trichomoniasis or candida infections. In the analysis of retrospective data, we conclude that bacterial vaginosis is associated with HPV infection and maintains a relatively high positive rate in cases of CIN+. In contrast, Candida infection appears to be more closely linked to lesions classified as CIN2+; however, Trichomonas has not been found to correlate with the progression of cervical cancer.

Conclusions: The summary of our findings suggests that increased attention should be directed towards the screening and treatment of bacterial vaginosis and candidiasis in cases where HPV infection or cervical lesions are diagnosis.

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#9448

HOST DNA METHYLATION AND CERVICOVAGINAL MICROBIOTA POTENTIAL ROLE IN HPV INFECTION PROGRESSION

18 - Microbiome

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Background/Objectives: Persistent infection with hr-HPV is the known etiological agent for cervical cancer development. Microbiome composition is being proposed for a potential role in the progression or regression of HPV infections. In fact it has been suggested that "Lactobacillus deplete microbiome composition may lead to a pro-inflammatory environment that can increase malignant cell proliferation and HPV E6 and E7 oncogene expression"(1,2). Regarding epigenetic biomarkers, several studies found linkage between some target genes methylation status and oncogenesis progression (3). The connection of epigenetic biomarkers and microbiota remains to be explored.

Methods: Cohort study with consecutive women referred for colposcopy in an organized cervical cancer screening program had colposcopy, biopsies and repeated hr-HPV testing. The ones that remained HPV negative at the time of colposcopy were now also tested with a panel of DNA methylation markers (ASTN1, DLX1, ITGA4, RXFP3, SOX17, and ZNF671). Cases with high methylation levels, hr-positive cases with lower levels of methylation and hr-HPV negative cases were selected in order to conduct 16s DNA sequencing to evaluate microbiome composition.

Results: The rate and level of methylation positively correlated with the severity of disease, while detecting 78.0% of the CIN3+ cases (3). 16s DNA sequencing experiments are still ongoing.

Conclusions: The studied methylation panel has a high sensitivity and specificity for CIN3+, correlating with the severity status of the lesions. The assessment of the potential relationship between methylation score and microbiota composition is still ongoing.

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#9435

Exploring the Interaction Between Cervix HPV, Oral-Nasal Microbiota, and Systemic Inflammatory Responses

18 - Microbiome

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Background/Objectives: The interaction between the microbiome and the immune system plays a distinct role in shaping the equilibrium in human health. Microbiota species have been identified as a key player in health regulation, but their impact on the cervix and oropharyngeal areas remains partially understood. This study aims to investigate the presence of HPV in the cervix and its interaction with the oral-nasal microbiota, as well as associated circulating hematological and inflammatory states.

Methods: We conducted an exploratory study with women attending gynecology appointments from 2022 to 2024. Participants were contacted by phone to complete a sociodemographic questionnaire. Subsequently, they were invited for an oropharyngeal swab to assess the microbiome. HPV genotyping and microbiome analyses were performed using Real-Time Polymerase Chain Reaction (RT-PCR), with additional microbiome species analyzed using Next-Generation Sequencing (NGS). Hemograms and inflammatory markers were assessed using standard procedures. Statistical analysis was conducted using SPSS software (v.27), with statistical significance set at $P<0.05$.

Results: We studied 30 women (mean age 41.8±11.9 years) for HPV presence in the cervix and characterized the oropharyngeal microbiota. Women with HPV-positive cervixes exhibited a higher circulating percentage of monocytes (P=0.018), a higher monocyte-lymphocyte ratio (P=0.006), and a trend toward lower eosinophils (P=0.085). Notably, vaccinated women showed an increased leukocyte count (P=0.036), with decreased monocyte percentage (P=0.004) and monocyte-lymphocyte ratio (P=0.006). Smokers presented with higher neutrophil percentages (P=0.062) and platelet counts (P=0.030). Women harboring potentially pathogenic oral bacteria had an elevated monocyte percentage (P=0.044), while those reporting oral sex showed higher platelet counts (P=0.034), platelet-lymphocyte ratio (P=0.024), leukocyte count (P=0.051), and a trend toward elevated C-reactive protein levels (P=0.078).

Conclusions: This project addresses the need for a deeper understanding of head and neck cancer's inflammatory pathways. Inflammation is a critical factor in numerous diseases, including head and neck cancer, which demands a comprehensive perspective. In this pilot study, we identified disruptions in inflammatory markers associated with pathogenic microbiome species and HPV positivity. A better understanding of these impacts could help lower healthcare costs associated with managing these conditions.

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#9251

Exploring the interplay of the vaginal microbiome, cervical cytology and HPV testing

18 - Microbiome

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Background/Objectives: This study evaluates the prevalence of different Lactobacilli species as a key component of the vaginal microbiome and their association with high-risk human papillomavirus (hrHPV) and cervical cytology outcomes.

Methods: A total of 166 reproductive-age women undergoing routine gynecological examinations at our hospital were included. Exclusion criteria comprised pregnancy, menstrual bleeding, other types of uterine or vaginal bleeding, recent antibiotic treatment (within one month), sexual intercourse (within three days), recent use of vaginal products, and transvaginal interventions (conization, biopsy, hysterosalpingography, hysteroscopy, and curettage) within the past month. Following informed consent, cervical and vaginal samples were collected with sterile swabs and sent for molecular identification of Lactobacillus species, which was analyzed at the Research Center for Genetic Engineering and Biotechnology using polymerase chain reaction (PCR) amplification of 16S rRNA genes and sequencing. A total of 147 women underwent liquid-based cytology (LBC), and 46 were analyzed for hrHPV.

Results: Positive cytology results were observed in 42 out of 147 women (28.6%). Among these, 32 had low-grade squamous intraepithelial lesions (SIL) (2 HPV; 29 CIN1), with Lactobacillus iners being the most prevalent Lactobacillus (19/ 59.34%), compared to Lactobacillus crispatus and Lactobacillus casei (3/ 9.37%). Four women exhibited atypical squamous cells of undetermined significance (ASCUS), three with Lactobacillus iners and one with a combination of Lactobacillus crispatus and Lactobacillus casei. Five had high-grade SIL (three CIN2 and two CIN3), where Lactobacillus iners was identified in two CIN2 cases, and in one CIN3 case; Lactobacillus delbrueckii in one CIN 3 case. One case of atypical glandular cells (AGC,NOS) had Lactobacillus crispatus and Lactobacillus casei and was hrHPV negative. Among the 46 hrHPV analyses, 30 were positive, with Lactobacillus iners most frequently associated with hrHPV (16/ 53.33%). Conversely, Lactobacillus crispatus was more prevalent among hrHPV-negative cases (7/ 43.75%). Notably, twelve hrHPV-positive women, treated with local application of carboxymethyl beta-glucan, tested negative upon follow-up 6-12 months later, with microbiome shifts from Lactobacillus iners to Lactobacillus gasseri and Lactobacillus crispatus observed in two cases.

Conclusions: Lactobacillus iners was more frequently identified in women with hrHPV compared to Lactobacillus crispatus, while Lactobacillus gasseri was exclusively identified in hrHPV-negative women. This interplay among different Lactobacillus species within the vaginal microbiome and their relationship with HPV, along with various other factors, is complex. However, ongoing research in this area holds significant promise for developing new screening methods aimed at predicting and preventing cervical cancer.

Loonen Anne
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#9425

Impact of DNA isolation method on a microbial community standard assessed by metagenomics nanopore sequencing - implications for vaginome research

18 - Microbiome

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Background/Objectives: The impact of an unhealthy vaginal microbiome (vaginome) is enormous and increases the risk of sexually transmitted infections, such as human papillomavirus (HPV). Shotgun metagenomic sequencing provides advantages over amplicon sequencing for analyzing the vaginome, but is a challenge to perform in lower microbial biomass samples with high human DNA content such as cervical scrapes. The ZymoBIOMICS microbial community standard is a well-defined mock community consisting of 3 Gram-negative bacteria (36%), 5 Gram-positive bacteria (60%) and 2 yeast strains (4%) with varying cell wall composition enabling validation of DNA extraction methods. In this study, the impact of three DNA extraction methods and 2 bioinformatics pipelines was evaluated on the community standard and cervical scrapes stored in PreservCyt buffer (Hologic).

Methods: After DNA extraction with the automated eMAG (Biomérieux), SwiftX DNA and SwiftX Hi-Sense (Xpedite Diagnostics) samples have been sequenced using the Native barcoding kit V14, flow cell R10.4.1 and MinION Mk1B. DNA yield was measured with Qubit dsDNA high sensitivity assay kit. Data was analyzed with both the EPI2ME Labs Metagenomic workflow (Oxford Nanopore Technologies) and the BugSeq Metagenomic sequencing pipeline.

Results: For the microbial community standard (30µl), DNA yield was 269ng with the eMAG method versus 127ng and 47ng for SwiftX DNA and SwiftX Hi-Sense, respectively. However, for the cervical scrape (3mL) eMAG resulted in a DNA concentration of 824ng and both Swift methods resulted in over 2300ng. Although the DNA yield for eMAG method was lower, this extraction method resulted in at least 4 times more nanopore reads for the clinical sample. Approximately, 94% of the obtained nanopore reads from the cervical scrape isolated with the automated eMAG system were of human origin. DNA extraction of the microbial community standard with eMAG, SwiftX DNA and SwiftX Hi-Sense resulted in 86%, 49% and 35% Gram negative bacterial reads, respectively. Furthermore, both Swift methods resulted in 36% (SwiftX) and 55% (Swift Hi-Sense) reads of other microorganisms (as compared to what is in the standard) or unclassified reads with the EPI2ME workflow. The BugSeq workflow showed similar results for the eMAG sample, however for the both Swift extractions a maximum of 18% reads of other microorganisms or unclassified reads was found. More Gram positives (35%) were recovered with BugSeq.

Conclusions: DNA extraction method and bioinformatics analysis have an impact on sequencing yield and species identification, indicating that both lab-based and bioinformatics methods need optimization. All extraction methods used show bias for Gram-negative bacteria. Currently, experiments are being performed with the ZymoBIOMICS DNA Miniprep kit as this lysis approach claims to eliminate bias associated with unequal lysis efficiencies of different micro-organisms. Fortunately, the vaginome does not contain a large diversity of microorganisms and is predominantly composed of Gram-positive bacteria, the bias towards Gram-negative bacteria may not play a significant role.

Salord Fiol Marina
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#9336

Efficacy of an intensive regimen of a multi-ingredient Coriolus versicolor-based vaginal gel in enhancing HPV clearance: results from the PALOMA Clinical Trial.

22 - Diagnostic procedures / management

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Background/Objectives: Cervical cancer is closely associated with persistent HPV infection. Although most of HPV infection will clear spontaneously within two years, certain factors, such as viral genotype, increase the risk of persistence. In the PALOMA clinical trial one of the reported secondary outcomes was to assess the efficacy of a Coriolus versicolor-based vaginal gel increasing viral clearance.

Methods: Randomised, multi-centre, open-label, parallel-group, clinical trial with a watchful-waiting control group. Unvaccinated HPV-positive women aged between 30-65 with ASCUS/LSIL cytology and concordant colposcopy were randomized (1:1:1) into 3 groups of different Coriolus versicolor-based vaginal gel treatment regimens: A) Standard regimen: once daily for one month, followed by every other day for five months; B) Intensive regimen: once daily for three months, followed by every other day for three months; C) Control group: watchful-waiting approach. Results of arm B vs C on HPV clearance are presented. HPV clearance was classified as either total clearance (defined as a negative HPV test or the disappearance of all species detected at baseline) or partial clearance (defined as the disappearance of at least one HPV genotype present at the baseline, along with normal cytology and concordant colposcopy observations).

Results: A total of 91 HPV-positive women were included in the study, with a mean age of 40,5 years. Among the 31 women in Arm B (intensive regimen), 24 were high-risk (HR)-HPV positive, while in Arm C (control group), 26 out of 31 women were HR-HPV positive. The intensive regimen showed significant increase of HPV clearance compared with the control group, both in total HPV (75.9% vs. 41.9%, p=0.0077) and HR-HPV positive (81.8% vs. 40.0%, p=0.0036) population.

Conclusions: After a 6-month treatment period, an intensive regimen of a Coriolus versicolor-based vaginal gel significantly increased HPV clearance in patients infected with HR-HPV genotypes compared to conventional watchful waiting approach. These findings highlight the Coriolus versicolor-based vaginal gel as an effective intervention for promoting HPV clearance and potentially reducing the risk of cervical cancer.

Hey Jana
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#9076

Cervicovaginal bacterial communities in adult Malagasy women of reproductive age with human papillomavirus infection and female genital schistosomiasis

18 - Microbiome

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Background/Objectives: The vaginal microbiome (VM) plays an important role for women's health and changes in its composition have been associated with several sexually transmitted infections. Specifically, the VM is described to have a role in the persistence of human papillomavirus (HPV) infection. Furthermore, recent findings suggest that female genital schistosomiasis (FGS), caused by a chronic infection with Schistosoma haematobium, might exacerbate the risk of both HPV infection and cervical cancer. Typical symptoms of FGS are non-specific and diagnosis is done using colposcopy. Few studies have described the characteristics and variability of the VM in association with FGS, showing different bacterial communities or abundant Trichomonas vaginalis. The objective of our study was to characterize the VM of women of reproductive age in Madagascar - a country with a high burden of both FGS and HPV infections.

Methods: A cross-sectional study was conducted at three Primary Health Care Centres in the district of Marovoay in the Boeny region of Madagascar, recruiting in total 500 women. Data was collected from women aged 18-49 years between March and August 2021, including socio-demographics, personal habits and clinical history. Cervicovaginal lavage fluids (CVL) were collected and all women were screened for HPV infection and presence of FGS, by performing E7-MPG using a Luminex bead-based technology and colposcopy, respectively. CVL samples were shipped to the Institute of Clinical Molecular Biology, Kiel, Germany, for 16S rDNA sequencing. Using speciateIT, taxonomy classifications on species level were inferred. VALENCIA was used to identify community state types (CST) in our population. Alpha diversity was calculated using the Chao1 index; beta diversity was displayed using principal coordinate analysis based on calculations with Bray-Curtis dissimilarity metrics.

Results: From 500 enrolled participants, 414 were included in the final analysis after quality check of testing results. The sequencing of 16S rDNA of these 414 women showed that the genera Gardnerella, Sneathia and Mycoplasma were more abundant in HPV-positive women, but no significant variations were observed among women with different FGS and HPV/FGS statuses. Moreover, five community state types (CST I - V) could be identified. The majority of VM (57.6 %) were characterized as CST IV (highly diverse and without Lactobacillus dominance), followed by 33.3 % with CST III (dominated by Lactobacillus iners). Variability in the alpha and beta diversity was associated with urbanicity, profession, diet behavior, antibiotics usage and dyspareunia.

Conclusions: To the best of our knowledge this is the first study describing the VM in a Malagasy population. Our preliminary results showed no Lactobacillus dominance in our Malagasy study population. Further studies are needed to characterize the role of VM for high burden gynecological disorders, especially those affecting the most neglected populations.

FC22 - Methylation II

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#9629

Hypermethylation of FAM19A4 and hsa-mir124-2 in vaginal self-samples.

17 - Methylation

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Background/Objectives: Cervical cancer screening has allowed for early detection and treatment of cervical cancer. Even though screening is efficient for identification of dysplastic lesions, not all women participate in screening. Self-sampling has shown to increase screening compliance although that the vast majority of self-sample-HPV-positive women have normal cytology. Testing for hypermethylation of promoters of genes FAM19A4 and hsa-mir124-2 might potentially be used for triage of self-sample high-risk HPV positive women. The aim of the study was to examine the association between hypermethylation among high-risk HPV positive self-samples and high-grade squamous intraepithelial lesion (HSIL) or worse.

Methods: In total, 155 vaginal self-samples were analyzed. We used a biobank with high-risk HPV-positive self-samples (APTIMA, sample transport medium (STM) tubes), stored at refrigerator temperature, collected from women attending screening between 2018-2021. The study population consisted of one case group and two control groups, all of which tested positive for high-risk HPV in self-samples (APTIMA). The case group (N=52) consisted of women with cervical histology of high-grade squamous intraepithelial lesion (HSIL) (N=2) and cancer (N=2). Control group 1 (N=50) and 2 (N=53) consisted of women with normal cytology who tested positive and negative for HPV at follow-up of cervical samples, respectively. The mean age was 43 years (range 30-69), and control samples were age matched (+/-4 years), using the HSIL+ group as reference. All data concerning diagnoses and HPV status were retrived from the pathology patient database registry. Methylation test: Self-collected samples were diluted 1:4 (100 µL sample and 300 µL water) and DNA was extracted (400 µL input and 50 µL output) by a MagDEA Dx SV 200 kit on a magLEAD 12cG robot. The bisulfite conversion and clean up were performed with the EpiTect Bisulfite Kit. The QIAsure methylation test was performed according to the manufacturer's instructions, where 2.5 µL bisulfite-converted DNA was used, and PCR conducted on the Rotor-Gene instrument. The Rotor-Gene Assay Manager automatically interpretated the results. Samples without Ct-values from the methylation markers were arbitrary given a maximum Ct-value of 40 cycles, and ΔΔCt-values were calculated by subtracting the Ct-values of ACTB from the given Ct-values of FAM19A4 and/or hsa-mir124-2. Statistical analyses were made by SPSS (SPSS statistics, version 28)

Results: Among self-samples, hypermethylation was detected in 35% (18/52) of the case group, including two hypermethylated cancer cases. The control group 1 and 2 showed hypermethylation in 14% (7/50) and 6% (3/53), respectively. Significant differences between hypermethylation in the case group compared to each control group were observed (p-value 0.021 and <0.001). Associations between greater hypermethylation values for FAM19A4 and increasing age were found in all subgroups (p-values <0.05).

Conclusions: This study showed increased proportion of hypermethylation among HPV positive self-samples from women with HSIL or worse. Among these cases the hypermethylation proportion was relatively low (35%). Speculatively, this hypermethylated subgroup might represent HSIL with increased risk for progression to cancer. Furthermore, we observed increased methylation signal in self samples along with age, regardless of cytology diagnosis. This is similar to a study of cervical samples showing increased hypermethylation by age (1).

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#9476

Performance of a six-methylation-marker assay on predicting post-LEEP pathological results of cervical HSIL patients: a retrospective study

25 - Cervical neoplasia

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Background/Objectives: The loop electrical excision procedure (LEEP) is a recognized therapeutic treatment for cervical intraepithelial neoplasia grades 2 and 3 (CIN2/3), primarily employed in patients preoperatively diagnosed with high-grade squamous intraepithelial lesions (HSIL). Subsequent assessment of postoperative pathological outcomes is routine. However, discrepancies between preoperative colposcopic biopsy results and postoperative pathological outcomes have been observed in certain patients. GynTect®, a six-methylation-marker assay tailored to measure the methylation status of six specific marker genes, has exhibited potential as a triage tool for cervical lesion detection and prognosis prediction. Therefore, the objective of this study was to assess the effectiveness of GynTect® in predicting post-LEEP pathological outcomes.

Methods: A retrospective analysis was conducted to examine the clinical profiles, GynTect® results, and postoperative pathology outcomes of 78 outpatients diagnosed with HSIL who underwent LEEP. Prior to surgery, cervical cytology samples, high-risk human papillomavirus (hrHPV) detection, and methylation analysis were obtained from each participant. Preoperative colposcopic impression and biopsy results were recorded. Statistical analysis and multivariate logistic regression were undertaken using IBM SPSS Statistics 25.

Results: Among the negative-GynTect® patients, 19 cases (57.6%) showed pathological downgrading post-LEEP, while 14 cases (42.4%) experienced sustained or upgraded pathological results. Among the positive-GynTect® patients, 8 cases (17.8%) showed downgraded pathological results post-LEEP, and 37 cases (82.2%) showed sustained or upgraded pathological results. The difference was statistically significant (p=0.001). Multivariate regression analysis identified positive GynTect® outcomes and colposcopic impressions suggestive of HSIL on the day of surgery as independent predictors of pathological upgrading following LEEP.

Conclusions: This study pioneeringly underscores the potential of GynTect® in predicting post-LEEP pathological outcomes, thereby showcasing its promising capacity to aid clinicians in selecting appropriate therapeutic regimens for patients with HSIL.

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#9424

Development of a Bisulfite-free DNA methylation marker-based diagnostic test for cervical cancer diagnostics

17 - Methylation

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Background/Objectives: An infection with high-risk human papillomaviruses (hr-HPV) may lead to precancerous lesions and cancer. In cervical cancer screening, HPV-testing was therefore implemented in several countries to either supplement or replace the cytology-based diagnostic measures (Pap test). However, these methods show their limitations, so reliable triage tests are needed tolimit invasive diagnostics and treatment to those who need it. ScreenYu Gyn® is such areliable triage test based on the detection of DNA methylation. In detail, one specific human genomic marker region (ZNF671) and one control marker (Beta-actin; ACTB) are analyzedby methylation-specific qPCR following a DNA bisulfite conversion of the diagnostic sample.To avoid the tedious DNA bisulfite treatment we aimed to replace it by using methylation-sensitive restriction enzymes (MSRE) to be able to detect methylated marker DNA in the background of unmethylated DNA. Based on this technique an MSRE qPCR assay was developed for the detection of DNA methylation in the marker region ZNF671.

Methods: For this study, cervical smears from 204 women with the cytology findings NILM (n=100), CIN I (n=17), CIN II (n=17), CIN III (n=66) and CxCa (n=4) were selected. All samples,collected and stored in liquid-based cytology medium (PreservCyt solution, Hologic), werepreviously tested using the ScreenYu Gyn® assay following manufacturer instructions. Regarding the MSRE-based assay, gDNA was isolated from the same 204 cervical smears, digested using methylation-sensitive restriction enzymes and afterwards amplified in a specific probe-based duplex qPCR. In this setting, only DNA that is methylated and thus not digested, will be amplified. The control marker ACTB has no restriction sites and thus provides a measure for the DNA input and a reference for quantitative evaluation (calculation ΔCtZNF671-ACTB).

Results: The 204 cervical smears were successfully tested with both assays, the ScreenYu Gyn® test as well as the MSRE qPCR-based assay for the detection of DNA methylation in the genomic marker region of ZNF671. The MSRE assay showed promising results. Regarding the assignment to the cytological findings six of the 100 NILM samples were false-positive in the MSRE assay. In the tested 17 CIN I and 17 CIN II samples, for each six were tested positive. In the CIN III cohort 42 of 66 samples were positive. All four CxCa samples were correctly detected. The invalidity rate of the MSRE assay results with 5,8 % compare to 0,9% in ScreenYu Gyn® higher. Furthermore, a clear connection could be observed between the ΔCtZNF671-ACTB and the severity of the underlying disease.

Conclusions: The developed MSRE qPCR based assay is an alternative method for the detection of DNA methylation. In contrast to established assays based on DNA bisulfite conversion, MSRE-based methylation assays provide the opportunity for further developments such as, fullyautomated tests in diagnostic laboratories or Point of Care tests e.g. for rural settings.

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#9229

Risk Stratification of HSIL Progression Using Longitudinal Methylation and HPV Genotype Analysis

17 - Methylation

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Background/Objectives: Women vaccinated against HPV are now entering the cervical cancer screening programs, creating a need for improved screening tests and methods to distinguish which cervical lesions will regress without treatment. A predictive test could change the landscape of screening and treatment of high-grade intraepithelial lesions (HSIL). This study investigated whether the S5 methylation panel could, over time, distinguish between lesion progression and regression in untreated cervical intraepithelial neoplasia grade 2 (CIN2) cases. We also examined the role of HPV genotypes in the context of HPV vaccinated and unvaccinated populations.

Methods: Pyrosequencing methylation assays and Luminex-based HPV genotyping were performed on exfoliated cervical cells from 171 women, aged 18-30, in an active surveillance study of CIN2 at Helsinki University Hospital, Finland (ISRCTN91953024). Participants were monitored every 6-months, for two years. Clinical outcome groups were categorized as progressed (≥CIN3) and regressed (<CIN1). HPV-genotypes were categorized into four groups based on hypothetical vaccination scenarios: unvaccinated, vaccinated with bivalent HPV vaccine, and vaccinated with the nine-valent vaccine.

Results: Out of the 171 women, 42 either persisted or progressed to HSIL or more severe lesions, while 129 regressed to normal histology. S5 methylation panel alone predicted lesion progression with an odds ratio (OR) of 1.14 (95% confidence interval (CI) 1.05-1.23) across all progressed cases. Interestingly, the mean S5 methylation levels remained stable throughout the 2-year surveillance period. Contrary to expectations, the S5 methylation levels closer to the time of HSIL treatment did not reveal stronger predictive associations compared to the baseline measurements, with mean S5 values ranging from 7.58(±SD 0.59) to 8.13(±SD 1.51). In cases involving non-vaccine-covered HPV types (39, 51, 56, 59, 66, 68, and 70), a borderline significant OR of 1.14 (95% CI 1.00-1.30) was observed for progression. When excluding HPV 16 and 18, the S5 classifier showed a similar association with progression as seen in unvaccinated women (OR 1.14, 95% CI 1.00-1.31). For lesions excluding all nine-valent vaccine types, the association was the strongest, with an OR of 1.16 (95% CI 1.01-1.32) for lesion progression.

Conclusions: The S5 classifier shows promise as an early prognostic biomarker for lesion progression in both HPV vaccinated and unvaccinated women. Initial findings suggest that S5 could be particularly useful for women vaccinated with the bivalent HPV vaccine and even for those receiving the nine-valent vaccine. However, further validation in larger cohorts of women from real-life HPV vaccination settings is needed to confirm these results.

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#9030

Novel triple-target panels utilizing methylation-sensitive restriction enzyme-based quantitative PCR for detecting advanced cervical precancers and cancers among high-risk HPV-positive women

17 - Methylation

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Background/Objectives: Optimal triage option for high-risk HPV-positive (hrHPV) women remains uncertain. We aimed to utilize methylation-sensitive restriction enzyme-based quantitative PCR (MSRE-qPCR) technique and develop triple-target human gene methylation panels to improve detection of advanced cervical precancers and cancers (CIN3+) among hrHPV women.

Methods: Eighteen candidate genes were detected by MSRE-qPCR in cervical samples from hrHPV women. All possible triple-target panels from these genes were generated by logistic regression models with repeated ten-fold cross-validation on a training set of 1223 women (180 CIN3+; 1043 <CIN3). Panels demonstrating satisfactory performance in a validation set of 937 women (69 CIN3+; 868 <CIN3) underwent qPCR redevelopment and retraining. Triage performance, screening efficiency and risk stratification of retrained panels were then compared with traditional triage strategies (Cytology [ASC-US], HPV16/18 genotyping, HPV16/18 genotyping combined with cytology [HPV16/18+Cytology]) within the validation set. Flowchart of the methodology can be found in Figure 1.

Results: Two panels were finally identified and retrained for CIN3+ detection. Panel1 includes JAM3, PCDHGB7, and SORCS1; while Panel2 consists of PAX1, ZNF671, and ASCL1. Compared to traditional triage strategies, both panels demonstrated superior AUC (Panel1: 0.799 [0.748-0.851]; Panel2: 0.790 [0.735-0.845]; Cytology: 0.532 [0.479-0.584]; HPV16/18 genotyping: 0.589 [0.528-0.650]; HPV16/18+Cytology: 0.515 [0.475-0.554]; all PAUC <0.001), with substantially higher specificity (83.06% [80.40%-85.50%]; 86.98% [84.56%-89.15%]; 29.49% [26.48%-32.65%]; 72.93% [69.84%-75.86%]; 14.52% [12.24%-17.04%]), comparable sensitivity (76.81% [65.09%-86.13%]; 71.01% [58.84%-81.31%]; 76.81% [65.09%-86.13%]; 44.93% [32.92%-57.38%]; 88.41% [78.43%-94.86%]), and requiring fewer colposcopies per CIN3+ case (3.77 [3.01-4.87]; 3.31 [2.64-4.29]; 12.55 [9.71-16.59]; 8.58 [6.20-12.41]; 13.16 [10.36-17.06]). However, Panel1 and Panel2 were statistically indistinguishable (PAUC=0.603; Ratiosensitivity: 0.92 [0.76-1.13]; Ratiospecificity: 1.05 [1.01-1.08]). Unlike traditional strategies (risks: 5.59%~17.97%), both panels exhibited excellent risk stratification capabilities, as evidenced by immediate CIN3+ risks below 4% for women tested negative on either panel (Panel1:2.17%; Panel2: 2.58%), supporting safe deferral for at least one year. Risk stratification results are illustrated in Figure 2

Conclusions: Two triple-target human gene methylation panels were successfully developed, each integrated into a single MSRE-qPCR system for one-tube detection. Both panels outperformed current triage strategies, indicating their potential as alternatives, though external validation acorss diverse settings and long-term followup are essential before clinical application.

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#8771

Primary ASCL1/LHX8 host-cell methylation analysis vs primary HPV screening in the IMPROVE primary HPV screening study

17 - Methylation

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Background/Objectives: The introduction of cervical cancer screening has substantially decreased the incidence of cervical cancer in high-income countries, but it remains the fourth most common cancer in women globally. Various molecular markers are under investigation as potential triage methods in HPV-positive women, including host-cell methylation analysis. Triaging however, adds to the complexity of screening and in settings where it is difficult to implement, it is therefore interesting to evaluate whether methylation assays can be used as a primary test, without additional triage testing. This study investigates ASCL1/LHX8 DNA methylation analysis as a potential primary screening test on self- and clinician- collected samples.

Methods: Data of two rounds of HPV screening were analyzed, comprising 10,651 women originally enrolled in the IMPROVE-study who were randomized to HPV self-sampling (n=5821) or clinician-sampling (n=4830) at baseline. Clinical performance of the HPV GP5+6+ PCR test and ASCL1/LHX8 methylation test were compared, stratified by enrolment collection method and age. Sensitivity and specificity of both tests for detection of CIN3+ were estimated by Bayesian techniques.

Results: For clinician-collected samples in women younger than 40-years, the sensitivity of the methylation test was lower than that of the HPV test (50.4% vs. 75.6%), but its specificity was higher (94.7% vs. 90.2%). In women 40-years or older, sensitivities of the methylation and HPV test were similar (81.3% vs. 81.8%) but the specificity was lower for the methylation than for the HPV test (89.7% vs. 94.7%). In self-collected samples, the methylation test was inferior to the HPV test with respect to both sensitivity and specificity, irrespective of age.

Conclusions: Primary methylation analysis on clinician-collected samples may be considered as a primary screening test in women younger than 40-years because of a favorable specificity when compared to HPV testing. However, the sensitivity for detection of CIN3+ was relatively low so that shorter screening intervals may be required. Primary methylation analysis on self-collected samples is not yet recommended.

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#9550

Assessing Methylation-Based Triage Assays in HPV Screening: A Proof-of-Concept Study Using Archived Cervical DNA Samples

17 - Methylation

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Background/Objectives: In the evolving field of HPV screening, molecular triage markers are emerging as tools for immediate reflex testing. Specific methylation signatures have shown substantial promise in distinguishing persistent oncogenic HPV infections from transient ones. However, assay-specific methylation markers present challenges for cross-assay comparisons and clinical translation. The ethical and logistical constraints of conducting long-term prospective studies further emphasize the need for alternative validation approaches. This study evaluated the performance of selected methylation assays to confirm compatibility with bio-banked DNA extracts.

Methods: DNA extracted from clinician-collected cervical samples of women participating in Belgium's national screening program since 2007, was retrieved from the AML - Sonic Healthcare Benelux biorepository. HPV-positive cases were selected based on predefined criteria: (1) a cytology-negative baseline collection point, (2) multiple HPV-positive collection points reflecting the natural history of disease progression, (3) confirmed histological endpoints (CIN 1/2/3 or cancer), and (4) an age-matched HPV positive healthy control. Archived DNA underwent initial quality assessments to confirm suitability for analysis. Subsequently, 60 archived DNA samples were bisulfite converted using either the EpiTect Fast Bisulfite Kit (QIAGEN) or the EZ DNA Methylation Kit (Zymo Research). Additionally, 20 paired LBC samples were directly converted using the EZ Direct Methylation Kit (Zymo Research) to evaluate concordance between fresh and archived samples. Six methylation assays were tested: the S5 methylation classifier, the GynTect assay (Oncgnostics), the Precursor-M+ test (Self-screen), the CONFIDENCE Marker (Neumann), the Methica CC kit (CC Diagnostics), and the DNA Methylation Detection Kit for Human PAX1, SOX1 and HAS1 Gene (YanengBio). Analytical parameters, including validity rate, accuracy relative to histology outcome, and methylation detection rates among controls and cases were analyzed.

Results: Archived DNA samples demonstrated adequate quality for bisulfite conversion and methylation analysis. Laboratory workflow parameters, such as hands-on time, throughput, and user-friendliness, varied across assays. Invalidity rates ranged from 0% to 41%, depending on the assay and sample type. Assay accuracy ranged from 51% to 71% for archived DNA and 53% to 80% for fresh LBC samples, with limited variability across assays. However, the proportion of methylation-positive controls and cases did exhibit a wide range: 3-39% and 21-83%, respectively, for archived DNA, and 0-20% and 10-80%, respectively, for fresh LBC samples. Concordance rates between paired archived and fresh samples ranged from 57% to 100%, depending on the assay.

Conclusions: Methylation assays exhibit strong potential as triage tools, though clinical validation remains constrained by practical challenges. This study highlights the feasibility of using bio-banked DNA to support assay validation, addressing critical workflow and result interpretation challenges. To advance the clinical application of these assays, a specialized working group, such as the proposed VALMETH framework, is necessary to establish standardized validation criteria (e.g., reproducibility, clinical sensitivity, and specificity) and evaluate the prognostic value of methylation markers across disease stages.

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#9100

Large scale clinical validation of the Methica CC Kit, a molecular triage test for cervical cancer screening

17 - Methylation

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Background/Objectives: High-risk human papillomavirus (hrHPV) testing opened the door to full molecular screening for cervical cancer. Although hrHPV screening is very sensitive for the detection of cervical abnormalities, specificity is low and additional triage of hrHPV-positive women is required. Analyzing promoter methylation of tumor suppressor genes with quantitative methylation specific PCR (QMSP) is a very promising potential molecular triage method. The Methica CC Kit detects promoter hypermethylation of C13ORF18, JAM3 and ANKRD18CP with high sensitivity for high-grade cervical intraepithelial neoplasia (CIN2/3) and cervical cancer lesions in cervical scrapings. Here, we analyzed the diagnostic performance using the Methica CC Kit on real-world hrHPV positive cervical scrapings.

Methods: Our real-world non-interventional study population consisted of physician-taken cervical scrapings from a consecutive cohort of 3421 hrHPV-positive women, collected within the Dutch population-based screening cohort. According to the Dutch screening protocol, on hrHPV-positive samples also triage cytology was performed to select women at high risk and referral for colposcopy. The pathological classification of the tissue biopsy was used as the gold standard for disease. HrHPV-positive women with two consecutive normal cytology results were considered as women without disease (NILM). DNA methylation analysis with the Methica CC Kit using bisulfite-converted DNA extracted from these cervical samples was performed. Hereafter, diagnostic sensitivity and specificity of the Methica CC Kit was determined.

Results: Distribution of pathology results of the 3421 cohort was comparable with the Dutch population and consisted of 2280 (66.6%) women with NILM, 162 CIN0 (4.7%), 299 CIN1 (8.7%), 265 CIN2 (7.7%), 397 CIN3 (11.6%) and 18 women with cervical cancer (0.5%). Methica CC Kit detected 100% of cervical cancer cases. The clinical sensitivity for CIN2+ was 67%, with a £ CIN1 specificity of 71%. The clinical sensitivity for CIN3+ was 75%, with a £ CIN2 specificity of 73%.

Conclusions: The Methica CC Kit shows good diagnostic performance in a large real-world cohort of consecutively collected samples. This supports the use of the Methica CC Kit as a reliable triage method for the detection of high-grade CIN and cancerous lesions.

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#9494

Evaluation of host gene methylation in HPV-negative women in a real-world clinical setting

17 - Methylation

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Background/Objectives: High-risk human papillomavirus (HR-HPV) tests are the mainstay for the screening of cervical cancer and its precursors, replacing cytology as the primary screening test in appropriate settings and age cohorts. These tests have, however, a moderate specificity and positive predictive value, resulting in unnecessary colposcopy referrals. DNA methylation has been shown to have a high sensitivity and specificity for cervical intraepithelial neoplasia (CIN) 2+, and especially for invasive cervical cancer. DNA methylation as possible triage in HPV-based cervical cancer screening settings is therefore of remarkable importance. The main objective of this study was access the negative HR-HPV results from our previous study, and to evaluate the impact of excluding these from colposcopy after the first HPV screening.

Methods: Cohort study with consecutive women referred for colposcopy in an organized cervical cancer screening program had colposcopy, biopsies and repeated HR-HPV testing. All HPV16/18 positive and ASCUS + HR-HPV women were selected. The ones that were tested HPV-negative at the time of colposcopy were now also tested with a panel of DNA methylation markers (ASTN1, DLX1, ITGA4, RXFP3, SOX17, and ZNF671).

Results: Samples from 96 patients, excluded from methylation testing in the main clinical study, were included in this study. Of these 96 samples 3 turned out to be methylation-positive (approximately 3% of positivity in GynTect® results).This value is concordant with the false positive cases described in the literature, and as stated by the provider in cytologically inconspicuous patients GynTect® is rarely false-positive (specificity around 96%). The 3 patients were discharged in normal colposcopy or colposcopy with minor changes.

Conclusions: The GynTect® methylation test is an effective tool for triaging HR-HPV positive cases in cervical cancer screening, significantly reducing unnecessary referrals while maintaining high detection rates for CIN3+. The high rate of negative methylation results in HR-HPV-negative cases indicates its potential to refine screening strategies even further, demonstrating that immediate triage with methylation testing could substantially decrease colposcopy referrals. One has to take into account that all the women in the study had previous HR-HPV tests so these findings cannot be extrapolated to the general screening population.

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FC24 - Economics and modeling

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#9562

The economic burden of human papillomavirus-related diseases in China

35 - Economics and modelling

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Background/Objectives: The burden of HPV-related cervical and non-cervical diseases in China is significant, yet the economic impact of which has not been fully quantified. This study aims to assess the annual economic burden associated with nine HPV-related diseases in mainland China: cervical cancer, vaginal cancer, vulvar cancer, anal cancer, penile cancer, oropharyngeal cancer, cervical intraepithelial neoplasia (CIN), anogenital warts (AGW), and recurrent respiratory papillomatosis (RRP), and provide evidence to inform national HPV prevention strategies.

Methods: A cost of illness study was conducted for the HPV-related diseases with disease burden and cost input from literature. We estimated the incidence and prevalence of the nine HPV-related diseases, and the fraction attributable to HPV infection and genotypes targeted bivalent (2v), quadrivalent (4v), and nonavalent (9v) HPV vaccines in China using cancer registries and epidemiological studies. A comprehensive literature review was conducted in both English (PubMed, Ovid, Embase, Web of Science) and Chinese databases (CNKI, Wanfang, VIP) to identify studies published between 2001 and 2024 reporting the costs of these diseases in mainland China. We extracted data on various cost categories and estimated the annual per-case direct medical, direct non-medical, and indirect costs for each disease. All costs were adjusted to 2023 values using the Consumer Price Index and converted to US dollars (1 USD = 7.0467 RMB). The overall economic burden of HPV-related diseases in 2023, and the cost attributable to genotypes targeted by the 2v, 4v, and 9v vaccines, was then calculated.

Results: In China, there are an estimated 160,721 new cases of HPV-related cancers annually, with a prevalence of 547,335 cases. This includes cervical cancer, vaginal cancer, vulvar cancer, anal cancer, penile cancer, and oropharyngeal cancer. Additionally, there are 217,028 new cases of CIN, 347,706 cases of AGW, and 2,250 cases of RRP each year. The per-case total costs for HPV-related cancers ranged from US$10,371 to 18,686 in the first year after diagnosis, with subsequent annual costs between US$2,618 and 4,368. For RRP, the annual per-case cost was US$5,111; for CIN and AGW, cost ranged from US$1,039 to 1,429. Overall, the total annual economic burden of the nine HPV-related diseases was estimated at US$3,490 million (range: US$1,888-6,716 million), with direct medical costs accounting for 67%. The combined annual costs of cervical cancer and CIN were US$2,772 (1,510-5,320) million, representing 79% of the total economic burden. Non-cervical HPV-related diseases contribute an additional US$718 (377-1,396) million in economic losses annually, with 55% of this burden borne by men and 45% by women. The annual costs attributable to HPV-16/18 (2vHPV), HPV-6/11 (covered by 4vHPV and 9vHPV), and HPV-31/33/45/52/58 (specific to 9vHPV) were estimated at US$2,146 (1,167-4,123) million, US$392 (192-803) million, and US$577 (320-1,088) million, respectively. The economic burden attributable to HPV types targeted by the 2v, 4v, and 9v vaccines represent 61%, 73%, and 89% of the total economic burden of HPV-related diseases, respectively.

Conclusions: Cervical cancer and CIN impose a significant economic burden in mainland China, with non-cervical HPV-related diseases also contributing substantially. Enhancing HPV vaccination efforts could lead to a marked reduction in the incidence of HPV-related diseases and their associated economic costs in both female and male.

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#9563

Assessing the Influence of Male Vaccination on Public Health Benefit of HPV Vaccines Against All HPV Related Diseases in China under Different Increasing VCR Scenarios: A Modeling Study

35 - Economics and modelling

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Background/Objectives: Gender-neutral vaccination (GNV) has been implemented in 89 countries globally, using either 2vHPV, 4vHPV, or 9vHPV vaccines. In real-world studies, GNV has been shown to reduce the prevalence of male and female anogenital and oral HPV infections as well as the incidence of anogenital warts (AGW). Previous modeling studies have also predicted that GNV will lead to substantial long-term reductions in the incidence of cervical and other HPV-related cancers among men and women. Despite China currently having five HPV vaccines for 3 types of valency that are all approved for women 9 - 30 years or 9 - 45 years, the vaccination coverage rate (VCR) for girls and women remains very low. Assuming different scenarios of increasing VCR for girls, we aimed to evaluate the impact of including boys' HPV vaccination on the public health benefit of current HPV vaccines against all HPV related cancers and diseases in China.

Methods: We adapted a dynamic transmission model of HPV infection and subsequent diseases to China. We compared two scenarios: (1) girls-only vaccination (GOV) at age 9 - 14, with VCR increasing from 30% to 60%, 70%, 80%, or 90% by 2030; and (2) GOV scenarios + boys' vaccination (GNV) at age 9 - 14 years, with boys' VCR increasing from 30% to 60% by 2030. For all scenarios, we considered vaccination with 9vHPV vaccine.

Results: The model predicted that, with a VCR increase from 30% to 60%, the GOV scenario compared to no vaccination would avert 2205 cervical cancer, 266 non-cervical cancer, and 4098 AGWRRP (AGW + recurrent respiratory papillomatosis) cases per 1000 populations between years 2024 and 2124. Compared to GOV strategy, the GNV strategy would avert an additional 590 cervical cancer, 184 non-cervical cancer, and 3194 AGWRRP cases per 1000 populations. In scenario where VCR in girls reach 90%, the GNV scenario had lesser impact on cervical cancer but not so much on other cancers and diseases, with additional averted cases of 134 cervical cancer, 140 non-cervical cancer, and 3130 AGWRRP cases per 1000 populations compared to the GOV scenario.

Conclusions: In China, where VCR for girls remain low and increasing slowly, adding male vaccination can help significantly reduce the burden of HPV-related cancers and diseases.

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#9397

AN ADAPTABLE MODELLING FRAMEWORK TO EXPLORE BENEFITS OF RISK-BASED CERVICAL CANCER SCREENING IN EUROPE: A CASE STUDY IN ITALY

35 - Economics and modelling

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Background/Objectives: Despite many risk factors are known and HPV-vaccinated women entering screening age, "one-size-fits-all" cervical cancer screening programs are still common practice worldwide, resulting in suboptimal allocation of health resources. We derived a modelling framework, adaptable for EU-27 countries, to evaluate the health-economic impact of screening strategies that account for different risk profiles based on woman's age, screening history, and HPV vaccination status.

Methods: A modelling framework was constructed interconnecting a dynamic population-based HPV transmission model and a cervical cancer progression microsimulation model. The models, for each EU-27 country, were informed using country-specific data on population demographics, sexual behaviour, HPV age-specific prevalence, and other epidemiological outcomes. For countries with lacking information, we used clustering methods to infer model data inputs. We evaluated 4 screening strategies: i) no screening; ii) an HPV risk-based strategy based on woman's HPV screening history; iii) an HPV risk- & age-based scenario based on woman's age and HPV-type screening history; and iv) an one-size-fits-all approach offering 3-year cytology screening (from age 24 to 30 years) and 5-year HPV screening (30 to 65 years). We considered the nona-valent HPV vaccine and two levels of vaccination impact (40% and 80%). Modelling outcomes were per 1000 women, reporting lifetime number of colposcopies, regressive lesions treated, and disability-adjusted life years (DALYs) prevented. Italy is used here, as case study, to illustrate the key findings of this EU-wide analysis.

Results: While all simulated screening strategies were found to reduce the burden of cervical cancer, we estimated that risk-based strategies were more efficient, requiring 51%-55% less colposcopies than the one-size-fits-all strategy in absence of vaccination. Among the risk-based strategies, HPV risk-based screening required less lifetime colposcopies than HPV risk- & age-based strategies. Overall, HPV vaccination sharply reduced the number of colposcopies under all screening strategies, with higher vaccination impact resulting in higher reductions. In addition, higher vaccination impact led to higher gain of efficiency by risk-based strategies as compared to the one-size-fits strategy. With vaccination impacts of 40% and 80%, the HPV risk- & age-based algorithm required, respectively, up to 61% and 78% less lifetime colposcopies compared to the one-size-fits-all strategy with a cost/benefits ratio <140 colposcopies per DALY avoided. Similar analyses were repeated for all EU-27 countries.

Conclusions: Risk-based cervical cancer screening allows for more efficient allocation of health resources, producing similar benefits than one-size-fits-all approaches. As costs related to screening are high, moving towards risk-based screening is crucial. As EU countries are entering the vaccination era, our modelling framework will assist EU decision-makers to design efficient screening programmes.

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#9173

Method for estimating age distribution of acquisition of causal HPV infection from CIN2+ diagnosis data: US and UK as case studies

35 - Economics and modelling

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Background/Objectives: Understanding the age distribution of human papillomavirus (HPV) acquisition is important for informing preventive strategies and public health interventions for cervical cancer and its precursors. This study presents a method for inferring the age distribution of causal HPV infections based on the observed age distribution of high-grade cervical intraepithelial neoplasia (CIN2+) diagnoses for the United Kingdom (UK) and the United States (US).

Methods: A published discrete event simulation model was modified to estimate the age-specific pattern of causal HPV infection and progression to CIN2+ diagnosis. We accounted for the natural history of HPV infection and screening behaviors. The model incorporates age at diagnosis, time from HPV infection to disease onset, and age at causal HPV infection. We track 1000 sampled females through three health stages while undergoing screening: HPV infection, CIN2+ onset and diagnosis. Data from vaccine trials, screening registries and pre-vaccine age-specific CIN2+ diagnosis were used. We assessed the impacts of different distributions of time to CIN2+ onset and censoring in the clinical trials on the age distribution of causal infection (by assuming 0%-20% of persistent infection or CIN1 (PPI) at the end of the clinical trial progress to CIN2+ post-trial) in scenario analyses.

Results: The method provided estimates of the age distribution of casual HPV infection that aligned with existing evidence. We found that the offset defined as the time between causal HPV infection and CIN2+ diagnosis,was 6.21 years (95% confidence interval [CI] 5.43, 6.99) for the UK and 4.10 years (95% CI 4.02, 4.18) for the US. In the UK, The median age at CIN2+ diagnosis was 32.35 (95% CI 31.83, 32.80) years, and the median age of causal infection was 26.27 (95% CI 25.52, 27.06), with a small proportion (1.14%, 95% CI 0.65%, 1.63%) were made after the maximum screening age of 64. In the US, the estimated median age of CIN2+ diagnosis was 28.63 (95% CI 27.93, 29.36), while the median age for acquiring causal HPV infection was 24.85 years (95% CI 23.80, 25.86), with 0.87% (95% CI 0.32%, 1.43%) of females were diagnosed after reaching the maximum screening age. Approximately 51.13% (95% CI 47.89%, 54.36%) and 44.86% (95% CI 40.38%, 49.33%) of causal HPV infections were acquired after the age of 26, for the UK and US, respectively. We observe no statistically significant difference when using gamma or exponential distribution for time between infection and CIN2+ onset on the offset (p-value > 0.1) for both countries. In both countries, scenario analyses showed that as the offset between infection and diagnosis and the proportion of PPI progressing to CIN2+ increase, the median age of infection decreased (p-value < 0.0001), while the age at diagnosis remained stable.

Conclusions: Using UK and US data, the method robustly estimated the age distribution of causal HPV infection with other relevant statistics. Insight from the method suggest the importance of using country-specific data in accurately estimating the age distribution of causal infection, as there are country-specific differences in the estimated values.

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#9049

Estimating the age of acquisition of disease-causal HPV infection in women who develop CIN2+ in England

35 - Economics and modelling

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Background/Objectives: Human papillomavirus (HPV) is a known cause of cervical cancer, for which cervical intraepithelial neoplasia (CIN) is a precursor. Women diagnosed with high-grade CIN (CIN2+) are at high-risk of progressing to cancer. A school-based HPV national immunisation program (NIP) was introduced in the United Kingdom in 2008, with catch-up vaccination available up to the age of 25, alongside a robust cervical cancer screening programme. However, several US modelling studies have shown that a significant proportion of HPV infection leading to cervical cancer and its precursors occur in women above the age of 25(1,2). The aim of the study is to estimate the age of the disease-causal HPV infection in women diagnosed with CIN2+ in England.

Methods: A published discrete event simulation model(1) was adapted to estimate the age of causal HPV infection for females diagnosed with CIN2+ in the UK. A sample of 1000 simulated females progressing through causal HPV infection, CIN2+ onset and CIN2+ diagnosis were used to determine the optimal time delay between causal infection and CIN2+ diagnosis by comparing the predicted age-distribution to the real-world diagnosis data. Progression rates from causal infection to CIN2+ onset were sampled from Gamma distribution, parametrized by the FUTURE I(3) and VIVIANE(4) clinical trials, and progression to diagnosis determined by real-world screening data(5) and test sensitivity (liquid-based cytology sensitivity of 80.1%)(6). Scenario analysis tested the impact of uncertainty in the average time from HPV infection to CIN2+ onset on model results by using alternate parameterisation of the gamma distribution to account for censoring in FUTURE I. In addition, a stability analysis based on 10 model iterations generated 95% confidence intervals for model estimations. The analysis used data from the year before the HPV NIP introduction in the UK to avoid confounding of vaccination on the model results.

Results: The model predicted the time from causal infection to CIN2+ diagnosis of 6.32 years, with median ages at causal HPV infection, CIN2+ onset and CIN2+ diagnosis of 26.88 (95% CI: 26.20, 27.55), 28.22 (95% CI: 27.64, 28.96) and 32.45 (95% CI: 31.59, 33.15) years, respectively. Additionally, the model estimated 61.7% of causal HPV infection occurs after 25 years of age meanwhile 1.40% of CIN2+ are diagnosed after the maximum screening age in the UK programme. The model results were robust to variations in inputs and parameterisation tested in the scenario and stability analysis.

Conclusions: Vaccinating women before acquiring HPV infection can prevent progression to CIN2+, and ultimately cervical cancer. This study estimates a substantial proportion of HPV infection occurs after the age of routine vaccination eligibility in England, suggesting a potential benefit of vaccinating women beyond the age of 25; and supports the need for catch-up opportunities for those who missed vaccination in school, however, further research is needed.

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#9391

An Almost Model-Free Method for Forecasting HPV-Related Disease

35 - Economics and modelling

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Background/Objectives: As models for HPV and HPV-related disease have increasingly sophisticated technical requirements, activities like model selection, use, and comparison become more challenging. One such difficulty that arises is integrating data on HPV-related disease which has been collected by clinicians and policy makers, and informing what data should be collected or made available to improve model forecasts. Dynamic mode decomposition (DMD) utilizes data to estimate the dynamics of a system without the explicit specification of a particular model. This model-free approach eliminates some of the hurdles involved with using HPV models. However, DMD requires sufficiently "rich" data to accurately approximate the system's dynamics. In cases where the data is not sufficient for the complete specification of the dynamics, the data or dynamics estimates can be "enriched" with a model or outputs from a model, leading to an almost model-free approach. Moreover, this approach can help to inform public health stakeholders on what data should be made available for forecasting of HPV-related disease. In this presentation, we will discuss implementation of DMD on currently available HPV-related disease data. We will also consider what additional data could be made available to expand the use of model-free methods in HPV.

Methods: We targeted data that would be well-suited for use with DMD: multiple temporal observations of a population-level quantity that would be representative of the dynamics of interventions for HPV-related disease (e.g. vaccination, screening). These data were assessed for limitations, particularly examining what dynamics could be reliably approximated with this data, and whether it was conducive for forecasting the future impact of interventions. DMD was then used to estimate the future dynamics of the data, and a simple Markov model was constructed to supplement the data for forecasting future disease incidence.

Results: Utilizing cervical cancer screening data from the United Kingdom (UK), we were able to identify data that showed the impact of interventions on severe dysplasia in women aged 20-29 years. DMD was used to estimate the dynamics from this data, and vaccination coverage data was used to extrapolate these results to older age groups to estimate the impact of HPV vaccination on dysplasia in the whole female population. A simple Markov model of progression from severe dysplasia to cervical cancer was then used to project the dysplasia dynamics to cervical cancer, estimating the future incidence of cervical cancer in the UK. Our estimates of the dynamics suggest that vaccination could reduce cervical cancer incidence by up to 62% by 2050. Moreover, if the UK maintains its current efforts, it could achieve cervical cancer elimination (less than 4 new cases per 100,000 women) by the year 2047.

Conclusions: Our work highlights the potential that almost model-free methods could have on forecasting HPV-related disease. However, these results are limited; additional data is required to be able to tease apart various elements of the dynamics to make more refined predictions: inclusion of HPV type in the dysplasia diagnoses; vaccination status in individuals with disease; multiple, granular temporal observations of HPV prevalence. These additional data are essential to validate the estimates of the dynamics, especially given the nonlinear interactions between vaccination, disease progression, and other factors.

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#9277

Potential health impact of therapeutic HPV vaccines in China: a modeling study

35 - Economics and modelling

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Background/Objectives: Cervical cancer prevention and control in China remains significantly behind the WHO 2030 targets. Therapeutic vaccines present a promising new approach for both prevention and treatment of HPV-related cancers or lesions. This study estimates the potential health impact of therapeutic vaccines.

Methods: We evaluated two potential therapeutic HPV vaccines(TxV) within HPV-based cervical cancer screening programs, targeting women aged 30-65 diagnosed with oncogenic HPV infection (TxV type 1) or cervical precancerous lesions (TxV type 2). In the base case scenario, TxV was assumed to cure HPV16/18 related infection or precancerous leisions. A two-dose schedule was considered and the vaccine efficacy was assumed to be 90% for two doses and 70% for one dose. We evaluated different scenarios with different prophylactic vaccination(PxV) and screening backgrounds. A previously validated transmission model was used to estimate the health impact on Chinese females over a 100-year time horizon. The primary outcomes were cervical cancer cases and deaths averted by TxV in 2025-2125. One-way sensitivity analyses was performed.

Results: In the base case, TxV type1(clearance of HPV infection) and TxV type 2(regression of CIN2/3) could avert 1.83 million and 0.92 million cervical cancer cases, respectively, and prevent 0.80 million and 0.33 million deaths by 2125. Notably, within the first 20-25 years of intervention, TxV type 2 is expected to avert more cervical cancer cases than TxV type 1. With expanded cervical cancer screening and prophylactic HPV vaccination reaching 70% and 90% coverage by 2030, the number of averted cases and deaths would decline, and the cervical cancer incidence would be similar regardless of TxV vaccination in the PxV eligible birth cohort (ie, 2020 birth cohort). The impact of TxV would further diminish with lower efficacy (70% efficacy: 28.7%/20.7% reduction in cases averted by TxV type 1/2) or delayed introduction (2040 year: 32.9%/15.2% reduction in cases cases averted by TxV type 1/2). Including additional targeted HPV types could increase the number of cases averted by TxV by 48.0-85.2% (for TxV type 1) and 37.2-58.4% (for TxV type 2) compared to TxV that targets only HPV16/18.

Conclusions: Our study demonstrates that integrating TxV within HPV-based cervical cancer screening programs can have a significant health impact, especially in scenarios where increasing prophylactic HPV vaccination coverage in the short term is challenging.

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#9221

The cost-effectiveness of the HPV screening program for unvaccinated, mixed, and vaccinated cohorts.

35 - Economics and modelling

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Background/Objectives: New data on diagnosis and treatment costs, along with recent changes such as the introduction of genotyping, have implications for the cost-effectiveness of the HPV screening program in the Netherlands. With these updates, we reassess the overall cost-effectiveness of the screening program.

Methods: The microsimulation model STDSIM-MISCAN-Cervix was employed to simulate three cohorts of women born in 1995: vaccinated, unvaccinated, and mixed. Each cohort is followed over their lifetime, with the first screening invitation occurring at age 30. To assess the effects and cost-effectiveness of the current screening program, we compared a scenario with screening to a scenario without screening. The screening scenario modeled represents the current program with realistic participation rates, accounting for individuals who never participate and those who attend one or more rounds. Harms of screening were defined as the total number and unnecessary colposcopy referrals (≤ cervical intra-epithelial neoplasia stage 1), while benefits included cancer cases and deaths prevented, and (Quality Adjusted) Life Years Gained (QALYs gained/LYG). Costs and (QA)LYs gained are discounted by 3%. Cost-effectiveness ratios (CERs) were calculated for screening compared to no screening.

Results: The screening program prevents approximately 209 cervical cancer deaths per 100,000 women born in the unvaccinated cohort, with health benefits diminishing in mixed (128 deaths prevented) and vaccinated (61 deaths prevented) cohorts. The program results in total costs of €4.7 million per 100,000 women in the unvaccinated cohort, increasing to €12.2 million in the mixed cohort and €18.5 in the vaccinated cohort. Cost-effectiveness ratios show €3,197 per LYG and €5,419 per QALY for unvaccinated women , with costs rising to €13,811 per LYG and €30,894 per QALY in the mixed cohort, and €46,115 per LYG and €2,938,811 per QALY for vaccinated women.

Conclusions: We showed that the current Dutch cervical screening program is cost-effective and saves lives in HPV unvaccinated women. The screening program is also cost-effective for cohorts with a mixed HPV vaccination status (considering a willingness-to-pay threshold of €50,000 per QALY gained), but not cost-effective in HPV vaccinated women. This highlights the importance of adapting the screening program for vaccinated women.

FC25 - Public health

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#9348

Insurance Instability and Rurality in the Western United States: Key Factors in HPV Missed Vaccination Opportunities Among Latino/a and American Indian/Alaska Native Children/Adolescents

39 - Public health

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Background/Objectives: This study examines the impact of rurality and insurance stability on missed HPV vaccination opportunities among children/adolescents. Despite the HPV vaccine being available for over a decade, U.S. adolescent vaccination rates remain low, with significant geographic disparities. Rural children/adolescents experience lower vaccination rates that lag their urban counterparts by 10-16 percentage points, contributing to preventable HPV-related cancers. Rural areas and certain racial/ethnic groups face unique barriers to vaccination, potentially exacerbated by fluctuations in insurance stability. Understanding these dynamics is crucial for developing targeted interventions to improve vaccination rates and reduce disparities. This study leverages a comprehensive dataset from the Utah Statewide Immunization Information Systems (USIIS).

Methods: We conducted a retrospective analysis using the USIIS dataset from January 2017 - May 2023. A total of 1,093,533 children/adolescents (C/A) aged 9-18 years who received over 5 million vaccinations were used in this analysis. Inclusion criteria required individuals to be within the specified age range at the time of vaccination, to have at least one vaccination recorded in the USIIS during the study period, and to have race and/or ethnicity data. Insurance stability was assessed by examining changes in insurance usage over the 6 year study period. Race/ethnicity was categorized into 1 of 16 race categories. Missed HPV vaccination opportunities were identified as instances where a vaccination visit occurred, but the individual received an immunization other than the HPV vaccine that was due or overdue. A total of n=685,614 individuals were included. Logistic regression and mediation analyses were performed, with variable selection guided by prior research and Directed Acyclic Graphs (DAGs). We evaluated the impact of rurality and insurance stability on missed HPV vaccination opportunities and examined Effect Measure Modification (EMM) to understand how these relationships vary across racial and ethnic groups.

Results: During the study period, 47.1% of adolescents aged 9-18 and 45.4% of those aged 11-18 did not receive any doses of the HPV vaccine. More than 70% of adolescents experienced at least one missed HPV vaccination opportunity, with an average of 2.14 missed opportunities per individual (SD=1.56). Adolescents in rural areas had a slightly higher likelihood of missing an HPV vaccination opportunity compared to their urban counterparts (OR=1.04, 95% CI: 1.02-1.06). Latino/a adolescents had higher odds (OR=1.26, 95% CI: 1.13-1.42) of missing HPV vaccination opportunities, whereas American Indian/Alaska Native, Biracial, Black, and Hawaiian/Pacific Islander adolescents had lower odds compared to White adolescents. The Effect Measure Modification (EMM) analysis revealed significant variations in how rurality and insurance stability impact missed HPV vaccination opportunities.

Conclusions: Our analysis supports the hypothesis that rurality and Hispanic ethnicity are associated with a higher likelihood of missed HPV vaccination opportunities. Rural adolescents and those identifying as Latino/a experience greater challenges in obtaining timely HPV vaccinations. However, the role of insurance stability adds complexity to this relationship. Insurance stability not only partially mediates the effect of rurality on missed vaccination opportunities ($p<0.01$) but also interacts differently across racial and ethnic groups.

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#9225

Readiness Assessment for Cervical Cancer Elimination in Europe

39 - Public health

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Background/Objectives: Human papillomavirus (HPV) is a well-established cause of cervical and other cancers. The World Health Organization (WHO) and European Commission released strategies and recommendations to facilitate cervical cancer (CC) elimination with a special focus on broad HPV vaccination, screening, and CC treatment availability, program implementation, and surveillance systems. We intended to assess readiness of 31 European countries to eliminate CC by defining status of programmes and policies, implementation, and existing data systems essential for decision-making.

Methods: The scoring framework used for this assessment comprised of three domains: vaccination, screening, and treatment, each comprising of two subdomains: decision- making and implementation. Countries were assigned scores based on availability of predefined parameters and tiered into one of four archetypes: low readiness (0-25% of maximum points collected), moderate-low readiness (26-50%), moderate-high readiness (51-75%), and high readiness (76-100%).

Results: Sweden, Ireland, and the United Kingdom achieved the highest overall scores, demonstrating the highest readiness for CC elimination (93%, 89%, and 87%, respectively). Northern countries generally outperformed Eastern and Southern European countries, with Romania, Bulgaria, Cyprus, and Greece showing lowest readiness. Vaccination domain scores were generally higher than screening and treatment domain scores with Sweden, Portugal, and Ireland showing highest readiness (91%, 88%, and 88%, respectively) and Czechia, Greece, Croatia, Poland, and Bulgaria showing lowest (50%). Across all three domains, countries generally scored lower across the implementation subdomain compared to the decision-making subdomain. One third of countries have limited/no vaccination and screening uptake monitoring systems or publicly reported rates essential for informed decision-making.

Conclusions: Our assessment highlights the diversity in decision-making and implementation of vaccination, screening, and treatment programmes across European countries. This framework illustrates current progress and highlights key areas for improvement to strive towards CC elimination as a public health problem.

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#9180

Failing to Eradicate Vaccine-Type HPV: The Long-Term Fiscal Burden of Neglecting a Public Good.

39 - Public health

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Background/Objectives: Under complete information, eradicating vaccine-type HPV should be considered a public good [1], implying a moral and political obligation for public health authorities to pursue this goal [2]. Failure to fully commit to an eradication strategy results in incomplete contracting [3], leading to long-term public implicit liabilities [4]. This study aims to quantify the economic consequences of various HPV vaccination strategies across different income-level countries.

Methods: Based on previously published predictions on time to HPV elimination [5], we developed a financial model to estimate the value of implicit public liability arising from the failure to eradicate vaccine-type HPV. Four scenarios were analysed: 90% universal coverage, 90% coverage of girls only, 40% universal coverage, and 40% coverage of girls only, all with twice-lifetime cervical screening. The model incorporated real-world hospital resource utilization from the NHS perspective, using 2022 international dollars (I$) per million people. We employed a growing perpetual debt formula, considering country-specific interest rates, population growth, and the rising incidence of oropharyngeal cancer.

Results: The study revealed that failing to eliminate vaccine-type HPV would place a significant financial burden on future generations, particularly in low-income countries. The value of implicit public liability for low-income countries ranged from I$ 43.4 million (90% girls-only coverage) to I$ 278.0 million (40% girls-only coverage) per million people. The cost of HPV vaccination was marginal compared to the potential financial burden that would arise from failing to eradicate vaccine-type HPV. Depending on the country's income level, the vaccination cost represents only 3.3% to 4.6% of the potential long-term liability. Notably, at 40% coverage, adding boys to the vaccination program almost halved the value of the implicit liability across all income levels.

Conclusions: Our findings strongly support adopting gender-neutral HPV vaccination policies across all income levels. Recognizing HPV eradication as a public obligation is crucial for maintaining fiscal stability and ensuring health equity over time. Governments must acknowledge the risks associated with inadequate commitment to this eradication strategy and consider the long-term financial implications of their health policies. By acknowledging the long-term financial implications of HPV vaccination strategies, policymakers can make informed decisions to maintain fiscal stability and ensure intergenerational equity in public health.

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#9084

Physician Perspectives on the HPV Decide Tool for Mid-Adult HPV Vaccination in the United States

39 - Public health

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Background/Objectives: In 2019, the HPV vaccine guidelines in the U.S. expanded to include HPV vaccination for unvaccinated 27-45-year-olds based on shared clinical decision-making (SCDM) with a health care provider. A patient-facing web-based decision tool, HPV Decide, was developed to support patients in the decision-making process. As health care providers are key stakeholders in the tool's implementation, we assessed their perceptions of the HPV Decide and recommendations for implementation.

Methods: We collected online survey data in 2024 from a U.S. sample of obstetrics-gynecology, internal medicine, and family medicine physicians (N=600) on perceptions of the tool's acceptability and usability in a clinical setting. Participants were presented with examples of HPV Decide. Descriptive statistics were estimated using SAS.

Results: Most (68.3%) providers were likely to use HPV Decide. Almost half (46.5%) favored clinic-based access, whereas others suggested that patients access the tool online independently (37.0%). Among those who favored clinic-based access, most providers identified the waiting room (29.0%) and pre-visit timing (27.6%) as ideal for tool use. The patient portal was the preferred delivery method (34.8%). Most providers (67.0%) agreed that the tool could be easily integrated into their practice, and a majority (54.0%) believed that patients would want to use this type of tool.

Conclusions: There were strong preferences for clinic-based access to the HPV Decide tool and electronic delivery (e.g., via patient portals). Moreover, there was agreement among providers that the decision aid tool should be used before the patient-provider interaction, ideally in the waiting room. These results underscore the potential of the HPV Decide tool to facilitate SCDM for mid-adult HPV vaccination. Future studies can test these implementation strategies in clinical settings.

References: This project was supported by the Merck Investigator Studies Program

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#9286

No Girl Left Behind: Integration of Multi-Sectoral Data to Identify Out-of-School (OOS) Girls in Bangladesh for HPV Vaccination

39 - Public health

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Background/Objectives: Cervical cancer, primarily caused by the Human Papillomavirus (HPV), is the fourth most common cancer in women globally and the second most common in Bangladesh. Gavi countries prioritize school-based HPV vaccination delivery; however, many girls in low- and middle-income countries (LMIC) are out of school (OOS). Bangladesh is a Gavi priority country and began rolling out HPV vaccination in 2023, targeting girls aged 10 to 14. However, accurately estimating the target population remains a significant challenge. This is largely due to difficulties in verifying beneficiary information, particularly among OOS girls and populations without valid birth registrations. These gaps make it difficult to establish denominators for the target population, posing a risk of missing vulnerable groups in the vaccination effort. Moreover, there is very limited understanding and data regarding effective (i.e., achieving high coverage) and efficient (i.e., cost-effective) strategies for reaching these populations and ensuring sustainable vaccine delivery. The aim of this project is to improve the estimation and identification of the OOS girls aged between 10-14 in Bangladesh by leveraging and triangulating multiple data sources, to provide critical insights for policymakers and program managers.

Methods: This study will be conducted over 12 months, integrating multi-sectoral data from various sources, such as the Ministry of Health and Family Welfare (MoHF&W), Ministry of Education (MoE), Bangladesh Bureau of Statistics (BBS), BRAC, International Centre for Diarrheal Research, Bangladesh (Icddr,b) etc. These datasets will be integrated with the existing EPI dashboard. This integrated data will be used to improve the estimation of the number of vaccine-eligible girls aged 10-14 years, including OOS girls, in Bangladesh. Integrating multi-sectoral data will aim to mitigate over- and under-reporting in existing databases. To validate estimates, Community Health Workers (CHWs) deployed by the MoHF&W, who conduct regular household visits, will enumerate the target population in selected areas. Finally, the study will compare the cost-effectiveness of two approaches: utilizing cross-verified multi-sectoral data versus data collected and validated by CHWs.

Results:

Conclusions: This verification exercise will provide valuable lessons on the accuracy of population enumeration for HPV vaccination, and on effective strategies for conducting future mapping efforts. Findings will guide micro-planning to improve vaccination coverage and ensure no one is left behind. The insights gained may apply to similar settings in low- and middle-income countries, and thus help enhance equitable vaccine delivery worldwide.

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#9421

Influences on HPV vaccine hesitant young adults across two cultures: youth voices

39 - Public health

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Background/Objectives: Cervical cancer is the fourth most common cancer in women globally.Cervical cancer is the fourth leading cause of death among women in Colombia, SA.By contrast, Israel has relatively low cervical cancer mortality rates that are attributable to the success of cervical cancer screening, the treatment of CIN earlier in the pathogenesis pathway to invasive cervical cancer, and protective factors among subpopulations.The routine administration of the HPV vaccine could effectively reduce the burden of HPV-related cancers in both countries.In Israel, HPV vaccines are routinely administered in grades 7-8.They are also administered in the kupot cholim (HMO's) to those who do not receive vaccines in school.The overall rate in 2021 was 62.9%.In Colombia, SA, the initiation of a free and compulsory school-based vaccination program began with girls in 2012-2013;Colombia experienced high rates of vaccine administration.Due to widely-reported incidents of some young women experiencing side effects after receiving the HPV vaccine,in the municipality of El Carmen de Bolivar in 2014,however, uptake rates dropped precipitously. HPV vaccination rates have increased,with the recent inclusion of boys,but the uptake rates are the lowest in the region at 37 percent.The aim of this study is to explore in depth the perspectives that influence HPV decision making among vaccine hesitant,age-eligible adolescents and young adults in two culturally distinct countries with free,school-based administration.

Methods: We conducted focus groups that were organized by age within both countries;the Israeli focus group respondents were older than the Colombian youth.Focus groups were video recorded and transcribed.Three members of the research team trained in qualitative approaches reviewed each transcript to inductively develop a codebook.At least two people independently applied descriptive codes from the codebook to all transcripts and memos;discrepancies were resolved by the team.A thematic analysis was conducted on data collected from information rich cases,those with lived experience relevant to the research question.

Results: The themes were discordant across the two countries,with less involvement of children in decision-making in Colombia than parents;older Israeli youth wanted more involvement in decision-making,however. Misinformation from the Carmen de Bolivar psychogenic incident in Colombia continued to influence these respondents.While primary provider recommendations were infrequent in both countries,Colombian respondents reported particularly high trust in primary care providers' recommendations for HPV vaccination.By contrast, across both countries, themes highlighted the importance of widely accessible,unbiased information about the HPV vaccine from a trusted source.An Israeli respondent noted that:"... school has a role not only in the HPV vaccination [but in] overall sexual education especially because not all parents give their children any information..."The school seems an under-used resource in both countries.

Conclusions: Enhancing the education of parents at the time of school-required permission forms may be a "teachable moment."Further,adapting dissemination approaches to primary care physicians and clinics,across both countries.Youths from the relevant subcultures could be engaged as champions of the HPV vaccine within both countries.Linking PCP's and public health dissemination and surveillance strategies are key to increasing HPV vaccine uptake.

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#9166

Understanding socioeconomic, racial, and geographic inequities in HPV-related health outcomes and health resource utilization in the US

39 - Public health

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Background/Objectives: Cervical cancer and other HPV related cancers are considered diseases of inequity, often occurring among the most vulnerable populations. These inequities may be associated with vaccination coverage, screening and follow-up, and access to treatment. In order to provide a comprehensive perspective of these inequities, we will be conducting a qualitative synthesis of the published evidence in the US to summarize inequities described above across different populations of interest.

Methods: Existing evidence highlighting disparities in HPV vaccination initiation and completion rates, cancer screening rates, as well as HPV-related disease burden for genital warts, abnormal cervical lesions, cervical cancer, anal and oropharyngeal cancers, will be examined in peer reviewed publications and gray literature, from 2010-2024. Overall disease management practices such as screening, follow up rates after abnormal results, and access to different types of treatment for HPV-related pre-cancers and cancers will also be evaluated. The population of interest will include different subgroups including but not limited to, racial or ethnic groups (Hispanics/Blacks/Native Americans/Alaska Indians), geography (rural/urban), immigrants and refugees, LGBTQ and publicly insured.

Results: Findings from this review could highlight critical gaps in care among certain hard to reach subgroups of the US population. It may also offer insights on finding ways to address those gaps and adopt a more holistic approach around preventive care in the context of HPV related cancers and diseases.

Conclusions: The evidence generated will provide insights into the multi-dimensional inequities related to HPV vaccinations, disease burden and treatment, and will offer guidance on incorporating equity issues when thinking about HPV care.

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#9290

Circulating genotypes of human papillomavirus in adult women of reproductive age from Madagascar: a cross-sectional study to explore needs and opportunities for HPV vaccination in the country

39 - Public health

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Background/Objectives: HPV virus is the most common sexually transmitted infection worldwide and associated to the vast majority of Cervical Cancers (CC) which is the fourth most frequent cancer among women worldwide. Different genotypes of the virus exist and they are generally classified as high-risk and low-risk depending on their association to cancer. Prevention through vaccination against HPV is considered one of the most effective control measures for CC. Three types of vaccine against HPV are available on the market, combining low and high-risk genotypes protection. In terms of cancer prevention, the bi- and quadrivalent vaccines are active against the HPV16 and HPV18 high-risk genotypes while the nona-valent vaccine covers five additional high-risk types: HPV31, HPV33, HPV45, HPV52, HPV58. In 2023 CC was reported as the most prevalent cancer in Madagascar, representing an estimate 26.6% of all gynecological cancers. The country, is characterized by a high CC incidence rate and limited access to screening and treatment facilities. Madagascar is one of the few countries where HPV vaccination has not yet been rolled-out except for a pilot study. In August 2024, the national vaccination program has established a strategy for the national implementation. This study aims to estimate the prevalence of HPV genotypes in rural Madagascar in order to support the planning of the national implementation strategy.

Methods: A cross-sectional study was conducted between March 2021 and December 2022 at three Primary Health Care Centres in the district of Marovay in the Boeny region of Madagascar, involving 18 to 49 years old women. Cervico-Vaginal Lavages (CVL) were collected and analysed for the presence of HPV DNA at the the International Agency for Research on Cancer (IARC) in Lyon, France. A total of 21 genotypes were investigated including 19 high-risk and possible high-risk HPV genotypes (HPV-16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73, 82) and two low-risk genotypes (HPV-6 and 11). The prevalence of each HPV genotype, as well as single and multiple HPV infections, was calculated as proportions with 95% confidence intervals.

Results: From a total of 1035 women enrolled, 927 were included in the final analysis of whom, 44.6% (n=413, CI: 41.3-47.8) tested positive for HPV. A single genotype was detected in 27.6% (n=256, CI: 24.8-30.6) participants, while 16.9% (n=157, CI: 14.6-19.5) were infected with multiple genotypes. The five most commonly detected high-risk genotypes were HPV52 - in 8.3% cases (n=77, CI: 6.6-10.3), HPV45 - 7.2% (n=67, CI: 5.6-9.1), HPV51 - 4.8% (n=44, CI: 3.5-6.3), HPV58 - 4.5% (n=42, CI: 3.3-6.1), and HPV18 - 4.0% (n=37, CI: 2.8-5.5). The prevalence of genotypes covered by the HPV vaccines was 7.4% (n=69, CI: 5.8-9.3), 10.8% (n=100, CI: 8.9-13.0), and 29.3% (n=272, CI: 26.4-32.4) for bi-, quadri-, and nona-valent vaccines, respectively.

Conclusions: Our preliminary results show that the most frequent strains circulating among women of reproductive age in Madagascar are those covered by the nona-valent vaccine. This data clearly suggests that for a vaccination strategy aimed at preventing CC, the adoption of a nona-valent vaccine would increase the impact of the program.

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#9500

Evolução da Epidemia de HIV/AIDS no Amazonas: Um Estudo Longitudinal de 2014 a 2023

33 - Sexually transmitted diseases and HIV infection

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Background/Objectives: Acquired Immunodeficiency Syndrome (AIDS), caused by HIV infection, severely compromises the immune system, making individuals highly susceptible to various opportunistic infections. The complexity of the epidemic, marked by social inequalities, stigma, and barriers to accessing health services, requires multidisciplinary and intersectoral approaches. Despite advances in antiretroviral treatment, new challenges constantly emerge, such as the emergence of new viral variants and the increase in drug resistance, demanding an agile and adaptive response from the health system. To study HIV-related morbidity and mortality, as well as its prevalence in hospitalizations in the public health system of Amazonas, between 2014 and 2023.

Methods: Retrospective, descriptive, and quantitative study using secondary data from the Brazilian Ministry of Health (SIH/DATASUS) on HIV-related hospitalizations in the public health system of Amazonas from 2014 to 2023. Variables used included region/federative unit, sex, age, race/ethnicity, costs, and deaths, excluding variables that did not meet the predetermined criteria

Results: The period between 2014 and 2023 showed a progressive increase in HIV-related hospitalizations, culminating in a peak in 2022, followed by a slight decrease in 2023. A total of 17,134 hospitalizations were recorded during this period. The brown race presented the highest proportion of cases (25.95%), followed by a significant percentage of cases with no declared race/color (69.56%). Males were predominantly affected (72.43%), with a higher prevalence in the age group between 30 and 39 years (36.04%). However, all age groups presented cases. Mortality associated with HIV hospitalizations was high, reaching 14.04% of cases. The average length of stay was 15.1 days, resulting in an estimated total cost of R$ 18,464,413.18 for the health system, evidencing a significant financial and care impact.

Conclusions: Epidemiological data reveal an alarming increase in HIV-related hospitalization and mortality rates in Amazonas, disproportionately affecting men aged 30 to 39. The vast territorial expanse, difficulties in accessing healthcare, especially in remote areas, and deep social inequalities exacerbate the situation, demanding urgent and coordinated actions. The implementation of effective public policies, focused on combined prevention, early diagnosis, timely treatment, and comprehensive care, is essential to reverse this trend. Primary healthcare, especially in remote areas, must be strengthened to ensure equitable access to health services. Research and community engagement are crucial for developing tailored prevention and treatment strategies, considering regional specificities and the needs of the most vulnerable populations.

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FC26 - Cervical neoplasia and others

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#9265

Long term risk of cervical carcinoma after CIN treatment: analysis of 6517 cases.

25 - Cervical neoplasia

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Background/Objectives: During the follow-up of patients treated for High Grade Cervical Intraepithelial Neoplasia (CIN), cases of invasive cervical cancer have been observed. However, the precise incidence rate remains uncertain, due to a lack of studies with extensive follow-up period. This study aims to assess the incidence rate and age at diagnosis of invasive cervical cancer in a large cohort of patients after cervical conization.

Methods: Conizations performed between 1997 and 2017 at the Colposcopy Unit of the S. Anna University Hospital, Torino Italy, were analysed. Unique identification codes of patients resident in Piedmont Region were cross-referenced with data from the Tumour Registry of the Piedmont Region. The analysed variables included adherence to organized screening, age at first conization, age at the onset of invasive neoplasia, follow-up process (if available), and final stage of invasive neoplasia.

Results: A total of 6517 cases of cervical conization were identified. Over a total of 56.965 person of follow up, 10 patients developed invasive carcinoma (9 squamous cell carcinomas and 1 adenocarcinoma), with an incidence rate of 17 per 100,000 woman-years. In 90% of cases, the first conization was performed after the age of 40 (50% over 50 years, only 20% over 60 years). The interval between the first conization treatment and the diagnosis of invasive neoplasia was less than 5 years in 7/10 cases, 10 years in 2 cases, 19 years in 1 case. All cases of invasive neoplasia occurred in patients older than 40 years (60% > 50 years and 30% >65 years). 60% of the patients who developed cancer in the follow up period were not enrolled into the organized cervical cancer screening program. Patients continuously adherent to the organized screening program had a lower tumour stage compared to those who did not adhere in the beginning or who had discontinued organized screening during follow-up (pT1a1 vs ≥ pT1a2).

Conclusions: The incidence of cervical carcinoma in patients treated for High Grade CIN was three times higher than Italian general population (17 vs 5.3 /100,000 women per year)1.Most cases occurred within five years of follow up consistently with the literature data2,3. Nevertheless 30% of invasive carcinomas developed more than five years after the initial intervention up to 19 years4,5. This long period could be due to the carcinogenesis process where dysplastic cells continue their neoplastic evolution entrapped within crypts of the previous treatment, undetectable by cytology and colposcopy, recommending long term follow up after conservative treatment6,7. Patients who maintained continuous adherence to the organized screening program presented with lower tumor stages.

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#8953

The expression of Nanog is associated with the progression and worse prognosis of cervical cancer.

25 - Cervical neoplasia

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Background/Objectives: Nanog protein is selectively expressed in pluripotent stem cells and it is a possible marker of Cancer Stem Cells (CSC). Stem cells from the transformation zone in the cervical epithelium are important for carcinogenesis due of their self-renewal and proliferativity. There are indications that CSC can originate from reserve cells. Considering the properties of CSC in tumorigenesis, the expression of NANOG should be hypothetically associated with the prognosis of cervical cancer, thus, its elimination might impact in treatment. From a clinical point of view, cervical cancer, is devoid of tumour markers or therapeutic targets of relevance. This study aimed to analyze the association NANOG expression as prognostic factors in women with cervical cancer.

Methods: This is a retrospective cohort, based on a convenience sampling, that analyzed Nanog expression as prognostic factors and indicative of progression in women with cervical cancer. The study was approved by Research Ethics Committees of the Federal University of Goiás (UFG) and Hospital Araújo Jorge (HAJ), registered under the codes 2.827.261 and 2.907.384. One hundred seven patients diagnosed with squamous cell carcinoma and adenocarcinoma had biopsies analysed for NANOG immunohistochemistry expression. The mean follow-up time was 115 months (SD± 51.8). Association analyses between categorical variables were performed using the chi-square or Fisher's exact tests and Mann-Whitney and Kruskal-Wallis tests were used for the numerical variables analyses The staging and degree variables of tumour differentiation were grouped: staging in I and II-IV and tumour grade in I-II and III. Survival curves were constructed using the Kaplan-Meier method, and the Log-Rank Test was used to compare the curves. Simple and multiple Cox Proportional Hazards Regression Analysis were as used to analyse the variables associated with specific survival and overall survival. Statistical analyses were performed with a confidence level of 95%, and it was considered statistically significant ($p < 0.05$) when the significance level was less than 5%.

Results: NANOG expression was significantly associated with advanced tumour stage ($p<0.001$), radiotherapy ($p<0.001$) and lymph node involvement ($p<0.001$). High NANOG expression showed low rates of specific survival ($p<0.001$) and overall survival ($p<0.001$). Multivariate Cox regression identified higher NANOG expression as the only factor associated with worse specific survival (HR: 40.29; 5.43 - 298.85); similarly, it identified higher NANOG expression (HR: 6.48; 2.48-16.90) and lymph node metastases (HR: 2.71; 1.26 - 5.84) as factors associated with worse overall survival. Higher NANOG expression was associated with specific (HR:30.07;1.77-511.54) and overall (HR:12.43; 2.48-62.30) survivals for women with Staging I cervical cancer. Similar findings on specific (HR:15.18; 2.02-113.92) and overall (HR:4.65; 1.58-13.70) survivals were observed for women with staging II-IV.

Conclusions: High protein expression of Nanog was associated with worse prognosis and progression of cervical cancer. These data reinforce Nanog expression as a prognostic marker and a potential therapeutic target in the clinical management of patients with this neoplasia.

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#9466

The value of folate receptor-mediated cervical special dyeing technique in the screening of cervical lesions

25 - Cervical neoplasia

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Background/Objectives: This study aims to evaluate the application value of the folate receptor-mediated cervical dyeing technique (FRD) in the screening of cervical lesions.

Methods: Between January and September 2022, a total of 2,000 women who underwent cervical cancer screening and FRD testing across multiple medical institutions in the Wenzhou area were selected. Data were collected from 130 women with complete records of FRD, human papillomavirus (HPV) testing, thinprep cytologic test (TCT), and colposcopy-guided cervical biopsy pathological results. The pathological results of cervical biopsies served as the gold standard for comparing the detection efficacy of FRD, HPV, and TCT in cervical lesion screening, as well as for analyzing the clinical effectiveness of the pairwise combinations of these three methods.

Results: In terms of specificity, the order was FRD (78.6%) > TCT (56.4%) > HPV (17.1%), with $P < 0.05$. No significant difference was observed in the negative predictive value (NPV) among these three methods ($P > 0.05$). The sensitivity for detecting high-grade cervical lesions reached 100% when HPV was combined with FRD, compared to 84.6% for TCT when combined with FRD. A significant difference in sensitivity was noted between the two combinations ($P < 0.05$). Furthermore, the sensitivity and NPV (100.0%) of the combination of HPV and FRD were equivalent to those of the combination of HPV and TCT.

Conclusions: This study demonstrated that FRD exhibits higher specificity in cervical lesion screening compared to TCT, while maintaining a comparable NPV. Additionally, the combination of HPV with FRD significantly enhanced the sensitivity and NPV of the HPV test. Given its low cost, ease of operation, and straightforward result interpretation, FRD represents a potentially valuable screening method, particularly suited for primary healthcare settings.

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#9044

Risk of non-cervical anogenital human papillomavirus-related cancer and precancer after active surveillance of cervical intraepithelial neoplasia grade 2: A POPULATION-BASED COHORT STUDY

25 - Cervical neoplasia

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Background/Objectives: Active surveillance (i.e., leaving the lesion untreated) for cervical intraepithelial neoplasia grade 2 (CIN2) has recently been introduced as an option for younger women with CIN2 in many countries. This is due to the high regression rates and the adverse effects of excisional treatment. However, a previous study reported an up to four-fold higher risk of cervical cancer in women undergoing active surveillance compared to those treated with loop electrosurgical excision procedure (LEEP). In this study, we aimed to investigate the risk of vulvar, vaginal, and anal cancer and precancer in women undergoing active surveillance compared to LEEP.

Methods: We conducted a nationwide population-based cohort study including all Danish women aged 18-40 years diagnosed with incident CIN2 between 1998 to 2020. Women were divided into two groups: active surveillance (i.e., a subsequent record of a biopsy/cytology) or LEEP (i.e., a subsequent record of a LEEP). We calculated weighted hazard ratios (wHRs) of vulvar, vaginal, and anal cancer and precancer using Cox proportional hazards regression and inverse probability treatment weighting. Age, region of residence, calendar year, and index cytology were considered confounders.

Results: We identified 27,505 women with CIN2, of whom 12,507 (45.5%) underwent active surveillance, and 14,998 (54.5%) underwent a LEEP. A total of 162 (0.6%) women were subsequently diagnosed with vulva, vaginal, or anal cancer or precancer. There was no difference in the risk of disease between women undergoing active surveillance and LEEP (wHR=0.89 (95% CI 0.61-1.30)). Similar findings were observed when stratifying by age at CIN2 diagnosis, site of lesion, and calendar time of CIN2 diagnosis.

Conclusions: In this population-based cohort study on women with CIN2, we found a low absolute risk of non-cervical anogenital cancer and precancer in women with CIN2. Importantly, we found that active surveillance for CIN2 was not associated with an increased risk of vulvar, vaginal, or anal cancer and precancer compared to LEEP.

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#9402

Cervical Cancer and Opportunistic Screening in Madeira Island - Portugal: a 24 year retrospective analysis

25 - Cervical neoplasia

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Background/Objectives: Cervical cancer remains a significant public health challenge worldwide. Organized cervical cancer screening in Portugal started in 1990 with the National Program for Oncological Diseases aiming at total national coverage. The Cervical Pathology activity in Madeira Island began in 1993. Until 2022 Madeira lacked an organized screening program, relying solely on opportunistic screening. The objective of this study is to analyze the cervical cancer cases and the activity and outcomes of the Cervical Pathology Unit in Madeira Island before the implementation of an organized screening.

Methods: A retrospective cohort study was conducted, analyzing all cases of histologically confirmed cervical cancer diagnosed in Madeira Island between 1998 and 2022. Data was extracted from Portuguese National Oncology Registry and hospital medical records, including patient demographics (age, parity, smoking status), clinical history, and diagnostic methods. Descriptive statistics were used to summarize demographic and clinical characteristics

Results: The Cervical Pathology Unit of Madeira Island was established in 1993 and conducted more than 31.000 medical appointments and 9.700 colposcopies until 2022. The opportunistic screening started in 1998 and the organized screening started in August 2022. There were 322 cases of histologically confirmed cervical cancer in Madeira between 1998 and 2022. Approximately 41% of them were diagnosed by our Cervical Pathology Unit. Stratification by age groups showed that cervical carcinoma in women under 30 was rare, representing only 0.6% of cases. Women aged 30-39 accounted for 12.5% of cases, those aged 40-49 represented 24.4%, and women aged 50-59 comprised 17.2%. Notably, the largest proportion of cases (45.3%) occurred in women over 60. The majority (64%) of women diagnosed during this period was multiparous. The number of carcinomas has decreased over time with the increased activity of our unit. The incidence of cervical cancer in Madeira in 1998 was 24.61 cases per 100.000 eligible women and in 2021 the incidence decreased to 8.86. There was also a shift in the patient profile, with carcinomas increasingly being diagnosed at earlier stages. However, even though our number of tests, colposcopies, biopsies and treatments increased significantly over the years, there is still a low cervical cancer screening coverage (being at 13.1% in 2021) and a high incidence of advanced stage carcinomas.

Conclusions: This retrospective analysis shows that opportunistic screening is not efficient to adequately fight cervical cancer. We need organized screening to significantly decrease the incidence and mortality of cervical cancer in Madeira.

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#9204

Prevalence of cervical premalignant/malignant lesions and their association with High-Risk HPV types and risk factors in Bafoussam, West Region, Cameroon: A cross-sectional study.

25 - Cervical neoplasia

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Background/Objectives: Background: Cervical cancer remains a significant burden in Africa, despite being preventable. While high-risk HPV (HR-HPV) is a major factor, other risk factors may contribute to its development. This study aimed to assess the prevalence of cervical lesions and their association with HR-HPV and risk factors.

Methods: Methods: A seven-month cross-sectional study was conducted from March to September 2024, involving sexually active women over 25 years old at the Bafoussam Regional Hospital. HIV serology, HR-HPV genotyping and cervico-uterine smears (Pap smear) were performed for all participants after administration of a questionnaire. Women with hysterectomies, cervical excision or undergoing cancer treatment were excluded. Data were analyzed using SPSS.22.

Results: Results: we enrolled 230 samples and 212 were analyzed. Participants were on average 46.8 ± 14.1 years. The prevalence of cervical lesions was 22.6%, with low- and high-grade squamous intraepithelial lesions (L/SIL and H/SIL) comprising 10.8% and 9.9% respectively, and squamous cell carcinoma 1.9%. HR-HPV infection was detected in 28.8% of cases, with non-16/18 subtypes being the most frequent (22.6%), subtypes-16/18 representing 3.8% and -16/OTHERS representing 2.4%. There was a weak, non-significant correlation between cervical lesions and HPV infection (p=0.12), where 19 HPV-negative patients presented with L/SIL and 14 with H/SIL while 4 HPV-positive patients presented with L/SIL and 7 with H/SIL. There were no significant differences in odds of developing cervical lesions between HIV-positive and HIV-negative patients (OR=1.987, 95%CI, [0.69, 5.69]) and HPV-positive and HPV-negative patients (OR=1.025, 95%CI, [0.51, 2.08]). According to risk factors, significant associations were found between cervical lesions, age (p<0.001), and number of pregnancies (p=0.001) while marital status, profession, and number of sexual partners showed no significant correlation. Educational level had a significant negative correlation (r=-0.357, p<0.001).

Conclusions: Conclusion: Cervical lesion prevalence is high, with a weak, non-significant association with HR-HPV. The findings suggest further investigation into HPV genotypes and other causative factors in Cameroon. Keywords: Prevalence, Cervical lesions, High-risk HPV, Clinical risk factors, Cameroon

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#9079

Locally advanced HPV associated cervical cancer in patients vaccinated against HPV prior to coitarche

25 - Cervical neoplasia

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Background/Objectives: The incidence of high-grade cervical lesions and cervical cancer has significantly decreased following the introduction of the human papillomavirus (HPV) vaccination, especially in those vaccinated prior to coitarche. However, optimal screening management of HPV vaccinated patients are still a concern and remain a clinical challenge. HPV 59 is a less common high-risk subtype, which is not included in any HPV vaccine type. Here we present a case report of HPV 59 positive patient vaccinated prior to coitarche with bulky cervical cancer.

Methods: A 27-year-old caucasian woman vaccinated against HPV before coitarche with the quadrivalent vaccine presented to our clinic with a bulky cervical tumor. From a clinical examination, ultrasonography and MRI staged as IB2 cervical cancer. After option consideration, patient opted for fertility sparing regime and was treated by neoadjuvant chemotherapy (NACT) followed by a successful fertility-sparing surgical treatment - SLNM (sentinel lymph node mapping) and pelvic lymphadenectomy followed by a simplex trachelectomy. Upon histopathological analysis from cervical biopsy prior to treatment and from the surgical sample testing HPV 59 was confirmed. The patient's post-operative course was uneventful, she was tested as HPV negative 6 months after treatment, and she subsequently achieved a pregnancy 1 year after her cancer treatment.

Results: This case displays a rare instance of cervical cancer in a young, vaccinated patient, and highlights the potential gaps in vaccine coverage, particularly against rarer HPV subtypes like HPV 59. As well as it raises awareness about the possibility of cervical cancer in vaccinated individuals and emphasizes the importance of ongoing cervical cancer screening and vigilance in vaccinated population. In Czech Republic we begin with HPV HR testing as a part of cervical cancer screening at 35. Is it time for a change? The successful use of NACT followed by surgical procedure provides valuable insights into fertility sparing treatment options for women of childbearing age diagnosed with cervical tumors IB2.

Conclusions: While HPV vaccination remains a main tool in the prevention of cervical cancer, cases of high-grade lesions and cervical cancer in vaccinated patients still occur. This case underscores the importance of proper cervical cancer screening even with vaccinated patients and raises a question about the screening itself. Should we for example move forward the first HPV testing in vaccinated patients, resulting in selection of group of patients with higher risk of high-grade cervical dysplasia?

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#9472

Effect of thermal ablation of Danish women ≥40 years of age with persistent HPV infection; a randomized clinical study

25 - Cervical neoplasia

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Background/Objectives: Nearly 10% of all infected HPV women HPV develops persistent genotype specific infections, which is a known cancer-risk enhancer and a clinical challenge. In clinical management, persistent HPV infection elicits extended monitoring or treatment. In Denmark, thermal ablation of the cervix is the primary treatment of contact bleeding, erythroplakia, chronic cervicitis and chronic discharge. Thermal ablation is a cervical heat treatment, where a smaller, defined area of the cervix is destroyed by a heated probe. Thermal ablation is less invasive and less extensive than i.e. a cone incision to treat benign conditions. We hypothesized that use of thermal ablation could destroy the HPV infected tissue in women with a persistent HPV infection, to the point of eradicating the infection as measured by HPV and DNA methylation status. The effects of thermal ablation in a time-study with HPV as outcome has not previously been evaluated. This small, randomized study evaluates whether thermal ablation eradicate persistent HPV infections and epigenetic changes in women ≥40 years.

Methods: In total, 120 women ≥40 years of age with screening defined HPV infection but without histologically verified neoplasia were enrolled. Sixty women were randomized for the intervention arm (thermal ablation) and 60 women constituted a control group (monitoring). At study conclusion, 40 women in the intervention arm and 43 women in the control completed the protocol. HPV and cytology status at baseline and effect measurements were monitored at 0-month (index, prior to ablation), 3 and 10-months after thermal ablation. For ablation, the WISAP Probe 6004/6005/6002 was used. Ablation treatment was administered 2-3 days apart; at 65 degrees celsius for 2 minutes, and at 100 degrees for 40 seconds. HPV testing was conducted using the BD OnclarityTM HPV test (BD Diagnostic Systems, Sparks, MD) paired with a full genotyping analysis (AnyplexII /A HPV28, Seegene, Seul, Korea). Methylation status was assessed using the QIAsureTM FAM19A4/miR124-2 methylation test (Qiagen, Hilden, Germany).

Results: Overall, 90% of women in the intervention arm (n=40) remained HPV positive for any genotype at conclusion of study versus at enrollment. In the control arm, 79% (n=34) remained HPV positive for any genotype at conclusion of study. No difference was observed between detection of high-risk HPV infections in the intervention and the control arms at any time point. At baseline, 60% of the women in the intervention arm were positive for FAM19A4 and 10% (n=6) for miR124-2 methylation. In the control group 33% (n=14) are initially FAM19A4 methylated and 7% (n=3) are miR124-2 methylated. FAM19A4 and miR124-2 methylation status initially decreases in both arms (-47%, n=17, - 20%, n=5, respectively) at the 3-month control but ends up increasing in both arms above the initial level after 10-months.

Conclusions: Here we show that the thermal ablation does not change the HPV infection status of the cervix. The observed temporary changes of methylation status on FAM19A4/miR124-2 could indicate a healing process in the cervix post thermal ablation. However, ultimately more women had a methylation positive profile. A larger study is needed to verify our findings. It is however worth considering that thermal ablation is suggested as treatment for cervical lesions in many countries, while this small study show that the underlying HPV infection is unaffected and hence could lead to recurrence.

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#9371

Clinical profile and risk factors of endocervical adenocarcinomas: impact of HPV status

25 - Cervical neoplasia

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Background/Objectives: Endocervical adenocarcinoma is an increasingly prevalent subtype of cervical cancer. Although Human Papillomavirus (HPV) infection is a well-established risk factor for many cases, a substantial portion of patients do not exhibit this viral association. The purpose of this study is to contrast the clinical characteristics and risk factors associated with HPV-dependent and -independent endocervical adenocarcinoma.

Methods: A descriptive, retrospective study was undertaken to characterize women with histologically confirmed endocervical adenocarcinomas treated at our center during a 6-year period (from 2018 to 2023).

Results: This study included 34 patients with a mean age of 51.9 ± 14.5 years (range: 29-89 years). Most cases were HPV-related cervical adenocarcinomas (ADC) (70.6% and n=24), while 23.9% (n=8) were HPV-independent. Patients with HPV-related ADC were younger at diagnosis (49.9 ± 13.2 years vs. 55 ± 16 years) and more likely to be asymptomatic (58.3% and n=14). Only one patient with HPV-independent ADC was asymptomatic at diagnosis. In both groups, the most common symptoms were abnormal uterine bleeding and postcoital bleeding. HPV 16 was the most common subtype in HPV-related ADC (n=12), followed by HPV 18 (n=5); in 7 cases, the associated genotype was not identified. Obesity and hypertension were more prevalent in the HPV-independent group. Regarding HPV vaccination, most patients in both groups were unvaccinated. Only two of HPV-independent patients and 62.5% (n=15) of HPV-dependent patients had regular cervical cancer screening. According to the FIGO classification (2018), most patients with HPV-dependent ADC were in the early stages of the disease (Stage 0: 37.5% and n=9 vs Stage 1: 41.7% and n=10), while patients with HPV-independent ADC were more likely to present at later stages. Large loop excision of the transformation zone was performed in one case of HPV-independent ADC and in 50% (n=12) of cases of HPV-dependent ADC for histological evaluation and treatment. In the latter group, 41.7% (n=5) also underwent surgical treatment. The most performed surgery was radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy. Chemotherapy and/or radiotherapy were used in 25% (n=6) and 33.3% (n=8) of this group, respectively. In the HPV-independent group, treatment consisted of surgery in 5 cases and radiotherapy in all cases (n=8). In 50% (n=4) of HPV-independent cases, a clear cell ADC was observed. In the HPV-related group, 41.6% (n=10) were in situ ADC, 20.8% (n=5) were endocervical ADC, and another 20.8% were usual-type ADC. Two recurrences of ADC in the vaginal fornix were verified. Both were submitted to chemotherapy and radiotherapy, and subsequently maintained under clinical surveillance.

Conclusions: This study demonstrates the heterogeneity of factors associated with cervical adenocarcinoma and the importance of considering HPV status, conducting HPV tests, and considering other risk factors and their management to define prevention strategies, such as vaccination, and early diagnosis of cervical cancer.

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#9422

Management and outcomes of adenocarcinoma in situ of the cervix: A seven-year retrospective study

25 - Cervical neoplasia

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Background/Objectives: Adenocarcinoma in situ (AIS) of the uterine cervix, first described in 1952, is considered a precursor lesion to invasive cervical adenocarcinoma. In recent decades, while the incidence of cervical squamous cell carcinoma has decreased in industrialized countries due to cytological screening programs, AIS incidence has remained stable or increased, now representing approximately 20% of cervical carcinoma cases. Risk factors include human papillomavirus (HPV) infection, particularly types 16 and 18, as well as oral contraceptive use. Due to its high endocervical location and potential for multifocal disease, AIS management is complex, particularly in women who wish to preserve fertility.

Methods: This retrospective seven-year study (2017-2024) was conducted at a reference cervical pathology center. We analyzed 23 cases of women diagnosed with AIS and followed their clinical outcomes. Data were collected from electronic medical records

Results: During the study period, 23 women were diagnosed with AIS through cervical biopsy or conization specimens, with an average age of 38 years. All patients underwent laser conization plus scissors. Negative margins were observed in 17 (73.9%) specimens, while 6 (26.1%) had positive margins. Among patients with positive margins, all also underwent re-conization, and 5 proceeded to hysterectomy, with 2 (33%) showing residual disease. In one case with positive margins, re-conization was performed, but the histopathological report is not yet available. Among patients with negative margins, 14 (82%) opted for hysterectomy, with only 1 case (7%) revealing AIS foci in the hysterectomy specimen. In 2 cases with negative margins, patients chose surveillance, with follow-up periods of 4 and 7 years showing no evidence of recurrence.

Conclusions: AIS treatment remains a subject of debate. Historically, hysterectomy was recommended due to the disease's multifocal nature and the limited predictive value of negative margins. However, considering the desire for fertility preservation, conservative approaches have gained prominence, provided patients understand the need for extended follow-up. For women wishing to preserve fertility, careful surveillance with endocervical cytology and high-risk HPV testing every six months for the first two years, followed by annual check-ups, is recommended. These findings support the use of laser conization plus scissors as a viable treatment option for AIS when performed with negative margins, maintaining recurrence risk at acceptable levels.

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#8951

Impact of HPV vaccination on the incidence of high-grade cervical lesions or worse in unvaccinated individuals: A Swedish register study

25 - Cervical neoplasia

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Background/Objectives: Human papillomavirus (HPV) is a prevalent sexually transmitted infection and the leading cause of cervical cancer. High-grade cervical lesions (HCL+), including cervical intraepithelial neoplasia of grade 2 and grade 3, are precursors to invasive cervical cancer. Although HPV vaccination has significantly reduced the incidence of cervical diseases among vaccinated individuals, understanding the indirect effectiveness (herd effect) in unvaccinated populations remains essential for evaluating vaccination programs. This study aimed to assess the incidence of HCL+ or worse in unvaccinated women born between 1985 and 2000 in Sweden, that are eligible for various vaccination programs.

Methods: We conducted a nationwide register-based cohort study using data from Swedish population-based registries. The study cohort included 827,373 unvaccinated women born between 1985 and 2000 who were free from HCL+ at study entry. The women were categorized into distinct birth cohorts: the pre-vaccination cohort (1985-1988), the catch-up cohort (1993-1998), and the school-based cohort (1999-2000). Participants were followed from age 10, or January 1, 2006, whichever came later, until they received HPV vaccination, were diagnosed with HCL+, emigrated, died, reached their 35th birthday, or the study ended on December 31, 2022. The study utilized multiple Swedish registries, including the Swedish Total Population Register, the Swedish HPV Vaccination Register, the Prescribed Drug Register, and the Swedish Cancer Register. Poisson regression was used to calculate incidence rate ratios (IRRs) across birth cohorts, adjusting for confounders. Kaplan-Meier survival curves visualized cumulative incidence rates across birth cohorts and illustrated the disease burden over time. We conducted a sensitivity analysis focusing on participants aged 23 years or younger to examine HCL+ incidence prior to the routine cervical cancer screening.

Results: The study identified 41,999 cases of HCL+ among 827,373 unvaccinated women, who contributed 9,314,082 person-years. Kaplan-Meier survival curves demonstrated clear differences in cumulative incidence among the four birth cohorts. Compared to the pre-vaccination cohort, both the subsidized opportunistic cohort and the catch-up cohort of unvaccinated women had a slightly, but statistically significant, increased risk of HCL+ (opportunistic: IRR 1.17, 95% CI: 1.14-1.20; catch-up: IRR 1.06, 95% CI: 1.03-1.09). In contrast, the school-based cohort showed a strong and statistically significant reduced risk compared to the pre-vaccination cohort (IRR 0.54, 95% CI: 0.44-0.67). The sensitivity analysis, focusing on women under 23 years of age, corroborated these findings and showed consistent patterns of lower risk among those who benefited from early vaccination efforts.

Conclusions: This study explores the complex relationships surrounding HPV vaccination programs and their effects on the incidence of high-grade cervical lesions among unvaccinated women. Women born in the pre-vaccination cohort and the catch-up cohort exhibited higher risks of developing precancerous cervical lesions. In contrast, those from the school-based cohort, likely benefiting from vaccination programs, had significantly lower risks. These findings highlight a complex interplay where unvaccinated individuals may experience indirect benefits from herd immunity, underscoring the need to optimize vaccine uptake and address disparities in cervical health prevention strategies.

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#9195

Managing cervical invasive carcinoma in pregnancy - a clinical case

25 - Cervical neoplasia

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Background/Objectives: Cervical cancer is one of the most common malignancies in pregnancy, with an estimated incidence of 0.8 - 1.5 / 10,000 births. 1-3% of women diagnosed with cervical cancer are pregnant or postpartum at the time of diagnosis; approximately 50% of these cases are diagnosed prenatally. A diagnosis of invasive cervical cancer in pregnancy poses major challenges to both the patient and her care providers. Given the complex ethical and medical issues present, management of cervical cancer in women who do not choose or are unable to terminate pregnancy requires individualized consideration of stage of disease, treatment options, patient preferences, and fetal viability.

Methods: We report the case of a 37-year-old pregnant black woman who presented to the emergency service at 11 weeks' gestation with vaginal bleeding.

Results: Upon gynecological examination, a 4 cm vegetative lesion of the cervix was identified. She had never undergone a screening test for cervical cancer. A pap-smear, HPV testing and colposcopy were performed, confirming an HPV-16 positive extensive lesion suggestive of invasive carcinoma. However, lesion biopsy showed high-grade squamous intraepithelial lesion (HSIL) but didn't confirm invasion. Due to discrepancy between colposcopy and histology a diagnostic conization was performed at 18 weeks gestation; the result was invasive epidermoid carcinoma of the cervix. An MRI classified it as stage IB2. The patient decided to continue with the pregnancy. She was proposed for neoadjuvant chemotherapy and re-staging after delivery. The pregnancy went on with no further intercurrences and the newborn was delivered via cesarian section at 34 weeks, with 2145 gr and an APGAR index of 8/9/10. Post-partum pelvic MRI had similar findings to the previous imaging study. She underwent Wertheim-Meigs radical hysterectomy 2 months after delivery with no surgical complications. At the present date, the patient is clinically stable and maintains follow-up at our institution.

Conclusions: There are no substantial randomized trial data to guide the management of cervical cancer in pregnant patients.1 Treatment strategies should be meticulously individualized, considering the stage of cancer, the patient's intention to proceed with the pregnancy, and the potential risks associated with modifying or deferring therapy.

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FC23 - HPV testing and genotyping

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#9404

HPV genotype distribution in HSIL/CIN2+ among women with chronic inflammatory disorders: population-based case-control study

14 - Genotyping

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Background/Objectives: Cervical screening algorithms recently started relying heavily on HPV-type risk profiles derived from a general female screening population, focusing on partial genotyping for HPV16 and HPV18. Women with chronic inflammatory disorders such as spondyloarthritis (SpA) and rheumatoid arthritis (RA) have an increased risk for high-grade cervical lesions [1]. Due to their inflammatory disease phenotype and/or immunomodulatory therapies, such women may display an overrepresentation of non-16/18 other high-risk (hr)HPV types acting in a carcinogenic manner. We therefore investigated which HPV types are prevalent in cervical lesions from this vulnerable patient population.

Methods: We performed a nationwide register-based cohort study of women with SpA or RA who started a first immunomodulatory treatment (here: TNF inhibitors) (n=8297 and n=14033), immunomodulator treatment-naive women with SpA or RA (n= 26186 and n=55506) and general population comparator women (age- and region matched 1:5, n=516211), followed up from 2007 to 2019. Our outcomes were incident screening-detected hrHPV infection, and cervical intraepithelial neoplasia (CIN) grade 2 or worse (CIN2+) during follow-up. HPV infection was categorized into hrHPV16/18-positive and non-16/18-other hrHPV-positive, respectively. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated through Cox regression models adjusted for the matching factors.

Results: Women with SpA or RA had a higher risk of screening hrHPV-positive (HRs of 1.17-1.24 vs comparators during follow-up), whether exposed to immunomodulatory drugs or not. RA cases not treated with such drugs had a higher risk for CIN2+ than their comparators from the general population (HR=1.19, 95% CI 1.06-1.33), but for RA cases treated with immunomodulators, and all SpA cases, no risk increase for CIN2+ was observed. Furthermore, the proportion HPV16/18 in CIN2+ lesions was similar between SpA/RA cases and their comparators, whether cases were exposed to immunomodulators or not.

Conclusions: Women with SpA and RA have a higher risk of high-risk HPV and thereto associated CIN2+ than the general female population. However, the HPV16/18 distribution in said lesions is similar, which is reassuring for HPV-based stratification algorithms based on partial genotyping.

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#9473

Distribution and role of high-risk human papillomavirus genotypes in women with cervical intraepithelial neoplasia: A retrospective analysis from Wenzhou, southeast China

14 - Genotyping

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Background/Objectives: To add the growing literature on baseline of high-risk human papillomavirus (HR-HPV) genotype distribution in cervical intraepithelial neoplasia (CIN) before the widespread using of HPV vaccines in Chinese mainland and to improve risk stratification of HR-HPV-positive women.

Methods: Retrospectively, the data of age, cervical HPV genotypes, cytology, and pathology were collected from 1166 patients who received loop electrosurgical excision procedure (LEEP). HPV genotypes were analyzed with Flowcytometry Fluorescence Hybridization Method. And then HPV prevalence, HR-HPV genotype distribution and the correlation of HR-HPV genotypes with CIN2+ (CIN2 or severer) were analyzed. The role of multiple HR-HPV types infection with or without HPV16/18 in the pathogenesis of CIN2+ was also analyzed.

Results: The 6 most common HR-HPV genotypes were HPV16, 58, 52, 33, 18, and 31 in descending order. Compared to HR-HPV-negative women, HPV16, 33 or 58 positive women had higher risk of CIN2+ (OR = 5.10, 95% CI = 2.68-9.70; OR = 3.09, 95% CI = 1.39-6.84; OR = 3.57, 95% CI = 1.85-6.89, respectively). And women who were infected by multiple HR-HPV types infection with HPV16/18 also had higher risk of CIN2+ (OR = 2.58, 95% CI = 1.35-4.92). However, multiple HR-HPV types infection without HPV16/18 did not increase the risk significantly (P = .08). Compare to bivalent Cervarix® and quadrivalent Gardasil®, HPV prophylactic vaccine targeting HPV31, 33, 52, and 58 might provide women more protection from HPV-induced cervical cancer in China. The women who infected by HPV16, 33, 58, or multiple HR-HPV types with HPV16/18 have higher risk of CIN2+ and need to be paid more attention in screening processes. And the role of multiple HR-HPV types infection without HPV16/18 needs be further identified in more studies.

Conclusions: This study aimed at providing a robust estimate of HPV prevalence and HR-HPV genotype distribution in CIN before the widespread using of HPV vaccines in Chinese mainland by analyzing the screening outcomes of 1166 patients who received LEEP retrospectively. In addition, to improve risk stratification of HR-HPV-positive women, the role of specific HR-HPV genotypes, and multiple HR-HPV types infection with or without HPV16/18 in the progress of CIN would be shown.

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#9335

Human papillomavirus genotypes distribution among women screened for cervical cancer in a rural healthcare facility in Eswatini

14 - Genotyping

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Background/Objectives: In Eswatini (South Africa), cervical cancer (CC) is the most common cancer and the first leading cause of cancer deaths in women. Infection from high-risk human papillomavirus (HPV) has a very high prevalence (46%) among women aged 15 to 49 years. In June 2023, a 4-valent anti-HPV vaccination, able to protect against HPV16, 18 (high-risk (HR) genotypes), and 6 and 11 (low-risk (LR) genotypes), was introduced for young girls aged 9-14 years. However, data regarding the HPV genotype distribution in the country are unavailable. The study aims to describe HPV genotypes infecting adolescent girls and women (AGW) participating in a urine-based HPV-DNA screening test at a rural health facility in Eswatini.

Methods: A cross-sectional study was conducted using specimens collected from a screening programme recruiting AGW aged 12-49 years self-presenting at St. Philip's Clinic for any health reason, Eswatini, between January 2023 and February 2024. Participants provided a urine sample and, if eligible (21-49 years), a cervix brush sample for cytology. Urine samples were concentrated and dried on filter paper (Dried Urine Spot, DUS) to be shipped to Italy. There, HPV-DNA was isolated using the NucliSENS EasyMAG® system (bioMérieux, France). In-house methods (i.e., PCR targeting L1 region of HPV genome and restriction length polymorphism method, or sequencing) and Ampliquality HPV-type express v3.0 (AB Analitica, Italy) were used for HPV-DNA detection and genotyping of all HPV types, including both HR and LR types.

Results: 440 DUS were tested, with HPV-DNA detected in 336 (76%) and genotyped in 333.The age-specific prevalence of HPV peaked at age 21-25 years (77/90, 86%). Most samples tested positive for multiple genotypes (210/333, 63%) ranging from 2 to 12 (median 2 genotypes) and for at least one HR-HPV (281/333, 84%). HPV35 (HR-HPV) was detected more frequently (80/333, 24%), followed by HPV16 (HR-HPV, 61/333, 18%) and HPV70 (HR-HPV, 52/333, 15%), HPV52 (HR-HPV, 50/333, 15%), and HPV31 (HR-HPV, 44/333, 13%) and HPV6 (LR-HPV, 44/333, 13%). At least one HR-HPV type was detected in 84% of samples (281/333), while the remaining tested positive only for LR-HPV (52/333, 16%). Cytology was performed in a subset of 175 women: 29 were classified as high-grade lesions. 76% (22/29) of women with high-grade lesions had infections preventable by 9-valent vaccine HR-types (HPV16, 18, 31, 33, 45, 52, and 58) vs. 41% (12/29), considering 2-valent and 4-valent vaccine HR-types (HPV16 and 18 types).

Conclusions: DUS samples represent a useful tool for wide-ranging molecular epidemiology study also "at the end of the road", rural St. Philips Clinic in Eswatini. To the best of our knowledge, this is the first study assessing the distribution of HR and LR-HPV genotypes in Eswatini. The high prevalence of HR-HPV genotypes, such as HPV35, calls for further research and tailored prevention strategies for cervical cancer in the country, including rapid molecular diagnostics and vaccines capturing the most prevalent HR genotypes. Evaluation of their impact on the development of cervical high-grade lesions and cancer awaits further studies. Our preliminary findings can inform policymakers and implementers in developing and adopting cost-effective prevention strategies for cervical cancer prevention.

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#9353

Cervical and Anal HPV Diversity in Women Living With HIV

14 - Genotyping

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Background/Objectives: Human papillomavirus (HPV) infection is a necessary condition for the development of cervical cancer and has also been associated with other malignancies, including anal cancer. People living with HIV are at higher risk of HPV infection, persistence, and related cancers. Anal cancer incidence has increased over the years supporting the screening for this cancer in high-risk populations, such as women living with HIV (WLWH). Women with cervical cancer or precancerous lesions have an increased risk of anal cancer, however this interaction remains to be clarified. Evaluating the relationship between anal and cervical HPV infection and their diversity is pivotal to the development of anal cancer prevention and screening strategies, especially among WLWH. The aim of this study is to characterize the diversity of HPV in the anal canal and cervix of WLWH to better understand the dynamics of HPV infection at these two sites.

Methods: Anal and cervical swabs were collected from WLWH recruited from hospitals in Rio de Janeiro, Brazil. HPV detection and genotyping were performed using reverse hybridization with the multi HPV flow chip kit (XGEN, Mobius). Cohen's kappa coefficient (k) was calculated to assess the agreement between HPV results from the two anogenital sites.

Results: To date, 56 women have been included in the study. Abnormal cytology was observed in six anal and three cervical samples. HPV infection was found in 29 cervical and 39 anal samples. Overall, 29 different HPV types were detected, and the most prevalent were HPV6 and HPV44/55 (11.6% each). HPV16 or 18 were identified in six anal and three cervical samples. Multiple HPV infection was observed in 13 cervical and 20 anal samples with an average of four HPV types per sample. HPV66 was found only in cervical samples (n = 3) while HPV33 and 71 were found exclusively in anal samples (n = 3 each). No agreement was found when comparing the presence of HPV, HPV16, high-risk HPV or multiple HPV infection between the two anogenital regions from the same women ($k < 0.21$).

Conclusions: HPV infection was higher in anal samples and the HPV status found was divergent between most cervical and anal samples of the same women, suggesting differences in susceptibility to HPV infection between the two anatomical sites studied. These results support the need for further studies evaluating the HPV types associated with anal cancer, and reinforce the importance of screening for this neoplasia in WLWH.

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#9396

Genotype Distribution of high-risk Human Papillomavirus Among Women in Azerbaijan

14 - Genotyping

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Background/Objectives: To determine the most common high-risk genotypes of HPV among women in Azerbaijan

Methods: For our study, cervical swabs were collected from 337 women aged 22-65 years at the National Oncology Center, from January 2020 to May 2024, and were tested for presence of Papillomavirus in cervical epithelium. Patients visited the hospital for various reasons, including physical examination, gynecologycal screening and gynecological tumors. For the detection of HPV DNA we used real time PCR test system (DNA-Technology) HPV QUANT-21 Quantitative REAL-TIME PCR Kit, which is intended for the specific identification and quantification of 3 low-risk (HPV 6, 11, 44) and 18 high-risk (HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82) HPV in human biological samples. DNA was extracted manually by the steps in specification using PREP-NA PLUS extraction kit (DNA-Technology). Amplification and detection of results was performed on 5-channel Detecting Thermocycler (DT 96, DNA-Technology).

Results: Using real-time PCR method we tested 337 urogenital swabs for the presence of HPV DNA, and obtained the following results. 201 tested samples (59,6%) were HPV DNA negative and in 136 samples (40,4%) HPV DNA was detected. Due to the fact that using method allows make screening and genotyping at the same time, we could analyze prevalence and distribution of HPV genotypes in our study group. So, among 136 women with positive result 64 (47,1%) of them was infected by one genotype of HPV (monoinfection), 72 (52,9%) of them infected by two or more HPV genotypes (multiple infection). The seven most common high-risk genotypes were 16 (23,5%), 68 (16%), 18 (15,4%), 56 (11,7%), 51(10,3%), 39 (10,3%), 31 (9,5%).

Conclusions: Cervical cancer is one of the most preventable and curable cancers worldwide, early screening and vaccination must be primary and secondary cervical cancer prevention strategies. But the most prevalent HPV genotypes among women can vary in different regions. So, in our study, we obtained results, that HPV genotypes specific for our region are 16, 68, 18, 56, 51, 39, 31. Therefore, specific HPV prevalence data are closely related to future vaccine developments

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•https://www.who.int/news-room/fact-sheets/detail/human-papilloma-virus-and-cancer •https://dna-technology.com/

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#9273

Distribution of circulating Human Papillomavirus genotypes in patients attending the national screening program in the Peruvian Amazon, 2024

14 - Genotyping

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Background/Objectives: Cancer is one of the diseases with the highest incidence and mortality in the world. In 2022, a worldwide incidence of almost 20 million new cases was estimated, in addition to a mortality of almost 10 million deaths. Among cancers affecting women, Cervical Cancer (CC) is the fourth most frequent cancer (1). In Latin America it is the third cancer with the highest incidence and mortality; and in Peru, it is the second most frequent neoplasm in women (2). In the Peruvian amazon regions (Loreto, Ucayali and Madre de Dios), there are greater difficulties in cancer control and prevention (3), with a higher cervical cancer mortality rate (more than 20 deaths per 100,000 women per year) compared to the rest of the country, as a result of lack of access to screening and treatment (4). It is known that 89-95.4% of CC is caused by persistent infection of the Human Papillomavirus (5), in that sense, in order of the designing and planning of appropriate interventions aimed at reducing the incidence of cases, morbidity and mortality from CC, information and evidence on the prevalence and distribution of HPV genotypes is required (6). The present study aims to determine the distribution of HPV genotypes in the Loreto region, a department of the Peruvian amazon.

Methods: Sampling: Cervical samples from women aged 25 to 55 years attending health facilities of the first level of care of the GERESA Loreto, within the molecular screening program for CC. Collected between May and August 2024 with Informed Consent approved by IRB of the Regional Hospital of Loreto. Genotyping: Qualitative molecular detection using a commercial kit (Allplex HPV 28) that detects 28 genotypes individually.

Results: We started with 377 samples, 374 of them obtained conclusive results, two samples were discarded from the study due to inadequate sample collection (excess blood) and one had insufficient transport medium to be processed. The mean age of the study participants was 39 years [32-46]. The overall prevalence of positive HPV was 51.3% (192/374). The prevalence of infection with a single HPV genotype was 56.3% (108/192), and the prevalence of multiple infection was 43.7% (84/192). The prevalence of infection with high-risk genotypes was 52.1% (100/192), with low-risk genotypes was 18.2% (35/192) and with both high- and low-risk genotypes was 29.7% (57/192). HPV 16 was the most prevalent HPV type, followed by 53, 52, 54 and 58, in descending order of prevalence. The five most prevalent low-risk HPV genotypes were (in descending order) HPV 54, 61, 70, 6 and 44.

Conclusions: First report on the distribution of HPV genotypes in the Loreto region, a remote area of the Peruvian Amazon. The high prevalences of general HPV infection and of high-risk genotypes indicate that Loreto is a region that should be better served by the national screening system in order to prevent CC. In a region with low HPV vaccination rates, it is important to know the distribution of genotypes to support the national vaccination program, which uses the tetravalent vaccine in Peru. We observed that of the 4 genotypes present in the vaccine, only one is among the most prevalent (HPV 16). This project generates evidence for a possible reorganization of the national vaccination program, which could increase its scope of application and the type of vaccine for a nonavalent tipe.

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#9096

Prevalence of Human Papilloma Virus Genotypes in Latvia Among Women Participating in Screening

14 - Genotyping

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Background/Objectives: Persistent infection of oncogenic human papilloma virus (HPV) is a well known risk factor for cervical cancer.1 HPV tendency to cause cervical cancer in tied with the specific genotypes2 and this study aims to provide insight into most prevalent HPV genotypes in Latvia among women. The data is drawn from the first two years of the reorganised state sponsored screening programme that now for the first time includes HPV genotyping as primary sceening method in 30 - 70 year old women and as a secondary screening method in women aged 25 - 30.

Methods: The conducted research was based on data obtained in an accredited clinical laboratory. Wilson score method, Chi-square test, one-sample binominal test and descriptive statistics were used for statistical analysis and graphical representation was made using Microsoft Office 365 Excel, IBM SPSS Statistics 28. The study process was in accordance with the Declaration of Helsinki, approved by the The Rīga Stradiņš University Research Ethics Committee.

Results: 81469 samples from 30 to 70 year old female patients in Latvia were collected as a part of state sponsored cervical cancer screening programme between July 1st 2022 and July 1st 2024. Overall HPV prevalence in this age group was 12,04%. Among these infections 81,82% women were positive for one HPV genotype, while 18,18% women were positive for infections caused by more than one HPV genotype. The study population with 9810 positive cervical samples tested positive for total of 12051 genotypes, making it 1.23 genotypes per positive sample on average. HPV 16 is the most prevalent HPV genotype, HPV 68 ranks second and HPV 31 comes in third, which is followed by HPV 16, HPV 68, HPV 31, HPV 66, HPV 52, HPV 56, HPV 51, HPV 45, HPV 33, HPV 39, HPV 18, HPV 58, HPV 59 and HPV 35 Across all age categories, a single infection was the most prevalent form. Age-specific infection, co-infection and genotype patterns in Latvian women are also analysed in this study.

Conclusions: The most prevalent genotypes were HPV16, HPV68, HPV31, HPV66 and HPV52, of which HPV68 and HPV66 are currently not covered by the vaccine. Regarding HPV infection, age seems to be a significant variable. These results offer significant epidemiological data that could be further used in cervical cancer screening, prognosis and the implementation of HPV vaccines targeting specific genotypes in this region.

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#9085

HPV HR test in the follow-up after fertility sparing surgery stage I cervical cancer

40 - Fertility and HPV

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Background/Objectives: In the Czech Republic, the overall incidence of cervical cancer in women of reproductive age has decreased since 2000. However, the number of women with invasive cervical cancer planning pregnancy has risen over the past 20 years. This increase may be attributed to the widening reproductive window, with the average age of first-time mothers now exceeding 30 years. (1) Consequently, fertility-sparing surgeries, such as laparoscopic lymphadenectomy and trachelectomy, have gained importance. These procedures show promising oncological and fertility outcomes in patients stage IA and IB1 with favorable prognostic factors (e.g., negative lymph nodes, clear surgical margins). (2)Despite these advances, optimal post-surgical follow-up protocols remain undefined, and there are no established guidelines regarding vaccination for these patients. Our follow-up protocol includes high-risk HPV (HPV-HR) testing since the year 2004. We began recommending HPV vaccination to patients in 2017. This study presents follow-up data from 53 non-vaccinated patients (2004-2016) and 14 vaccinated patients (2017-2021).

Methods: We conducted a prospective follow-up using HPV-HR testing (6 months and 30 months after surgery), cytology every 6 month, gynecology examination and colposcopy every 3 month, ultrasound every 6 month, and MRI 1 year after the surgery. In HPV-HR positive cases with colposcopy abnormal findings, biopsy was performed.

Results: In the non-vaccinated group, 53 patients were enrolled. Six months post-trachelectomy, 9 were HPV-HR positive. Biopsies revealed 4 cases of LGSIL, 1 HGSIL, and 4 with no dysplasia (HPV+ only). At 30 months, among the remaining 44 patients (HPV HR negative at 6 month), 13 were HPV-HR positive, with 7 cases of LGSIL, 1 HGSIL, 1 carcinoma, and 4 with no dysplasia. In the vaccinated group (14 patients), one was HPV-HR positive at 6 months and HPV positivity persist at 30 months and no new HPV-HR positive cases were detected at 30 months.

Conclusions: This study highlights the significant role of HPV testing in follow-up and underscores the importance of vaccination in this young, high-risk population. Despite the small sample size of the vaccinated group, the data show a statistically significant reduction in HPV reinfection and lesion development, potentially reducing the need for more radical, fertility-compromising surgeries. These findings advocate for HPV vaccination as a critical measure in preventing recurrent disease and improving long-term outcomes.

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#9005

Optimization and Analytical Validation of the Allplex HPV28 Genotyping Assay for Use in First-void Urine Samples

09 - HPV testing

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Background/Objectives: Despite first-void urine (FVU) being increasingly recognized as a credible specimen for HPV detection, there is a lack of well-validated testing methods providing full quantitative genotyping required for vaccine impact monitoring from FVU samples. The Allplex HPV28 assay, capable of individually detecting 28 HPV genotypes, presents a promising method. We aimed to evaluate its genotype-specific performance on FVU samples, following optimization of FVU preanalytics.

Methods: We selected 701 FVU samples collected using a Colli-Pee device (20 mL, with UCM), enriched for HPV-positivity (n = 630) based on previous testing with GP5+/6+ -PCR-based reverse line blot (GP5+6+ RLB) and E7 multiplex genotyping bead-based assay (E7-MPG) after Amicon filtration (AF). We first evaluated comparability and agreement of Allplex HPV28 genotype-specific positivity according to different preanalytics, i.e., pre-centrifugation with automated DNA extraction, direct automated extraction, and direct manual DNA extraction. Subsequently, we conducted genotype-specific comparison of Allplex HPV28 with GP5+/6+RLB AF and E7-MPG AF.

Results: No significant differences in HPV positivity by Allplex HPV28 testing were observed when comparing pre-centrifuged versus non-centrifuged DNA extraction, nor when comparing manual versus automated DNA extraction. Good genotype-specific agreement was observed between Allplex HPV28 and GP5+/6+RLB AF, with Allplex HPV28 being slightly more sensitive for all 28 HPV genotypes (average Allplex HPV28:GP5+/6+RLB AF ratio of 1.729). Compared to E7-MPG AF, Allplex HPV28 exhibited lower sensitivity for all 21 overlapping HPV genotypes (average Allplex HPV28:E7-MPG AF ratio of 0.588).

Conclusions: Findings of this study, combined with practical considerations for real-world implementation, support the use of Allplex HPV28 testing after automated or manual DNA extraction without requirement for pre-centrifugation, for HPV studies based on FVU samples, most notably those for vaccine impact monitoring on HPV prevalence.

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#9390

High rate of non-vaccine high-risk HPV genotypes in cervical cytology samples classified as atypical in women from Mpumalanga and Gauteng, South Africa

09 - HPV testing

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Background/Objectives: In the setting of low vaccine coverage in low-and middle-income countries, secondary prevention strategies such as cytology remain the backbone of cervical precancer detection.1 However, atypical or indeterminate results pose a clinical and diagnostic challenge.2 These indeterminate results require further investigation and risk loss-to-follow up. Molecular methods for screening of cervical cancer have been recommended owing to its superior performance; highly multiplexed real-time polymerase chain reaction assays allow for the detection of high-risk HPV genotypes and may assist in streamlining the referral of patients with atypical cytology if co-testing strategies are employed. Such molecular methods also give insight into circulating genotypes allowing the development and selection of epidemiologically relevant diagnostic kits and assays. Therefore, the aim of this study was to perform hrHPV genotyping on remnant liquid-based cervical cytology samples classified as atypical from women living in understudied areas. .

Methods: A laboratory based cross-sectional study was performed at the National Health Laboratory Services / University of Pretoria Department of Medical Virology. LBC cervical specimens submitted between March- August 2024 as part of routine screening from facilities in Gauteng and Mpumalanga and classified as atypical (atypical squamous cells of undetermined significance or atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion) by qualified cytologists were included in the study. Once all quality control checks were completed, remnant samples underwent automated extraction and PCR setup using the Nimbus liquid handling robot (Seegene Inc, Korea) after which amplification and detection for 14 hrHPV types were performed using a real-time PCR kit, the Allplex HPV HR assay (Seegene Inc, Korea).

Results: After applying exclusion criteria, 388 (ASC-H n= 75; ASCUS N= 313) samples were included in the analysis. The median age was39 [32-49]. Overall, 80.2% of samples tested positive for one of the 14 hrHPV types targeted by the assay. HPV 58 was the most commonly detected (20.6%) followed by HPV 35 (19.85%). 42.4% of samples had 2 or more genotypes detected with 34.7% having a single genotype. The most common hrHPV genotypes that presented as single infections were HPV16 (3.74%%), HPV58 (2.80%) and HPV35 (2.34%). The age group >=41 had the highest frequency of multiple infections. 64% of positive samples had a non-vaccine type detected. Types 16,18 and 45 were detected in 50% of samples ($p<0.05$)

Conclusions: Our study sheds insight into the circulating genotypes in understudied South African populations and demonstrates the high frequency of both hrHPV vaccine and non-vaccine genotypes present in LBC samples classified as atypical. Types 16,18 and 45 that require immediate further clinical intervention according to local guidelines were also commonly detected. Our study also highlights the high frequency of HPV 35 and the need to include this genotype in epidemiologically relevant vaccines.

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#9419

Human papillomavirus (HPV) genotype-specific prevalence and progression of high-grade cervical lesions (CIN2/3+) and cancer in HPV-positive women: a European pooled analysis

14 - Genotyping

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Background/Objectives: Many European countries with organised screening have shifted from traditional cytology-based screening to primary human papillomavirus (HPV) testing over the last decade, making the first step toward implementing risk-based screening over current "one-size-fits-all' approaches. As the first cohorts of women vaccinated against oncogenic HPV types begin reaching cervical cancer screening age, current HPV-based screening guidelines may require reassessment as the distribution of prevalent HPV genotypes shifts. For the development of new screening programs, it is necessary to accurately assess the risk of progression and prevalent high-grade precancerous lesions and cancer based on individual baseline risk factors, such as high-risk HPV types.

Methods: We applied a previously developed prevalence-incidence model which decomposes the biological process of HPV infections progressing to (pre-)cancerous lesions into easily interpretable parts by including parameters for disease prevalence at baseline as well as progression and clearance rates based on individual risk factors. By pooling data from six population-based cervical cancer screening studies conducted across Europe we were able to estimate genotype-specific effects on progression from HPV infection to endpoint CIN2+, CIN3+ or cancer, and probability of disease at baseline in HPV-positive women. For CIN2+ and CIN3+, 8 individual genotypes (HPV 16, 18, 31, 33, 35, 45, 52, and 58) were included as covariates. For endpoint cancer, genotypes were grouped according to the IARC stratification for carcinogenicity: (1) HPV16, (2) HPV18/45 and (3) HPV Group 1 a9 (HPV types 31, 33, 35, 52, and 58), and the model was fit with the three genotype groups as covariates. The reference category was "HPV other" consisting of types 39, 51, 56, 59, 66, or 68. Lastly, the predicted cumulative risk over a 15-year period was compared across the three endpoints.

Results: HPV16 had the greatest impact on the disease risk at baseline and over 15 years of follow-up across all endpoints. HPV18/45 had the second-highest disease risk at baseline for endpoint cancer but not for CIN2+ or CIN3+, and also the second-highest cancer progression risk during follow-up. HPV31 and HPV33 had a high progression risk for CIN2+ and CIN3+, but not for cancer. Additionally, HPV35 and HPV52 were associated with a relatively high risk for endpoint CIN2+.

Conclusions: The results align with general knowledge that HPV16 is the most prevalent and aggressive type associated with CIN2/3+ as well as cancer, whereas HPV18 is associated with a risk of cancer. Overall, our results suggest that extended genotyping of high-risk HPV types beyond HPV16 and HPV18 may primarily serve to rule out the presence of CIN2 or 3 lesions, while genotyping for HPV16 and HPV18 could be used to identify lesions with a high risk of progressing to cancer.

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#9556

A Multimatrix Approach to HPV Testing: Evaluating the HPV PLUS ELITe MGB Kit Across FFPE, Semen, and Urine Samples

09 - HPV testing

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Background/Objectives: Validation processes are fundamental for ensuring the performance and reproducibility of human papillomavirus (HPV) assays, in alignment with established standards. However, limited data are available regarding assay validation for non-standard sample matrices, such as formalin-fixed, paraffin-embedded (FFPE) biopsy material, sperm, and urine. These matrices are increasingly recognized for their potential in HPV diagnostics but present challenges due to factors such as DNA degradation, inhibitory substances, and matrix-specific variability. Greater emphasis on addressing these gaps is necessary to enhance the applicability of HPV assays and to support accurate diagnostics in diverse clinical contexts. This pilot study aims to assess the feasibility and compatibility of validation approaches for HPV assays in these challenging sample types.

Methods: This research presents a proof-of-concept study assessing the HPV PLUS ELITe MGB Kit (ELITechGroup, A Bruker Company, EG) assay's compatibility across diverse sample matrices using the ELITe BeGenius system (EG). Specimens were obtained with patient consent from AML - Sonic Healthcare Benelux. Twenty samples (10 positives and 10 negatives) for each matrix, i.e., FFPE, sperm, and both primary and buffered in Colli-Pee® urine, were selected using the RIATOL qPCR HPV assay as comparator test. Workflow efficiency was quantitatively analyzed at a Ct-level of internal control (IC). Categorical HPV detection accuracy was calculated using kappa coefficient of agreement and false positive/negative rates (FPR, FNR).

Results: All matrices showed successful compatibility with the ELITe BeGenius system, without modifications to the standard protocol. Overall, the total invalid rate across all sample types was 3%, with FFPE samples showing the highest invalid rate of 10%, while sperm, raw urine, and Colli-Pee urine samples exhibited no invalid results. Invalid FFPE samples were retested with a 2-factor dilution of the eluate, where valid results were obtained and included for further accuracy analysis. The IC values were consistent among matrices, averaging from 23.08-27.90, with FFPE showing the highest mean IC value (27.90). HPV concordance rates exceeded 90% for all matrices, with an average of 94% (kappa: 0.781). FPR were generally low, ranging from 1.5% (sperm and urine in Colli-Pee®) to 7.4% (FFPE). However, FNR were more variable, with the highest observed in FFPE and sperm samples (25% and 23.1%, respectively), while both non-buffered and Colli-Pee® urine demonstrated lower FNRs of 0% and 14.3%, respectively.

Conclusions: Our research shows that molecular testing is reliable in non-customary sample types and it shows the potential to expand HPV diagnostics beyond conventional cervical specimens. These changes greatly improve cancer screening programs for people in need and in places where usual methods are hard to use. Detecting HPV in different sample types helps us understand its epidemiology, transmission, and role in non-cervical cancers better. These improvements create a thorough framework for HPV management and prevention and they improve public health outcomes globally.

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#9123

Triage management method research of high risk HPV 5+9 genotyping in the population with ASC-US in cytological initial screening: A multicenter research from China

14 - Genotyping

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Background/Objectives: To evaluate the performance of different high-risk human papillomavirus (HR-HPV) genotype models in triaging women with cytological diagnosis of atypical squamous cells of undetermined significance (ASCUS).

Methods: After acquired the ethical permission from the ethical committee of West China Second Hospital of Sichuan University, patients from West China Second Hospital of Sichuan University, Henan Cancer Hospital and Changzhi Medical College were selected to join this research, between Apr. 2017 and Dec. 2020. Those subjects were referred for further screening by colposcopy and biopsy. Cervical intraepithelial neoplasia grade 2 or worse (CIN2+) were treated as the endpoint. The sensitivity, specificity, positive predictive values (PPVs), negative predictive values (NPVs), positive likelihood ratio (PLR) and negative likelihood ratio (NLR) of different HR-HPV genotype combination models were estimated. This research was signed by Chinese Clinical Trial Regeistry (ChiCTR2200055287).

Results: As a results of 1096 subjects with ASCUS were recruited, and 3.19% (35/1096) women were diagnosed as CIN2 lesions, 3.65% (40/1096) cases diagnosed as CIN 3 and there was no cervical cancer diagnosed. Among those with ASCUS who were identified as having CIN2+, the HR-HPV infection rate was 93.3% (70/75). Compared to other HR-HPV-type combination models, the HPV16/18/33/52/58 model achieved a higher sensitivity [85.33% (74.58-92.1)], specificity [69.54(66.6-72.33)], PPV [17.07 (13.48-21.35)], NPV [98.47 (97.2-99.2)], PLR [2.08 (2.46-3.20)] and NLR [0.21(0.1221 ~ 0.3644)] for the triage of ASCUS patients.

Conclusions: This study presented an opinion that the specific Hr-HPV genotype of HPV16/18/33/52/58 is an alternative strategy for ASCUS triage and can effectively reduce the high burden of colposcopy referrals in China.

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IVDR Implementation: Analytical and Clinical validation of genotyping in FFPE samples

14 - Genotyping

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Background/Objectives: As of May 26, 2022, the new EU in vitro diagnostic medical devices regulation (IVDR) came into effect, bringing new challenges to the laboratories regarding the validation processes. However, this shift has also created a valuable opportunity to thoroughly analyze the data obtained during these validations. The goal of this project was to validate FFPE samples and correlate the results with histological outcomes thereby proving the accuracy value of the tests conducted in these samples.

Methods: A total of 45 cases of hr and lr-HPV genotyping tests were selected for histological comparison. The Seegene Anyplex HPV28 test was performed on samples extracted from paraffin blocks during 2022 and 2023. The genotyping results from these paraffin section samples were categorized based on histological findings related to lesions in the genital region. The categories included Histological Diagnosis Negative, which encompassed diagnoses such as lichen, molluscum contagiosum, and cases lacking morphological characteristics indicative of HPV infection, and Histological Diagnosis Positive, which included diagnoses of condylomas, low-grade and high-grade dysplasia, as well as carcinomas. Samples were chosen based on a strong clinical and scientific correlation.

Results: Of the total of cases, 93% were positive for HPV and only 7% were negative. The most prevalent HPV type was HPV 6 in 30 cases, and 10 samples exhibited infection by multiple HPV types. The PPV was 94,8% and NPV was 78,1%. The clinical sensitivity was 88,7% and clinical specificity 89,3%.

Conclusions: The validation of this test was successful and showed excellent clinical correlation with histological findings and immunohistochemistry biomarkers. This establishes the test as a valuable tool to complement pathological diagnoses.

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#8892

Recommendations for the implementation in Chile of extended genotyping for human papilloma virus in screening and follow-up

23 - Risk management

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Background/Objectives: This summary corresponds to the work sent to "The Chilean journal of gynecology and obstetrics" which is currently in the peer review phase (code RECHOG/0091/24). Introduction. Most cases of cervical cancer occur in women without current screening (either due to lack of coverage or adherence to prevention programs) and/or poor screening (it is estimated that 1 in 3 women with cancer had a current PAP screening). In Chile, it is estimated that 2 women die a day from this cancer, which is, without a doubt, a worrying figure. Local epidemiological data regarding HPV - its causal agent - is scarce. The few local genotyping studies demonstrate that the most prominent genotypes in Chile are, arranged in descending order, in screening, HPV16, 31, 58, 59 and HPV66; and from biopsies of patients over 25 years of age, HPV16, 33, 31, 52, 35 and HPV18. In this way, the need arises to incorporate screening with extended genotyping in real time into the prevention program, which allows clarity and understanding regarding the local epidemiology. By understanding which genotype infects patients, efforts can be focused on those who are at greater oncogenic risk, improving the capacity for early detection and making control more flexible in those who have less dangerous genotypes. This means better use of available resources, which are always limited. Objective. To generate recommendations that allow optimizing the cost-effectiveness of HPV-PCR screening and follow-up to to suggest them to the Chilean Ministry of Health (MINSAL) through a scientific publication.

Methods: Materials and methods. A critical review of scientific articles and clinical guidelines, both national and foreign, is carried out and recommendations compatible with current national guidelines are prepared by consensus by a multidisciplinary panel of specialists (expert consensus).

Results: Results. A guide of recommendations. Some of the key points were: -We recommend a universal definition of "high-risk patient." -Prioritize the distribution of tests to high-risk patients. -Implement reflex cytology. -CIN1: Observation is preferable to treatment. -Post-treatment surveillance with PCR-HPV. -Viral load was decided to be omitted for now. -Colposcopy. During colposcopic evaluation, a lesion or suspicious area of lesion should be observed for sampling. -Algorithm for first time PCR-HPV/PAP: high risk. Referral to colposcopy additionally considers genotype(s) 45 and/or 33. The rest of the genotypes can be managed according to their risk in: control at 1 year and; control at 3 years. Only those cases that prove to be persistent infection by the same genotype are referred to colposcopy. Genotype 66 can be considered low-risk HPV. -Algorithm for previous negative PCR-HPV (5 years) and/or previous negative PAP (3 years): lower risk patient. Colposcopies can be limited to what is strictly necessary, with 16 and 18 being mandatory. -Report. It is suggested to work with the template presented in order to help the clinician and educate the patient regarding the result.

Conclusions: Conclusions. The implementation of extended genotyping allows the development of a cost-effective strategy based on stratification and monitoring according to oncogenic risk, a comprehensive concept that helps prevent overtreatment, giving the possibility of redistributing resources and reducing cancer.

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Exploring HPV Genotyping: A New Horizon for FFPE Samples

14 - Genotyping

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Background/Objectives: At the time of this data´s publication, there were few studies regarding HPV prevalence in FFPE samples. The main purpose of this project is to describe the most prevalent cases of HPV in the different body locations, while establishing a correlation with the literature and evaluating the performance of hr-HPV and lr-HPV genotyping in these samples.

Methods: A selection of all the hr and lr-HPV genotyping cases performed since 2017 to date was analyzed in order to obtain information about positivity of the different HPV types in FFPE samples from different body locations. The tests were performed with Seegene Anyplex HPV28 kit and extraction was made on a Kingfisher Flex with MagMax Viral/Pathogen kit after paraffin digestion.

Results: From the 219 tests performed, 21% were women and 79% were men. The cases comprised different topographies namely: 10% head and neck region, 11% female genitalia, 52% male genitalia, 18% anal, 9% skin and others. For head and neck samples the most commonly found HPV type was 16, followed by HPV 6. In the male genitalia the majority of cases were HPV6 and 20% of the cases corresponded to multiple infections. For female genitalia the main causative agent was HPV6 as well, although as expected HPV16 is in the second place. For anal histological samples almost half of the lesions were caused by HPV 6, followed by HPV11 and 16. Occasional skin samples and other locations were also considered for this evaluation and the findings were surprising with 45% of HPV16 and HPV6.

Conclusions: The applicability of the HPV tests in the market goes beyond its basic utility, and it is relevant to study the FFPE lesions excised to obtain more information. The growth of these studies is notorious particularly in head and neck cancer suspicions. In such lesions the vaccine influence has not yet been seen, partly due to the age of the cohort that has an average of 49 years old. In the overall analysis almost half were due to HPV 6, around 17% to HPV 16 and 6% to HPV 11 and 17% of the cases had multiple infections.

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