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ABSTRACTS

FREE COMMUNICATIONS SESSIONS

FC02 - Self-sampling I

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#7125

IMPROVING COMMUNICATION AND MANAGEMENT FOLLOWING A POSITIVE HOME HPV SELF-SAMPLING KIT RESULT: DATA FROM THE U.S. HOME AND STEP TRIALS

13 - Self-sampling

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Background/Objectives: Mailed HPV self-sampling kits improve cervical cancer screening adherence. Qualitative findings from our HOME trial in a U.S. integrated healthcare system found unmet information needs and anxiety among patients with a positive kit result. The subsequent STEP trial tested optimized implementation strategies for: 1) educating patients when offering the kit, and 2) when explaining results and recommended follow-up. We evaluated if optimized implementation strategies in the STEP trial improved result communication processes and addressed informational needs compared to HOME.

Methods: The STEP trial provided an educational pamphlet to explain the purpose of HPV testing (especially difference to Pap testing), and added a centralized nurse to communicate about and arrange follow-up for all with positive kit results.Telephone interviews were conducted from December 2021 to March 2022 with 29 patients (56% of invited) who had a positive kit result. The interview guide was similar to the one deployed in the HOME trial.1 Transcripts were analyzed in two phases. In Phase 1, five coders applied similar codes from the HOME trial using iterative content analysis to identify overarching themes for the STEP interviews alone. One code was added to document references to the COVID-19 pandemic. In Phase 2, coders discussed which HOME and STEP trial elements were similar versus different. We expected less heterogeneity in STEP participants' description of, information needs after, and anxiety from the result communication due to centralized management by nurse (versus handled by each primary care team in HOME). Two coders created a table to organize and juxtapose coding data from STEP and HOME trials and then the group discussed whether data were different or similar as posited. This planned comparison between HOME and STEP codes and themes helped evaluate if implementation strategies worked as intended.

Results: Response rates for qualitative interview participants from both trials were similar. Most were older, White, not Hispanic, and had a prior Pap. Comparison of codes across trials found one theme remained consistent - convenience of the home-based kit. Some STEP participants were still worried about kit accuracy due to concerns of doing the sample collection "right". Patients equated the discomfort of clinician using a speculum to collect the cervical specimen for the Pap with it being a better test. This suggests that some patients still did not understand the difference between Pap and HPV tests. Though STEP patients still experienced fear after receiving a positive kit test result, they felt more supported during results communication. All reported feeling reassured after talking with the nurse and understood next steps in the management process. Though an educational pamphlet was provided with the kit, most participants did not recall receiving it or using it to understand their kit results. Most STEP participants (69%) preferred the kit. All (100%) agreed that kit instructions were easy to understand, 90% were sure they sampled the right place, and 86% believed kit results were correct.

Conclusions: Unlike the prior HOME trial, there was less negative affect expressed by patients after receiving results. This suggests patients received the information needed to continue with the screening process and supports the value of a centralized nurse. Providing educational materials at multiple timepoints may further improve results communication in the future.

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A SURVEY TO ASSESS BELIEFS AND ATTITUDES TOWARDS HPV SELF-SAMPLING AS PART OF THE NATIONAL CERVICAL SCREENING PROGRAMME IN THE REPUBLIC OF IRELAND

13 - Self-sampling

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Background/Objectives: The WHO recommended that HPV self-sampling should be made available as an additional method of cervical cancer screening in their 2022 update on self-care interventions (1). The importance of understanding a country's context before implementation has been emphasised in HPV self-sampling research (2-3). Ireland's current cervical screening coverage is 73% of 25 - 65 year olds and 79% of 25 - 60 year olds. We aimed to determine the acceptability of HPV self-sampling in the Irish context, particularly in under- and never screened populations while also determining the preferences of regular attenders to better understand their cervical screening behaviours and inform any future changes to the cervical screening programme.

Methods: This study was an anonymous, cross-sectional survey of the views of women aged 20 - 65 living in the Republic of Ireland on HPV self-sampling, using quota sampling. The questionnaire used was based on a similar cross-sectional survey conducted in England and adapted with permission for the Irish context (4). The attitudes and preferences of participants to HPV self-sampling were assessed before and after exposure to information about self-sampling. Questions also focused on preferred location for completing self-sampling and any perceived advantages to self-sampling. Responders were categorised as under-screened (attended more than 6 months after invite), never screened (never attended screening), pre-eligible (20-24 years) and regular attenders (attended within 6 months of invite).

Results: In total, 2024 surveys were completed, 1522 online and 502 face-to-face administered by an interviewer. Of the total sample, 59% (n=1194) were regular attenders to cervical screening, 14.8% (n=300) were under-screened, 18.8% (n=381) never screened and 7% (n=149) were under 25 (pre-eligible). Pre-explanation, 51% of all women would choose a form of self-sampling as their first choice, 42% would continue with screening as usual, 6% did not know and 1% would not attend for cervical screening. Post-explanation, 54% of all respondents would choose some form of self-sampling, 42% would continue screening as usual, 4% did not know and 1% would not attend at all. Based on screening participation category, 65% of never screened and 62% of under-screened women would choose self-sampling compared to 41% of regular screening attenders. Privacy (71% & 75%), more comfort (63% & 64%), convenience (77% & 77%) and less embarrassment (66% & 66%) were cited by the under- and never screened groups as motivators for self-sampling, respectively. 88% of those preferring clinician-based screening would be more confident that the test was done correctly, 86% feel they would have greater trust in the result and 73% are used to getting their cervical screening done in that way.

Conclusions: This is the first study to assess the preference of women to HPV self-sampling in Ireland. The findings demonstrate that if a self-sampling option was offered through CervicalCheck, a substantial proportion of regular attenders would continue to opt for clinician-based screening, while many from the never-screened and under-screened populations would consider being screened using a self-sampling option.The results indicate the potential demand of self-sampling in Ireland and that if introduced, HPV self-sampling has the potential to increase screening participation of under- and never screened populations.

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Acceptability of Self-Sampling vs. Routine Clinician Sampling for Cervical Cancer Screening in Two Rural Settings of Cuenca, Ecuador.

10 - HPV screening

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Background/Objectives: Background: In Ecuador, 4 out of every 10 women have never undergone cervical cancer screening during their lifetime due to several barriers. The use of Self-Sampling tests could take away some of these barriers due to their convenience and properties and consequently improve screening adherence. Objective: The main objective is to compare the acceptability and uptake of Self- Sampling tests for human papilloma virus (HPV) versus routine clinician sampling in two rural communities in Cuenca, Ecuador.

Methods: Methodology: A quasi-experimental study was conducted in two rural parishes of Cuenca, Ecuador, between February and September 2023. In both communities, identical educational sessions were conducted on cervical cancer screening prevention. A prepositive sample size of 130 women participated in each community. After the educational session, women of community A, the intervention community, were offered the possibility of Self-Sampling, while in community B, women were referred to routine screening at healthcare facilities. Three months after the educational session, women from community B were contacted by phone to follow-up whether they had undergone cervical cancer screening in routine care.

Results: Results: Community A consisted of 130 participants with a median age of 43 years, 55 (42%) had a basic educational level, and 92 (70%) were in a stable marital status. Community B consisted of 130 participants with a median age of 38 years, 62 (47%) with a secondary educational level, and 97 (74,6%) in a stable marital status. In community A, 117 (90%) participants accepted Self-Sampling, while 13 (10%) refused the test. Among these women, 8 (61.5%) were menstruating at the time, 2 (15,4%) preferred to have the sample taken by a health professional, 2 (15,4%) were concerned about not performing the sampling correctly or causing self-harm, and 1 (7.7%) cited a lack of time. In community B, 25 (19,2%) participants underwent screening after 3 months of follow-up, 12 (9,2%) women were lost to follow-up, and 93 (71,5%) did not go for screening

Conclusions: The study highlights the substantial impact of utilizing Self-Sampling tests for human papilloma virus (HPV) in increasing cervical cancer screening adherence, especially in rural communities facing barriers to routine clinician sampling. Implementing this approach can play a pivotal role in improving cervical cancer screening rates, particularly among women in underserved regions, thereby contributing significantly to early detection and prevention efforts in Ecuador and similar settings worldwide.

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#6808

WOMEN'S REASONING AND EXPERIENCE IN THE CERVICAL CANCER SCREENING PROGRAM WHEN OFFERED A SELF-SAMPLING HPV-TEST: A QUALITATIVE STUDY

13 - Self-sampling

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Background/Objectives: The HPV vaginal self-sampling test was implemented in the southern part of Sweden in September 2021 to increase the attendence in the cervical cancer screening program. The objective in this study was to explore women's reasoning and experience when offered a self-sampling HPV-test.

Methods: A qualitative study design and content analysis with an inductive approach was applied to the data. Questionnaires with nine open-ended questions were used to collect narratives from the invited women. Women were eligible if they had been offered a self-sampling device since the implementation in September 2021 and resident in the southern part of Sweden. To achieve purposive sampling with maximum variation, both adherent attenders to the screening program and non-attenders (absence for >7 years), as well as a certain number of women with cervical dysplasia were deliberately recruited. In total, 1915 women fulfilling the inclusion criteria received an invitation to participate in the study.

Results: The preliminary results from 168 answered questionnaires indicate that the women appreciated preventive measures and felt positive and grateful for the self-test. Reasons for taking the self-test were that it is time- and cost-efficient, saves resources, no need of transportation and serves as a good alternative to reduce the need of having a test taken by a health care professional. A vaginal examination was described as unpleasant despite friendly health care professionals. There was a varied perception on women's own capacity to perform the self-sampling test. The majority of women described being anxious about a potential and detected HPV-infection. Women experienced in general a negative impact on the mental well-being due to cervical dysplasia, some women expressed death anxiety, depression, and fear of not becoming a mother in the future. The sex life was also affected negatively for most women. Little reflections on HPV as a sexual transmitted disease was described.

Conclusions: The results suggest that most women appreciate the self-test, although there are varied perceptions on women's own capacity to perform the self-sampling test. More knowledge about HPV and cervical dysplasia could benefit women to increase the acceptance to the self-test and furthermore increase the attendance in the screening program.

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HE TAPU TE WHARE TANGATA - A MODEL FOR EMPOWERING RURAL SOLUTIONS: POINT OF CARE TESTING FOR HUMAN PAPILLOMA VIRUS IN AOTEAROA NEW ZEALAND

13 - Self-sampling

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Background/Objectives: Māori the Indigenous peoples of Aotearoa New Zealand face inequitable high rates of cervical cancer and are almost three times more likely to die than non-Māori. Data shows that Māori experience specific barriers to access of diagnostic and treatment services following an abnormal cervical screening test. This study utilises Point-of-Care Testing (PoCT) technology in two rural communities, testing self-taken vaginal swabs for high-risk HPV (HPV) providing timely results. This allows for immediate referral to colposcopy appointments for follow up of positive tests. We hypothesise that this intervention will lead to earlier colposcopy and treatment.

Methods: This is a cluster-randomised crossover trial comparing two pathways for cervical screening and follow-up in two rural areas (sites) in partnership with Iwi (tribal) groups (1). Pathway 1 is HPV self-testing with onsite PoCT results (GeneXpert) in one-hour, face-to-face provision of information, support, and immediate referral for colposcopy for women with positive HPV results - a community-controlled pathway. Pathway 2 is HPV self-testing and laboratory analysis, followed by usual result giving, information and support, and standard referral pathways for those with positive HPV results - current standard pathway. Each site was randomised to implementing either Pathway 1 or Pathway 2 in the first study period (15 months), then crossing over to implement the other pathway in the second study period. The primary outcome is the proportion of women with HPV positive results having a colposcopy within 20 working days from HPV test. A range of quantitative and qualitative secondary outcomes were explored, including the successes and challenges of both pathways from the perspectives of a range of stakeholders and women being tested.

Results: Study recruitment began February 2021 and period 1 finished April 2022. After a three-week washout, period 2 recruitment began in May 2022 and finished July 2023. Initial results: Pathway 1 (PoCT); 619 eligible participants undertook an HPV self-test and PoCT, with 49 positive results (7.9%). Median age 48. Approximately 30% under/never-screened in period 1, 13% in period 2. Pathway 2; 779 eligible participants undertook an HPV self-test, with 78 positive results (10.0%). Median age 48. Approximately 30% under/never-screened in period 1, 17% in period 2. The use of PoCT was found to be highly acceptable to both clinicians and patients. Full pathway results available in February 2024.

Conclusions: This study involved governance of local Iwi and community. It showed positive engagement by community and primary care clinics in the successful use of PoCT and acceptability of HPV self-testing and local control of the pathway.

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HPV SELF-SAMPLING WITHIN NATIONAL CERVICAL CANCER SCREENING PROGRAM: AN IMPLEMENTATION PROJECT IN ESTONIA 2022

13 - Self-sampling

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Background/Objectives: In Estonia, cervical cancer incidence and mortality rates rank among the highest in Europe, even though a national screening program has been in place since 2006. One of the reasons of low effectiveness of the organised cervical cancer screening program is its low participation rate. HPV self-sampling feasibility and a pilot study were conducted in 2020 and 2021, with the findings suggesting that this method is effective in boosting screening rates. The objective of this implementation project was to provide women with the self-sampling option, to pilot the provision of HPV self-sampling kits in pharmacies, and thereby preparing the groundwork for the inclusion of HPV self-sampling method in the screening program.

Methods: The project was conducted within the framework of the national cervical cancer screening program in 2022. It targeted 52,843 women in the screening-eligible group who had not participated in screening in the first half of the year. These women were given the choice between performing a self-sampling or going to a healthcare facility for an HPV test. Self-sampling kits could be ordered online through a dedicated platform. Also, a pilot project was initiated in Ida-Viru county, an area in North-Eastern Estonia with the lowest cervical cancer screening participation rates. In this region, women had the option to obtain a self-sampling kit from a pharmacy. Participation rates were calculated for each screening method within the entire screening-eligible group of 74,109 women. Additionally, the distribution of participants based on age and place of residence was examined. A questionnaire was administered as part of the pharmacy pilot to assess user satisfaction with the counselling provided in pharmacies, and the overall self-sampling experience.

Results: In total, 42,932 women (58% of the targeted population) participated in cervical cancer screening in Estonia in 2022, according to Estonian Cancer Screening Registry data. In total, 5,263 (12%) women opted for self-sampling, with 285 of them having received the self-sampling kits from pharmacies. In addition, 68 women outside the target group performed self-sampling. Altogether 595 self-sampling kits were distributed by 28 pharmacies in Ida-Viru county. Highest proportion of screening participants who chose self-sampling was seen in Ida-Viru county (19%) and in Võru county (15%); among younger women aged 35 (18%) and 30 (17%). Among those who received self-sampling kits from pharmacies and completed the questionnaire 94% expressed satisfaction with the counselling provided in pharmacies, 97% found self-sampling to be easy, and 92% expressed a willingness to use self-sampling in the future. In comparison to the previous year, the overall screening participation rate increased by 7%, with the most significant increase noted in southern regions Viljandi (12%), Võru (10%) and Tartu (10%). Notably, in Ida-Viru county, where the number of screenings increased by 7%, nearly one in every five screening participants opted for self-sampling, and almost half of them received the test kits from pharmacies.

Conclusions: The interest and confidence in HPV self-sampling have been steadily increasing in Estonia each year. Providing individuals with the choice of screening methods has proven to be efficient increasing screening attendance, especially in remote areas. Additionally, the distribution of HPV self-sampling kits in pharmacies has proven to be an effective supplement to make these kits more available.

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CATCH-UP SCREEN: OFFERING AN AT-HOME URINE HPV TEST TO WOMEN AGED >65 IN THE UK

13 - Self-sampling

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Background/Objectives: The NHS Cervical Screening Programme replaced primary cytology with primary HPV testing in 2019. In England, where almost half of all cervical cancer deaths are now among women aged 65 years or over, the age at stopping screening has remained at 65 since the screening programme was introduced in 1988. Women currently being discharged from the screening programme with a negative HPV test will be at extremely low risk of developing cervical cancer, but the lifelong risk will be substantially higher in women who were screened only with cytology.

Methods: "Catch-Up Screen" is a research project offering a catch-up HPV test to women aged 65-79 who have not had a primary HPV test. The first stage will be a feasibility study inviting 3,000 women (stratified by their screening history) to test the methodology and determine the uptake, and the second stage will be a wider roll-out inviting about 15,000 women to estimate the rates of pre-cancer detection and cancer prevention. The aim is to screen about 10,000 women over 3 years. A Colli-pee urine collection device (Novosanis) will be sent by post to women living in two areas of the north of England (Manchester and Hull) and consenting participants will return their sample by free post to the laboratory. The Colli-pee device is easy to use, less invasive than other devices and avoids the embarrassment of a speculum examination which older women often find uncomfortable. It is hoped that this will encourage women who were not screened regularly to take part. The BD Onclarity assay will be used to test the urine samples. HPV positive women will be invited to repeat their urine test after 6 months, and persistently positive women will be referred to colposcopy. The project is funded by Yorkshire Cancer Research.

Results: Recruitment began in November 2023. Uptake rates, overall HPV prevalence and HPV genotyping will be presented for the first ~650 women aged 65-79 who have been invited to take part. Analyses will be stratified by age, previous screening history, ethnicity and education.

Conclusions: We hope to demonstrate that a national HPV catch-up programme is feasible and an effective way to reduce cancer in this older age group. We anticipate that at-home urine tests will address common barriers to screening and will increase the uptake among previously under-screened women.

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SELF-COLLECTION FOR CERVIX SCREENING IN NEVER AND UNDER-SCREENED IN BRITISH COLUMBIA'S ORGANIZED CERVIX SCREENING POPULATION-BASED PROGRAM: PROGRAM FINDINGS

13 - Self-sampling

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Background/Objectives: Following the WHO call to action to eliminate cervical cancer, Canada has set a target of 2040 for elimination, with implementation of primary HPV screening as a priority. HPV-based self-collection (HPV-SC) for cervix screening has the potential to improve coverage, particularly for the under-screened. As part of the transition from cytology to an HPV-based screening program, the British Columbia (BC) Cervix Screening program offered HPV-SC to never/under-screened in select regions to assess impact on screening coverage.

Methods: Individuals never-screened and >10yrs overdue for screening (Cohort 1), and those 5 to less than 10yrs overdue (Cohort 2) in select BC regions were invited to participate in a provincial HPV-based self-collection pilot study. Individuals were randomized 2:1 to: 1) mailed invitation to participate by requesting an HPV-SC kit (Opt-in) or 2) mailed an invitation to participate with an HPV-SC kit included (Opt-out). Kit return rates and Opt-in vs Opt-out risk ratios are presented. Feedback surveys were sent to a subset of all invited participants. A summary of acceptability is included.

Results: From Dec 2021-July 2023, 41,065 never or under-screened individuals were invited to participate: Cohort 1=21,815; Cohort 2=19,250. In Cohort 1, of 15,099 Opt-in participants, 2,518 (17%) requested a kit and 1,537 returned the self-collection kit that was sent (overall return rate 10%). In Cohort 1, of 6,716 Opt-out participants, 1,545 (23%) returned the self-collection kits. In Cohort 2, of 13,506 Opt-in participants, 3,306 (24%) requested self-collection kits and 2,018 returned the kits (overall return rate 15%). In Cohort 2, of 5,744 Opt-out participants, 1,603 (28%) returned kits. Opt-out participants were significantly more likely to return kits in Cohort 1 [RR: 2.26 (95%CI: 2.12, 2.41)], and Cohort 2 [RR: 1.87 (95%CI: 1.76, 1.98)]. Invitations to complete a feedback survey were sent to 306 HPV-negative participants, of which 105 (34.3%) responded. Overall, participants were highly satisfied with the self-collection experience (92%) and were likely to do self-collected cervix screening in the future (86%).

Conclusions: Findings from the first Canadian HPV-SC cervix screening implementation project embedded within a population-based screening program illustrate that mailed HPV-SC has the potential to increase screening coverage in the never and under-screened, with an Opt-out approach having a higher return rate. Post-participation surveys indicate HPV-SC is an acceptable and preferred method for future screening. To accelerate elimination of cervical cancer, screening programs across Canada, and in similarly resourced settings, should consider HPV-SC as a feasible, acceptable, and safe alternative to provider collected cervix screening.

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#6594

CLINICAL EVALUATION OF HPV DNA DETECTION IN URINE COLLECTED AT HOME USING A NEW GENERATION FIRST-VOID URINATION DEVICE

13 - Self-sampling

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Background/Objectives: Evidence is growing on similar clinical accuracy of high-risk (hr)HPV testing on self-collected urine, compared to paired clinician-collected cervical samples. Standardized collection of the initial part of the urine stream (first-void urine), immediate DNA preservation, and use of a clinically validated PCR-based hrHPV assay are fundamental for its use in screening programs. In combination with a self-sampling device that is suitable for postal delivery to reach un(der)-screened females by offering home-based screening interventions. In the diagnostic test accuracy study reported here, we evaluated the analytical and clinical performance of the Alinity m HR HPV assay (Abbott) on a new generation first-void urination device (Colli-Pee® UCM® FV-5010, Novosanis).

Methods: Paired first-void urine and cervical samples from 298 females attending colposcopy (NCT04530201) were analysed using the Alinity m HR HPV assay. Participants were requested to collect the first-void urine sample at home, one day prior to colposcopy. Cervical samples (Cervex-Brush, Rovers in PreservCyt Solution, Hologic) were collected before colposcopy. Colposcopy applied to all females followed by colposcopy-directed biopsy for disease verification (when indicated by the clinician) was used as reference standard.

Results: Paired hrHPV results were available from 297 females (median age 38; IQR: 30-49; 72.39% infCIN2 and 27.61% CIN2+). HrHPV testing in first-void urine (median volume 10.2 ml; IQR: 9.2-10.9) was found to be less sensitive for CIN2+ (ratio 0.91; 95% CI: 0.83-0.99), though equally specific (infCIN2; ratio 1.04; 95% CI: 0.92-1.19) compared to cervical samples at the manufacturer validated cut-off for cervical samples. Adjusting the cut-off for first-void urine (exploratory defined cycle number cut-off) improved relative clinical sensitivity for CIN2+ (ratio 0.96; 95% CI: 0.89-1.03), whilst maintaining equal specificity for infCIN2 (ratio 1.00; 95% CI: 0.88-1.14). Good and excellent HPV agreements were observed between paired samples at both cut-offs, for hrHPV and individual genotyping channels (Cohens Kappa range: 0.642-0.846).

Conclusions: As no assay cut-off for first-void urine has been clinically validated for the Alinity m HR HPV assay, an exploratory cut-off was defined. At this cut-off, no difference in clinical sensitivity (CIN2+) nor specificity (infCIN2) was observed for hrHPV testing in urine using a new generation first-void urination device, compared to cervical samples. This study demonstrates the importance of validating self-sample-specific cut-offs for hrHPV assays that have been clinically validated on cervical samples.

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CAN VAGINAL SELF-COLLECT MATCH CERVICAL SAMPLING? - NEW LEARNINGS AND OPTIMIZED WORKFLOW FOR PRECANCER SCREENING

13 - Self-sampling

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Background/Objectives: Meta-analyses and randomized controlled trials (RCTs) demonstrate that HPV self-collection from the vagina has non-inferior sensitivity to physician-collected cervical samples and self-collection is now being implemented in several national screening programs. The majority of studies have used liquid-based-cytology (LBC) media to reconstitute self-collected samples because it is the gold-standard reference method for physician-collected samples. This also enables laboratories to use existing automation to process self-collected samples. However, recent evidence strongly suggests that this assumed equivalence is an over-simplification and can lead to sub-optimal results. Here we investigate the technical parameters underpinning these data.

Methods: We performed a structured literature review from 2020-2023 to investigate the impact of different self-collection methods on performance of paired self-collected versus physician-collected samples. We also performed wet lab testing of different resuspension methods and recovery media using pooled vaginal samples and compared the respective cell recovery using human beta-globin Ct scores as a proxy for cell counts.

Results: The literature review revealed two trends: resuspension volume was inversely associated with agreement with physician-collected samples, with smaller resuspension volumes having higher agreement and improved sensitivity for CIN2+ disease. Vortexing of samples was also more effective than swirling the device in the media and then discarding it. In-house wet lab testing confirmed these findings: Depositing swabs in SurePath media versus swirling the swab in the media and discarding it, resulted in approximately a 2-fold increase in cell recovery. We also observed a 2.35 lower median Ct value when comparing physician-collected versus the 10 mL self-collection swirl method (equivalent to a greater than 4-fold increase in recovery for the physician sample). Depositing self-collected swabs directly into 3 mL lytic media versus fixative media can off-set this difference, with these samples showing an increased cell recovery of approximately 4-fold.

Conclusions: Recent published studies confirm that resuspension volume is a critical parameter for HPV self-collected samples and that earlier assumptions of sample type equivalence between the cervix and the vagina are invalid. The results imply that the target load in the cervix and the vagina are different. A recent study by Li et al confirmed that this is in fact the case. (1) They sequentially sampled the same women from the perineum, lower vagina, upper vagina and cervix and compared HPV positivity and ability to detect CIN2+ disease. They reported higher viral loads in the cervix but higher overall positivity in the vaginal canal. This apparent contradiction can be explained by the tropism for high-risk HPV for the transformation zone and a higher non-specific infection rate in the vagina. This also helps explain the findings from implementation studies where a significant proportion of women positive for a self-sample do not retest positive at physician follow-up. (2) The results presented here demonstrate that the recovery method and media type also have a large impact on target recovery and should be carefully considered in the design of self-collection workflows. All of these factors can be combined to ensure optimal sample recovery and target detection in self-collected samples. The relevance of these results for national screening programs will be discussed.

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FC03 - Health education and public health

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National survey on knowledge, attitude and perception among Italian dental students toward HPV disease: are they ready?

37 - Health education

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Background/Objectives: Human Papilloma Virus (HPV) infection is the most common worldwide sexually transmitted infection, and long-lasting infection, especially with high-risk serotypes (16 and 18), is associated with cervical, ano-genital and oropharyngeal (mouth, throat, tongue, and tonsils) cancers. A multidisciplinary approach therefore becomes essential and, considering that approximately 70% of oropharyngeal tumors are HPV+, dental students need to be aware of their future role in the HPV-diseases primary and secondary prevention. The aim of this investigation was to assess knowledge, attitude and perception on HPV infection, HPV-related OP-cancer and HPV vaccination among Italian dental students, and whether it was necessary to strengthen programs HPV training in dental school curricula.

Methods: This cross-sectional study enrolled Italian dental students from the first to the sixth year of attendance between February 2023 and May 2023. Through a self-administered questionnaire, data on participants' socio-demographic characteristics, knowledge, attitude and perception concerning HPV-related OP-cancer, HPV infection, and HPV vaccine were acquired for a total of 82 questions. Statistical analysis was conducted utilizing the Pearson's chi-square, Kruskal-Wallis and Mann-Whitney tests, and statistical significance was determined by considering a p-value of less than 0.05 for all conducted tests.

Results: 412 dental students filled out the questionnaire. Based on the correct answers, the general knowledge rate was 69.5%. Among 3 items analysed, the highest percentage of correct answers concerned knowledge of the vaccine, followed by HPV+ OP-cancer and infection items. Almost all of respondents were aware of the possibility that HPV caused OP- and cervical cancer but only about 50% to 60% knew the relation with anogenital cancer. Overall, students showed good perception of their future role against HPV disease; in fact, 82.5% and 91.1% of participants agreed about dentist's role in preventing infection and educating patients on the link between HPV and OP-cancer, respectively. Additionally, 87.9% of respondents generally promoted vaccination. Therefore, most of the Italian students would acquire more information on HPV+ diseases during the attendance of the degree course. For attitude, most of participants would feel comfortable talking about HPV topics with patients and agreed that they will routinely screen them for oral cancer; however, only about 50% of them would be inclined to recommend the vaccine regardless of gender. Female students and students attending last years of degree course demonstrated a more positive attitude and perception than male students and students attending the first years of degree course, respectively.

Conclusions: As the incidence of HPV+ OP cancer is increasing, dentists could play a crucial role in the management of HPV disease by educating patients about the risks of infection, promoting vaccination and screening for oral cancer. Findings from the current study are encouraging, since Italian dental students showed a satisfactory knowledge, attitude and perception towards HPV+ OP-cancer, infection and vaccine, although it is necessary to further strengthen the content of these topics in the curricula of dental schools. In conclusion, students demonstrated readiness to collaborate in a multidisciplinary team of health professionals in primary e secondary prevention to reduce the burden of the disease and the overall impact that HPV infection has on society.

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KNOWLEDGE AND UNDERSTANDING OF CERVICAL SCREENING AND HUMAN PAPILLOMAVIRUS BY SOCIO-ECONOMIC GROUP IN IRELAND: FINDINGS FROM A NATIONAL SURVEY

39 - Public health

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Background/Objectives: Between 2014-2018, women in lower socio-economic groups (SEG) in Ireland had an 84% higher incidence rate of cervical cancer compared to those in higher SEG.1 Inequalities also exist in cervical screening participation with those from lower SEG less likely to attend cervical screening.2 We aimed to examine the knowledge and understanding of cervical screening and human papillomavirus (HPV) of women by SEG in Ireland, to provide information for future screening awareness promotion.

Methods: In 2023, an online survey examining views on cervical screening was sent by a market research company to a quota-based sample of women and people with a cervix aged 25-65 years. The sample was categorised into high (n=432) and low (n=597) SEG, based on the NRS Social Grades classification .3 Survey response data on cervical screening and HPV knowledge were collated and analysed using the Chi-squared test.

Results: Of 1,029 survey respondents, 42% (n=181) in the high SEG believed they had a good understanding about cervical screening compared to 28% (n=167) in the low SEG ($p<0.05$). Both high and low SEG believed that attending cervical screening when invited could prevent cervical cancer from developing (87% vs 85%, respectively, $p=0.791$) and the majority of both groups plan to attend their next screening appointment (91% vs 89%, $p=0.806$). Both groups cited the feeling of fear/anxiety as one of the main reasons for not attending cervical screening in the past but this was significantly more likely in the low SEG (50% vs 64% $p<0.05$). Significantly more in the higher SEG were aware of the change in the national screening programme from cytology to HPV cervical screening (70% vs 57%, $p<0.05$) and knew that HPV can cause genital warts (49% vs 39%, $p<0.05$). A minority of both groups knew that HPV could clear itself (32%: high SEG; 22%: low SEG, $p<0.05$). Both groups knew that HPV causes cervical cancer (75%: high SEG; 70%: low SEG, $p=0.480$) but a significantly higher proportion of women in the high SEG believed that availing of the HPV vaccine would reduce the risk of cervical cancer (66% vs 50%, $p<0.05$).

Conclusions: Respondents in the high SEG were more knowledgeable about cervical cancer screening and HPV and less likely to feel fear/anxiety around the screening process compared to the low SEG. Future strategies to reduce cervical cancer should consider these findings and focus on providing information about HPV screening and increasing awareness on the benefits of HPV vaccination in people from low SEG.

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SURVEILLANCE HESITANCY POSES A SERIOUS WEAKNESS IN CERVICAL SCREENING

22 - Diagnostic procedures / management

Background/Objectives: Primary high-risk HPV DNA detection has been adopted widely as a primary cervical cancer screening method. Positive predictive value of HPV testing for high-grade lesions is low and triage tests are recommended for selecting women for colposcopy and diagnostic evaluation. A substantial number of women without high-grade lesions for immediate treatment and those who are not immediately referred for colposcopy after triage testing are managed with follow-up surveillance. Available literature on this aspect of cervical screening program is scarce. It is well-recognized that good compliance of management of abnormal results is important for effective cervical screening. To fill the information gap, we performed this study to investigate the rate of follow-up surveillance and outcomes for positive HPV results in cervical screening in Singapore.

Methods: This was a retrospective study approved by the Institutional Review Board of the health authority. Women on surveillance by repeat HPV testing were identified in a prospectively managed database. Data retrieved included women's age, country residence status, history of colposcopy, HPV-DNA status on the first and repeat tests, dates of follow-up during the 5 years since the initial screening, and histological diagnosis of cervical lesions. The main outcome measures were compliance rate for repeat HPV testing, regression and persistence rates of HPV subtypes, and detection rate of high-grade lesions (CIN2+).

Results: This analysis included 680 natural residents in the community, mean age 44.8 (95% CI 20.1 to 69.5) years. The initial HPV positivity included 105(35.9%) HPV-16, 46 (15.8%) HPV-18 and 529 (48.3%) HPV-12others. The compliance rate of repeat testing was 28.2% at 12 months and, cumulatively, 42.8% for the entire 5-year follow-up period. The rates were unaffected by age (p=0.5829) nor prior colposcopy (p=.1607). There were 5 (1.7%) cases of CIN2+ detected. On longitudinal follow-up, the regression rate was 90.3% for HPV-16, 87.0% for HPV-18 and 65.2% for HPV-12others (p=.0001). Some women with multiple HPV infection cleared one but not the other subtype(s). The annualized HPV regression rates were similar for HPV subtypes and for each follow-up years. Thus, of 391 women, 194 (60.8%) cleared their HPV infection.

Conclusions: This study found that, despite a high regression rate of HPV, the prevalence rate of high-grade lesions among women on follow-up of positive HPV DNA test was high. It highlights the clinically significance of surveillance. However, there was an alarmingly high incidence of surveillance hesitancy. The findings of this study call for attentions in management of abnormal screening results.

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HOW MUCH DO POLISH STUDENTS KNOW ABOUT HPV VACCINATION?

37 - Health education

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Background/Objectives: Human papillomavirus (HPV) is a common sexually transmitted infection that can cause both benign and malignant changes in the body. HPV vaccines, preferably given prior to the onset of sexual activity, have demonstrated remarkable efficacy in preventing HPV-related cancers. The impact of a healthcare provider's recommendation on HPV vaccine acceptance is substantial. Therefore, it is imperative that medical students undergo thorough training in this domain. This study aims to compare the fundamental understanding and viewpoints regarding HPV and anti-HPV vaccines among Polish students pursuing medical and nonmedical sciences. We aim to identify the differences in knowledge and opinions between the two groups and genders. The findings from this study can shed light on any gaps in knowledge and highlight the need for modifying the approach to educating and disseminating information within the academic setting.

Methods: The study was based on the authors' questionnaire and the results were statistically analyzed. Participants in the study were 1,025 students (medical sciences students - 520 respondents in total; and nonmedical sciences students - 505 respondents in total). The study was carried out between 1 June and 31 July in 2023. The Bioethics Committee approved it at Poznan University of Medical Sciences (540/22) in conformity with the Helsinki Declaration guidelines.

Results: According to the results, the knowledge of medical students about the consequences of HPV infection and vaccination against HPV is significantly greater. Almost the entire medical group (98.8%) marked the answer "cervical cancer" and in the non-medical group - 70.3% ($p<0.001$). Indeed, fewer non-medical students marked the answer "oropharyngeal cancer" - 22.2% vs 72.9% (medical group) or "anal cancer" - 21.6% vs 65.4% (medical group). Despite significant differences in the results among the groups, the low awareness of the medical group about the consequences of persistent, long-term infection with oncogenic HPV genotypes is noteworthy. In the medical group, 74.2% answer "condylomas", 40% - "smelly discharge, pelvic pain", 39.8% - "bleeding after intercourse" and 37.1% - "hoarseness, cough". Knowledge about the possibility of preventing primary infection varied significantly between the groups of respondents (91.7% medical believe it is preventable, 68.5% - non-medical). The responses about the cervical cancer prevention program in Poland (85.5% vs 61.6%) and HPV vaccination (98.3% vs 67.7%) were similar. Noteworthy is the high percentage of responses among medical students regarding the value of vaccination after starting intercourse (84.4%) and recommending vaccination in men (79.2%).

Conclusions: To date, there have been numerous publications describing the knowledge of particular social, gender, parents, etc., groups about vaccination, but the knowledge of students at different universities - medical and other - has not been compared. Social awareness is still insufficient, even in group of medical students. There is much to be done in terms of educating and encouraging preventive behavior in those not receiving primary prevention in early childhood.

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Stop HPV- all in one place, all in one side

37 - Health education

Background/Objectives: Our organization started in 2013, working along two main lines. One line is the prevention of the Human Papilloma Virus (HPV), the other line is the help of gynecological cancer patients. The first line includes education and campaign programs, editing brochures, online PTA meetings, informational videos, the second involves managing the entire patient journey from symptoms through therapies to rehabilitation. We co-operate with the professionals, doctors, district nurses, nurses.

Methods: The Mallow Flower Foundation works with many professionals, we cover the country with Mallow Flower Stations (Points). In Hungary, several people deal with this topic, mostly professionals, authorities, there are several websites and other information channels. However, there was no such platform where the interested party could obtain all the information in its entirety. Which contains authentic and up-to-date information about HPV as a virus, vaccination and screenings. We designed and implemented an interface that contains all information, whether it is about the history of screenings, HPV topics during pregnancy, the psychology of HPV infection, changes caused by the virus, tumors, creams, gels, immune strengthening. Additionally we created parts of What to do? If you have heard that..., and in the useful part, we can look out into the wider world, learn about other programs of the foundation (such as the Cooltas teens comic, the Gladiolus men's project, for example), we can read about intimate hygiene and find the HPV specialists working in the country. The site also has a special feature. This is the HPV algorithm, which we drew as a map with experts for lay people, so that if they get a positive result from the HPV test, they know where the road leads. This is also special because the profession manages the positive HPV path differently, and we also show the way through the algorithm, through Hungary's leading specialists.

Results: The site shows the need to create a closed section. We prepare this for HCPs, e-academy, which we prepare not only with the help of Hungarian but also foreign (ESGO) specialists, as well as domestic and foreign publications, useful information that will help the work and communication of healthcare workers in the future. After confirming the closed page, we plan an HPV conference.

Conclusions: It is important that all information and specialists can be found in one place. Also, it is not only the population that needs to be trained, but also health workers. A PAG cannot do this alone, but by supporting the profession it can achieve great results, since the Mályvavirág Foundation is like a bridge that connects the participating parties.

References: https://stophpv.hu/

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#6634

Knowledge regarding human papillomavirus and cervical cancer prevention among medical students in Thailand

37 - Health education

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Background/Objectives: Cervical cancer is one of the leading causes of death among women in Thailand. In their primary healthcare role—the role most accessible to the general population—general practitioners perform a crucial function in the cervical cancer screening program. This study aims to determine the level of knowledge of cervical cancer and human papillomavirus (HPV) infection, HPV vaccination, and cervical cancer screening among last-year medical students at Chulalongkorn University in Bangkok, Thailand.

Methods: A cross-sectional study was conducted among sixth-year medical students at Chulalongkorn University using an electronic self-administered questionnaire. The two-part questionnaire comprised demographic data and 12 true/false questions that assessed knowledge regarding HPV infection, HPV vaccination, and cervical cancer screening recommendations. Pilot testing revealed a high Cronbach's alpha and test-retest reliability coefficient.

Results: A sixty-seven percent response rate was achieved. Among the 198 respondents, only one (0.5%) student correctly answered over 80% of the questions while most respondents (172, 71.7%) correctly answered less than 60% of the questions. Less than 50% of respondents correctly indicated that only high-risk HPV causes cervical cancer and accurately identified the recommended age for a two-dose series of the HPV vaccine, the sensitivity level of cytology compared with HPV testing, and the recommended frequency of cervical cancer screening for women at average risk.

Conclusions: This study highlights a lack of understanding of HPV infection and vaccination and cervical cancer screening guidelines among Thai medical students. The medical school curriculum should promote education, communication, and awareness of these topics.

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#7029

RURAL-URBAN DIVIDES AND CULTURAL DYNAMICS: THE EFFECTS OF RURALITY, RACE, AND ETHNICITY ON HPV AND COVID-19 VACCINE HESITANCY IN THE UNITED STATES

39 - Public health

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Background/Objectives: Human papillomavirus (HPV) infection is responsible for about 80% of cases of genital cancers in the United States. However, only 47% of young adults in the U.S. ages 18-26 years have received one or more doses of the HPV vaccine despite their eligibility. We sought to understand differences in HPV vaccine hesitancy among young adults by socio-demographic characteristics such as rurality, gender, race, and ethnicity in the western United States because young adult HPV vaccine uptake often differs by these socio-demographic characteristics. These data will be used to inform targeted HPV vaccine interventions.

Methods: Young adults across 12 western U.S. States in 2020-2021, during the era of COVID-19, self-reported to an online survey in rural and urban communities. We assessed vaccine hesitancy scales that were created from this online survey of young adults using factor analysis. These scales were evaluated by rurality, gender, race and ethnicity for odds of vaccine hesitancy using logistic regression. Race and ethnicity, rurality, and gender were examined as the main exposures of interest. Vaccine hesitancy was measured by a series of survey questions regarding HPV infection and HPV vaccination. Factor analysis was utilized to create coarse factor scores for three scales of vaccine hesitancy: HPV vaccine confidence, HPV infection complacency, and HPV vaccine complacency. Intent to vaccinate against COVID-19 was also assessed.

Results: Participants (N=2,937) were young adults (ages 18-26 years). Hispanic young adults had higher odds of HPV vaccine hesitancy across all three scales, compared to non-Hispanic White/Caucasian young adults: HPV vaccine confidence (OR=1.55 [95%CI:1.23-1.96]), HPV infection complacency (OR=1.53 [95%CI:1.22-1.93]), and HPV vaccine complacency (OR=1.28 [95%CI:1.01-1.61]). Rural young adults were more likely than urban young adults to have high vaccine hesitancy in the domains of confidence (OR=1.66 [95%CI: 1.37, 2.01]) and HPV vaccine complacency (OR=1.79 [95%CI:1.48-2.17]), but not in the domain of HPV infection complacency (OR=1.06 [95%CI:0.88-1.28]). Among Hispanic adults, those living in rural communities had higher odds of vaccine hesitancy than those living in urban communities for the domains of HPV vaccine confidence (OR=2.13 [95%CI:1.33-3.49]) and HPV vaccine complacency (OR=2.11 [95%CI:1.33-3.40]), but not HPV infection complacency (OR=0.84 [95%CI:0.54-1.32]). Rurality was also an important determinant of COVID-19 vaccination intent by ethnicity and by gender; rural Hispanic young adults had lower odds of vaccination intention compared to urban Hispanic young adults (OR=0.57 [95%CI: 0.38, 0.87]), as did both rural female (OR=0.44 [95%CI: 0.35-0.54]) and male young adults (OR=0.45 [95%CI: 0.33, 0.63]), compared with their urban counterparts.

Conclusions: Rurality and Hispanic race/ethnicity are correlated with increased levels of HPV vaccine hesitancy. Rural Hispanic young adults have higher levels of HPV vaccine hesitancy than urban Hispanic young adults, suggesting that variation in HPV vaccine hesitancy exists within the broad category of Hispanic adults. Results suggest that generalization of Hispanic adults as a single category may not be sufficient to address HPV vaccine hesitancy. Interventions to increase HPV vaccination must consider different dimensions of vaccine hesitancy by demographics of rurality and race/ethnicity, as well as variations within demographic groups.

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FC01 - HPV Vaccines I

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#6708

A systematic review of factors associated with high coverage of HPV vaccination programs in the EU

06 - HPV prophylactic vaccines

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Background/Objectives: Highly effective HPV vaccines which protect against the most common oncogenic HPV types have been available in the European Union (EU) since 2006. The European Code Against Cancer (1) includes an official recommendation of participation in HPV vaccination as a cancer prevention measure for all girls. Yet, coverage of HPV vaccination at the population-level varies substantially across EU member states; from virtually no coverage to high coverage (>80%) in several countries in 2021 (2). In this systematic review, we will synthesize knowledge about features of HPV vaccination programs on the local, regional, and national levels and relate these to achieved vaccination coverage. This review is part of the EU4Health program co-funded consortium PROTECT-EUROPE (https://www.protect-europe.org/) which aims to advance HPV vaccine coverage to reduce cancers caused by HPV in Europe.

Methods: We searched databases PubMed/MEDLINE, Web of Science, the Cochrane Library REVIEWS and CENTRAL, Embase, and Open Research Europe using a search string containing terms such as HPV, vaccine, coverage, program, and strategy, to identify relevant items. Studies were included if they 1) report at least one strategy/feature of an HPV vaccination program in the EU, 2) report on coverage of the vaccination program as proportion of the eligible population that has received at least one dose of any HPV vaccine, 3) focus on the pre-adolescent and adolescent population (10-17 years), and 4) are published in a peer-reviewed journal in English between January 2006 and June 2023. Rayyan (https://www.rayyan.ai/) was used to manage the screening process and all items were screened independently by two blinded investigators. A planned future extension of the study will also include synthesis of knowledge related to strategies/features of HPV vaccination programs related to resilience of HPV vaccine coverage. The study protocol is published on PROSPERO (3).

Results: In total, we identified 1,710 items in the searches after removal of duplicates. After title and abstract screening, 311 items remain for full text screening. Common reasons for exclusion at the title and abstract stage included study not conducted in the EU, wrong scope, not original research, and wrong focus (e.g., screening or HIV).

Conclusions: Although 311 studies are included in the full text screening stage, our preliminary results suggest that there is a lack of high-quality systematic data on programmatic aspects of HPV vaccination programs and how they relate to vaccine coverage in the EU. Further challenges include lack of established instruments to assess study quality and risk of bias for the wide range of studies that will need to be included in the systematic review, and the difficulty to infer conclusions of causality for vaccine coverage related to programmatic aspects in the absence of large-scale randomized trials on the individual or cluster level.

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Implementation of HPV vaccination programs - lessons learned from the Scandinavian countries

06 - HPV prophylactic vaccines

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Background/Objectives: A major component in the elimination of cervical cancer is the implementation of nation-wide HPV vaccination programs with high coverage. As HPV is mainly a sexually transmitted virus, the optimal age of vaccination is before early sexual debut age, i.e., around 10-12 years of age. In addition to childhood vaccination, many countries offer catch-up programs for adolescents and young adults. The three Scandinavian countries, Norway, Sweden and Denmark, have offered such programs, but the timing has varied greatly, from before or around the initiation of childhood vaccination programs (Sweden and Denmark), to seven years later (Norway).

Methods: We looked at cervical cancer incidences in 25-30-year-old women between 2010 and 2020 in Norway, Sweden and Denmark using NORDCAN (https://en/nordcan.iarc.fr/). Smoothing by lowess was employed to visualize the main trends.

Results: In Sweden and Denmark, cervical cancer incidences in 25-30-year-old women decreased markedly from 2016, while Norway showed steadily increasing incidences for the same age group until 2020.

Conclusions: As the three Scandinavian countries are very similar in important factors for cervical cancer incidence rates (sexual habits, HPV distribution, cervical screening, childhood vaccination), the difference in recent incidence trends among young women is most likely due to differences in the catch-up vaccination. Many countries are yet to implement national HPV vaccination programs. Based on the experience from the Scandinavian countries the take-home message is clear: By starting off offering multicohort vaccination to all age groups at risk of HPV infection and not restricting the vaccination to single cohorts of 10-12-year-olds, the time to cervical cancer elimination may be reduced by several years.

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TARGETED HPV VACCINATION FOR GAY, BISEXUAL AND OTHER MEN WHO HAVE SEX WITH MEN ATTENDING SPECIALIST SEXUAL HEALTH SERVICES IN ENGLAND 2016-2022: CHARACTERISTICS OF THOSE DECLINING OFFER OF VACCINATION

06 - HPV prophylactic vaccines

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Background/Objectives: The national human papillomavirus (HPV) vaccination programme for gay, bisexual and other men who have sex with men (GBMSM) in England has opportunistically offered vaccination to GBMSM under 46 years of age attending specialist sexual health services (SHSs) and HIV clinics since April 2018, following a successful pilot from June 2016-March 2018. The proportion of eligible GBMSM reported to decline the offer of HPV vaccination has been low since programme implementation; nevertheless, it may be useful to understand more about those declining this safe and effective vaccination.

Methods: HPV vaccination events (including declining the offer) and sociodemographic and clinical characteristics are reported to the GUMCAD STI Surveillance System (GUMCAD) by all SHSs in England. GBMSM are defined as men who self-reported as gay or bisexual at any attendance. GBMSM eligible for HPV vaccination were defined as attendees aged under 46 years and not known to be previously vaccinated. Those who were reported to have ever declined were identified for this analysis. Pearson's χi2 analyses were used to describe differences across sociodemographic and clinical factors (age group at first attendance, HIV status, ethnicity, country of birth and Indices of Multiple Deprivation (IMD) quintile) among those who had ever declined an offer of HPV vaccination. A multivariable logistic regression model was created to sequentially assess associations of key sociodemographic and clinical characteristics with ever declining vaccination, using a backward stepwise methodology, adjusted for age group at first attendance.

Results: Of 333,472 eligible GBMSM attending SHSs from 1st June 2016-31st December 2022, only 8,396 (2.5%) had ever declined HPV vaccination. One third of these attendees (2,663) went on to receive vaccination at a later attendance. In the multivariable model, compared with having "White' ethnicity, belonging to "Asian or Asian British' (adjusted odds ratio [aOR]: 1.3, 95% CI: 1.2-1.4), "Black or Black British' (aOR: 1.2, 95% CI: 1.1-1.4), "mixed' (aOR: 1.1, 95% CI: 1.0-1.2), or "not specified" (aOR: 1.3, 95% CI: 1.2-1.4) ethnic groups, and compared with being born in the UK, being born outside of the UK (aOR: 1.3, 95% CI: 1.3-1.4) gave higher odds of ever declining vaccination. Living with HIV was associated with lower odds of ever declining vaccination (aOR: 0.54, 95% CI: 0.49-0.60). There was no apparent association with IMD quintile.

Conclusions: While the proportion of eligible GBMSM reported to decline HPV vaccination has been consistently very low since the beginning of the national programme, minority ethnic groups in England and those born abroad have higher odds of declining vaccination. These findings are in line with previous studies in the literature that report belonging to a minority ethnic group as a predictor of higher vaccine hesitancy and/or lower uptake. Improving our understanding of the reasons for GBMSM declining HPV vaccination (possibly including language barriers, cultural beliefs, a lack of trust in or poor experience with healthcare) may help to tailor messaging to some GBMSM to improve uptake and reduce any inequalities in protection against the harms of vaccine preventable disease.

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THE EFFECT OF A NATIONAL HPV VACCINATION PROGRAM TARGETING GIRLS ON THE INCIDENCE OF CIN2+ AND CYTOLOGY SCREENING PERFORMANCE: FIVE-YEAR CERVICAL SCREENING RESULTS FROM SLOVENIA

06 - HPV prophylactic vaccines

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Background/Objectives: Women who are vaccinated for Human Papilloma Virus (HPV) when they were girls (age 9-14) are expected to have the most protection from the HPV vaccine. However, observed data on the effect of implementing HPV vaccination program targeting those women on screening outcomes is extremely limited. This is because women in routine-age vaccine-targeted birth cohorts are not yet invited for screening in many countries. Since 2018, those women have been invited for cytology screening in Slovenia.

Methods: Using Slovenia's cervical screening programme and registry (ZORA), we compared screening results of women who were born in the latest non-vaccine-targeted cohorts (birth years 1994-1997) with those of the first vaccine-targeted cohorts (birth years 1998-2001). We calculated the Incidence Rate Ratio (IRR) of Cervical Intraepithelial Neoplasia (CIN) 2 or worse (CIN2+) using Poisson Regression and compared screening performance indicators such as colposcopy referral rate, CIN2+ Positive Predictive Value (PPV) for low and high-grade cytology results, and CIN2+ detection rate using chi-square tests.

Results: The national coverage for quadrivalent HPV vaccine in vaccine-targeted cohorts was between 48.7% and 55.2%. We included 28,187 and 26,080 women from non-vaccine-targeted cohorts and vaccine-targeted cohorts, respectively. We found 40% lower incidence of CIN 2+ in vaccine-targeted cohorts (IRR 0.60 95% CI 0.50 - 0.72). Direct referral rate, PPV, and detection rate were found to be lower in vaccine-targeted cohorts ($P < 0.05$).

Conclusions: Even with imperfect but substantial coverage of HPV vaccination, substantially lower incidence of CIN2+ is observed in vaccine-targeted population. This demonstrates the effectiveness of scaling up HPV vaccination targeting routine-age girls as an organized and nationally implemented program. Lower cytology screening performance indicators observed in vaccine-targeted cohorts may indicate a shift in harms-and -benefit ratio of cytology screening in this population which may require further interventions.

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#6804

EFFECTIVENESS OF SINGLE DOSE OR TWO DOSES OF BIVALENT HPV VACCINE (CERVARIX) IN FEMALE SCHOOL STUDENTS IN THAILAND

06 - HPV prophylactic vaccines

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Background/Objectives: A single-dose (SD) schedule of HPV vaccine can offer significant cost savings and help with overall delivery challenges. To generate evidence on SD HPV vaccination in young women, we conducted a community vaccine effectiveness (VE) study comparing HPV SD and two dose (2D) regimen (0, 6 months) of Cervarix in Thailand among Grade 8 schoolgirls. VE at 2-year and 4-year post vaccination are presented.

Methods: In 2018, eligible Grade 8 schoolgirls under 15 years old in Udon Thani (SD) and Buriram (2D) provinces (~8,000 in each province) were offered HPV vaccine per assigned dose regimen. Concurrently, a baseline cross-sectional survey (CSS) of HPV prevalence was conducted in typically 16 year-old Grade 10 (N=2,600 in each province) and 18 year-old Grade 12 (N=2,000 in each province) girls. HPV was assessed in urine using PCR assay detecting HPV 16, 18 and 12 additional types. When vaccinated Grade 8 schoolgirls reached Grade 10 and Grade 12 in 2020 and 2022 respectively, CSSs were repeated in each province. Two-year and four-year post-vaccination VE were estimated by comparing prevalence of HPV 16 and/or 18 between baseline CSS (2018) and vaccinated schoolgirls in Year-2 (2020) and Year-4 (2022) CSS. Adjustment methods were used in the analysis to account for potential changes in sexual behavior due to non-contemporaneous comparison. Non-inferiority comparison of SD and 2D VE was made using a margin of 10% at 4-years post-vaccination.

Results: Prevalence of HPV 16 and/or 18 in baseline CSS among Grade 10/Grade 12 schoolgirls was 2.90% (95% CI 2.54-3.31)/3.98% (95% CI 3.52-4.49) and 3.87% (95% CI 3.46-4.34)/6.13% (95% CI 5.56-6.75) for Udon Thani and Buriram, respectively. In Year-2 CSS the prevalence among vaccinated Grade 10 schoolgirls was 0.57% (95% CI 0.42-0.77) for Udon Thani and 0.31% (95% CI 0.21-0.47) for Buriram. Two-year post-vaccination crude VE for SD was estimated at 80.4% (95% CI: 73.9-86.9), and 2D at 91.9% (95% CI: 88.5-95.4). In Year-4 CSS the prevalence among vaccinated Grade 12 schoolgirls was 0.37% (95% CI 0.25-0.56) for Udon Thani and 0.28% (95% CI 0.18-0.45) for Buriram. Four-year post-vaccination crude VE for SD was estimated at 90.6% (95% CI: 86.6-94.6), and 2D at 95.4% (95% CI: 93.2-97.6). All adjustment methods minimally impacted VE for SD and 2D. At 4-years post-vaccination, the difference in VE between SD and 2D was -4.79% (95% CI: -9.32 to -0.25), meeting the study's non-inferiority criteria.

Conclusions: Our study demonstrated that both SD and 2D of HPV vaccine significantly decreased HPV 16/18 point-prevalence 2-years and 4-years post vaccination. Crude VE at 4-years post-vaccination was greater than 90% for both SD and 2D; SD was not inferior compared to that of 2D. These data show that SD of HPV provides high levels of protection when given to schoolgirls younger than age 15 years.

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Analysis of indirect effectiveness of the bivalent human papillomavirus vaccination program in the Netherlands: preliminary results of a cohort study

06 - HPV prophylactic vaccines

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Background/Objectives: This study aims to assess the indirect effect of the bivalent human papillomavirus (HPV) vaccine by comparing the incidence of HPV infections in unvaccinated women from the first birth cohort eligible for HPV vaccination in the Netherlands (birth cohorts 1993/1994; vaccination coverage 49-53%, 3D schedule) with those in unvaccinated women from birth cohort 2001 up to 13 years after introduction of HPV vaccination.

Methods: Longitudinal data from two cohort studies (HAVANA and HAVANA2) were used in which participants were annually asked to complete a web-based questionnaire and to collect a vaginal self-sample for determination of HPV by the SPF10-LiPA25 assay, which is able to detect 25 HPV types. Unvaccinated women participating in the HAVANA study (2010/2011-2015/2016) and HAVANA2 study (2017-2022) were included. The indirect effect of the HPV vaccination program against incident type-specific HPV infections and combined HPV-types was estimated using Poisson regression. The combined incidence of non-cross-protective HPV types 39, 51, and 56 was included in the analyses to correct for differences in the background prevalence between the two cohorts. The incidence rate ratios (IRRs) defined as the ratio of the incidence rate of a specific HPV type(s) and the incidence rate of non-cross-protective types were calculated for each cohort. Subsequently, the ratio between the IRRs of both cohorts and the 95% confidence interval (95%CI) was calculated. For sensitivity analysis, the indirect vaccine effectiveness (VE) was calculated using Cox proportional hazards regression. VE estimates were adjusted for age, ever had sex, contraception use, urbanisation degree, and educational level.

Results: In total, 1588 unvaccinated participants were included in the analyses, of whom 41.6% were eligible for a 3D scheme in 2009/2010 (HAVANA participants) and 58.4% were eligible for a 2D scheme in 2016 (HAVANA2 participants). A reduction of 68.4% (95%CI, 43.2-82.4%) of incident HPV16 infections was observed among unvaccinated women over time in the HAVANA-2 versus the HAVANA cohort. For incident HPV18 infections, this reduction was estimated to be 37.3% (95%CI, -20.4-67.4%). For cross-protective HPV types 31 and 45, the reductions were 23.2% (95%CI, -31.9-55.2%) and 64.4% (95%CI, 0.2-87.3%), respectively. In sensitivity analyses, an adjusted indirect VE of 75.7% (95% CI, 57.9-86.0%) against incident HPV16 infections was observed among unvaccinated women over time in the HAVANA-2 versus the HAVANA cohort. The adjusted VE against incident HPV18 infection was 53.3% (95%CI, 11.5-75.4%). For HPV types 31 and 45, VE estimates were 42.9% (95%CI, 5.6-65.5%) and 76.2% (95%CI, 32.5-91.6%).

Conclusions: High indirect effect of the bivalent vaccine against vaccine type HPV infections and several cross protective types can contribute to the success of the HPV vaccination program 13 years after its introduction in the Netherlands. Our results suggests herd protection which is specifically important for countries where the HPV vaccination coverage is suboptimal.

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HPV VACCINATIONS IMPACT ON PRETERM BIRTH RATES

06 - HPV prophylactic vaccines

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Background/Objectives: Human papillomavirus (HPV) vaccines have been in used for almost two decades and the knowledge of their efficacy against cervical cancer is well recognised. There is some evidence that prophylactic HPV vaccination could also impact on the reproductive field of women by reducing the preterm birth (PTB) incidence. PTB remains the leading cause of perinatal mortality and lifelong morbidity worldwide. In this registry-based study our aim was to evaluate the PTB rate further with an extended registry follow-up of the HPV vaccinated women.

Methods: The study population comprised 6200 HPV vaccinated, and 1667 hepatitis B virus (HBV) vaccinated women born in 1992-1993 and reference cohort 19 473 unvaccinated women born in 1990-1991. Age-aligned data were collected up to age 28 for both cohorts. The HBV and unvaccinated women were combined as the non-HPV-vaccinated group for this study. PTBs were categorized as early preterm (pregnancy durations of gestational age (GA) of 22+0-33+6 weeks), late preterm (GA 34+0-36+6 weeks) and term (GA ^{3}37+0 weeks). The rate of PTB was compared between the HPV vaccinated and non-HPV-vaccinated women by using the data from nationwide Finnish Medical Birth Registry.

Results: Overall 23.9 % (n=1484) of HPV-vaccinated and 28.5 % (n=6018) of the non-HPV-vaccinated women had at least one childbirth recorded by the age 28. A total of 4,1 % (n=91) of HPV-vaccinated and 4.7 % (n=454) of non-HPV-vaccinated women had a PTB £37 GA weeks. Majority of these were at late preterm among both groups, 3.1 % and 3.5 %, respectively. The incidence rate for PTB per 10 000 person years at late preterm was 9 (95%CI 7-12) for HPV-vaccinated and 13 (95% CI 12-15) for non-HPV-vaccinated women. In the early preterm the PTB rate was 3 (95% CI 2-4) for HPV vaccinated and 5 (95% CI 4-6) for the non-HPV-vaccinated women. Similar trends for PTBs were seen if only the first childbirth of these women was considered.

Conclusions: Our results with the extended follow-up reinforces the previous observations that prophylactic HPV vaccination is likely to reduce the incidence of PTB. The decrease of PTB is crucial to reduce the need for extensive and costly postnatal care as also prevent from life-long morbidity. These results can further help to improve the HPV vaccination programs and coverage as HPV vaccine offers a major improvement for public health via cancer prevention and offering women a safer reproductive health.

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ASSOCIATION BETWEEN HPV VACCINATION AND ANAL HPV INFECTIONS IN GAY, BISEXUAL, AND OTHER MEN WHO HAVE SEX WITH MEN

06 - HPV prophylactic vaccines

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Background/Objectives: Gay, bisexual, and other men who have sex with men (gbMSM), especially those living with HIV, are at an increased risk of HPV-related cancers, particularly anal cancer. In the general population in Canada, anal cancer incidence is 1-2 cases per 100,000 individuals, whereas incidence is estimated at 19 per 100,000 individuals in HIV-negative gbMSM and 85 per 100,000 individuals in gbMSM living with HIV. gbMSM under the age of 26 have been eligible for vaccination against HPV since 2014 in Quebec, Canada. The few observational studies that examined the association between HPV vaccination and anal HPV infection in gbMSM reported prevention of incident infection by vaccine-protected types. We assessed the association between HPV vaccination and anal HPV prevalence and incidence in HIV-negative and HIV-positive gbMSM participants in the Lubricant Investigation in Men to Inhibit Transmission of HPV Infection (LIMIT-HPV) randomized controlled trial.

Methods: The LIMIT-HPV trial enrolled (2016-2020) 258 gbMSM (69 HIV-positive) in Montreal, Canada. Participants attended follow-up visits at months 1, 2, 3, 6, 9 and 12, where they self-completed an electronic questionnaire on sociodemographic and behavioral risk factors and provided a nurse-collected anal sample. Samples were tested for HPV using polymerase chain reaction (PCR) assays. We collapsed the treatment (carrageenan-based gel) and placebo arms and analyzed the data using a cohort framework. A participant was considered to be HPV vaccinated if they reported receiving 1+ doses at baseline and/or during follow-up. To assess the cross-sectional association between HPV vaccination and prevalent anal HPV infection, we used logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI). To assess the longitudinal association between HPV vaccination and anal HPV infection acquisition, we used Cox proportional hazards regression to estimate hazard ratios (HR) and 95% CI. HPV vaccination status was treated as a time-varying variable and study arm assignment was included as a covariate for the Cox regression models. Analyses considered HPV16/18 and HPV6/11/16/18 as the outcome of interest and were conducted at the individual level (i.e., unit of observation= gbMSM) and HPV-level (i.e., unit of observation= HPV infection), overall and stratified by HIV status.

Results: Of the 258 participants (mean age: 36.6 years), 60 (23.3%) reported to be HPV-vaccinated at baseline. At the individual level, there was no association between HPV vaccination and HPV16/18 prevalence (n=234, OR=0.87, 95% CI: 0.37-2.03) or incidence (n=181, HR=0.16, 95% CI: 0.02-1.21). There was also no association between HPV vaccination and HPV6/11/16/18 prevalence (n=234, OR=1.04, 95% CI: 0.53-2.02) or incidence (n=152, HR=0.33, 95% CI: 0.08-1.46). Analyses at the HPV-level showed consistent results with those conducted at the individual-level (HPV16/18 prevalence: n=468, OR=0.77, 95% CI: 0.34-1.71; HPV16/18 incidence: n=390, HR=0.18, 95% CI: 0.02-1.35; HPV6/11/16/18 prevalence: n=936, OR=0.90, 95% CI: 0.52-1.55; HPV6/11/16/18 incidence: n=775, HR=0.24, 95% CI: 0.06-1.01).

Conclusions: Although all estimates of effect were consistent with protection by vaccination, they did not reach statistical significance regardless of analytical framework. We will further explore these associations by adjusting for potential risk factors for HPV infection.

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THE IMPACT OF GERMANY'S HUMAN PAPILLOMAVIRUS VACCINATION PROGRAM ON ANOGENITAL DISEASES AMONG 28-32-YEAR-OLD WOMEN

07 - HPV therapeutic vaccines

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Background/Objectives: Human papillomavirus (HPV) is the most common sexually transmitted infection, responsible for anogenital warts and multiple anogenital cancers, including almost all cervical precancers and cancers(CIN2+). In Germany, HPV vaccination was first officially recommended and included in STIKO's vaccination schedule for 12- to 17-year-olds in 2007 and has since been reimbursed by statutory health insurances. However, vaccination coverage in Germany remains suboptimal and data on the real-world impact of HPV vaccination in Germany are lacking. This study examined the population-level impact of the German HPV vaccination program on HPV-related anogenital diseases among young women.

Methods: We conducted retrospective analyses of claims data comparing disease prevalence among 28 to 33-year-old women before (1980 birth cohort) and after (1990-1991 birth cohort) introduction of the HPV immunization program in Germany. Claims data from the InGef research database, representing approximately two thirds of German health insurances, were used. Outcomes included prevalence of anogenital warts, CIN2+, vulvar and vaginal precancers/cancer based on corresponding ICD-10-GM codes from outpatient settings (verified diagnosis) or inpatient settings (primary or secondary discharge diagnosis) during an individual's observation period. To account for differing lengths of observation within the cohort, prevalence rates were annualized. As detection of CIN2+ depends on cervical cancer screenings, for analyses of CIN2+, the sample was restricted to women who received cervical cancer screening during their observation period.

Results: Cervical cancer screening was recorded in 81.8% of evaluated women. The prevalence of CIN2+ significantly decreased by 51.1% from 0.92% (95-%CI=0.78%,1.08%) to 0.45% (95-%CI=0.38%,0.53%). Significantly lower prevalence rates were found among vaccine-eligible women for severe dysplasia of the cervix (N87.2), malignant neoplasms of the cervix (C53), and carcinoma in situ of the cervix (D06). We observed a 38.6% decline in anogenital warts prevalence from 0.44% (95%-CI=0.36%,0.54%) to 0.27% (95%CI=0.22%,0.32%) and 75.0% decline in vaginal precancer/cancer prevalence from 0.04% (95%CI=0.02%,0.07%) to 0.01% (95%-CI=0.00%,0.02%).

Conclusions: The German HPV immunization program has led to significant declines in female anogenital disease among young women in Germany, highlighting the importance of the vaccination. Moreover, the findings suggest that increasing vaccination coverage in Germany could further strengthen the public health impact of its HPV immunization program and increase the likelihood of HPV elimination in Germany over time.

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#6884

HPV types and variants among women who developed HSIL/LSIL in sixteen years post HPV vaccination

02 - Viral and molecular biology

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Background/Objectives: The strong association between high-risk HPV and cervical cancer is well established and the vaccines against these viral infections have been implemented worldwide. Here we investigated the HPV type and within type diversity distribution between vaccinated women with lesion progression and healthy controls.

Methods: Samples were collected from HPV-vaccinated women during the 16-year follow up of the Finnish HPV vaccine trial. Cervicovaginal swab samples were obtained from 81 HPV vaccinated women who developed cervical HSIL or LSIL during sixteen years post-vaccination and from similarly aged HPV-vaccinated healthy controls (N= 396). HPV type and variant level prevalence and diversity distribution was assessed.

Results: The HPV types showed that virtually all the HSIL and LSIL cases were associated to non-vaccine targeted oncogenic HPVs and the type level distribution differed significantly from the controls. Furthermore, prevalence of HPV variants was assessed among the HPV positive SILs and controls.

Conclusions: Our results indicate a shift in cervicovaginal HPV - host interactions post HPV vaccination.

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#6465

Post-marketing surveillance of human papillomavirus (HPV)-related high-grade cervical disease in a cohort of Chinese women who received the 4-valent HPV vaccine

06 - HPV prophylactic vaccines

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Background/Objectives: Cervical cancer is the 3rd leading cause of female cancer and the 2nd leading cause of cancer death in Chinese women 15 to 44 years of age. Nearly all cases of cervical cancer are caused by HPV. The 4-valent HPV (4vHPV; Gardasil 4 [Merck & Co., Inc., Rahway, NJ, USA]) vaccine has been approved in China for women aged 20-45 years old since May 2017. However, real world evidence of the impact of 4vHPV vaccine for the prevention of high-grade cervical lesions in Chinese women is not yet available.

Methods: Women aged 20-45 years old who received ≥1 dose of the 4vHPV vaccine were identified from the Ningbo Regional Health Information Platform (NRHIP) retrospectively. The primary 4vHPV vaccinated cohort included women vaccinated per protocol (3 doses administered within 12 months; ≥8 weeks between doses 1 and 2). A sub-cohort of 4vHPV vaccinated women who had cervical HPV negative and TCT (Thinprep Cytology Test) negative results within one year prior to the cohort enrollment date (vaccinated test-negative sub-cohort) and a matched unvaccinated test-negative cohort, were also assessed. Outcomes were the occurrence of new-onset high-grade cervical disease (cervical intraepithelial neoplasia 2/3 [CIN2/3]), adenocarcinoma in situ (AIS), and invasive cervical cancer (ICC).

Results: From 9 January 2018 to 31 March 2021, 195,457 doses of the 4vHPV vaccine were administered and 76,118 women received at least one dose of 4vHPV. The 4vHPV vaccinated cohort, vaccinated test-negative sub-cohort, and matched unvaccinated test-negative cohort comprised 50,051, 1,129, and 3,311 women, respectively. In the 4vHPV vaccinated cohort, twenty-three cases of CIN2/3 were identified in women with unknown HPV and cytological testing status at enrollment, therefore HPV infection prior to vaccination could not be excluded. No new-onset CIN2/3 cases were observed in the vaccinated test-negative sub-cohort as well as in the matched unvaccinated test-negative cohort. One AIS case and no ICC case were observed in 4vHPV vaccinated cohort. No AIS or ICC cases were observed in the vaccinated test-negative sub-cohort and the matched unvaccinated test-negative cohort.

Conclusions: These findings demonstrate that new-onset high-grade cervical disease can be monitored through surveillance of Chinese women registered in the NRHIP. However, considering the limited number of vaccinated women and the short follow-up period, it needs more time to assess the real-world effectiveness of 4vHPV vaccination in China.

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#6652

INDUCED ABORTION RATES AMONG HPV VACCINATED WOMEN

37 - Health education

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Background/Objectives: The first birth cohorts of human papillomavirus (HPV) vaccinated women are soon reaching the age of 30 in Finland. Women that are HPV vaccinated in their early adulthood have the possibility to receive comprehensive sexual health education as they meet nurses or doctors during the vaccination visits. On the other hand, HPV vaccinated women might feel to be more protected from sexually transmitted diseases and therefore be more liberal in sexual relationships, which might lead to greater risk for unintended pregnancies. In this study we investigated the differences in the induced abortion rates between HPV vaccinated and unvaccinated women.

Methods: This study consists of 7867 women from the 1992-1993 birth cohorts that took part to the HPV vaccination trial in 2007-2008 and a reference cohort of 19473 unvaccinated women born in 1990-1991. Participants of the HPV vaccination trial received the bivalent HPV16/18 vaccination (n=6200) or hepatitis B (HBV) vaccination (n=1667) at age of 12-15. Age-aligned registry data up to the age of 28 years was collected from The Register on Induced Abortions of Finland to compare the possible differences in the induced abortion rates between the groups of HPV vaccinated and unvaccinated women.

Results: A total of 18.3% (n=4702) of the women, 1052 HPV-vaccinated and 3650 unvaccinated, had at least one induced abortion in the past. Incidence rate of induced abortions per 10 000 person years during the follow-up of 12 years was 145.6 (95% CI 137.1-154.5) among HPV vaccinated and 161.4 (95% CI 156.4-166.7) among unvaccinated women. Socioeconomic concerns were the most common reason for induced abortion in both groups, with person-time rate of 135.6 (95% CI 127.5-144.2) among HPV vaccinated and 150.4 (95% CI 145.5-155.4) among unvaccinated women. Mean age at the time of induced abortion was 22 years in both groups. The proportion of abortions induced under the gestational week of 9+0 was significantly higher among the HPV vaccinated women (74.1%) compared to the unvaccinated women (70.7%) (p=0.002). No differences were observed in the number of induced abortions per person: in both groups 72% had one induced abortion, 19% had two and 9% had 3 or more induced abortions.

Conclusions: Our preliminary results show that HPV vaccinated women have a lower induced abortion rate compared to unvaccinated women. Also, gestational weeks at the time of induced abortion were lower among HPV vaccinated women, when the procedure is clinically considered easier and safer. These differences might be explained due to education and guidance on sexual health that the HPV vaccinated women received as part of the vaccination trial compared to the unvaccinated women. Our results indicate that besides cervical cancer prevention, HPV vaccination programs also influence greatly on women's sexual health by the health care professionals' guidance on the options of contraceptive measures and choices in the occurrence of unintended pregnancies.

FC05 - Cervical neoplasia and cancer

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#6653

HPV type-specific regression in women untreated for cervical intraepithelial neoplasia grade 2

25 - Cervical neoplasia

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Background/Objectives: In recent years, many countries have implemented active surveillance as an alternative option to excisional treatment in younger women with cervical intraepithelial neoplasia grade 2 (CIN2). However, little is known on potential biomarkers predicting regression of CIN2, thereby supporting active surveillance. Here, we aimed to describe HPV genotype-specific regression in women undergoing active surveillance for CIN2.

Methods: We conducted a historical cohort study on women aged 23-40 years diagnosed with CIN2 at Aarhus University Hospital, 2000-2010. Women were identified through the Danish Pathology Data Bank (DPDB) and were considered as undergoing active surveillance if they had a first record of cervical biopsy within two years after index diagnosis and no excisional treatment prior to this. Archived tissue samples underwent HPV genotyping using the HPV SPF10-DEIA-LiPA25, version 1 system (DNA ELISA kit HPV SPF10 and RHA Kit HPV SPF10-LiPA25). Regression was defined as having a record of £CIN1 in the DPDB defined on the last record of cervical punch biopsy or cone biopsy specimen during follow-up. We estimated the relative risk (RR (95% CI)) of regression using a modified Poisson model with robust variances.

Results: From the source population (n=3,623), 1,496 women were evaluated for eligibility, and 455 were included. Two-thirds were £ 30 years (73.8%) at index diagnosis, and nearly half of women had a high-grade index cytology (48.8%). Overall, 47.8% of all women regressed to £CIN1 during follow-up, with major differences across HPV genotypes. HPV16 was associated with a significantly lower likelihood of regression (RR 0.53 (95% CI (0.40-0.68)) compared to non-HPV16. The risk of regression was lowest in HPV16-positive women with a high-grade index cytology compared to HPV16-positive women with a low-grade cytology (RR 0.56 (95% CI (0.34-0.94)), while no significant differences were observed across age groups. Furthermore, women testing positive for HPV56, HPV33, HPV52, HPV45 and/or HPV31 were less likely to regress. In contrast, women with HPV68/73, HPV51, or HPV59 at CIN2 diagnosis had a significantly higher likelihood of regression.

Conclusions: HPV16 and extended HPV genotyping may be useful for clinical management of CIN2 as risk of regression varies by HPV genotype. Lowest risk of regression was observed among HPV16-positive women, in particular those with an associated high-grade cytology, suggesting that upfront excisional treatment in this subset of women may reduce risk of CIN3+.

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#6276

HPV status as a triage mechanism in the follow-up of patients with adenocarcinoma in situ and microinvasive adenocarcinoma of the uterine cervix - a retrospective study.

22 - Diagnostic procedures / management

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Background/Objectives: Treatment and follow-up of glandular precancerous lesions of the uterine cervix are different from squamous lesions mostly due to the risk of discontinuous spread of dysplasia in endocervical mucosa ("skip lesions") and insufficient efficacy of diagnostic methods such as cytology or colposcopy. The aim of our study was to investigate the safety of fertility sparing treatment of adenocarcinoma in situ (AIS) and pT1a adenocarcinoma (AC) in the long-term and identify factors associated with recurrence.

Methods: We retrospectively reviewed all patients with histopathologically verified AIS or FIGO 2018 IA cervical AC treated in a single center between years 2002 and 2023. Analyzed were specimens from consecutive surgeries in order to acquire the occurrence of skip lesions. Factors associated with recurrence were assessed in 86 patients after fertility sparing treatment with availability of long-term follow-up data (mean follow-up length was 57 ± 45 months).

Results: Generally, 143 patients (112 with AIS and 31 with AC) were included in the analysis. Skip lesion was identified in 11 of 33 (33%) patients who underwent secondary cervical surgery (repeated cone biopsy or hysterectomy). Recurrence rate after fertility sparing treatment was 9% (12% for AIS and 4% for AC). In the follow-up, no HPV negative patient experienced recurrence. In HPV positive patients, recurrence rate was 38%. HPV 16/18 positivity was strongly associated with the risk of recurrence than other high-risk genotypes; however, the difference was not significant (83% vs. 10%; p=0.083, log-rank).

Conclusions: In our retrospective study of 143 patients after fertility sparing treatment of AIS and microinvasive AC, we found that the risk of recurrence was strongly associated with HPV status. Long-term follow up based on HPV testing and genotyping poses a safe alternative to hysterectomy in such patients.

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#6878

PROGNOSTIC IMPLICATIONS OF HPV-RELATED HISTOPATHOLOGICAL VARIANTS IN ADENOCARCINOMA IN SITU OF THE CERVIX: A RETROSPECTIVE ANALYSIS

03 - Epidemiology and natural history

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Background/Objectives: Cervical adenocarcinoma in situ (AIS) is often incidentally detected during follow-up for squamous preneoplastic lesions. Screening strategies, effective in detecting squamous cell carcinoma and precursor lesions, are less effective in identifying endocervical glandular abnormalities. There has been a notable increase in the incidence of AIS without a corresponding decline in subsequent invasive disease, which has raisen from 5% to 20-25% in recent years. The updated 2020 World Health Organization (WHO) classification, divides endocervical adenocarcinomas (EACs) into two main groups: human papillomavirus-associated (HPVA) and human papillomavirus-indipendent (HPVI) deseases. The HPVA group is the most prevalent and exhibits a less aggressive course. Nevertheless, the WHO classification further subdivides histological variants of HPV-related adenocarcinomas, including villoglandular, mucinous NOS, intestinal, signet-ring cell, serous, clear-cell histotypes, and a novel variant known as "Stratified Mucin-Producing Intraepithelial Lesion (SMILE)". These subtypes are less common and, therefore, exhibit less predictable clinical outcomes when compared to the so-called "Usual Type" histotype HPV-associated cases. The present study aims to provide a detailed review of a cohort of patients treated for histologically-confirmed AIS by conization. Our primary goal was to identify histological variants in the HPVA group and observe their prognostic behaviour.

Methods: We retrospectively collected clinical and histological data from a cohort of 122 patients diagnosed with cervical AIS HPV-related after cervical conization, between 2000 and 2022, at the European Institute of Oncology, Milan, Italy. We classified the adenocarcinoma histotypes and their variants according to the updated WHO classification.

Results: The distribution of histological HPVA variants was as follows: 112 (91.8 %) patients had HPVA EACs, and 10 (8.2 %) had HPVI EACs. The "usual type" was the most common among HPVA (104/122; 85.2 %). Stratified mucin-producing and intestinal types were observed in 11 (9 %) and 7 (5.7 %) cases, respectively. The mean age at diagnosis of patients with these two histological variants was 42 years ± 11.19 years (range: 26-70). Overall, HPV 16 was the most prevalent detected genotype, followed by HPV 18, regardless of histotype, in both the "usual type" (38.4 % and 50 % respectively) and "non-usual type" (32.7 % and 44.4 % respectively) groups. There was only one case (0.8 %) of intestinal type AIS in which HPV 18 infection has persisted. Clear-cell, signet-ring cell and serous types were not found in our case series. None of the HPVA histological variants resulted in disease recurrence or progression during a follow-up period of at least five years.

Conclusions: Endocervical HPV-related AIS has a better prognosis than HPV-indipendent cases. In our case series, we found some uncommon histological variants in the HPVA group with an equally favourable prognostic behaviour, as none of them relapsed or progressed to invasive cancer.

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#6698

FOUR NOVEL DNA METHYLATION MARKER REGIONS ARE ABLE TO RELIABLY DETECT CIN3+ LESIONS IN CERVICAL SWABS IN A CYTOLOGY-SCREENED REFERRAL POPULATION

25 - Cervical neoplasia

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Background/Objectives: DNA methylation serves as an important marker for mis-regulation of gene expression in cancer, it can be used for the diagnosis of cancers, to classify tumors and to monitor disease progression and predict treatment outcome.

Methods: We used MeD-seq, a method that facilitates genome-wide methylation marker discovery, to successfully identify methylation changes associated with pre-cancer and cancer. Four novel marker regions, two intragenic and two intergenic, were selected and developed into a qMSP assay. These novel qMSP assays were used to detect cancer and pre-cancerous lesions in the EVAH study, a cytology-screened referral population.

Results: The EVAH study consists of cervical swabs of 1204 women of which 272 were tested using our four novel qMSP assays. The tested sample set consisted of 109 control, 42 CIN1, 73 CIN2, 45 CIN3 and 3 cancer samples. Detection of CIN3+ lesions varied between individual marker regions (sensitivity range 48-92%, specificity range 66-87%), however using combinations of two out of our four novel marker regions helped to increase the test reliability. The most sensitive two marker combination had a sensitivity of 94% with a specificity of 66%, whereas the most specific combination had a specificity of 78% with still a sensitivity of 71%. In addition, we found a very high consistency when scoring CIN1-3 lesions with our four individual marker assays, with the majority (64%) of CIN1-3 samples scoring either positive (23%) or negative (41%) for all four marker assays.

Conclusions: Using MeD-seq we selected and developed four novel marker regions into qMSP assays. These four novel DNA methylation assays were able to reliably detect CIN3+ lesions in the EVAH study. Individual CIN lesions score very consistently on all four qMSP assays (23% score positive and 41% score negative for all four assays) reveal the biological heterogeneity of CIN lesions. The presence of consistent cancer related hypermethylation in CIN lesions might predict CIN lesion outcome.

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#6291

A promising new model？the establishment of patient-derived organoids model covering HPV-related cervical precancerous lesions and corresponding cancer

25 - Cervical neoplasia

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Background/Objectives: The development of HPV infection to cervical intraepithelial neoplasia and finally to cervical carcinogenesis is a long 5-10 years process, but the lack of human-derived in-vitro models that recapitulate cervical precancerous lesions has been the bottleneck in researching HPV infection-associated precancerous lesions and cancers for a long time. We wish to describe a long-term 3D organoid culturing protocol for high-grade squamous intraepithelial lesion (HSIL) and cervical squamous cell carcinoma (SqCa) that stably recapitulate the two tissues of origin, demonstrate the fidelity of these two organoid models from multiple perspectives and perform some applications in this platform.

Methods: In this study, the organoid culture system was established and optimized, and high-grade cervical intraepithelial neoplasia (n=26) and cervical squamous cell carcinoma tissues (n=18) were included for culture. Subsequently, the established organoids were characterized in terms of morphology, sub-microstructure, genomics, and tumorigenicity, and the real structures of the organoids were presented by three-dimensional reconstruction. Further, in this study, the established organoid platform was simply applied for drug sensitivity screening, and the co-culture model of cervical tumor organoids and immune cells was explored for HPV antigen peptide screening.

Results: Originating from human-derived samples, a small biobank of cervical pre-tumoroids and cervical tumoroids that faithfully retained genomic, transcriptomic characteristics and also the causative human papillomavirus (HPV) genomes were established. In this study, we simultaneously established stably transmissible cervical pre-tumoroids and cervical tumoroids in the context of HPV, with success rates of 84.6% (22/26) and 83.3% (15/18), respectively, and successfully described the three-dimensional structures, microstructure, and cellular function of these two types of organoids. Originating from human-derived samples, a small biobank of cervical pre-tumoroids and cervical tumoroids that faithfully retained genomic, transcriptomic characteristics and also the causative human papillomavirus (HPV) genomes were established. Cervical pre-tumoroids and cervical tumoroids showed differential responses to common chemotherapeutic agents and grew differently as xenografts in mice. Most interestingly, by coculture of organoid models with PBMC stimulated by HPV antigenic peptides, we illustrated both organoid models responded differently to immunized PBMC cells, supporting 3D organoids are reliable and powerful tools to study virus-specific T-cell responses and screening of therapeutic HPV vaccines.

Conclusions: By successfully establishing a small biobank of cervical pre-tumoroids and cervical tumoroids, this study has broken through the bottleneck of human-derived cervical precancerous lesion models and established an experimental platform and biobank for in vitro mechanism research, therapeutic vaccine screening and future personalized treatment of HPV-related cervical diseases. It also provides support for the precise treatment of HPV persistent infection, especially for patients with advanced cervical cancer, and lays the foundation for the clinical promotion and application of organoid individualized drug sensitivity technology.

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#7085

High-throughput microRNA screen using 3D cell cultures identifies potent thermoradiation sensitizers for cervical cancer

25 - Cervical neoplasia

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Background/Objectives: Chemoradiation is the standard treatment for women with locally advanced cervical cancer, but often comes with severe side effects. A well-established and better-tolerated alternative is the combination of radiotherapy with hyperthermia (thermoradiation). However, there is still need for further improvement of thermoradiation and accurate prediction of treatment response. Dysregulation of microRNAs (miRNAs) is commonly found in cancer and growing evidence indicates their value as predictive biomarkers and therapeutic targets. The conventional clonogenic assay for assessing radiosensitizing effect is time-consuming and unsuitable for high-throughput studies. Therefore we established a high-throughput miRNA screen using spheroid cell cultures on ultra-low-attachment (ULA) plates and cell viability as readout of radiosensitivity.

Methods: We performed a discovery screen, introducing miRNA overexpression using ~400 miRNA mimics in four cervical cancer cell lines on ULA plates. Twenty-four hours after transfection, cells were treated with irradiation (2Gy) and hyperthermia (42°C for 60mins) or were kept in incubator as treatment control. Cell viability was assessed 72h post-treatment and analyzed using ShrinkHT, a statistical model designed for small sample sizes. The identified 55 miRNA candidates and 13 controls were then subjected to a validation screen in six cervical cancer cell lines and four head and neck cancer cell lines. The validation screen revealed nine miRNAs with strong sensitizing potential that are currently being validated for functional relevance by RT-qPCR, luciferase reporter assay, and western blot.

Results: The discovery screen in four cervical cancer cell lines yielded 55 miRNAs with sensitizing potential for thermoradiation. The validation screen in ten extended cancer cell lines identified nine out of 55 miRNAs that significantly reduced cell viability and had an additive effect on thermoradiation. RT-qPCR in SiHa cells showed downregulation of genes related to DNA damage response (RAD51, MDM4 and SMC1A) upon overexpression of the miRNA sensitizer.

Conclusions: Cell viability measurement of spheroid cultures provides a promising alternative for clonogenic assays to study radiosensitizing effects in a high-throughput setting. The identified miRNAs with strong sensitizing potential could provide new therapeutic options for treatment and biomarkers for predicting treatment effect of thermoradiation in cervical cancer.

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#6589

CIRCULATING CELL-FREE HPV DNA IS A STRONG MARKER FOR DISEASE SEVERITY IN CERVICAL CANCER

15 - Molecular markers

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Background/Objectives: For cervical cancer (CC), circulating cell-free HPV DNA (ccfHPV) may establish disease severity. Furthermore, HPV integration has been correlated to viral load and survival.

Methods: Plasma from 139 CC cases; 50 primary surgery patients, 22 primary surgery+adjuvant oncological therapy patients, and 67 primary oncological therapy patients, was collected (2018-2020) before treatment. Furthermore, plasma from 25 CIN5 patients were collected, and plasma from 15 healthy women were included as controls. Two NGS panels were used to establish ccfHPV presence and HPV16 integration status.

Results: ccfHPV was detected in four primary surgery (8.0%), eight primary surgery+adjuvant oncology (36.4%), and 54 primary oncology (80.6%) patients. For primary oncology patients with HPV16 related cancer (n=37), more ccfHPVneg than ccfHPVpos patients had HPV16 integration (p=0.04), and in patients with HPV16 integration (n=13), ccfHPVpos patients had higher disease stages than ccfHPVneg patients (p=0.05).

Conclusions: ccfHPV presence is related to disease severity and may add to the much debated Sedlis criteria used for identifying patients for adjuvant oncological therapy. However, ccfHPV detection seems to be influenced by HPV integration status and disease stage, and these factors need to be considered in ccfHPVneg patients.

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#6556

Vvax001, an alphavirus-based therapeutic cancer vaccine, against HPV-induced premalignant cervical lesions: a phase 2 clinical trial

07 - HPV therapeutic vaccines

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Background/Objectives: Human papillomavirus (HPV) infection is the major cause of (pre)malignant genital lesions. We previously demonstrated that Vvax001, a replication-incompetent Semliki Forest virus (SFV) vaccine encoding HPV type 16 (HPV16) E6 and E7, induced potent anti-E6 and -E7 immune responses (1). Here, we report data of the ongoing phase 2 trial evaluating efficacy, HPV clearance and safety of Vvax001 in patients with HPV16 positive cervical intraepithelial neoplasia grade 3 (CIN3).

Methods: 18/18 patients with newly diagnosed HPV16 positive CIN3 were recruited. Patients received 3 immunizations of Vvax001 (5x107 infectious particles) with a three-week interval. Patients were monitored by colposcopy every two months for up to 19 weeks after the last immunization. A biopsy was taken at the last visit (19 weeks after the last immunization) to evaluate efficacy histologically. After the last visit, responders (histopathological regression from CIN3 to CIN1 or no dysplasia) did not receive standard-of-care loop excision (LLETZ), while non-responders (still CIN2 or CIN3) underwent the standard-of-care LLETZ. Next to colposcopic and pathologic response rates, treatment-related adverse events (trAEs), and immune correlates of treatment were assessed.

Results: At this moment 15/18 (83%) patients have been fully immunized and completed all study visits. Colposcopic examination revealed a reduction in size of CIN3 lesions in 14/15 patients (93%), which was already evident 3 to 11 weeks after the last immunization. A vaccine-induced histopathological complete response was observed in 7/15 patients (47%). HPV16 clearance was observed in 9/15 (60%) patients. TrAEs were mild to moderate local injection site reactions.

Conclusions: Vvax001 is safe and well-tolerated with promising activity against HPV16 positive CIN3 lesions.

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#6224

Unraveling the role of surgery in the prognosis of small cell carcinoma of the cervix patients: A representative study based on the SEER database and a Chinese multicenter registry

25 - Cervical neoplasia

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Background/Objectives: Small cell carcinoma of the cervix is an uncommon subtype of cervical cancer, accounting for only 0.5-1.0% of all cervical cancers. Despite the available therapeutic methods, patients diagnosed with small cell carcinoma of the cervix face a poor prognosis, with a 5-year overall survival rate of less than 30%. NCCN guidelines recommend different treatment approaches based on the stage of the cancer. For cases where the cancer is confined to the cervix, options include surgery or chemoradiation with brachytherapy or neoadjuvant chemotherapy, depending on the size of the tumor. For locally advanced tumors (stage IB3-IVA), non-surgical methods are primarily used as the first-line treatment. However, due to the rarity of this type of cervical cancer, conducting prospective studies can be challenging. Therefore, current therapy guidelines are mainly extrapolated from the treatment strategies used for squamous cell carcinoma, adenocarcinoma of the cervix, or small cell lung cancer. To date, there is a scarcity of multicentre, cross-racial, large-scale studies examining different treatment outcomes for patients with small cell carcinoma of the cervix. Consequently, there is a need for more retrospective studies to provide valuable insights into the diagnosis and treatment of this rare and aggressive form of cervical cancer.

Methods: In this retrospective study, we collected data from the Surveillance, Epidemiology, and End Results (SEER) 18 registries cohort and a Chinese multi-institutional registry. Kaplan-Meier analysis, propensity score matching, and Cox-regression analyses were used to assess treatment outcomes and risk factors. Landmark analysis was uesde as a sensitivity analysis in the Chinese cohort to reduce immortal-time bias.

Results: 1288 participants were included in the study; 610 in the SEER cohort and 678 in the Chinese cohort. Both univariable and multivariable Cox regression analysis (SEER hazard ratio [HR] 0·65 [95% CI 0·48-0·88], p=0·0058; China HR 0·53 [0·37-0·76], p=0·0005) showed that surgery was associated with a better prognosis. In subgroup analyses, surgery remained a protective factor for patients with locally advanced disease in both cohorts (SEER HR 0·61 [95% CI 0·39-0·94], p=0·024; China HR 0·59 [0·37-0·95]; p=0·029). Furthermore, the protective effect of surgery was observed among patients with locally advanced disease after propensity score matching in the SEER cohort (HR 0·52 [95% CI 0·32-0·84]; p=0·0077). In the China registry, surgery was associated with better outcomes in patients with stage IB3-IIA2 cancer (HR 0·17 [95% CI 0·05-0·50]; p=0·0015).

Conclusions: The results of our study using the SEER database and the Chinese multicentre cohort suggest that surgery might improve outcomes in patients with small cell carcinoma of the cervix, surgery might be beneficial for patients with locally advanced disease, and that surgery is potentially protective for patients with stage IB3-IIA2. These findings should inform consensus best practice guidelines for the treatment and management of patients with small cell carcinoma of the cervix. The findings from this study suggest that the efficacy of different treatments might depend on the stage of the disease, which emphasizes the need for tailored treatment approaches. Furthermore, our study might offer potential research directions for future prospective studies.

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FC06 - HPV Screening I

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#6754

RANDOMIZED NONINFERIORITY TRIAL OF THE EFFECTIVENESS OF FREQUENT VERSUS INFREQUENT SCREENING CERVICAL CANCER SCREENING AMONG 22-TO-28-YEAR-OLD HUMAN PAPILOMA VIRUS-VACCINATED FINNISH WOMEN.

10 - HPV screening

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Background/Objectives: A decade after the implementation of the national human papillomavirus (HPV) vaccination programs, HPV vaccinated cohorts are now entering national cervical screening programs. Both the changing HPV type-distribution and immunity against the most common hrHPV types is reducing the positive predictive value of primary cytology-based screening implying the screening should be less intense in these birth cohorts. We launched a randomized trial to assess the effectiveness and safety of infrequent screening compared to frequent screening (current policy) among vaccinated young-adult women (NCT02149030).

Methods: In 2013,6963 1992-95 born women who received HPV16/18 or hepatitis B virus vaccination at 12-to-15 years 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. In parallel, 1334 women who received the HPV16/18 vaccine at 18 were invited to an infrequent-screening safety arm at the age of 22 and 25 (A3). Cervical samples were HPV-genotyped using MALDI-TOF-MS and/or the BD Onclarity platform for extended genotyping. We evaluated the noninferiority of the infrequent screening to detect CIN2+ among A2 compared to infrequent-screening A1-participants. The prevalence of HPV and abnormal cytology at 22, 25 and 28 are being compared between the arms.

Results: 2744, 2885 and 1334 women participated in the frequent (A1), infrequent (A2) and safety (A3) screening arms respectively at the age of 22. Participation at the ages of 25 was of 2472, 2640, and 1219 women A1, A2 and A3 arms respectively and of 1991 and 2123 (A1 and A2) women at the age of 28. Noninferiority of screening results will be presented.

Conclusions: The results of this randomized trial will estimate the accuracy and safety of less frequent screening among HPV-vaccinated women.

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NATIONWIDE MULTI-LABORATORY HPV SCREENING USING EXTENDED GENOTYPING AND NEAR REALTIME QUALITY ASSURANCE MONITORING IN THE NETHERLANDS

10 - HPV screening

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Background/Objectives: Back 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: As of July 2023, 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 for quality assurance purposes regarding e.g. intra- and inter-laboratory comparisons of assay performance, equipment monitoring, and longitudinal trend analysis of reagents and controls.

Results: Given the recent adaptations of the Dutch screening program, performance data will be presented on results generated in the first 6 months after the switch (July - December 2023). The use of the near-real-time quality assurance monitoring system will be demonstrated both from the individual screening laboratory's perspective as from the national perspective. Stability of performance of the screening systems within and between laboratories is monitored longitudinally for both assay control samples and clinical samples. Examples and observations will be presented. Furthermore, HPV screening results and typing information will be presented for both GP collected cervical scrapes and self-collected samples.

Conclusions: Starting mid-2023, the cervical cancer screening program in the Netherlands has implemented HPV based screening on both cervical scrapes and self-collected samples, using an HPV assay that applies extended genotyping. 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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HPV TESTING VERSUS CYTOLOGY FOR CERVICAL CANCER SCREENING AMONG THOSE 50 YEARS AND OLDER: EVIDENCE FROM HPV FOCAL RANDOMIZED CONTROLLED TRIAL.

10 - HPV screening

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Background/Objectives: Most global recommendations regarding age to exit cervical cancer screening were based on previous experiences with cytology-based testing. The lack of consensus regarding the appropriate upper age limit to stop HPV based cervix screening raises critical questions about the optimal screening approach for older women. No clinical trial has yet directly compared the effectiveness and testing intervals of HPV testing compared to cytology in women ≥50 years. Aim of this study was, 1) to evaluate the effectiveness of HPV testing compared to cytology in detecting histologically confirmed incident cervical intraepithelial neoplasia grade 2 or worse (CIN2+ and CIN3+) among women ≥50 years, (with up to 48 months follow-up); and 2) to compare the number of CIN2+ detections missed by primary HPV testing at 48-month exit with co-testing.

Methods: This analysis includes all participants aged >50 who participated in the HPV For Cervical Cancer (FOCAL) randomized clinical trial. A total of 6471 women aged >50 were randomly allocated to receive liquid-based cytology (LBC) (Control arm) (3248, 50.19%) or to receive HPV testing (intervention arm) (3223, 49.81%) at baseline. Participants in both arms received co-testing (HPV and cytology) at the 48-month exit. Objective 1: we calculated incidence rates and risk ratios for CIN2+ detection at exit by arm. Objective 2: we also compared CIN2+ lesions missed by cytology alone in the control arm to those missed by HPV alone in the intervention arm.

Results: Objective 1: at 48 months, individuals who received HPV at baseline had considerably less CIN2+ detection than those who received cytology at baseline. Among those negative at baseline, at 48 months, the incidence of CIN2+ was 1.61/1000 (95% CI, 0.52, 3.76) in those who received HPV testing compared to 5.36/1000 (95% CI, 3.13, 8.59) in those receiving cytology, with a risk ratio of 0.30 (95% CI, 0.11, 0.81). Objective 2: at the 48-month exit, cytology every two years missed 50% of CIN2+ cases, while HPV testing every four years missed none.

Conclusions: Our findings suggest that HPV-based screening is more effective than cytology in detecting pre-cancerous lesions among those ≥50 years. Findings also indicate cytology co-testing did not add value to HPV-based screening among those ≥50 years. These findings are important for Canadian and global cervical cancer screening programs as they plan for implementation of HPV-based screening.

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Quality assurance of HPV screening services using confirmatory testing of "HPV- negative" HSIL

10 - HPV screening

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Background/Objectives: Some high-grade cervical lesions and cervical cancers (HSIL+) may test negative for human papillomavirus (HPV) with PCR based analysis. Re-analysis of "HPV-negative" HSIL+ samples with repeat testing and extended analyses including whole genome sequencing is a strategy for quality assurance of HPV screening services. An international quality assurance guidance on this procedure has been developed through an iterative consensus process among national HPV reference laboratories (NRLs) from 13 countries.

Methods: The Swedish NRL received 185 initially HPV-negative cervical specimens (HSIL+) since February 2019 (136 liquid-based cytology samples and 49 histopathology specimens) from HPV laboratories all over Sweden. The samples were re-tested, using broad general primer -PCR with genotyping for 37 different HPV-types. Specimens still "HPV-negative" were analyzed using whole genome sequencing of the whole specimen using SMARTer Stranded Total RNA-Seq Kit v2 - Pico Input Mammalian (Takara Bio USA, San Jose, CA) and NextSeq 550 system (Illumina, San Diego, CA) at 2×150 bp in different runs (10 samples max per run), aiming for >30 million paired end reads/sample.

Results: The standard general primer PCR targeting the L1 region detected HPV in 53% (n=98) of initially "HPV-negative" samples, with HPV 16 being the most common HPV-type (n=15). Whole genome sequencing of PCR-negative samples detected HPV in an additional 16 specimens with HPV 18 being the most common HPV-type (n=4).

Conclusions: Most cases of "HPV-negative" HSIL in routine HPV screening do contain HPV when re-tested at an NRL. Confirmatory testing strategies may be useful to minimize false negativity in HPV screening.

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#6850

RISK OF CERVICAL CANCER AFTER POSITIVE HUMAN PAPILLOMAVIRUS TEST WITH NEGATIVE CYTOLOGY TRIAGE BY HPV GENOTYPE: LONG-TERM FOLLOW-UP FROM A RANDOMIZED HEALTHCARE POLICY TRIAL

10 - HPV screening

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Background/Objectives: In human papillomavirus- (HPV-) based cervical screening, management of positive HPV test with negative cytology triage is challenging. We performed long-term follow-up of a randomized healthcare policy trial in the population of Stockholm, Sweden on the endpoint of invasive cervical cancer development, in women tested positive for HPV with negative cytology triage.

Methods: The randomized healthcare policy trial involved 395,725 women living in Stockholm, Sweden, who were 30-64 years of age between 2014 and 2016. Half were randomized to HPV primary screening with cytology triage, and half to cytology primary screening. In HPV arm, 7093 women were tested positive for HPV and negative in cytology triage. We linked these women to the Swedish Total Population Registry for death and emigration information, and to the Swedish National Quality Register for Gynecological Cancer for diagnosis of invasive cervical cancer, up to the end of 2021. We compared the cumulative incidence proportion of invasive cervical cancer between women tested positive for HPV16/18 and other oncogenic HPV types, with negative cytology triage.

Results: Among 7093 women tested HPV positive cytology negative, 1199 were positive for HPV16, 428 for HPV18, and 5466 for the mix of other 12 oncogenic types (HPV31,33,35,39,45,51,52,56,58,59,66 and 68). During 5-7 years of follow-up, 23 women positive for HPV16 developed invasive cervical cancer (1.92%). The corresponding cervical cancer cases for HPV18 and other HPV types were 6 (1.40%) and 2 (0.04%), respectively. By one screening interval of 3.5 years, the cumulative incidence of invasive cervical cancer was 0.93% (95%CI=0.56%-1.55%) in women positive for HPV16/18 with negative cytology triage, and 0.04% (95%CI=0.01%-0.15%) in women positive for the mix of other oncogenic HPV types. By 7 years of follow-up, the cumulative incidence in HPV16/18 group was 3.0% and no further cervical cancer case was diagnosed in the group positive for other oncogenic HPV types. The difference was statistically significant (Pinf0.0001).

Conclusions: Women tested positive for HPV16/18 with negative cytology triage in HPV-based screening should be prioritized to close follow-up. But this appears to not be required for women who are positive for other HPV types with negative cytology.

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#7026

EVALUATION OF THE TATA MD CHECK HPV HR GENOTYPE TEST FOR THE DETECTION OF HIGH-RISK HPV IN CERVICAL CANCER SCREENING

10 - HPV screening

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Background/Objectives: The TATA MD CHECK HPV HR Genotype test which identifies and differentiates 15 high-risk HPV genotypes (HR-HPV) was compared with the Cobas 4800 and AmpliSens HPV HCR genotype-titre-FRT PCR kit for detecting HR-HPV types in clinical referral and follow-up patients to evaluate its value for cervical cancer screening.

Methods: Aliquots of 99 HPV positive samples [(HPV 16 (n=14), HPV 18 (n=18), HPV HR (n=67)] and 98 HPV negative samples preserved at -800 C were included in the study. Inclusion Criteria: For a sample to be negative, it should be negative in both Cobas HPV test and AmpliSens HPV HCR genotype-titre-FRT PCR kit. (CE-IVD approved) For a sample to be positive, it should be positive in both Cobas HPV test and AmpliSens HPV HCR genotype-titre-FRT PCR kit. (CE-IVD approved) DNA was extracted from the aliquots using the QIAamp DNA Mini kit (Qiagen) and then PCR was performed with TATA MD CHECK HPV HR Genotype test, qualitative real time PCR assay. This kit is manufactured by TATA Medical and Diagnostics Ltd., Sriperumbudur, Chennai and waiting approval from DCGI, India

Results: A total of 197 samples were used for the clinical performance study of Tata MD CHECK HPV HR Genotype Kit. Among 98 HPV negative samples, 94 samples were detected as true negative. Among 99 HPV positive samples, 14/14 samples were positive for HPV 16 genotype, 18/18 Samples were positive for HPV 18 genotype and 65/67 Samples were positive for HPV HR. There were three discrepant results, wherein HR 68 genotype could not be detected by the TATA MD kit in two cases and HR 73 genotype was detected by TATA MD kit only. While the overall agreement rate was 98 % for 14 high-risk HPV types, the test kit under study, demonstrated 98 % sensitivity and 96 % specificity.

Conclusions: The study showed that Tata MD CHECK HPV HR Genotype kit detected all the genotypes claimed in the kit. All the co-infected samples (containing more than one HPV HR type) were detected as positive for HPV. The kit was found to be satisfactory, of standard quality and thus can be used for cervical cancer screening.

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#6792

A NEGATIVE HPV TEST IS ASSOCIATED WITH LONG-TERM PROTECTION AGAINST INVASIVE CERVICAL CANCER FOR POST-MENOPAUSAL WOMEN: EVIDENCE FROM A REGISTRY-BASED COHORT STUDY

10 - HPV screening

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Background/Objectives: Cervical screening has transitioned from primary cytology test to primary HPV test, and from a 5-year interval to a 7-year interval for women above 50 years of age. Results of previous studies evaluating the effectiveness of HPV tests compared to cytology typically use CIN2+/HSIL+ as the outcome. Whether one negative HPV test would be enough to provide long-term protection against invasive cervical cancer among post-menopausal women remains unknown. We performed a registry-based study, to investigate safety of the current recommended 7-year interval for HPV negative post-menopausal women, using invasive cervical cancer (ICC) as the outcome.

Methods: All women eligible for screening and resident in the capital Stockholm-Gotland region of Sweden aged 56-61 years (n=42,752) were randomized to primary cytology test or primary HPV test between 2012 Jan 1st and 2014 May 31st. We identified 14,165 women in the randomized trial with negative screening results through the Swedish National Cervical Screening Registry. There were 6909 women in the primary HPV negative group and 7256 women in the primary cytology negative group. We used the Gynecological Cancer Quality Registry to identify the invasive cervical cancer until Dec 31st 2021, including squamous cell carcinoma (SCC), adenocarcinoma (AC), adenosquamous carcinoma (ASC), and other more rare histological types still deemed as HPV-associated. We calculated the cumulative incidence of ICC and the relative risk (RR) of the two groups at 7 years and stratified on baseline test status (HPV negative or cytology negative). We also calculated the incidence rate and the incidence rate ratio over the entire follow-up (maximum of 10 years). All estimates are presented with 95% confidence intervals (CI).

Results: The average age of women who participated was 58 years old at the beginning of follow-up and 66 years old at the end of follow-up. We identified only 1 cervical cancer (histology type: SCC) in the HPV negative group and 7 cervical cancers (histology type: 5 SCC, 2 AC) in the cytology negative group over 7 years of follow-up. This meant that the 7-year cervical cancer cumulative incidence was 14.7/100,000 women versus 97.4/100,000 women in the HPV negative and cytology negative group, respectively. The RR of ICC in the cytology negative group compared to the HPV negative group was 6.6 (95% CI 0.8-53.8). Extending the whole follow-up period to the maximum of 10 years, we still only identified 1 cervical cancer (histology type: SCC) in the HPV negative group and a total of 9 cervical cancers (histology type: 7 SCC, 2 AC) in the cytology negative group. This corresponded to an incidence rate of 1.7/100,000 person-years versus 14.4/100,000 person-years in the HPV negative and cytology negative group, respectively. The resulting IRR in the cytology negative group compared to the HPV negative group was 8.6 (95% CI 1.1-67.7).

Conclusions: For post-menopausal women, a negative HPV test provides much higher reassurance against ICC than a negative cytology result. The low incidence of ICC at 7 years supports the current recommendation in this age group.

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#6908

HPV screening with extended genotyping in cytologically negative women aged 35, and 45 years from the Czech Republic - large-scale study

10 - HPV screening

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Background/Objectives: The Czech Republic has an organized nationwide cervical cancer screening program based on cytology with an optional reflex HPV test for women with atypical cellular findings. Since 2021, the screening algorithm has been extended to include an HPV screening test for all women aged 35 and 45 years with negative cytology as a highly sensitive test with long-term negative predictive value. Most HPV screening tests detect 12-14 high-risk (HR) HPV types, with separate information on the presence of HPV16/18. Extended genotyping included in HPV screening tests could provide both information on the prevalence of HPV types in a particular population and a possible triage of women based on detected HPV groups reflecting the risk of progression to cancer. The Alinity m HR HPV screening test (Abbott) detects DNA of 14 HR HPV types and also gives the result of extended HPV typing, namely the separate presence of HPV16, HPV18, HPV45, other HR HPV types covered by the nonavalent HPV vaccine (group A: HPV31,33,52, and 58) and the remaining HR HPV types not covered by the nonavalent HPV vaccine (group B: HPV35,39,51,56,59,66, and 68). The aim of our communication is to present the data obtained in almost 3 years of use of the Alinity m HR HPV Assay for HPV screening of more than 76,000 cytologically negative women aged 35 and 45 years who were screened in the Bioptical Laboratory Ltd.

Methods: Between April 2021 and September 2023, 33,183 women with normal cytology aged 35 years and 43,031 women with normal cytology aged 45 years who attended their annual gynecological check-up were tested with the Alinity m HR HPV Assay. Overall positivity and positivity rates for separate HPV groups were calculated for each age group. Furthermore, positivity rate and genotype prevalences were compared to those retrieved from the same age groups but tested after abnormal cytological results.

Results: Out of 33,183 cytologically negative women aged 35 years, 3,485 (10.5 %) tested positive for any of the 14 detected HR HPV types. The positivity rate of the same age group who were tested after abnormal cytology was 28.2 %. Out of 43,031 cytologically negative women aged 45 years, 3,086 (7.2 %) tested positive for any of 14 detected HR HPV types. The positivity rate of the same age group who were tested after abnormal cytology was 19.7 %. The most commonly detected were HPV types from group B, namely 41.9% (of all positives) in the 35-year-old group with negative cytology and 47.7 % (of all positives) in the 45-year-old group with negative cytology.

Conclusions: The overall HR HPV positivity in cytologically negative women aged 35 and 45 years from the Czech screening cohort seems a little higher than expected in a pilot study LIBUSE. However, the majority of positive samples contain one or more of the less aggressive genotypes HPV35,39,51,56,59,66, or 68.

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#6661

THE RISK OF VAGINAL, VULVAR, AND ANAL PRECANCER AND CANCER ACCORDING TO HIGH-RISK HPV STATUS IN CERVICAL CYTOLOGY SAMPLES

10 - HPV screening

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Background/Objectives: High-risk human papillomavirus (hrHPV) is the cause of virtually all cervical cancer cases and some vulvar, vaginal, and anal cancer cases. In cervical cancer screening programs, HPV testing is increasingly becoming the primary screening method. As a result, more information about the potential link and risk for other subsequent HPV-related anogenital cancers following a positive cervical hrHPV test is required. The objective of this prospective cohort study was to estimate the association between cervical hrHPV infection and the subsequent risk of vulvar, vaginal, and anal cancer and precancer or worse (VIN2+, VaIN2+, and AIN2+). We further assessed if age, a history of previous anogenital precancerous lesions, and HPV vaccination modified the risk.

Methods: The study population consists of 455,349 women who had a cervical hrHPV test in Denmark between 2005 and 2020. We used Cox proportional hazard regression models to calculate hazard ratios (HRs) and 95% confidence intervals (CI) and the Aalen Johansen estimator to calculate the absolute risk of vulvar, vaginal, and anal cancer and precancer or worse. We adjusted the models for age, calendar year, and HPV vaccination status.

Results: 15% of the 455,349 women were hrHPV positive at baseline. A positive cervical hrHPV test was associated with an increased hazard of vulvar, vaginal, and anal squamous cell carcinoma (SCC) (Vulvar SCC: HR 3.7 (95%CI; 2.5-5.4), vaginal SCC: HR 19.9 (95%CI; 2.5-5.4) and anal SCC: HR 2.2 (95%CI; 1.4-3.4)). HrHPV-positive women also had an increased absolute risk of VIN2+, VaIN2+, and AIN2+; the highest difference was seen for VIN2+, where hrHPV positive had a 5-year absolute risk of 0.45% compared to 0.14% for hrHPV negative.

Conclusions: In conclusion, our study confirms the association between cervical hrHPV infection and non-cervical anogenital precancers and cancers. Currently, no established risk threshold or guidelines exist due to the rarity of these diseases. As HPV testing becomes the primary method for cervical cancer screening, future data will help define high-risk groups and acceptable risk thresholds.

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#6917

PERFORMANCE COMPARISON BETWEEN THE INNOVATIVE DYSPLASIA DETECTION TEST QUANTIGENE-MOLECULAR-PROFILING-HISTOLOGY AND 5 GUIDELINE-COMPLIANT HPV SCREENING TESTS.

10 - HPV screening

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Background/Objectives: Background: WHO recommends HPV testing for cervical cancer screening worldwide. In Germany, HPV and cytology co-testing was introduced as primary screening since 2020. Due to low specificity (20-50%) for detection of CIN2+, HPV-based screening may lead to overdiagnosis and referral to colposcopy. A positive HPV test indicates a risk for dysplasia but not its actual presence or severity. Triage testing is necessary, such as cytology, dual-stain, methylation marker, HPV genotyping. This is challenging especially in high prevalence situations like in LMIC (20%-30% HR-HPV prevalence at screening age) or immunosuppressed populations like WLWH (up to 60%-80%). The innovative dysplasia test QuantiGene-Molecular-Profiling-Histology (QG-MPH) quantifies HPV oncogene expression (E7 mRNA) and cellular dysplasia stage-associated biomarkers and enables stage-specific dysplasia diagnosis from the first screening LBC smear. Objective: To compare accuracy (sensitivity and specificity) for the detection of CIN2+ of QG-MPH assay to guideline-compliant HPV tests and an estimation of health economic benefits.

Methods: METHODS: Selected samples (n=162) with definitive histomorphologic-pathologic results from patients with various degrees of dysplasia severity were tested by QG-MPH and with the HPV tests Cobas, Onclarity, Anyplex HR-HPV Detection, Aptima, and MPG (in-house). The results of each HPV test, as well as their concordance, were determined and compared with those of QG-MPG. A description of the complexity and a health economic estimation of the total screening effort when using QG-MPH assay in the German algorithm or in an LMIC setting was performed.

Results: Results: All HPV tests studied had high sensitivity (88.9% - 93.7%) for detection of CIN2+ but varied widely in specificity (20.2% - 53.5%). The QG-MPH test showed a slightly reduced sensitivity (71.4%) but with higher specificity (58.6%) than any PCR-based test. The higher the histomorphological dysplasia diagnosis, the better was the accuracy of QG-MPH with >80% for identifying CIN2 and CIN3, and 92% for invasive cancer. The estimation on basis of the German screening algorithm of cost for co-testing, including cytology, HPV testing and colposcopy versus QG-MPH showed a cost savings of more than 50% and a high time advantage. In a LMIC setting the test is suitable for mobile outreach and decentralised point of care testing and treatment due to robust and portable devices.

Conclusions: Conclusion: In this purposively selected well-characterized sample pool, the probe-based, mRNA quantifying QG-MPH dysplasia assay showed comparable results to PCR-based and RNA amplifying assay methods. By inclusion of dysplasia-specific expressed cellular biomarkers and assessment by risk-score formulas, the QG-MPH indicates the severity of the underlying dysplasia from the initial screening smear. Theoretical complexity and cost estimations suggest a health economic benefit. This will be especially important in LMIC where higher HPV prevalences pose a problem for using PCR-based tests with low specificity and in turn induce high cost and workload for triage and diagnosis. Mobile screen and treat approaches will be necessary to reach 70% of all women worldwide. QG-MPH assay was designed to circumvent pathology services and support decentralized local screening.

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#6989

Modeling the cost-effectiveness of cervical cancer screening with HPV self-sampling and molecular triage for women 60-69 years

10 - HPV screening

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Background/Objectives: To estimate the cost-effectiveness of cervical cancer screening for women 60-69 years. Evaluation of screening methods focusing on postmenopausal women is of particular interest, as this group differs from younger cohorts and because the fact that this group is to be released from the screening program. In this cost-effectiveness analysis, the currently implemented Swedish screening strategy is compared with HPV self-sampling strategies with cytology or molecular triage (methylation and/or genotyping) for triaging HPV-positive samples.

Methods: A decision tree was constructed using transition probabilities derived from a Swedish self-sampling study for women 60-69 years. This population-based screening study included women who attended the organized screening with professional sampling and additionally performed vaginal self-sampling. Paired sample types were then analyzed for HPV, triaged with cytology and molecular triage, and followed up according to the national guidelines for screening. The time perspective of this analysis is one screening cycle (from initial screening test to eventual colposcopy), and the main outcome is identified number of HSIL+ (high-grade squamous intraepithelial lesion or invasive cancer) detected in histopathological examinations. Sensitivity analyses will be conducted.

Results: When comparing the current screening program and several self-sampling strategies with molecular or cytology triage, preliminary results indicate that a self-sampling strategy followed by cytology triage is the most cost-effective for this age group.

Conclusions: Molecular triage is described as potentially promising methods for replacing cytology and increasing screening specificity. However, when these methods are evaluated in the older screening population, they appear to be less specific than cytology and lead to a higher colposcopy burden. This prompts further discussions on how these methods can be adapted for older women.

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#6648

MODELING FEASIBILITY AND EFFECTIVENESS OF POINT-OF-CARE LIMITED HPV GENOTYPE SCREENING

10 - HPV screening

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Background/Objectives: Cervical cancer remains a significant cause of morbidity and mortality, especially among women in sub-Saharan Africa, where only 15% of women have undergone screening. To address these substantial screening gaps, the WHO recommends human papillomavirus (HPV) DNA detection as the primary screening method. One strategy to improve screening coverage is the use of limited HPV genotype target tests which can be offered as true point-of-care (POC) tests. However, understanding the conditions under which limited genotype target tests can compete with full high-risk HPV (hrHPV) genotype screening remains a barrier to their development and adoption. We explored the trade-offs between accessibility, retention, costs, and test performance to inform the development of new POC limited genotype target tests.

Methods: We developed a once-off HPV screening model to investigate the potential use cases and required specifications of limited genotype target POC tests. We estimated the proportion of cases of cervical intraepithelial neoplasia grade 2+ (CIN2+) and the testing costs per case identified for three screening scenarios: (1) limited genotype target tests alone, (2) full hrHPV tests, and (3) rule-in limited genotype target tests followed by full hrHPV testing for those screening negative. We compared screening program performance across ranges of screening coverage, genotype target coverage, loss to follow-up, and test price to identify the conditions where limited genotype screening was non-inferior to full hrHPV screening.

Results: When access and retention following full hrHPV screening were high, limited genotype target tests were only competitive at a very low cost. However, with either modest increases (≥5%) in screening coverage with limited target tests or higher loss to follow-up after hrHPV testing (≥19.8%), an 8-genotype target test could identify the same number of CIN2+ cases as hrHPV screening, but must cost less than US $8.50 to be cost-equivalent. Adding hrHPV testing following a rule-in 4-genotype target test would be as effective as full hrHPV screening in the number of CIN2+ cases identified and would be cost-equivalent if the limited genotype target test cost less than US $2.20.

Conclusions: Our modeling supports screening with an 8-genotype target point-of-care HPV test priced at less than US $8.50 for cost-equivalence with full hrHPV screening. A rule-in 4-genotype target test will be cost-equivalent if priced at less than US $2.20. These insights can support product development to enhance screening access and support elimination of cervical cancer in sub-Saharan Africa.

FC07 - Anus

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#6924

Risk Factors for Anal Cancer in Women in a Large Integrated Health System, 2006-2020

27 - Anal neoplasia

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Background/Objectives: Anal cancer incidence rates are increasing in women. There are no national or international screening guidelines for anal cancer, yet experts agree that higher risk groups should undergo screening. Our objective was to determine risk factors for anal cancer among women, that may help to guide screening practices.

Methods: A nested case-control study was conducted among women in Kaiser Permanente Northern California (KPNC). Cases were women with incident invasive anal cancers ascertained from the KPNC SEER-contributing Cancer Registry for those aged greater than or equal to 18 years old with long-term membership history (greater than or equal to 2 years) between 2006-2020. Using the same eligibility criteria, women without cancer were selected as controls at the time when each case occurred (i.e., incidence density sampling), matched 10:1 by age, membership, and KPNC service area. Clinical and demographic factors were ascertained from the electronic health record. We report odds ratios (OR) with 95% confidence intervals (CI) from conditional logistic regression models.

Results: A total of 699 incident anal cancers were identified in women during 2006-2020. Among 699 cases and 6985 controls, Black, Asian/Pacific Islander, Hispanic, and Other race/ethnicity were at decreased risk of anal cancer compared with White women, with ORs and 95% CI, respectively: 0.58 (0.41-0.83), 0.13 (0.08-0.21), 0.56 (0.43-0.74), and 0.27 (0.11-0.66). Factors associated with a decreased anal cancer risk included a negative cervical HPV test in the 4 years prior to the index date compared with those not tested (0.80; 0.65-0.98), and overweight/obesity (0.79; 0.67-0.93) compared with normal/underweight. Factors associated with an increased anal cancer risk included non-HIV immunosuppression (inclusive of Crohn's disease, systemic lupus erythematosus, solid organ transplant, and ulcerative colitis; 2.00; 1.25-3.22), former (1.60; 1.33-1.91) or recent (3.05; 2.4-3.89) smoking versus never smoking, Hepatitis B history (1.70; 1.36-2.13), anal warts (4.59; 1.44-14.63), and non-HPV related anal disease (1.25; 1.05-1.49).

Conclusions: We were able to identify risk factors for anal cancer in a general population of women. Many of the identified risk factors are likely related to HPV acquisition and persistence. More research is needed to understand the racial disparities in anal cancer and to inform targeted screening protocols.

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#7122

The influence of home versus clinic anal human papillomavirus sampling on high-resolution anoscopy attendance in the Prevent Anal Cancer Self-Swab Study

10 - HPV screening

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Background/Objectives: Anal cancer disproportionately affects men who have sex with men (MSM) living with HIV. High-resolution anoscopy (HRA) is an in-clinic procedure that detects precancerous anal lesions and cancer, yet prospective data on HRA attendance are lacking. Our objective was to investigate whether home-based versus clinic-based anal cancer screening was associated with HRA uptake and to examine HRA acceptability.

Methods: The Prevent Anal Cancer Self-Swab Study recruited MSM and trans persons 25 years and older to participate in an anal cancer screening randomized clinical trial. Home participants were mailed an anal self-swab kit and clinic participants received anal swabbing at a clinic. All were asked to attend in-clinic HRA. Using data from those who engaged in baseline screening (n=196), we examined HRA attendance and acceptability.

Results: 62.8% of participants who engaged in screening attended HRA. Although not significant (p=0.13), a higher proportion of participants who engaged in clinic-based screening attended HRA (68.5%) compared to home-based participants (57.9%). Overall, HRA uptake was higher among participants with anal cytology history (aRR 1.44, 95% CI 1.11 - 1.87) but did not differ by race or HIV serostatus. In the clinic arm, persons living with HIV had lower HRA attendance (42.9%) versus HIV-negative participants (73.3%) (p=0.03) and Black non-Hispanic participants had lower HRA attendance (41.7%) than White non-Hispanic participants (73.1%), (p=0.04); however, no differences in HRA attendance by race or HIV status were observed in the home arm. Age was significantly associated with reporting some or a lot of pain during the HRA. Participants ages 25 to 34 years old represented the highest proportion of those who reported some pain or a lot of pain during the HRA (52.0%) compared to other age groups such as those age 55 years and over (28.0%) (p=0.02). Nearly all (95.5%) of HRA participants strongly agreed or agreed that HRA is something they are willing to do.

Conclusions: While important significant differences emerged by HIV status and race among those who engaged in clinic screening, no differences in HRA attendance by HIV status or race were found among those who completed mailed home-based anal HPV self-sampling. Given that persons living with HIV and Black MSM are disproportionately affected by anal cancer, interventions are needed to support their clinic attendance.

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#6658

INTER-OBSERVER AGREEMENT IN THE INTERPRETATION OF ANAL CYTOLOGY

27 - Anal neoplasia

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Background/Objectives: Anal cytology has been proposed as a tool for anal cancer screening in high risk populations, given its quite good accuracy for high-grade lesions. Besides accuracy, one important aspect to be considered is the reproducibility of the interpretation. However, differently from cervical cytology, the inter-observer agreement in anal cytology interpretation has been scarcely investigated. In this study we evaluated the concordance of the anal cytologic interpretation between cytopathologists with expertise in cervical cytology.

Methods: We assessed the inter-observer agreement between two cytopathologists in the interpretation of a series of anal liquid-based cytologic slides from HIV-negative MSM. Cytology was evaluated using the Bethesda system, blinded to HPV test results (Linear Array HPV Genotyping Test, Roche Diagnostics), or individuals' age. In case of a discordant interpretation, the slide was revised and a consensus report was reached. For the agreement, weighted Cohen's kappa (linear weights) and 95% confidence intervals (CI) were calculated.

Results: We analyzed a series of 713 anal thin-layer cytologic slides adequate for interpretation, obtained from individuals with a median age of 33 years (inter-quartile range, IQR: 27-40). Among them, 620 (87.0%) were also genotyped for HPV. Taking into account a dichotomous interpretation, i.e. negative for intraepithelial lesion or malignancy (NILM) vs. atypical squamous cells of undetermined significance (ASC-US) or worse, the crude agreement between the two raters was 93.3% (k=0.82; 95% CI 0.77-0.87). Apart from the only 2 high-grade squamous intraepithelial lesions (HSIL), for which the two observers agreed, the best agreement was found for the 528 NILM (96.8%) and the 66 low-grade squamous intraepithelial lesions (LSIL; 81.8%). The 117 ASC-US cases showed a lower concordance (76.9%). Considering the individual cytologic categories, the overall agreement was 92.1% (k=0.85; 95% CI 0.81-0.89). Agreement of each cytopathologist with the consensus report was very good (k=0.91; 95% CI 0.88-0.94 and k=0.93; 95% CI 0.91-0.96). The discordant interpretations were not associated with High-risk HPV infection and individuals' age. Differently, median number of HPV types, presence of Low-risk types, and, in particular, HPV6 infection, were significantly higher in discordant cases.

Conclusions: We observed a very good agreement between the two cytopathologists who independently evaluated anal cytology in HIV-negative MSM. This is a prerequisite for adoption of cytology as a primary test in anal cancer screening. Disagreement in the interpretation was not associated with High-risk HPV infection.

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#6994

ONCLARITY PERFORMANCE IN HPV DNA DETECTION OF ANAL SAMPLES

27 - Anal neoplasia

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Background/Objectives: Anal cancer is a relatively rare disease in the general population. However, it occurs at a higher rate in specific at-risk groups, including immunosuppressed individuals (e.g. those with HIV or post-organ transplantation), men who have sex with men, and women with HPV-related lower genital tract dysplasia or cancer. The causal link between HPV infection and the development of anal pre-neoplastic lesions and carcinoma is well-established. While HPV detection is not typically performed on anal liquid-based cytology (LBC) specimens, it could be a valuable addition to clinical assessment and patient management. HPV tests are traditionally designed for cervical cytological samples, with clinical cut-off mainly focused on CIN2+ detection. The aim of the present study is to evaluate the performance of the BD Onclarity HPV test genotyping assay on anal samples.

Methods: We enrolled high-risk men and women for anal cancer during endoscopic or gynecological visits at the European Institute of Oncology (IEO) in Milan from September 2022. For each patient, a LBC sample was collected, followed by histology and/or cytology examinations. The Onclarity HPV test was performed on the same LBC sample.

Results: To date,105 patients were enrolled, with 4 samples deemed unsuitable due to the absence of human beta-globin. Preliminary data from 101 samples reveal an overall HPV genotype positivity prevalence of 50%, with HPV16 being the most commonly detected genotype at 36%. Sixteen sample exhibited single infections, while 35 samples showed multiple infections.

Conclusions: Our data indicates a high prevalence of HPV in anal samples among a high-risk population, suggesting the utility of the Onclarity assay in anal cancer screening. Implementing HPV genotyping methods on anal specimens could simplify the screening process for anal cancer without the need for invasive procedures, such as high-resolution anoscopy, and making it more patient-friendly.

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#6840

HOST AND VIRAL GENOME METHYLATION IN DETECTION OF ANAL HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS

27 - Anal neoplasia

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Background/Objectives: Anal cancer is a common cancer in sexual minority men, especially those with HIV. The high incidence of anal cancer makes the choice of an appropriate triage strategy a pressing need for high risk groups. The primary cause in the vast majority of anal cancers is persistent infection with high-risk human papillomavirus (hr-HPV). Hr-HPV genotyping could be used as a potential anal cancer screening tool but its major limitation is a relatively low specificity. Novel, more specific diagnostic biomarkers are needed. In the process of carcinogenesis, human genes and the HPV genome are subject to large changes in DNA methylation and those epigenetic events can be used as a temporal biomarker, with the great potential to predict whether the hr-HPV infection will lead to high-grade disease. We have developed a triage DNA methylation test (S5) for the detection of cervical high-grade lesions, which is based on the DNA methylation levels of HPV16, HPV18, HPV31 and HPV33 combined with the human gene EPB41L3. We investigated the potential of the S5 test to identify anal intraepithelial neoplasia grade 2 (AIN2) or higher (AIN3+) using samples from participants of the Prevent Anal Cancer (PAC) Self-Swab Study. Having access to samples from this unique study, which mimics an anal cancer screening program, allowed us to test the effectiveness of our methylation score as a potential screening tool for high-risk groups.

Methods: HIV+ and HIV- men having sex with men (MSM) and transgender persons were randomised to either home-based self-sampling (HBSS) or clinical sampling in Milwaukee, Wisconsin. From HBSS participants we obtained paired self- and clinician-collected samples at baseline and 12 months, while from clinic arm participants there was one clinician-collected sample at each time point. All participants were offered a clinic-based high-resolution anoscopy (HRA)-directed biopsy with abnormalities classified as low-grade squamous intraepithelial lesions (LSIL) or high-grade squamous intraepithelial lesions (HSIL). HPV genotyping was performed at the Moffitt Cancer Centre and Research Institute. DNA was extracted from all samples and the S5 assays were performed as previously described (Brentnall et al, 2015).

Results: Histopathology results were available for 107 participants including 57 with normal histology, 24 with LSIL (AIN1) and 26 with HSIL (7 AIN2 and 19 AIN3). In clinician-collected samples combined from both study arms the S5 showed good separation between infAIN2 and AIN2+ and infAIN3 and AIN3 for both baseline and 12-month swabs, with the strongest association between score and AIN3 at 12 months (Mann Whitney test, p=inf0.05). A similar but non-significant trend was observed in self-collected samples. S5 scores were similar in paired clinician and self-collected samples (n=124, pinf0.001). Higher methylation levels were observed in HIV+ compared with HIV-participants. Finally, there was a significant difference in methylation scores for participants with persistent hr-HPV infection vs non-persisters (pinf0.05).

Conclusions: Our methylation classifier could potentially be useful as a biomarker of anal disease and tool for screening of high-risk populations.

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#6862

HPV E6/E7-MRNA TESTING FOR THE DETECTION OF ANAL HIGH-GRADE DYSPLASIA IN HIV-POSITIVE MEN

27 - Anal neoplasia

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Background/Objectives: Anal HPV-infection and dysplasia are very frequent in HIV-positive men who have sex with men (HIV+MSM), and progression of low-grade (LSIL) to high-grade lesions (HSIL) occurs faster than in HIV-negative persons. We compared the diagnostic accuracy of high-risk (HR)HPV-E6/E7-mRNA and HR-HPV-DNA-testing for the detection of anal dysplasia in HIV+MSM. Additionally, we monitored the time of HSIL-free survival in a long-term follow-up.

Methods: 3,299 intraanal swabs from 882 HIV+MSM participating in an anal cancer screening program (anal cytology/histology, high resolution anoscopy, HPV-DNA-testing) were collected every 6- to 12 months between May 2010 and November 2021. In the baseline samples HPV DNA genotyping as well as HPV E6/E7-oncogene mRNA-detection of 14 HR-HPV-types (APTIMA® HPV assay, Hologic) were performed. Follow-up samples with cytology/histology and HPV-DNA genotyping were collected from 669 patients up to 120 months after the first visit.

Results: Results: So far, 659 baseline swabs have been evaluated (238 normal, 84 ASCUS, 226 LSIL, 111 HSIL by cytology/histology). For the detection of LSIL+HSIL sensitivity, specificity, negative and positive predictive values were 88.7%, 23.0%, 66.1%, 54.7% for HR-HPV-DNA-testing and 78.6%, 44.4%, 66.5%, 54.9% for E6/E7-mRNA-testing. For the detection of HSIL, the respective values were 95.5%, 19.5%, 95.5%, 19.4% for HR-HPV-DNA-testing and 91.0%, 37.4%, 95.3%, 22.7% for E6/E7-mRNA-testing. 46 of 206 (22.3%) patients with an E6/E7-mRNA-positive swab and a cytology ≤ LSIL at baseline developed HSIL within the next 36 months compared to 7 of 116 (6.0%) of those who were E6/E7-mRNA negative at baseline.

Conclusions: HPV oncogene mRNA detection has an (almost 2-fold) increased specificity and a slightly decreased sensitivity for the detection of anal dysplasia in HIV+MSM compared to HR-HPV-DNA-testing. Furthermore, E6/E7-mRNA detection at baseline could be predictive of future HSIL development and thus could be a useful marker for refining anal cancer screening programs.

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#6537

RECEPTIVE ANAL INTERCOURSE IS ASSOCIATED WITH SEROPOSITIVITY FOR HIGH-RISK HPV AMONG YOUNG MEN WHO HAVE SEX WITH MEN

03 - Epidemiology and natural history

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Background/Objectives: Receptive anal intercourse (RAI) increases the risk for anal HPV among MSM, so RAI might be an important risk factor for seropositivity. However, previous studies showed conflicting results on the association between RAI and seropositivity. It is unclear which risk factors are shared between seropositivity and anal and/or penile DNA-positivity, as no study has assessed these within the same study population. Therefore, we aimed to assess potential risk factors of HPV seropositivity in MSM, and to compare these to risk factors for anal and penile HPV DNA-positivity within the same study population.

Methods: Data of the repeated cross-sectional study PASSYON (2009-2021) were used. Clients of various sexual health clinics throughout the Netherlands aged 16-24 years were invited to participate by completing a questionnaire and by providing samples. For MSM, these samples were an anal and a penile swab, and a venous blood sample. HPV seropositivity, and anal and penile HPV DNA-positivity was assessed for 7 high-risk HPV types. Logistic regression models using GEE were conducted to assess risk factors for sero- or DNA-positivity among MSM who provided all three samples. First including RAI ever, and in a sub-analyses with RAI in the previous six months. Differences in the distribution of type-specific antibody titres in relation to RAI were assessed with Kruskal-Wallis tests.

Results: Among 1,019 MSM, HPV-16 and -18 were the most prevalent HPV types: seroprevalence for HPV-16 was 18.4%, and for HPV-18 this was 15.1%. Seropositivity was more common among MSM reporting RAI ever. Multivariable regression models, including the 657 MSM who provided all three samples, showed a strong association between RAI ever and seropositivity (aOR: 3.50; 95%CI: 1.56-7.88); associations with anal DNA-positivity (aOR: 1.81; 95%CI 0.94-3.47) and with penile DNA-positivity (aOR: 0.86; 95%CI 0.35-2.12) were not statistically significant. RAI in the previous 6 months was significantly associated with seropositivity (aOR: 2.17; 95%CI: 1.44-3.26) and with anal DNA-positivity (aOR: 1.67; 95%CI: 1.09-2.56), but not with penile DNA-positivity (aOR: 0.91; 95%CI: 0.49-1.70). Finally, MSM reporting RAI ever had higher median antibody titres for all genotypes, which was statistically significant for HPV-16/18/33/58.

Conclusions: Recent RAI is associated with anal HPV DNA-positivity, and both RAI ever and recent RAI with HPV seropositivity. Both RAI measures were the strongest associated risk factor for seropositivity in their models. This is suggestive for RAI leading to anal HPV infections and consequently to seroconversion. Further, as the two genotypes that are preventable by three HPV vaccines were most common, and these are most oncogenic, our results underline the importance of gender-neutral vaccination.

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#6899

Anal self-sampling is suitable for anal cancer screening among men who have sex with men in Togo

27 - Anal neoplasia

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Background/Objectives: Anal cancer screening guidelines exist only locally or nationally for some at-risk population like MSM living with HIV. In sub-Saharan Africa, there is no access to anal cytology analysis and proctologic consultations. There is a need to implement HPV detection strategy to screen most at-risk patients. The aim of this study was to evaluate anal self-sampling (ASS) for HPV detection compared to anal swab carried out by the practitioner (ASP) concomitantly.

Methods: In 2021, the ANRS 12400 DepIST-H cohort included 200 MSM in Togo, half living with HIV, prospectively followed up with yearly anal sampling and proctologic exam. During the month-12 (M12) visit, ASS was proposed to MSM before clinical consultation. A flyer explaining the procedure accompanied FloqSwabs®(Copan) for ASS, which was discharged into eNAT®(Copan). The practitioner conducted afterwards anal exam, anal sampling with a cytobrush (Rovers) discharged in ThinPrep®(Hologic). All samples were analyzed by the Virology lab of a French Universary Hospital with AnyplexII® for detection of 14 high-risk HPV (HR-HPV). Albumin quatification was performed with real-time PCR described in (1). HPV16 viral load was quantified with in-house real-time PCR described in (2).

Results: A total of 188 MSM came to the M12 visit, with a median age of 23 years-old. Almost all participants (99%) found the ASS procedure easy to carry out and 60% of them would prefer ASS to ASP at next visit while 19% had no preference. ASS was suitable for HPV detection since only 5% of ASS samples were uninterpretable compared to 7% for ASP (p=0,77). Albumin quatification reports a higher cellularity in ASS than ASP with median quantity of 2.9 ng/mL [0.5-10.0] vs 0.16ng/mL [0.05-0.33], respectively, pinf0.0001. This can be in part explained by the difference of medium volume in which swabs were discharged (1.5 mL for eNAT® and 20mL for ThinPrep®). Overall, at least one HR-HPV was detected in 83% (n=148/178) and 77% (n=135/176) of ASP and ASS, respectively, and 28% and 26% were positive for HPV16. ASP and ASS showed substantial agreement (89.7%) for HR-HPV detection with Kappa's coefficient of 0.66 (Figure 1). The agreement for HPV16 was 90.3% (Kappa's coefficient = 0.75). HPV16 median viral loads were higher in ASS (n=46) than ASP (n=45) (7652c/mL, IQR=[236-232773] vs 575c/mL [135-7052] respectively, p=0.009). Regarding the 16 samples with discordant result for HPV16 detection, HPV16 viral loads were low (119 c/mL [34-7949] for ASS and 13 c/mL [7-114] for ASP in median).

Conclusions: To our knowledge, this is the first time ASS and ASP are carried out concomitantly and compared for HPV detection performance. The concordance of the two sampling methods, the acceptability of ASS and the facility to implement self-sampling are in favor of using ASS for HPV detection in anal cancer screening programs. The HPV detection implementation worldwide for cervical cancer screening following the WHO's 2020 guideline will enable anal cancer screening implementation in LMIC by molecular diagnosis.

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#7631

DETECTION OF PATIENTS WITH RECURRENT HPV-DRIVEN ANAL CANCER USING CIRCULATING TUMOR HPV DNA

27 - Anal neoplasia

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Background/Objectives: Circulating tumor HPV DNA has emerged as a powerful biomarker with established performance in HPV-driven head and neck cancers. Anal squamous cell carcinoma (ASCC), although rare, is an HPV-driven malignancy with steadily increasing incidence over the past decade. Standard-of-care treatment with chemoradiotherapy can result in a complete response for ASCC patients, but up to 30% of patients experience persistent and/or recurrent disease. Here we assessed the performance of the circulating cell-free tumor tissue-modified HPV DNA (TTMV-HPV DNA) test ordered during routine clinical practice for the post-treatment surveillance of patients with ASCC.

Methods: This central IRB-approved retrospective clinical case series included forty-six patients from three U.S. sites who were ≥3 months post-definitive treatment for ASCC and who had one or more TTMV-HPV DNA tests (NavDx®, Naveris Inc., Waltham, MA) between February 2020 and August 2023. TTMV-HPV DNA for HPV subtypes 16, 18, 31, 33, and 35 was analyzed with ultrasensitive droplet digital PCR. Clinical evidence of anal cancer, using anoscopy, radiologic imaging (CT, MRI, PET-CT, endoanal ultrasound) evaluations, and/or tissue biopsy provided the reference method for performance evaluation.

Results: Patients were primarily female (32/46, 69.6%) and HPV positive (39/46, 84.8%), with seven patients having unknown HPV status. Of the thirty-three patients with surveillance TTMV HPV DNA testing, 6/33 had one or more positive tests (18.2% positivity rate; TTMV-HPV DNA Score range: 21-5282). All six of these patients were diagnosed with recurrence. The remaining 27/33 patients (81.8%) did not test positive and had a total of seventy-four negative TTMV-HPV DNA tests, including one patient with recurrent disease. The one patient had a negative TTMV-HPV DNA test followed roughly one month later by a positive biopsy that showed diffuse p16-positivity. Pretreatment testing was positive for HPV16, albeit with a low TTMV-HPV DNA Score of 23. Overall, TTMV-HPV DNA testing demonstrated a per-test sensitivity of 93.8% (95% CI: 81.9-100), specificity of 100%, PPV of 100%, and NPV of 98.6% (96.0-100), in line with what is observed for HPV-driven oropharyngeal cancer. Per-patient sensitivity was 86% (6/7) in this small series.

Conclusions: These findings demonstrate the clinical validity and utility of circulating TTMV-HPV DNA testing in daily clinical practice as an effective surveillance tool for identifying patients with active and occult recurrent HPV-driven ASCC.These data will help inform clinical and guideline-endorsed strategies concerning the inclusion of circulating TTMV HPV-DNA as a biomarker of molecularly detectable HPV-driven anal SCC in the setting of recurrence surveillance.

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#6820

USE OF A CARRAGEENAN-BASED GEL HAD NO IMPACT ON ANAL HPV16/18 VIRAL LOADS IN GAY, BISEXUAL, AND OTHER MEN WHO HAVE SEX WITH MEN.

23 - Risk management

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Background/Objectives: The longitudinal Lubricant Investigation in Men to Inhibit Transmission of HPV Infection (LIMIT-HPV) double-blind, randomized control trial in gay, bisexual, and other men who have sex with men (gbMSM) found that use of a carrageenan-based gel neither reduced acquisition of incident anal HPV infections nor influenced infection clearance. To investigate carrageenan's lack of protective effect, we compared the change in anal HPV16 and HPV18 viral loads following carrageenan use compared to placebo gel use.

Methods: The LIMIT-HPV study enrolled 258 gbMSM (2016-2020) in Montreal, Canada. Participants attended follow-up visits at months 1, 2, 3, 6, 9 and 12, where they provided a nurse-collected anal sample and self-completed an electronic questionnaire on sociodemographic and behavioral risk factors. Samples were tested for HPV using polymerase chain reaction (PCR) assays; HPV16- and/or HPV18-positive samples were assayed for viral load using real-time PCR. We restricted the analyses to participants who had completed at least 4 study visits and had a valid baseline anal sample (n=161, 54 HIV-positive). For participants who had tested HPV16-positive and/or HPV18-positive at least once across visits 1 to 4, we described the change in type-specific viral load between visits 1 and 2 as well as the net change in type-specific viral load across visits 1 to 4 using the median and interquartile range; these were compared between study arms using the Mann-Whitney U test. We conducted the analyses overall and stratified by HIV status.

Results: Of the 161 included participants (mean age 39.1 years), 29 tested HPV16-positive and 10 tested HPV18-positive at least once over the first 4 visits. The HPV16 viral load was lower in the treatment than placebo arm at baseline; however, at visits 2 to 4, the mean was higher in the treatment than placebo arm. The HPV18 viral load was higher, on average, in the treatment than placebo arm at baseline and over visits 2 to 4. The median change in HPV16 viral load between visits 1 and 2 was similar between study arms (0.00 versus -0.01 copies/cell, P=0.36), whereas that for HPV18 was higher in the treatment than placebo arm (0.92 versus 0.24 copies/cell, P=0.83). The median net change in viral load across visits 1 to 4 was higher in the treatment than placebo arm (HPV16: 0.68 versus 0.18 copies/cell, P=0.60; HPV18: 18.32 versus 10.12 copies/cell, P=0.52). Results did not differ by HIV status.

Conclusions: Carrageenan use did not impact anal HPV16 or HPV18 viral load in HIV-negative or HIV-positive gbMSM.

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

27 - Anal 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.

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

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

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Circulating tumor tissue modified viral-human papillomavirus DNA (TTMV-HPV DNA) is a biomarker of response to pembrolizumab in anal cancer

08 - Immunotherapy - Immuno-oncology - New treatments

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Background/Objectives: Anal squamous cell carcinoma is a rare gastrointestinal malignancy associated with human papillomavirus (HPV) in more than 90% of cases. HPV circulating tumor (ct)-DNAis an emerging biomarker for monitoringsome HPV-driven cancers, however, its role in anal cancer remains undefined. We investigated the efficacy of pembrolizumab in patients with anal cancer and aimed to determine whether a specific type of HPV ctDNA that employs fragment size profiling analysis (tumor-tissue modified viral [TTMV]-HPV DNA) is a feasible biomarker of disease response.

Methods: We conducted a multicenter, single-arm phase II clinical trial (NCT02919969) of pembrolizumab in patients with advanced anal cancer (n=32). Enrolled patients had metastatic or locally advanced incurable anal squamous cell carcinoma and received pembrolizumab 200 mg IV every three weeks. The primary endpoint was objective response rate (ORR) by RECIST v 1.1, and exploratory objectives included analysis of TTMV-HPV DNA (NavDxTM, Naveris, Waltham, MA) using serially collected plasma samples. Clinical benefit rate (CBR) was defined as best response of complete response (CR), partial response (PR), or stable disease (SD) ≥ 6 months. Progression-free survival (PFS) was defined as time from first dose of therapy to progression or death. The date of second plasma blood draw was used as the landmark initial timepoint for PFS of change in TTMV-HPV DNA score.

Results: The investigator-assessed ORR was 9.4% (95% CI: 2.0-25.0) including 1 CR and 2 PR.The CBR was 21.9% (95% CI: 9.3-40.0). Median PFS was 2.2 months (95% CI: 1.9-4.1). TTMV-HPV DNA was detected in 86.2% (25/29) of patientswithabaseline sample available (score range: 4-2,462,500). Pre-treatment TTMV-HPV DNAscores positively correlated with greater tumor burden, as defined by baseline RECIST measurements (Pearson coefficient, r=0.71, p<0.0001) and were significantly associated with clinical benefit (median score372 in those with clinical benefit versus 35,046 in patients without benefit, p=0.01).The percentage change in TTMV-HPV DNA score from baseline to cycle 3 (6 weeks) was significantly associated with clinical benefit to pembrolizumab (median 72% decrease in TTMV-HPV DNA scorewith clinical benefit versus 70% increase of TTMV-HPV DNAscorewithout benefit, p=0.01). No patients with a CR, PR, or SD ≥ 6 months had an increasing TTMV-HPV DNA score at the start of cycle 3. Patients who had a decreasing TTMV-HPV DNA score at 6 weeks had a median PFS of 3.0 months (95% CI: 0.66-11.9) versus 0.7 months (95% CI: 0.6-2.5) in patients with a rising TTMV-HPV score (HR: 0.37; 95% CI: 0.14-0.99, log-rank p=0.04).The patient with a CR had a detectable TTMV-HPVDNA score at baseline which became undetectable by 18 weeks of treatment (26 weeks prior to radiographic resolution of disease). The patient completed two years of pembrolizumab and continues to have no evidence of disease 5.3 years after enrollment.

Conclusions: Pembrolizumab is efficacious in a subgroup of patients with anal cancer, and TTMV-HPV DNA appears to be a circulating biomarker ofimmunotherapy response, representing a dynamic monitoring tool with the potential to enable rapid assessment of therapeutic response ahead of radiographic assessment of disease.

FC08 - Epidemiology I

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GLOBAL BURDEN OF CERVICAL HPV INFECTIONS AMONG OLDER WOMEN WITH NORMAL CYTOLOGY (A SYSTEMATIC REVIEW AND META-ANALYSIS)

03 - Epidemiology and natural history

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Background/Objectives: Cervical cancer is the fourth most incident cancer in women worldwide, with incidence peaks reported in women outside of the screening age in some countries. Given the higher mortality rates among older women, their lower self-perceived risk, and the lack of up-to-date data on HPV infections, we conducted a systematic review and meta-analysis aiming to estimate the global HPV prevalence among women aged 50 years and older with normal cytology.

Methods: We searched three databases (PubMed, Scopus, and Web of Science) for quantitative studies reporting HPV prevalence among women 50 years and older with normal cytology findings published until 31 May 2022. Two researchers independently extracted information on study characteristics and prevalence. The risk of bias was assessed using a modified Newcastle-Ottawa Scale (NOS). The pooled prevalence and 95% confidence intervals (95%CI) of any-HPV and high-risk (HR)-HPV were estimated using random-effects models. The prevalence was also estimated by world region and subregion, HPV testing method, and recruitment setting. These predictors, as well as number of HPV types tested, study year and risk of bias were considered in multiple meta-regression models. Additionally, we estimated pooled HPV prevalences by 5-year age groups and HPV genotyping prevalence overall and by world region.

Results: We identified a total of 9 099 articles, of which 130 were included in the qualitative synthesis. The studies were mainly conducted in Asia (33.8%), the Americas (28.5%), and Europe (28.5%). Africa and Oceania were underrepresented with only 6.2% and 2.3% of the studies, respectively. We estimated a global pooled any-HPV prevalence of 12% (95%CI, 10-14%) and an HR-HPV prevalence of 6% (95%CI, 5-8%). The HPV prevalence varied across geographical regions, with the highest estimates in Western and Middle Africa and Central America and the lowest in Western Europe. Worldwide, HPV estimates declined after age 55, rose slightly at 65-74, and then decreased again. HPV types 16 and 53 were the most prevalent among older women with normal cytology globally.

Conclusions: Considering the substantial HPV burden among older women, higher HPV persistence and higher mortality from cervical cancer, a re-evaluation of the current screening guidelines should be considered. Additionally, more research is needed, focused specifically on older women, to further explore the HPV burden in certain regions (e.g. Africa, Oceania) and patterns of HPV persistence and reactivation to better estimate cancer risk.

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#6907

Routine program audit of cervical cancer to identify remaining risks and guide elimination efforts

03 - Epidemiology and natural history

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Background/Objectives: Recurrent audits of the screening process are recommended in the European Guidelines for Quality Assurance in Cervical Cancer Prevention 2008 in order to systematically monitor and evaluate cervical cancer screening. Audits have been reported in studies covering 1999-2011 with validated, registry-based data to evaluate cervical cancer risk in the population, stratified by screening status, history, and clinical work-up. Presented here is a model for routine annual audits that has been adopted and implemented nationally.

Methods: All cancer cases between 2018-2021 were collected from the Swedish Quality Register of Gynecological Cancer (SQRGC) where date of diagnosis, age, FIGO stage, histopathology, and mode of treatment were registered. Data on screening invitations and screening history and status were collected from the National Cervical Screening Registry (NKCx). Process related causes related to organization and sampling, lab procedures or management of positive tests was interpreted from register data. Case confirmation and verification of process-related causes was performed by reviewing local medical charts. Incidence of cervical cancer was estimated by risk group to demonstrate where improvements in the screening program chain are needed.

Results: Data from the register are stable with more than 98% conformity between register data and medical records. Advanced cancer cases are still dominating, especially among older women, who have left the screening program without a negative HPV-test, and who have a late detection by symptoms. However, cancers cases in younger women are mostly screen detected in early stages allowing for fertility preserving treatments. All cases were classified according to where in the chain of events there have been failures related to development of cancers (process-related causes); failure in screening invitations and participation, deficiencies in detection of abnormalities in screening samples or triage, and/or deficiencies in investigation of screening detected abnormalities, or in treatment or long time follow up. The dominating cause of cancer is failure in screening participation. The sensitvity of cytology has decreased in the last decade, manifested as that about 26% of cervical cancer cases can be explained by deficiencies in detection of abnormalities in samples. Many cancer cases can be explained by delayed or insufficient management of abnormalities.

Conclusions: Annual national register based audits with local review of clinical charts are an important part of screening program quality assurance and can be used to identify patterns of increased risk. Differences in incidence between different regions and over time can be demonstrated and adjustments of guidelines could be performed after analyses of audit data. Annual national audits like the Swedish model should be performed to routinely identify patterns of increased risk and guide program optimization.

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#6620

HIGH-RISK HPV AND CERVICAL DYSPLASIA IN INTRAUTERINE DEVICES USERS AND CONTROLS: A CROSS SECTIONAL STUDY

03 - Epidemiology and natural history

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Background/Objectives: Intrauterine devices (IUDs) are common contraceptive methods for women globally, and both the copper-containing IUD and the hormonal IUD, are highly effective in preventing pregnancy, but their side effects, positive as well as negative, differ (1). A meta-analysis published in 2017 found that women who reported ever use of an IUD were less likely to develop cervical cancer (OR 0.64; 95% CI 0.53, 0.77), but this meta-analysis was unable to examine the influence of IUD type (2). The mechanisms behind this is unclear. It is speculated that the insertion of IUD induce a cellular immune response that might clear HPV infections and preinvasive lesions, and that the copper-containing IUD is associated with a higher clearance rate compared with the hormonal IUD (3). In the HPV based screening programme for cervical cancer in the Region Örebro County, Sweden, the participating women report the use of contraceptive methods at the time of the screening. This provides a unique opportunity to analyse HPV status and cervical dysplasia in relation to contraceptive method. The objective of this study was to examine the prevalence of high-risk human papillomavirus and cervical dysplasia, and the clearance rate of HPV infections, in users of different kinds of IUDs and other contraceptive methods.

Methods: A cross-sectional register-based study was performed that included all women aged 30-49 years who participated in the screening programme for cervical cancer in Region Örebro County in 2017-2018. Data on contraception from their screening records was paired with the HPV test results, eventual cytological and histological follow-up tests and subsequent HPV test.

Results: The odds for an HPV-positive screening test were not significantly different in users of copper-containing IUD compared to women with no reported use of contraception (aOR 1.01; 95% CI 0.81-1.27). Use of hormonal IUD and hormonal contraception were associated with higher odds for HPV infection when adjusted for age (aOR 1.21; 95% CI 1.04-1.41, aOR 1.41; 95% CI 1.22-1.63, respectively). The odds for histological HSIL+ were significantly higher among women using hormonal contraception, aOR 1.56 (1.13-2.16 95% CI) or hormonal IUD, aOR 1.45 (1.02-2.06 95% CI), but not in women using copper-containing IUD. No significant differences were found in HPV clearance rates in different contraception groups. No data on condom use, number of sexual partners, smoking or other risk factors were available.

Conclusions: Hormonal IUD and hormonal contraception were associated with a higher prevalence of HPV infections and histological HSIL+ compared to no reported use of contraception or use of copper-containing IUD.

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#6885

Association between female lower genital tract pathogen infection and the persistence of cervical high-risk HPV

03 - Epidemiology and natural history

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Background/Objectives: To explore the effects of different non-HPV sexually transmitted infections (STIs) on hrHPV persistence in a female population detected with baseline hrHPV infection

Methods: From 2018 to 2019, 3128 women from southwest China were recruited for cervical cancer screening. After informed consent, a one-on-one questionnaire survey was conducted, and cervical exfoliated cell specimens were collected for high-risk HPV (hrHPV) detection and cytological diagnosis. The leftover of cytological samples was transferred to the ultra-low temperature refrigerator at -80℃ for storage. Women who tested positive for hrHPV or had a cytological diagnosis of abnormality (baseline period) were followed up annually. There were 503 out of 3128 women tested hrHPV positive at baseline, and a total of 489 baseline hrHPV-positive women were followed up for 3 years, of whom 245 completed continuous follow-up. During follow-up, exfoliated cervical cytological specimens were collected and hrHPV testing was performed. High-risk HPV persistent infection is defined as two continuous positive tests within the corresponding interval, for example, 12 months of persistent infection is defined as two positive HPV tests within the interval of 12 months. Based on the leftover of cytological specimens at baseline, STIs were detected by next-generation sequencing, which identifies Chlamydia trachomatis (CT), gonorrhoeae (NG), ureaplasma Uticyticum (UU), herpes simplex II (HSV2), Mycoplasma hominis (Mh), Mycoplasma genitalium (MG), and ureaplasma micus (UP), simultaneously.

Results: The persistent rates at 12th, 24th and 36th months were 61.9%, 54.8% and 43.9% for 14 types of hrHPV, 51.3%, 34.4% and 24.1% for HPV16/18, 60.3%, 53.3% and 42.9% for other 12 types of hrHPV, respectively. Stratified by STI infection status, the persistent rates of hrHPV infection at 12th, 24th and 36th month were 60.9%, 50.0% and 40.0% in women with baseline hrHPV-positive & STIs negative, and 59.8%, 47.1% and 38.5% in women with baseline hrHPV-positive & STIs single infection, and 64%, 63.2% and 50.8% in women with baseline hrHPV-positive & STI multiple infection, respectively. There was significant difference in 24-month hrHPV persistence rate among STI negative, single infection and multiple infection (P=0.029). The 24-month hrHPV persistence rate of the other 12 types of hrHPV-positive in women coinfected with STIs negative, STIs single infection and multiple infection was statistically different (P=0.045), which were estimated at 47.6%, 46.1% and 61.9%, respectively.

Conclusions: Women who were detected with hrHPV positive coinfected with multiple STIs had higher risk of hrHPV persistence, and surveillance should be strengthened for this part of the female population.

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#6770

HPV16/18 VIRAL CLEARANCE AND PROGRESSION TO CIN2+ AMONG WOMEN AGED 18-25 YEARS ENROLLED IN THE COSTA RICA HPV VACCINE TRIAL

03 - Epidemiology and natural history

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Background/Objectives: Cervical cancer is a leading cause of cancer death among women worldwide. Limited access to preventive interventions (vaccination against HPV and screening and treatment of pre-cancerous lesions) presents a challenge for global cervical cancer control, particularly in low-resource settings. Therapeutic vaccines are an emerging secondary prevention strategy that can become an additional tool to address the growing public health problem. Therapeutic HPV vaccines phase II trials have shown partial efficacy on the histological resolution of cervical intraepithelial neoplasia (CIN) grades 2 or 3. Other endpoints considered are immunological outcomes (e.g., HPV-T cell response) and DNA viral clearance. We provide data on DNA viral clearance and progression to CIN2+ in women aged 18-25 years from Costa Rica to inform assumptions underlying therapeutic HPV vaccine trials.

Methods: Costa Rica Vaccine Trial (CVT), a randomized, double-blind, controlled trial, was designed to assess the efficacy of a bivalent HPV vaccine for the prevention of cervical HPV16/18 infection and associated precancerous lesions. At each study visit, sexually active women underwent pelvic examinations to collect cervical cells for cytological assessment and HPV DNA. Women with abnormal cytology were referred to colposcopy, biopsy, and treatment as needed. Broad-spectrum PCR-based HPV DNA testing was performed on all collected cervical samples. This analysis included 646 women who tested HPV16/18 DNA positive at the enrollment visit. Inclusion was independent of treatment assignment because prophylactic HPV vaccination does not change the natural history of existing infections. Clearance was calculated as the percentage of women with prevalently detected cervical HPV16/18 infections that cleared the infection by months 6, 12, and 24. Progression of prevalently detected cervical HPV16/18 infections was estimated as the percentage of women with a CIN2+ diagnosis by months 12 and 24, based on histological findings by expert pathologists. Progression analysis excluded women with high grade squamous intraepithelial lesions or CIN diagnosed at the enrollment visit.

Results: At enrollment, there were 676 prevalently detected HPV16/18 infections (458 HPV16, 158 HPV18, and 30 positive for both HPV16 and HPV18). Overall, 29.1% (95%CI 22.9-35.2) and 46.5% (31.9-61.1) of the women cleared a prevalently detected HPV16 and HPV18 infection, respectively, over approximately 6-months after initial detection. The majority cleared the HPV16 and HPV18 prevalent infections by month 24 [79.6% (61.6-97.6) and 89.3% (47.8-100), respectively] (Table 1). Among women with prevalently detected HPV16 infections, 4.2% (2.5-6.5) progressed to CIN2+ by 12 months [median 13.3 (interquartile range, IQR 9.0-17.5) months] and 6.7% (4.5-9.4) progressed to CIN2+ by 24 months [17.8 (IQR 11.6-25.8)]. In women with prevalently detected HPV18 infection, 1.3% (0.2-4.1) progressed to CIN2+ by 12 months [12.7 (IQR 7.9-18.1)] and 1.9% (0.5-5.1) progressed to CIN2+ by 24 months [19.2 (IQR 9.7-25.7)].

Conclusions: Our data confirms that 80-89% of the prevalently detected HPV16/18 infections clear by 24 months in a cohort of healthy women aged 18-25 years. Less than 7% of the women with prevalently detected HPV16/18 infection progressed to CIN2+ by 12 to 24 months of follow-up. These data suggest that viral clearance of HPV16/18 and/or progression to CIN2+ may be useful endpoints for therapeutic vaccination trials.

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#6888

ANALYSIS OF HUMAN PAPILLOMAVIRUS (HPV) GENOTYPE-SPECIFIC VIRAL LOADS ASSOCIATED WITH SEVERITY OF CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)

15 - Molecular markers

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Background/Objectives: The introduction of molecular methods for the triage of HPV-positive women, such as high-risk HPV (hrHPV) genotyping and genotype-specific viral load, could improve the risk stratification of HPV-positive women reducing the number of unnecessary colposcopies and biopsies. This ongoing study investigates the role of these possible biomarkers for the stratification of cervical lesions.

Methods: Liquid-based cervical cytology (LBC) samples collected from women referred to colposcopy and undergoing biopsy and/or conisation with a single hrHPV infection were investigated. All specimens were analysed using Fluent 480 liquid handler, in combination with Quick-DNA/RNA MagBead for nucleic acid extraction and OncoPredict HPV® Quantitative (QT) assay for the determination of 12 hrHPV genotype-specific viral loads. Viral loads were expressed as hrHPV copies/104 cells.

Results: Presently 175 cervical samples from women with documented single-genotype infections have been analyzed; 104 (59.4%) of these women showed associated high-grade lesions (infCIN2) and 71 (40.6%) low grade CIN (infCIN2). A different distribution of high-risk HPV genotypes was observed among the two groups of women as reported in Figure 1. Analyzing the results obtained for the most common genotype detected, HPV16, a higher percentage of positivity was observed among women with supIN2 lesion (49/104; 47.1%) compared to women with infCIN2 (16/71; 22.5%). In general, high-risk HPV types showed median viral load values which differed among genotypes. Moreover, in women with HPV16 infections higher median viral loads were associated with infCIN2 as compared to infCIN2 lesions (1.93E+04 vs 8.98E+03 copies/104 cells).

Conclusions: Preliminary data on women with single hrHPV infections have indicated the possible use of genotyping and genotype-specific viral load cut-offs for cervical lesion stratification. Future analysis involving a greater number of samples will provide a better understanding on the possible role of these two molecular biomarkers.

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#6646

RECONSTRUCTING PATTERNS OF HUMAN PAPILLOMAVIRUS AGE-SPECIFIC PREVALENCE IN EUROPE

39 - Public health

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Background/Objectives: Age-specific human papillomavirus (HPV) prevalence data are crucial for stakeholders to predict the future impact of public health policies. However, in the European Union (EU), the availability of this data is heterogenous across countries (and sometimes missing) therefore evaluating the impact of HPV vaccination or HPV-based screening can be challenging. This study reviewed type- and age- specific HPV prevalence data in the EU and identified clusters of countries sharing similar patterns to fill in the needed missing information on HPV prevalence.

Methods: Publications used for our analysis were selected in two steps. First, we systematically reviewed studies from 2009 to 2022 assessing type- and age- specific HPV prevalence in normal or general population, in EU countries. A second search, for countries without recent data, was conducted for papers published prior to 2009. The studies identified were then selected using a quality algorithm, assessing the sample population, and the availability of the aggregated age-prevalence data. For studies without HPV16-specific data, imputation was performed from available high-risk (hr)HPV data considering the proportions of hrHPV subtype prevalence. Finally, model-based clustering methodology was applied to group countries with similar HPV16 trajectories (in 2 to 4 typical groups) accounting for statistical heterogeneity. The final cluster was selected according to BIC criteria (adequacy of data) and the epidemiological relevance of the clusters obtained.

Results: A total of 28 studies were included, representing 20 EU countries and 467 704 women. For 16 EU countries, HPV16 age-specific prevalence trajectories were imputed from hrHPV data. Overall, prevalence trajectories were similar across European countries. The optimal cluster selection produced 3 typical patterns which were mainly differentiated by varying HPV prevalence rates at age 20.

Conclusions: The findings of our study showed that the level of heterogeneity in the trajectories of age-specific HPV16 prevalence across Europe was limited: EU countries could be clustered into 3 mains categories based on their similar HPV age-specific prevalence trajectories differing mainly in magnitude. These trajectories can be used to model typical EU countries, and fill gaps for countries without HPV age-prevalence information using similar geographical or sexual behaviour data. Although good quality HPV type-specific prevalence surveys are crucial for informing cervical cancer control strategies, our results provide the missing information for EU countries to evaluate the impact of cancer prevention policies.

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#6432

HIGH PREVALENCE OF HUMAN PAPILLOMAVIRUS AT DIFFERENT STEPS OF ASSISTED REPRODUCTION TECHNOLOGY PROCEDURES: A MULTICENTER PROSPECTIVE STUDY -AMPAMAVIR

40 - Fertility and HPV

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Background/Objectives: Despite human papillomaviruses (HPV) are mostly transmitted via sexual activity, no recommendation exists on the risk related to HPV during Assisted Reproductive Therapies (ART) procedures. The main objective of this prospective multicenter study was to evaluate the HPV prevalence at the different steps of an ART program. Secondary objectives investigated the correlation between HPV detection and infertility or ART outcomes.

Methods: 914 consenting couples enrolled in ART in Saint-Etienne and Bordeaux University Hospitals were included. HPV DNA testing was performed and typed in semen, cervicovaginal smears (CVS), follicular fluids (FF), embryo culture media (ECM) and newborns.

Results: The prevalence of HPV DNA was 14.8% in semen (13.2% in seminal plasma and 1.6% in the final sperm fraction) and 19.1% in CVS. As previously reported, sperm mobility was impaired by the presence of HPV DNA in semen (p=0.04). The percentage of high-risk genotypes (mainly 31, 39, 51 and 52) was 63.7% and 65% in semen and CVS, respectively. Among HPV positive women enrolled in an ART program, 26.5% of FF and 9.1% of ECM were also tested positive for HPV DNA (without HPV transmission to newborn in the 4 resulting pregnancies). At birth, 4 of 253 newborns tested positive for HPV at the throat level. No correlation was found between HPV detection and procreation success.

Conclusions: Our findings highlight the huge prevalence at several stages of ART procedures and raise the question of a revision of guidelines in Reproductive Biology related to the management of HPV positive samples.

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#6639

Time trends in human papillomavirus prevalence and genotype distribution in vulvar carcinoma in Norway

26 - Vulvar diseases and neoplasia

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Background/Objectives: Approximately 25-43% of all vulvar carcinomas are associated with human papillomavirus (HPV). In many countries, vulvar carcinoma incidence rates are increasing, possibly due to higher HPV exposure. However, studies exploring changes in HPV prevalence and genotype distribution in vulvar carcinoma over time are scarce. Our aim was to evaluate time trends in HPV prevalence and genotype distribution in vulvar squamous cell carcinoma in an unselected, nation-wide sample of Norwegian women. Further, we explored clinical and histopathological aspects in relation to HPV status and investigated if HPV status was associated with survival.

Methods: All vulvar squamous cell carcinoma cases from 1970-75 and 2000-05 were extracted from the Cancer Registry of Norway and corresponding tissue blocks were retrieved. After detailed histology review, HPV testing was conducted using real-time TaqMan PCR. Overall survival rates were calculated using the Kaplan-Meier method. Multivariable Cox regression analysis was performed to estimate hazard ratios adjusted for age at diagnosis, stage and diagnostic period.

Results: Histological review was performed on 352 vulvar squamous cell carcinoma cases. For 282 cases, we were able to obtain valid HPV analysis results. Overall, 29.8% (95% CI: 24.5%-35.5%) of cases were high-risk HPV (hrHPV)-positive. When comparing the two periods, we found that the percentage of hrHPV-positive tumors increased significantly from 23% (95% CI: 16.0%-31.4%) in 1970-75 to 35.3% (95% CI: 27.8%-43.3%) in 2000-05 (P = 0.025). The predominant genotypes were HPV 16 (73%), 33 (21%), and 18 (6%) with similar distributions in both periods. In the more recent cohort, several additional genotypes were detected: HPV 6, 11, 39, 45, 52, 58, and 66 were found in smaller percentages, ranging from 1.8% to 3.6%. In univariate analysis, patients with HPV-positive tumors showed improved overall survival compared to patients with HPV-negative tumors (HR=0.65; 95% CI 0.48 - 0.86).

Conclusions: The prevalence of HPV in vulvar squamous cell carcinomas in Norway was significantly higher in 2000-05 compared to 1970-75. The three predominant genotypes were HPV 16, 33, and 18 in both time periods. However, several other HPV genotypes have emerged over the last decades. HPV-positivity was associated with better overall survival.

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FC09 - Epidemiology II

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#6690

SEX-SPECIFIC DIRECTIONALITY OF TRANSMISSION OF HPV INFECTION IN RECENTLY FORMED HETEROSEXUAL COUPLES

32 - HPV transmission

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Background/Objectives: While HPV is mostly perceived as a women's health issue, HPV infection is also common in males. Studies indicate that transmission rates are higher from females to males than from males to females. Rates of new HPV infections in females decline after early adulthood, but in males, remain constant through adulthood [1]. We calculated sex-specific rates of HPV first incidence, persistent incidence (total number of detections of an HPV type not present at baseline), and transmission, in newly formed heterosexual couples and determined sex-related directionality, and the effect of HPV vaccination on that directionality.

Methods: We used data from the Transmission Reduction and Prevention with HPV Vaccination study, a randomized, double-blinded, controlled trial that enrolled couples aged 18-45 (2014-2022) in Montreal, Canada, who were together for ≤ 6 months pre-enrolment. Participants were randomized to receive the intervention HPV vaccine (quadrivalent or nonvalent after July 15, 2015) or active control (hepatitis A vaccine). Genital samples were collected at enrolment and at 2, 4, 6, 9, and 12 months; they were tested for 36 HPV types (Linear Array assay). Participants filled out self-administered electronic questionnaires at each visit, providing information on sociodemographic factors, sexual behaviors, and sexual health history. We calculated male/female rate ratios (RR) and 95% confidence intervals (provided below in parentheses) via survival analysis for all three outcomes. We used the following units of analysis: 1) type-specific HPVs; 2) any HPV; 3) HPVs grouped by subgenera (subgenus 1 - low oncogenicity, subgenus 2 - high oncogenicity, and subgenus 3 - commensal); and 4) grouped vaccine-target HPVs (6, 11, 16, 18, 31, 33, 45, 52, and 58), stratified by HPV vaccination status.

Results: Incidence: Type-specific RRs were above 1 for 24 out of 33 HPV types detected. The RR was 1.24 (0.97-1.60) for all HPV types combined. For grouped vaccine-target HPVs, the RR was 1.94 (0.91, 4.11) among unvaccinated participants and 1.58 (0.59, 4.24) among those who received the HPV vaccine. Specifically for HPVs 16 & 18, the RR was higher among unvaccinated than vaccinated participants [4.58 (0.54- 39.21) vs 1.21 (0.24-5.97)]. Persistent incidence: Type-specific RRs were above 1 for 18 out of 33 types detected. The RR was 1.01 (0.83, 1.23) for all HPV types combined. For grouped vaccine-target HPVs, the RR was 1.88 (1.03, 3.41) among unvaccinated participants and 0.82 (0.39, 1.70) among those who received the HPV vaccine. Specifically, for HPVs 16 & 18, the RR was higher among unvaccinated than vaccinated participants [9.01 (1.15, 70.38) vs.0.67 (0.23, 2.01)]. Transmission: Type-specific RRs were above 1 for 16 out of 25 types for which transmission occurred. The RR was 1.60 (1.02, 2.51) for all HPV types combined. For grouped vaccine-target HPVs, the RR was 4.01(1.00, 16.04) among unvaccinated participants and 2.29 (0.42, 12.5) among those who received the HPV vaccine. There were no transmissions of HPV 16 or 18 to females.

Conclusions: Results shed light on HPV transmission dynamics and may help inform optimal vaccination policies. Findings indicate that, in new relationships, there is a preponderance of risk for males being more likely to acquire HPV infections than females, but vaccination nullifies this directionality. These findings support gender-neutral vaccination and indicate that there are benefits to vaccination for adult males.

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#6903

OTHER HPV RELATED CANCERS ARE INCREASING AND NOW EXCEEDS CERVICAL CANCER INCIDENCE RATES IN NORWAY: A POPULATION-BASED REGISTRY STUDY

03 - Epidemiology and natural history

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Background/Objectives: Human papilloma virus (HPV) is the most common sexually transmitted virus, and persistent infection with high-risk types may cause cancer [1]. Each year, about 600 new cases of HPV-related cancers are reported in Norway. About half of these are cervical cancer (CC) [2]. HPV-related cancers in other sites are steadily increasing, especially oropharyngeal cancers (OPC), and this is likely caused by increased prevalence of HPV infections acquired through sexual behavior [3]. In Norway, HPV-vaccine was implemented in the childhood vaccination program for girls in 2009, and for boys in 2018. Girls below 26 years of age were also offered a two-year catch-up vaccination starting in 2016. HPV vaccination programs are now starting to make an impact on CC incidence, but for other HPV-related cancers it is still several years away.

Methods: This is an observational registry-based study. Incident cases of HPV-related cancers (CC, vulva-, vagina-, oropharyngeal-, anal- and penile cancer) during 2020-2022 were extracted from the Cancer Registry of Norway. For the main analyses we used incidences of SCC and adenocarcinoma (ADC) for CC, and SCC for the other HPV-related cancers. To estimate the number of cases attributable to HPV, we multiplied the total number of incidences for each cancer type with the following HPV attributable fractions: CC: 100% of SCC and ADC, vulva: 69%, vagina: 75%, oropharynx: 70%, anus: 91%, penis: 63%, based on [4].

Results: Figure 1 shows the incidence of HPV-related cancers from 2000-2020 in Norway. Among women, CC is by far the most common HPV-related cancer type and the only one that shows a decreasing trend (Figure 1 A).Among men, all HPV-related cancer types are steadily increasing, and the greatest increase is seen for oropharyngeal cancer (Figure 1 B). The combined incidence of SCC of the oropharynx, anus, vulva, vagina, and penile cancer surpassed the incidence of SCC and ADC of the cervix around 2008 (Figure 1 C). Adjusting for HPV attributable fraction for every cancer type, we found that from 2015 HPV caused more other types of cancers than CC, and in 2022 the difference was 43% (Figure 1D).

Conclusions: The incidences of other HPV-related cancers are steadily increasing over time and recently exceeded the incidence of CC in Norway. The greatest increase is seen in oropharyngeal cancers among men. Due to vaccination, the prevalence of CC is only now beginning to decline in Norway. Other nations with long-standing national vaccination programs have already observed this trend [5]. As more HPV-vaccinated cohorts reach cancer ages, CC rates should continue to decline. The incidences of other HPV-related malignancies are predicted to keep rising. This is due to the fact that these cancers often develop at a considerably older age than CC and that HPV-vaccination for boys began several years later than for girls, suggesting that the impact of vaccination on other HPV-related conditions will not be detected for several years.

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#6752

LONGITUDINAL ANALYSIS OF CERVICAL INTRAEPITHELIAL NEOPLASIA PROGRESSION AND REGRESSION AMONG WOMEN WITH HIV IN ZAMBIA

03 - Epidemiology and natural history

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Background/Objectives: Cervical cancer screening tests and treatment of precancerous lesions perform inferiorly among women living with HIV (WLWH) compared to women without HIV. The dynamics of high-risk (HR) human papillomavirus (HPV) infection and cervical disease among regularly screened WLWH are poorly understood. We describe the prevalence of HR-HPV and cervical disease at two time points over 36 months and examine factors potentially associated with cervical disease persistence, progression, or regression.

Methods: We included women who participated in a cervical screening test accuracy study in Lusaka, Zambia, in 2019-2020 (baseline) and at a follow-up visit (30-36 months). All included women had cervical biopsies taken at both time points and had complete cervical histology results available at baseline and follow-up. We also assessed the HR-HPV status on liquid-based cytology at baseline and follow-up using GeneXpert (Cepheid, Sunnyvale, CA). Histological results were categorized into normal, low-grade disease (LSIL), and high-grade disease (HSIL). All women who were CIN2+ on histology or VIA-positive were offered treatment. We also asked all women if they received precancer treatment outside the study, and included that data at follow-up. Based on women's cervical disease state at baseline and follow-up, we categorized them into women with disease persistence, progression, or regression. We assessed the cervical disease distribution at baseline and follow-up and performed a multivariable multinomial logistic regression to identify factors potentially associated with cervical disease persistence, progression, and regression. We set disease persistence as the reference category for the multinomial logistic regression.

Results: We included 241 WLWH (median age: 38 years; interquartile range [IQR] 32-45) who returned for a follow-up visit after a median duration of 34 months (IQR: 31-37). The prevalence of any HR-HPV reduced from 44% (95% confidence interval [CI] 38-51%) at baseline to 26% (95% CI 19-31%) at follow-up. Similarly, the proportion of women with high-grade disease decreased from 25% (95% CI 20-31%) at baseline to 9% (95% CI 5-13%) at follow-up. In an analysis adjusted for age, CD4 cell count, HIV RNA viral load, and precancer treatment, HR-HPV infection at baseline did not show a strong association with either cervical disease progression (odds ratio [OR] 1.10, 95% CI 0.53-2.27) or regression (OR 0.93, 95% CI 0.47-1.81; Table). Women who underwent cervical precancer treatment were more likely to have disease regression (adjusted OR 3.12, 95% CI 1.53-6.40) and less likely to have disease progression (adjusted OR 0.48, 95% CI 0.17-1.35). However, among 21 women with high-grade disease at follow-up, 43% (n=9) had undergone precancer treatment during the study period (Figure).

Conclusions: Although cervical precancer treatment was strongly associated with cervical disease regression, a substantial proportion of women had high-grade cervical disease at follow-up despite prior precancer treatment. Improving the effectiveness of precancer treatment among WLWH is essential for the prevention of cervical cancer.

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#6870

CHANGES IN THE DISEASE BURDEN OF HPV-RELATED CANCERS IN THE NORDIC COUNTRIES

03 - Epidemiology and natural history

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Background/Objectives: Despite the population-based screening of cervical cancer in the Nordic countries, an increase has been reported for its annual incidence in Finland during the last decade. The rate is now even higher than before the organized screening program was implemented in 1963. For many other HPV-related cancers no screening exists and thus, monitoring their annual incidence remains important.

Methods: We report the NORDCAN results for selected HPV-related cancers from the years 2015-2020. Our primary goal was to study whether decreasing trends can already be observed in the annual rates of cervical, vulvar, vaginal, anal, penile, and oropharyngeal cancers. The secondary aim was to discuss possible variations between the Nordic countries that would relate to their HPV vaccination programs.

Results: The age-standardized incidence ratio for cervical cancer showed a plateau or an increasing trend over the study period in Finland and Norway, but a clear decreasing trend in Sweden and Denmark. For oropharyngeal cancer, for both sexes, no decreasing trend was seen in these countries. For penile cancer only in Denmark a decreasing trend was evident, although in general, the numbers were small. All Nordic countries showed an increasing trend in the ratios of anal cancer.

Conclusions: We searched for any early decreasing trends in the age-standardized incidence ratios of HPV-related cancers in the Nordic countries. However, these ratios were somewhat variable, and no remarkable decreasing incidence could be identified. The increasing cervical cancer rate in Finland was a surprise. Similarly, increasing trends for anal cancer in the Nordic countries were unexpected. Anal cancer is generally more common in men than in women. The rates of oropharyngeal cancer continued to increase and around two thirds of them have been reported to be HPV positive. This is in accordance with reports from other high-incidence areas. One key point is that the implementation of the national HPV immunization programs, although school-based, took place at different time points, and for example Finland started late (2013 for girls; 2020 for boys). Furthermore, cancer as an endpoint is rare in young individuals, so the impact of HPV vaccination programs on these major trends will become evident later. Also, vaccination coverage rates differ between the Nordic countries being clearly lowest in Finland.

References: https://nordcan.iarc.fr/en/

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#6606

ESTIMATED NUMBER OF CASES OF HIGH-GRADE CERVICAL LESIONS DIAGNOSED IN THE UNITED STATES BY HISTOLOGICAL GRADE, 2008 AND 2019

25 - Cervical neoplasia

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Background/Objectives: Since the introduction of HPV vaccination in 2006, data measuring the impact of the HPV vaccination program in the United States have documented declines in overall cervical intraepithelial neoplasia (CIN) 2+ diagnoses and specifically those attributable to HPV types 16 and 18. Through 2015, most vaccine used in the United States was quadrivalent vaccine, targeting HPV 6/11/16/18; since the end of 2016, only 9-valent vaccine (9vHPV), which additionally targets 31/33/45/52/58, has been available. We estimated the total number of females diagnosed with CIN2, CIN2/3, and CIN3/adenocarcinoma in situ (AIS) in the United States in 2008 and 2019 and estimated the number of these cases attributable to vaccine types.

Methods: To estimate U.S. CIN2+ numbers, age-specific rates by diagnosis were calculated from a 5-site, population-based cervical precancer surveillance system and applied to the age-specific, annual U.S. female population. The five sites included in the surveillance network were chosen for their diverse populations and geographic representativeness; approximately 1.5 million females reside in the catchment areas. For cases in females aged 20-39 years, HPV typing was performed on archived diagnostic specimens. The number of cases positive for 16/18, 31/33/45/52/58, other high-risk HPV types, and other low-risk HPV types or no HPV were estimated by multiplying the proportion positive for each type group by the estimated number of cases, overall and for each grade and age group.

Results: In 2019, an estimated 155,662 CIN2+ diagnoses occurred in females aged ≥20 years: 75,121 CIN2 (48%), 31,765 CIN2/3 (20%), and 48,776 CIN3/AIS (32%) cases (Figure). These numbers represent a decrease of 19.6% from 2008 (n=193,642) when an estimated 93,354 CIN2 (48%), 33,298 CIN2/3 (17%), and 66,990 CIN3/AIS (35%) cases were diagnosed. CIN2+ cases decreased by 83% in 20-24-year-olds and 22% in 25-29-year-olds; there was an increase or no change in older age groups. HPV16/18 were no longer the most prevalent types among CIN2+ diagnoses in 2019 (n=58,280, 37% compared with n=102,727, 53% in 2008). Estimated CIN2+ cases attributable to HPV 16/18 decreased from 29,036 to 11,670 in 20-24-year-olds and 27,329 to 10,586 in 25-29-year-olds. Estimated CIN2+ cases attributable to the five additional 9vHPV types decreased from 11,670 to 3,738 in 20-24-year-olds.

Conclusions: We estimated that there was a 19.9% decrease in CIN2+ cases diagnosed in females aged ≥20 years in the United States in 2019 compared with 2008, which is likely due to a combination of vaccination and screening changes (e.g., later initiation and longer intervals) during this period. Decreases were observed for CIN2 and CIN3/AIS. The disproportionate decline in HPV 16/18 cases in 20-24-year-olds suggests specific impact of HPV vaccination since this is the age group most likely to have been vaccinated as part of the routine vaccination program. While HPV16/18 no longer causes the majority of estimated CIN2+ cases, these types still drive the burden in CIN3/AIS diagnoses. The continued use of 9vHPV in the United States can prevent CIN2+ cases due to HPV 16/18 and the five additional 9vHPV types.

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#6880

THE INFLUENCE OF EBV ANTIBODY LEVELS ON ORAL AND GENITAL HPV INFECTION OUTCOME

03 - Epidemiology and natural history

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Background/Objectives: Epstein-Barr virus (EBV) and Human papillomavirus (HPV) are both common viruses that a majority of people will be infected with at some point in their life. Both are known for their oncogenic properties, EBV associated especially with nasopharyngeal carcinoma and lymphomas and HPV being the known cause for cervical cancer as well as having an impact on the development ofhead and neck cancers.The connection between the two viruses is still unclear, despite both having been found at similar anatomical sites and being associated partly with similar malignancies. The aim of this work is to examine the effect of EBV serology on the outcomes of oral and genital HPV infections.

Methods: This study included a total of 280 women from the original Finnish Family HPV study, from the Turku University hospital and University of Turku, Finland. Oral and genital sampling and blood samples were collected at baseline, 12-, 24- and 36-month follow-up visits. The serum IgG antibodies of Zebra (transcriptional trans activator protein), EA-D (early antigen-diffuse), EBNA (EBV nuclear antigen) and VCAp18 (viral capsid antigen 18)for EBVwere analyzed with fluorescent bead-based multiplex serology and HPV genotyping was performed using Luminex. Unconditional logistic regression was used to measure the strength of the association between different variables.

Results: A total of 98.2% (n=275) women were seropositive to at least two EBV antibodies and all antibody levels stayed consistent throughout the three-yearfollow-up. Reported atopy significantly increased the likelihood of high Zebra and VCAP18-antibody levels, ORs of 2.11 and 2.45 (95% CI range of 1.07 to 4.83). Other health or sexual behavior factors were evaluated, however none of these wereassociated with elevated EBV antibody levels. Women were protected from long term persistent genital HPV16 infection, lasting over 24-months, if elevated VCap18 antibody levels, OR of 0.18 (95% CI 0.05-0.71) were detected. However, this was not seen when only extremely high titres of VCAP18 antibodies were considered. No associations betweenEBV serology and the oral HPV infection wasfound. Additionally,therewas no association between theEBV antibody levels and different HPV serological outcomes.

Conclusions: Nearly all women were EBV seropositive as expected. History of atopy associated with increased EBV antibody levels among healthy young women. Only EBV VCAp18 antibody levels showed a protective role for persistent genital HPV infections.Interestingly, EBV serology showed no association to oral HPV infections. Further studies are warrantedto shed light on the possibleassociation between these two oncogenic viruses.

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M. GENITALIUM ANTIBODY LEVELS IMPACT ON PERSISTENT ORAL AND GENITAL HPV INFECTION AMONG WOMEN

33 - Sexually transmitted diseases and HIV infection

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Background/Objectives: Mycoplasma genitalium is acknowledged as an established sexually transmitted pathogen, responsible for the induction of cervicitis and pelvic inflammatory disease (PID) in women. Persistent high-risk human papillomavirus (HPV) infections are known as the main agents involved in cervical and in some part of oral carcinogenesis. Several sexual transmitted diseases are known to increase the risk of HPV infection persistence. The knowledge on M. genitalium role in the natural history of HPV infection outcome are so far scanty.

Methods: This study included 329 women from the prospective Finnish HPV Family cohort study (FFHPV), from Turku University Hospital and University of Turku, Finland. Women were all pregnant at recruitment and were subsequently followed-up for six years. Genital and oral scraping and blood samples were collected at baseline, 12-, 24- and 36-months follow-up visits. Serological assays for M. genitalium IgG antibodies of MgPa and rMgPa were done with fluorescent bead-based multiplex serology. The median fluorescence intensity (MFI) cut-off value for M. genitalium seropositivity was MFI>1000 for both MgPa and rMgPa. HPV genotyping was performed using Luminex multiplex HPV genotyping. Persistent HPV infection was defined as being subsequently HPV positive for two or more visits.

Results: M. genitalium antibody levels persisted among 12.9 % (n=35) women and 82.7 % (n=225) women were always seronegative during the three-year follow-up. Persistent oral and genital HPV infection were detected among 20.1 % (n=66) and 32.8 % (n=108) of women during the follow-up. Antibody levels of women that were M. genitalium seropositive were further divided into low and high levels. No association was seen between low or high M. genitalium antibody levels and the persistence of oral or genital HPV infections. Regarding persistent oral HPV16 infections, a tentative correlation with M. genitalium antibody persistence was seen, but the findings were not statistically significant. Interestingly however, all persistent M. genitaliumantibodies co-occurred in the oral mucosa only with HPV16 infection, while in the genital site HPV infections showed a broader representation of genotypes among these women.

Conclusions: Our investigations could not show any association between M. genitalium antibody levels and detected persistent oral or genital HPV infection among women. Nevertheless, a potential connection especially in the oral cavity might exist, warranting further investigations with larger cohorts.

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#6771

GLOBAL HPV PREVALENCE AMONG WOMEN 50 YEARS AND OLDER WITH UNKNOWN CYTOLOGY

03 - Epidemiology and natural history

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Background/Objectives: According to the World Health Organization (WHO), in 2020, cervical cancer was the fourth most common cancer among women worldwide, with most new cases and deaths occurring in low- and middle-income countries (LMIC). It is estimated that around half of cervical cancer cases worldwide occur in women over 50 years of age. Therefore, this systematic literature review and meta-analysis aimed to provide a global estimate of overall and high-risk HPV (hrHPV) prevalence among this previously underrepresented population.

Methods: A systematic literature search was conducted in Medline via PubMed, Web of Science, and Scopus. Publication years included were between January 1990 and May 2022, and the eligible study designs were observational studies and randomized-controlled trials (RCTs). HPV pooled prevalence was calculated using random-effects models with a restricted maximum likelihood estimator (REML). The analyses considered the following variables: continent of study conduct, 5-year age group, mode of recruitment, HPV test used, and HPV genotype. A modified Newcastle-Ottawa Scale was used to assess the quality of the included studies. Heterogeneity of the included studies was observed with I^2 and Cochranes Q, while Egger's test was implemented to test for publication bias. The statistical analyses were conducted in R version 4.2.2.

Results: 145 eligible studies were identified, and 110 of these provided sufficient data for the meta-analysis. The global overall HPV prevalence was 13.7% (95% CI 12.1-16.5), whereas the pooled hrHPV prevalence was 12.2% (95% CI 10.5%-14%). Subgroup analysis by continent detected the highest overall and hrHPV prevalence in older women in Asia. The analysis by 5-year age group showed a slightly decreasing HPV prevalence with increasing age. Study populations recruited from clinical settings resulted in higher HPV prevalence. PCR test other than GP5/6, GP5/6+, MY09/11, or PGMY09/11 gave a higher HPV prevalence. The most common hrHPV genotype in women above 50 years of age was HPV16.

Conclusions: The study detected a substantial global HPV prevalence among older women. These results offer valuable and novel insights since no similar large-scale meta-analyses have been conducted before in older women. Additionally, due to the limited number of studies reporting on hrHPV genotypes in older women, further research is needed to understand the regional distribution of different HPV types.

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#7152

MOLECULAR EPIDEMIOLOGY AND ULTRASTRUCTURAL CELL MORPHOLOGY OF HUMAN PAPILLOMAVIRUS IN BRAZIL

39 - Public health

Background/Objectives: Cervical cancer is the most common cancer in developing countries induced by Papillomaviruses. Circular double-stranded DNA genome, around 8 kb non-enveloped belong Papillomaviridae family. More than 200 HPV genotypes and several HPV types, associated to particular diseases as oral lesions, anogenital warts, Epidermodysplasia verruciformis have been described. Clinical trial has showed human papillomavirus (HPV) as responsible for 99.8% of cervical cancer cases and 90% of genital warts in females. The Brazilian Immunization Program recommended the vaccine to be administered at 9 to 14 years of age before most adolescents became sexually active. The study reports the HPV infection prevalence among unimmunized women and the co-factors as demographic, behavioral and biological variables associated to cervical cancer.

Methods: A cross-sectional study was performed in women randomly selected at Public Family Health Program. The responders without a previous history of immunosuppressive disease, not pregnant and sexually active regardless of age were included in the cohort epidemiological. Cervical samples collected with a cytobrush were analyzed by PCR amplification of L1 ORF. HPV-DNA positive samples were detected by consensus (MY09/MY11), Nested PCR and high-types specific primers (HPV16/18/31/45). In order to evaluate the viral DNA quality, swab samples collected were amplified by ß-globin PCR primers. Restriction fragment length polymorphism (RFLP) assay patterns for mucosal HPVs were used for genotyping. Chi-square test was used to analyze the risk factors associated with HPV infection in 18 socio-demographic variables.

Results: The group of 100 women was divided into six age groups (≤25 y.o [15%, 95% CI]; 26 to 30 y.o [15%, 95% CI]; 31 to 35 y.o [25%, 95% CI]; 36 to 40 y.o [5%, 95% CI]; 41 to 45 y.o [5%, 95% CI]; ≥45 y.o [35%, 95% CI]). Distribution among racial/ethnic groups representative were white (47%), black (53%) and other race/ethnicities. Most women were currently not married (56%) and married or cohabitating (44%) ($p<0.05$). Psychosocial and psychosexual issues demonstrated that six percent of the women exhibit history of sexually transmitted diseases, except HIV, with 85% of women having sex with until to five sexual partners ($p<0.03$) by chi-squared tests and 14% started sexual activity under the age 17. About 27% used alcoholic, 40% reported having had at least one abortion, 15% used oral contraceptives, while 71% did not use any type of condom ($p<0,03$). About the employment status of all the participating women, 90% reported having had at least one until four basic salaries. Only 5% women have had higher education. The most women (87%) have had secondary and fundamental education. Prevalence of 20% positive samples of cervical HPV-DNA was confirmed. HPV-18 was the most prevalent genotype (8%). High cellular activity in cervical keratinocytes and virus-like particles (VLP) were detected by electron microscopy.

Conclusions: This molecular study estimates a high prevalence of HPV unimmunized women and may be useful to future epidemiological surveillance reports and evaluation of new clinical and subclinical cases of cervical intraepithelial neoplasia and genital warts. These findings suggested a strong cellular activation in these cervical keratinocytes and point to the potential to induce tumors that probably involves mechanisms of oncoproteins to produce virions and differentiation of keratinocytes in the epithelial layers remains to be elucidated.

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#6759

Cumulative incidence of high grade CIN2+ and CIN3+ lesions in Slovenian non-attenders of the organised cancer screening programme ZORA: A 7-year follow up study

11 - Screening for women difficult to reach

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Background/Objectives: Cervical cancer is largely preventable through HPV vaccination and organised screening. However, despite the success of the nationally organised population-based cervical cancer screening programme (ZORA) in Slovenia, some women don't attend the screening (non-attenders) and may be at higher risk of developing cancer. HPV testing via self-sampling represents an avenue to reduce the burden of disease in non-attenders. The goal of this study is to describe the trends in high grade HSIL/CIN2/3+ in non-attenders and calculate the cumulative incidence of CIN2/3+ over time across different modes of recruitment of non-attenders (study arms).

Methods: Secondary data analysis of an existing randomised trial of ZORA non-attenders will be performed (N = 26,556). Women aged 30 - 64 years from two Slovenian regions were enrolled and randomised into 3 study arms; opt-in (N = 14,000), opt-out (N = 9.556), and control group (N = 2.600). Women could decide to perform an HPV self-sample or visit a gynecologist for conventional cytology screening. Kaplan-Meier method will be used for the calculation of cumulative incidence of CIN2/3+ over the seven-year period.

Results: Within the first year, 33.8% (N = 8.972) of women responded with self-sample for HPV test and/or cytology. Response rates were 37.7%, 34.0% and 18.4% for opt-in, opt-out and control groups, respectively. We will present the cumulative incidence over seven years in all three study arms relative to the self-sampling approach (HPV self-sampling, cytology) and according to the positive and negative cytology results.

Conclusions: Cervical cancer is almost entirely preventable through early detection of high grade CIN2/3+ lesions and early intervention. Our work addresses an important question of further management of women according to their HPV self-sampling outcome in the present and subsequent screening rounds. The results will not only contribute evidence towards understanding if HPV self-sampling presents a feasible option for screening of hard-to-reach women, but also inform the revision of national screening guidelines.

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#7107

Community - Based Study To Assess Cytological Pattern In Combination With Schistosomiasis Infestation, Among Women Of White Nile State / Sudan

11 - Screening for women difficult to reach

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Background/Objectives: Cervical screening programs play an important role in decreasing the morbidity rate that occur as a result of cervical cancer by early detection of precancerous lesions and to facilitate prevention and treatment of and neoplastic development. There are many virulence factors lead to cervical cancer such as HPV, TV and others. Schstiosoma is one of virulence factors that detected in some cases in developed countries from African patients. Recent research indicates that patients had Female Genital schistosomiasis may have susceptibility to stimulate cervical cancer. Therefore the association between schistosomiasis and cervical cancer should be studied to reduce mortality rate resulting from both diseases. The purpose of this study is to assess cytological screening pattern in combination with schistosomiasis infestation, among women of White Nile State / Sudan.

Methods: This descriptive study, Convectional Pap smears were taken from 165 women and also questionnaires are filled to have an idea about factors such as age, history of Schistosomiasis infection, and using of contraceptive pills. All these factors were considered in assessment of cervical cytology. Standard plastic cyto-spatula (szalay cytospatula) were used to collect the cytological smears from patients, specula were used to visualize the cervix for sample collection. the scraped cells were smeared then rapidly fixed with 95% ethyl alcohol, The smears were stained with Papanicoulaou stain. All slides were screened by investigators and the results were confirmed by expert cytologist (Dr. Abdulla Hassab El-nabi and Mr. Emanwell Edward Siddig). The collected data were analyzed using SPSS. Frequency tables, and X2-test and Odd ratio were used as statistical tests (P-value ˂0.05 was considered positive).

Results: Some of women with history of shistosomiasis infection 90(54.4%) and others without 75(45%). Analysis of the cytological smear identified 61 % (102) were normal, 30(18.1%) associated with inflammatory conditions. precancerous lesions were presented among 28(16.9%) of which 8(4.8%) were LISL (Low grade Squamous Intra Epithelial Lesion),13(7.9%) were HISL (High grade Squamous Intra Epithelial Lesion), 6(3.6%) were reported as atypical squamous cells of unknown significance (ASCUS), and only 1 case considered as atypical granular cells of unknown significance (AGUS). Look at the figures attached in supplementary file.

Conclusions: Cervical screening program is essential to estimate the actual magnitude of cervical carcinoma and its precursor lesions. Schistosomiasis infection may be protective or risk factor for HPV infection, and therefore for precancerous and cancerous lesions. Also theses lesions may be due to factors other than HPV or Schistosomiasis infections. Recommendations: advanced tools as HPV testing are important to correlate such studies to rule out the effect of HPV in developing cancerous and precancerous lesions, more efforts and research should be done to reduce the morbidity due to female genital Schistosomiasis and to study the relationship between Female Genital Schistosomiasis and HPV and/or cervical neoplasia.

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FC04 - HPV Vaccination and public health

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#6735

ATTITUDES TOWARDS HPV VACCINATION - HOW TO ACHIEVE BETTER VACCINATION COVERAGE IN FINLAND?

36 - Advocacy, acceptability and psychology

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Background/Objectives: Background The burden of disease caused by human papillomavirus (HPV) is globally high. With primary prevention i.e. by vaccination, the virus causing the disease burden can be eradicated and the disease burden eliminated. There are more research data on the effectiveness and safety of the HPV vaccines than of any other vaccine. In Finland, all children and young people are equally offered the right to the HPV vaccine. Despite the meritorious HPV vaccination information provided by the Finnish Institute of Health and Welfare, our vaccination coverage is clearly lower than the goals set by the EU and WHO. The HPV vaccination coverage in Finland is lower than in the other Nordic countries although the vaccination coverage of other vaccines in the pediatric national vaccination program has traditionally been high in Finland. However, high vaccination coverage would be of primary importance in achieving good herd protection. While the Internet has made the world more united in terms of access to information, variable and conflicting information is challenging. In the absence of critical assessment, differentiating true information from false information is difficult.

Methods: Objectives The objective of this project is to increase understanding of the factors that influence vaccination coverage and to provide means to eliminate HPV-associated life-debilitating and potentially fatal diseases from the world.

Results: Conclusions We can increase vaccine coverage with effective responsible communication, reliable information sharing and cooperation. Health policy decisions must be based on true and solid research data and expert assessment. In addition, health care professionals must understand human emotions when choices are made. Disinformation and fear related to HPV-vaccination must be handled so that the individual and population level benefits are understood and accepted by the vaccine recipients and parents. Expertise of the healthcare professionals plays a key role in providing such information, not only to individuals representing the target population, but also to the decision makers.

Conclusions: In Finland, an HPV network of professionals from various specialties was established in 2022, which has actively sought to bring information related to HPV infection to both lay people and health care representatives.

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#6819

SOCIODEMOGRAPHIC FACTORS ASSOCIATED WITH NON-UPTAKE OF HPV VACCINATION IN HIGH-INCOME COUNTRIES WITH SCHOOL-BASED VACCINATION PROGRAMMES: A SYSTEMATIC REVIEW

39 - Public health

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Background/Objectives: Background Lower uptake of human papillomavirus (HPV) vaccines in certain population subgroups could exacerbate inequalities in cervical cancer prevention. Uptake is generally high in high-income countries with school-based vaccination programmes, such as the UK, with many countries on track to reach the WHO elimination target of 90% coverage; however, differences in access might persist.

Methods: Methods Six electronic databases were searched for articles published between September 2006 and 20 February 2023. Search strings were developed based on three key fields: HPV vaccination, sociodemographic factors (e.g., ethnicity, parental education, religion, socioeconomic status (SES)), and high-income countries with school-based vaccination programmes. Titles, abstracts, and full text articles were screened for eligibility criteria to identify quantitative studies, representative of the general population, with individual-level data in settings where routine vaccination in girls was reported by at least one sociodemographic measure. The Joanna Briggs Institute critical appraisal checklist was used to ascertain risk of bias. A second independent reviewer screened 20% of articles at each stage. A narrative synthesis was used to summarise findings.

Results: Results In total, 24 studies based in 8 countries (UK, Canada, Australia, Norway, Sweden, New Zealand, Belgium, Switzerland) were included. Studies reported vaccination uptake by individual-level SES, area-level SES, parental education, religion, ethnicity, and/or country of birth. 19 of 24 studies reported more than 70% vaccinated (Range: 50.7%-93.0%). Despite high vaccine coverage, there were inequalities in uptake. Lower SES was associated with non-uptake of HPV vaccination across most studies. Where studies examined ethnicity and country of birth, minority ethnic groups and migrants were found to have lower vaccine uptake than White groups and non-migrants. However, associations with other sociodemographic characteristics, such as parental education and religion, were less clear.

Conclusions: Conclusions This systematic review demonstrates inequalities in uptake of HPV vaccination in countries with routine, school-based programmes, with lower SES and minority ethnic groups less likely to be vaccinated. These groups may benefit from additional catch-up vaccination programmes to mitigate the effects of these inequalities. Additionally, as high vaccination coverage prompts changes to cervical cancer screening programmes, these findings could inform a targeted approach to cervical cancer screening among these groups.

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#7214

INCREASING HPV VACCINATION RATES AMONG ADULT WOMEN IN MANITOBA

39 - Public health

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Background/Objectives: The human papilloma virus (HPV) vaccine is one of the best tools in preventing cervical cancer. In 2015, it was estimated that 3,829 cases of cancer in Canada were caused by HPV (1). In Manitoba, Canada, most females receive their publicly-funded HPV vaccine in middle school (age 12) through Public Health recruitments targeting parents (guardians) of middle school girls. Manitoba's HPV vaccination uptake is 69%, below the Canadian target of 90%. Fortunately, the province maintains a once eligible, always eligible policy, so individuals can continue into adulthood to receive their publicly funded vaccination if they missed the school-based program, or if their parents had opted them out (2). Objectives To determine if an HPV vaccine letter campaign would increase uptake in unvaccinated Manitoba women aged 20 to 25 years. To evaluate the sustainability/feasibility of incorporating HPV vaccine letters into routine CancerCare Manitoba operations by leveraging the impact of letters on HPV vaccine uptake with the cost to implement.

Methods: Methods Approximately 14,000 randomly selected women meeting the pilot study inclusion criteria were randomized to three study arms: Group I: 4,650 women mailed an invitation letter. Group II: 4,650 women mailed an invitation and a reminder (if needed) letter. Group III: 4,650 women identified as control. In consultation with public advisors, the campaign was developed to meet the needs of the target audience, and address issues affecting young adults. Campaign components were translated in French and English and the letter package included an "HPV (human papillomavirus) Vaccine" frequently asked questions (FAQ) insert. Analysis - For each of the study groups, HPV vaccine uptake is defined as receiving at least one dose of an HPV vaccine within six months of the first letter mailout date. In pilot study objective 1, vaccine uptake in Groups I and II was evaluated by calculating the number of women who record at least one dose of an HPV vaccination within six months of the invitation divided by the total number of women within the study group. Vaccine uptake in Group III was evaluated by calculating the number of women who record at least one valid dose of an HPV vaccination within six months of the invitations sent out in Groups I and II divided by the total number of women in the control group. A chi square test of homogeneity will determine whether HPV vaccination uptake differs across the three study arms, and then logistic regression will be used to assess the strength of the relationship between the dependent variable (vaccine uptake) and the independent variable (study arm). In pilot study objective 2, the sustainability and feasibility of continued HPV vaccine invitation letters would be assessed leveraging HPV vaccination participation rates and CancerCare Manitoba capacity (cost to print and distribute letters, and human resource levels).

Results: In May 2023, 9300 letters of invitation were sent to HPV vaccine eligible women 20 to 25 years of age. Distribution was integrated within standard CancerCare Manitoba program and has been determined that the letter campaign is sustainable. As the study timeframe does not close until January 2024, final results are not available to share in this abstract, however early numbers indicate that the intervention was successful. Final results will be available at time of Eurogin March 13-15, 2024.

Conclusions: Study will inform future adult vaccination strategies in Manitoba.

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#7112

Uptake of HPV Vaccination Among Women treated for HPV-related cervical lesions in the Province of Ancona, Italy

07 - HPV therapeutic vaccines

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Background/Objectives: The Human papillomavirus (HPV) vaccine was found to be highly effective against cervical cancer (Lei et al, NEJM 2020), and evidence is also growing about its prophylactic effectiveness against recurrent cervical lesions after surgical treatment (Bogani et al, Gynecol Oncol 2020; Del Pino et al, Vaccines 2020). This study aims to assess the frequency of treatments of the cervix due to HPV-related Cervical Intraepithelial Neoplasia (CIN) grade 2, CIN3, or cervical carcinoma, and the uptake of HPV vaccination in these treated women, in one Italian province.

Methods: Since October 2021, the Local Health Agency of the Province of Ancona, Italy, has started to actively offer free HPV vaccination to women who had undergone a documented treatment of HPV-related lesions of the cervix, without a time limit from the treatment. Data were collected from the official registries of the Local Health Agency on women that participated to the screening programme, and underwent treatment for HPV-related cervical lesions between 2017 and 2023. The main outcomes were the histological result of either the pre-treatment biopsy or the surgical specimen (registering the higher-grade result), and the uptake of HPV vaccination from 30 days before the treatment date and up to April 2023.

Results: A total of 63,385 women, aged between 25 and 64 years, participated to cervical screening between 2017 and 2023 in the study area. Out of the screened women, 0.5% (n=319) underwent treatment, and had average age 41.7 years (standard deviation 9.6 years). Among the treated, 4.7% (n=15) were still waiting for the histology results, 43.6% (n=139) had CIN2, 46.4% (n=148) had CIN3, 2.8% (n=9) had in-situ squamocellular carcinoma, 1.6% (n=5) had in-situ adenocarcinoma, and 0.9% (n=3) had invasive squamocellular carcinoma. Women who opted for both the treatment and the HPV vaccination were 42.0% (n=134), however data on vaccination was still lacking for 7.5% (n=24). The uptake increased from 20.4% among women treated between 2017 and 2019, to 63.1% among women treated between 2020 and 2022 ($p<0.001$).

Conclusions: The histological results of women who underwent treatment for HPV-related cervical lesions was CIN2/3 lesions for the great majority. The uptake of vaccination against HPV among the treated women was more widespread after its offer became active and free. Data on the effectiveness of vaccination against recurrent cervical lesions will become available in the near future.

References: Lei et al. HPV Vaccination and the Risk of Invasive Cervical Cancer. NEJM (2020) 383(14): 1340-1348. Del Pino et al. HPV Vaccination as Adjuvant to Conization in Women with Cervical Intraepithelial Neoplasia: A Study under Real-Life Conditions. Vaccines (Basel) 2020;8(2) Bogani et al. Recurrence rate after loop electrosurgical excision procedure (LEEP) and laser Conization: A 5-year follow-up study. Gynecol Oncol 2020;159(3):636-41.

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#6583

EQUAL ACCESS TO HPV-VACCINATION: PRELIMINARY RESULTS OF A CROSS-SECTORIAL INTERVENTION OF SCHOOL-BASED HPV-EDUCATION AND -VACCINATION.

39 - Public health

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Background/Objectives: Human Papillomavirus (HPV)-related cancer diseases can be prevented with vaccination, but despite free access to vaccination through the Danish Childhood Vaccination Program, children with ethnic minority background attend substantially lesser than native children (65% vs. 93%). This tendency is reflected internationally in various HPV-vaccination programs. Practical barriers such as language and insufficient understanding of prevention in terms of vaccination, as well as emotional barriers regarding sexuality and cultural taboos, need to be accommodated, to achieve increased participation in a healthcare program. In collaboration with multiple stakeholders, we developed a culturally adapted intervention consisting of school-based HPV-education and -vaccination aiming to improve HPV-vaccination coverage by 10%-point for ethnic minority pupils.

Methods: The study is a non-randomized implementation study. The cross-sectorial intervention was developed and conducted according to guidelines from the Complex Interventions Framework. The intervention was implemented throughout school year 2022-2023 and consisted of three core elements: 1) school-based parental HPV-education, 2) pupil HPV-education, and 3) school-based HPV-vaccination of pupils. All pathways of counselling, written material, video-material as well as an animation were developed with user-representatives from every layer of potential impact on decision making regarding HPV-vaccination. User-representatives were political and administrative staff in the municipality, school nurses, school leaders, medical doctors, local representatives with an ethnic minority background, parents, and children in the age of 10-13 with various ethnic background. Intervention group was 670 nine-13-year-old pupils at five schools in the Municipality of Aarhus, Denmark, with proportion of pupils with ethnic minority background varying from 26% to 91%. The control group was 3000 children comparable in age and community.

Results: Analysis of quantitative and qualitative results are ongoing, and preliminary results will be presented. Primary outcome is difference in HPV-vaccination coverage between intervention and control group. Secondary outcome is HPV-vaccination coverage for siblings to intervention-group, to investigate the effect of parental HPV-education alone. Further, the intervention has been qualitatively evaluated in 10 focus-group interviews regarding user perspectives.

Conclusions: The study has potential to increase the attendance in HPV-vaccination by breaking down barriers to participation. It may serve as a means, to obtain equity in HPV-related cancer prevention for all children regardless of ethnical background.

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#6905

INCREASING HPV VACCINATION IN PEDIATRIC SETTINGS: MOTIVATORS, BARRIERS AND FACILITATORS IN A QUALITY IMPROVEMENT INTERVENTION

39 - Public health

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Background/Objectives: Practice facilitation is an evidence-based implementation strategy to improve provider adherence to clinical guidelines through provision of training, technical support, and resources to conduct quality improvement (QI). However, little research has applied practice facilitation to HPV vaccination. In a recent implementation trial, we compared two formats for delivering practice facilitation to pediatric clinics, and both arms demonstrated increases in HPV vaccination. In this analysis, we examined feedback from the clinics regarding their motivators to participate in the QI project, factors that contributed to successful implementation, and challenges they experienced.

Methods: We recruited 21 community-based pediatric clinics in Tennessee, USA, to participate in the implementation trial. Clinics were randomized to the coach-based facilitation arm (periodic in-person coach visits) or web-based facilitation arm (web-based resource portal). The same content and data feedback reports were provided in both arms. Each clinic identified a Physician Champion (PC) and Operations Champion (OC) as internal leaders of the 12-month QI project. We conducted post-intervention qualitative interviews (N=21 PC, N=13 OC) and performed thematic analysis of the interview transcripts.

Results: When asked what motivated clinics to participate, many champions mentioned the incentives offered through the study: physicians earning credits for pediatric Maintenance of Certification (MOC) requirements and free access to a population health dashboard. Additional motivators included the desire to increase HPV vaccination rates, seeking strategies to address parental HPV vaccine hesitancy, ability to receive data feedback reports, and alignment with previous QI efforts. Intervention-related factors that contributed to successful implementation included the training module content, guidance on planning internal process changes, patient education materials, data feedback reports, population health dashboard, and technical support. General factors included assistance from office staff and buy-in of other clinic physicians. In the coach arm, champions consistently cited the beneficial role of the coach, including guidance, responsiveness, and reminders to stay on track. In the web arm, champions liked being able to access the web portal, materials, and data reports at any time within their busy schedules. Intervention-related challenges experienced by champions included learning how to use the population health dashboard, MOC paperwork and documentation, and some delays in data reporting. In the web arm, champions said it was challenging not having a person to give them clinic-specific guidance and having technical issues with the web portal. General challenges included limited time, coordinating and training clinic staff, getting buy-in from physicians and staff, and turnover of physicians and staff.

Conclusions: Future efforts to recruit pediatric clinics into practice facilitation interventions for HPV vaccine may consider showing clinics they have suboptimal coverage rates, offering resources to address parental hesitancy, and offering MOC credits. Each delivery format offers unique advantages that can contribute to the successful implementation of HPV vaccine QI projects. Future efforts could attempt to minimize time burden, optimize ease-of-use for technology-based tools, and provide resources for generating internal buy-in and coordination.

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#6744

ESTIMATING THE TIME REQUIRED TO REACH HPV VACCINATION TARGETS ACROSS EUROPE

39 - Public health

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Background/Objectives: In 2018, the World Health Organization (WHO) called for coordinated action globally to eliminate cervical cancer as a public health problem. In addition to screening and treatment targets, the WHO has urged countries to take action to prevent cervical cancer by setting a target for Human papillomavirus (HPV) vaccine coverage rate (VCR) of 90% for girls aged 15 years old to be fully vaccinated by 2030. However, national elimination plans do not always provide guidance on implementable actions to reach the WHO VCR targets, leading to the false view that no accelerated efforts are required to reach the targets by 2030. The aim of this study is to estimate the number of years needed to reach the WHO vaccination target in Europe.

Methods: To estimate the time required to reach the WHO VCR target, a framework was developed using the WHO's publicly available VCR data (2017-2022). Several univariate regression models (linear, exponential, logarithmic, power, 2nd order and piecewise linear regressions) were fitted to the observed VCR data of each country in order to extrapolate and estimate future VCRs. R2 index was calculated to determine goodness of fit and the highest ranked R2, together with visual inspection, determined the most appropriate regression model for each country. The tool estimates the number of years required to reach the target and the change in annual VCR required to reach vaccination targets by a given year.

Results: WHO's database contained VCR data in 24 of 30 European countries (No VCR data was available for Poland, Czechia, Slovakia, Romania, Croatia, and Greece). Based on the WHO VCR data, Norway, Iceland, and Portugal have already achieved a 90% VCR. Our estimates show that only five countries (Sweden, Hungary, Spain, Denmark and Ireland) are projected to achieve a 90% VCR before 2030. France, Germany, Netherlands, Switzerland, Estonia, Austria, and Cyprus are expected to reach 90% VCR between 2030 and 2040. The 9 remaining countries (Belgium, Bulgaria, Latvia, Finland, Italy, Lithuania, Luxembourg, Malta, Slovenia) are currently expected to achieve 90% VCR after 2040. It is important to note that a number of countries, showed stagnation in VCR over a period of time such as Bulgaria, which remained around 7-9% between 2018 and 2022 and Finland, which has had a VCR of 67% since 2018. In the countries expected to achieve a 90% VCR between 2030 and 2040, a 30% to 80% increase in the annual VCR growth is required in order to be able to accelerate reaching the target by 2030.

Conclusions: Our study estimates that the majority of countries are currently unlikely to meet a target of 90% VCR by 2030. However, for the countries that are expected to achieve a VCR of 90% between 2030 and 2040, a modest increase in the rate of VCR increase is required to meet the target by 2030. This study highlights the importance of prioritizing HPV vaccination programmes in order to meet WHO HPV VCR targets by 2030 and stay on the path to cervical cancer elimination.

References: WHO's HPV vaccination coverage database: https://immunizationdata.who.int/pages/coverage/hpv.html?GROUP=Countries&ANTIGEN=15HPVC_F&YEAR=&CODE=

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#6952

Partnering with Social Media Influencers to Increase Confidence in the HPV Vaccine for Children and Adolescents: A Mixed Method Study

37 - Health education

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Background/Objectives: Despite HPV vaccination reducing the prevalence of cervical cancer by 90%, vaccination rates remain lower, especially among communities of color in the U.S. The COVID-19 pandemic exacerbated these trends. The public health community has long utilized trusted messengers to deliver vaccine messaging but the effectiveness of social media influencers is an under-examined area of study. This presentation will review a mixed-method study designed to understand how influencers of color frame HPV vaccine messages and understand the effects of those messages on their followers' knowledge, attitudes, and beliefs.

Methods: Working closely with an organization specifically focused on influencers of color, the study team recruited 10 female influencers who had children aged 9-14. These influencers used a provided factsheet to draft social media posts about HPV vaccination. Influencers were interviewed about their post and also recruited a sample of their followers to complete a pre-post survey. The team assessed changes in HPV vaccine knowledge, attitudes towards HPV-related cancer, and intentions to vaccinate their children. Mean scores/frequencies were calculated for all variables. Changes in survey variables were assessed with repeated measures t-tests. Qualitative data were analyzed using Nvivo. The study team: determined a set of codes; coded a sample and obtained a Kappa score; and finalized the codebook and coded all interviews/posts. The team collaboratively interpretated the data, resolved differences, and identified the main themes.

Results: Of the 10 social media influencers, four were African American and 6 were Hispanic. All were female; their mean age was 44; most had 2 or 3 children. Almost all had a college degree; all but one were married. The average time as an influencer was 9.5 years. 134 followers viewed a post from their influencer and completed a survey. The majority (86%, n=115) were women; 59% (n=79) were African American. The team observed significant positive changes, after viewing a post, in almost all outcome measures: knowledge about the vaccine ($p<0.001$), perceiving HPV infection to be serious ($p<0.001$), perceiving the vaccine to be safe ($p<0.001$), and intentions to vaccinate their children against HPV ($p< 0.001$). All followers had a high level of trust in their influencer. The qualitative analyses conducted revealed several things. Most influencers were hesitant to talk about vaccinations for fear of backlash. Most committed to writing because they were compelled to support important health topics. All used the power of storytelling to convey the messages and highlighted their personal journeys of vaccine decision making. Influencers highlighted the struggles of parenting and talked about how HPV vaccine decision making prompted emotional feelings about their child growing up. Influencers believed that they could help people make the decision to vaccinate.

Conclusions: As more health information is shared and consumed on social media, partnerships with novel trusted messengers are important for delivering accurate and culturally tailored information. Findings from this study indicate that exposure to these messages can increase knowledge and intention to vaccinate. They also reveal how personal the decision to vaccinate is and the emotional context within which parents are being asked to vaccinate their children. Approaches and best practices for working with influencers on vaccination-related projects will also be shared.

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#6923

Measures of the behavioural and social drivers of HPV vaccination: a review

39 - Public health

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Background/Objectives: Understanding the behavioural and social drivers (BeSD) of HPV vaccine uptake can support interventions to address the underlying causes of under-vaccination. This review sought to characterize available survey measures of the BeSD of HPV vaccination to support the World Health Organization's development of a standardized survey tool.

Methods: The review was prospectively registered with PROSPERO (CRD42023386935).We systematically searched 8 databases (MEDLINE ALL, Embase, PsycINFO, CINAHL, LILACS, Cochrane Database of Systematic Reviews, Web of Science, and Scopus) from January 2006 to March 2023.We also searched the grey literature, reviewed reference lists of included studies, and approached content experts to identify relevant tools. We included primary studies that reported on the development and psychometric evaluation (e.g., reliability) of a quantitative survey on the BeSD of HPV vaccination. We then categorized the survey items into the BeSD Framework's 4 domains: Thinking and Feeling, Social Processes, Motivation, and Practical Issues.

Results: The review identified 49 studies meeting inclusion criteria that reported on 43 unique survey instruments. The majority of studies (80%) were conducted in high-income countries. All surveys (98%) were available in English, except one that was only available in French. Surveys asked parents or caregivers about the vaccination of their child (41%), but a substantial minority asked adolescents (8%), young adults (37%), or adults (14%) about their own drivers for vaccination. The review identified 950 survey items. Most of the items were in the Thinking and Feeling BeSD domain, and the fewest were in the Motivation domain, but few surveys addressed the domains comprehensively.

Conclusions: Our review identified survey constructs and items that are informing the development of WHO's BeSD HPV vaccine survey. These findings highlight the need for a comprehensive BeSD HPV survey tool to be validated for use in global contexts with diverse samples and in multiple languages.

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#6736

No increased risk of infectious disease hospitalization after receipt of human papillomavirus vaccine: Nationwide register-based cohort studies among Danish, Finnish, Norwegian, and Swedish girls

39 - Public health

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Background/Objectives: Human papillomavirus (HPV) vaccines are non-live and primarily offered to girls in early adolescence to prevent cervical cancer. It has been suggested that non-live vaccines may increase susceptibility to non-targeted infections and that such deleterious non-specific effects are more pronounced in girls. However, there are few studies on non-specific effects of HPV vaccines. We aimed to study whether receipt of an HPV vaccine was associated with an increased risk of infectious disease hospitalization in girls from four Nordic countries.

Methods: Nationwide cohort studies based on detailed individual-level data from national registries were performed in Denmark, Finland, Norway, and Sweden. The cohorts consisted of girls aged 11-14 years in Denmark, Finland, and Norway, and girls aged 10-14 years in Sweden. Girls from the following birth cohorts, eligible for HPV vaccination through national immunization programs, were included: 1996-2004 in Denmark; 1998-2004 in Finland; 1999-2005 in Norway; 2003-2004 in Sweden. Cox regression with age as the underlying time scale was used to estimate hazard ratios (HRs) of infectious disease hospitalization according to time-varying HPV vaccination status. The model was adjusted for multiple potential confounders related to the participants health and socioeconomic status.

Results: In total, 754 458 girls were included in the analyses: 284 824 in Denmark, 165 707 in Finland, 202 774 in Norway, and 101 153 in Sweden. Uptake of at least one dose of HPV vaccine was 85.1% in Denmark, 67.3% in Finland, 88.2% in Norway, and 80.5% in Sweden. The number of infectious disease hospitalizations during follow-up was 4446 in Denmark, 1404 in Finland, 2782 in Norway, and 1148 in Sweden. Comparing HPV-vaccinated to HPV-unvaccinated person time, the HR (95% confidence interval) was 0.81 (0.72, 0.90) in Denmark, 0.69 (0.60, 0.80) in Finland, 0.76 (0.66, 0.88) in Norway, and 0.59 (0.49, 0.71) in Sweden. In Denmark, Finland, and Norway, the association was slightly stronger 1-90 days after vaccination as compared to more than 365 days after vaccination, whereas it was slightly weaker in Sweden. However, decreased risk was observed in all time intervals after HPV vaccination.

Conclusions: Receipt of HPV vaccine was consistently associated with a decreased risk of infectious disease hospitalization among girls in the Nordic countries. Thus, our study does not indicate that non-live HPV vaccines have deleterious non-specific effects that result in increased susceptibility to infections requiring hospitalization.

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#6635

HEALTHCARE PROVIDER PERSPECTIVES ON HPV VACCINATION AMONG 27-45 YEAR OLDS IN THE UNITED STATES

39 - Public health

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Background/Objectives: In the United States, HPV vaccination is recommended for 11-12-year-olds with catch-up vaccination until age 26. In 2019, the guidelines expanded to include HPV vaccination for unvaccinated 27-45-year-olds based on a shared clinical decision with a healthcare provider. Since the guideline implementation, little is known on provider perceptions on this recommendation. The purpose of this study was to elucidate healthcare provider perspectives on HPV vaccination for 27- to 45-year-olds in the United States.

Methods: A convenience sample of 9 family medicine and 9 OB/Gyn healthcare providers was recruited in 2023. Semi-structured interviews were conducted virtually with 18 healthcare providers regarding current HPV vaccination practices for 27-45-year-olds, perceptions of the guideline, and shared clinical decision-making needs. Thematic analysis was conducted using interview transcripts, and interrater reliability achieved for >10% of the transcripts.

Results: The sample included 39%physicians, 44% nurse practitioners, and 17% physician assistants. Overall, most participants reported that they have recommended HPV vaccination to patients aged 27-to-45-year-olds; however, they applied various criteria to guide these discussions. Some participants considered the patients'relationship statuses, sexual partnerships, past HPV infection history, and age. Potential needs to facilitateshared clinical decision-making processes included medical record prompts and brief educational materials.

Conclusions: While most healthcare providers in this sample discussed HPV vaccination with their patients ages 27-to-45 years old, there were inconsistencies in the interpretation of the guideline. The lack of specificity in the recommendation will likely result insignificantand potentially inequitable implementation difficulties. As such, decision support tools are needed to facilitate the shared clinical decision-making process and implement this vaccine guideline into clinical practice in the United States.

References: Funding: This project was supported by the Merck Investigator Studies Program

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#7895

ATTITUDES of DUTCH YHCWS REGARDING HPV AND MENACWY VACCINES FOR ADOLESCENTS

39 - Public health

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Background/Objectives: Vaccination in the Dutch NIP are executed by physicians and nurses working for Youth Health Care organizations, further called Youth Health Care workers (YHCWs). Since 2010 girls in the Netherlands get offered the HPV-vaccine at the age of 13. In 2018 the MenACWY-vaccine for adolescents at the age of 14 was introduced because of an outbreak of meningococcal type W disease. In 2018 the HPV-vaccine coverage for girls born in 2004 was 45,5%. The preliminary coverage for MenACWY for adolescents born in 2004 was 87,1% (1). In 2019 the HPV-vaccine coverage for girls born in 2005 was 53,0%. The MenACWY coverage for adolescents born in 2005 was 87,0% (2). In 2022 the HPV-vaccine uptake for the girls born in 2008 was 58,5% and for MenACWY for the 2007 cohort 80,3%. The HPV-vaccine uptake keeps lagging behind compared to the MenACWY-vaccine uptake and the uptake of other vaccines in the NIP (3). YHCWs are the cornerstone of the execution of the NIP. Since recommendation of a vaccine by a health care provider is an important factor in vaccine confidence, it is relevant to know their attitude towards the NIP and how they see their role within the NIP. This study aims to gain insight into these attitudes and to the perceived role of YHCWs working with adolescents.

Methods: This study consisted of 15 semi structured interviews with 8 nurses and 7 physicians working with adolescents. Thematic analysis of the interviews took place using MAXQDA (version 2018.2). Interviews took place between May and September 2019.

Results: The attitudes of the YHCWs towards the NIP in general and the NIP for adolescents in specific were positive. Some hesitancy existed about the amount of vaccines being added to the NIP. Meningococcal disease was perceived as more severe and more terrifying than an HPV-infection, contributed by the sudden onset and rapid deterioration and deaths of healthy youngsters. HPV-infections were perceived as less severe. MenACWY and HPV-vaccinations are offered at least twice a year in a mass campaign event. YHC-organizations offer one or more adolescent well-visits during secondary school. Sometimes a health questionnaire is used as a risk assessment tool. Visits take place at school, mostly alone with the adolescents. Vaccines are not a standard topic during these visits. Some YHCWs ask about the vaccination status of the child. The introduction of the MenACWY-vaccine seems to have made YHCWs more pro-active in bringing up the topic of vaccination. YHCWs who talk about vaccines see it as their role to inform and not to convince. Sometimes having a conversation is perceived as difficult. Perceived barriers were the age of the adolescents, seeing them without their parents, the perceived policy of their organization not to discuss vaccination with adolescents during school visits.

Conclusions: The attitudes of YHCWs towards the NIP for adolescents is positive. Some knowledge gaps seem to exist about the benefits of HPV-vaccinations for boys and the benefits of the HPV-vaccine as primary prevention compared to the secondary prevention of the cervical cancer screening program. Not all YHCWs talk about the NIP with adolescents or their parents. When they do have conversations about vaccines they see it as their role to inform. Including vaccination status on the health questionnaire can increase the possibility to talk about vaccines. From a public health point of view it would be preferred that all YHCWs talk about vaccines and also give recommendations to be vaccinated.

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FC11 - HPV Vaccines II

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#6857

DURABILITY OF SINGLE-DOSE HPV VACCINE IMMUNE RESPONSES UP TO 5 YEARS POST-VACCINATION IN GIRLS PARTICIPATING IN THE DORIS TRIAL IN TANZANIA

06 - HPV prophylactic vaccines

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Background/Objectives: Recent evidence from the first randomised trial of the efficacy of single dose HPV vaccine has shown high efficacy against persistent human papillomavirus (HPV) 16/18 infection in sexually active young women. Durability of immune responses after a single dose in the target age for vaccination is critically important. We investigated the stability of immune responses over 5 years after a single dose of HPV vaccine in the first randomised controlled trial of single dose HPV vaccination in girls in the target age range for vaccination.

Methods: Tanzanian girls aged 9-14 years were randomised to receive 1, 2 or 3 doses of the 9-valent HPV vaccine, Gardasil-9®, or the 2 valent HPV vaccine, Cervarix®. Blood samples were collected at regular intervals up to Month (M)36 and tested by VLP ELISA for HPV16 and HPV18 IgG antibodies. Girls in the 1 and 2 dose arms will be followed to M108. The proportions of HPV16 and HPV18 seropositive participants at M60 were compared between trial arms using pre-defined non-inferiority margins. The stability of HPV16 and HPV18 antibody geometric mean concentrations (GMC) over time was examined within each arm.

Results: Seropositivity at M60 for HPV16 IgG antibodies after a single dose of either vaccine was >99% and was non-inferior compared with two doses. HPV18 seropositivity at M60 after a single dose was 98% for the 2-valent vaccine and 93% for the 9-valent vaccine, although the non-inferiority criteria were not met. HPV16 and HPV18 antibody GMCs in the one dose arms of both vaccines remained stable from M12 through M60, with no evidence of a decline. The ratio of HPV16 antibody GMC comparing M60 with M12 was 1.06 (95% confidence interval (CI)=0.96-1.17) for the 2-valent vaccine and 1.00 (0.92 -1.09) for the 9-valent. HPV18 antibody GMC ratios were 1.14 (1.02 -1.26) for the 2-valent vaccine and 1.01 (0.92-1.11) for the 9-valent.

Conclusions: A single dose of HPV vaccine in girls from a malaria endemic area who were aged 9-14 years at the time of vaccination continues to provide robust and stable immune responses 5 years after vaccination.

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#6587

COMPARISON OF SEROPREVALENCE OF 9-VALENT HUMAN PAPILLOMAVIRUS VACCINE TYPES USING CLIA AND MULTIPLEXED M9ELISA ASSAYS, UNITED STATES, 2005-2006

19 - Serology

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Background/Objectives: Prior to implementation of the US vaccination program, sera collected through the National Health and Nutrition Examination Survey (NHANES) were tested using a competitive Luminex immunoassay (cLIA) to estimate national HPV type-specific seroprevalence. Serologic testing in some future cycles will be performed using a more recently developed multiplex virus-like particle-based IgG ELISA (M9ELISA). Both assays are type-specific, but the cLIA, used in 9-valent vaccine clinical trials, measures a subset of neutralizing antibodies whereas M9ELISA measures both neutralizing and non-neutralizing antibodies. We present a comparison of HPV seroprevalence using cLIA and M9ELISA among US females and males aged 14-59 years using samples collected in the prevaccine era.

Methods: Sera collected in the 2005-2006 NHANES survey were originally tested for the 9 HPV types in the 9-valent HPV vaccine (9vHPV; HPV6/11/16/18/31/33/45/52/58) using a cLIA assay. Specimens were retested using the M9ELISA assay. Type-specific seroprevalence and 9vHPV seroprevalence (seropositivity for at least one 9vHPV type) were estimated separately for females and males aged 14-59 years, overall and by age group (14-19, 20-29, 30-39, 40-49, 50-59 years), using each assay. Estimates were compared using Wald Chi-square tests.

Results: M9ElISA seroprevalence estimates for individual 9vHPV types ranged from 4.0% for HPV45 to 26.0% for HPV16 among females and 2.8% for HPV58 to 16.9% for HPV16 among males. M9ELISA seroprevalence estimates were higher than cLIA estimates for all individual HPV types among both females (range: 1.4% for HPV45 to 19.6% for HPV6) and males (0.8% for HPV45 to 9.3% for HPV6) (all p-values inf 0.05). Using M9ELISA, 47.5% of females and 26.0% of males were positive for at least one 9vHPV type. 9vHPV seroprevalence using cLIA was lower at 40.5% for females and 19.4% for males (p-values inf 0.0001). Seroprevalence for 9vHPV and all individual types varied by age group in both males and females (all p-values inf 0.05); both assays showed similar patterns in seroprevalence by age. Among females, for nearly all types, seroprevalence was highest among those ages 20-29 or 30-39 years and lowest among those aged 14-19 years. Among males, seroprevalence was highest among those aged 40-49 years and lowest among those aged 14-19 or 20-29 years for most HPV types.

Conclusions: This unique dataset allows comparison of cLIA and M9ELISA from samples collected in an HPV vaccine naïve population. Seroprevalence using M9ELISA was significantly higher than estimates using cLIA. These recently released baseline M9ELISA HPV serology data will be helpful as a historical comparison in future analyses of NHANES serologic data.

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#6990

VACCINE EFFECTIVENESS OF BIVALENT HPV VACCINATION: COMPARISON OF ROUTINE VACCINATION VERSUS CATCH-UP CAMPAIGN FOR 13-16 YEAR OLD GIRLS

06 - HPV prophylactic vaccines

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Background/Objectives: Previous post-licencing observational vaccine effectiveness (VE) studies on bivalent human papillomavirus (HPV) vaccination often mainly included women vaccinated in catch-up campaigns. VE may be lower in catch-up campaigns than in routine vaccination, as girls receiving HPV vaccines at an older age are more likely to be sexually active. The Netherlands had a catch-up in 2009 for girls aged 13-16 years, and started routine HPV vaccination for girls aged 12 years in 2010. As the Netherlands is one of few countries which only used the bivalent HPV vaccine, it is uniquely placed to assess VE of the bivalent vaccine. This study aims to assess type-specific VE of the bivalent HPV vaccine, and to assess potential differences in VE between routine vaccination and the catch-up campaign for women aged 13-16 years.

Methods: The current study reports updated and elaborated VE estimates of the PASSYON study, a Dutch biennial repeated cross-sectional study (2011-2021) among young sexual health clinic clients. Participants filled in a questionnaire, and provided self-collected vaginal swabs, tested for HPV DNA and typed with DEIA-LIPA-25. Type-specific and grouped VE estimates against genital HPV positivity were assessed, adjusted with propensity score stratification. Adjustments were made for possible inter-study-round differences in study population, and differences between vaccinated and unvaccinated women. With stratified analyses, differences in VE for targeted genotypes and a set of grouped VE estimates were assessed between the women who had been eligible for vaccination in the catch-up and routine vaccination.

Results: The PASSYON study included 4,488 female participants who had been eligible for HPV vaccination in either the catch-up or routine vaccination. Overall, 6.7% of the participants tested positive for HPV-16 and/or HPV-18 (n=299) and 56.4% for at least one high risk (hr) HPV genotype (n=2,532). VE against genital HPV-16 was 93.5% (95%CI: 89.8; 95.9), and against HPV-18 89.5% (95%CI: 83.0; 93.6). Outside of the two vaccine targeted genotypes, statistically significant protection was found against HPV-31 (63.9%), HPV-33 (51.5%), HPV-35 (48.5%), HPV-45 (79.6%), HPV-52 (18.0%) and HPV-58 (31.4%). Stratified analyses did not show different VE estimates between women eligible for the catch-up campaign and routine vaccination: the VE against HPV16/18 for women who had been eligible for catch-up was 92.1% (95%CI: 87.8; 94.9) and for routine vaccination 91.8% (95%CI: 86.0; 95.1).

Conclusions: We observed high VE against genital HPV-16/18 positivity among young women in the Netherlands. Additionally, significant cross-protection was found for 6 other hrHPV genotypes. These eight genotypes are responsible for 89% of cervical cancers worldwide. These findings should inform cost-effectiveness studies concerning vaccine choice in National Immunisation Programmes (NIPs). Moreover, we showed that catch-up campaigns focussed on women up to the age of 16 years can provide the same level of protection as routine vaccination at an earlier age. This provides important insights for other countries as roll-out or changes in HPV vaccination in countries' NIPs are often combined with catch-up campaigns.

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United States

#6586

VACCINE EFFECTIVENESS AGAINST ANAL HPV INFECTION AMONG MEN WHO HAVE SEX WITH MEN AGES 18-45 - UNITED STATES, 2018-2022

06 - HPV prophylactic vaccines

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Background/Objectives: Men who have sex with men (MSM) are disproportionately affected by human papillomavirus (HPV) infections and HPV-related diseases. In the United States, HPV vaccination has been recommended for MSM through age 26 since 2011; shared decision-making with healthcare providers regarding vaccination has been recommended for some adults through age 45 since 2019. Quadrivalent vaccine (4vHPV) was the first HPV vaccine used; 9-valent (9vHPV) vaccine, introduced in 2015, has been the only vaccine available in the U.S. since the end of 2016. We assessed HPV vaccine effectiveness (VE) against anal HPV among MSM.

Methods: Residual anal specimens from MSM ages 18-45, submitted for gonorrhea/chlamydia testing at clinics in 3 U.S. cities in 2018-2022, were tested for 28 HPV types. Demographic and vaccination history data were obtained from clinic records or vaccine registries. People living with HIV were excluded from analysis. We calculated prevalence of 4vHPV and non-9vHPV types among vaccinated (≥1 documented vaccination ≥30 days before specimen collection) and unvaccinated MSM. Non-9vHPV-type (i.e., not prevented by any vaccine) prevalence was used as a measure of sexual exposure. Log-binomial regression was used to calculate adjusted prevalence ratios (aPR) and 95% confidence intervals (CI) for associations between vaccination and HPV infection, adjusting for city and race/ethnicity. Joint and separate effects of age at vaccination (inf18, 18-26, >26 yrs) and time since vaccination (inf1, 1-inf2, ≥2 yrs) were evaluated. Analyses were stratified by age group (18-26, 27-45 yrs). VE was calculated as (1-aPR)x100.

Results: Among 2289 MSM ages 18-26, 45% were vaccinated; of those, 43% were vaccinated at age inf18 and 57% at age 18-26, and 15% were vaccinated inf1 yr, 12% 1- inf2 yrs, and 72% ≥2 yrs before specimen collection. Compared with unvaccinated MSM, 4vHPV-type prevalence was lower in vaccinated MSM (aPR=0.81, CI:0.68-0.96, VE=19%; Table), those vaccinated at age inf18 (aPR=0.12, CI:0.07-0.22, VE=88%), and those vaccinated ≥2 yrs before specimen collection (aPR=0.53, CI:0.42-0.67, VE=47%). Among 2751 MSM ages 27-45, 24% were vaccinated; of those, 2% were vaccinated at age inf18, 41% at age 18-26, and 57% at age >26, and 25% were vaccinated inf1 yr, 22% 1- inf2 yrs, and 54% ≥2 yrs before specimen collection. Compared with unvaccinated MSM, 4vHPV-type prevalence was lower in vaccinated MSM (aPR=0.78, CI:0.68-0.90, VE=22%) and those vaccinated at ages 18-26 (aPR=0.64, CI:0.51-0.80, VE=36%). While there was no VE in MSM vaccinated at age >26 years overall, prevalence was lower among MSM vaccinated at age >26 if time since vaccination was ≥2 yrs (aPR=0.63, CI:0.45-0.89, VE=37%). In both age groups, non-9vHPV-type prevalence was similar in vaccinated and unvaccinated MSM.

Conclusions: Among MSM ages 18-26, we found high VE against anal 4vHPV-type prevalence when age at vaccination was inf18. Among MSM ages 27-45, few had been vaccinated at age inf18. VE was 36% when vaccination occurred at ages 18-26 and 37% when vaccination occurred at age >26 yrs if ≥2 yrs before specimen collection. Using a lag period between vaccination and specimen collection to estimate VE among MSM, so that some prevalent HPV infections at the time of vaccination may have cleared, allows VE against new infections to be observed. While ideally vaccination should be given before sexual exposure, vaccination can prevent future HPV infections even in this highly exposed population.

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#6619

EVALUATION OF POSSIBLE HUMAN PAPILLOMAVIRUS (HPV) TYPE REPLACEMENT AFTER VACCINE INTRODUCTION, OVERALL AND BY RACE AND ETHNICITY, UNITED STATES

03 - Epidemiology and natural history

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Background/Objectives: In the United States, routine HPV vaccination was recommended for females aged 11-12 years and catch-up through age 26 starting in 2006. Quadrivalent vaccine (4vHPV) was the first HPV vaccine introduced; 9-valent vaccine, introduced in 2015, has been the only vaccine available since the end of 2016. The possibility of HPV type replacement following vaccine introduction, increases in high-risk (HR) types not targeted by vaccination, has been explored in several countries. While increases in some non-vaccine types have been observed, findings are not consistent. To explore potential type replacement in the United States, we determined type-specific HR HPV prevalence among 14-49-year-old females overall and in non-Hispanic White (NHW) and non-Hispanic Black (NHB) females using National Health and Nutrition Examination Survey (NHANES) data.

Methods: We analyzed HPV DNA positivity from self-collected cervicovaginal specimens among sexually experienced females in two vaccine periods, 2011-2014 and 2015-2018, and in the pre vaccine era, 2003-2006. We limited the analysis to females ages 14-29 and 30-49 years who had adequate HPV typing results; 30-49-year-olds were included for comparison as impact of vaccination in this age group was expected to be minimal. HPV DNA was detected using an L1 consensus PCR assay. We estimated weighted prevalences of 14 individual HR types (HPV16,18,31,33,35,39,45,51,52,56,58,59,66,68), two low risk types (HPV6,11), any HPV16/18, any 14 HR type, and any non-4vHR type. Prevalence ratios (PRs) were calculated comparing prevalences in each vaccine period to pre vaccine era prevalences. Significant differences were defined as PRs with a confidence interval that does not include 1. We also present self-reported receipt of ≥1 HPV vaccine dose in the two vaccine periods.

Results: During 2011-2014 and 2015-2018, reported ≥1 dose HPV vaccine coverage among 14-29-year-olds was 40.1% and 51.4%, and among 30-49-year-olds was 3.5% and 6.9%. Among 14-29-year-olds, between 2003-2006 and 2011-2014, there was a significant decrease in HPV16/18 prevalence (12.3% vs. 6.2%, PR 0.50 [95% CI 0.37, 0.70]) and no significant increase in any or any individual non-4vHR HPV type. From 2003-2006 to 2015-2018, we observed a decrease in HPV16/18 prevalence (12.3% vs. 4.3%, PR 0.35 [95% CI 0.21, 0.57]) and no significant increase in any or any individual non-4vHR HPV type overall (Table). By race and ethnicity, there were similar decreases in HPV16/18 among NHB and NHW (Table). There was an increase in HPV35 prevalence among NHW (1.0% vs. 3.5%, PR 3.55 [95% CI 1.03, 12.21]) but not among NHB females, and there was an increase in HPV68 among NHB (3.0% vs. 7.0%, PR 2.35 [95% CI 1.02, 5.38]) but not among NHW females. Among 30-49-year-olds, there were no significant decreases in HPV 16 or 18 and no increases non-4vHR HPV types in 2011-2014 or 2015-2018 compared with the pre vaccine era overall or in either racial/ethnic group (data not shown).

Conclusions: We found no evidence of type replacement up to 12 years after introduction of HPV vaccination in the United States among 14-29-year-olds overall. In this age group, increases in prevalence were seen for HPV35 among NHW but not NHB females and for HPV68 among NHB but not NHW females in the most recent vaccine period examined. Continued monitoring can provide additional information as vaccine coverage increases further. Overall, these data show no strong evidence of type replacement, consistent with studies in other countries.

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#7067

RISK OF CIN2 PROGRESSION BY HPV VACCINATION STATUS

23 - Risk management

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Background/Objectives: Background: HPV infection may lead to development of cervical precancer graded as CIN1 (mild), CIN2 (moderate], CIN3 (severe) and cancer. Historically, CIN2 has been removed surgically, but as this is associated with an increased risk of preterm birth, fertile women are now recommended active surveillance with semi-annual follow-up visits for up to 2 years. Some of these women will progress to CIN3+ and identification of those at increased risk of progression is clinically relevant. However, we are lacking knowledge on clinical variables that identifies high-risk patient groups. We therefore aimed to investigate whether HPV-vaccinated women undergoing active surveillance for CIN2 are less likely to progress to CIN3+ compared to unvaccinated women.

Methods: Methods: We conducted a nationwide population-based cohort study of all Danish women aged 18-40 who were diagnosed with incident CIN2 during 2007-2020. We obtained information on HPV vaccination status as the primary exposure. Primary outcome was CIN3+, and women contributed with time-at-risk from date of CIN2 diagnosis until date of CIN3+, hysterectomy, emigration, death, or end of follow-up (28 months after CIN2 diagnosis), whichever occurred first. We calculated risk ratios (RR) using modified Poisson regression to evaluate the association between vaccination status and risk of CIN3+.

Results: Results: We included 7,904 women of whom 3,876 (49%) had received the HPV vaccine at least 1 year prior to CIN2 diagnosis. Vaccinated women were younger (median age 25 (IQR 23-27)) than unvaccinated women (29 (IQR 25-33)), and 17.5% of vaccinated women were vaccinated before the age of 15. Overall, HPV vaccination was not associated with a lower risk of progression to CIN3+ compared to no vaccination (RR 0.98 (95% CI 0.93-1.04)). Stratified by age at vaccination, women vaccinated before age 15 (RR 0.65 (95% CI 0.57-0.75)) and between age 15 and 20 (RR 0.86 (95% CI 0.79-0.95)) had a lower risk of progression to CIN3+ compared to unvaccinated women. For women vaccinated after age 20, the risk was comparable to that in unvaccinated women (RR 1.02 (95% CI 0.96-1.09).

Conclusions: Conclusion: HPV vaccination administered before the age of 20 is associated with a lower risk of progression of CIN2. These findings are of highly clinical importance, and may be used in risk stratification of clinical management of CIN2, as well as clinical counselling and shared decision-making.

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#7044

REDUCTION OF PRECANCEROUS LESIONS AND CANCER IN THE CERVIX AMONG THE JAPANESE HPV VACCINATION GENERATIONS？NATIONAL DATA SUGGESTS THE EFFECTIVENESS OF THE VACCINE

39 - Public health

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Background/Objectives: The incidence and mortality rates of cervical cancer show a negative correlation with socioeconomic development. In advanced countries that have implemented effective cervical cancer screening programs and HPV vaccination, the incidence and mortality rates are stable or decreasing (1). However, in Japan, more than 10,000 people are diagnosed with cervical cancer annually, and approximately 3,000 people die from it. The incidence rate per 100,000 has increased significantly from 9.1 people in 2000 to 16.8 people in 2019 (2). This is due to the fact that the Japanese Government started HPV vaccination recommendations for 13 to 16 year olds in 2010, but withheld the recommendations in 2013 as a result of a negative campaign of vaccine adverse reactions. In a study comparing the "vaccination generation" (born between 1994 and 1999, vaccination rate: 55.5% to 78.8%) with the "vaccine-suspension generation" (born between 2000 and 2005, vaccination rate: 14.3% to 0%), the abnormal cell rate in screening was found to be increasing in the vaccine-suspension generation, close to the expected rate based on the trend of the "pre-introduction generation" before vaccination started (2). However, this study was limited to data from only about 10% of the entire Japanese population in 24 municipalities and did not include results from precise examinations. Therefore, we compared the discovery rates of precancerous lesions and cancer in cervical cancer screening between the "vaccination generation" and "vaccine pre-introduction generation" using national cervical cancer screening statistics data that includes results from precise examinations.

Methods: First, we collected data on precancerous lesions and cancer (HSIL+ & AIS) in cervical cancer screening from the Ministry of Health, Labour and Welfare's Report on Regional Public Health Services and Health Promotion Services (2014, 2016, 2018, and 2020) and calculated their discovery rates. Next, we divided people aged 20-59 into eight groups every five years and examined the trends in discovery rates of precancerous lesions and cancer for each group. Currently available national cancer screening statistics data only goes up to 2020, and since vaccine-suspension generations are not yet included in cancer screening targets, this study only compared discovery rates between vaccination generations and pre-introduction generations.

Results: The number of precancerous lesions and cancer cases decreased in people in their early twenties belonging to the vaccination generation. The number remained stable after a temporary increase in people in their late twenties in 2016. Discovery rates were generally increasing for six groups aged over thirty belonging to pre-introduction generations.

Conclusions: We used national cervical cancer screening statistics data to examine changes in discovery rates of precancerous lesions and cancer in cervical cancer between vaccination generations and pre-introduction generations. The discovery rates decreased for vaccination generations but increased for pre-introduction generations. This study only examined trends based on collected data from national cancer screening results; however, it can be said that HPV vaccine effectiveness is supported by national statistics. The Japanese government resumed its recommendation for HPV vaccination in November 2021; however, it is necessary to strengthen calls for vaccination including catch-up vaccinations for vaccine-suspension generations (born between 2000 and 2009.)

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#7084

Human papillomavirus type-specific distribution in cervical intraepithelial neoplasia and cancer in The Gambia prior to HPV immunization programme: A baseline for monitoring the quadrivalent vaccine

06 - HPV prophylactic vaccines

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Background/Objectives: In the Gambia, cervical cancer ranks as the most frequent cancer among Gambian women and the 1st most frequent cancer among reproductive aged women 15 - 44 years with an age standardised incidence rate of 42.9% and age standardised mortality rate of 33.9% (IARC., 2023). Eighty percent (80%) of Gambian women diagnosed with cervical cancer do not attain the 5-year relative survival rate due to late-stage diagnosis of the disease. In 2019, the Gambia rolled out the HPV vaccination program of girls aged 9-14 years with a coverage of 68%. Although, there are studies on the distribution of circulating HPV genotypes in the Gambia (Bah et al., 2018), there are no recent studies, characterising HPV genotypes in archived formalin fixed paraffin embedded (FFPE) biopsy cervical cancer tissues. Aim: To establish an association between specific HPV types and the development of cancer to determine the potential effectiveness of the quadrivalent vaccine in the Gambia in future.

Methods: Method: Study design: The study was a retrospective cross-sectional study. A total of 223 FFPE tissue samples with either precancerous or cervical cancer were retrieved from the pathology department and sectioned for HPV DNA screening. 104 samples failed to amplify the internal housekeeping gene and were removed from screening. 119 samples adequately amplified the internal housekeeping gene and therefore were screened for HPV DNA using the line gene 9200 (Atila Biosystem). Statistical analysis: Epidemiological data was stored using Epi-Info version 7 (https://www.cdc.gov/epiinfo) software and was linked to both the clinical data and the HPV genotyping results. The final data base was analysed using IBM SPSS version 20.0. Analysis was primarily descriptive with proportions of each HPV type detected in the cancers. Fisher's exact tests were used to determine the primary outcomes of interest at a p-value of < 0.05 and 95% confidence intervals (CI) were considered statistically significant.

Results: HPV prevalence in the FFPE samples was found to be 87% (104/119). HPV 16 accounts for 53% (56/104) of the HPV genotypes found in the cervical tissues, followed by HR-others 17% (18/104), and HPV 18 accounts for 15% (16/104). Ninety-three percent (93%, 97/104) of HPV positive samples were squamous cell carcinoma and HPV 16 were the majority (54,6%). However, only 5 adenocarcinoma cancers were positive for HPV and HPV 18 accounts for 40% (2/5). Overall, HPV DNA was not detected in approximately 15/119 (13%) of cancers. The data showed that HPV 16 related cancer was more prevalence in the 43 -53-year-old (18.3%). 39% of the cervical cancer biopsies that were HPV positive were from the Mandinka ethnicity. A bivariate analysis showed there was no significant association between ethnicity, residential area of the participants and their diagnosis with cervical cancer, HPV result and HPV Genotype ($p > 0.05$). However, there was a strong association between participants' age with their diagnosis with cervical cancer ($p = 0.023$) and HPV Genotype ($p = 0.038$).

Conclusions: Conclusion: There is no difference in the distribution of HPV 16 genotypes in cervical cancerous cases in The Gambia in comparison with the global distribution. However, other HR-HPV are also linked to causing cervical cancer in the Gambia. The Gambia will certainly benefit from the nonavalent vaccine for an effective cervical cancer elimination.

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#6773

Mortality trends from Human Papillomavirus (HPV)-related cancers and vaccination coverage in Brazil

03 - Epidemiology and natural history

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Background/Objectives: In Brazil, there are few studies on mortality trends due to the anal canal/anus, vulva/vagina and penis, cancers related to the human papillomavirus (HPV), and therefore preventable, as well as cancer of the cervix and oropharynx. In the world, in 2012, it is estimated that approximately 100% of cervical cancer, 88% of anal canal cancer, 78% of vaginal cancer, 50% of penile cancer, 24.9% of vulvar cancer are caused by HPV, while for oropharyngeal cancer the attributable fraction varies around the world, being highest in developed countries (more than 40% in Europe and North America), and 13% in Latin America (de Martel et al, 2017). In Brazil, HPV vaccination has been included in the National Immunization Program (PNI) since 2012.Objective: To describe the rates and trends of mortality from HPV-related cancers in Brazil and its states from 1996 to 2019, as well as the doses of HPV vaccines administered in Brazil in 2022.

Methods: Data on mortality from HPV-related cancers (C01-02, C05, C09-10, C21, C51-53, C60) were extracted from the Sistema de Informações sobre Mortalidade (SIM) of the Departamento de Informática do Sistema Único de Saúde (DATASUS). States with more than five years without data on mortality from HPV-related cancers in the DATASUS database were excluded from the analysis for each studied site. Age-standardized mortality rates were calculated. The average annual percent change (AAPC) was calculated using the Joinpoint Regression Program. Results were considered statistically significant when p inf 0.05. The number of vaccine doses administered in Brazil and its states for HPV in females and males was extracted from the DATASUS database according to the PNI. The total vaccine coverage, as well as coverage for the first dose (D1) and second dose (D2) in 2022, for girls aged 9 to 14 years and boys aged 11 to 14 years, was calculated using the cumulative coverage method stratified by age cohort. The numerator was the cumulative sum of vaccine doses administered to each cohort since the first year they became eligible. The denominator was the number of eligible girls and boys residing in each locality for vaccination in 2022.

Results: In Brazil, during the studied period, there were 214,513 deaths, including 116,216 (54%) deaths from cervical cancer, 74,437 (35%) from oropharyngeal cancer, 9,546 (4%) from vulva/vaginal cancer, 7,385 (3%) from penile cancer, and 6,929 (3%) deaths from anal cancer. Mortality rates and AAPC for anal and oropharyngeal cancers in both sexes, vulva/vaginal and penile cancers showed an increasing trend, while cervical cancer remained stable. The highest increases in mortality rates for HPV-related cancers were concentrated in the northern and northeastern regions. In Brazil, the HPV vaccination coverage for the first dose among females was 76.71%, with higher coverage rates in the states of Paraná (94.96%) and Santa Catarina (90.89%), and lower rates in Acre (22.52%) and Amapá (61.79%). For the second dose, the coverage was 55.11%, with the highest coverage in Paraná (77.53%) and the lowest in Acre (21.55%). The HPV vaccination coverage for males was 53.09% for the first dose and 34.01% for the second dose. The highest coverage was observed in Paraná (59.22%), while the lowest was in Acre (7.99%).

Conclusions: In Brazil, mortality from HPV-associated cancers demonstrated stability for cervical cancer and increases in all other topographies. Vaccination continued to have low coverage, especially among males.

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#6816

HEALTHCARE WORKERS' SENTIMENTS ON RECOMMENDING THE HPV VACCINE: A SYSTEMATIC REVIEW

06 - HPV prophylactic vaccines

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Background/Objectives: Human papillomavirus (HPV) is linked with 74% of cancers among women, most of which are cervical cancers. The HPV vaccine has been introduced in many countries over the past two decades but rollout is slow globally. Healthcare workers are the most trusted advisor affecting patients' or parents' vaccine decision-making. Thus, in an era of increased vaccine hesitancy, understanding healthcare workers' vaccine beliefs and recommendation behaviors is critical. The aim of this systematic review is to investigate the evidence that exists on healthcare worker's sentiments on recommending the HPV vaccine to their patients.

Methods: A literature search was conducted based on a search strategy developed in Medline (Ovid) in collaboration with librarians at Karolinska Institutet University Library. The databases searched were Medline, Web of Science, CABI: CAB Abstracts, and Global Health and Sociological Abstracts, and as a complementary search Publicly Available Content database. Inclusion criteria were that the articles needed to address healthcare workers' recommendation sentiments or behavior, and could not be proposals, abstracts, or reviews. The JBI quality assessment tool for cross-sectional or qualitative studies was used. For the data analysis, a qualitative synthesis approach was used.

Results: 40 articles were included in the final review. The majority (30/40) of the studies were conducted in high-income countries and after 2010 (36/40). Recommendation behavior varies widely based on the context, the time since the vaccine introduction in the study context, and based on the patient's gender. 19 out of 40 articles concluded a high likelihood to recommend, with 16 of these studies being in high-income countries. 12 had a medium likelihood to recommend and nine concluded a low likelihood to recommend. 4/9 of the low likelihood to recommend were in low-middle-income settings. When vaccination of adolescent males was studied, the likelihood to recommend was lower than for females. Barriers to HPV vaccine recommendation were the cost of the vaccine, lack of evidence on efficacy, that the vaccine is too new, parental hesitancy, concerns about safety, and resistance to discussing sexuality. Several of the cross-sectional studies utilizing a survey or questionnaire did not discuss the validity or reliability of the tool used.

Conclusions: Healthcare worker recommendation behavior varies across contexts with a higher likelihood to recommend in high-income countries and among female patients. Low willingness to recommend the HPV vaccine is concerning for improving vaccine uptake. In particular, there were healthcare worker concerns related to the vaccine cost, efficacy, and the need to discuss sexuality.

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#6683

CROSS-SECTIONAL STUDY TO ESTIMATE HPV VACCINE COVERAGE RATE IN A SPECIFIC HIGH-RISK POPULATION IN SPAIN, COVAR STUDY

06 - HPV prophylactic vaccines

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Background/Objectives: In Spain, HPV vaccination is funded in some adult unvaccinated high-risk groups, including since 2018, women undergoing cervical excisional therapy due to cervical precancerous lesions (SIL/CIN)1. Currently, there is no published information about the HPV vaccination coverage rate (VCR) in this population. Our study aimed to estimate the HPV VCR in this group of women, to describe their sociodemographic characteristics, and the impact of the COVID-19 pandemic on the number of cervical excisions and the HPV VCR.

Methods: Non-interventional, multicentric, cross-sectional, retrospective study conducted by gynecologists within Cervical Pathology Units of 6 public hospitals in Spain, using data from medical charts. Inclusion criteria were females who had undergone cervical excisional treatment due to SIL/CIN from 1 January 2019 to 31 December 2021. A descriptive analysis was carried out using mean and standard deviation for continuous variables and percentages for categorical variables.

Results: 1300 women were included. Mean age was 40 (SD 10.0) years, 34.8% (453/1300) were nulliparous and 5.4% (70/1300) had immunosuppression. Overall, 87.3% (1135/1300) of women received at least one dose of HPV vaccine. The VCR was higher in younger women (90.8% (375/413) in 28-35 yo vs. 63.2% (12/19) in >65 yo; pinf0.001). Among vaccinated women, 88.5% (1005/1135) received peri-treatment HPV vaccination: 58.3% (662/1135) started vaccination after the conization and 30.2% (343/1135) after SIL/CIN diagnosis but prior to the excisional treatment, and 11.5% (130/1135) received it prior SIL/CIN diagnosis. Vaccines were mostly administered in primary outpatient settings (public primary care and private outpatient clinics; 66.9% (759/1135)). The number of conizations decreased during COVID-19 pandemic and so was the HPV VCR (adjusted per year). Comparing the pre COVID-19 period with the first restrictions period, the proportion of women receiving cervical excisional treatment decreased from 32.7% to 19.6% (pinf0.001), and the proportion of women who started vaccination was reduced from 30% to 20.7% (pinf0.001).

Conclusions: Our study shows a high HPV VCR in this population, mostly peri-treatment HPV vaccination. However, there is still a percentage of women not vaccinated. VCR was higher in women under 35 years old and most of them received the vaccines in primary outpatient settings. This study also evidences the detrimental effect of the COVID-19 pandemic on the number of cervical excisions and the HPV VCR. Findings of this study are key to ensure a correct implementation and success of this type of vaccination programs.

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FC12 - Economics and modeling

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#6826

Cost-effectiveness analysis of single-dose or 2-dose of 2vHPV, 4vHPV, or 9vHPV vaccine in a low/middle income country setting.

35 - Economics and modelling

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Background/Objectives: This study endeavors to assess the health impact and economic benefits of one dose or two doses of 2-valent (2vHPV), 4-valent (4vHPV), or 9-valent (9vHPV) HPV vaccine compared to no vaccination, in conjunction with primary HPV screening in a low/middle income country setting, specifically focusing on Thailand.

Methods: A Markov model was employed to simulate HPV infection and cervical cancer in a cohort of 100,000 12-year-old girls free of HPV. The study scrutinized nine strategies: one dose and two doses of 2vHPV (Cervarix®), 2vHPV (Cecolin®), 4vHPV (Gardasil®), 9vHPV vaccine (Gardasil9®), and no vaccination. The primary outcome measure was the quality-adjusted life year (QALY) associated with each strategy. Incremental cost-effectiveness ratios (ICER) were estimated over a lifetime horizon, accompanied by univariate and probabilistic sensitivity analyses were conducted for uncertain variables across various scenarios. Interpretation of ICER was based on the willingness-to-pay (WTP) threshold in Thailand of 160,000 THB (4,552.50 USD) per QALY gained for reimbursing new life-saving treatment.

Results: In the base case scenario, all vaccination programs yielded in 41,298-71,057 QALYs gained accompanied by cost savings of 14,914,186-19,821,655 USD compared to no vaccination. The incremental analysis revealed that administering two doses of 9vHPV vaccine emerged as the most cost-effective strategy, boasting an ICER of 406 USD/QALY, within a lower willingness to pay threshold. Sensitivity analysis demonstrated an 80% probability of the cost-effectiveness of the two-doses 9vHPV vaccine regimen. Furthermore, uncertainty around the costs of vaccination and vaccine efficacy exerted the most substantial influence on the cost-effectiveness outcomes.

Conclusions: Opting for two-doses of 9vHPV vaccine in conjunction with a primary HPV screening for screening program represent the most cost-effective option for implementing a school-based HPV vaccination program targeting 12-year-old girls in Thailand. Such findings provide valuable insights for policymakers in the realm of cervical cancer prevention.

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#6938

Cost-effectiveness analysis of HPV vaccination for women with cervical intraepithelial neoplasia treatment

35 - Economics and modelling

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Background/Objectives: Cervical intraepithelial neoplasia (CIN) is a pre-malignant condition of the cervical epithelium. High-grade disease often requires surgical excision to mitigate the risk of progression to cervical cancer. However, women have undergone CIN treatment are at an increased risk of subsequent disease, highlighting the importance of preventive measures to further reduce the risk of cervical cancer development. Vaccination against HPV is an effective public health measure to prevent HPV infections and related cervical neoplasia. The study aims to assess the cost-effectiveness of prophylactic, nonavalant, HPV vaccination for women undergoing treatment for CIN2+ in conjunction with post-treatment surveillance in the United Kingdom (UK).

Methods: To evaluate the economic implication of peri-treatment HPV vaccination on reducing the risk of subsequent disease, a Markov model was developed to account for disease progression dynamics of clinical outcomes attributed to HPV including cervical infection and associated cancers (i.e. cervical, vaginal, vulvar, anal, head and neck), and diseases (i.e. genital warts and recurrent respiratory papillomatosis). Various scenarios are explored including the impact of vaccine cost and coverage, age at treatment, incremental utility, cancer cases and deaths avoided, the potential associated healthcare cost savings. Data were obtained and derived from published sources.

Results: At a 3.5% discount rate and the list price vaccine, the incremental cost-effectiveness ratio (ICER) for vaccination with regular post-treatment surveillance compared to surveillance only was calculated to be £18,925 per quality adjusted life years (QALY). Moreover, the incremental cost per HPV-related cancer and cancer death avoided were estimated at £55,767 and £68,186, respectively. These findings suggest that peri-CIN 2+ treatment vaccination is a cost-effective intervention, as it offers significant health benefits with the incremental cost per QALY gained that is below the accepted cost-effectiveness threshold of £20,000/QALY gained in the UK. Scenario and sensitivity analysis showed that discount rate, HPV incidence, price of vaccine and age of conization and receiving vaccination are key factors impacting variations in the economic evaluations of peri-CIN2+ treatment vaccination for reducing the likelihood of subsequent cervical cancer development.

Conclusions: The analysis suggests that addition of prophylactic HPV vaccination to post-treatment surveillance for women undergoing treatment for CIN for prevention of HPV-related diseases is a cost-effective intervention. The ICER and per HPV-related cancer avoided are within the acceptable threshold, supporting the integration of peri-treatment vaccination as part of a comprehensive strategy for reducing the burden of HPV-related cancers and diseases.

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#6721

MODELLING THE IMPACT OF CONCOMITANT HUMAN PAPILLONAVIRUS (HPV) VACCINATION AND HPV-BASED SCREENING FOR AN EVEN FASTER ELIMINATION OF HPV IN SWEDEN

35 - Economics and modelling

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Background/Objectives: Although several European countries successfully implemented vaccination against human papillomavirus (HPV) and organized cervical HPV screening, population-based declines of cervical cancer seem not yet close to the WHO elimination threshold. There is therefore an interest in assessing strategies that could result in an even faster elimination of HPV and cervical cancer, especially those implementing concomitant HPV vaccination and HPV screening (previously suggested under the name of HPV-Faster or Even Faster [EF] interventions).[1] In this study, we estimated short-term impact of implementing EF on incidence of high-risk HPV infections in Sweden.

Methods: We used an established dynamic, population-based, and single-type HPV transmission model to predict HPV16 and HPV18 incidence in the entire population of Sweden.[2] First, we adapted the model using age-specific HPV prevalence data among unvaccinated women in Sweden. Then, we validated our model against observed HPV prevalence of the Swedish birth cohorts (1994-1998) targeted by organized catch-up vaccination (coverage around 55%), which started in 2007. Finally, we predicted HPV16 and HPV18 incidence during 2020-2024, simulating EF in 2021 for women born in 1994-1998 and assuming, respectively, none, 30%, and 90% participation in the intervention. Our simulations also assumed school vaccination at age 12 starting in 2007 (coverage around 80%) for women born after 1998.

Results: Our model predicted that EF could reduce the incidence of high-risk HPV infections among women born in 1994-1998. Considering incidence of HPV16, the model predicted a reduction from 9.1 (per 100 women-year) in 2020 to, respectively, 3.6 and 1.5 in 2024 assuming 30% and 90% adherence in the intervention. In contrast, in absence of EF, incidence was predicted to decline from 9.1 to 5.6 (per 100 women-year). Similar patterns were predicted for HPV18.

Conclusions: The findings of this study illustrated how EF would lead to an accelerated decline of high-risk HPV infections in Sweden. As consequence of this decline, risk-based cervical cancer screening policies are under construction, experimenting which screening intensity is needed in the situation with very low HPV incidences.

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#7128

Under which realistic circumstances is hrHPV self-sampling increasing cervical screening effectiveness in a partly vaccinated population? A modelling study

35 - Economics and modelling

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Background/Objectives: High-risk human papillomavirus (HrHPV) self-sampling can increase attendance rates for screening. However, observed lower sensitivity and loss-to-follow-up (LTFU) of self-sampling could reduce programme effectiveness when attenders of clinician sampling switch to self-sampling. We determined the tipping point for effectiveness (based on life years gained (LYG)) of self-sampling and the consequences for cost-effectiveness, taking into account waste.

Methods: We used the STDSIM-MISCAN-Cervix microsimulation model to simulate self-sampling deployment scenarios (e.g. direct-mail) in the Dutch hrHPV screening programme. We simulated a cohort of Dutch women born in 2000 (50% vaccinated [sensitivity analysis: 0-100%], 70% screening attendance [sensitivity analysis: 60-80%]). We varied the percentage of original attenders switching to self-sampling and the percentage of new attendance from non-attenders. Main outcome measures are Life years gained (LYG) and cost-effectiveness (cost per quality adjusted (QA)LYs gained) compared to the current programme.

Results: Compared to no screening, the current screening programme leads to 537 LYG. If self-sampling does not reach non-attenders, life years cannot be gained. When reaching 10% or 30% of non-attenders the tipping point lies at ≤40% and ≤100% switchers to maintain programme effectiveness, respectively (+4 LYG and +10 LYG). Scenarios were cost-effective (<€50,000/QALY) if at least 10% of non-attenders could be reached. Full opt-out improved cost-effectiveness substantially.

Conclusions: Self-sampling deployment strategies need to reach at least 10% of non-attenders to maintain programme effectiveness and cost-effectiveness in a partly vaccinated population. A well-functioning opt-out system further improves cost-effectiveness.

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#7150

Cost-effectiveness Analysis of Alternative Screening Strategies for the detection of Cervical Cancer among poor women in Western Kenya

35 - Economics and modelling

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Background/Objectives: While cervical cancer incidences have dropped in high income countries due to organized cytology-based screening programs, it remains the leading cause of cancer death among women in Eastern Africa. Therefore, the WHO now urges providers to transition from widely prevalent but low performance VIA screening to primary HPV DNA testing. Due to high HPV prevalence, effective triage tests are needed to identify those lesions likely to progress and so avoid over treatment. To identify the optimal cost-effective strategy, we compare the VIA screen-and-treat approach to primary HPV DNA testing with p16/Ki67 dual stain cytology or VIA as triage.

Methods: We use a Markov model to calculate the budget impact of each strategy with incremental quality-adjusted life years (QALY) and incremental cost-effectiveness ratios (ICER) as the main outcome.

Results: Deterministic cost-effectiveness analyses show that the screen-and-treat approach is the most cost-effective (ICER 2336 Int$), while screen, triage and treat with dual staining is the most effective and more cost-effective than triage with VIA (ICER 9049 Int$ compared with 9575 Int$). One-way-sensitivity analyses shows that the results are most sensitive to discounting, VIA performance and test prices. In the probabilistic sensitivity analyses, the triage option using dual stain is the optimal choice above a WTP threshold of 9580 Int$ being cost-effective as per WHO standards.

Conclusions: This study shows, that strategies of primary HPV testing plus triage testing with either dual stain cytology or VIA perform better than the exclusive VIA screening strategy in detecting precancerous lesions in low resource settings with dual stain cytology being the more cost-effective triage option. The cost of such two-step approaches are highly context related and there are several options to increase their cost-effectiveness, including the reduction of test prices and the utilisation of HPV self-sampling strategies. Future research needs to assess the feasibility and cost-effectiveness of such innovative strategies for different low resource settings.

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#7664

CERVICAL CANCER ELIMINATION IN THE UK

35 - Economics and modelling

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Background/Objectives: The National Health Service of the United Kingdom (UK) recently announced its commitment to the elimination of cervical cancer (CC) as a public health problem by the year 2040 i.e. achieving an incidence of less than 4 per 100,000 woman-years. The World Health Organization (WHO) has defined three key interventions to realize this goal: 90% vaccination coverage rate (VCR) in adolescent girls, 70% coverage of cervical screening, and treatment for 90% of women diagnosed with cervical disease. The UK has achieved high VCR among adolescent boys and girls and has had an organized call/recall cervical screening program since 1988. The aim of this study is to adapt a mathematical model of HPV to the UK and assess how current interventions will contribute to the elimination of CC, and how improvements in the CC screening and vaccination programs would impact the timing of reaching CC elimination.

Methods: A mathematical model of HPV transmission, infection and disease was adapted for the UK. Model outputs were validated against two sets of data: the proportionate drop of HPV prevalence from 2010 to 2020, and the age-standardized rate of CC from 2006 to 2017. The model captures historical changes in screening programs and HPV vaccination (including the transitions to gender neutral vaccination, HPV DNA-based screening, and a 9-valent vaccine). CC incidence was forecasted from 2024 through 2124 under various scenarios including: 1) Current levels of vaccination and screening; 2) Various vaccine coverage rates; 3) Increased follow up of abnormal screens; 4) Increased screening coverage in under-screened populations; 5) Combinations of the above scenarios that include the WHO targets.The results were compared to other relevant CC elimination modeling results for the UK. Consistent with other CC elimination modeling in high-income countries, we also considered an aspirational threshold of <1 new case of CC per 100,000 woman-years.

Results: The model results fit the calibration data well, estimating the baseline number of cervical cancers within 3% of the data, and the number of HPV infections within 5% of the target data. The model accurately reproduced the validation data from 2006 to 2020 for both HPV prevalence and CC incidence. At current screening levels and VCR, estimates from the model suggest that the UK may potentially achieve CC elimination by 2050. To achieve elimination by 2040, the model shows that improved follow up of abnormal screens, and increased uptake of CC screening in under-screened populations is necessary. The aspirational threshold of <1 new case per 100,000 woman-years was only achieved in scenarios with both improved screening and high vaccination rates. These results are consistent with other UK specific model results.

Conclusions: UK, through the past successes of its CC control programs, is on track to eliminate CC as a public health problem before 2050, but improvements to the screening program will be necessary to meet the 2040 goal. Improvements in follow-up of abnormal screens and decreased heterogeneity in screening have the greatest impact on reducing the estimated time to CC elimination, as the delayed benefits of vaccination are less influential in reaching the elimination threshold. However, more aspirational goals can only be achieved by combining screening improvements with a high coverage of vaccination.

FC10 - Colposcopy / Management I

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#7117

A prospective cohort study of active surveillance of CIN2 in young women - predicting factors for progression and regression

24 - Colposcopy

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

Methods: This prospective cohort study at Helsinki University Hospital included 258 women aged 18-30 years with histologically confirmed CIN2 lesions. Women were tested for 34 different HPV-types at baseline and followed with colposcopy every 6 months up to 24 months. The rates of regression and progression of CIN2 and their predicting factors were calculated. Risk ratio was used to estimate the relative risks for regression and progression. Regression was defined as normal histology and/or cytology normal or ASC-US, progression to CIN3+, persistence of CIN2 and partial regression defined as histological or cytological LSIL.

Results: Of the recruited women, 205 (84.4%) completed the study. The overall regression rate of CIN2 lesions was 64.4.% (n=132) while 16.1% (n=33) of the lesions progressed to CIN3+. Strongest indicators of progression were initial large cervical lesion (>50%) RR 3.06 (CI 1.40-6.69) and high-grade referral cervical cytology RR 4.73 (1.18-19.03). HPV16 positivity was associated with increased risk of progression, RR 2.03 (95% 1.04-3.96) compared with HPV16 negativity whereas women with low-risk HPV or negative HPV-test had increased probability to regress compared to those with high-risk HPV positivity. Smoking, age, use of combined oral contraceptives or colposcopic impression at baseline did not affect the likelihood of regression or progression. LLETZ was performed to 22.4% of women (n=46) whereas 13.1% of women with minor changes (n=27) remained in active surveillance after the study period.

Conclusions: The majority of CIN2 lesions regress in young women. However, it is of clinical importance to understand factors associated with progression and regression to inform management decisions.

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#7070

Conservative treatment of coexisting high SIL and adenocarcinoma in situ of the cervix: Case report

40 - Fertility and HPV

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Background/Objectives: Adenocarcinoma-in-situ (AIS) of the uterine cervix is a precursor to cervical invasive adenocarcinoma and may co-exist with high-grade squamous intraepithelial lesions of the uterine cervix. Studies show that 55% of women with AIS had co-existing squamous intraepithelial neoplasia. For fertility sparing reasons, conservative treatment is considered and the patient is well informed about the follow-up. On screening cytology there is a lower likelihood of detecting glandular lesions compared to precancerous squamous lesions, due to the fact that the glandular lesions are generally high in the cervix or deep within the glands. Because of the location of glandular disease inside the endocervical canal and in the glandular clefts, the cervical cytology of both squamous and glandular lesions may indicate only squamous cell abnormality. Particular attention is needed to obtain adequate endocervical samples

Methods: We present a case report of 31 years old patient with coexisting Squamous cell carcinoma in situ and Adenocarcinoma in situ AIS. She was referred at our hospital and underwent a cervical biopsy, endocervical sampling and HPV testing. The histopathology result showed high grade squamous intraepithelial lesion and high risk HPV18 positive. The patient was then treated with a cold knife conization. The surgery was uneventful. The histopathology report showed that it was a case of cervical squamous cell carcinoma in situ and adenocarcinoma in situ- HPV related. The patient didn`t accept hysterectomy and after consliar examination of gynecologist and pathologist, was asked to be follow up by endocervical cytology, endocervical biopsy for histological evaluation and human papillomavirus testing every 4 months. We evaluated the effect and safety of cervical coniseation with additional imunostimulators and recurrence or progression of disease in 18 months follow up period in these women.

Results: /////

Conclusions: Conclusion Conservative treatment of coexisting squamous cell and adenocarcinoma in situ cervical cancer is possible with intensive follow up after conservative treatment. Intensive monitoring should preferably be done by endocervical cytology, and human papillomavirus and deviations should be subjected to further histological examination.

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#6955

Can adequate follow-up of women treated for high grade squamous intraepithelial lesions prevent the development of invasive cervical and vaginal cancer?

03 - Epidemiology and natural history

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Background/Objectives: Women previously treated for HSIL have an increased risk of developing recurrent HSIL and invasive cervical or vaginal cancer compared to the general population. Follow-up after treatment is recommended, but the role of the first test after HSIL treatment (test of cure) in relation to subsequent testing is unknown. Furthermore, an appropriate time interval between tests has not been established.

Methods: Women aged above 22 treated for HSIL or invasive cervical or vaginal cancer in Sweden between 1999-2018 were identified through the National Cancer Register. Women were linked to the Swedish National Cervical Screening Registry to retrieve information on cervical screening history including cytology and HPV results. Further linkages were made to the Patient Register (hysterectomy data) and the Cause of Death Register. Women treated for HSIL or cancer before 1999 were excluded. Adherence to follow-up was defined by Swedish national guidelines as having a test of cure within a year after treatment and subsequent testing every 3 years, irrespective of age.

Results: There were 78844 women with HSIL at baseline, and 69,7744 women still at risk one year after HSIL and assessed for cancer after cure test. Out of the 69,744 women, 246 were identified as having a subsequent cervical or vaginal cancer corresponding to an overall absolute risk for cancer after HSIL of 0,7%. The main analysis was split by follow-up time into four screening states: 1) before initiation of screening, 2) regular screening, 3) irregular screening or 4) no screening at all. For each screening state, we found an excess risk of invasive cervical or vaginal cancer for women without a test of cure: before initiation (HR=3.8, p=0.005) regular screening (HR=1.3, p=0.307), irregular screening (HR=2.1, p=0.03), no screening (HR=8.5, p=0.05), though the excess was modest and statistically not significant for regular screening. Adjustments were made for age at HSIL, calender period and education. Sensitivity analyses was performed for women under and above age 38.5 at HSIL diagnosis as well as by excluding all HSILs 2016-2018 when definitions of HSIL changed, but did not affect results.

Conclusions: The risk for cervical or vaginal cancer was elevated in women without a cure test and subsequent irregular or no testing, with a statistically significant substantial extra risk during the time period after being eligible for the test of cure before initiating screening.

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#6762

Underdiagnosis of cervical intraepithelial neoplasia by colposcopy and its association with thin high-grade squamous intraepithelial lesions

24 - Colposcopy

Background/Objectives: The relationship between the thickness of the epithelium and the colposcopic diagnosis is controversial. The present study was conducted to determine whether colposcopic underdiagnosis of cervical intraepithelial neoplasia (CIN) is associated with thin high-grade squamous intraepithelial lesions (HSILs) of the cervix.

Methods: We retrospectively analyzed 136 cases of HSIL confirmed by pathological biopsy in Peking University People's Hospital between June and October 2021; 79 cases were CIN2 and 57 cases were CIN3; The number of epithelial layers and thickness were analyzed according to different colposcopy impression.

Results: In the low-grade colposcopic impression group, the number of epithelial layers (12.8±4.2 vs. 17.8±4.2) and epithelial thickness (105.2±41.9 μm vs. 150.3±50.0 μm) of CIN2 lesions were significantly lower compared with the high-grade colposcopic impression group; however, the differences for CIN3 were not statistically significant. CIN2 lesions had significantly fewer (12.8±4.2 vs. 17.2±5.4) and thinner (105.2±41.9 μm vs. 140.4±48.6 μm) epithelial layers than CIN3 lesions in the low-grade colposcopic impression groups. In the high-grade colposcopic impression group, however, there were no significant differences in the number or thickness of epithelial layers between CIN2 and CIN3. In 12 cases of thin HSILs, 91.6% of the colposcopic impressions were low-grade.

Conclusions: Thin HSILs are likely associated with underdiagnosed colposcopic findings, particularly for CIN2. Thin HSILs usually present with small to minute lesions and lack the typical colposcopic appearance of classic HSIL, which may help to explain why thin HSILs are easily underestimated under colposcopy.

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#6881

EVALUATION OF THE DIAGNOSTIC PERFORMANCE OF COLPOSCOPY IN THE DIAGNOSIS OF HISTOLOGIC CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN2+) IN A TERTIARY-LEVEL HOSPITAL IN MADEIRA, PORTUGAL - A QUALITY CONTROL SURVEY

24 - Colposcopy

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Background/Objectives: Colposcopy is a fundamental step as part of screening programs for detection of pre-cancer cervical lesions and the success of the preventive strategy depends on the diagnostic accuracy of the procedure. It is essential to define indicators and to access quality systems in our clinical practice. Improving protocols and techniques is crucial and it is important to evaluate the performance and effectiveness of colposcopy practice in order to reduce the incidence and mortality from cervical cancer in Portugal, without overtreatment. The main goal of this study is to perform an evaluation of the performance of our Colposcopy Unit and application of quality criteria from the European Federation of Colposcopy (FEC).

Methods: Retrospective analysis of women who underwent excision of the transformation zone (ETZ) from January 2021 to December 2022. From the 6 quality criteria defined by the FEC, we collected data that allowed the evaluation of 4 of these.

Results: The sample contains 181 cases. All users underwent colposcopy before EZT, and in all cases, the transformation type and the colposcopy findings were identified and documented in the clinical file. From a sociodemographic point of view, we found that the patients ages ranged from 24 to 71 years, with an average age of 42.2 years. Regarding the obstetric history, 24,9% (n=45) had 2 vaginal deliveries and 17,7% (n=32) had 3 or more. Regarding risk factors for cervical cancer, 52% (n=94) were smokers, 28,2% (n=51) had 2 sexual partners, 23,8% (n=43) had 3 partners and 48% (n=87) had 4 or more partners. 129 women (71,2%) were vaccinated against HPV, in which, 8,5% (n=11) were vaccinated in the national vaccination program, 42,6% (n=55) after medical assistant advice before EZT and 48,9% (n=63) were vaccinated after EZT. Regarding the cervical cytology results, in 48,1% (n =87) of cases, HSIL was detected, ASC-H in 17,7% (n=32), ASC-US in 12,6% (n=22) and LSIL in 16% (n=29) of cases. The main reasons for performing TZ excision were: CIN2+ in the biopsy (n=126; 69.6%), followed by persistence of LSIL (n=28; 15,5%) and colposcopy-histological discrepancy (n=24; 13,3%). When analyzing the histology of the excision specimens from the TZ, we found: squamous cell carcinoma (n=6; 3,31%), adenocarcinomas (n=2; 1,1%), CIN2+ (n=128, 70.7%), CIN1 (n= 26, 14,3%), and in 10,5% (n=19) of cases, dysplasia was not found. In 61,3% (n=111) of cases, the margins of the TZ excision specimen were free of dysplasia.

Conclusions: In our sample, the colposcopic examination was always performed before any treatment and the type of ZT was documented in all cases. The percentage of excisional treatments with lesion-free margins was inferior to the target of 80% and the percentage of excisional treatments with definitive CIN2+ histology was less than 85%. This colposcopy unit fulfilled 2 of the 4 criteria evaluated. This quality survey is fundamental in order to improve our performance and effectiveness colposcopic practice or to promote changes in standard requirements for operators.

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#6700

ACTIVE SURVEILLANCE OF CIN2 IS NOT ASSOCIATED WITH LOWER RISK OF PRETERM BIRTH

22 - Diagnostic procedures / management

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Background/Objectives: In recent years, active surveillance for cervical intraepithelial neoplasia grade 2 (CIN2) has been implemented in many developed countries, mainly because excisional treatment is associated with increased risk of preterm birth and due to high regression rates of CIN2. However, it remains unclear if active surveillance results in lower risk of preterm birth as cervical dysplasia itself is associated with a higher risk of preterm birth. Here, we compare the risk of preterm birth between women with CIN2 undergoing active surveillance or immediate loop electrosurgical excision procedure (LEEP).

Methods: We conducted a population-based cohort study using Danish nationwide healthcare registers. We included women with a first-time record of CIN2 and a subsequent singleton birth in Denmark during 1998-2018. Women with prior record of CIN3+ or LEEP were excluded. We categorized women into two groups based on their first cervical sample after CIN2 diagnosis. Women with a cervical biopsy and/or cytology were classified as undergoing active surveillance, while women with a record of a LEEP were classified as such. The active surveillance group was further subdivided based on whether a delayed LEEP was performed during the surveillance period. We calculated relative risks (RR) of preterm birth (inf37+0) using modified Poisson regression. Inverse probability treatment weighting of the propensity scores was used to adjust for age, parity, calendar year, index cytology, and smoking.

Results: We identified 10,537 women with CIN2 and a singleton birth, with 869 births (8.2%) being preterm. The risk of preterm birth was comparable between the active surveillance and the immediate LEEP group (RR 1.03 (95% CI 0.90-1.18)). However, for women undergoing a delayed LEEP during the surveillance period, the risk of preterm birth was higher compared to women undergoing an immediate LEEP (RR 1.29 (95% CI 1.08-1.55)). In contrast, the risk was slightly lower for women completing active surveillance without LEEP than those undergoing an immediate LEEP (RR 0.88 (95% CI 0.74-1.04)).

Conclusions: In this study, active surveillance for CIN2 was not associated with lower risk of preterm birth. Importantly, a delayed LEEP was associated with a 30% higher risk compared to immediate LEEP. These findings points to the importance of early identification of women at increased risk of a delayed LEEP.

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#6562

Endocervical brush after cervical conization as an alternative to endocervical curettage for predicting high-grade squamous intraepithelial lesion persistence

22 - Diagnostic procedures / management

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Background/Objectives: Endocervical curettage (ECC) is the gold standard for estimating the risk of persistent disease after cervical conization for high-grade squamous intraepithelial lesions (HSIL). However, ECC has a high rate of unsatisfactory samples and may be uncomfortable for women. Recently, endocervical sampling with brush (ECB) has been proposed as a procedure with an accuracy similar to ECC, which, in addition to the cytological evaluation, allows performing HPV testing using the same sample. We compared ECC and ECB performed immediately after conization to identify women with persistent HSIL

Methods: Design: prospective single-centre study Setting: a specialized colposcopy unit in a tertiary care hospital Population: 518 patients who underwent conization over a ten-year period (2012-2021) Methodology: immediately after treatment conization, we performed ECB sampling followed by ECC to all patients. We evaluated the accuracy of the two techniques for diagnosing persistent HSILduring follow-up. Main outcome measure: persistent HSIL after cervical conization

Results: The mean follow-up time was 24.8±13.6 months. In total, 46 (8.9%) patients developed persistent HSIL. The mean time to the diagnosis of persistent HSIL was 10.0 ± 11.8 months. Persistent HSIL was identified in 46/518 women (8.9%). 93/518 (18%) of the ECC samples and only 37/518 (7%) of ECB cytology were unsatisfactory (pinf0.001). In the univariate analysis, HSIL in both the cytological evaluation of the ECB sample and in the ECC significantly increased the risk of persistent HSIL (HR = 9.0 [95% CI 4.9-16.7], pinf0.001 and HR: 12.1 [95% CI 6.1-24.1], pinf0.001, respectively). A positive HPV testing result in the ECB sample and a positive endocervical surgical margin were also correlated with a higher risk of persistent HSIL. In contrast, a positive exocervical margin did not increase the risk of persistent HSIL. In the multivariate ECB model analysis, both the cytological result and positive HPV testing in the ECB sample, but not the status of the margins of the conization specimen, were associated with persistent HSIL. In the multivariate ECC model analysis, ECC diagnosis and positive margins were also associated with persistent HSIL. The accuracy of detecting persistent HSIL was similar for ECB and ECC (89.0%, 95% confidence interval [95% CI]: 85.9-91.5 vs. 90.8%, 95% CI: 87.7-93.2; p=0.797). Adding HPV testing to ECB cytological evaluation increased the accuracy to 91.5%(95% CI: 88.8-93.6).

Conclusions: This is the first study comparing the accuracy of ECB and performed after cervical conization ECC to predict persistent HSIL. This study, including more than 500 women who underwent cervical conization, shows that that cytological evaluation of the ECB sample performed immediately after excision has a similar accuracy as that of ECC for predicting persistent HSIL during follow up, with a lower rate of inadequate samples and patient discomfort.In addition, ECB allows performing HPV testing in the same sample, which, as shown in the present study, provides useful information for identifying women at risk of persistent HSIL. This study was funded by Instituto de Salud Carlos III (ISCIII) through the project PI21/00928 and co-funded by the European Union.

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#7066

Predicting the follow up regimen three years after treatment of cervical intra-epithelial neoplasia: does dual staining add to the equation?

22 - Diagnostic procedures / management

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Background/Objectives: To investigate the association between p16/Ki-67 dual stain test (DST) results, obtained prior to- and 6 months after a LLETZ procedure for treatment of CIN, and the follow up regimen three years after treatment.

Methods: Secondary analysis of a prospective cohort study that took place in the University Hospital of Leuven between 10/2016 and 02/2017. A consecutive series of women referred for a LLETZ procedure were invited to participate. A cervical cytology sample was obtained just prior to- and 6 months after the LLETZ. Samples underwent conventional liquid-based cytology (LBC) staining, p16/ki-67 dual staining (DST) and hrHPV genotyping. Women were managed based on the LBC and hrHPV test results, with clinicians being blinded to the DST results. Case-records were reviewed in 03/2023 to document the follow up regimen on average three years after treatment: women had either been advised to return to routine follow up, or to undergo more intensive posttreatment surveillance. Factors associated with the need for more intense posttreatment follow up were investigated in univariate and multivariable logistic regression analyses.

Results: The follow up regimen was recorded in 79/110 women originally recruited (72%). The need for intense posttreatment follow up was associated with older age (46.0y vs. 39.9y, p=0.024), a type 3 transformation zone before treatment (78.6% vs. 35.6%, p<0.001), hrHPV infection at follow up (79.3% vs. 18.0%, p<0.001), including presence of type 16 or 18 (27.6% vs. 10.0%, p=0.042), a positive DST result at baseline and follow up (41.4% vs. 84.0%, p<0.001 - 55.2% vs. 16.0%, p<0.001), and persistent cytological anomalies at 6 months (37.9% vs. 16.0%, p=0.028). In multivariable logistic regression analysis, a positive DST at baseline (aOR 20.1, 95%CI 2.03-199.1), a type 1 or 2 transformation zone before treatment (aOR 0.01, 95% CI 0.001-0.31 - aOR 0.05, 95% CI 0.003-0.73), and a negative hrHPV test result at follow up (aOR 0.02, 95% CI 0.002-0.20), were the only factors independently associated with the follow up regimen. A model including these three parameters, was able to correctly predict the follow up regimen in 90.2% of cases (Nagelkerke R2 0.742)

Conclusions: A positive dual stain test obtained at the time of LLETZ is an independent predictor for the need of more intense posttreatment surveillance multiple years after treatment.

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#6687

A NEW APPROACH IN THE CONSERVATIVE MANAGEMENT OF CERVICAL HSIL

32 - HPV transmission

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Background/Objectives: Human papilloma virus (HPV) is behind 99% of cervical cancer cases and its precursor lesions. According to the American Society of Colposcopy and Cervical Pathology (ASCCP), 50% of CIN 2 cases managed conservatively regress spontaneously. The aim of this study was to evaluate the effect of a Coriolus versicolor-based vaginal gel in the conservative management of HSIL/CIN 2 lesions compared to the wait and see approach.

Methods: This was an observational, prospective, single-centre, with two non-synchronous cohorts including HPV positive women ≥ 25 years-old, diagnosed with CIN 2. Inclusion criteria were based on the Spanish Society of Colposcopy and Cervical Pathology (AEPCC) guidelines for HSIL conservative treatment: adequate colposcopy image with visible transition zone, completely visible lesion affecting less than 2 quadrants, non-affected endocervix and accepting cytology/colposcopy after 6 months. The treated cohort was administered with 1 cannula/day for 1 month + 1 cannula/alternate days for 5 months of a Coriolus versicolor-based vaginal gel. The untreated cohort was managed with a wait and see approach. Baseline and 6-month biopsies and cytology were performed in both cohorts to compare the results. Compliance and satisfaction with the vaginal gel were also evaluated.

Results: A total of 47 patients were included in the Coriolus versicolor-based vaginal gel conservative treatment cohort (mean age= 36,1 years) and 117 patients were included in the wait and see/untreated cohort (mean age= 35,91 years.). A complete treatment compliance/adherence was obtained in 44 patients in the treatment group with a satisfaction score of 4,73/5. After 6-months of treatment period, 68.2% of the treated cohort showed a regression by biopsy to CIN1 or normalization, 13,6% persisted on CIN 2, and 18,2% progressed to CIN 3. On the other hand, 55,6% of the patients in the untreated cohort showed regression, 31,6% persisted on CIN 2, and 12,8% progressed to CIN 3. Regarding the cytological results, the 80% of the patients who were treated with Coriolus versicolor-based vaginal gel showed a regression or normalization, meanwhile the 67,86% of the untreated patients showed regression or normalization.

Conclusions: The Coriolus versicolor-based vaginal gel 6-month treatment seems to increase the regression of the CIN2 lesions (68.2% at 6 months) compared with spontaneous resolution (55,6 % at 6 months) and could represent a clinical advantage compared with the "wait and see" approach in patients meeting the conservative treatment criteria for CIN2 lesions.

FC13 - Screening methods & Women difficult to reach

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#6890

COMPARISON AND CORRELATION OF VISUAL INSPECTION WITH ACETIC ACID AND PAP SMEAR FOR CERVICAL CANCER SCREENING .

16 - Screening methods

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Background/Objectives: Cervical cancer is the second most cancer in women in India. One of the reasons being lack of structured screening program. Screening methods such as VIA and PAP smear in the presence of good training and sustained quality assurance, is an effective method to prevent cancer cervix. The target set by FIGO in 2018 is that by 2030, 70% of the world's eligible women must have at least one screening and 90% of that screened positive must receive treatment. The Objectives of the study were:1. To screen high-risk participants coming to gynaecological OPDs between the ages of 21 and 60 years by VIA and PAP smear.2. To compare the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of VIA and PAP smear. 3. To compare the colposcopy guided biopsy- histology from positively screened women in both VIA and PAP smear.

Methods: In this cross-sectional study spanning for 18 months, 540 women who satisfied the inclusion criteria were subjected to VIA and PAP smear testing. If any abnormality was detected in either of the two or both, were further subjected to Colposcopy guided biopsy which is gold standard in diagnosis. A pre-designed, structured proforma was filled by the evaluator which included general information about the subject to stratify as high risk, clinical findings at pelvic evaluation, results of VIA, PAP test and Colposcopy and biopsy when indicated.

Results: Among the 540 participants on whom the study was conducted, 322 of the participants were subjected to biopsy, almost 66% of women had no malignant or pre malignant lesions on pap smear. Positive cytology reported as LSIL, HSIL, ASCUS, Squamous cell carcinoma in 106 out of 540 participants (19.6%). VIA positive accounted for 58.88% (318/540), 41% were VIA negative. A total of 322 women who had either positive cytology or positive VIA or positive in both modalities, underwent biopsy. Among them, 162 (50.3%) of the participants were found to have normal histopathology. CIN 1 was seen in 20.8%, CIN 2 in 22% CIN 3 in 6% and 0.93% had Squamous cell carcinoma. Biopsy when taken as gold standard, VIA had sensitivity, specificity, positive predictive value and negative predictive value of 98.73%, 57.44%, 48.74%, 99.10% respectively. PAP smear had sensitivity, specificity, positive predictive value and negative predictive value of 87.62%, 85.06%, 58.60%, 96.61% respectively. Hence sensitivity of PAP smear is higher than that of VIA and is a better diagnostic tool.

Conclusions: The high incidence of cervical cancer is attributed to lack of awareness among the population for the screening methods and their uses. The present study showed that the accuracy of PAP smear was found to be better than that of VIA. Hence cytology continues to be an efficient method for screening in the developing / low resource setup like ours. Aided visual inspection of the cervix because of its easy availability, low cost, immediate results and optimal sensitivity and specificity can also be used as an alternative to PAP smear-based screening programme at grass root levels in developing countries. Biopsy had excellent diagnostic accuracy as in our study 100% of the VIA and PAP smear positives came positive on biopsy.

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#6704

HPV GENOTYPING FOR CERVICAL CANCER RISK STRATIFICATION IN VIA-BASED PRIMARY CERVICAL CANCER SCREENING PROGRAM IN INDIA.

16 - Screening methods

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Background/Objectives: The national cervical cancer screening program in India recommends Visual Inspection with Acetic acid [VIA] as a primary screening. Most screen positive women do not have clinically significant disease due to low specificity and low positive predictive value of VIA test. Screening algorithms using genotype-specific risk stratification may allow for more precise colposcopy referral recommendations and reducing overtreatment. Present study was undertaken to assess the utility of HPV genotyping as a method for the triage and risk stratification of cervical cancer risk during baseline screening .

Methods: Women in the age group of 25-65 years were screened with the primary screening test VIA. VIA test positive women were further offered secondary screening tests of HPV E6/E7 mRNA test and HPV genotyping. The reference standard for final disease status was Histopathology.

Results: Out of the total 1003 women tested positive on VIA primary screening test, 106 were [10.6%] were positive for HPV mRNA_E6_E7. Overall distribution of Single HPV Genotypes was as follows; HPV 16 [14.2], HPV 18 [15.1] , HPV 31 [8.5], HPV 33 [6.6], HPV 45 [2.8]. Mixed Infection of HPV 16_31 was found in 50 [47.2%] followed by HPV 31_45 in 2 [1.9%]. For histologically confirmed CIN 2+ category lesions, percentage distribution of HPV genotypes in descending order was as follows, HPV16_31 [68.3%], HPV 16 [14.6%], HPV 18 [4.9%] , HPV 45 [4.9%], HPV 33 [2.4%] and HPV 31 [0.00 %]. When both 16 and 31 were positive the risk of developing malignancy was 3.818 [Odds Ratio] for CIN2 and above lesions

Conclusions: Mixed Infection of HPV 16 & 31 [47.2%] contributed to the highest burden of HPV positive infections. Multiple HPV genotype 16-31 was associated with3.8 fold increase in the risk of developing malignancy. The study provides evidence for customizing the HPV Partial Genotyping Assays conforming to the High Risk pattern within the region.

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#6828

CERVICAL CANCER SCREENING BY SELF-SAMPLING FOR HPV AND DYSPLASIA MOLECULAR TESTING INTEGRATED IN A WOMEN'S HEALTH AND WELL-BEING COMPREHENSIVE APPROACH

11 - Screening for women difficult to reach

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Background/Objectives: The C3UC3 program, implemented by women's health and protection associations and Research Center , aims to integrate awareness-raising, education and participation in cervical cancer screening and prevention (CCU) into an holistic approach to women's well-being through HIV care and mental health support. Yaounde's Cité Verte health district harbours 129.118 women between age 25 and 50 eligible to accessing health centers and being visited in communities by health community workers. They invite to meetings about causes and prevention of cervical cancer, explain, propose screening and make appointments. They collect samples door-to-door and provide the results in complete confidentiality. In HIV care units, social workers are responsible for raising awarness among women and offering them the test. We are studying screening tests of differing sensitivity and specificity (accuracy for CIN2+ detection) to document the effectiveness of the tests.

Methods: In this 2 year longitudinal cohort study 2,000 women (1,000 living with HIV, 1,000 in the general population) will be recruited. Cervico-vaginal self-sampling will be carried out in HIV health care units and in the community using Evalyn brushes. Smear material is extracted and analyzed by PCR (reporting genotypes 16, 18/45, and "other" subgroups) and the innovative dysplasia test QuantiGene-Molecular-Profiling-Histology (QG-MPH) testing viral and cellular biomarkers resulting in a diagnosis of dysplasia (CIN2+, CIN3+, Cervical Cancer) and individually reporting 18 HR-HPV genotypes. Following, diagnostic VIA supported by smartscope image analysis is done in clinics. Biopsies from PCR positive participants are collected and evaluated as a gold standard

Results: Study started on September 11, 2023, and until October 07. 2023, 392 women were included, giving 200 self-samples and 192 refusals. 331 women were recruited in the community and 61 in HIV health care units. Refusal rate in general population and HIV+ women, was 48,97% and 14.75%. (Initial results updated during the congress). While HPV-PCR based GeneXpert has a very simple technical hands on time, it has a low sample turnover and demand an additional visit to avoid over treating, the QG-MPH technic is able to identify cervical dysplasia in one step. In addition it has a high throughput, with 92 samples run in parallel, suitable for busy clinics.

Conclusions: This study, funded by L'Initiative of Expertise France and supported by the Ministry of Health in Cameroon aims to test if integrating cervical cancer screening activities into general health care is feasible and acceptable in HIV clinics and communities. Comparing the standard screening strategy to one using a more specific test, the study will show if screening programs could focus funds and resources on women who really need treatment, reducing unnecessary follow up, i.e. cost and effort, and the burden, fear and risk of overtreatment.

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#6909

EXPLORING HPV SELF-SAMPLING ACCEPTABILITY AMONG MOROCCAN AND PAKISTANI WOMEN PRIOR TO THE IMPLEMENTATION OF A POPULATION BASED CERVICAL CANCER SCREENING PROGRAM IN CATALONIA, SPAIN

11 - Screening for women difficult to reach

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Background/Objectives: Immigrant women have lower rates of cervical cancer (CC) screening uptake compared to European native women, which increases the risk of being diagnosed in later stages and reduce probability of survival. Innovative strategies are being implemented across Europe to improve overall screening rates and reduce this health disparity. The necessary cause for CC development is the persistent infection with oncogenic human papillomavirus (HPV). In Catalonia (Spain), CC screening is transitioning to a population-based program and HPV testing is being implemented using self-sampling, with pilot studies conducted since 2022. We carried out a multi-method qualitative study to explore the knowledge and perceptions of Moroccan and Pakistani women about CC and screening, and their views on HPV self-sampling implementation.

Methods: Semi-structured interviews (N=22) and focus groups (N=51) were organized with women aged 24-65 years from Morocco and Pakistan, and in-depth interviews were conducted with health providers (N=13). Recruitment was through Moroccan and Pakistani key informant networks and community health agents. After a short demonstration, all participants (N=73) were invited to use two different self-sampling devices and complete an acceptability questionnaire. Thematic content analysis was conducted to identify themes using a framework matrix, and descriptive statistics were performed to assess acceptability.

Results: Participants lacked information about CC and most of them never heard of HPV and its connection with CC. Women also were confused about the purpose of the test and believed that CC screening was part of the routine pregnancy check-ups, which might undermine regular participation in screening programs. 57.5% of the participants would like HPV self-sampling to be considered as a new method for CC screening. After testing either of the devices -with a higher use of FloqSwab (N=38; Pakistan N=15; Morocco N=23) than EvalynBrush (N=34; Pakistan N=16; Morocco N=18)-, most of them would use it again. Lack of confidence to perform the sampling correctly was one of the main identified barriers. Oral and visual communication with the presence of a female "expert' with the same cultural and linguistic background was proposed for future interventions introducing HPV self-testing

Conclusions: While initial motivation for HPV self-testing in Moroccan and Pakistani women appeared modest, most of them were willing to use it. This study highlights the crucial aspect of education to ensure correct self-sampling. Health providers and trained women from their own communities will play a key role to foster confidence and empower women, and advocate for the adoption of HPV self-sampling.

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#6859

INNOVATIVE URINE-BASED HPV-DNA SCREENING FOR CERVICAL CANCER PREVENTION IN A RURAL PRIMARY CARE CENTRE IN ESWATINI

11 - Screening for women difficult to reach

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Background/Objectives: In Eswatini, high-risk HPV (HR-HPV) infection has a very high prevalence (46%), leading to 341 new cervical cancer (CC) diagnoses and 214 deaths from CC per year (2020 estimates). Socio-economic and cultural factors hinder access to CC screening and retention to care. Other factors, such as test invasiveness and sampling modalities, are known to further reduce women's participation in screening programmes. In 2020, the World Health Organization (WHO) launched the Global Cervical Cancer Elimination Initiative. It recommended using HPV DNA detection as the primary screening test and taking advantage of existing technological diagnostic platforms already being used to implement screening in low-middle-income countries. Our study aims to introduce a urine-based HPV DNA screening test using the GeneXpert® System (Cepheid, USA) in a rural healthcare facility in Eswatini to increase access to, and acceptability of, CC prevention among adolescents and young girls.

Methods: Starting on 20 January 2023, all women aged 12-49 years self-presenting at St. Philip's Clinic (Lubombo, eSwatini) were enrolled in the study, regardless of human immunodeficiency virus status (HIV). For each woman, a urine sample was collected, centrifuged to concentrate viral particles, and eliminate debris, and tested with the Xpert® HPV test (Cepheid, USA) to detect 14 HR-HPV genotypes pooled in 5 different channels (HPV 16, HPV 18/45, P3, P4, and P5). Women aged 21-49 years were offered, on a voluntary basis, the collection of cervical brush samples for cytological analyses performed at Mbabane Central Pathology Laboratory. Only women collecting both urine and cervical brush samples were included in this analysis.

Results: At the time of analysis, 117 women (median age 33 years, range 21-49 years) were enrolled in the study. Five women were diagnosed with CC, 19 with a high-grade squamous intraepithelial lesion (HSIL), 7 with a low-grade squamous intraepithelial lesion (LSIL), and 16 with atypical squamous cells of undetermined significance (ASC-US) or where HSIL could not be excluded (ASC-H). Sixty-two women declared to be HIV positive (53%). The Xpert HPV® test yielded a valid result in samples collected from 111 women (98%), with the detection of at least one HR-HPV genotype in 50% (58/117, median age 31 years). HIV and HPV coinfection were found in 36 women (36/62, 58%). Forty-two urine samples tested positive for a single Xpert® channel (72%), with the P3 channel (HPV31, 33, 35, 52, and 58) being the most frequently detected (29/58, 50%). HPV DNA was detected in 24 women with normal cytology (24/70, 34%) and in 34 women with lesions of different grades (34/47, 72%). The Xpert® HPV test on urine samples could detect HR-HPV infection in all women diagnosed with CC, in 74% (14/19) of those diagnosed with HSIL, and 86% (6/7) in those with LSIL.

Conclusions: The study is still in progress and aims to reach 500 enrolled women for a full evaluation. Results obtained so far suggest that the Xpert® HPV test performs well when adapted to detect HR-HPV infections in fresh urine, as HR-HPV infection was detected in all women with CC and almost all those with HSIL and LSIL. A recent cross-sectional study conducted in Eswatini highlighted how fear of pain is one of the main reasons for non-adherence to invasive CC screening methods. Using urine samples for CC screening is a promising strategy to promote access to prevention, including in younger girls, through higher adherence.

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#6940

Impact of health-related behavioral factors on participation in a cervical cancer screening program: The Lifelines Population-Based Cohort

11 - Screening for women difficult to reach

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Background/Objectives: Regular participation in cervical cancer screening is critical to reducing mortality. Although certain sociodemographic factors are known to be associated with one-time participation in screening, little is known about other factors that could be related to regular participation. Therefore, this study evaluated the association between health-related behavioral factors and regular participation in cervical cancer screening.

Methods: The Lifelines population-based cohort was linked to data for cervical cancer screening from the Dutch Nationwide Pathology Databank. We included women eligible for all four screening rounds between 2000 and 2019, classifying them as regular (4 attendances), irregular (1-3 attendances), and never participants. Multinomial logistic regression was performed to evaluate the association between behavioral factors and participation regularity, with adjustment made for sociodemographic factors.

Results: Of the 48,325 included women, 55.9%, 35.1%, and 9% were regular, irregular, and never screening participants. After adjustment for sociodemographic factors, the likelihood of irregular or never screening participation was increased by smoking, obesity, marginal or inadequate sleep duration, and low physical activity, while it was decreased by hormonal contraception use.

Conclusions: An association exists between unhealthy behavioral factors and never or irregular participation in cervical cancer screening.

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#7176

THE INDIGENOUS WOMEN OF THE AMAZON RAIL FOREST - TRUE CUSTODIANS -SAVING THE PLANET

11 - Screening for women difficult to reach

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Background/Objectives: The Indigenous women of the Amazon Rain Forest (ARF) have the highest prevalence of HPV infection, lack early screeening and treatment ,present with advanced cervical cancer, and too many die before age 30, because of thier ISOLATION. Social, cultural, lack of economic opportunity, and no empowerment, with little access to Timely Health Information result in a very high prevalence. These women have many risk factors which result in this tragic Preventable cancer. These women are the Only true Custodians of the ARF who will Protect, Defen and Preserve the ARF our last hope to Prevent Climate destruction. The ARF has the richest source of Biodiversity and Genetic material with Medicinal Plants , and small insects and animals to Provide medicines to cure all that ails us. We have worked with these women to provide Health Information , change thier perspective on this important Preventable Cancer , issue accept our Program , and are then Literate or educated . We provide HPV Screening , Early Detection and offer Curative treatment including HPV Vaccination. The future of this planet to prevent Climate Destruction may rest on the success of this and similar programs . We owe it to future generations to prevent this tragedy . IF NOT NOW WHEN?

Methods: These women are difficult to reach, Guyana has 83,000 more than 90 % ARF, access is difficult these people can only by small aircraft, boats and 4 wheel all terrain motorbikes, and hiking. It is expensive to undertake these trips with many challenges , but we persist and persevere. The Villages of Imbambadi, Phillipai, Quebanang, Akawinin ,Wakapoa,and Jawalla among many others were visited. our team would interact and gain permission from the village Elder Touchau, with the health worker , we would hold public discussions , lectures, question & answer sessions with Posters, Leaflets to provide information on the Self Collection of Vaginal swabs, Prior to this the exclusion criteria would be established. 48 hours prior to testing, No Sex , No Menstruation, No Special Vaginal wash . The names ,DOB, Contact details and HPV vaccination status would be recorded with signed consent to do the self collection of the swabs. Demonstrations of Swab collection was done by the team. Samples were collected in small labelled tubes, and cold storage to be transported to The PCR Molecular Lab to be tested in Georgetown at the certified Diamond Grove PCR Lab . The Test Kits and Testing were provided by my good friend and colleague at Atilla Prof Youxiang Wang Calif USA , we have had a long and successful collaboration prior to Covid . We Recognise and thank him for his support.

Results: Results returned to the Health worker , AND counselled Negative test and no HPVVaccine , these women eligible to receive the Quadrivalent Vaccine two doses, and rescreened in 3-5 years . Rescreened if sympotamic If the test is Positive Colposcopy or VIA, and LEEP with curative treatment if required. If No lesions are present a repeat HPV in a year. Total tests 505, # HPV + 107, HPV NEG 398, HPV + 16 = 16 , HPV 18 = 43, OTHER ONCOGENIC TYPES = 65 - SOME HAD MULTIPLE HPV ONCOGENIC TYPES

Conclusions: THE WOMEN OF THE ARF HAS THE HIGHEST PREVALENCE ,COMPARED TO WOMEN IN GEORGETOWN, AND THOSE WITH BETTER PAID JOBS WERE SIGNIFICANTLY LESS INFECTED. AIDS PATIENTS WERE > 65 % POSITIVE . THESE WOMEN ARE TRUE CUSTODIAN OF THE ARF. SAVE THEM -SAVE THE PLANET
FUNDING BY VAN Oord NETHERLANDS
NO WOMAN SHOULD DIE FROM A PREVENTABLE CANCER

References: PREVENTION IS THE CURE CNIAMATALI PREVENTION SCREENING AND CURATIVE TREATMENT -NO WOMAN SHOULD DIE FROM A PREVENTABLE CANCER THE ELIMINATION OF A PREVENTABLE CANCER AMONG THE INDIGENOUS WOMEN CUSTODIANS OF THE RAIN FOREST MUST BE AN URGENT PRIORITY - SAVE THEM SAVE THE PLANET

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#6930

Turning the Tide: Recommendations to Increase Cervical Cancer Screening Among Women who are Under-screened - a White Paper by the ACCESS Consensus Group

11 - Screening for women difficult to reach

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Background/Objectives: Cervical cancer is a largely preventable disease, yet far too many women still die from it. HPV vaccination is a highly effective prevention intervention but it will take many years for it to offer population-wide protection. In most high-income countries, organised cervical cancer screening programmes have been in place for decades and have helped significantly reduce the incidence and mortality rates of the disease. Despite this success story, participation rates in screening programmes remain suboptimal. In Europe, screening participation rates vary hugely between countries, at 80% in some but as low as 25% in others1, and are stagnant or have declined in some countries in recent years.2,3,4 Women who do not receive regular screening are at higher risk of developing cervical cancer and, when diagnosed, they are more likely to have advanced disease and poorer outcomes. It is recognised that there are groups of women who are consistently under-screened due to a wide range of factors including, among others, lack of awareness, lack of access or cultural beliefs. Empowering women in these groups to take up the offer of screening would deliver both individual health and societal benefits.

Methods: In light of these challenges, the ACCESS Consensus Group has come together as an international, multi-disciplinary group of leading clinicians, researchers, patient advocates and women's representatives from Europe, Canada and the US to accelerate cross-border collaboration on cervical cancer screening participation, share best practices and ensure policy reflects the latest scientific evidence and programmatic experience. Their first initiative was to develop a White Paper containing a set of consensus recommendations intended to serve the ongoing efforts of policymakers and those involved in planning and delivering cervical cancer screening programmes to increase participation rates. In order to develop the content and recommendations of the White Paper, group members participated in a written survey and collaborated via structured virtual workshops. They submitted written comments on drafts of the paper, facilitated by the group's secretariat, and approved the final consensus paper.

Results: The ACCESS Consensus Group reached consensus on six key recommendations for policymakers aiming to protect women's health by improving cervical cancer screening participation: 1. Develop cervical cancer national elimination plans with goals for elimination by a defined date, including ambitious national screening programme participation targets at the population level 2. Implement targeted and culturally-relevant education, information and awareness-raising initiatives, particularly focused on under-screened women 3. Improve the accessibility of cervical cancer screening 4. Support healthcare professionals to increase participation in cervical cancer screening 5. Encourage and support the creation of national cervical cancer patient advocacy groups and national cervical cancer prevention coalitions 6. Ensure that health insurance appropriately covers screening in all high-income countries

Conclusions: By implementing these recommendations, policymakers can help turn the tide and reverse the stagnation and decline in cervical cancer screening uptake in higher-income countries for the benefit of under-screened women.

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#6845

A BENCHMARK ANALYTICAL VALIDATION OF THE COPAN UNIVERSE® PRE-ANALYTICAL INSTRUMENT INTEGRATION ON THE RIATOL QPCR WORKFLOW FOR CERVICAL CANCER SCREENING

20 - New technologies

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Background/Objectives: Cervical cancer screening is transitioning worldwide from cytology to primary HPV screening. Recent society guidelines prioritize risk-based, clinical threshold-driven screening, highlighting the essential need for validated HPV assays. Nonetheless, when transitioning a validated HPV test to a new high-throughput platform, potential changes in test characteristics must be considered. Here, the analytical validation of UniVerse® (COPAN Group) is demonstrated as a new pre-analytical liquid handling robot for management of ThinPrep® liquid-based (Hologic Inc.) samples in the RIATOL qPCR workflow (Sonic Healthcare Benelux).

Methods: Residual material of cervical specimens collected in LBC medium was obtained with informed consent of woman participating in the Belgian screening program. The clinically validated RIATOL qPCR HPV genotyping assay was used in a head-to-head comparison between the UniVerse® coupled to an external loading carousel and the ThinPrep® 5000 Sample Transfer System (Hologic Inc.) liquid handling robot in order to demonstrate non-inferiority performance based on HPV and B-globin (BG) human gene amplification. To this end 377 samples, among which at least 10 positives for each HPV genotype, were processed on both systems. The degree of qualitative agreement in HPV detection and genotyping between the two workflows, was determined based on Kappa statistics. Quantitative agreement was evaluated based on arithmetic differences and linear correlation of the BG measurements. Furthermore, in order to fully validate the Universe® system intra- and inter-run reproducibility was determined by triplicate testing of 5 HPV negative and 15 HPV positive samples including multiple infections, and determining the coefficient of variance. At last, the risk of cross-contamination was evaluated based on a carry-over experiment including 20 samples and 20 blanks arranged in alternating order.

Results: Development of an automated aliquoting protocol on the new high-throughput UniVerse® instrument was tailored to replace with identical pre-analytics as the well-validated STS. Parallel analysis of 377 samples run on both workflows demonstrated an HPV genotyping concordance of 0.993 and an excellent Kappa coefficient of agreement of 0.857. Regarding BG detection, samples showed a correlation coefficient of 0.625 and an arithmetic mean difference of 0.03 on a Cq-level. Passing and Bablok regression revealed no systematic nor proportional differences on an analytical level and no significant deviation from linearity (Cusum test, p=0.75) between both methods. Excellent reproducibility of results using Universe® instrument was demonstrated both in an intra-run setting (BG and HPV covariance average of 0.017 and 0.034, respectively) and inter-run (0.023 and 0.046), scattering clearly within the acceptable criteria. Sample mixing, de-/re-capping and liquid-handling on the new instrument showed no carry-over of cross-contamination for both BG and HPV positive samples.

Conclusions: The pre-analytic phase of RIATOL qPCR assay was successfully validated on the versatile and high-throughput Copan UniVerse® instrument. Results were found to be non-inferior to the previous workflow for analytical HPV accuracy, while demonstrating a strong intra- and inter-run reproducibility. The combination of RIATOL qPCR assay-specific characteristics with the UniVerse® instrument's high efficiency and capacity proves to be an excellent combination for HPV primary cervical cancer screening.

FC16 - Methylation I

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#7009

Cervix cytology samples revealed increased methylation of the human markers FAM19A4/miR124-2 up to eight years before adenocarcinoma

17 - Methylation

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Background/Objectives: Methylation analysis of the promoter region of tumour-suppressor genes, has previously shown high sensitivity for detection of high grade cervical intraepithelial neoplasia (CIN) and cancer (1,2).HPV-testing has a high sensitivity to identify women at risk of developing cancer, and has been implemented in the cervical screening program in several countries. But most HPV-positive women will clear the infection and never develop cancer. Testing for methylation could help to identify women who have potentially progressive cervical disease and need more close follow-up. The goal of the present study was to investigate the potential use of methylation as a triage test of HPV-positive women in the screening program.

Methods: A collection of liquid-based cytology (LBC) samples from 106 women, collected between four months and eight years before histologically confirmed cervical cancer or CIN3, was analysed for hypermethylation of the human genes FAM19A4 and miR124-2.

Results: Methylation was detected in 45% (33/73) of normal LBC samples from women who later developed CIN3+, compared to 10% (3/31) of normal LBC samples from women without subsequent dysplasia (p=0.0006). Overall, methylation was detected in 39% (14/36), 51% (19/37), 61% (14/23), and 70% (7/10) of LBC samples, from women who later developed CIN3, adenocarcinoma in situ (AIS), squamous cell carcinoma (SCC) and adenocarcinoma (ADC), respectively. Positive methylation analysis was not significantly more frequent than abnormal cytology of ASCUS+ (atypical squamous cells of unclear significance or worse) in LBC samples collected 4 months-8 years before SCC or AIS, but prior to the development of ADC, methylation was observed among 7 of 10 LBC samples, despite normal cytology. Overall, LBC samples collected before invasive cancer (ADC and SCC) were more frequently positive in the methylation analysis, than positive for cytology ASCUS+ (p=0.048). For LBC samples collected more than two years before the development of AIS, SCC or ADC, methylation analysis showed a higher positivity rate than cytology.

Conclusions: Testing for methylation of FAM19A4/miR124-2 as a triage for HPV-positive women would be useful to identify women at risk of cancer development, especially adenocarcinoma. Further studies are needed to estimate the cost-effectiveness, before introducing methylation testing in the screening program.

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#6991

MED-SEQ, A METHOD FOR GENOME-WIDE DNA METHYLATION DETECTION, CAN BE USED TO CHARACTERIZE TUMORS, DETECT HPV SUBTYPES AND IS COMPATIBLE WITH LIQUID BIOPSIES

17 - Methylation

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Background/Objectives: DNA methylation serves as an important marker for mis-regulation of gene expression in cancer. DNA methylation can be utilized for cancer diagnosis, for classification and origin determination of tumors. Promising applications such as personalized medicine include treatment outcome prediction and disease monitoring.

Methods: We created a new, low-cost method to facilitate the genome-wide methylation profiling and the identification of new methylation markers for pre-cancer and cancer. The technique involves isolation and purification of DNA from formalin-fixed paraffine-embedded (FFPE), fresh biopsies or liquid biopsies (only 5-50ng DNA is needed). This Methylated DNA sequencing (MeD-seq) assay is very robust, allowing detection of DNA methylation at more than 50% of the 30 million CpGs present in our genome as well as detection of HPV integrated DNA. With respect to costs and sequencing depth MeD-seq is superior to all available technologies and requires no disruptive DNA bisulphite treatment.

Results: We compared MeD-seq profiles of different types of cancers from vulva, cervix, endometrium, fallopian tube, and ovary between cancers vs controls and cancers vs other cancers. Identification of Differentially Methylated Regions (DMR) was achieved by comparing MeD-seq profiles with genome wide statistical testing using a sliding window approach. Data was visualized through the Integrative Genomics Viewer (IGV). In addition to DNA methylation data, MeD-seq generates sequencing data which enables the detection of Human Papilloma Virus (HPV) DNA that is incorporated in the genome of HPV-infected cells. Around half of the gynecological cancer types in our study are HPV-associated and we were able to detect HPV genomic integration and call HPV subtypes.

Conclusions: MeD-seq is a reliable low-cost technology to establish genome-wide DNA methylation profiles able to interrogate >50% of all the CpGs in the human genome. Its exceptional feature of requiring only a minimal amount of DNA sets it apart from other methods and makes MeD-seq seamlessly compatible with cell-free DNA/ liquid biopsy samples, tumor enrichment in FFPE material by laser capture microdissection (LCM) and small populations of FACS-sorted cell types. MeD-seq can be applied to both FFPE and fresh tumor samples for tumor classification. We found that MeD-seq is also able to detect and genotype integrated HPV subtypes.

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#6703

HIGH-RISK HPV GENOTYPES AS POTENTIAL BIOMARKERS IN EARLY DIAGNOSIS OF CERVICAL CANCER

17 - Methylation

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Background/Objectives: Cervical cancer ranks fourth among women worldwide, primarily affecting those aged 35-44. In 2020, there were 604,000 new cases and 342,000 deaths, with 90% occurring in low- to middle-income countries. Detecting cervical cancer early is key to prevention. Persistent high-risk human papillomavirus (hrHPV) infection causes almost all cervical cancers, with HPV16 and HPV18 responsible for 70% of cases. Other high-risk HPV genotypes, like HPV39, HPV45, HPV51, HPV52, and HPV58, vary by ethnicity and location. Cervical cytology, the gold standard for over 50 years, has limitations, prompting the exploration of methylation patterns in host and viral genes for hrHPV-positive women. The S5 classifier (HPV16, HPV18, HPV31, HPV33, and EPB43L1) shows promise in distinguishing disease stages. However, it lacks other prevalent hrHPV genotypes. This study assesses methylation levels of L1 and L2 regions in these other high risk genotypes as potential biomarkers for early cervical cancer diagnosis.

Methods: In this study, we designed primers targeting the L1 and L2 regions of high-risk HPV genotypes (HPV 39, 45, 51, 52, 58). We extracted DNA from patients who tested positive for high-risk HPV across different cervical intraepithelial neoplasia (CIN) grades. Subsequently, we prepared the samples for methylation analysis through bisulfite conversion and determined methylation levels at CpG sites using pyrosequencing. Finally, we conducted a validation of the primers and performed statistical analysis of the methylation data

Results: As of the time of this abstract submission, further validation are being carried out and preliminary data will be presented at the conference.

Conclusions: Beyond HPV16, HPV18, HPV31, and HPV33, our study identifies methylation in L1 and L2 regions of other hrHPV genotypes (HPV39, 45, 51, 52, 58) as potential biomarkers for early cervical cancer detection. These findings suggest the potential to enhance the sensitivity and specificity of cervical cancer diagnosis by incorporating these additional genotypes into the current S5 classifier

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#6757

DIRECT COMPARISON OF THE PERFORMANCES OF THE SINGLE-MARKER ASSAY SCREENYU GYN AND THE SIX-MARKER ASSAY GYNTECT

17 - Methylation

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Background/Objectives: Accurate clarification of women with HPV positive test results or abnormal cytology findings during routine screening is important in order to reduce both, overtreatment as well as long, psychologically stressful watchful waiting periods. Different strategies are discussed, among others DNA methylation markers show a high potential. Detecting DNA methylation is, however, not yet automated, and detecting a set of markers is still expensive and time-consuming. We compared GynTect, comprising six methylation markers (ASTN1, DLX1, ITGA4, SOX17, RXFP3 and ZNF671) with ScreenYu Gyn, based on a single methylation marker (ZNF671), regarding detection of cervical precancerous lesions and cancer using cervical scrapes.

Methods: GynTect is a Eva-Green based singleplex real-time PCR for the detection of six methylation markers ASTN1, DLX1, ITGA4, SOX17, RXFP3 and ZNF671, as well as two control marker regions ACHE and IDS-M, using bisulfite converted (EpiTect Fast DNA Methylation Kit, Qiagen) clinical samples. ScreenYu Gyn is a duplex methylation-specific real-time PCR assay using TaqMan probes for the detection of the amplicons. ZNF671 as methylation marker and ACTB as quality control are amplified in a single-tube reaction after bisulfite conversion (EZ DNA Methylation Lightning Kit, Zymo Research) of the clinical sample. To compare clinical performance between these two assays, a clarification cohort comprising >600 residual cervical scrapes, collected in Thinprep PreservCyt (HOLOGIC), were analyzed with both assays.

Results: Valid results were obtained in both assays for 611 samples: 334 NILM, 46 CIN1, 44 CIN2, 179 CIN3 and eight cervical cancer samples. Both assays detected all eight cervical cancer samples. Among high grade cervical lesions, ScreenYu Gyn showed a slightly higher detection rate than GynTect: 60.9% and 45.5%for CIN3 and CIN2, vs. 56.4% and 34.1%, respectively. Detection rate for CIN1 samples was 17.4% with ScreenYu Gyn and 19.6% with GynTect. The detection rate in the NILM group was slightly higher for ScreenYu Gyn with 7.8% compared to GynTect with 4.2%. HPV status was unknown for the NILM group. Sample status ScreenYu Gyn GynTect NILM (n = 334) 7.8% 4.2% CIN1 (n = 46) 17.4% 19.6% CIN2 (n = 44) 45.5% 34.1% CIN3 (n = 179) 60.9% 56.4% Cancer (n = 8) 100% 100%

Conclusions: GynTect shows a slightly better specificity, whilst ScreenYu Gyn has a slightly better sensitivity for CIN2+ and CIN3+ detection. Overall, both assays showed concordant results in 91.2% of the assays, according to Cohen's kappa assessment an almost perfect agreement. The single-marker assay ScreenYu Gyn has clear advantages regarding hands-on time and overall duration. It provides an excellent basis for further development of an even simpler and automatable DNA methylation marker test for cervical cancer diagnostics.

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#6764

GynTect® DNA METHYLATION MARKERS DETECT RECURRENT DISEASE IN PATIENTS TREATED FOR CIN3 WITH HIGH SENSITIVITY AND SPECIFICITY IN A RETROSPECTIVE CASE-CONTROL STUDY

17 - Methylation

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Background/Objectives: Post-treatment follow-up in women with high-grade cervical lesions (CIN3) is mandatory due to relapse in up to 10% of patients. Standard follow-up based on hrHPV-DNA/cytology co-testing has high sensitivity but limited specificity. The aim of our case-control study was to evaluate the performance of the methylation markers comprising the cervical cancer diagnostic GynTect® as a means for the timely detection of recurrent CIN2/3 during follow-up.

Methods: Residual clinical material from an observational study with a focus on HPV/cytology co-testing was analysed (PMID34282754). We studied a sample of 48 patients (median age 31 years) comprising 17 cases with recurrent CIN2/3 diagnosed within 24 months and 31 controls. All of them had at least one follow-up visit. DNA from cervical scrapes at baseline (before CIN3 surgery) and follow-up visits were analysed for 13hrHPV types and the GynTect® methylation status.

Results: Overall 15 of 48 patients were GynTect-negative at baseline. Of the 33 GynTect-positive patients at baseline 12 were diagnosed with recurrent disease. Two of these patients were neither hrHPV- nor GynTect-positive during follow-up. One patient was hrHPV-positive but GynTect-negative and 9 patients were hrHPV- and GynTect-positive during follow-up. Sensitivity was not significantly different for GynTect (75%, 95% CI 46%-92%) and hrHPV (83%, 95% CI 55%-96%) (McNemar p=1.00). Two of 21 patients who were GynTect-positive at baseline but without evidence for recurrent disease were both hrHPV- and GynTect-positive during follow-up. Six patients were hrHPV-positive but GynTect negative and 13 patients were negative for both tests. Specificity was significantly higher for GynTect (90%, 95% CI 71%-98%) compared to hrHPV (62%, 95% CI 40%-80%) (McNemar p=0.03).

Conclusions: For initially GynTect-positive patients both hrHPV and GynTect® assays detect recurrent disease with similar sensitivity but the GynTect® assay has a significantly higher specificity. A future study will have to show whether cytology/GynTect® co-testing will out-perform cytology/hrHPV co-testing in post-treatment surveillance for this subgroup of CIN3 patients.

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INTEGRATIVE ANALYSIS OF GENE EXPRESSION AND DNA METHYLATION IN HPV+ PENILE SQUAMOUS CELL CARCINOMA IN PUERTO RICO

17 - Methylation

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Background/Objectives: Penile squamous cell carcinoma (PSCC) is a disease with a high morbidity and mortality among developing countries. Although PSCC is a relatively uncommon cancer in developed countries, its incidence is nearly four times higher in Puerto Rico when compared with other racial and ethnic groups in the United States.1 It is still unclear how PSCC works on a molecular level. One epigenetic modification that is present in cancer cells is DNA methylation, which can affect cellular function and gene expression. This study aims to identify and correlate differentially expressed genes and analyze DNA methylation patterns in HPV+ and HPV- PSCC tissues in Puerto Rican men.

Methods: PSCC fresh tissue was obtained from surgically intervened cases. The Affymetrix GeneChip® Human Gene 2.0 array was used to identify and assess the global gene expression profile from twenty-four fresh PSCC tissue samples from Puerto Rican patients. HPV status and genotyping were determined using the DNA ELISA kit HPV SPF10 protocol. DNA was amplified and hybridized using PCR. To identify and compare average DNA methylation levels (%), we performed a DNA methylation assay using the Infinium Methylation EPIC v2.0 BeadChip Kit. Logistic regression to model HPV status as a function of the genetic data and clinical data.

Results: Several pathways involved in cell division were enriched for HPV+ PSCC, suggesting a highly proliferative state of the cancer cells in these samples. Other pathways were involved in DNA damage response and p53 function, consistent with the activity of the HPV E6 oncoprotein to induce degradation of the tumor suppressor protein p53 via the ubiquitin pathway. Our results demonstrated 43 loci significantly different between HPV-positive and HPV-negative samples, with an adjusted p-value inf0.1 (Benjamini-Hochberg method). Most of the hypermethylated loci were present in HPV-negative tumor samples. Additionally, we identified four methylated-differentially expressed genes: ANXA4, CACNA1C-AS1, UBXN2A, and DUOX1, which are found as uncharacterized proteins (open reading frames, ORFs) of the human genome with adjusted p-value inf0.05.

Conclusions: Studies revealed that specific DNA methylation patterns could be linked with cancer development and progression. This study will provide much-needed data to aid studies on early detection, prognosis, and development of therapeutic agents to reduce the morbidity and mortality from PeCa.

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VALIDATION OF METHICA CC KIT AS TRIAGE TEST FOR CERVICAL CANCER SCREENING

17 - Methylation

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Background/Objectives: The introduction of high-risk human papillomavirus (hrHPV) testing as the primary screening tool created a full molecular screening for cervical cancer. This is even more emphasized by the increased use (5% in 2017 to up to 30% in 2022) of self-sampling in the Netherlands. Although hrHPV screening is very sensitive for the detection of cervical abnormalities, the specificity is low and additional triage of hrHPV positive women is required. Analyzing promoter methylation of tumor suppressor genes with quantitative methylation specific PCR (mQMSP) is a promising molecular triage method. The Methica CC Kit enables detection of promoter hypermethylation of C13ORF18, JAM3 and ANKR18CP identifying high-grade cervical intraepithelial neoplasia and cervical cancer (CIN2+) lesions in physician-taken cervical samples and importantly also in self-sampled samples. Here, we analyzed the evaluation of the repeatability and reproducibility using the Methica CC Kit.

Methods: Cervical scrapings were selected from 20 hrHPV-positive women, from the Dutch population-based screening cohort. DNA methylation analysis was performed using the Methica CC Kit using bisulfite-converted DNA extracted from these cervical samples. Ten cases were selected to be methylation negative for all three markers and 10 cases were selected to be methylation positive (e.g., for at least one of the three markers). These bisulfite-converted DNA samples were analyzed with the Methica CC kit at 3 centers (UMCG, JBZ and Radboud). Concordance was determined for both repeatability and reproducibility resulting in 24 and 40 separate runs per sample, respectively.

Results: The methylation-negative samples showed a concordance of 99.1% and 99.3% for the repeatability and reproducibility, respectively, whereas in the methylation positive samples the concordance was higher (100% concordance for both repeatability and reproducibility). Including all 20 bisulfite-converted DNA samples, the concordance for the Methica CC kit was 99.6% for the repeatability and the reproducibility.

Conclusions: The Methica CC Kit showed a high concordance for both repeatability and reproducibility in a selected series of DNA samples. This suggests a reliable method for the detection of clinically relevant CIN lesions. Currently the intra-laboratory workflow agreement and the inter-laboratory workflow agreement is under evaluation. Additionally large-scale validation of the Methica CC Kit is ongoing.

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TOWARDS SIMPLIFIED ANAL CANCER SCREENING: BIOMARKER DISCOVERY BY GENOME WIDE METHYLATION PROFILING ON ANAL SWABS

17 - Methylation

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Background/Objectives: Only a subset of people at increased anal cancer risk is currently screened due to limited capacity and expertise of high-resolution anoscopy. Hence there is an urgent clinical need for an objective minimally invasive screening test on anal swabs. We previously showed that testing for DNA methylation markers on anal biopsies can accurately detect high-grade anal intraepithelial neoplasia (HGAIN) at risk of progression to anal cancer (i.e., advanced HGAIN)(1). This study aimed to develop a methylation test applicable to anal swabs to detect advanced HGAIN by genome-wide methylation analysis on anal swabs.

Methods: Genome-wide methylation profiling was performed on anal swabs of 36 cases (i.e., AIN3), 34 controls (i.e., infAIN1), and 7 anal cancer patients using the 850K Infinium MethylationEPIC BeadChip (Illumina). Candidate methylation markers were selected using logistic regression penalized with adaptive multi-group ridge penalties using co-data and derived with an empirical Bayes approach (ecpc) comparing cases with controls. Candidate markers were tested by quantitative methylation specific PCRs (qMSPs) on anal swabs of anal cancer patients and controls (n=21) and are currently evaluated on a larger independent series of anal swabs (n=170).

Results: Ecpc yielded 50 candidate markers with a combined area under the curve of 0.80 for AIN3. Sixteen CpGs corresponding to 10 genes showed significant differences between disease categories (i.e., infAIN1, advanced AIN3, and anal cancer). qMSP analysis showed significantly elevated methylation levels in anal cancer versus control swabs (pinf 0.003). Further evaluation is currently ongoing.

Conclusions: We successfully performed methylation profiling on anal swabs resulting in the identification of 10 new candidate markers for anal cancer screening. First qMSP results indicate a good marker potential, but further evaluation is to be awaited.

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FC18 - Genotyping

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#6572

Epidemiological Overview of HPV Genotypes Co-circulation Related to Genital Malignancies and Appraising of Human SNPs, miRNAs, Methylated Genes and Lead (Pb) Exposure among the Unvaccinated Community: A Research of Molecular Diagnostic Laboratory

14 - Genotyping

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Background/Objectives: Co-circulation of multiple human papillomaviruses (HPV) infections with low, probably high, and high-risk genotypes are to be associated with various grades of infections and cancer progression. In addition, environmental risk factors, epigenetics, human single nucleotide polymorphisms, and sexually transmitted infections can have synergistic effects on HPV disorders. The aim of the current study was to investigate and wrap up eight of our previous molecular diagnostic laboratory studies in Tehran, Iran as an unvaccinated community.

Methods: We performed genome extraction from 1340 archival women's genital scrapings (LBCs) and genital tissue specimens (530 HPVs undetected vs 810 HPVs detected). The HPVs molecular diagnosis, STD infections, SNPs, and miRNAs detection were conducted on categorized participants using INNO-LiPA® HPV Genotyping, In-House TaqMan Real Time PCR, and PCR-RFLF procedures.

Results: The top 6 dominant HPVs (in women ages 25-34 years) in single and multiple genotypes were HPV6 (43.4%), HPV16 (16.9%), HPV31 (11%), HPV53 (10.2%), HPV11 (9.5%), and HPV52 (9.5%). Moreover, single, multiple, and un-typeable HPV genotypes were diagnosed as follows: 1 type (48.5%), 2 types (24.8%), 3 types (12.7%), 4 types (6.5%), more than 5 types (5.3%), and 1.4% un-typeable among the study population. The prevalence of M. genitalium, C. trachomatis and HSV2 in 195 specimens was 3 (1.54%), 24(12.3%) and 1(0.5%), respectively ($p \geq 0.05$). Findings suggested there was a significant association between the MTHFR 1298 CC, Cyp2C9*3, and GSTO1 A140D gene polymorphisms among 50 cervical intraepithelial neoplasia (CIN) cases compared to 98 HPV-positive subjects and 47 non-cancerous/non-HPV cases as healthy controls (P inf 0.05). However, there were no significant differences in MTHFR 677, JAK2 V617F, GSTO2N142D genotype, Cyp2C9*2, and VKORC1 SNPs between outcomes ($P \geq 0.05$). Moreover, miRs expression analysis presented there was a significant increase in miR-21 and a decrease in miR-29 expressions in cancerous samples in comparison with the control groups (P inf 0.0001). In addition, there was a correlation between the expression of miRs and the ROC analysis (diagnostic value) in CINs and HPV-positive cases. The MethyLight analysis of C13orf18 and C1orf166 (MULAN) demonstrated there were not any significant differences among the 112-study population. Measurement of Lead (Pb) exposure from outdoor air pollution: as a potential risk factor for CINs related to HPV genotypes showed higher Pb concentration was associated with higher risk for cervical malignancy in comparison with non-HPV infected/non-cancerous subjects, after controlling for age effect (aOR = 4.55, 95% CI: 1.55-15.07, P inf 0.01).

Conclusions: Distribution of various oncogenic HPV genotypes with effects of environmental and epigenetic risk factors among the normal population as asymptomatic forms is still challenging in unvaccinated communities. Although it has not been launched as a reliable gene biomarker for prognostication of genital neoplasia yet. Hence, the preventive and organized surveillance programs for HPV screening need to be compiled by health policymakers of low or unvaccinated countries.

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MONITORING OF HPV PREVALENCE AND GENOTYPE DISTRIBUTION IN A VACCINE SURVEILLANCE PROGRAMME USING URINE SAMPLES FROM BOYS AND YOUNG MEN

14 - Genotyping

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Background/Objectives: In Norway, the HPV vaccine was introduced into the childhood immunisation programme in 2009, initially targeting all girls at age 12, with inclusion of boys from 2018. To evaluate the impact of the immunisation programme, a national surveillance programme for the HPV vaccine was established by the Norwegian Institute of Public Health (NIPH) to monitor the HPV prevalence and genotype distribution in young males and females. The aim of this study was to investigate HPV prevalence and type distribution in urine samples from boys and young men.

Methods: 17-year-old unvaccinated boys born in 2002 and 21-year-old unvaccinated men born in 1997 and 1999, who belonged to cohorts where girls had received the Gardasil HPV vaccine at age 12, were invited to participate in the study. Approximately 4.100 urine samples were collected and analysed for the presence of HPV by using a modified GP5+/6+ (MGP) PCR protocol, followed by a multiplex Luminex technology assay detecting and genotyping 37 HPV types [1]. Sample adequacy was evaluated through a real-time quantitative PCR targeting the human beta-globin gene (HBB) and Exogenous Internal Positive Control (EIPC).

Results: Among 4092 urine samples, EIPC was detected in all samples except one, while HBB was detected in all samples except 12 (0.3%). The prevalence of HPV was 1.8% in urine samples from 17-year-old boys (n = 2265) and 17.0% in urine samples from 21-year-old men (n = 1827). In urine samples from 17-years old boys the most common HPV types were HPV66 and HPV90 (0.4%), while the most common HR-HPV types were HPV59 (0.2%) and HPV16/HPV18/HPV52/HPV56/HPV39/HPV51 (0.1%). The most common HPV types found in urine samples from 21-year-old men were HPV90 (3.0%) and HPV42 (2.7%), while the most common HR-HPV types were HPV51 (2.2%), HPV56 (1.8%), HPV52 (1.2%), HPV59 (1.1%), HPV16/HPV39 (0.8%) and HPV33 (0.7%).

Conclusions: Our data indicate that the HPV prevalence in urine samples from unvaccinated boys and young men is low compared to the HPV prevalence previously found in urine samples from unvaccinated Norwegian 17-year-old girls (19.9%) and 21-year-old young women (45.4%) [2,3]. The low prevalence of vaccine-targeted HPV types (HPV6/11/16/18) in boys and men can be explained by herd protection due to the high vaccine uptake among girls in the same age cohorts (1997 and 2002, respectively) and which has been observed in unvaccinated girls [3]. In particular, HPV16 was not among the most commonly detected HPV type in our male populations.

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EVALUATION OF HPV PERSISTENCE AND NEW INFECTIONS IN THE CERVICO-VAGINAL SAMPLES FROM THE NTCC2 STUDY

14 - Genotyping

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Background/Objectives: HPV persistence has been recognized a main factor associated with the risk of developing a high-grade cervical lesion. We used the samples from the NTCC2 study to assess how many persistent HPV positive results at 1-year retesting actually were only new infections. We aimed at estimating the impact of genotyping in distinguishing persistent from new infections to the end of managing them differently, i.e. not referring to immediate colposcopy. We also evaluated whether this impact varies according to baseline genotype, multiple infections, cytology, and other biomarkers status.

Methods: Using the BD Onclarity HPV assay, we genotyped the NTCC2 baseline HPV-DNA positive samples, obtained with Cobas 4800 or HC2 assay. In this study we included BD positive samples from women who did not have any CIN2+ lesion at baseline and had another BD positive sample obtained at least 10 months after the baseline. We defined as persistent the cases with at least one channel in common between baseline and follow up (FU) specimens, whereas the cases that at FU were negative for the baseline channel/s but positive for different channel/s were considered as having new infections.

Results: Among the 568 samples that were positive for BD Onclarity both at baseline and 1-year retesting, 500 had persistent positivity for at least one channel, while 68 (12%) had only new infections. At 1-year retesting, 15 CIN2+ were found in samples with persistent positivity and 3 in samples with new infections. The proportion of only new infections was lower for women that had multiple infections at baseline (5.9%, OR 0.38; 95%CI 0.16-0.79) and in p16/ki67 positives (7.9%, OR 0.50; 95%CI 0.26-0.92), while cytology and E6/E7 mRNA findings had small and non-significant effects (OR for positive vs negative cytology = 0.75, 95%CI 0.41-1.42; OR for positive vs negative E6/E7 mRNA = 0.59, 95%CI 0.31-1.19). Considering the baseline genotype, the proportion of only new infections was lower for HPV16 (9.8%) and for channel 33/58 (7.8%), but differences were compatible with random fluctuations

Conclusions: According to many current screening algorithms, the women who are positive at 1-year retesting are referred to colposcopy, independently from cytology. Applying genotyping, we could classify about 12% of 1-year-HPV positive cases as new infections that could be managed differently from persistent infections. Considering that, in the Italian protocol, 1-year retesting accounts for more than 60% of the colposcopy referrals from first level screening, this proportion would correspond to about 7% of the total colposcopies. Baseline genotype, multiple infections and p16/ki67 results might influence this proportion. On behalf of NTCC2 Working Group

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THE 2023 GLOBAL HPV DNA TYPING PROFICIENCY STUDY

14 - Genotyping

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Background/Objectives: The International HPV Reference Center supports quality and order in HPV research and diagnostics. Notably, the center assigns HPV type numbers to novel HPV types, maintains a reference clone repository, and issues international proficiency panels for HPV genotyping and screening. Correct genotyping is essential in the follow up and monitoring of HPV vaccination. In 2023, we issued two different proficiency panels: The HPV DNA genotyping panel assesses the proficiency of the different HPV genotyping assays as used in different laboratories

Methods: Participating laboratories were asked to perform HPV testing and typing using one or more of their usual assays on coded samples composed of purified whole genomic plasmids of fifteen HPV types (HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68a and 68b) in a background of human cellular DNA. Proficient genotyping requires detection in both single and multiple infections of 10 International Units of HPV 16 and HPV 18 DNA/ ul and 100 genome equivalents / ul for the other HPV types included, with no false positive results reported.

Results: The 2023 genotyping proficiency study was subscribed to by 95 different laboratories worldwide, that have ordered 111 genotyping panels. This is an increase in participation compared to last year. The panels are distributed worldwide during October 2023 to public health laboratories, research laboratories and diagnostic test manufacturers.

Conclusions: A continuing global proficiency program will promote reliable laboratory services for genotyping in HPV vaccine research and monitoring.

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PRE-VACCINE ERA DISTRIBUTION OF HPV GENOTYPES IN CERVICAL CANCER AND PRECANCEROUS LESIONS IN NORWAY

14 - Genotyping

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Background/Objectives: In Norway, HPV vaccine has since 2009 been offered free of charge to all girls born in 1997 and later at age 12 years through the childhood immunization program. Uptake of the first dose reached 93% in 2022. Additionally, a temporary catch-up program was implemented in 2016-2018, offering the vaccine to women born 1991-1996 (uptake 59%). To monitor the vaccine's impact, the Norwegian Institute of Public Health established a surveillance program including nationwide HPV genotyping of archived tissue samples from all women diagnosed with cervical cancer, as well as a subset of high-grade precancerous lesions. Sample management, processing, and HPV genotyping is conducted at the Norwegian HPV Reference Laboratory at Akershus University Hospital. Our aim is to describe the distribution of HPV genotypes in cervical cancer and high-grade precancerous lesions among mostly unvaccinated women.

Methods: HPV test results are reported to the Norwegian Surveillance System for Communicable Diseases (MSIS). MSIS-data was linked to the Norwegian Immunization Registry using personal ID. In our preliminary analysis, we included cases of cervical cancer and high-grade precancerous lesions from 2017-2020. The data included PCR test results for 37 HPV genotypes along with information about the tissue morphology, as well as age and vaccination status of the cases. Morphology was categorized as cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3), adenocarcinoma in situ (ACIS), or invasive cervical cancer (ICC). We calculated the prevalence of positive results for each HPV genotype.

Results: In total, 1082 cases of ICC, 599 cases of ACIS and 2505 cases of CIN2/3 were genotyped and included in our preliminary analysis. The majority of cases were born before 1990 and thereby not in a vaccine eligible cohort (75% of CIN2/3, 57% of ACIS and 95% of ICC). Less than 1% of CIN2/3 and ACIS and 0% of ICC were born 1997 or later and were offered HPV vaccine at 12 years through the immunization program. The remaining CIN2/3 (24%), ACIS (43%) and ICC (5%) cases were among the catch-up population. The proportion of HPV-positive samples was 94%, 95% and 96% for ICC, ACIS and CIN2/3 respectively. Infections with multiple HPV genotypes were more common in CIN2/3 (19%) and ACIS (19%) compared to ICC (4%). The prevalence of HPV 16 and/or 18 (with or without other types) was 70% in ICC, 81% in ACIS and 49% in CIN2/3. The HPV genotype distribution according to morphology, age and vaccination status will be presented.

Conclusions: Our data provide the first nationwide overview of HPV genotype distribution in cervical cancer and high-grade precancerous cervical lesions in Norway. The systematic surveillance of HPV genotype distribution in cervical lesions contributes to evidence-based vaccine policy and facilitates post-vaccination monitoring.

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#6779

DIFFERENCE IN OBSERVED HPV73 PREVALENCE IN URINE SAMPLES FROM YOUNG WOMEN IN A VACCINE SURVEILLANCE PROGRAMME USING MGP-LUMINEX AND IN-HOUSE QPCR

14 - Genotyping

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Background/Objectives: In Norway, the HPV vaccine was introduced in the childhood immunisation programme in 2009, initially offered to all girls at age 12 years and extended to include boys from 2018. To evaluate the impact of the immunisation programme, a national surveillance programme for the HPV vaccine was established by the Norwegian Institute of Public Health (NIPH) to monitor the HPV prevalence and genotype distribution in urine samples from pre-screening cohorts. Method development and optimisation, including quality assessment using plasmids, revealed challenges in reliably detecting HPV73 using modified GP5+/6+ primers (MGP) in combination with Luminex technology [1]. Previous studies [2,3,4] have reported difficulties in amplifying or detecting HPV73, potentially leading to underreporting its prevalence and relevance in cervical cancer and high-grade precancerous cervical lesions. This highlights the need to evaluate alternative detection methods to better assess HPV73 prevalence and the aim of this study is to investigate the prevalence of HPV73 using PCR with type-specific primers targeting a different segment of the genome than MGP primers, in younger women.

Methods: Urine samples from vaccinated 21-year-old women born in 1997 were collected, and HPV genotyping was performed using an MGP PCR protocol, followed by hybridization of type-specific oligonucleotide probes linked to fluorescence-labelled polystyrene beads (Luminex technology) for the detection and genotyping of 37 HPV types [1]. These included the high-risk types HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59, as well as the probably and possibly high-risk types HPV26, 30, 66, 67, 68, 69, 70, 73 and 82. In addition the method detects the low risk and unknown risk types HPV6, 11, 40, 42, 43, 54, 61, 74, 81, 83, 86, 87, 89, 90 and 91. Sample adequacy was assessed through real-time quantitative PCR targeting the human beta-globin gene (HBB) and Exogenous Internal Positive Control (EIPC). Furthermore, the same DNA eluates underwent additional analysis with an in-house qPCR assay, specifically targeting the HPV73 E6 gene.

Results: Our preliminary analyses indicate a threefold increase of HPV73 prevalence when analysed with E6 type-specific qPCR. MGP PCR and Luminex technology detected HPV73 in 1.7% of the samples collected from 21-year-old women vaccinated with Gardasil, while type-specific qPCR showed a prevalence of 5.4%. All samples tested positive for HBB and EIPC.

Conclusions: Preliminary data may suggest a potential systematic underreporting of HPV73. We will investigate the need for further analysis or adoption of an alternative detection method for this specific genotype in the surveillance programme to get a better understanding of HPV73 prevalence in unvaccinated and vaccinated populations.

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HIGH RATE OF NON-VACCINE-TARGETED HIGH-RISK HPV GENOTYPES IN EASTERN ETHIOPIA: Its implication in future vaccine selection

14 - Genotyping

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Background/Objectives: Since the distribution of high-risk [hr] HPV genotypes varies across countries, genotype-based vaccination is widely recommended to control the burden of cervical cancer. As of 2018, an HPV vaccination program is underway in Ethiopia for girls aged 9-14 years against HPV-6, HPV-11, HPV-16, and HPV-18. However, the rate and distribution of non-vaccine-targeted genotypes are not well characterized. Therefore, by determining the prevalence and characterizing their genotypes, we assessed the level of multiple infections with other vaccine-targeted genotypes in Ethiopia.

Methods: A health facility-based cross-sectional study including 110 women with positive HPV DNA results was conducted from April to August 2021. We used a structured questionnaire to collect demographic and clinical data and collected cervical swabs using L-shaped FLOQSwabs®. We, then, stored them in eNAT nucleic acid preservation and transport® medium. Women's cytological profile was determined based on Pap smear test results, and we made automated nucleic acid extraction using STARMag 96 ProPrep Universal Extraction Kit. We have used a real-time amplification assay to amplify and identify the HPV Late 1 [L1] gene used for genotyping. After the collected data was entered into Epi data version 3.1 software, the analysis was done with STATA version 14.

Results: Among 901 women who underwent HPV DNA testing, only 110 women [age range 30 to 60 years, mean age = 36.5 years and SD±6.9] had positive HPV DNA results and were included in the study. Among these, 108 women had valid co-testing [Pap test and HPV DNA test] results for further analysis, and the results of the remaining 2 women were rejected. Overall, the prevalence of non-vaccine-targeted HPV was 51.8% (95% CI: 0.424- 0.611), of which 28 women (25.4%, 95% CI: 0.181- 0.345) had a single non-vaccine HPV genotype infection. The remaining 29 women (26.4%, 95% CI: 0.190- 0.355) experienced multiple infections. The non-vaccine-targeted genotypes of HPV-35 (10%, 95% CI: 0.056- 0.173), HPV-68 (8.2%, 95% CI: 0.043- 0.151), HPV-56 (7.3%, 95% CI: 0.036- 0.140), and HPV-66 (7.3%, 95% CI: 0.036- 0.140) were found in higher numbers. In addition, out of these 108 women, 93 (86.1%, 95% CI: 0.781- 0.915) had low-grade squamous intraepithelial lesions, 13 (12%, 95%CI: 0.071- 0.198) no intraepithelial lesion or malignancy, and two (1.9 %, 95%CI: 0.004 - 0 .072) high-grade squamous intraepithelial lesions. Furthermore, there was no statistical difference (p=0.755) between vaccine-targeted and non-vaccine-targeted genotypes as the primary cause of cervical lesions.

Conclusions: In Ethiopia, non-vaccine-targeted HPV genotypes are highly prevalent, including HPV-35, HPV-68, HPV-56, and HPV-68. More than a quarter of women had multiple infections, which increased their risk of developing cervical cancer. Therefore, changing from the current vaccine that protects against four HPV types to the vaccine that covers seven HPV genotypes will have better outcomes in preventing cervical cancer.

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A comprehensive, user-friendly and cost-efficient HPV and sexually transmitted infections Assay

14 - Genotyping

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Background/Objectives: There are more than 30 different bacterial, viral and parasitic pathogens known to cause sexually transmitted infections (STIs). STIs represent a major public health burden worldwide, however, there is a paucity of literature on their burden and trends globally. HPV and Chlamydia trachomatis are the most prevalent STDs worldwide. Essentially, HPVs and STIs cannot be regarded as an isolated problem since multiple HPV/STI co-infections are rather common contributing synergically to diseases. These infections are often asymptomatic or may induce non-specific symptoms. Selective testing of HPVs and STIs does not provide sufficient STD overview and multiple assays are expensive. There is clearly a need for a comprehensive, user-friendly and cost-efficient HPV/STI method to provide a far-reaching overview of HPV and STI co-infections at a cost matching a simple PCR test.

Methods: The ChapterDx HPV-STI assay utilizes a combination of type-specific primers targeting 29 HPVs (including HPV68a and 68b) and 13 STIs, including Chlamydia trachomatis serovars and the GAPDH internal control. Amplification and barcoding/indexing of each sample is simultaneously performed in a single tube and a single PCR reaction. After amplification, all the amplicons are pooled in a single tube. The pooled PCR products are then analyzed by Illumina MiniSeq platform. The hr-HPV types include HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68a, 68b, 73, 26, 53, 82 and lr-HPV types include HPV6, 11, 40, 42, 43, 44, 55, 61, 81, 83. The 13 STIs include Chlamydia trachomatis, Treponema pallidum, Mycoplasma genitalium, Trichomonas vaginalis, Neisseria gonorrhoeae, HSV-1, HSV-2, Mycoplasma hominis , Ureaplasma urealyticum , Ureaplasma parvum (UP), Varicella zoster virus, Haemophilus ducreyi. The Chlamyida serovars include L1, L2, B, D, E, F and G. For HPV genotyping study, a set of 75 samples previously analyzed by Genomica Clart HPV assay, were analyzed by ChapterDx HPV-STI NGS assay. The assay was also evaluated for amplification biases and type-suppression.

Results: In a previous study, ChapterDx HPV-STI assay and Roche cobas HPV test exhibited an overall agreement of 97.5% for hr-HPV, and 98.5% for both HPV16 and HPV18. In this study, we compared genotyping agreement with Genomica Clart HPV assay and the overall genotyping agreement was 98.7% (74/75), the full agreement was 92% (69/75) and the partial agreement was 6.7% (5/75). ChapterDx HPV-STI assay detected more types due to significantly decreased PCR biases and type-suppression. ChapterDx HPV-STI NGS assay also detected other non-HPV STIs in the genotyping sample group, which included C. trachomatis, N. gonorrhea, T. vaginalis, M. hominis, and U. parvum.

Conclusions: ChapterDx HPV-STI NGS assay demonstrates excellent concordance for HPV genotyping without the issues of PCR biases and type-suppression, common among assays using consensus/degenerate primers. Furthermore, ChapterDx assay detected non-HPV STIs revealing that many samples harbor other STIs that go undiagnosed in selective HPV testing. In our other studies (data not shown) we observed that the rate of multiple co-infections of HPV-STI varies in different populations. The ChapterDx NGS assay is a user-friendly and easy-to-automate method that provides accurate and comprehensive results for a wide spectrum of HPVs and STIs. The assay is rapid, cost-competitive with a simple PCR assay and can be applied to low, medium, and high-throughput sample scales.

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#6781

"YOU'RE NO LONGER MY TYPE!" - IMPACT OF QUADRIVALENT VACCINATION ON US HPV PREVALENCE AND DISEASE

14 - Genotyping

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Background/Objectives: The quadrivalent vaccine was licensed in the US in 2006 and young women who were vaccinated as pre-teens now represent an annually increasing number of routinely screened women. While 3-dose coverage in the US has lagged behind other nations, the recent realization that 2- and even 1-dose regimens provide protection against HPV 16/18 infections means that many States now have herd immunity. The BD OnclarityTM HPV Assay is an FDA-approved HPV test that provides extended genotyping information focused on the nonavalent high-risk HPV types responsible for 90% of cancers. Here we describe the emerging results from an IRB-exempt study of routine screening data to examine recent changes in US HPV prevalence and disease, benchmarked against prior published pre-vaccination numbers and data from the BD Onclarity US pivotal where ~90% or enrolled women were unvaccinated.

Methods: Routine screening and follow-up HPV extended genotyping data were de-identified and, where available, linked to cytology and histology outcomes. Results were stratified by age and location and compared to published pre-vaccination data and PMA trial data from approximately 10 years prior, using standard statistical methods. State vaccination surveys were used to infer vaccine coverage and the potential for herd immunity

Results: The BD Onclarity PMA trial enrolled up to 10% of women who self-declared that they had received the quadrivalent vaccine. We previously reported a significant decrease in HPV16/18 and cross-protected high-risk types and a reduction in LSIL cytology and CIN2+ disease in women with HPV16/18 infections who had received the vaccine (1). Here, we re-examined the impact of vaccination in women screened in the last 2 years (up to 10 years later). HPV 16/18 prevalence is continuing to decline over time with HPV 16 representing approximately 6% of screened women pre-vaccination, reduced to inf 2% in the PMA trial, and down to inf 1% in more recently screened women. HPV18 showed similar levels of decline from over 4% to inf 1% over the same period. Cross-protected types such as HPV 31 showed more modest declines with less than 50% reduction in prevalence. The most striking change observed was in the contribution to disease where HPV16/18 are now only contributing about 1/3 of the total disease cases (reduced from approximately 70%, pre-vaccination) with the majority being attributable to the non-16/18 types, especially HPV 31, HPV 52 and HPV33_58.

Conclusions: The quadrivalent vaccine continues to have a significant impact on both HPV prevalence and disease in the US and there is evidence of herd immunity from published studies. This ongoing decline was confirmed using real-world-evidence from three different clinical laboratories who routinely report out extended genotype information. We discuss these results in the context of recent reports documenting an increase in non-vaccine type disease and the current standard of care HPV 16/18 triage paradigm in the United States and other countries. We conclude that HPV16/18 triage is no longer an optimal management strategy based on the reduced prevalence of these types in the population.

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FC17 - Methylation II

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UTILITY OF DNA METHYLATION MARKERS FAM19A4/MI124-2 FOR RISK-STRATIFICATION OF WOMEN ≥45 REFERRED FOR COLPOSCOPY

17 - Methylation

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Background/Objectives: The performance of colposcopy is often impaired in older women because the transformation zone retracts into the cervical canal, which makes sampling difficult and thereby increases risk of underdiagnosis. We recently showed that cervical biopsies missed more than 50% of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) lesions as compared to a diagnostic cone biopsy in older women without a fully visible transformation zone. To reduce the risk of overtreatment and its consequential harms, but without increasing risk of underdiagnosis, there is a need to explore the utility of biomarkers for risk-stratification.Host-cell DNA methylation has been shown to be useful for triage of women with an HPV-positive screening test and to predict risk of regression in women with CIN2. Especially FAM19A4/miR124-2 has shown potential as a triage marker when tested in large multicentre studies. Yet, the value of DNA-methylation as a risk stratification tool for older women at colposcopy is unknown. Therefore, this study evaluated the clinical utility of host-cell DNA-methylation markers FAM19A4/miR124-2 in the accurate identification of older women with CIN2+.

Methods: We conducted a cross-sectional study during 2019-2021. Eligible women were ≥45 years, referred for colposcopy due to an abnormal screening result, and did not have a fully visible transformation zone. Each woman had a cervical cytology sample and biopsies collected followed by a loop electrosurgical excision procedure. Cervical samples were analysed for host-cell methylation markers FAM19A4/miR124-2 using the QIAsure Methylation test. The sensitivity and specificity of the methylation markers for CIN2+ detection will be calculated using the loop electrosurgical excision result as the reference standard.

Results: Out of 102 eligible women, the cytology sample was invalid for 6 women, and 10 samples tested invalid using the QIAsure Methylation test, leaving a total of 86 women to be included for final analysis. The DNA methylation analyses are currently in progress and the final results will be presented at the conference.

Conclusions: If host-cell DNA methylation has a high sensitivity and specificity for older women with CIN2+ detection, the markers FAM19A4/miR124-2 may be useful for risk-stratification at the time of colposcopy. This may enable the implementation of targeted treatment for older women at high risk of CIN2+, while allowing older women at lower risk to undergo clinical follow-up.

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#6548

A NOVEL DNA METHYLATION PREDICTOR FOR CIN3 PROGRESSION OF HR-HPV POSITIVE WOMEN CAN HELP IN EARLY DETECTION OF CERVICAL CANCER RISK

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]. Cervical cancer is preceded by cervical intraepithelial neoplasia (CIN) which are lesions detected on the surface of the cervix, categorized into stages, with stage 1 (CIN1) being the mildest and stage 3 (CIN3) being the closest in severity to cancer. 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 CIN leading to a more invasive histological biopsy for definitive diagnosis. DNA methylation has been found to be a prospective biomarker that can help in the early detection of CIN3 progression [3] and next generation sequencing can provide genome-wide detection of potentially methylated positions (CpGs) in the genome.

Methods: DNA was isolated from cervical tissue samples of healthy hr-HPV infected women enrolled in the ARTISTIC cohort [4] and was sent for reduced representation bisulfite sequencing (RRBS). Each participant was monitored for a period of up to 6 years during which histology testing was conducted to determine the incidence of CIN3. The differentially methylated positions (DMPs) between the women who remained healthy and the women that developed CIN3 during the follow up period were used as features in a supervised machine learning model using support vector machines.

Results: 1331 CpGs were found to be differentially methylated between the two groups of women and 31 of them were ranked as the most important ones using a bootstrap resampling method and recursive feature elimination. The final classifier was built using these 31 DMPs and exhibits 93.3% sensitivity and 94.4% specificity.

Conclusions: 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 up avenues for new targeted prevention and treatment strategies.

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#6839

A multicenter study on the accuracy of detecting PAX1/JAM3 double gene methylation in cervical scraping cells as a clinical predictor of cervical cancer

17 - Methylation

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Background/Objectives: The cervical cancer screening guidelines recommend the use of high-risk human papillomavirus (hrHPV) DNA testing as the primary test, but the specificity of hrHPV testing is relatively low. There is an urgent need for a new type of triage tool to improve the accuracy and specificity of cervical cancer screening, in order to reduce the referral rate of colposcopy.The purpose of the study is to explore the value of DNA methylation detection in cervical scraping cells as a clinical predictor of cervical cancer as a triage method of high-risk HPV (hrHPV) for hospital opportunistic cervical cancer screening programme.

Methods: This study was a prospective multicenter study conducted from May 2022 to October 2022. Women with cytology and hrHPV testing results were enrolled in gynecological outpatient clinics for the study. Cervical scraping cells were collected for PAX1/JAM3 dual genes methylation testing (PAX1m/JAM3m). Colposcopy evaluation and biopsy were performed according to guidelines. The clinical performance of various testing methods and their combinations were compared based on histological diagnosis.

Results: More than 6000 women participated in this study, including the pathological results of 1643 cases of cervical intraepithelial neoplasia and cervical cancer. For detecting CIN3+, the area under curve of PAX1m/JAM3m testing 0.850(0.827-0.873) was significantly superior to cytology testing 0.554(0.528-0.581), P values inf 0.005. The PAX1m/JAM3m testing for detecting CIN2 or more severe lesions (CIN2+) were over 74% sensitivity and over 94%specificity, respectively. The sensitivity and specificity of PAX1m/JAM3m testing for detecting CIN3+ were over 87% and 85%, respectively. No any cancer was miss diagnosis by PAX1m/JAM3m testing in the study.

Conclusions: Due to its high specificity of the PAX1/JAM3 dual genes methylation testing could be used as triage method of hrHPV DNA testing for cervical cancer screeing.

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#6793

Methylation analysis to detect CIN3+ in hrHPV-positive self-samples from the population-based cervical cancer screening programme

17 - Methylation

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Background/Objectives: Since 2017, self-sampling has been introduced to the Dutch population-based screening programme (PBS). However, routine triage cytology cannot be performed on self-sampling material. Methylation analysis, an alternative triage method, can be performed directly on DNA extracted from self-samples. Recently, we tested 15 published cervical intraepithelial neoplasia grade 3 or worse (CIN3+)-specific methylation markers, and found a panel of three markers with a sensitivity of 82% and a specificity of 74%. In this study, we compared the diagnostic performance of two commercial methylation assay (QIAsure Methylation Test and Gyntect® assay) with our previously identified panel, and searched for the best diagnostic marker panel by combinning all markers.

Methods: DNA from the same cohort of high-risk human papillomavirus (hrHPV)-positive self-sampled material obtained through the PBS from women with CIN2 or less (infCIN3, n=208) and women with CIN3+ (n=96) was used. QIAsure Methylation Test and Gyntect® assay were performed using quantitative methylation-specific PCR (QMSP) according to manufacturer's protocol. Diagnostic performance was determined by area under the curve (AUC) of receiver operating characteristic (ROC) analysis. Self-samples were divided into a train and test set. Both hierarchical clustering analysis and model-based recursive partitioning and robustness analysis to construct a predictive model were applied to design the best marker panel.

Results: QIAsure Methylation Test (comprising two markers) showed a 65% sensitivity with 72% specificity, while Gyntect® assay (comprising 6 markers) showed a 59% sensitivity and 91% specificity for CIN3+. Comparing all individual 23 methylation markers, ROC analysis showed an AUC of ≥0.7 for 11/23 markers (pinf0.001). By model-based recursive partitioning and robustness analysis, we found a panel with better sensitivity compared to QIAsure and Gyntect® (pinf0.001). This new panel including ITGA4, ASCL1 and FAM19A4, has a 84% sensitivity and 70% specificity, similar to our previous panel (ANKRD18CP, LHX8 and EPB41L3).

Conclusions: Summarising, in addition to our previously identified panel, combination of ITGA4, ASCL1 and FAM19A4 showed good diagnostic performance and potentially can replace cytology thereby avoiding additional doctor's visit for many women and reducing time of referral to the gynaecologist.

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#6851

Preliminary results of DNA-methylation analysis in a population-based screening program

17 - Methylation

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Background/Objectives: Growing evidence have been demonstrated that the methylation of specific cell promoter genes is one of the most common epigenetic mechanisms in normal cell physiology and in tumorigenesis. In particular, hypermethylation of host and viral HPV-genome increases with the severity of lesions in cervical cells, providing a useful potential biomarker in triage of hr-HPV-positive women and during treatment. The high heterogeneity in study settings, variability in targeted population and genes, as well as different analytical protocols represents potential limits in introduction of methylation test into clinical practise. To evaluate the clinical performance of FAM19A4/miR124-2 methylation-based triage, a cross-sectional study was performed among women recruited into the cervical screening program in Italy.

Methods: The DNA methylation assay was carried out in LBC samples, stored at -20°C, using the available commercial kit PreCursor-M+ (distribute by Fujirebio Europe), a multiplex real-time PCR test starting with bisulfite-converted DNA, performed by EZ DNA methylation Kit (Zymo Research). For each patient, clinical results (i.e., cytology, HPV-DNA test, colposcopy, and histology) were retrospectively collected. We calculated the sensitivity (Se), specificity (Sp) and negative/positive predictive values (PPV/NPV) of DNA methylation VS clinical results to evaluate the potential adoption of these markers into screening program.

Results: A total of 61 cases were included, of which 70% classified as boundary or mild dyskaryosis (i.e. ASCUS/LSIL) and 90% were positive for at least one hr-HPV-genotype. 50/61 women were referred to colposcopy and more than half have a histology examination, with 4/28 diagnoses of CIN2+. Clinical Se, Sp and PPV/NPV of DNA methylation analysis VS cytology, HPV-DNA, colposcopy, and histology results were reported in table 1 (Supplementary). The clinical Se and Sp of DNA methylation VS cytology was 23.3% and 88.9%, respectively, similar to result observed between DNA methylation and HPV-DNA test (22% Se, 100% Sp). The Se of methylation versus colposcopy and histology was 38.5% and 50%, whereas the Sp was 91% and 83.3%, respectively. The PPV of DNA methylation compared with other tests was higher than 0.80, except of histology where the PPV was 0.33. Conversely, the NPV was higher if compared with histology (0.91), but descreases VS cytology, HPV-DNA, and colposcopy. To evaluate the role of methylation in detection of progression/regression of cervical lesions, 22 patients were evaluated at baseline (T0) and follow-up visit (T1). The Se of DNA methylation VS colposcopy at T0 and T1 was respectively 38.5% and 27.3%, whereas the Sp was 85.7% at T0 and 100% at T1. Moreover, the PPV at two different time points was 0.83 and 1.00. The NPV was 0.43 and 0.50 at T0 and T1, respectively.

Conclusions: Our results evidenced a good specificity of DNA methylation in risk stratification of HPV-positive women, with a reliable discrimination for patients with negative-histology. We demonstrated that the combination of test, as HPV-DNA and methylation, may improve the accuracy of test as predictor of severe diseases. As we expected, the hypermethylation status decreased in treated group at follow-up. Larger samples size could provide consistent support for the introduction of FAM19A4/miR124-2 as reliable biomarkers for the management of HPV-positive women in cervical screening program, as well as, during the monitoring of patients treated for high-grade cervical lesions.

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#6933

AUTOMATED WORKFLOW FOR FAM19A4/miR124-2 METHYLATION ANALYSIS ON HPV+ CERVICAL SCREENING SAMPLES

17 - Methylation

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Background/Objectives: Triage testing of HPV-positive women by methylation analysis to select women with (pre)cancerous lesions who need colposcopy is an emerging strategy for clinician-taken and self-collected screening samples. Methylation detection assays require pretreatment of the sample DNA with sodium bisulfite conversion to separate methylated from unmethylated cytosines, which often involves manual laboratory steps. Bisulfite-conversion performed directly on the clinical sample without prior DNA extraction (i.e. direct bisulfite conversion) has fewer handling steps thereby improving the throughput. Automation can further improve throughput, reproducibility, and accuracy of the methylation assay for better risk stratification. A novel automated workflow for methylation analysis comprising sample pretreatment and PCR set-up on a liquid handler system was developed for application with the FAM19A4/miR124-2 methylation assay. In this study the novel automated workflow for FAM19A4/miR124-2 on cervical samples in PreservCyt medium was compared to two reference protocols using either isolated genomic DNA as input for bisulfite-conversion or the direct bisulfite-conversion protocol.

Methods: The novel workflow was developed on the Dynamic Devices LM1200 platform and is capable of handling 96 samples simultaneously. The sample in liquid-based cytology medium serves as input for the workflow and all sample handling (e.g. lysis, bisulfite-conversion and PCR setup) is performed on-deck. A dedicated user interface guides the complete process from sample loading, logging, up to data interpretation of the FAM19A4/miR124-2 assay and is capable to report results through LIMS. The FAM19A4/miR124-2 methylation test is a CE-IVD and commercially available as PreCursor-M+ (Self-screen B.V.) or QIAsure Methylation Test (QIAGEN). The assay detects methylation of the FAM19A4 and miR124-2 genes relative to the housekeeping gene ß-actin using quantitative methylation-specific PCR. Sample validity is based on ß-actin Ct values indicating sufficient DNA quality and quantity and the assay scores samples as hypermethylation-positive when positive for the FAM19A4 and/or miR124-2 target. Sixty eight cervical smears of women collected in PreservCyt were used for the comparisons.

Results: The success rate of the automated workflow was equal to that of both reference protocols (>97%). The agreement for methylation assessment when compared to the reference protocols was high, being for both assays ≥97.5% (kappa scores ≥0.82). The workflow has reduced hands-on time >80% for to both reference protocols and easily performs 96 samples within an 8-hour work shift from sample to result.

Conclusions: The novel automated workflow for methylation analysis performs equivalent to the reference protocol and offers an automated workflow for FAM19A4/miR124-2 methylation analysis with significantly reduced hands-on time.

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#6742

High performance of DNA methylation analysis among HPV-positives: a retrospective cohort study with 12-year follow-up time.

17 - Methylation

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Background/Objectives: HPV-based screening provides a high sensitivity for detecting high-risk HPV infections, but it lacks specificity for identifying women at risk of serious high-grade cervical precancerous lesions or cancer. Therefore, 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 cellular methylation markers. This is based on the evidence that DNA methylation of host cell genes has been shown to correlate with the severity of cervical lesions and the presence of carcinogenic HPV types. In this retrospective cohort study, we mimic a real-world setting by utilising 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 screening samples.

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). Excess samples which have been processed and stored in our biobank were analysed by the Gyntect® DNA methylation assay (Oncgnostics, Jena Germany). The outcome of cervical disease was known through linkage with health registries. Two study groups of HPV-positive women were generated: HPV-controllers, who only had normal cytology recorded in the cervical cancer screening programme, and HPV-progressors, who developed cervical intraepithelial neoplasia (CIN) grade 2 or worse either at LBC screening or during the follow-up time of up to 12 years. For each HPV-progressor, we identified an HPV-controller matched on age and HPV type at LBC screening. For the HPV-progressors, concordance between HPV types found in the screening sample and in the cervical lesion developed during follow-up time will be examined. Performance indicators of the methylation assay were determined by comparing the number of methylation positive and negative samples between the two groups.

Results: We identified 188 HPV-progressors and matched HPV-controllers and performed DNA methylation analyses. In total, 99.2% of the samples provided a valid result. Interestingly, the specificity of the DNA methylation test was very high, as 97.3% of the HPV-controllers had a Gyntect® negative score. Test sensitivity (proportion of HPV-progressors with positive test) will be presented once HPV type in lesions has been confirmed (ongoing analysis).

Conclusions: These results indicate that the Gyntect® DNA methylation assay can be used to improve specificity in HPV-based screening. This could in the future help reduce overdiagnosis and overtreatment.

References: Dillner J, et al. Vaccine 2018;36(26)

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#6887

Construction and preliminary validation of a primary screening model for cervical cancer based on host DNA methylation

17 - Methylation

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Background/Objectives: Background: Cervical cancer is the most common cancer among women, and screening is an effective prevention method. The current screening methods mainly include cytology and HPV testing, but both methods have their limitations. Therefore, it is still necessary to explore new biological markers. Increasing evidence suggests that DNA methylation detection is one of the effective methods for cervical cancer screening. These studies mostly use host methylation gene promoter regions as predictive factors, without considering multiple host genes or the relationship between different CpG sites within genes. Therefore, Further research needed for DNA methylation in cervical cancer screening. Objectives: To construc a multigene machine learning model for predicting the level of cervical cancer and precancerous lesions in cervical cancer screening using methylation profiles of host genes.

Methods: Host DNA methylation testing was performed on samples. Gene fragments associated with high lesions and cervical cancer were selected by the bioinformatics analysis method of CpG high-density, high correlation, and high methylation screening (MHL screening) and LASSO regression algorithm. With lesions of CIN2 and above as the research endpoint, three machine learning models were constructed: Random forest model, Naive Bayesian model, and Support vector machine model. The histologic diagnosis results were used as the gold standard to compare the detection of CIN2 and above lesions under different screening methods.

Results: 224 women were recruited, with 144 divided into the training set and 80 into and validation set. The mean age of the training set was 47.90±9.90 years old, with the HPV positivity rate of 29.90% and 85 cases of CIN2 and above; the mean age of the validation set was 46.90±10.20 years old, with the HPV positivity rate of 35% and 31 cases of CIN2 and above. The correlation coefficient of MHL and the level of cervical cancer lesions was 0.72. 6 genes (containing 7 detectable CpG locus regions) were screened out from the 47 genes to develop models. On the validation set, the AUC of the random forest model, the naive Bayesian model, and the support vector machine model was 0.90 (95% CI: 0.82-0.98), 0.88 (95% CI: 0.78-0.97), and 0.82 (95% CI: 0.69-0.94), respectively, with the specificity of 73.47% (95% CI: 63.29%~ 83.14%), 93.88% (95% CI: 88.62%-99.13%), and 95.92% (95% CI: 91.58%-100.00%) respectively.

Conclusions: The methylation of human host genes is closely related to the level of cervical cancer and precancerous lesions. The NB and SVM model in this study had better specificity and might hold the potential to be combined with HPV testing in cervical cancer screening to optimize the screening strategy.

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#7656

A novel DNA Methylation marker for prediction of Cervical Intraepithelial Neoplasia grade 2 progression

17 - Methylation

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Background/Objectives: Historically, Cervical Intraepithelial Neoplasia grade 2 (CIN2) has been the cut-off to proceed to local surgical treatment of the cervix. However, treatment has been shown to increase the risk of poor future reproductive outcomes, and there is increasing evidence to suggest that a large number of CIN2 lesions will regress. DNA methylation has recently been proposed as a novel molecular technique, which may be accurate for both diagnosis and prediction of future oncological outcomes.

Methods: DNA was extracted from liquid-based cytology samples in a subset of 58 women aged 16-24 managed conservatively for histologically-confirmed CIN2, with known outcomes (12 progressors, 31 regressors, and 15 late regressors). Extracted DNA underwent bisulphite conversion and an Illumina 850k EPIC Methylation array. Data were processed using R; minfi package and a bespoke statistical pipeline.

Results: Quality control was met for all 58 samples. Data were adjusted for principal components, previous pregnancy, and smoking status. Beta values were compared between groups using linear regression. In progressors (n=12) as compared to regressors (n=46) one CpG was statistically significantly differentially methylated (FDR <0.1).

Conclusions: Previous work with DNA methylation in prediction of CIN2 progression has typically focused on known CpG sites. We have identified a novel CpG site which may assist in predicting progression of CIN2. This CpG site is within the promoter region of a gene involved in immune regulation, and thus biological plausibility exists for its role in malignant development. Larger prospective cohort studies are needed to validate these findings.

FC14 - Self-sampling II

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#7114

PROMOTING PARTICIPATION THROUGH SELF-SAMPLING: SOCIODEMOGRAPHIC DISPARITIES IN SCREENING UPTAKE AMONG LONG-TERM NON-ATTENDING WOMEN - A RANDOMIZED CONTROLLED TRIAL

11 - Screening for women difficult to reach

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Background/Objectives: Sub-optimal screening coverage is a significant risk factor for cervical cancer. While self-sampling technology can address some screening barriers, it's important to note that individuals with higher socioeconomic status tend to adopt new health interventions more readily. To address inequalities, we utilized data from a recent randomized controlled trial (ClinicalTrials.gov NCT03873376), which showed that HPV self-sampling significantly increased screening uptake. Among long-term non-attending women, participation rates were 27.7% in the 'send-to-all' arm, 17.0% in the 'opt-in' arm, and 4.8% in the control arm (Aasbø et al. 2022). Sociodemographic data for each participant were collected from Statistics Norway to further examine associations with self-sampling participation. This study represents the first investigation of participation inequalities related to self-sampling among long-term non-attending women.

Methods: We analyzed sociodemographic factors affecting screening participation in 6,000 women aged 35 to 69 who hadn't been screened in over a decade. These women were randomly assigned to three screening strategies: (i) regular screening reminders (control), (ii) optional self-sampling kit request (opt-in), or (iii) unsolicited self-sampling kit (send-to-all).

Results: Long-term non-attending women across all sociodemographic levels (i.e. income level, education level, and labor market status), have a far higher cervical screening participation when offered send-to-all HPV self-sampling than when receiving the standard reminder letter to schedule a clinician-collected cervical screening exam. In the send-to-all arm, increased screening participation ranged from 17.1% (95% confidence interval (95%CI)=10.3% to 23.8%) to 30.0% (95%CI=21.5% to 38.6%) between sociodemographic groups. In the opt-in arm, we observed smaller, and at times, non-significant increases within the range 0.7% (95%CI=-5.8% to 7.3%) to 19.1% (95%CI=11.6% to 26.7%). Thus, send-to-all self-sampling benefits women in all sociodemographic groups more than opt-in self-sampling. Moreover, larger absolute inequalities were observed for women in the send-to-all arm than women in the control arm for income level, education level, labor market status, and country background. Women from high-income countries with high socioeconomic status were most likely to take advantage of being offered self-sampling.

Conclusions: Self-sampling increases participation among long-term non-attending women of all sociodemographic backgrounds in the context of a national cervical screening program. However, considerable inequalities in participation remain for all screening modalities investigated, and some sociodemographic inequalities are exacerbated by self-sampling. Attention should be paid to reducing participation inequalities if self-sampling is offered to long-term non-attending women in a screening program.

References: Aasbø, G., Tropè, A., Nygård, M. et al. HPV self-sampling among long-term non-attenders to cervical cancer screening in Norway: a pragmatic randomized controlled trial. Br J Cancer 127, 1816-1826 (2022). https://doi.org/10.1038/s41416-022-01954-9

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#7151

MAILED, AT-HOME SELF-SAMPLING FOR HPV TESTING TO INCREASE SCREENING PARTICIPATION AMONG UNDER-SCREENED PATIENTS IN A U.S. SAFETY NET HEALTH SYSTEM: RESULTS OF THE PRESTIS TRIAL

13 - Self-sampling

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Background/Objectives: The Prospective Evaluation of Self-Testing to Increase Screening (PRESTIS) Trial is the first pragmatic randomized controlled trial (RCT) in the United States (U.S.) to evaluate the effectiveness of mailed, at-home self-sampling for HPV testing in a safety net health system setting.1 Safety net systems are a critical setting as they provide care to medically underserved individuals who are at disproportionate risk for cervical cancer. We hypothesized that patients who were mailed an unsolicited self-sampling kit would have higher screening participation compared to those receiving usual care; and that patient navigation, a patient-centered intervention to address barriers to care, would enhance self-sample HPV testing uptake.

Methods: PRESTIS is a three-arm pragmatic RCT of n=2,268 patients in a U.S. safety net health system who are underscreened for cervical cancer (i.e., no Pap in 3.5 years or no Pap/HPV co-test in 5.5 years). Eligible participants were identified through the electronic health record (EHR) and randomized to one of three arms: 1) telephone recall to provider-performed screening (usual care); 2) telephone recall + mailed self-sampling kit for HPV testing; or 3) telephone recall + mailed self-sampling kit for HPV testing + telephone-based patient navigation. Kits were tested for high-risk (HR-) HPV, with reflex testing for HPV 16, 18/45. Results were documented in the EHR; HR-HPV+ patients were navigated to cytology or colposcopy. The primary outcome, screening participation, was ascertained by EHR review at 6 months post-randomization and defined as return of a completed kit or attendance for provider-performed screening.

Results: Participants were enrolled 02/2020-08/2023. Primary outcomes have been ascertained for n=2,115 participants (93%); 100% will be ascertained by 02/2024 (present estimates may change slightly). Trial participants were predominantly Hispanic/Latina (68.6%); 53.4% indicated Spanish as their primary language; 60.3% were uninsured; and 60.6% had a primary care provider. Average age was 47.9 years; time since last screening test was 10 years. In intent-to-treat analyses, screening participation was 15.3% (95% CI 13.0 - 17.9%) in Arm 1; 44.0% (40.4 - 47.6%) in Arm 2; and 51.4% (47.7 - 55.0%) in Arm 3. Relative risk (RR) of screening in Arms 2 and 3 compared to Arm 1 was 2.90 (2.42 - 3.47) and 3.36 (2.82 - 4.01), respectively. Relative risk of screening in Arm 3 compared to Arm 2 was 1.16 (1.04 - 1.29).

Conclusions: Compared to usual care, mailed at-home self-sampling increased screening participation among underscreened safety net health system patients by almost three-fold when used alone and by over 3.3-fold when supplemented with telephone-based patient navigation. Improvements in screening participation are consistent with pooled estimates for mailed self-sampling versus usual care from a recent meta-analysis (RR=2.5).2 Screening participation in the self-sampling arms of the PRESTIS trial is significantly higher than the meta-analyses' pooled participation estimate (24.3%). Once approved by the U.S. Food and Drug Administration (FDA), self-sampling for HR-HPV testing has the potential to dramatically increase participation in cervical cancer screening in underserved populations.

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#6713

HIGH ACCEPTABILITY AND ACCURACY OF ANAL SELF-COLLECTION BY VEIL COLLECTOR DEVICE FOR HIGH RISK-HPV SCREENING BY MULTIPLEX REAL-TIME PCR AMONG MEN WHO HAVE SEX WITH MEN LIVING IN AFRICA

13 - Self-sampling

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Background/Objectives: Persistent infection by a high risk-HPV (HR-HPV) is the leading cause of anal squamous cell carcinoma, especially in men who have sex with men (MSM). We herein assessed the usability, satisfaction and accuracy of veil-based canal anal self-sampling in MSM living in Africa, a vulnerable population at high risk for HR-HPV anal shedding, HIV and anal cancer (ANAUTO Study).

Methods: The acceptability, practicability, and satisfaction of self-collection method with veil (Veil Collector V-Veil Up, V-Veil-Up Production SRL, Romania; https://hpv-veil.com) by reference to clinician-based anal swabbing were assessed in 100 MSM living in N'Djamena, the capital city of Chad. Participants were first randomized between the initial use of self-collected anal veil or anal swab collected by medical staff, and the two sampling methods were carried out 2 hours apart. The acceptability, practicability and satisfaction questionnaires were completed after using the veil and anal swab with face-to-face questionnaires. The acceptability was assessed using an arbitrary quantitative Likert scale (1) from 1 (most difficult) to 4 (very easy or comfortable). The satisfaction was assessed using another arbitrary quantitative Likert scale from 1 (less favorable) to 4 (most favorable). The accuracy of veil-based sampling for HPV DNA detection was compared in subgroup of unselected MSM to clinician-collected anal swabs (as reference collection). Frozen samples were subjected to HPV DNA molecular detection by fluorescence-based multiplex HPV DNA genotyping kit (Bioperfectus Ltd., China).

Results: Acceptability of collection methods. Participants reported feeling much better cared for during the veil-based self-collection (mean note, 3.1/4) compared to swab-based clinician-collection (mean, 2.3; Pinf0.02) and also more in privacy handled during self-collection (mean, 3.4) compared to clinician-collection (mean, 1.6; Pinf0.01). When asked to choose one collection method, the majority (95.7%) of study MSM responded that they would prefer the self-collection method. Most participants (91.3%) reported that they would be willing to perform veil collection at home and bring the specimen with them to clinic. Satisfaction of self-sampling by veil. The verbal explanations on how to use the collection device showed higher mean note according to the Likert scale of satisfaction (written vs oral explanation: 1.9/4 and 3.7/4, respectively). The large majority of MSM (95.9%) were able to recognize correctly the component's device, with high notes (3.8/4). The veil was generally (97.6%) correctly placed with the applicator. All items concerning the general satisfaction of the Veil Collector V-Veil Up showed high mean notes from 3.1 to 3.7. Finally, only 4 (4%) MSM reported some difficulties with performing the self-collection. Prevalences of HPV detection. HPV and HR-HPV detected in 75.2% and 58.6% by veil and 71.9% and 60.8%, respectively, of anal samples, without statistical differences, mainly HPV-35, HPV-58, HPV-59 and HPV-31, with frequent (67%) multiple HR-HPV in HIV-positive MSM.

Conclusions: These observations highlight the high burden of anal HR-HPV infection in MSM living in Central Africa. Veil Collector V-Veil Up would constitute a simple, highly acceptable and powerful tool for self-collection of anal secretions for further molecular screening of HR-HPV that could be easily implemented in national anal cancer prevention programs in Africa.

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#7121

REGIONAL ORGANIZED CERVICAL CANCER SCREENING IN NON-ATTENDEES WOMEN INVITED FOR FIRST-VOID URINE HOME SELF-SAMPLING REGARDING THEIR SOCIAL-ECONOMICS LEVEL AND AGE STATUS (THE PAPU ACCESS STUDY)

13 - Self-sampling

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Background/Objectives: To increase patient's compliance with cervical cancer (CC) screening, home self-sampling for Human Papillomavirus (HPV)-DNA detection could be an alternative to clinician sampling. Home vaginal self-sampling is recommended in France for difficult-to-reach women. We found in the prospective multicentre PapU APV study, with 461 included women, that first-void urine (FVU) self-sampling showed similar results than self-collected vaginal for HPV-DNA screening but with about two-third of preference to FVU. The aim of the PapU Access study was to evaluate the FVU home self-sampling in non-attendees women in an organised CC screening in Brittany.

Methods: From 2021 to 2022, 12473 women of 25-65 years old were invited to realise FVU home self-sampling after a first invitation for cervical HPV screening during the organised CCS. This study group was randomized by age and social-economics level (with EDI scores, MapInMed platform from Caen university) and compared to a control group of 12415 women with a recall for cervical screening. FVU samples were send by post mail to the Brest virology lab for HPV-DNA quantification by real-time PCR and genotyping, with a signed consent and a questionnaire for sampling evaluation. Cytology and histology results follow-up were also recorded up to October 2023.

Results: Among the study group with FVU, 2784 had a HPV testing (22.3%), with 394 HPV positive test (14.1%), compared to the control group, with 1370 cytology or HPV cervical screening (11%), women in the study group having 80% more chance to be screened (OR=2.02; 95% IC [1.87;2.18]). Women over 50 years old and with low social-economics EDI 4 and 5 scores were significantly less to respond compared to younger women or with EDI 1 and 2 scores ($p<0.001$). However, older women and women with EDI 4 score respond better to FVU than those in the control group ($p<0.01$). During follow-up of the 394 HPV+ women from the study group, 112 had a normal cytology and 55 had abnormal cytology with 32 colposcopies and 4 CIN1 and 2 CIN3 at histology up today.

Conclusions: The invitation with first-void urine home self-sampling was showed in our regional study to increase the participation to organised CC screening in non-attendees women, mostly in older women (over 50) and with average and lower social-economic levels. A cost-efficiency study is ongoing with the ECEVE unit. Grants from the French Health Ministry, Prevention PREPS program 2018.

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#7143

Urine high risk human papillomavirus testing as an alternative cervical screening strategy: the ACES Studies

13 - Self-sampling

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Background/Objectives: Cervical screening saves lives but only 69.9% of those eligible attend in the UK. The main barriers include inconvenience, embarrassment and fear of the speculum examination. Urine human papillomavirus (HPV) testing shows promise as an alternative cervical screening strategy and may be an attractive option for non-attenders. The aim of this study was to (1) determine the clinical performance of optimised urine HPV testing for CIN2+ detection in colposcopy referral and general screening populations; and (2) ascertain its acceptability to both regular and poor attenders of cervical screening, including people from LGBTQIA+ and ethnically diverse backgrounds.

Methods: We collected matched cervical and urine samples from colposcopy clinic attendees and a general primary care screening population. Colposcopy clinic attendees were randomised to provide a first void urine sample using the Colli-Pee® device (Novosanis, 10mls with preservative) or a standard urine collection pot. Primary care attendees collected their urine using the Colli-Pee device. Samples were tested for high risk HPV using Roche cobas 8800 at cervical thresholds. We assessed concurrent acceptability in trial participants and prospective acceptability in people from LGBTQIA+ and ethnically diverse backgrounds using a co-created national survey.

Results: 465 colposcopy (standard pot n=230, Colli-Pee n=235) and 1059 primary care attendees provided matched cervix and urine samples (total n=1517). Their median age was 35.0 years (IQR 29-44) and 77.5% were of White British ethnicity. Urine HPV test sensitivity for CIN2+ detection was higher with the Colli-Pee (90.3%, 95%CI=83.7-94.9, 112/124) than the standard pot (73.4%, 95%CI=64.7-80.9, 91/124, p=0.0005). In the 1287 Colli-pee collected urine samples, sensitivity for CIN2+ detection was 91.2% (95%CI=85.2-95.4) vs 98.5% (95%CI=94.8-99.8, relative sensitivity 0.93) in matched cervical samples and specificity was 78.5% (95%CI=76.0-80.9) vs 80.5% (95%CI=78.1-82.8, relative specificity 0.98). Concurrent acceptability for urine based cervical screening was good with 62.4% of all study participants preferring urine or having no preference for future screening method. People from ethnically diverse backgrounds had a higher preference for cervical sampling than those from White British/Irish backgrounds (49.6%; n=184/371 vs 30.8%; n=328/1066, p=<0.001). Prospective acceptability of urine sampling was assessed in 503 and 260 individuals from LGBTQIA+ and ethnically diverse backgrounds, with 47% of the n=211 individuals identifying as transgender choosing urine as their preferred sampling method, while 43% of individuals from ethnically diverse backgrounds preferred routine cervical sampling.

Conclusions: HPV tested Colli-Pee-collected urine shows similar test accuracy for CIN2+ detection compared to routine cervical screening, meeting Meyer's criteria for a candidate novel screening test for NHS implementation. Improved test accuracy could be achieved with urine-specific thresholds for HPV positivity. Urine is broadly acceptable especially to groups less likely to attend such as the LGBTQIA+ community. However, clinician-based cervical sampling remains a preference for some and should continue to be offered within the NHS cervical screening programme. Urine based screening may increase attendance in current non-attenders, however, requires further optimisation including how best to offer self-screening methods for maximal uptake.

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#7127

EVALUATION OF RETRIEVAL OF HPV FROM A NOVEL SELF-SAMPLING DEVICE COLLECTION SUBSTRATE

13 - Self-sampling

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Background/Objectives: A vaginal self-collect device utilizing a novel collection substrate (polyurethane (PU) foam) was developed by Teal Health ("Teal wand') to present an alternative to the current validated self-collection devices. This study assessed the analytical performance of the Teal wand including comparisons with current standard of care methods for cervical collection, stability (including pre-collection shipping conditions), and sensitivity.

Methods: Collection devices (Rovers Cervex-Brush and PU foam) were inoculated with HPV18 positive cell lines and eluted into a Hologic Thinprep vial (20 mL PreservCyt). Sample stability was assessed at room temperature (20 - 23°C). Pre-conditioning was done across a range of conditions mimicking desert, tropical and frozen environments. All samples were tested on the Roche cobas HPV test using the Roche cobas 6800 system.

Results: This study is ongoing but preliminary data is available on the Teal wand performance. The Teal wand has demonstrated the ability to capture and release material in a manner that is not significantly different ($p > 0.05$) from the Rovers Cervex-Brush which is the standard of care device for clinician-collected samples from the cervix. Even at low concentrations of HPV (<3x LOD) the Teal wand demonstrated sensitivity equivalent to current methods that was not inferior ($p > 0.05$). The Teal wand demonstrated no significant loss of sensitivity when stability was assessed for an initial paradigm of 7 days at room temperature ($p > 0.05$) compared with baseline performance. Even when the Teal wand has been exposed to a range of environmental conditions to mimic a wide range of shipping conditions prior to specimen collection there is no indication of a loss of sensitivity.

Conclusions: The Teal wand, which utilizes a novel PU foam substrate, has undergone preliminary experiments to assess the performance in terms of function, sensitivity, and stability. Further experimentation is being undertaken to assess performance with a range of individual HPV types that are examined using clinically validated HPV NAAT assays used in HPV-based cervical screening programs. There are few clinically validated self-collection devices and acceptability is likely to vary depending on the different social and cultural conditions under which self-collection for HPV-based cervical screening is offered. The Teal wand offers a novel approach to self-collection devices, and the outcomes of this analytical validation, when combined with a separate clinical validation underway are showing promising signs that performance of this device will be comparable with other established self-collection devices.

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#7013

PREDICTORS 5.2. COMPARISON OF HIGH-RISK HPV POSITIVITY OF A VAGINAL SELF-SAMPLE AND URINE SAMPLE WITH A CLINICIAN TAKEN CERVICAL SAMPLE TAKEN AT THE SAME SCREENING VISIT

13 - Self-sampling

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Background/Objectives: The gold standard method for cervical screening uses a sample collected by a clinician. The sample is tested for the presence of high-risk human papillomavirus (hrHPV) types. Clinical investigation in those who test positive is a highly effective method for identifying precursors to cervical cancer, high-grade cervical intraepithelial neoplasia (CIN2+). This enables early treatment to prevent cervical cancer and associated mortality and morbidity. Unfortunately, in some settings there are not enough clinicians or resources available for tests on a population basis. Clinician-collected samples are also unacceptable to some women and people with a cervix and may be painful or uncomfortable. New approaches to cervical screening based on women taking their own sample for testing (self-sampling) may help to improve this. There is evidence that self-sample tests identify women with precursors to cervical cancer but also evidence that not all are equally effective, including from our earlier Predictors 5.1 study. The main aim of this study is to evaluate aspects of performance of different self-sampling tests, compared with clinician-collected samples in women invited for routine cervical screening in England, when they attend their appointment at their General Practice (GP).

Methods: Phase 1 is designed to generate data to help ensure that sample collection protocols in the main study (Phase 2) are adequate. Each participant will be asked to provide two vaginal self-samples, a clinician-collected cervical sample, and a urine sample at the Royal London Colposcopy clinic; and an optional second urine sample returned to the lab within a week by post. In a prior study (Predictors 5.1) we found 1% "Wet" and 14% "Dry" vaginal samples had low quality of sample DNA (Genomic DNA Quality Score (GQS) <1.5). We aim to surpass "Dry" quality with the tests taken forward to the main phase. This will be based on a 95%CI for the DNA quality score failure rate of each self-sampling process (device and time to test) using a Wilson confidence interval less than 14%. Self-sample tests evaluated will be urine (Colli-Pee device, 10ml and 20ml); Copan FLOQSWAB (transported dry, wet in Copan or BD medium); and time to assay (and resuspension for dry), from 0 to 2 weeks after being received at the laboratory. At least n=72 participants will be recruited for each device / timing combination. Phase 2 will test whether the self-sample tests are non-inferior for hrHPV detection to clinician-taken samples using a prospective paired-sample design. Primary analysis will evaluate agreement of hrHPV positivity in the self-sample with the clinician-collected sample in 2000 participants. Non-inferiority is defined to be achieved when the 95% one-sided confidence interval for the false-negative rate of self-sampling is less than 5%, compared with the gold-standard clinician sample. Secondary endpoints include CIN2+, HPV genotype, and DNA methylation. Participants will also be invited to complete a questionnaire on acceptability and ease of use of different devices.

Results: Recruitment is planned for 2024. Preliminary data will be presented at the conference.

Conclusions: Different self-sample HPV tests have not been robustly evaluated in an English screening population. This study will help determine accuracy and acceptability of different self-collection HPV tests in this setting.

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A SURVEY OF HPV SAMPLETAKERS' KNOWLEDGE, BELIEFS AND ATTITUDES TOWARDS HPV SELF-SAMPLING FOR CERVICAL CANCER SCREENING IN IRELAND

13 - Self-sampling

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Background/Objectives: Self-sampling for human papillomavirus (HPV) is an alternative method to provider-collected HPV testing for cervical screening. It has been introduced in a minority of countries and the WHO recommends it as an additional method for cervical screening.[1-3] Understanding sampletakers' attitudes towards and support for HPV self-sampling is crucial, as they play an integral role in screening and negative attitudes among them may lead to issues with implementation and adherence. The objectives of this survey are to assess HPV sampletakers' support for HPV self-sampling as a potential, additional cervical screening method in Ireland, as well as their knowledge and beliefs about self-sampling.

Methods: An anonymous, online, cross-sectional survey of HPV sampletakers in Ireland was conducted. The survey content was informed by an extensive literature review and consultations with key stakeholders. It consisted of 18 mostly closed questions focusing on support for HPV self-sampling, preferred delivery modality and location, as well as knowledge about and perceived advantages and disadvantages of self-sampling. The survey was disseminated via email to all HPV sampletakers registered with CervicalCheck, Ireland's organised cervical cancer screening programme, who had previously indicated a willingness to be contacted by the National Screening Service. Ethical approval was granted by the Royal College of Physicians of Ireland's Ethics Committee. Analyses were performed on SPSS Version 27.

Results: In total, 200 HPV sampletakers registered with CervicalCheck participated in the survey, 88% of whom were nurses or midwives. 73% of respondents reported to be aware that HPV self-sampling existed and 51% reported to be aware that the WHO recommends it as an additional screening method; 96% reportedly were aware that a positive HPV self-sampled test requires a subsequent provider-collected sample for cytology triage. Two thirds (67%) of respondents supported HPV self-sampling as an additional screening method, while 9% did not support it and 24% were unsure. The main reason proponents of self-sampling cited for supporting it was increasing cervical screening uptake (62%), followed by reducing patient anxiety (17%) and self-sampling being less invasive than provider-collected HPV samples (10%). Opponents of self-sampling primarily cited a potential lack of trust among screening participants in self-sampled tests (33%), lack of opportunities for sampletakers to counsel participants about screening (28%) and missed opportunities for sampletakers to visualise the cervix and examine screening participants (22%) as the reasons for not supporting self-sampling. The majority (73%) of respondents believed a participant's home would be the optimal location for self-sampling to take place, while 9% believed it should take place in participants' general practitioners' (GP) practices. Half (50%) of respondents believed self-sampling tests should be sent directly from CervicalCheck, and not from participants' GPs.

Conclusions: Knowledge levels about HPV self-sampling among HPV sampletakers in Ireland appear to be high. A majority of sampletakers report to be in favour of self-sampling as a potential, additional cervical screening method in Ireland and would prefer it to take place in participants' home. Sampletakers perceive the main benefit of self-sampling to be increased cervical screening uptake. Perceived disadvantages should be further explored to address potential barriers to HPV self-sampling.

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Designing an inclusive study of HPV self-sampling in the transgender population

10 - HPV screening

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Background/Objectives: Transgender (trans) persons may be at higher risk of HPV-related cancers than cisgender persons. Trans men and non-binary people with a cervix are less likely to undergo cervical screening or have an adequate sample. Trans women and non-binary people assigned male at birth may have not received vaccination due to later implementation of a gender neutral programme, and have higher rates of HIV infection which can result in HPV persistence. Both groups can experience stigma and discrimination in medical settings and may benefit from HPV self-testing. The Self-TI study set out to codesign an inclusive pilot study of HPV self-testing for trans individuals in collaboration with members of the UK trans community.

Methods: Self-TI is a collaboration between the US National Cancer Institute and the UK Queen Mary University of London. Self-TI aims to assess feasibility and acceptability of HPV self-testing across multiple body sites. Participants will complete demographic and medical history forms, followed by HPV self-testing and an acceptability questionnaire.The Self-TI leads are an epidemiologist, and an oncologist and gender identity clinician, both with experience of conducting research with the trans community. Self-TI is co-produced with trans and non-binary individuals, including a study team member who is non-binary and CEO of an LGBTIQ+ cancer charity, and a community advisory board (CAB) that reviews the study protocol, advertising strategy, and other materials. CAB members are remunerated and receive presentations on trans health topics as a form of knowledge exchange. CAB attendees are surveyed on their experience after each meeting.

Results: Iterative protocol development and extensive review meant the study took two years from idea generation to submission to the Research Ethics Committee in September 2023 Six community members attended six CAB meetings May 2022--August 2023. CAB members included transfeminine, transmasculine, and non-binary individuals to represent the target population. CAB feedback included preferred terms and language, and suggestions to improve accessibility on forms, surveys, information, and advertisement materials. The CAB suggested that Self-TI create an instructional video to support participants collecting their specimens. Self-TI contracted a prominent member of the UK trans community to narrate this video and to produce a study advert. The CAB highlighted that remuneration of study participants was critical. Self-TI found it difficult to recruit CAB members from diverse backgrounds and to find mutually agreeable times for them to meet. In response, feedback was also solicited via email in addition to meetings.

Conclusions: Codesign of research studies is crucial to successful research, particularly with the trans community. Subject matter experts are important to have on the study team and in peer review but do not replace the expertise of lived experience, particularly when the goal is ethical research design. This is pertinent to HPV research given the inequalities that exist with regards to disease burden and access to vaccination, as well as screening and treatment of HPV-associated cancers. CAB recruitment benefits from being considered in its geographical, cultural, and intersectional relevance. CAB members should be compensated for their time and input as they are lived experience experts. We encourage other HPV researchers to adopt similar approaches to their research with underserved communities.

FC15 - Low incomes countries and at risk situations

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DYNAMICS OF HPV PERSISTENCE, CLEARANCE AND INCIDENT INFECTION ACCORDING TO GENOTYPE CARCINOGENICITY IN A COHORT OF WOMEN LIVING WITH HIV IN SEMI-RURAL TANZANIA

38 - Low resource settings

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Background/Objectives: HPV infection is common in women living with HIV (WLWH), and multiple infections and lasting persistence lead to increased risk for transformation, progression and cervical cancer (CxCa). HPV genotypes differ in their contribution to CxCa with HPV 16 and 18 present in around 70% of CxCa cases. Also, HPV genotypes with comparable carcinogenicity can be grouped together. The prevalence of infection does not adequately represent the genotype contributions to CxCa. The persistence of genotypes is related to their carcinogenicity,and persistence is a prerequisite for CxCa development. In WLWH, the persistence of genotypes is increased but also new incident infections are more common and contribute to HPV test positivity. This may impact the usefulness of HPV tests that report pools of high-risk (HR-) types. In a cohort of WLWH, we analyzed the genotype and risk-group specific persistence, clearance and new infections in a screening implementation study in order to understand the necessity of full genotyping or HPV-group testing.

Methods: We implemented CxCa screening in the preexisting Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) in semi-rural Tanzania in women aged 18-65 years. After cervical self-sampling (Evalyn®Brush, Rovers, The Netherlands), HPV testing was done using the Seegene AnyplexTM II 28 HPV Detection Test (19 HR-HPV and 9 low-risk (LR-) HPV genotypes). In HPV positive women, triage was done by colposcopy. Women with abnormal colposcopy were treated by thermoablation or LEEP-conisation, depending on the colposcopic findings. All HPV-positive women were followed and a second self-sampled HPV test was performed after 6 (+/- 2) months. HPV-types were grouped by carcinogenicity as deduced from healthy populations post hoc. Groups: super-risk (HPV 16,18); high-high risk (HPV 16/18,31,33,45,52,58); intermediate risk (35,39,51,56,59); probable risk (66,68,26,53,73,82) and descriptive statistics with calculation of prevalence, persistence, clearance and incident infections were performed.

Results: 1504 WLWH with a median age of 45 years (18-65) were enrolled. Median time of HIV diagnosis was 9 years ago (3 month-25 years). At baseline, HR-HPV was undetectable in 1008 (67%) and detected in 496 (33%) WLWH. Multiple infections by any HPV-type at baseline were present in 16.6% (n=250) of HPV positive WLWH and with HR-types in 12.3% (n=184). Preliminary results show a positive result within the group of HR-HPV positive women at baseline for the super-risk group 31.6%; the group of high-high risk 76.2%; intermediate-risk 41.5%; probable-risk 36.1%. In women with baseline HPV positivity after 6 (+/-2) months the rates of persistence, clearance and incident new infections were in the super-risk group 57.5%, 15.7% and 26.8%, respectively; in the high-risk HPV group 62%, 17.4% and 20.6%; in the intermediate-risk group 46.2%, 16.5%, 37.3% and in the probable-risk group35%, 25%, 40%, respectively.

Conclusions: This study provides valuable epidemiological information about HPV prevalence, persistence, clearance and incident infections in a cohort of WLWH. The dynamics of new infection in this group is high. Using full genotyping tests allows discrimination of incident from persistent infections. This discrimination is critical for the risk evaluation of recurrence and decision for re-treatment.

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#6863

MOLECULAR EPIDEMIOLOGY OF HUMAN PAPILLOMAVIRUS (HPV) INFECTION IN A RURAL HEALTHCARE FACILITY CATCHMENT AREA IN ESWATINI

39 - Public health

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Background/Objectives: In Eswatini, cervical cancer (CC) is the most common cancer and the first leading cause of cancer deaths in women. Infection from high-risk (HR) human papillomavirus (HPV) has a very high prevalence (46%) among women aged 15 to 49 years (i.e., nearly 175,000). In June 2023, 4-valent anti-HPV vaccination, able to protect against HPV 16, 18 (HR genotypes), and 6 and 11 (low-risk (LR) genotypes), has been introduced for young girls aged 9-14 years. However, up-to-date, data regarding the HPV genotype distribution in the country are not available. This study aims to describe HPV genotypes in Swazi women with normal or abnormal cytology enrolled in a project using a urine-based HR-HPV testing approach.

Methods: Adolescent girls and women aged 12-49 years, spontaneously presenting at St. Philip's Clinic (Lubombo, Eswatini) were asked to provide a 30 mL urine sample for HPV DNA testing and, only for those aged 21-49 years, a cervix brush sample for Pap smear. After concentration, 10 mL of urine were used to prepare four filtered papers (dried urine spot, DUS), two to be tested locally with Xpert® HPV test (Cepheid, USA) and two to be shipped to, and tested at, the University of Milan, Italy. From the DUS received in Italy, 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.

Results: Two-hundred and ten DUS were received and 183 (87%) tested positive for HPV. Overall, 50 (27%) HPV infections were sustained by a single genotype and 133 (73%) by multiple genotypes (max 12, median 3), for a total of 38 different infecting genotypes. Most of the infections were due to HR-HPV types (135/183, 74%), with HPV35 being the most frequent (61/183, 33%), followed by HPV70 (39/183, 21%), HPV16 (36/183, 20%), and HPV52 and 45 (34/183, 19%). Pap smear results were available for a subset of 117/210 (56%) women enrolled in the study: 47/117 (40%) were diagnosed with abnormal cytology, 5 of which with CC (5/47, 11%). HPV infection was found in 59 women with normal cytology (59/70, 84%), in 39/45 (93%) women with pre-cancerous lesions, and in 5/5 (100%), diagnosed with cervical cancer.

Conclusions: To the best of our knowledge, this is the first study assessing the distribution of HPV genotypes in Eswatini. The proportion of HPV infection observed in women with normal cytology (84%) was much higher compared with that reported from Sub-Saharan Africa (24%) and globally (12%). In the majority of women diagnosed with CC (4/5, 80%), the diseases would have been potentially prevented through an earlier introduction of HPV vaccination in the country. Our data suggest that, although the adoption of 4-valent vaccine is helpful to reduce the burden of CC in Eswatini, the introduction of the 9-valent one would be more effective. However, several HR-HPV types identified are not included in the available HPV vaccine formulations. Although the study is still in progress, data collected in St. Philips are revealing crucial information and generating evidence to support policymakers in implementing cost-effective prevention strategies.

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#7153

The implementation of human papillomavirus testing using point-of-care diagnostics for the screening of cervical cancer in women living with HIV in Malawi

10 - HPV screening

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Background/Objectives: Malawi has the world's highest incidence and mortality rates due to cervical cancer. This is despite cervical cancer being one of the most preventable and treatable malignant conditions worldwide. Human papilloma virus (HPV) testing has been found to be more effective in screening for cervical cancer than conventional and liquid-based cytology. The emergence of point-of-care (POC) HPV tests have made it possible to implement HPV testing in low-resource settings, and this may be the best strategy for cervical cancer screening in such settings. Objectives: To describe the prevalence of cervical abnormalities and high risk HPV in women living with HIV who present for cervical cancer screening; to determine the incidence of high-risk HPV serotypes in HIV infected participants presenting for cervical cancer screening; to determine the diagnostic yield of Xpert HPV testing for cervical abnormalities identified on VIA screening; to determine the proportion of women with acute complications after Thermoablation following a positive Xpert HPV test result

Methods: This study is a prospective cohort study of diagnostic accuracy. Participants are 300 adult females presenting for routine cervical cancer screening at Thyolo District Hospital. Study procedures include sterile speculum examination wherein cervical cytobrush samples for Cepheid Xpert® HPV point-of-care test and cervical cytobrush sample for real-time (RT) reverse transcriptase polymerase chain reaction (PCR) are collected, Visual Inspection with acetic acid (VIA) and HIV testing and linkage to care.

Results: The study is actively recruiting and has to date recruited 136 participants. For the 23 participants who have already been recruited, 75.7% (103/136) were HIV positive, of whom 12.6% (13/103) were positive for HPV 16, 2.9% (3/103) were positive for other high-risk HPV, and 26.2% (27/103) were positive for HPV 18/45. Only 1/103 (1%) HIV positive participant had a positive VIA screen and was positive for other high-risk HPV. The median CD4 count was 682 cells/mm3 (interquartile range - IQR: 589.5 to 872.5).

Conclusions: The implementation of Xpert HPV testing for cervical cancer screening in women living with HIV in Malawi shows promising early results, with high recruitment rates and a considerable proportion of HIV-positive participants testing positive for high-risk HPV. The results will inform large-scale implementation efforts in the country, ultimately reducing the burden of cervical cancer in this high-risk population.

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#6919

IMPLEMENTATION OF AN INTEGRATED CERVICAL SELF-SCREENING PROGRAM IN RURAL UGANDA

38 - Low resource settings

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Background/Objectives: The WHO call for cervical cancer elimination includes a target of 70% of women screened twice by age 45; however, many LMICs are falling short with less than 20% of women in sub-Saharan Africa having ever had cervical screening. Innovative and feasible strategies are urgently needed to achieve global elimination targets. The most common form of cervical screening in LMICs is visual inspection with acetic acid (VIA), however this requires attendance at a clinic and a pelvic exam. In contrast, HPV testing can be done on self-collected specimens, increasing the accessibility of cervix screening, which is especially critical in LMICs, including Uganda where cervical cancer incidence rates are among the highest in the world. This study aims to evaluate an integrated self-collection HPV-based cervical cancer screening program within the existing community-based primary health care services in a rural sub-county of Uganda.

Methods: The integrated HPV-based cervix screening program serves women aged 30-49 living in 11 villages in the Malongo sub-county. HPV-based self-collected cervical screening is offered through door-to-door visits conducted by village health teams (VHTs) to women who have never had cervical screening. The samples are transported to a local health centre for HPV testing. HPV results are returned during community health days, and women undergo VIA to confirm HPV positivity, and thermocoagulation if they need treatment. At the initial outreach visit, women are invited to complete a survey, which collects information about demographics, past health system interactions, and future screening preferences. The survey is available in both English and local dialect, Lusoga. HPV screen results are presented, in addition to, number of specimens collected, and participant demographic information. The research is ongoing and the findings presented are from preliminary analyses. Although not currently available, rates of compliance with follow-up will be presented when available.

Results: This interim analysis includes a total of 1499 enrolled participants who completed HPV-based self-collection. Of those, 1414 (69%) completed the baseline survey. The median age at enrollment was 36yrs (interquartile range (IQR), 31-42). There were 1217 (86%) participants who reported being in a relationship (married, cohabitating, or other), and the majority (1254, 88.7%) had primary or lower education. The median number of pregnancies per woman was 7 (IQR, 5-9). Among 1473 participants who completed HPV testing and whose samples have been received at the lab, 411 (27.5%) were HPV-positive and required follow-up. HPV positivity ranged from 23 to 39% across the eleven villages. Although not currently available, rates of compliance with follow-up will also be presented.

Conclusions: Offering HPV-based self-collection through VHT led community outreach visits, has been highly successful. Through this research, an extremely under-screened population has received screening, and for those who are HPV positive, treatment is readily accessible. Integration with existing community health services and community health teams has been critical to the feasibility of HPV-based self-collected screening. As this research continues, the RE-AIM framework will be used to define both the qualitative and quantitative indicators of program success and determine public health impact of the intervention in a real-world environment.

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#6982

POSITIVITY RATES OF CERVICAL SCREENING TESTS OTHER THAN VISUAL INSPECTION IS DOUBLED IN HIV POSITIVE SOUTH AFRICAN WOMEN

16 - Screening methods

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Background/Objectives: HIV has been shown to exacerbate human papillomavirus (HPV) carcinogenicity and as expected, high incidence and prevalence of cervical intraepithelial neoplasia (CIN) have been reported in our country with its high HIV burden. The cost of any screening program will be influenced by these high rates of positive screening. Here we report on cervical screening test results in a cohort of both HIV-positive and -negative South African women.

Methods: HIV-negative and positive women, aged 25-65 years, unscreened in the preceding 5 years, were enrolled to this cross-sectional multicentre study. Health care workers performed visual inspection with acetic acid (VIA) and Lugol's iodine (VILI), followed by sample collection for cytology and HPV DNA tests, cobas HPV as well as Qiagen digene Hybrid Capture2 (HC2). Cervical biopsies were taken of suspicious lesions, and blind biopsies in a number of screen negative women. Participants who qualified for treatment were offered large loop excision of the transformation zone. Worst grade histology was regarded as final diagnosis.

Results: Enrolled were 699 women, mean age 40.9 years, 48.8% (341/699) HIV-positive. Positivity rates were significantly higher in HIV-positive v HIV-negative women: for VIA 43.7% (149/341) v 15.9% (57/358) [Positivity Ratio (PR) 2.74, p<0.0001], for VILI 46.2% (160/341) v 17.9% (64/358) [PR 2.62, p<0.0001], and for cytology (cutoff atypical squamous cells of undetermined significance) 33.4% (114/341) v 17.0% (61/358) [PR 1.96, p=0.0001] respectively. Both HPV tests displayed comparable results, and again positivity in HIV-positive women was almost twice than HIV uninfected women: for cobas HPV 45.7% (156/341) v 23.7% (85/358) [PR 1.93, p<0.0001] and for HC2 44.6% (152/341) v 21.8% (78/358) [PR 2.05, p<0.0001] respectively. HPV16/18 were identified in 15.8% (54/341) HIV-positive v 9.2% (33/358) [PR 1.72, p=0.0134] HIV-negative participants. Histology results were available for 73.9% (252/341) HIV-positive and 64.0% (229/358) HIV-negative women. Positivity rates for HIV-positive v HIV negative women were: CIN3+ 24.6% (62/252) v 12.7% (29/229) [PR 1.94, p=0.0025]; cancer 2.0% (5/252) v 0.9% (2/229) [PR 2.27, p=0.35].

Conclusions: VIA and VILI positivity in HIV-positive women are nearly three times higher than HIV-negative women, while all other screening test had a positivity ratio of almost 2:1, suggesting that visual inspection is not specific enough in HIV-positive women. Disease prevalence maintained the ratio of about 2:1 for HIV-positive v HIV-negative women, for both CIN3+ and cancer.

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#7120

RISK MANAGEMENT OF SUSPICIOUS CARCINOMA OF VIA/VILI FOR CERVICAL CANCER SCREENING IN LOW RESOURCE SETTINGS

38 - Low resource settings

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Background/Objectives: Screening remains essential for cervical cancer prevention globally, especially in developing countries. VIA/VILI is recommended as a triage method for cervical cancer screening in low-resource settings. This study aimed to evaluate the risk of cervical cancer and precancer lesions if the women had suspicious carcinoma of VIA/VILI in low-resource settings.

Methods: Since 2016, a full-coverage cervical cancer screening program for women aged 35-64 years has been conducted to build up a long-term screening system in Ordos, China. careHPV test as the primary method was offered to participants every five years. In order to reduce the lost rate of follow up, the sample collection of the careHPV test and VIA/VILI examination were conducted at the same time. HPV-positive women with abnormal results of VIA/VILI were recalled for a colposcopy. The suspicious carcinoma of VIA/VILI was called for colposcopy immediately.

Results: A total of 187,863 women received the first round of screening for cervical cancer and had valid results in 2016-2020. Among them, 688 women were suspicious carcinoma of VIA/VILI and were involved in the analysis, with a mean age was 44.2 ± 6.5 years. In the HPV-positive arm, the detection rate of cervical intraepithelial neoplasia (CIN) 2 or worse, CIN3+ and cancer were 51.2%, 44.2% and 30.2%, respectively. In the HPV-negative arm, the results were 2.2%, 1.4% and 0.8%, respectively. The detection rate of CIN2+ peaked at 44−54 years and significantly declined for women aged over 55 years (Ptrend=0.000). A comparable pattern was observed for CIN3+.

Conclusions: With continuous training and quality assurance, the HPV test as a primary screening method with VIA/VILI triage might act as a temporary substitutional screening strategy that is preferred for cervical cancer in low-resource settings. The suspicious carcinoma of VIA/VILI referred to colposcopy immediately is necessary.

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#6686

Utility of extended HPV genotyping as primary cervical screen in an unscreened population with high HIV co-infection

38 - Low resource settings

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Background/Objectives: Screening with primary HPV testing has been evaluated in highly pre-screened populations with lower HPV and Human Immunodeficiency Virus (HIV) prevalence that what is the case in South Africa. High prevalence of HPV, and underlying pre-cancer, in women living with HIV (WLWH) affect the clinical performance of screening tests significantly. This study investigates the utility and performance of an extended genotyping HPV test in detection of pre-cancer in a population with a high co-infection rate with HIV.

Methods: 1001 women aged 25 to 65 with no cervical cancer screening in the preceding five years were tested with cytology and primary extended genotyping HPV testing. The cohort of 1001 women included 430 Women Living with HIV (WLWH) (43.0%) and 564 HIV negative (56,3%) women.

Results: Abnormal cytology (ASCUS+) was significantly higher in WLWH (37,2%, vs 15,9%,) and HSIL or above (23,5% vs 5,2%). WLWH had a higher rate of any HPV+ (20,1%) when the cytology was reported as NILM when compared to HIV negative (8,2%). P=0.1177 WLWH also tested positive more often for any HPV type (44,3% vs 19.6% pinf 0.0001) The specificity for CIN 2+ at 91,2% of a combination of HPV types, 16/18/45 (Very High Risk) and 31/33/58/52 (Moderate Risk), support referral to colposcopy.

Conclusions: The potential contribution of extended genotyping is demonstrated. The ideal choice of sensitivity and specificity ultimately depends on the health budget. More information will allow a screening algorithm, guiding management according to risk.

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#7069

ENHANCING CERVICAL CANCER PREVENTION IN SOUTH AFRICAN WOMEN: PRIMARY HPV MRNA SCREENING WITH DIFFERENT GENOTYPE COMBINATIONS

38 - Low resource settings

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Background/Objectives: Cervical cancer prevention in regions with limited access to screening and HPV vaccination necessitates innovative approaches. This study explored the potential of a test-and-treat strategy using mRNA HPV tests to impact cervical cancer prevention in a high-prevalence HIV population.

Methods: A cervical screening study was conducted at three South African hospitals involving 710 under-screened, non-pregnant women (25 to 65 years) without known cervical diseases. Cytology, HPV testing, colposcopy, and biopsies were performed concurrently. Histopathologists determined final histological diagnoses based on biopsy and LLETZ histology. mRNA-HPV-genotyping for 3 (16, 18, 45) to 8 (16, 18, 31, 33, 35, 45, 52, 58) high-risk types was performed on leftover liquid-based cytology material. The preventive potential of the test-and-treat approach was estimated based on published data, reporting the causative HPV types in cervical cancer tissue from South African women. Treatment was provided as needed.

Results: HPV positivity rate more than doubled from 3-type (15.2%; 95% CI: 12.6-17.8) to 8-type mRNA (31.5%; 95% CI: 28.8-34.9) combinations, significantly higher among HIV-positive women. CIN3+ prevalence among HIV-positive women (26.4%) was double that of HIV-negative women (12.9%) ($p<0.01$). The 6-type combination showed the best balance of sensitivity, specificity and treatment group size, and effectiveness to prevent cervical cancer. A 4-type combination (16, 18, 35, 45) could potentially prevent 77.6% (95% CI: 71.2-84.0) of cervical cancer burden by treating 20% and detecting 41.1% of CIN3 cases in the study group. Similarly, a 6-type combination (16, 18, 31, 33, 35, 45), treating 25% and including 62% of CIN3 cases, might prevent 85% of cervical cancer cases (95% CI: 79.6-90.6) among HIV-positive and negative women.

Conclusions: Employing mRNA HPV tests within a test-and-treat approach holds huge promise for targeted cervical cancer prevention in under-screened populations. Testing for mRNA of the 6 highest-risk HPV types in this population and treating them all is projected to effectively prevent progression from CIN3 to invasive cervical cancer while reducing overtreatment in resource-constrained settings.

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#7232

LAMP-Based Lateral Flow Point-of-Care Diagnostic Test for all 14 High-Risk Types of Human Papillomavirus

38 - Low resource settings

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Background/Objectives: In 2018, cervical cancer - nearly always caused by human papillomavirus (HPV) - was the fourth most common cancer in women (1), with people in low-resource settings more frequently affected. The World Health Organisation (WHO) outline the requirements for an HPV diagnostic test that is validated for use in low-resource settings. Importantly, they require it to be a nucleic acid amplification test (NAAT), diagnosing all 12 high-risk types of HPV (hrHPVs) (2). No such test exists yet. Point-of-Care (PoC), or Point-of-Need, diagnostics involve testing close to the patient- minimising or removing the need for lab requirements, such as temperature control or trained personnel, making it an attractive option for diagnostic tests in low-resource settings. Loop-Mediated Isothermal Amplification (LAMP) is a type of NAAT that can be used in PoC diagnostics (3). It is isothermal, negating requirements for expensive thermocycling equipment required in typical alternatives, such as Polymerase Chain Reaction (PCR), and results can be read on low-cost lateral flow strips. Self-taken vaginal swabs can be used instead of invasive cervical swabs (which need to be taken by experienced clinicians, and are required for cervical smears, as the current gold standard diagnostic). A key challenge is the detection of all 12 hrHPVs in a single test. We aim to amplify any HPV genomes present (using LAMP), and then select for high-risk types using CRISPR-Cas12a technology (4). Our objective is to develop an affordable, LAMP-based diagnostic test for all 12 hrHPVs, with lateral flow readout, for use at the PoC.

Methods: LAMP assays, coupled with LFS, were developed for HPV16, HPV18, and a human control gene (BRCA1) using synthetic DNA. The analytical performance was established with a 10X serial dilution of spiked samples.

Results: Limits of detection (in synthetic DNA) were identified as follows: HPV18 LAMP (1000 copies/reaction); HPV16 LAMP (1000 copies/reaction); BRCA1 LAMP (1000 copies/reaction). The assays meet the acceptable limit of detection, defined by the WHO, at 24-7500 copies/reaction. The PoC cassette, coupled to a minimal heater, allows nucleic acid extraction and amplification to be performed directly from a swab.

Conclusions: A NAAT for all 12 hrHPVs is required. Individual LAMP assays for HPV16, HPV18, and BRCA1, and a LAMP-CRISPR assay for the other 10 hrHPVs, will be integrated into a PoC diagnostic test, with lateral flow readout, using self-taken vaginal swabs. We aim to then test the cassette in the field. This follows the development workflow of other NAAT PoC devices within our research group (5).

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#6341

STUDY OF THE IMPACT OF THE COVID-19 PANDEMIC ON HPV VACCINATION INITIATION AMONG FRENCH GIRLS

01 - HPV disease and COVID-19

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Background/Objectives: In France, human papillomavirus (HPV) vaccination is reimbursed in 11-14 (routine vaccination) and 15-19-year-olds (catch-up) girls since 2007 and boys since 2021. The COVID-19 pandemic led to significant disruptions in health care. Our aim was to explore the implications for HPV vaccination, particularly for adolescents at the upper limit of the recommendations, who have not been vaccinated due to lack of access to the vaccine during this period.

Methods: We studied girls eligible for the HPV vaccine in 2017-2021 using French claims data (SNDS). They were considered to have initiated HPV vaccination if they were dispensed at least one dose of HPV vaccine. Boys were not included in the analysis due to insufficient hindsight on vaccination data among them. The effect of COVID-19 pandemic was investigated by estimating the monthly proportion of initiation (mPI) in a given year. Moreover, the annual HPV vaccination initiation rate was described from 2017 to 2021, and compared between 2019, 2020 and 2021 at age 19.

Results: In all, 1,408,645 girls initiated HPV vaccination between 2017 and 2021. Lower mPI were observed at the time of the first lockdown (March-May 2020) compared to the same period in previous years. While annual HPV initiation rates increased from 1.3% in 2017 to 3.4% 2019 in 19 y.o., it was significantly lower in 2020 (3.1%) compared to 2019 (pinf0.0001), showing that some 19-year-olds have come out of the recommendations without being able to get vaccinated. Annual HPV initiation rates were significantly higher in 2021 (3.9%) than in 2020 among 19-year-olds (pinf0.0001).

Conclusions: The COVID-19 pandemic slowed the progress of HPV vaccination coverage in 2020, and certainly excluded some girls targeted by the recommendations from getting vaccinated. Our results support the importance of the extension of recommendations to adolescents aged 19 years and older in France to give them an additional opportunity to be vaccinated.

FC19 - HPV Screening II

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#6898

Prolonged persistent genital HPV infections and the future risk of cervical carcinogenesis

10 - HPV screening

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Background/Objectives: Persistent human papillomavirus (HPV) infections predispose to long follow-ups in cervical cancer screening. Little is known about individual HPV genotypes' persistence times and their potential to induce cervical carcinogenesis. Our aim was to examine the role of different persistent HPV genotypes in causing cervical disease in long-term follow-up.

Methods: This study included 69390 women that took part in the primary national Finnish cervical cancer screening program between 2012-2023 in the Tampere region, Finland. Screening samples were genotyped as part of the routine screening by Abbott Realtime High-Risk HPV test (2012-2020) and Roche Cobas 4800 HPV assay (2021-2023) that detect HPV16, HPV18 and further 12 high risk (hr) HPV genotypes as grouped. Women were divided into 3 age groups (inf40, 40-50, >50). We examined partial HPV genotypes persistent with NILM (Negative for Intraepithelial Lesion or Malignancy) or ASCUS (Atypical Squamous Cells of Undetermined Significance) cytology at baseline. We examined which of the mentioned HPV genotypes cause the longest persisting infections and their risk in developing high grade squamous intraepithelial lesion or worse (HSIL+) during follow-up.

Results: Out of 4526 baseline HPV-positive results with NILM/ASCUS cytology a total of 1721 (38.0%) women had a type-specific persistent HPV detected. Time between the consecutive persistent samples varied from 0.5 to 4 years. On average, other hrHPVs were associated with the highest persistence frequency considering all age groups, ranging between 37.8% to 44.4%. Incidence of persistent HPV16 was the most consistent in all age groups, 39.4% to 41.6%, respectively. Taking into account all genotypes the average persistence time was longest in women inf40 with 17.6 months and decreasing in time by increasing age from 15.6 months to 14.9 months with 40-50 age group and women >50. In women >50 years old, single HPV18 persistence was associated with the shortest average time of 18.7 months to the diagnosis of HSIL+ compared to the younger age women. Interestingly, with persistent HPV18 and a combination of other hrHPV the time to HSIL+ was much more prolonged among women of 40-50 years with 27.1 months.

Conclusions: Our results demonstrate the oncogenic and persistent potential of the selected partial HPV genotypes acting differently on women of different age. Further research on genotype specific HPV persistence is needed to improve the current treatment and follow-up guidelines of cervical disease.

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#7096

HPV infection and CIN2/3 rate over two screening rounds of a randomized primary HPV self-sampling trial (IMPROVE study)

10 - HPV screening

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Background/Objectives: The IMPROVE study is a randomized non-inferiority trial set up in a regular screening population in the Netherlands to evaluate the performance of HPV testing on self-collected samples versus clinician-collected samples. An evaluation of the first screening round of the IMPROVE study (enrolment 2015-2016, follow-up < 4 years) confirmed that HPV testing on self-collected samples and clinician-collected samples have similar sensitivity and similar specificity. The aim of the present study is to evaluate the performance of primary HPV self-sampling over two screening rounds. At the second screening round, women in both randomized arms received an invitation for cervical screening as per the new HPV-based screening programme. In the new programme, women have the possibility to choose between the two sampling methods.

Methods: NA

Results: NA

Conclusions: This presentation will address the round-two probability of opting for screening using a self-sample, the HPV infection risk, the risk of cervical intraepithelial neoplasia grade 3 or worse (CIN3+) and risk of cancer. The results from this study will be used to evaluate the safety of primary HPV self-sampling with a 5 screening year interval.

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#6894

EVALUATION OF ALGORITM TO DISTINGUISH PRIMARY AND SECONDARY HPV SCREENING IN REGISTRY DATA

16 - Screening methods

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Background/Objectives: It has taken until 2022 for all 21 regions in Sweden to adapt their cervical screening organiztion from the old policy, using primary cytology and reflex HPV-test, to implement primary HPV-based screening which was mandated in 2015. The capital region (Stockholm) introduced primary HPV screening as a randomized health care policy already in 2012. Because of the concomitant use of primary and secondary HPV screening in Sweden during almost 10 years it is difficult to analyze and interpret data and assess quality indicators throughout this time. As all laboratories register samples in different series to facilitate handling and analysis of incoming samples, we previously investigated if it was possible to use the sample series to classify the samples according to indication. We developed a simple algorithm based on treshold values. The aim is to evalute how the algorithm, based on data from 2012 to 2018, performs on new data from 2019 until 2022 and compare with known indication for testing throughout this time. Furthermore, the algorithm was adjusted to reduce the proportion of samples with unknown indication for HPV-testing.

Methods: The algorithm was based on individual-level data of all HPV-tests and cytologies performed in Sweden between 2012 and 2018. Data was analyzed per sample year, per laboratory and per registered series at the laboratory. Threshold values were derived based on assumptions of appropriate policy and used to discriminate the sample series into four groups: a) primary HPV-screening, b) secondary HPV-testing (triage of primary cytology), c) self-sampling HPV-testing, d) other/ unknown indications for HPV-testing. To reduce the proportion of unknown indication two further categories was examined to improve the algorithm: co-testing (with both HPV and cytology) and HPV-testing on clinical referral. Data from 2019 to 2022 was then compiled in the same way and used to evaluate the performance of both the new and the old algorithm, comparing with the known indication for testing.

Results: Between 2012 and 2018 there were 919 998 HPV-tests performed in Sweden, of which 52% were classified as primary HPV screening, 34% as other/ unknown indication, 9% as secondary HPV screening and 5% as HPV self-sampling by the algorithm with a known misclassification rate of 3.4% and an unknown proportion of 24% of the samples with no or ambiguous information of the indications for testing. The results of the modification of the algorithm and the evaluation with data from 2019 to 2022 will be presented at the conference.

Conclusions: Using very basic assumptions and a simple classification algorithm based on threshold values it is possible to classify the indication for HPV-testing in Sweden. This talk will provide updated results on the performance of the algorithm.

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#6896

Cervical cancer out of Portuguese age screening limits - are the age range enough?

25 - Cervical neoplasia

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Background/Objectives: Cervical cancer (CC) is one of the most common types of cancer in women worldwide. High-risk human papilloma virus (hrHPV) infections are responsible for virtually all CCs. Screening is an important tool for detection and treatment of cervical neoplastic lesions that can evolute to neoplasia and to reduce the incidence of CC. In Portugal, an organized CC screening takes place in women between 25 and 65 years old. The aim of this study were a descriptive analyses of the CC diagnosed in a Central Hospital and analyse the cases out of the age range of the Portuguese CC screening.

Methods: Cervical cancers diagnosed between 2017 and 08/2023 in a Central Hospital Cervical Pathology Unit Care were reviewed and analyzed with SPSS 23.

Results: A total of 117 CCs were diagnosed in the study period, from this 36 (30.8%) were out of the screening age range (median age 74, and one patient with 22 years old). Between the cases identified out of screening range, the mean number of sexual partners were 5.6 and only 2 (5,6%) were smokers, and only 2 (5,6%) were vaccinated. Overall cases, 8 (6,4%) referred by other specialties in the Hospital, 41 (35,0%) from the screening Primary care, 25 (21,4%) from private medicine, 42 (35,8%) referred by the emergency department (1 missing value). In this group, the previous last cytology results were ASC-US - 1 case (0,86%), HSIL - 3 cases (2,6%), LSIL - 3 cases (2,6%) and NILM - 50 cases (42,4%) and 32 never did any screening test (27,4%). Smoking increases the 2,5 times the risk of CC in the age range of the screening (OR 2.55, CI 1,048-4,047, pinf0,001). During the COVID19 pandemic (2020-2022) 52 cases (44.4%) were diagnosed. From the 36 cases diagnosed out of the screening age, 20 (50,6%) were during the pandemic period (28 cases missing data).

Conclusions: Although we know that increasing cervical screening coverage involves more than merely increasing screening participation, probably, a future review should consider more broad age limits for screening in order to identify more CC cases. The COVID-19 pandemic might have worsened existing inequalities in screen coverage; it has temporarily disrupted cervical cancer prevention activities in many countries, however, it might also create opportunities for more efficient prevention, including the extension of HPV testing with self-sampling or the introduction of innovative digital, mobile, and artificial intelligence technologies to assist in the delivery of cervical screening.

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#6886

LONG-TERM EFFECTS OF COVID-19 ON THE DUTCH CERVICAL CANCER SCREENING PROGRAMME

01 - HPV disease and COVID-19

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Background/Objectives: Organization of a screening programme influences programme resilience to a disruption as COVID-19. Due to the COVID-19 pandemic, short-term participation rates were lower, response times were temporarily longer and self-sampling usage was higher in 2020 compared to 2018/19 in the Dutch cervical cancer screening programme.The aim of this study was to investigate programme resilience by examining the impact of the pandemic on longer-term outcomes of the Dutch cervical cancer screening programme.

Methods: Data from the Dutch national screening organisation and the Dutch nationwide pathology databank (Palga) were used. Main outcome measures include long-term (i.e. 32-months of follow up) participation rates by age, screening region and invitation month, self-sampling usage, time between colposcopic referral and compliance and detection rates after referral. Invitation year 2020 was compared with 2018/19. A follow-up period of 32 months was used.

Results: Using 32-months of follow-up, participation rates of 2020 were comparable to 2018 and 2019 (62.7%, 64.3%, and 61.6%, respectively), for every age category and screening region. Participation rates were still slightly lower in 2020 in women invited in January, February, March and July compared to women invited in these months in 2018/19 (mean difference: -0.9%, -2.2%, -2.9% and -3.0%). No differences were observed in time between colposcopic referral and compliance between 2020 and 2018/19. Self-sampling usage remained higher in 2020 compared to 2018/19 after including women who participated later (max follow-up 32 months). Detection rates of all cervical abnormalities (CIN1/2/3 and cervical cancer) were slightly lower in 2020 compared to 2018/19 per 100,000 women screened, for both clinician-collected sampling and self-sampling, except for CIN1 (2020 vs 2018: +0.2%). Per 100,000 women referred, CIN1 detection rates were higher in 2020 compared to 2018 and 2019 (difference +4.5% and +0.7% respectively), in both clinician-collected sampling and self-sampling. CIN2, CIN3 and cervical cancer detection rates were lower in 2020 compared to 2018 (-1.7% CIN2, -2.4% CIN3 and -6.6% cervical cancer), but slightly higher compared to 2019 (+0.7% CIN2, +0.2% CIN3 and +5.8% cervical cancer) per 100,000 women referred. This pattern was mainly seen in women that used clinician-collected sampling, except for CIN3 (2020 vs 2019: -1.4%). However, no clinically relevant differences in detection rates were observed between the years. In women that used self-sampling, detection rates of CIN2, CIN3 and cervical cancer were lower in 2020 compared to both 2018 (-16.2% CIN3, -24.8% cervical cancer) and 2019 (-4.8% CIN2, -3.6% CIN3, -4.8% cervical cancer) per 100,000 women referred, except for CIN2 (2020 vs 2018: +3.0%). The group of women that used self-sampling in 2020 was different from 2018/19, which was less of a high-risk population.

Conclusions: Due to the well-organised programme and measures taken to catch-up participation, the impact of COVID-19 on the screening programme remained small.

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#7075

Diagnostic and clinical outcome at 24 months re-test after HPV+ index and 12 months re-test in HPV screening using extended genotyping and cytology triage

10 - HPV screening

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Background/Objectives: In 2021, the Danish cervical cancer screening program initiated a phased implementation of HPV screening for women 30-59 years. In the Capital Region of Denmark, the HPV screening triage is conducted using extended genotyping and cytology combined. The HPV screening algorithm is risk based including one or two potential re-tests for least risk scenarios. These include women with an HPV positive index screening and concurrent NILM cytology or ASCUS/LSIL in combination with HPV genotypes 35, 39, 45, 51, 56, 58, 59, 66, or 68, who are referred to a re-test after 12 months. A 2nd re-test after further 12 months is recommended if the 1st re-test sample is HPV positive for HPV 35, 39, 45, 51, 56, 58, 66, or 68 with concurrent NILM cytology. If the 2nd re-test is HPV positive, the woman is referred to colposcopy regardless of triage testing. Here we evaluate the diagnostic and clinical outcome of the 2nd re-test, 24 months after an HPV positive index and re-test sample.

Methods: All women residing in the Capital Region of Denmark, aged 30 to 59 years, and undergoing HPV screening in March to August 2021 with a valid HPV positive index sample and a referral for re-test were included (n=1317). Outcome of 1st and 2nd re-test were analysed descriptively. Screening and outcome data were retrieved from the Danish National Pathology Database by October 2023.

Results: Adherence to referral for 1st re-test was 87% (1140 out of 1317 referred women), the median time from index to re-test sample was 387 days (IQR: 344-469 days). At re-test 44% (n=498) of the women cleared their HPV infection and returned to regular screening. Of the re-test HPV positive women (n=642), 11% (n=71) had concurrent ≥ASCH, 18% (n=117) had ASCUS or LSIL independent of HPV genotype, 38% (n=243) had HPV16, 18, 31, 33, 52 and NILM cytology. These women were referred to colposcopy. The remaining 33% (n=211) with HPV 35, 39, 45, 51, 56, 58, 59, 66, or 68 and NILM cytology were referred to a 2nd re-test. At data retrieval, 47% (n=100) of the referred women (n=211) had a 2nd re-test sample registered. The median time from 1st to 2nd re-test sample was 369 days (IQR: 338-410 days). At 2nd re-test 38% (n=38) cleared their HPV infection and 62% (n=62) were referred to colposcopy. Out of those, 63% (n=39) had a biopsy and this resulted in 72% NILM (n=28), 23% CIN1 (n=9), and 5% CIN nos (n=2). No high-grade lesions were registered.

Conclusions: The risk-based HPV screening algorithm includes two potential re-tests for the lowest risk groups. In this analysis, at 1st re-test 44% women cleared their HPV infection and 38% cleared the infection at 2nd re-test. Out of the included 1317 women with an HPV positive index sample and a referral for re-test, 493 (37%) in total were referred to colposcopy, 62 (5%) after 2nd re-test. For those who remained HPV positive in the 2nd re-test, 95% had a histology outcome of ≤CIN1. The 1st and 2nd re-test allow women additional time to clear the underlying HPV infection and reduces overtreatment. Despite the small dataset, the lack of detected high grade lesions at 2nd re-test for the lowest risk groups indicate that the 2nd re-test might be unwarranted and constitute overtreatment. These women could with benefit return to next regular screening round already after 1st re-test.

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#7137

LONGITUDINAL PERFORMANCE OF MRNA HPV TESTING IN CERVICAL CANCER SCREENING. HIGH PROTECTIVE VALUE OF A NEGATIVE TEST AND POSITIVE PREDICTIVE VALUE AFTER EIGHT YEARS OF FOLLOW-UP

10 - HPV screening

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Background/Objectives: Longitudinal studies of high-risk HPV (hr-HPV) testing are useful to establish the safety of screening intervals by analyzing their negative predictive value (PPV) for a preneoplastic or neoplastic cervical lesion (CIN2+). In addition, the positive predictive value (PPV) of the test also reflects its clinical performance assuming that most women with a positive result will have a non-progressive infection. This information is valuable to design triage strategies and to detect the percentage of unnecessary colposcopy referrals in a screening program. Detecting hr-HPV mRNA of viral E6/E7 is considered more specific than hr-HPV-DNA testing in cervical cancer prevention because these oncoproteins are related to cell proliferation during oncogenesis. Since mRNA-based assays are newer than most DNA HPV tests, there is scarce literature demonstrating the predictive values of the Aptima hr-HPV (APTIMA) test for the detection of CIN2+ in the European population (1-4). We analyzed the protective value of a negative test and the PPV of APTIMA after 8 years of follow-up (FU).

Methods: Longitudinal prospective study from a screening population comprising 3 cohorts of women aged 25-65 years: A) those (n=1973) with a negative initial cotest with APTIMA and ThinPrep cytology that were actively recruited for a second cotest 3 years later. B) A group (n=81) of women with a negative APTIMA test and abnormal cytology; C) women (n=327) with a positive APTIMA test undergoing colposcopy and biopsy. All groups were followed-up according to the current screening guidelines. Predictive values and cumulative detection rates of CIN2+ lesions were analyzed.

Results: The average FU was 8,3 years. At 5 years, the NPV was 99,95% and the cumulative risk of CIN2+ eight years after a negative APTIMA test was 0,006% (12/2.054). In contrast, the immediate risk for CIN2+ was 25,4% (83/327) and the added risk after 8 years of FU was 10,6% after a positive APTIMA test. The 8-year cumulative incidence of CIN2+, was significantly higher in women with abnormal cytology (65,9%) than in women with positive APTIMA test and negative cytology (22,2%). The PPV of APTIMA was 35,2%.

Conclusions: This study provides longitudinal evidence of performance of the mRNA-based APTIMA test over 8 years. It shows a very high protection against squamous CIN2+ lesions after a negative test, with a risk of CIN2+ lower (0,006%) than those reported for some DNA tests (5-6). Accordingly, the NPV at 5 years is 99,95%, indicating a safe screening interval. The clinical performance of the test gathers a PPV higher than most DNA tests, reflecting the value of the E6/E7 gene detection in progressive HPV infections by APTIMA. The lower rate of false positive results demonstrated here, allows for a more efficient strategy on reducing unnecessary colposcopies and related costs in HPV-based screening programs.

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#7094

SCREENING AND VACCINATION: RESULTS ON NUMBER OF VACCINE DOSES FROM THE ITALIAN STUDY EVALUATING BEST STRATEGIES ON HOW TO SCREEN VACCINATED WOMEN

10 - HPV screening

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Background/Objectives: First women invited for HPV-vaccination when 15-16 years old in Italy in 2007/08 reached the age for cervical screening (25 years) in 2017. A study was conducted to provide evidence about the best screening protocol for vaccinated women, and evaluate the vaccination impact in a real-world Italian setting. We consider the impact of vaccine on type-specific HPV infection prevalence (IP), colposcopy referral (CR) and CIN2+ and CIN3+ detection (CIN2+D, CIN3+D).

Methods: Women born in 1993-1996 invited in Florence, Turin-Piedmont and Savona organised screening in 2018-2022 were eligible after informed consent. They were tested for high-risk HPV (Hybrid-Capture 2 or Cobas), genotyped by Anyplex. Positives triaged by cytology, were referred to colposcopy if ASCUS+. IP analysis considered infections, CR and CIN2+, and CIN3+ cases were hierarchically attributed to the pool of HPV16/18, or HPV31/33/45, or other-types. We estimated relative outcomes and 95%Confidence Interval (CI), adjusted by centre and birth cohort, by binomial regression. The Ethical Committees approved the study.

Results: Participation to screening was higher in vaccinated women (unvaccinated: 35.2%, ≥2 doses: 56.9%), and among them with increasing number of doses (40.4% among vaccinated with 1 dose, 42.1% among vaccinated with 2, 46.8% among vaccinated with 3 doses). Of 14,512 enrolled women with valid genotyping, 34% had no vaccination, 65% ≥2 doses. Bivalent vaccine and vaccination at <=16 was more frequent in women vaccinated with 2 or more doses. Comparing women vaccinated with ≥2 doses to the unvaccinated, we observed: a decrease in overall IP (0.84, 95%CI 0.79-0.91), CR (0.81,0.71-0.93), CIN2+D (0.68,0.49-0.95), CIN3+D (0.72, 95IC% 0.45-1.14). CIN2+ with HPV16/18 were reduced by 93%(0.07,0.02-0.20), the ones with HPV 31/33/45 by 36% (0.64,0.33-1.23). Among women with one dose, no infection by HPV16/18 was detected; no other significant outcomes reduction vs. no-vaccination was observed.

Conclusions: In women vaccinated with ≥2 doses, a significant decrease in HPV-IP, CR and CIN2+D was observed, with protection almost complete for HPV16/18 infections and relevant for HPV31/33/35. Risk reduction is plausibly due to reduced infection but also to high propensity to participation in screening, this low risk population needing low-intensity screening. Active policies are needed for the higher-risk unvaccinated population. When comparing results on lesions (CIN2+, CIN3+) hierarchically/not hierarchically attributed to infection from single genotypes, our data suggest that hierarchical classification is not proper. To address this issue we are HPV Genotyping CIN2+ lesions of women infected with more than one type of HPV to correctly attribute lesions, and use the statistical approach proposed by Lissenberg-Witte et al (Epidemiology 2019;30: 590-596) to estimate CIN2+ and CIN3+ detection. In order to provide evidence about the best screening protocol for management of vaccinated women, we will estimate the same outcomes and PPV considering also groups of HPV types according to available data on HPV type-specific risks of CIN3+/cancer

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#7097

Mapping Opportunities for HPV Vaccination and Screening Engagement and Uptake in Trans Men and Gender Non-Binary Individuals Assigned Female at Birth: The MOVE UP Study

10 - HPV screening

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Background/Objectives: Transgender ("Trans') men and gender nonbinary ("GNB') individuals assigned female at birth are significantly underrepresented in scientific health research, including research on HPV and its impactsvi. Additionally, Trans men and GNB individuals assigned female at birth, including especially those living with HIV and / or who also self-identify as gay, bisexual, or men who have sex with men ("GBMSM') may be disproportionately impacted by HPV, as they may share HPV risk factors of both cisgender male and female individuals, and may lack access to important prevention and screening programs. This may impact HPV awareness and vaccination, screening, and treatment opportunities for Trans men and GNB individuals assigned female at birth, potentially leading to later development of HPV pre-cancers, and associated cervical, vaginal, vulvar, and anal cancers. With no Canadian specific research yet conducted, essential data is not available. New research is necessary to understand HPV, including prevention and specific screening tools, in Trans men and GNB individuals assigned female at birth. 1. Describe and analyze provincial/territorial (P/T) HPV vaccination, pre-cancer and cancer awareness programs, and HPV pre-cancer and cancer screening programs for Trans men and GNB individuals assigned female at birth. 2. Determine the educational needs of Health Care Providers and stakeholders for the successful implementation of HPV vaccination and HPV pre-cancer and cancer screening programs for Trans men and GNB individuals; identify the social and structural determinants of HPV vaccination and HPV pre-cancer and cancer screening program uptake among Trans and GNB individuals.

Methods: In the proposed pilot, the research team will utilise an exploratory qualitative study design. The applicant will conduct one-on-one semi-structured, web-based interviews with study participants from two distinct cohorts. In the first cohort, the applicant will conduct interviews with 40 Trans and GNB individuals (including individuals who also identify as GBMSM, both individuals living with HIV and HIV-negative individuals, and GNB-identifying individuals with and without vaginal, vulvar, and cervical tissues). Interview questions for this cohort will relate to four predetermined domains: (1) Participant knowledge and awareness of HPV and its potential risks and impacts in Trans and GNB individuals; (2) Overall participant sexual health and bacterial STI literacy and self-efficacy; (3) HPV-specific awareness and screening self-efficacy; and (4) The impacts of Trans and GNB-specific health promotion messaging on HPV-related sexual health behaviours. In the second cohort, the applicant will conduct interviews with twelve healthcare providers (i.e., doctors and nurses) working in both primary care and clinical sexual health settings. Interview questions for this cohort will relate to two domains: (1) Participant knowledge and awareness of HPV and its potential risks and impacts in Trans and GNB individuals; (2) Awareness of existing and/or needed Trans and GNB specific HPV awareness, screening, and treatment programs; (3) Self-identified needs and resources to better deliver Trans and GNB specific HPV awareness, screening, and treatment programs.

Results: Study is currently underway

Conclusions: Study is currently underway

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#7188

CHANGES IN HPV PREVALENCE AND GENOTYPE DISTRIBUTION AS HPV VACCINATED WOMEN ENTERS THE CERVICAL SCREENING PROGRAM IN DENMARK

10 - HPV screening

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Background/Objectives: To inform on future changes in age specific HPV prevalence and genotype frequencies amongst women participating in cervical cancer screening, we have generated data on women age of 23-59 years participating in cervical cancer screening in 2021. We compare the 2021 HPV prevalence and genotype frequency against a historical study cohort from 2011 consisting of HPV vaccine naïve, HPV tested screening samples. Here, women 23-29 vs 30-59 years of age are particular interesting as 23-29 old has been offered childhood vaccination. The vaccine coverage is between 78% (birth cohort 1993) to 92% (birth cohort 2000), with an approx. 85% average across the birth cohorts 1993-1998. For women older than 30 years, HPV vaccine is only opportunistic.

Methods: In Denmark, cytology is the screening method for 23-29y, and 999 consecutive, unselected screening samples from this age group were collected in 2021 and subsequently genotyped as a quality development initiative. For 30-59 y, the 2021 cohort attending cervical cancer screening in the Capital Region of Denmark consisted of 41,319 SurePath collected, HPV screened cervical samples. All 2021 samples were analyzed using the BD Onclarity HPV test (BD Integrated Diagnostic Systems, Sparks, MD). HPV prevalence and genotype frequency in the 2011 cohort were recalculated from Bonde et al, BMC Inf. Dis, 2014. The study is a quality development study approved by AHH-Hvidovre Hospital.

Results: HPV prevalence, 2011 versus 2021, was age group specific with 37.7% vs. 25.2% for 23-29 years old, 21.1% vs. 17% for 30-39y, 12.8% vs. 7.6% for 40-49y, and 9.7% vs. 6.3% for 50-59y. HPV genotype frequency out of all HPV positive findings in 23-29y unvaccinated (2011) vs 23-29y offered vaccination (2021) was 29.5% vs. 2% for HPV16, 9.8% vs. 0.8% for HPV18, 20.2% vs. 5.2% for HPV31, 23.1% vs. 15.1% for HPV33/58, 18.1% vs. 32.1% for HPV 35/39/68, 19.4% vs. 25% for HPV52 & 28.9% vs. 34.9% for HPV56/59/66. HPV genotype frequency in largely unvaccinated 30-59y, 2011 vs 2021, was HPV18 (9.3% vs 4.9%), HPV51 (10.9% vs. 7%), HPV33/58 (18.7% vs 11.2%), HPV45 (6 % vs 9.6%), HPV52 (16.5% vs. 14.2%), HPV31 (12.9% vs. 12.1%), HPV16 (21.5% vs. 16.4%), HPV56/59/66 (22.2% vs. 21.9%) & HPV35/39/68 (17.3% vs. 22.3%).

Conclusions: The purpose of this study is to establish a 2021 reference on HPV prevalence across the screening ages 23-59 year. For women aged 23-29, we observe a substantial reduction in HPV prevalence compared to 2011 and the almost but eradication of HPV16 and 18. HPV16 and 18 remain amongst the most frequent genotypes in women above the age of 30. A limitation of the study is that the 2011 genotyping assay was more analytical sensitive than the BD Onclarity HPV assay used in routine cervical screening today. Screening algorithms using extended genotyping allows for ongoing, real-time monitoring of changes in prevalence and frequencies. Furthermore, the HPV prevalence reduction amongst young women could lead to considering also this age group for primary HPV screening, as is indeed already implemented in Sweden and Norway but not Denmark. In conclusion, these data can inform on how screening designs in the future can accommodate both largely vaccinated and unvaccinated birth cohorts.

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#6731

PILOT PROJECT FOR CERVICAL CANCER SCREENING BY HPV TESTING IN THE REPUBLIC OF UZBEKISTAN

10 - HPV screening

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Background/Objectives: Determination of HPV positive women in the Republic of Karakalpakstan and the city of Chirchik, Tashkent region

Methods: The first UNFPA-WHO pilot project on HPV-based cervical cancer screening is underway with funding from the Government of Japan, technical assistance from WHO, IARC and UNFPA, and some support from the French Embassy. The project was approved by the Ministry of Health of the Republic. The planned target group was 50,000 women in the Republic of Karakalpakistan and 6,000 women in the city of Chirchik, Tashkent region, aged 30-55 years. The Xpert HPV Assay is a qualitative in vitro diagnostic test for the detection of the E6/E7 region of high oncogenic risk human papillomavirus (HPV) genomic DNA in patient specimens. The analysis was performed on a Cepheid Gene Xpert system. The Xpert HPV test specifically identified HPV 16 and HPV 18/45 types in two separate detection channels and reported the presence of 11 other high risk virus types (31, 33, 35, 39, 51, 52, 56, 58, 59, 66 and 68) as a combined result.

Results: The study included 54,710 (98%), of them in the Republic of Karakalpakstan 49,002 women were screened, of which HPV positive 3303 (6.7%), coverage 98%. The results of HPV testing showed that in the central regions the percentage of HPV positive was higher and amounted to 9.5%, in remote areas it was lower, i.e. 6%. In the city of Chirchik, out of 6,000 women, 5,708 women were examined, screening coverage was 95%, of these, 525 (9.2%) women were HPV positive. Distribution by HPV types: among HPV-positive women HPV 16 - 28%; HPV 18/45-7.6%; HPV 31.33.35.52-23.9%; HPV 51-11.6%; HPV 39.56.66-18.4%; mixed forms - 10.2%. Erroneous tests were 2.9%. The age of HPV positive women was 35-45 years.

Conclusions: In the studied regions, HPV types 16,31,33,35,52 were most often detected, which should be taken into account when developing the country's national screening program. Also, given the age-specific prevalence of HPV, may be considered for the target group of cervical cancer screening of women aged 35 and 45 years, which is more acceptable for a developing country.

FC23 - Molecular markers and viral and molecular biology

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HIGH RISK HPV LINEAGES AND SUBLINEAGES ASSOCIATED WITH CERVICAL CANCER AND PRECURSOR LESIONS: A SYSTEMATIC REVIEW

15 - Molecular markers

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Background/Objectives: Despite the identification of 200+ human papillomavirus (HPV) types, only 12 are categorised as high-risk HPV (hrHPV) and associated with cervical cancer development. They are distinguished based on >10% difference in the L1 gene. Therefore, the question remains whether smaller genetic differences, on a lineage (1.0-10%) and sublineage (0.5-1.0%) level, also contribute to determining the disease risk. As such, this review explores whether identifying hrHPV (sub)lineages has any diagnostic or predictive value.

Methods: Three databases for health sciences were searched: PubMed, Web of Science and Scopus. Data was extracted from eligible publications regarding: (1) hrHPV type, (2) (sub)lineages, (3) geographics, (4) study population, (5) sample size, (6) sample type, (7) detection method, (8) gene(s) sequenced, (9) study results (and when provided odds ratios) and (10) year of publication. A prospective protocol was registered on PROSPERO (CRD42023464090).

Results: The query yielded 768 records of which 69 were included in the analysis after the selection process. The majority of the studies reported on HPV16 (n=38), followed by HPV18 (n=14), HPV52 (n=10), HPV58 (n=9), HPV31 (n=7), HPV45 (n=5) and HPV56 (n=5). The remaining hrHPV types are all covered less than 5 times. In addition, the majority of publications were performed in an Asian population (49%), whereas papers focussing on African and Oceanian populations were lacking. Moreover, E6 and E7 were most frequently sequenced to determine the (sub)lineage. For HPV16, 23/38 studies rendered significant results, most (21) suggesting an increased disease risk of non-European (sub)lineages A4, B, C and D. Six out of 14 publications on HPV18 found significant differences of which most (5) discovered an increased presence of lineage A in cases vs. controls. Furthermore, lineages A and B of HPV31 had an elevated risk (in 4/7 studies), as well as sublineage A1 of HPV33 (3/4) and HPV35 A1 in a Caucasian population (2/3). However, the latter was not the case in African-American women, where HPV35 A2 was described as associated with disease (1/3). Other significant results included HPV45 B2 (3/5), HPV51 B (1/2), HPV52 C (3/10) and B (2/10), HPV56 B (2/5) and HPV58 A1 and A3 (2/9). HPV39 and 59 were studied three times and once resp., yet without any significant differences between cases and controls. Finally, several studies found the disease risk of (sub)lineages to be associated with population characteristics as well, suggesting an interaction between the host and viral genome that causes these nuances.

Conclusions: While these results suggest the increased disease risk of specific (sub)lineages, further research needs to explore the potential clinical value in risk stratification as well as the influence of population origin. Indeed, specific populations such as in Africa or Oceania should also be covered more extensively. Moreover, the detection of (sub)lineages should be standardised as well as the nomenclature. Currently, there are two classifications being used, either geographical names or letters. Furthermore, the nature of the included studies is heterogeneous due to different study designs in which different groups are compared and sometimes pooled. In addition, both histological as well as cytological endpoints are used. Consequently, comparison of these studies is complicated. Instead, standardised study design could simplify the determination of the true clinical value of (sub)lineage identification.

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#6582

MUTATIONAL DIFFERENCES BETWEEN HUMAN PAPILLOMAVIRUS (HPV)-ASSOCIATED AND HPV-INDEPENDENT PENILE SQUAMOUS CELL CARCINOMAS AND PRECANCERS.

04 - Pathogenesis

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Background/Objectives: Penile invasive squamous cell carcinoma (SCC) are divided into human papillomavirus (HPV)-associated and HPV-independent SCC, mainly for prognostic reasons. While HPV induced carcinogeneses and precursor lesions are well characterized, their precursor lesions of HPV independent penile SCC are insufficiently characterized.

Methods: We analyzed peritumoral precursor lesions of 150 invasive SCC (50% HPV-induced and 50% HPV independent) with known mutational profile. HPV genotyping was performed on formalin-fixed and paraffin embedded tissues for 41 genotypes and mutational profile was evaluated with the cancer hot spot panel analyziing 50 cancer relevant genes.

Results: Less than 30% of HPV induced SCC carried somatic mutations, mainly in the PIK3CA gene. Precursors adjacent to HPV-induced SCC were full thickness basaloid lesions called high-grade squamous intraepithelial lesions (HSIL). HPV-negative invasive penile SCC showed somatic mutations in about 90%, manly tumorsuprressor genes. They showed 4 histologically different precursor lesions. 60% SCC showed basal keratinocyte proliferation with variously elongated epithelial rete with nuclear atypica, increased mitotic rate, and premature squamatization, but regular superficial cornification, termed differentiated penile intraepithelial neoplasia (d-PeIN). They were associated with chronic inflammatory dermatoses lichen planus and occassionally with lichen sclerosus in 76%. They overexpressed p53 and were associated with SCC that featured hotspot mutations in TP53, CDKN2A or both in 62%. A rare cytoplasmic p16ink4a overexpression in HPV negative d-PeIN correlated with somatic missense mutations in the CDKN2A gene. In all, 30% of peritumoral precursor lesions were cornified verrucous or non-cornified verruciform precursors with minimal atypia and wild-type p53 adjacent to verrucous or papillary SCC which harbored mutations in HRAS and/or PIK3CA. About 10% of peritumoral p16ink4a-negative HPV-negative precursors were undifferentiated full-thickness lesions with inconclusive genetic characteristics.

Conclusions: In summary, HPV-induced precursor lesions arise as result of the oncogenic effects of E6/E7 of high-risk HPV and acquire somatic mutation with invasion. In contrast, HPV-independent SCC represent a heterogeneous group. Three highly differentiated HPV-independent penile precursor lesions can be assigned to 2 distinct genetic / biological pathways with characteristic precursors requiring different clinical management decisions. These include a) mostly keratinizing SCC with TP53/CDKN2A mutations arising via p53 overexpressing d-PeIN in chronic inflammatory dermatoses, and b) verrucous / verruciform p53 wildtype SCC with mutations in oncogenes PIK3CA and HRAS developing through verrucous and verruciform precursors not associated with dermatoses. These two pathways have clinical and therapeutic consequences similar to vulvar precancers. d-PeIN needs to be considered a rapidly progressing precursor that can recur multifocally in residual lesions of chronic inflammatory dermatoses, which should be treated to lower risk of cancer development. These patients need close clinical follow-up for early detection of recurrent SCC. Verrucous precursors are typically solitary lesions and complete resection should suffice in therapeutic management.

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#7056

Identification and correlation with prognosis of specific molecular signatures of HPV virus in early cervical cancer without pelvis nodes metastasis by HPV Capture technique coupled with NGS (Next-Generation Sequencing).

02 - Viral and molecular biology

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Background/Objectives: Background: The persistent infection with human papillomavirus (HPV) causes almost all cervical cancers. It is known that patients with early cervical cancer (ECC) without lymph node metastases (N0) have a better prognosis than those with lymph node involvement (N+), however 15% of N0 patients will have recurrences with an lower survival rate equivalent to N+ patients. In this context, we decided to evaluate the prognostic value of the specific HPV molecular statuses obtained by the HPV capture technique coupled with NGS (Next-Generation Sequencing) carried out on the primary tumors of these patients. Objectif : Identify specific molecular signatures of HPV virus by HPV Capture technique coupled with NGS (Next-Generation Sequencing) in ECC patients without histologically lymph node metastasis and correlate them with prognosis

Methods: Forty tumors from patients meeting our selection criteria could be analysed and the molecular signatures obtained by the HPV Capture technique correlated with the prognosis.

Results: As expected, HPV 16 genotype was the most frequent (55% of patients). Different molecular statuses of HPV viral genomes have been described: - Pure episomal status: HPV viral genome is not integrated into the human genome - Pure integrated status: HPV viral genome with total loss of a defined area of the HPV viral genome framed by chromosomal marks confirming the complete integration of the HPV genome into the human genome - Mixed status: viral genome both present in episomal and integrated form For the HPV16 genotype (22 patients), in 100% of cases we found the episomal form (20 pure episomals (90.9%) and 2 mixed (9.1%)). On the other hand, the HPV18 genotype (9 cases) was most often found in integrated form (5 pure cases (55.6%) and 2 mixed (22.2%)) as already described in the literature. Only 2 patients (22.2%) had pure episomal status for the HPV18 genotype. This correlation between molecular status and viral genotype is highly significant (p=0.00002). In our entire cohort, 7 recurrences and 3 deaths were documented. In 100% of these cases, the HPV16 genotype was found in episomal form. Thus, a significant correlation between the risk of recurrence and the presence of the HPV16 genotype in the episomal state (p=0.007) was identified in these patients

Conclusions: An increased risk of recurrence seems associated with the episomal molecular status of the HPV16 genotype in patients with EEC N0.

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#7015

Association of HPV E6/E7 mRNA expression with IL-10 c. -592C>A single nucleotide polymorphism

15 - Molecular markers

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Background/Objectives: High-risk HPV persistent infections with HPV E6/E7 mRNA expression are a highly predictive marker for the progression of cervical intraepithelial lesion toward cervical cancer (CCa). Still, in only a low percentage of HPV-positive women, the infection remains persistent with continuous HPV E6/E7 mRNA expression. The individual host's immune response is an important factor that influences viral biological activity as well as HPV E6/E7 mRNA expression. Immunomodulatory effects of cytokines such as IL-10 and its genetic variants may confer variation in host response toward HPV clearance as well as the influence of the expression of these viral oncogenes.

Methods: This study evaluates the association of IL-10 c. -592C>A single nucleotide polymorphism (SNP) with HPV E6/E7 mRNA positivity. We conducted a case-control study that included 159 HPV DNA-positive women and 113 HPV DNA-negative women with no prior history of HPV positivity or cervical abnormality, as a control group. Women from both groups were genotyped for IL-10 c. -592C> A using RFLP analysis. Additionally, the cases group was tested for HPV E6/E7 mRNA expression using commercial test. The statistical significance of the association was assessed by the chi-square test and the OD ratio.

Results: The results showed the CC genotype (59.3%) was significantly more common in women positive for both tests compared to those positive only for HPV DNA (39.2%) [p = 0.018; OR = 2.25 (95% CI: 1.14-4.45)], and compared to control and HPV DNA positive groups together [p = 0.04; OR: 1.68 (95% CI: 1.03-2.75)], but not compared to the control group alone (49.6%). The frequency of the C allele in the HPV E6/E7 mRNA positive group (78.2%) was significantly more frequent [p = 0.016, OR= 1.88 (95% CI: 1.11-3.16)] than only HPV DNA positive (65.7%) and with borderline significance compared to both HPV E6/E7 mRNA negative groups [p = 0.04,;OR=1.88 (95% CI: 1.11-3.16)].

Conclusions: In conclusion, the C/CC variant of IL-10 c. -592C>A SNP may influence a more frequent rate of HPV E6/E7 mRNA expression after the onset of HPV infection. This genotype is not associated with susceptibility to this infection given the absence of association with HPV DNA alone. These results should be confirmed in a larger epidemiological study involving a much larger number of women.

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#6699

THE PROOF-OF-PRINCIPLE OF MED-SEQ, A METHOD FOR GENOME-WIDE DNA METHYLATION PROFILING FOR MARKER DISCOVERY TO DETECT DIFFERENT GYNECOLOGICAL CANCERS

17 - Methylation

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Background/Objectives: DNA methylation acts as a crucial indicator for the mis-regulation of gene expression in cancer and can be used as a diagnostic tool. DNA-methylation markers can be utilized to diagnose cancer, categorize tumors, and monitor disease progression and therapy responses.

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

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

Conclusions: MeD-seq is a reliable low-cost technology to establish genome-wide DNA methylation differences between cancer and controls and can be used to call DMRs for the rapid development of PCR-based assays.

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#6772

Binding of HPV16-E2 protein on E2 binding sites is blocked in case of T310K mutation on E2

15 - Molecular markers

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Background/Objectives: Although HPV16 is the leading cause of anogenital and oropharyngeal cancers, the degree of oncogenicity may depend on variations along the HPV16 genome. By studying a longitudinal cohort of women with a cervical HPV16-infection, our group previously described a T310K mutation inside the HPV16-E2 protein. This protein plays a key role in the regulation of the E6 and E7 viral oncogenes through its fixation on E2 binding sites (E2BS) located in the Long Control Region (LCR) of the HPV16 genome. Therefore, this study aimed at determining the phenotypic impact of the T310K mutation on the E2/E2BS interaction.

Methods: The T310K mutation was reproduced in a pCI-neo-plasmid containing E2 by directed mutagenesis. Adequate expression of the non-mutated and the T310K-mutated plasmids was determined by RT-PCR and western blotting. A second plasmid containing the HPV16-LCR and the luciferase gene (Luc) was used as a reporter. Co-transfection of these two plasmids was performed in U-2 OS cells (HPV negative). CaSki cells were used as a model of HPV-positive cells.

Results: Co-transfection of the non-mutated pCI-neo-E2 plasmid and the reporter plasmid triggered the expression of the Luc gene, reflecting an appropriate binding of E2 with E2BS. Conversely, the Luc gene expression was abolished in the presence of the T310K-mutated form of E2, suggesting a loss of binding of the mutant E2 with E2BS. In the model of HPV16-positive Ca Ski cells, the expression of E6 was not affected by the presence of non-mutated or T310K-mutated forms of E2.

Conclusions: Our results suggest that the T310K mutation in HPV16-E2 protein blocks the binding of E2 with E2BS and may favor a deregulated expression of E6 and E7 oncogenes. Further studies on HPV-positive cells are ongoing to confirm these results.

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#7088

DISTRIBUTION OF GENITAL AND ANAL HPV 16 VARIANTS AMONG MEN IN THE HUMAN PAPILLOMAVIRUS INFECTION IN MEN (HIM) STUDY.

02 - Viral and molecular biology

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Background/Objectives: The prevalence of HPV 16 variants in multiple anatomical sites among men has not been fully investigated. Our aim was to estimate the distribution and proportion of HPV 16 variants among men with detectable HPV 16 at the external genitals and anal canal who participated in the multi-national Human Papillomavirus Infection in Men (HIM) Study.

Methods: The HIM study cohort enrolled ~4500 men aged 18-70 year who had genital and anal swabs collected over a series of eleven 6-monthly visits. Those who had at least one HPV 16 positive anal or genital swab were included for HPV 16 variant characterization using PCR-sequencing. Amplicon sequences were compared with the HPV-16 prototype sequence (sublineage A1) (GenBank no. K02718) and classified into 4 lineages (A, B, C, and D) and 16 sublineages (A1-4, B1-4, C1-4, and D1-4). Summary statistics were performed in STATA 17.0.

Results: At baseline, a total of 301 men tested positive for genital HPV 16, whilst 48 tested positive for anal HPV 16. 209/301 (69.4%) and 42/48 (87.5%) had HPV 16 lineages and sublineages that could be classified on the genital and anal specimens, respectively. For both anogenital sites, HPV 16 A1 was the most commonly detected variant; 175/301 (58.1%) from the genital and 34/48 (70.8%) anal anatomic sites at baseline. Prevalence of the other variants detected at baseline are listed in Table 1. The A1 variant remained the most commonly detected across 11 biannual clinical visits; detected in 57-93% and 57-100% of genital and anal specimens, respectively. Concurrent HPV 16 variant detection at both anatomic sites was observed among 14 men, of whom 6 were at baseline and were all positive for the A1 variant (Table 1). The total number of men with A1 infections at each of the 11 clinical visits is shown in Figure 1.

Conclusions: The HPV 16 A1 variant was detected in a relatively high proportion of HPV 16 infected men an is the most common variant detected in both anogenital sites studied. These data set a baseline for multi-anatomical site studies of HPV variant distribution, and contribute to an increasing understanding of the molecular epidemiology of HPV 16 variants.

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#7065

LINE-1 HYPOMETHYLATION CORRELATES WITH TP53 MUTATION IN OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

17 - Methylation

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Background/Objectives: The autonomous non-LTR retrotransposons long interspersed nuclear element-1 (LINE-1) are the only active human retrotransposons, and account for 17% of the entire genome, thus representing a widely accepted surrogate of overall genomic DNA methylation content. LINE-1 hypomethylation has been associated with a poorer overall and/or progression-free survival in many different tumor types, including oropharyngeal squamous cell carcinoma (OPSCC) (1, 2). Somatic TP53 mutations are a common feature in HPV-negative OPSCC, whereas their presence has been reported in only a small subset of HPV-related OPSCC. TP53 mutations often result in overexpression and nuclear accumulation of mutant p53, whereas TP53 nonsense, frameshift or splice-site mutations usually associate with p53 negative staining in tumor cells (3). At present, however, little is known about the correlation between LINE-1 methylation and p53 expression status and/or TP53 mutation in OPSCC (2).

Methods: Presently, 115 OPSCC patients with molecular characterization from one retrospective cohort of investigation and an ongoing prospective study were included. Methylation of LINE-1 repetitive sequences was evaluated by methylation-specific real-time quantitative PCR in FFPE tissues. HPV16 DNA quantification was performed by using specific primers for the amplification of a region spanning the E6 genes of the HPV16 genome. p53 expression was detected by immunohistochemical staining. TP53 exon mutations were analyzed by by Next Generation Sequencing on Illumina platform. LINE-1 RNAs quantification was performed using the tool L1EM (4) considering samples mutated and not in TP53, from the Head and Neck Squamous Cell Carcinoma - TCGA dataset. Only LINE-1 RNAs with a FDR≤0.05 or less were considered for further analysis.

Results: The correlation between LINE-1 hypomethylation and p53 expression has been evaluated in OPSCC patients. According to published cutoffs, p53 expression was categorized into three groups (0%, 1-49%, and ≥50%) based on the overall intensity of nuclear staining of the tumor cells. p53 was considered null, overexpressed, or wild type when its nuclear staining was 0 %, ≥50%, or ranged between 1% and 49%, respectively. Following p53 immunohistochemistry, LINE-1 methylation levels were compared among the different p53 expression groups. Of note, the highest level of LINE-1 methylation was observed in OPSCC tissues with nuclear p53 staining between 1% and 49% (57.8%), whereas OPSCC patients with p53 expression ≥50% showed a decline of LINE-1 methylation levels (40.6; p=0.026). Interestingly, LINE-1 methylation was lower in OPSCC patients harboring TP53 mutations in both HPV16-negative (24.8%) and HPV16-positive (24.0%) OPSCC patients, even if statistical significance was reached only in the HPV-negative group (p=0.015). Finally, TGCA analysis indicated increased LINE-1 mRNA expression in TP53 mutant OPSCC patients.

Conclusions: Although preliminary, results of this study suggest that mutations within TP53 gene might influence LINE-1 methylation and expression in OPSCC, irrespective of HPV status. Further studies are required to elucidate the mechanism through which p53 affects LINE-1 methylation status in OPSCC.

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#6800

Metabolic Profiling of Vaginal Discharge Differentiates Persistent High-Risk Human Papillomavirus Infection and Cervical Lesions

16 - Screening methods

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Background/Objectives: Cervical cancer ranks as the fourth most common malignancy in women worldwide. Early prediction and diagnosis are crucial for reducing the incidence and mortality of cervical cancer. The objective of this study was to identify potential biomarkers for distinguishing persistent high-risk human papillomavirus (HR-HPV) infection and associated cervical lesions through vaginal metabolic profiling.

Methods: Vaginal secretion samples were collected from various groups including 8 healthy controls (Control), 12 patients with persistent HR-HPV infection(HR-HPV), 8 with high-grade squamous intraepithelial lesion (HSIL), and 8 with cervical cancer (CC). Liquid chromatography-mass spectrometry(LC-MS) was performed to analyze the vaginal secretion samples and determine the differential metabolites and pathways among different groups.

Results: Potential biomarkers distinguishing different groups were identified. Three metabolites (N-Desthienylethyl-rotigotine, Dihydrohydroxy-O-methyl sterigmatocystin,1'-Hydroxybufuralol) were discriminated between persistent HR-HPV infection and healthy controls (area under the curve (AUC) value > 0.8).On the basis of persistent infection of HR-HPV, 4-Hydroxy-4-(3-pyridyl)-butanoic acid, N-Acetyl-b-glucosaminylamine increased and Zalcitabine, Arg Val Phe, NAD+ decreased(pinf0.05) with the aggravation of cervical lesions, indicating that they have the potential to be used as potential biomarkers to predict different stages of cervical lesions. Furthermore, metabolic pathway analysis revealed amino acid metabolism, atrazine degradation, and glycerophospholipid metabolism as key pathways associated with cervical lesions.

Conclusions: By measuring the metabolome of vaginal secretions, specific metabolites can effectively distinguish persistent HR-HPV infection and different grades of cervical lesions, which may become an important means for early screening and diagnosis of cervical cancer.

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#6831

The clinical relationship between the cervical administration of Chinese medicine (Paiteling) and HPV E6E7 mRNA expression

02 - Viral and molecular biology

Background/Objectives: To explore the clinical relationship between the cervical administration of Chinese medicine (Paiteling) and HPV E6E7 mRNA expression.

Methods: From January 2021 to July 2022, a total of 198 patients with pathological CIN3 and below were enrolled in Peking University Shenzhen Hospital. According to the treatment method, patients were divided into non-surgical and surgical groups before Paiteling administration. All patients were diagnosis with HPV E6E7 mRNA positive before Paiteling administration in 2 groups. Inclusion criteria: ① women over 20 years old; ② no previous history of cervical physical therapy or surgery. Exclusion criteria: no follow the treatment and / or diagnosis protocol and the patients withdrew from the study. Petaline was administered according to the instructions, and the course of treatment was 6 weeks. Patients in the control group were only observed and followed up without treatment. TCT and E6E7 test were examined in one years after enrollment or treatment.

Results: 47 percent of invasive treatment patients (average 41.9 years) and 48 percent of non-invasive treatment or observation patients (average 38.5 years) were treated with Paiteling Chinese medicine via cervical administration. The other patients with no Paiteling Chinese medicine treatment were defined as the Chinese medicine control group. The negative conversion rate of HPV E6E7 in Petaline/ control of invasive treatment group were 84.8% / 71.7% and 89.1% / 82.6%, in the 6th and 12th months (Pinf0.05), respectively. The negative conversion rate of HPV E6E7 in Petaline treatment vs control of non-invasive treatment or observation group were 81.3% / 45.8% and 89.6% / 75.0% in the 6th and 12th months (Pinf0.05), respectively. The E6/E7 copy levels were decreased significant after Petaline Chinese medicine treatment in the invasive and non-invasive groups (Pinf0.05).

Conclusions: The Petaline Chinese medicine treatment by cervical administration can reduce E6E7 mRNA expression of patients with cervical precancer in the invasive and non-invasive group. The results showed the Chinese medicine could reduce the HPV-E6E7 mRNA expression.

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#6861

Understanding false HPV-negativity in cervical cancer diagnostics by HPV whole genome sequencing

02 - Viral and molecular biology

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Background/Objectives: Human papillomavirus (HPV) testing has been implemented as the primary screening test for all women attending the cervical cancer screening program in Norway. Although being a clinically very sensitive test, women occasionally develop cervical lesions or cancer despite an HPV-negative primary test result. True HPV-negative cases include HPV-independent cancer or cases where the HPV infection has caused the cellular lesion, but is no longer necessary for driving tumorigenesis. False HPV-negative cases represent lesions caused by another HPV type than the ones tested for, or cases where the HPV target sequence possibly contains mutations or might be lost. In this project, we aim to understand the causes behind false HPV-negative results, with one explanation being a result of genomic events occurring within the HPV-DNA.

Methods: For HPV whole genome sequencing in our laboratory, the tagmentation-assisted multiplex PCR enrichment sequencing (TaME-seq2) method is used, with simultaneous identification and characterization of mutations, gene rearrangements and chromosomal integrations. TaME-seq will be performed on false HPV-negative samples identified in a quality assurance project of the cervical cancer screening program, including samples obtained from 2015-2028. In addition, extended genotyping and E6/E7-directed assays are performed as part of reference diagnostics, with samples showing results of interest for whole genome sequencing.

Results:

Conclusions: Results from the TaME-seq analysis will be presented. Although fortunately few false HPV-negative cases are observed, increased knowledge on genomic rearrangements, deletions or mutations affecting common target genes for screening purposes is important for improved and personalized cervical cancer screening procedures and cancer diagnostics in the future.

FC21 - Triage of HPV positive women

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#7080

PERFORMANCE OF A 7-TYPE HPV MRNA TEST IN TRIAGE OF HPV DNA PRIMARY SCREEN POSITIVE WOMEN COMPARED TO LIQUID-BASED CYTOLOGY

12 - Triage of HPV positive women

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Background/Objectives: A plethora of data supports HPV-based screening to be the preferred strategy for cervical cancer prevention. The shift to a more sensitive first-line test brings the need for effective triage up for discussion. Currently, most algorithms apply cytology as triage of HPV-DNA-positive women. This study compared the performance of a 7-type HPV-mRNA test to cytology.

Methods: From 2019-01-01, until 2022-12-31, cervical samples from 67,068 women were examined at the University Hospital of North Norway. 36.9% (24,750/67,068) fulfilled the criteria for HPV-DNA primary screening. All positive samples were triaged by cytology and followed up according to national guidelines through October 2023. Additionally, a 7-type HPV-mRNA test was applied. The study endpoint was a histologically confirmed high-grade lesion (CIN2+).

Results: 5.4% (1348/24,750) had positive HPV-DNA test, 99.1% (1336/1348) with valid HPV-mRNA results. 53.4% (713/1336) had abnormal cytology (ASC-US+) and 35.7% (477/1336) had positive HPV-mRNA test. 14.5% (194/1336) had CIN2+. The sensitivity (CIN2+) of cytology versus the HPV-mRNA test was 74.7% (145/194) versus 71.1% (138/194), p=0.49. The specificity was 50.3% (574/1142) versus 70.3% (803/1142), p<0.001. PPV was 20.3% (145/713) and 28.9% (138/477), p<0.001 respectively. The number of colposcopies per CIN2+ detected by cytology and HPV-mRNA test was 4.9 and 3.5.

Conclusions: The 7-type HPV mRNA test was significantly more specific than cervical cytology in the triage of HPV-DNA-positive women. Using this biomarker as the threshold for colposcopy may better balance the benefits and harms of screening.

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#7050

IMPACT OF THE QUALITY OF CERVICAL PAP SMEARS ON REFERRAL RATES AND CLINICAL OUTCOME OF A CERVICAL SCREENING PROGRAM.

12 - Triage of HPV positive women

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Background/Objectives: Since 2017, the Netherlands has a renewed cervical screening program with primary HPV testing and cytology triage after an HPV-positive result. Between 2017 and 2020, 24% percent of the participants have cytological thin-layer preparations of inferior quality, mainly due to lack of endocervical cells and squamous metaplasia (EC-). Each year an 11% increase of EC- Pap smears is evident. To investigate the consequences for the effectiveness of the program, a study was undertaken to relate the quality of cervical smears to follow-up histological outcomes, using data from the Dutch nationwide pathology databank (PALGA).

Methods: A cohort of 146,000 consecutive participants of the screening program between 2017 and 2020 was selected with at least 1.5 year of follow-up after an HPV-positive result. All cytological reports contained an assessment of the quality of the specimens according to the Dutch KOPAC system. Within this cohort, two groups were defined, i.e. EC- and EC+ samples. Comparisons between groups were statistically analysed with chi2-tests. Analyses were repeated for 3 age cohorts (30-39,40-49,50+).

Results: The referral rate was higher in the EC+ group compared to the EC- group (42% ve 27%, p<.0001). The CIN2/3 and cancer rate were also higher in the EC+ group than in the EC- group (CIN2/3: 23% vs 12%, p<.0001, cancer: 0.47% vs 0.21%, p0.1). Similar associations were found in all age cohorts.

Conclusions: The sensitivity of the cytology test for CIN2+ and CIN3+ outcomes is higher in specimens classified as EC+ compared to EC- and warrants measures to increase the quality of cervical specimen collection for cytology. Although the overall quality of cytology testing in the Netherlands was already of a high standard, we now have tools at hand to further improve the quality of cytology results for all participants.

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#6867

ASSESSMENT OF ASCCP CIN3+ RISK-GUIDED TRIAGE: A STUDY ON 125,750 CHINESE WOMEN

12 - Triage of HPV positive women

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Background/Objectives: The American Society of Colposcopy and Cervical Pathology (ASCCP) released updated guidelines for managing cervical cancer screening abnormalities in 2020. These guidelines proposed a statistical model to estimate the immediate risk of cervical intraepithelial neoplasia 3+ (CIN3+) based on the Kaiser Permanente Northern California (KPNC) cohort, a ten-year prospective study involving 1.5 million patients. According to these guidelines, CIN3+ risk can be estimated using historical and current screening data to provide triage recommendations. This risk-based approach is now available on http://www.asccp.org and has been proven cost-effective and applied successfully in other American cohorts. However, it is crucial to access the applicability of these guidelines in Chinese cohorts due to variations in human papillomavirus (HPV) prevalence, lifestyles, and other risk factors unique to China.

Methods: We analyzed screening data from 125,750 Chinese women, focusing on 10,055 cases with confirmed pathology diagnoses. Data were obtained from nine large-scale screening projects conducted between 2006 and 2019. Using the online estimation model, the immediate CIN3+ risk and triage recommendations were determined for each case based on the age and HPV genotypes, which was compared with the pathology diagnosis for the assessment.

Results: Among 10,055 cases, 9,495 were included into the analysis after excluding 560 cases without online recommendations. The majority recommended for return in 5 years showed ≤ CIN1 pathology (99.4%). Similarly, those recommended for return in 3 or 1 year exhibited ≤ CIN1 pathology, with rates of 98.7% and 97.0%, respectively. Cases advised for colposcopy or aggressive procedures had a ≥ CIN3 diagnosis rate of 15.6%. In cases with CIN3+, 95.8% received colposcopy or expedited treatment. A comparison with the ASCCP-recommended immediate CIN3+ risk threshold (4%) revealed a threshold of 4.85% in our analysis, with an AUC of 0.926, sensitivity of 87.1%, and specificity of 82.5%. The new guidelines significantly reduced colposcopic referrals without compromising CIN3+ detection.

Conclusions: Despite population differences, our study demonstrated a consistency between ASCCP recommendations and real-world pathology results in Chinese women. The risk-based guidelines, originally developed in the U.S., proved effective in the Chinese context. However, considering the study's limitations, cautious interpretation of these results is necessary.

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Triage options of hpv positive women: a real world study from China

12 - Triage of HPV positive women

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Background/Objectives: Improvement in managing HPV positive women is urgently needed to maximize the screening benefits while minimize the harm. We aimed to evaluate the clinical performance of multiple triage strategies in comparison with cytology triage among high-risk (hrHPV) positive women from rural China.

Methods: A total of 2188 women from Kashi, China were screened with HPV DNA testing and liquid-based cytology. Any positive results triggered colposcopy and biopsy if indicated. Here, we focused on hrHPV positive women either by DH2 HPV test (a hybrid capture-based HPV test targeting 14 hrHPV types) and a sureX HPV test (a PCR-based HPV test targeting 14 hrhpv types and 9 low-risk HPV types) and evaluated the sensitivity, specificity and predictive values of the multiple triage algorithms to detect cervical intraepithelial neoplasia grade 2 or higher (CIN2+), using the histology diagnosis as the gold standard.

Results: A total of 252 (11.9%) and 258 (12.2%) women were tested hrHPV positive by DH-2 and sureX HPV test, respectively. Among a single triage strategies, the sensitivity of reference strategy (hrHPV with triage of cytology (ASC-US+)) were 84.2% and 86.7% for triage of DH2 positive and sureX HPV positive women. HPV16/18, cytology (LSIL+), p16/ki67, careme methylation (targeting the host cell gene EPB41LE and HPV16/18 DNA L1/L2 regions) showed a slightly lower sensitivity (78.9-80.0%), with higher specificity and more efficient colposcopy for CIN2+ than cytology (ASC-US) triage of hrHPV positive women either by DH2 or sureX HPV. While achieving the highest specificity (97.5%), gonganli methylation test (targeting the host gene ASTN1、DLX1、ITGA4、RXFP3、SOX17、ZNF671) showed the lowest sensitivity at 75%. Triage strategy with extended genotyping using HPV 16/18/31/33/45 achieved significantly higher sensitivity (93.3%) and comparable specificity (95.3%) compared to the reference triage. Regarding to the triage strategies with a combination of two tests, HPV 16/18 genotyping with reflex cytology (ASC-US+) demonstrated significantly increased sensitivity at 94.7% at the cost of decreased specificity at 94.3% compared to the reference strategy (ASC-US+ only). While, HPV 16/18 genotyping with reflex p16/ki67 or cytology LSIL+ achieved comparable sensitivity (86.7%) and specificity (~95%). Of note, both methylation triage tests showed the highest positive predictive values at ~20%, and the extended genotyping with HPV 16/18/31/33/45 showed the highest AUC value (0.942).

Conclusions: Our study demonstrates the several promising alternatives for cytology triage, some superior in sensitivity such as HPV16/18 genotyping with reflex cytology, extended genotyping (HPV16/18/31/33/45), some superior in specificity such as cytology triage with LSIL threshold, HPV16/18 genotyping, and methylation. Among them extended genotyping as the most easy-to-perform (merged into primary HPV screening) and objective methods, might be the most promising alternatives for cytology triage, especially for the areas that lack of sufficient well-trained cytologists. Different settings need to consider the resource availability and balance the benefits and harms of different screening algorithms when incorporating them into practice.

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SHOULD WE USE RISK SELECTION TESTS FOR TYPE 16/18 POSITIVE CASES: COMPARISON OF p16/Ki67 AND CYTOLOGY

12 - Triage of HPV positive women

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Background/Objectives: 13-14 high-risk types of human papillomavirus (HRHPV) are strongly associated with cervical cancer development, with the highest risk for types 16 and 18 [1-3]. The introduction of primary HPV-based cervical cancer screening with its high sensitivity, raised questions of need for triage tests to determine the risk and establish an optimal management. Major screening abnormalities in pre-colposcopic stage are test results that imply direct referral to colposcopy (and/or expedited treatment - treatment without colposcopic biopsy and histology result) without additional high-grade squamous intraepithelial lesions or worse (HSIL+) risk selection tests [4-5]. The American Society for Colposcopy and Cervical Pathology 2019 Consensus Guidelines based on primary HRHPV test with limited HPV 16/18 genotyping advise colposcopy after reflex cytology in all HPV type 16 and/or 18 positive cases (HPV 16/18+) [6,7]. However, the U.S. Food and Drug Administration indicates a reflex p16/Ki67 dual-stain (DS) in HPV 16/18+ patients together with the physician's evaluation and professional guidelines as an acceptable management [8]. Currently, both clinically validated HSIL+ risk selection tests (reflex cytology and reflex DS) are being compared for use in primary HPV-based screening, but there is still no sufficient data available for comparison of their performance.

Methods: Among 30,066 liquid-based cervical cancer screening tests results, a group of 332 women, aged over 25 years old, was selected with available HRHPV test results with limited 16 and 18 genotyping, liquid-based cytology, DS and histology results from standardized colposcopy with biopsy. In HPV 16/18+ cases, three triage approaches (M1 - a reflex cytology was performed in all positive cases; M1A - a reflex cytology was used in all positive cases combined with DS done as a second triage test in patients with NILM, ASC-US and LSIL results, while patients with ASC-H or worse results were referred to colposcopy and/or expedited treatment; M2 - a reflex DS was performed in all positive cases) were retrospectively analyzed. PPV for detection of HSIL+ was calculated for all triage models.

Results: Both triage models with DS used (reflex cytology followed by DS, and reflex DS alone in all cases) had significantly higher PPV for HSIL+ than strategy with reflex cytology alone (44.2%/45.7% vs. 28.3%; pinf0.0001). However, there was no statistically significant difference in PPV between models with DS performed, M1A and M2 (44.3% vs. 45.7%; p=0.0843). In models with DS less colposcopies were required (95/92 vs. 152) and less colposcopies were needed per HSIL+ detection (2,26/2,19 vs. 3,54). Only 1 HSIL+ case was missed in both models with DS incorporation.

Conclusions: p16/Ki67 dual-stain may be an effective alone or combined with cytology triage test to detect HSIL+ in patients with major screening abnormalities in primary HPV-based cervical cancer screening. The use of DS as a triage test allows a reduction in number of colposcopy referrals while ensuring safety for the patients. Performing a reflex cytology as a first triage test before DS, improves the strategy by allowing selected cases to be referred to expedited treatment. Further studies are required to confirm these findings.

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#6868

CLINICAL RELEVANCE OF PARTIAL HPV GENOTYPING IN CERVICAL CANCER SCREENING TRIAGE IN FINLAND

10 - HPV screening

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Background/Objectives: Cervical cancer (CC) incidence has significantly decreased due to the national CC screening program in Finland. Currently CC screening is done with human papillomavirus (HPV) primary testing with combined cytology triage testing on women that test HPV-positive. While HPV-test has shown to be highly sensitive, there are concerns regarding its poor specificity, which leads to overdiagnosis and unnecessary screenings that bottleneck the healthcare system. The lack of specificity may be overcome by the introduction of other triage tests such as extended genotyping. In many countries, like Sweden and Norway, the HPV 16 and 18 positive women are directed straight to the colposcopy. In Finland, CC screening with different genotypes has not yet been studied. The aim of this study was to assess whether testing HPV16 and 18-genotypes separately would offer a better specificity for CC screening and thus decrease unnecessary testing in the Finnish population.

Methods: This study included 76 369 women that took part to the Finnish national CC screening program at the city of Tampere and its' surrounding municipalities between the years 2012 and 2023. The partial HPV genotyping for HPV16, HPV18 and other 12 high-risk HPV types combined was done using Abbott RealTime High-Risk HPV test (2012-2020) and Roche Cobas 4800 HPV assay (2021-2023). Information on the follow up of the HPV positive women were retrieved from the hospital charts. The association between partial HPV genotyping results and the detection of cervical precancers at follow-up was assessed.

Results: Among the 5943 HPV-positive women, precancerous lesions were almost two times more prevalent in HPV16 positive women (n=782) compared to overall HPV-positives (27.1% and 13.8%, respectively). Also, with HPV18 (n=294) the precancerous lesions seemed to be more prevalent (16.7%) compared to overall HPV-positive women. Between different age groups the cumulative incidence of HSIL+ was highest among women under 41 years with HPV16 and other high-risk HPV infections. Instead, with HPV18 the cumulative incidence of HSIL was at the same level among the women under 41 years and women 41-51 years. Age group 51+ had the lowest incidence rate for HSIL+ among all the HPV genotypes studied. The overall prevalence of precancerous lesions decreased by age: among the 29-41 years-old it was 16.9%, among the 41- 51 years-old 12.3%, and among the 51 years or older 8.1%, respectively.

Conclusions: Partial HPV16 and 18-genotyping seems to offer an improvement of triage within the Finnish CC screening. It is possible that cervical precancerous lesions might be detected more efficiently, if HPV16 and HPV18 positive women were referred straight to colposcopy. Further investigations on further extended high-risk HPV genotyping should be also evaluated to gain the best possible HPV testing option to the national Finnish CC screening setting.

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#7006

TO TREAT OR NOT TO TREAT; THAT'S THE QUESTION.

12 - Triage of HPV positive women

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Background/Objectives: HrHPV-DNA testing in cervical scrapes is increasingly implemented in cervical cancer screening programs because of its high sensitivity. The downside is the low specificity, which is partially solved by cytology (PAP-staining, LBC), either as triage or as co-test. Despite triage cytology, in the Netherlands rates of overdiagnoses and colposcopy referrals without any findings are 60-70%. CiRNAseq is a targeted RNA next generation sequencing technology that can quantitatively detect thousands of transcripts in hundreds of samples simultaneously (1). The objective of this study is to develop a CiRNAseq-based diagnostic triage test for HPV-DNA positive cervical smears with increased specificity of predicting CIN2+.

Methods: CiRNAseq was performed according to standard procedures on RNA, isolated from hrHPV-DNA positive tested cervical scrapes from the Dutch screening program (n=2,017). The assay was performed with a set of 2,913 molecular inversion probes designed for targeted detection of E2, E6, E6* and E7 RNA from 20 HPV genotypes, and of >600 gene transcripts with a general involvement in cancer development and progression. Clinical metadata were collected with a median clinical follow up time of 7 months. Differentially expressed genes between women with clinical outcome no CIN and CIN1 versus CIN2+ were identified, based on robust statistical analysis. Machine learning was performed on the data to build a model for predicting CIN2+.

Results: Of 277 HPV-DNA positive scrapes with cytology PAP1, in only 26% hrHPVE6_7 RNA was detected (any genotype). These percentages increased to 65% (ASCUS), 81% (LSIL) and 87% (HSIL). Based on HPV-RNA sequences, HPV genotypes could be annotated on the individual level and their gene transcripts quantified. Concordance was 97% with COBAS-reported HPV genotypes (HPV16, 18 and other). A number of cellular biomarkers was identified that discriminate CIN3 from cancer with high significance, among which were biomarkers involved in, e.g. inflammation, cell cycle, stem cell markers and proteases. Machine learning on the data resulted in a model that predicts CIN2+ with a specificity of 0.75 (2).

Conclusions: CervicaDx can be used to detect HPV oncogene transcriptional activity with simultaneous detailed HPV genotyping and detection of biological pathways that are induced by HPV oncogenes or spontaneously activated on the way to cancer. The high throughput character of the test makes it suitable for cost-effective testing in a centralized setting. By combining HPV expression data with human gene expression data, sensitivity is combined with an enhanced specificity with the potential of unburdening healthcare systems.

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#6766

EVALUATION OF HOST GENE METHYLATION AS A TRIAGE TEST FOR HPV POSITIVE WOMEN IN A REAL-WORLD CLINICAL SETTING

12 - Triage of HPV positive women

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Background/Objectives: High-risk (HR) human papillomavirus (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, as most positive cases represent prevalent HPV infection and will not develop relevant disease. 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 objective of this study was to evaluate the impact of a strategy of triage of all HR-HPV positive cases with a methylation assay (GynTect® [ASTN1, DLX1, ITGA4, RXFP3, SOX17, and ZNF671 DNA methylation markers]) in an organized cervical cancer screening program, in comparison to routine standard of care, as well as the possible influence of the variation of the rate of HPV16/18 in its performance.

Methods: Cohort study with consecutive women referred for colposcopy in an organized cervical cancer screening program had colposcopy, biopsies and repeated HPV testing,. The ones that remained HPV positive at the time of colposcopy were tested with a panel of DNA methylation markers. The performance of the test was evaluated and compared to standard practice.

Results: The DNA methylation marker test had a sensitivity and specificity for CIN2+ of 60.8% (49.1-71.6%) and 88.4% (83.2-92.5%), respectively. For CIN3+, it was of 78.0% (64.0-88.5%) and 86.0% (80.8-90.2%), respectively. The rate and level of methylation positively correlated with the severity of disease. The use of methylation reduces the referral for colposcopy to 25.5%, while detecting 78.0% of the CIN3+ cases. Referral of all HPV16/18 positive cases and triaging the other high risk HPV positive cases with methylation, detects 90.0% of the cases of CIN3+, while reducing the number of referrals to 43.2%. The variation in the rate of HPV16/18 does not relevantly affect the performance of the methylation panel.

Conclusions: The GynTect® methylation test has a high sensitivity and specificity for CIN3+ and significantly reduces the rate of referrals for colposcopy. The level of methylation positively correlated with the severity of disease. A model in which all cases that test positive for HPV16/18 sent directly to colposcopy and the other HR-HPV sent after triage with methylation, may be the best option to reduce the number of referrals for colposcopy, while detecting 90% of the cases of CIN3+.

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#6937

Could HLA-DPB2 rs4713607 and rs3117039 polymorphisms detection benefit HR-HPV triage based on HPV primary screening for cervical cancer?

12 - Triage of HPV positive women

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Background/Objectives: Effective triage of high-risk human papillomavirus (HR-HPV) women is warranted to avoid unnecessary referral and overtreatment. Therefore, the study aimed to evaluate the performance of the Single-Nucleotide Polymorphisms (SNPs) test in triaging HR-HPV (+) women.

Methods: The study is a multi-center study including 2628 women from Fujian, and 1999 women from Shenzhen. All participants underwent PCR-RDB HPV test, and some patients underwent cytology and pathology test. We designed kompetitive allele-specific PCR (KASPTM) methods to determine the association of single-nucleotide polymorphisms (SNPs) with HPV infections and cervical cancer, and evaluated the triage efficacy. The sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) between HPV primary test and HPV & SNP test were calculated.

Results: We find that HLA-DP rs4713607 showed a higher risk of HPV infection (OR=2.51, P□0.001) and cervical cancer (OR = 1.61, P = 0.02). HLA-DP rs3117039 showed a lower risk of cervical cancer (OR = 0.48, P = 0.01). Besides, HPV & SNP (rs4713607 AA or rs3117039 AG/GG) test achieved comparable sensitivity with HPV primary test in the detection of CIN2+ (93.06% vs 93.56%) and CIN3+ (93.39% vs 93.39%). Although there was no statistically significant difference, the HPV & SNP test dictated a slightly higher specificity compared to that of the HPV primary test in the detection of CIN2+ (42.98% vs 38.94%) and CIN3+ (37.17% vs 33.63%). More importantly, HPV & SNP test reduced colposcopy referral rate (34.97% vs 36.59%) and the cost of the detection of CIN3+(¥ 6081 vs ¥ 6139).

Conclusions: The SNP (rs4713607 AA or rs3117039 AG/GG) test may serve as a triage test for HR-HPV (+) women, especially in developing countries with large populations, because the test had comparable sensitivity, slightly higher specificity and lower cost of the detection of CIN3+.

FC24 - Immunology, immuno-therapy, treatment & microbiome

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#6818

DEFINING HPV16 AND HPV18 SEROPOSITIVITY THRESHOLDS IN YOUNG UNVACCINATED WOMEN USING TRAJECTORY MODELLING

19 - Serology

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Background/Objectives: Given low seroconversion rates following HPV infection, estimating HPV seroprevalence using fixed external cut-offs may lead to classification errors. The use of data-driven approaches to distinguish heterogeneity in seroreactivity may be more appropriate for setting a seropositivity threshold in the presence of repeatedly measured HPV seroreactivity over time. We evaluated the use of finite mixture modelling (FMM) and group-based trajectory modelling (GBTM) on cross-sectional and longitudinal serological data, respectively, among unvaccinated HPV-exposed women to define study-specific HPV16 and HPV18 seropositivity thresholds.

Methods: We used data from 399 unvaccinated sexually active women (mean age: 21 years) in Montreal, Canada, who were enrolled (2005-2011) in the HPV Infection and Transmission Among Couples Through Heterosexual Activity (HITCH) cohort. Participants provided blood samples at 6 study visits spanning 2 years. Multiplex serology was used to measure antibody titers specific to bacterially expressed L1 glutathione S-transferase (GST) fusion proteins of HPV16 and HPV18. Primary serum antibodies were quantified as median fluorescence intensity (MFI). We applied separate two-component FMMs and GBTMs for baseline cross-sectional and repeated measures of antibody titers, respectively, assuming various data distributions (FMM: normal, skew normal, skew T; GBTM: zero-order, linear, quadratic, cubic), to identify seronegative and seropositive women for HPV16 and HPV18 antibodies. We then generated study-specific seropositivity thresholds as 5 standard deviations (SD) above the mean baseline seronegative antibody titer, as previously done to create fixed cut-offs (1). We evaluated the agreement (kappa) and performance (Youden index) of each study-specific threshold relative to external reference cut-offs (HPV16: 422 MFI; HPV18: 394 MFI), derived from Korean women aged 15-29 years with evidence of HPV non-exposure (had reportedly never engaged in penetrative sexual intercourse nor had evidence of genital HPV DNA for the tested HPV types) (1).

Results: Study-specific thresholds based on FMM ranged from 40.8 to 58.4 MFI for HPV16 and from 87.0 to 150.0 MFI for HPV18. Corresponding thresholds based on GBTM ranged from 304.9 to 305.7 MFI and from 222.8 to 344.3 MFI. Seroprevalence estimates using study-specific thresholds were higher than those based on external reference cut-offs. Agreement between study-specific thresholds based on FMM and external reference cut-offs were no more than moderate for HPV16 (range 0.26-0.46) and HPV18 (range 0.20-0.56). Conversely, agreement based on GBTM was high; the corresponding values were 0.92 - 0.92 and 0.82 - 0.99. Since sensitivity estimates for study-specific thresholds relative to external reference cut-offs were all equal to 100%, the Youden index values were equivalent to the specificity estimates; these ranged from 63.3% to 80.8% for HPV16 and from 55.9% to 86.7% for HPV18 FMM thresholds. Youden index values for GBTM-derived HPV16 and HPV18 thresholds were 98.3 - 98.3% and 95.9 - 99.7%, respectively.

Conclusions: Our findings support the use of FMM and GBTM for cross-sectional and longitudinal continuous serological data, respectively, to derive study-specific thresholds and seroprevalence estimates without requiring prior classification rules. Notwithstanding, GBTM thresholds generally had stronger agreement and higher performance than FMM thresholds, relative to reference cut-offs.

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#6825

THE HPV SEROLOGY STANDARDIZATION INITIATIVE: KEY ACHIEVEMENTS

19 - Serology

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Background/Objectives: Protection against Human Papillomavirus (HPV) infection after vaccination is believed to be mediated by HPV-specific antibodies. However, the lack of standardized assays, procedures, and qualified critical reagents accessible to the scientific community has precluded the comparison of different studies evaluating immunogenicity of HPV vaccines. With an increase in the number of trials relying on immunobridging for approval of new dosing schedules or vaccine formulations, there has been an increased interest in serology standardization 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, working with the National Cancer Institute (USA) and The Bill & Melinda Gates Foundation to lead standardization and harmonization efforts for HPV serological testing within vaccine trials. The main goal has been to expedite serology assay standardization by assisting with the development of serology standards for HPV-6, 11, 31, 33, 45, 52, and 58, as well as testing samples from several one dose vaccine trials and immunobridging studies. Furthermore, assay standard operating procedures are also accessible on our laboratory website (https://frederick.cancer.gov/research/vaccine-immunity-and-cancer-directorate/hpv-serology-laboratory).

Results: HPVSL co-developed WHO International Standards for HPV-6, 11, 31, 33, 45, 52, and 58, which are available through the NIBSC website. The laboratory also developed secondary standards calibrated against available WHO International Standards, reference HPV Virus-Like Particles (VLP) and a serology-based proficiency panel for the 9 HPV types included in licensed vaccines. These materials have been shared with many serology laboratories. Forty-two material transfer agreements or collaborative agreements have been executed with different organizations. HPVSL has also transferred technology and has helped establishing various serology laboratories across the globe.

Conclusions: Achievement of these aims has promoted standardization and serology testing capabilities globally. These efforts enable comparisons of data across different HPV vaccines and different studies and will facilitate vaccine development and implementation of new vaccine recommendations.

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#7115

TIME-RESOLVED FLUORESCENCE (TRF) FOR TOTAL IGG AND HPV16-SPECIFIC ANTIBODY DETECTION IN FIRST-VOID URINE AND SERUM: A COMPARATIVE STUDY

05 - Immunology

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Background/Objectives: Detection of human papillomavirus (HPV) specific antibodies (Abs) in self-collected, non-invasive first-void urine (FVU) samples, would present a major advantage for monitoring HPV infection and HPV vaccine impact. Recent studies have described three immunoassays for the detection of HPV-specific Abs in FVU: one bead-based immunoassay, GST-L1-MIA, and two VLP-based multi-spot ELISAs, M4ELISA and M9ELISA. These assays have shown promising results with FVU samples. However, the Ab concentrations in FVU samples are frequently very close to the detection limit of these assays, which makes distinction between uronegative and low positive results sometimes challenging. Therefore, we evaluated the potential of a novel HPV16-specific Dissociation-Enhanced Lanthanide Fluorescent Immunoassay (DELFIA) and compared it to the already existing immunoassays. DELFIA is based on time-resolved fluorescence (TRF) and uses the properties of lanthanide fluorescent compounds to achieve a highly sensitive result. We also compared two assays to quantify the total human IgG in the samples as this may be applied in the future to normalize the HPV Ab levels in FVU.

Methods: In this study, paired serum and FVU samples from two cohorts of healthy female volunteers were analyzed. For cohort 1, samples from 53 female volunteers were included, of which 36 were fully vaccinated with a bivalent or quadrivalent vaccine (NCT02714114). For cohort 2, samples from 57 female volunteers, collected before and at two timepoints after complete nonavalent vaccination, were included (NCT03542227). Total human IgG concentrations were measured on all samples using the homogeneous TRF (HTRF®) human IgG kit and the BioPlex ProTM Human Isotyping Assay. HPV-specific Ab concentrations were determined using our in-house developed HPV16-specific DELFIA. Correlation between the two total IgG results and their potential as a normalization parameter will be assessed. For cohort 1, HPV16-specific Ab results were compared to available M4ELISA and GST-L1-MIA results, and for cohort 2 to M9ELISA results.

Results: Very strong correlations of the HPV Ab levels determined by GST-L1-MIA, M4ELISA, and DELFIA were seen for cohort 1; between GST-L1-MIA and DELFIA for FVU ($Rs = 0.79$, $p < 0.001$) and serum ($Rs = 0.82$, $p < 0.001$), and between M4ELISA and DELFIA for FVU ($Rs = 0.96$, $p < 0.001$) and serum (0.95, $p < 0.001$). For cohort 2, very strong correlations of HPV Ab levels were found between DELFIA and M9ELISA for both FVU ($Rs = 0.94$, $p < 0.001$) and serum (0.95, $p < 0.001$). The correlation of total IgG levels between the BioPlex ProTM Human Isotyping Assay and the HTRF assay is moderate in FVU samples ($Rs = 0.42$, < 0.001), but very weak and not significant for serum samples ($Rs = -0.06$, $p = 0.466$).

Conclusions: The result of the DELFIA measuring anti-HPV16 Abs is comparable to the M4ELISA, M9ELISA, and the GST-L1-MIA assay. Nonetheless, we were unable to show the benefits of the time-resolved fluorescence (TRF) in combination with the lanthanide compounds. However, the DELFIA assay's good sensitivity, high throughput, and possibility for multiplexing make it a potential assay for testing in large-scale epidemiological or follow-up studies. The correlation between the two assays measuring total human IgG is not significant for serum samples. This unexpected observation, only seen for serum samples, warrants further investigation.

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#7138

RELATIONSHIP BETWEEN MALE HPV SEROSTATUS AND FEMALE HPV INFECTION AMONG HETEROSEXUAL COUPLES

19 - Serology

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Background/Objectives: Research suggests that HPV antibodies acquired from natural infection are modestly protective against subsequent homotypic infections (i.e., of the same HPV type) among women but not men. However, it is unclear whether naturally acquired antibodies in males reduce HPV transmission to their female partners. We evaluated the risk of HPV acquisition among females, dependent on their male partner's serostatus.

Methods: We used data from 386 heterosexual unvaccinated couples (females aged 18-24, males 18+) in Montreal, Canada, who were enrolled (2005-2011) in the HPV Infection and Transmission Among Couples Through Heterosexual Activity (HITCH) cohort. Couples attended study visits (females: 1 baseline, 5 follow-ups at 4, 8, 12, 18, and 24 months; males: 1 baseline and 1 follow-up at 4 months) for collection of blood and genital (self-collected vaginal; nurse-collected penile and scrotal) samples. HPV DNA status was detected by polymerase chain reaction (PCR; Linear Array HPV genotyping assay). Multiplex serology was used to measure antibody titers specific to bacterially expressed L1 glutathione S-transferase (GST) fusion proteins of 14 HPV genotypes (HPVs 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 58, 59, and 68). All analyses were conducted at the HPV level (i.e., type-specific), with the exposure of interest being male partner's HPV serostatus and the outcome being female HPV positivity. Since male baseline antibody titer distributions were unimodal, we used type-specific median antibody titers as the cut-off to define male partner-HPV serostatus (high/low) for each of the 14 HPV types. We correspondingly categorized females as 14 monotypic female-HPV units into the two strata of partner-HPV serostatus. We estimated the rate ratios (RR) and 95% confidence intervals (CI) of the females' HPV infection rates over the follow-up period (study visits 2+) according to partner-HPV serostatus for 4 analytical scenarios: 1) episodic infections among all female-HPV units (least restrictive), 2) episodic infections among female-HPV units of HPV-positive males at baseline (less restrictive), 3) episodic infections among HPV-negative female-HPV units of HPV-positive males at baseline (moderately restrictive), and 4) incident infections among HPV-negative female-HPV units of HPV-positive males at baseline (most restrictive).

Results: Using the least restrictive scenario, the rate of episodic vaginal HPV infection did not differ between female-HPV units having high partner-HPV serostatus and female-HPV units having low partner-HPV serostatus (RR=1.09, CI=0.96-1.25). Similarly, no significant differences were observed using the less restrictive scenario (RR=1.02, CI=0.83-1.27). The RRs using the moderately restrictive and most restrictive scenarios were 1.83 (95% CI=1.05-3.26) and 1.26 (95% CI=0.59-2.77), respectively.

Conclusions: Overall, the evidence of a relationship between a male partner's serostatus and the female's risk of infection is weak. Naturally acquired HPV antibodies in males likely do not provide additional protection for their female partners. Increased rates of HPV infection among females with high partner serostatus may be confounded by sexual behaviours/history, which will be explored in future studies.

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#6865

A pre-existing coordinated immune response is pivotal to treatment response to imiquimod in primary and recurrent vulvar high-grade squamous intraepithelial lesions

08 - Immunotherapy - Immuno-oncology - New treatments

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Background/Objectives: Imiquimod has been proven to be a safe and effective form of topical immunotherapy as a non-invasive alternative to surgery for treatment of vulvar high-grade squamous intraepithelial lesions (vHSIL), with complete response rates up to 80% [1]. Previous research shows that response to imiquimod therapy in primary vHSIL is related to a pre-existing coordinated immune response [2]. Moreover, in cervical HSIL a biomarker based on the pre-treatment immune infiltrate can predict the response to imiquimod treatment [3]. The aim of this study was to identify an immune profile predicting therapy responses to imiquimod in vHSIL. Furthermore, we performed an in-depth analysis of the tumor microenvironment of vHSIL to evaluate the immunologic differences between primary and recurrent vHSIL in relation to therapy responses to imiquimod.

Methods: Pre-imiquimod treatment vHSIL biopsies of 38 patients included in the PITVIN trial [1] were stained with two multispectral immunofluorescence panels to identify pre-existing T cell and myeloid cell immune composition. Slides were scanned with the Vectra multispectral imaging system and automatically phenotyped and counted using QuPath [4] analysis software.

Results: The immune microenvironment of complete responders (CR) to imiquimod show a coordinated influx of CD14+ inflammatory myeloid cells and type 1 CD4+ and CD3+CD8+ T cells, both in and between epithelial and stromal compartments. The persistent lesions (PR) did not display such a coordinated immune response. Importantly, recurrent vHSIL are able to respond to imiquimod in a comparable manner to primary vHSIL if the pre-existent immune infiltrates show the coordinated influx of inflammatory myeloid cells and type 1 T cells.

Conclusions: In conclusion, this study emphasizes the pivotal role of a coordinated influx of type 1 T cells and myeloid cells in achieving a complete response to imiquimod therapy in vHSIL, irrespective of primary or recurrent vHSIL. Topical imiquimod therapy is able to enhance the pre-existing pro-inflammatory immune infiltrates to induce lesion regression, however if the pre-existing immune microenvironment does not exhibit this coordinated influx of pro-inflammatory cells regression of the lesion is less probable. At present we are analyzing predictive biomarkers in this context via which we expect to personalize patient selection for imiquimod and other therapeutic options, and to improve patient outcomes in vHSIL management.

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#6945

EVALUATION OF T- AND B-CELL IMMUNITY AFTER HPV VACCINATION BY MULTI-COLOUR ELISPOT ON A SINGLE CELL LEVEL

05 - Immunology

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Background/Objectives: Human papillomaviruses (HPV) are the causative agents for the great majority of anogenital and oropharyngeal cancers as well as anogenital warts [1-3]. Safe and highly protective HPV vaccines have now been available for more than a decade. Vaccination against Human Papillomaviruses (HPV) with virus-like particles (VLPs) consisting vaccines is recommended in Germany for children from nine to fourteen years [4-6]. The aim of this work was to evaluate mechanisms of the T- and B-cell mediated immunity and a putative cross-reactivity against L1-VLPs of the HPV-Types 6, 11, 16 and 18 by fluorescent Enzyme-Linked-ImmunoSpot (EliSpot) Assay [7].

Methods: To evaluate T-cell mediated immunity, IFNy, IL-2 and IL-5 were simultaneously detected in one well. Our underlying hypothesis says, that fully vaccinated donors should express the most IFNy, whereas partly vaccinated donors should express less IFNy when stimulated with VLPs, in contrast to almost no IFNy expression in non-vaccinated donors. The individual T-cell reaction has been monitored over time to elucidate dynamic changes in T-cell patterns. Therefore, IFN-y (active immune response), IL-2 (memory immune response) and IL-5 (transient secretion during vaccination regime) were detected. HPV specific B-cells were detected using fluorescently labeled VLPs from HPV types 6, 11, 16 and 18 to investigate potential cross-reactivity.

Results: For HPV- reactive T-cells, this was proved with the EliSpot assays and the groups were clearly distinguishable. Also, fully vaccinated donors showed the highest IL-2 expression. Furthermore, IL-5 expression was only detectable in vaccinated donors, which indicates functional T helper 2 T-cells against VLPs from HPV 11, 16 and 18. For evaluating functional B-cells, and cross-protection potential of the different available vaccinations, VLPs from HPV 6&11 (low-risk-mix) and 16&18 (high-risk-mix) were labeled with different fluorescent dyes to evaluate B-cell numbers for both mixes in one well in parallel. We were able to detect a dose-dependent spot number for all HPV types in vaccinated donors which were for all types higher than for non-vaccinated donors. Also, B-cell reactions to the low-risk pool from patients exclusively vaccinated with high-risk strains (Cervarix) could be observed. This indicates a cross-protective cellular immune reaction after vaccination.

Conclusions: The range for an effective vaccination should be confirmed by further investigations with more and well characterized donors. Furthermore, these trials could facilitate the detection of significant differences between vaccinated and non-vaccinated donors and open the possibility to define effectiveness of vaccination for cellular immune responses.

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#6630

Effects of HPV16 E7 protein on the immune microenvironment of HPV-associated tumors by inhibiting the type I interferon signaling pathway

08 - Immunotherapy - Immuno-oncology - New treatments

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Background/Objectives: The component and infiltration level of immune cells in tumor immune microenvironment are important factors for tumor immunotherapy. Human papillomavirus (HPV) oncogenic protein E7 plays an important role in tumor development and immune escape. However, the role of E7 protein on tumor immune microenvironment remains to be studied. The research explores the mechanism of HPV16 E7 affects the tumor immune microenvironment and immunotherapy to promote the exploration of HPV-related tumor immunotherapy strategies.

Methods: The RNA-seq and immune infiltration data of head and neck cancer and cervical cancer were downloaded from the public databases TCGA and TIMER2.0. The relationship between the HPV16 E7 gene expression and immune cells infiltration of tumors was analyzed. HPV16 E7 in cell lines was overexpressed with lentivirus. RNA-seq, Realtime PCR, Western Blot, immunohistochemistry, flow cytometry, co-culture experiments and animal models were used to explore the mechanisms of HPV16 E7 affecting tumor immune cells infiltration and immunotherapy.

Results: Through TCGA and TIMER2.0 data analysis, it found that the expression of HPV16 E7 was correlated with tumor immune cells infiltration level in cervical cancer and head and neck cancer, and samples with high E7 expression showed decreased microenvironment score and immune score. The infiltration levels of B cells, CD8+ T cells and NK cells decreased in head and neck cancer with high expression of E7. B cell infiltration level decreased in E7 high expression cervical cancer. In vivo, it was found that in E7-overexpression subcutaneous tumors in mice, the infiltration of CD8+ T cells decreased, and the T regulatory cells (Tregs) and M2 macrophages infiltration level increased, at same time, the treatment response to PD-1 inhibitor was poor. E7 down-regulated the expression of type I interferon (IFN-I), TLR9 and STING . In vivo, TLR9 agonist CpG oligonucleotide (CpG) and STING agonist MSA-2 were used in tumor-bearing mice, which enhanced the therapeutic effect of PD-1 inhibitor and improved the infiltration level of CD8+ T cells.

Conclusions: The expression of HPV16 E7 is related to the level of immune cell infiltration in tumors. HPV16 E7 inhibits the expression of IFN-I by down-regulating TLR9 and STING, leading to changes in tumor immune microenvironment, thereby inhibiting tumor immunotherapy response. This study explores the mechanism by which the HPV16 oncogene E7 affects immune cell infiltration and immunotherapy, providing new ideas for immunotherapy strategies for HPV-related cancers.

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#6949

RESULTS OF THE MULTICENTER STUDY ON LOCAL CARBOXYMETHYL BETA-GLUCAN AND POLYCARBOPHIL TREATMENT IN HIGH-RISK HPV (PCR+) PATIENTS.

08 - Immunotherapy - Immuno-oncology - New treatments

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Background/Objectives: The lack of data in the Spanish population and in real clinical practice using this medical device (MD) prompted us to conduct the present study to assess the effectiveness of local treatment with carboxymethyl beta-glucan and polycarbophil. This is the first study in Spain involving over 500 High Risk (HR) HPV+ patients, comparing local treatment to a control group. While there have been four published studies on the Italian population with this MD, none have been conducted in a real clinical practice. The goal is to evaluate the effectiveness of this treatment in achieving HR HPV negativization by PCR in the Spanish population.

Methods: The lack of data in the Spanish population and in real clinical practice using this medical device (MD) prompted us to conduct the present study to assess the effectiveness of local treatment with carboxymethyl beta-glucan and polycarbophil. This is the first study in Spain involving over 500 High Risk (HR) HPV+ patients, comparing local treatment to a control group. While there have been four published studies on the Italian population with this MD, none have been conducted in a real clinical setting. The goal is to evaluate the effectiveness of this treatment in achieving HR HPV negativization by PCR in the Spanish population. Favourable opinion of the CEIC Quirónsalud-Catalunya Hospital Group on 28 July 2022

Results: The average age of participants was 38.6 years in the treatment group and 34.5 years in the control group. In the treatment group, both age and the number of pregnancies were statistically higher, whereas physical activity was statistically higher in the control group. Other factors such as tobacco use, the number of sexual partners, years of HPV persistence, and vaccination were statistically balanced between the two groups. Notably, 44% of participants were vaccinated at the study's commencement. The primary objective was to assess the effectiveness of local treatment with carboxymethyl beta-glucan and polycarbophil in achieving HPV negativity in patients with normal cytology/ASCUS/LSIL (CIN1) based on HPV PCR results. The study revealed that 50.1% of HPV+ patients achieved complete negativity at 6 months with treatment, compared to 24% in the wait&see group. This was a statistically significant difference ($p<0.0001$). When considering total or partial HPV negativity (at least one genotype), 58.3% of patients achieved complete or partial negativity at 6 months in the treatment group, as opposed to 43.3% in the wait&see group ($p=0.0073$). Focusing on HPV-16, it was present in 20.6% and 20.9% of the control and treatment groups, respectively. The negativization of HPV-16 was 50.7% in the treatment group, compared to 9.2% in the wait&see group, making it 5 times more effective ($p=0.0291$). Notably, ectopy disappeared in 12.6% of the treatment group compared to 6.4% in the control group ($p<0.0001$).

Conclusions: These findings align with results from previous publications involving this medical device. We can confidently conclude that this treatment is effective in achieving HR HPV test negativization after 3 months, which is twice as effective as wait&see ($p<0.0001$) at 6 months. Consequently, we have a therapeutic option to consider for patients with high-risk HPV, particularly for those who are genotype 16 and over 35 years of age, as it provides both efficacy and speed.

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#6810

Treatment with the demethylating agent decitabine represents a promising novel therapeutic concept for HPV-transformed lesions at the vulva

08 - Immunotherapy - Immuno-oncology - New treatments

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Background/Objectives: Vulvar intraepithelial neoplasias (VIN) and vulvar squamous cell carcinomas (VSCC) are caused by infection with oncogenic human papillomavirus (HPV) types in about 90 % and 20 % of cases, respectively. From studies on cells of the uterine cervix, it is known that expression of the HPV oncoproteins E6 and E7 is tightly controlled by the HPV protein E2 in non-transforming stages of HPV infection. Hypermethylation of the E2 binding sites (E2BSs) within the HPV genome represents an important mechanism how this regulatory mechanism can be disrupted, resulting in substantial E6/E7 overexpression and consequent uncontrolled cell proliferation, which may trigger the development of (pre-)cancerous lesions. Treatment with demethylating agents, such as the DNA methyltransferase 1 inhibitor decitabine, can reverse this aberrant hypermethylation, representing a promising new treatment concept against HPV-transformed lesions. Only few studies analysing epigenetic alterations during carcinogenesis at the vulva have been conducted to date. The aim of this study is to analyse distinct methylation patterns within the HPV and host genomes and assess the therapeutic potential of the demethylating agent decitabine on HPV-transformed cells at the vulva.

Methods: Twenty-four HPV-induced (i.e. HR-HPV DNA-positive and p16INK4a-positive) VIN and nine HPV-induced VSCC specimens were analysed for the expression of DNA methyltransferase 1 by immunohistochemistry. From the same samples, the lesion areas containing transformed cells were specifically isolated by manual or laser microdissection, and methylation at the viral E2BSs 1, 3 and 4 and global methylation of the human genome (via LINE-1 methylation as surrogate marker) were determined after DNA isolation and bisulfite conversion by pyrosequencing. To assess the efficacy of demethylating treatment, an HPV-transformed vulvar cancer cell line (UM-SCV-6) was treated with decitabine at a concentration range of 0.1 µM - 1.0 µM over one and two weeks. Treatment effects were quantified via determination of vital cells and HPV oncogene expression analyses by qPCR and Western Blot.

Results: Overexpression of DNA methyltransferase 1 in comparison to normal epithelium was detected in all (24/24) VIN and all (9/9) VSSC. Methylation at the E2 binding sites 3 and 4 was higher in HPV-transformed VSCC compared to VIN (p=0.0388). Demethylating treatment of the HPV-transformed vulvar cancer cell line UM-SCV-6 led to a significant dose- and time-dependent reduction of vital cells at all tested concentrations. HPV oncogene mRNA (E6*I and E7) expression in the treated cells was significantly reduced in a dose- and time-dependent manner, with a particularly pronounced decrease in the second week of treatment. These effects were confirmed on the protein level by a decrease of HPV oncoprotein E7 expression and an increase of the p53 and Rb proteins as surrogate markers of a decreased HPV oncoprotein expression.

Conclusions: Overexpression of DNA methyltransferase 1 in HPV-transformed VIN and VSCC and high sensitivity of HPV-transformed vulvar cancer cells to decitabine treatment indicate a promising potential of demethylating treatment for HPV-transformed lesions at the vulva.

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#6869

Association between sexually transmitted infections, cervical-vaginal microbiome and high-risk HPV infection: a study based on a prospective cohort

18 - Microbiome

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Background/Objectives: Persistent infection of high-risk human papillomavirus (hrHPV) is necessary for developing of cervical cancer. Emerging data suggest that the hrHPV infection was associated with the cervical-vaginal microbiome (CVM), meanwhile, other sexually transmitted infections (STI) may also impact the vaginal microbiome and hrHPV infection, but evidence was limited. This study aimed to evaluate the association among STI, CVM and hrHPV infection.

Methods: From Oct. 2018 to Apr. 2019, 540 women from the southwest China were enrolled into the study after informed consent. At the time of enrollment (baseline), cervical-vaginal swab samples and exfoliated cell samples were collected sequentially by gynecologic physicians. The cervical-vaginal swabs sample was stored in buffer solution for 16S rRNA sequencing, and cervical exfoliated cell samples were collected for baseline hrHPV detection, and the leftover of cervical exfoliated samples were stored at −80°C. At the 3rd year, 373 women were followed up to detect the hrHPV infection and histology result. A specially developed targeted high-throughput sequencing was performed using the leftover of cervical exfoliated cell samples for baseline STI detection, which could detect Chlamydia trachomatis, Neisseria gonorrhoeae, Ureaplasma urealyticum, HSV, Mycoplasma hominis and Mycoplasma genitalium, simultaneously. The baseline and follow-up stage of hrHPV infection was detected by a HPV Genotyping Assay, which individually detects 14 hrHPV genotypes (HPV16/18/31/33/35/39/45/51/52/56/58/59/66/68). The vaginal microbiota was detected using 16S rRNA sequencing targeted 16SV4_515F (GTGYCAGCMGCCGCGGTA), 16SV4_806R (GGACTACHVGGGTWTCTAAT), along with barcode sequences to amplify V4 region of the 16S rRNA gene.

Results: Cross-sectional analysis based on 540 women showed that, compared with STI negative, OR of hrHPV was 1.59(95%CI:0.88-2.89) for STI single infection group and 4.99 (95%CI:2.82-8.84) for STI multiple infection group. OR of hrHPV increased with the a diversity, compared with the lowest quartile (Q1) of Shannon index, ORs were 1.32 (95%CI:0.75-2.35), 2.11 (95%CI: 1.23-3.67), and 2.83 (95%CI:1.66-4.90) for Q2, Q3, and Q4 of Shannon index, respectively. In addition, ORs increased with the observed ASVs, compared with the Q1 of observed ASVs, ORs for Q2, Q3, and Q4 of observed ASVs were 2.02 (95%CI: 1.17-3.59), 2.30 (95%CI:1.31-4.13), and 3.93 (95%CI: 2.29-6.91), respectively. The a diversity was not significantly different between hrHPV negative and positive group in women detected with baseline STI infection, however, it was significantly higher in hrHPV positive group compared with hrHPV negative group in women with no STI infection. Relative abundance of g__Lactobacillus showed no obviously decrease in STI single infection than in STI negative group, but decreased in multiple STI infection group. Prospective analysis showed that, in women detected with baseline STI negative, STI single infection, and STI multiple infections, the Shannon index was lower in the hrHPV cleared group compared with persistence group (not significantly), and it was also lower in persist negative group than hrHPV incident infection group (not significantly).

Conclusions: Only when women were detected with multiple STI positive, the hrHPV risk was relatively high. Lower a diversity was associated with higher risk of hrHPV persist infection and hrHPV incident infection. And STI infection showed not obvious influence on the hrHPV infection or persistence.

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#6921

THE INTERPLAY BETWEEN HPV AND MICROBIOTA OF ORAL-NASAL-INTESTINAL MICROENVIRONMENTS IN HEAD AND NECK CANCER

18 - Microbiome

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Background/Objectives: Head and neck cancer is the 7th most prevalent type of cancer worldwide, and HPV infection is becoming to be identified as one of the main risk factors for the development of this type of cancer. With the advances of therapeutics, HPV-positive head and neck cancer have increased response to chemo- and radiotherapy, as well as enhanced prognosis. Recently, microbiota colonization species were isolated in head and neck cancer, which may represent a key-player unknown until now. Therefore, our main goal is to characterize this oral-nasal-intestinal microbiota of head and neck cancer. Furthermore, there is the intention to access the differences between healthy individuals and cancer patients, alongside with the possibility of healthy microbiota establishment after the treatment of head and neck cancer. Finally, we would like to understand if oral microbiota augments the susceptibility to HPV infection, and, their respective genotype.

Methods: This is a national, longitudinal, observational, and prospective study that has 4 groups, with controls, composed by around 30 participants in each group, with the following composition: 1) Healthy individuals without oral HPV; 2) Healthy individuals with oral HPV; 3) Individuals with recent diagnostic of head and neck cancer HPV-positive; 4) Survivors of head and neck cancer HPV-positive. DNA was isolated from nasal and oral swabs, as well as faeces, followed by purification and another isolation through bacterial 16s RNA was analysed by NGS. Statistical analysis was performed in SPSS v 24.0. An alpha of 0.05 was considered statistically significant, and 95% confidence intervals were reported when appropriate.

Results: We are expecting that the microbiome from healthy individuals compared to cancer patients will be significantly different. However, all the microbiotas (oral, nasal, and gut) from survivors from head and neck cancer will be more similar to healthy individuals, when compared to recently diagnosed patients. Furthermore, it will be possible to notice that the modifications of the microbiota in each site will be related to each other, either in terms of taxonomic or functional groups, allowing us to define an oral-nasal-intestinal microbiota axis of head and neck cancer HPV-positive. Finally, we will be able to understand the composition of oral microbiota would be important for the definition of HPV infection and their respective genotype.

Conclusions: We keep getting closer to a personalized medicine, that will allow us to detect cancer in its early stages, enhancing the chances of more effective therapies, as well as better patient's prognosis and quality of life. Furthermore, this project will permit to comprehend the oral-nasal-intestinal microbiota axis of head and neck cancer. Moreover, it will get us one step closer to understand the physiopathology of the development of head and neck cancer after the infection with HPV. At last, it will represent the first step towards a non-invasive, low-cost, test that will enhance the opportunity for better screening for a wider range of the population.

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#6591

Single-Cell and Spatial Transcriptome Analysis Reveals that HPV promotes malignant phenotype via reinforcing TCRaß+CD4-CD8- (Double Negative) T Cells in Cervical Cancer

05 - Immunology

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Background/Objectives: Cervical cancer poses a substantial global health burden, primarily attributed to persistent high-risk Human Papillomavirus (HPV) infections. However, the precise mechanisms through which HPV drives carcinogenesis and disease progression, particularly at single-cell and spatial transcriptome resolution, remain elusive.

Methods: In this study, we employed single-cell and spatial transcriptome analysis using HPV+ and HPV- cervical cancer samples to elucidate the intricate molecular intricacies shaping the tumor microenvironment in the context of HPV infection. Multiple deconvolution-based and multiplex immunohistochemical analyses were used to validate the expression patterns of TCRaß+CD4-CD8- (double negative) T cells in tumor samples. We also leveraged the Clinical Proteomic Tumor Analysis Consortium (CPTAC) and The Cancer Genome Atlas Program (TCGA) datasets, along with organoid culture models, to explore the mechanisms of TCRaß+CD4-CD8- T cells in cervical cancer.

Results: Our single-cell and spatial transcriptome analysis unveiled an elevated presence of TCRaß+CD4-CD8- T cells in HPV+ cervical cancer samples, concomitant with a decreased proportion of CD8+ T cells, NK cells, and myeloid cells within the tumor microenvironment. The presence of TCRaß+CD4-CD8- T cells correlated with immunosuppressive characteristics and the dysregulation of pivotal immune checkpoints. Furthermore, CPTAC and TCGA datasets corroborated the downregulation of cytolytic activity of T cells in the tumor microenvironment of HPV+ tumor samples. Notably, organoid culture models demonstrated that TCRaß+CD4-CD8- T cells were associated with disease progression and aggressive tumor behavior, primarily through the modulation of the IFN-γ/PD-L1 axis within the cervical cancer tumor microenvironment.

Conclusions: Our findings unveil a previously uncharted population of TCRaß+CD4-CD8- T cells within the tumor microenvironment of HPV+ cervical cancer. These T cells play a pivotal role in promoting a malignant phenotype by regulating the IFN-γ/PD-L1 axis. Our study illuminates promising therapeutic avenues, suggesting that interventions targeting the interactions between HPV and double-negative T cells may offer the potential to restrain cervical cancer progression and ultimately improve patient outcomes.

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#6918

HOST IMMUNE RESPONSE TO HPV INFECTION: USING DECONVOLUTION TOOLS FROM NON-INVASIVE SAMPLES LOW-VOLUME RNA-SEQ DATA FOR TUMOR MICROENVIRONMENT PROFILING IN CERVICAL CANCER PROGRESSION AND RISK STRATIFICATION, A PILOT STUDY.

05 - Immunology

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Background/Objectives: HPV infection is essential but not sufficient to cervical epithelial cells transformation,and several cofactors influence oncogenic process,particularly host immune response[1].HPV promotes its own DNA integration and persistence through oncoproteins E6 and E7,by influencing the host immune system through immune evasion mechanisms,leading to the so-called PIM[2,3],within MDSCs limits local immunity by restricting effector T and NK cells proliferation,while Treg are recruited[5,6].Regarding clinical aspects,Treg and TAMs augmentation are associated with CIN and HPV-associated tumors patient prognosis, respectively[5-7].Therefore,PIM supports viral persistence,propagation,and promoting CIN pathogenesis first,and then invasive carcinoma[2,3].PIM biomarkers could be predictive not only of malignant transformation but also of CC prognosis. Our aim is to describe,by non-invasive samples low-volume transcriptomics analysis,the HPV infection immunologic signatures at different stages of CC progression from dysplasia to full-blown cancer,with the intent to evaluate their functional role in immune escape and potentially identifying their correlation with prognosis.

Methods: This is a pilot prospective non-interventional cohort study on cytological samples (Thin-prep) from patients undergoing surgical treatment at IRCCS Regina Elena National Cancer Institute for CC and pre-cancerous lesions CIN 1-2-3. Control samples were also analyzed. Total RNA from thin preps was extracted using a RNA-based kit magnetic microspheres: MagMAXTM mirVanaTM Total RNA Isolation Kit and RNA integrity was evaluated. RNA libraries for sequencing were generated using the same amount of RNA for each sample (Illumina Stranded Total RNA Prep kit) and quantified by qPCR and sequenced in paired-end mode (NovaSeq 6000- llumina, CA). Quality control of data was performed. RNA-seq analysis was performed through the nf-core dedicated pipeline rnaseq. Later, in-silico deconvolution was performed with the xcell algorithm on TMP normalized counts, as well as signature quantification. Although more granular patients' classes were considered, samples were aggregated into three major comparisons and clustering:healthy, displasia and tumor. General performance evaluation of the sequencing and the alignment by multiQC yielded to the exclusion of two samples that did not meet the minimum requirements of properly aligned reads.

Results: We first validated our methodology: 1.Through enrichment analysis, in terms of biological processes and transcription factors, of the most expressed gene within each group of patients in our cohort, we found they matched with those ones most representative in the literature. 2.Then, through comparison with TCGA-UCEC vs our cohort, we almost found the same immune populations relative abundances within the TIME. Then,by selecting the most representative immune cells and prognostic signatures in CC, we estimate their trend from healthy to cancerous, via dysplasia samples (fig. 1,2,appendix).

Conclusions: We describe a new non-invasive methodology for total RNA seq analysis in cervical cancer, which matches results from tissues, in terms of expressed genes and immune cells populations and signatures within the TIME. Next step will be to enlarge our cohort to be able by studying the TIME composition to predict CIN evolution in bloom cancer and CC prognosis, and therefore to stratify patients according to their immune response to HPV infection, by creating an A.I. algorithm.

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FC22 - HPV Testing

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#7793

BUILDING AN HPV GENOTYPING LAB IN COSTA RICA: TRANSFER OF TECHNOLOGY TO PERFORM A NEXT-GENERATING SEQUENCING-BASED ASSAY FOR HPV GENOTYPING SAMPLES COLLECTED IN LARGE HPV VACCINE TRIALS.

14 - Genotyping

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Background/Objectives: HPV vaccine trials that investigate virologic endpoints require affordable, accurate, reproducible and high-throughput human papillomavirus genotyping assays. The US National Cancer Institute's Cancer Genomics Research Laboratory (NCI) developed and validated a novel next-generating sequencing (NGS)-based assay (TypeSeq2) that detects 51 HPV genotypes. NCI demonstrated high positive agreement for most HPV genotypes between TypeSeq2 and SPF10-LiPA25 and estimates of vaccine efficacy against HPV16/18 were higher when using TypeSeq2 compared to SPF10-LiPA25. The NGS assay technology was transferred to ACIB-Costa Rica to generate capacity for HPV genotyping. Here, we describe the technology transfer process and present the results of the validation in Costa Rica.

Methods: We implemented a horizontal (lab-to-lab) transfer of technology from NCI to ACIB-Costa Rica, for non-commercial use (no profit). Initial steps of the transfer included guidance for lab requirements on infrastructure, reagents/consumables, and equipment; development and translation of documentation (manual of procedures, quality assurance plan, supplementary information); execution of automated methods, instrument programs, custom analysis plugin; training (virtual and onsite); and shipments of custom assay components (e.g., multiplexed PCR primer pool, HPV16/18+ cellular lysis controls, spike-in controls). Next steps of the transfer included testing in ACIB-Costa Rica as follows: (1) a training set with single-HPV type synthetic controls to demonstrate lab's proficiency of the assay; (2) testing a set of Proficiency Panel samples with good representation of HPV16, HPV18, multiple infections, other carcinogenic types, with different viral load concentrations, to demonstrate that the lab can produce similar results as NCI; and (3) the assay validation to demonstrate that the lab generates similar sensitivity and specificity as in NCI. A set of 1,195 cervical samples previously tested with SPF10-LiPA25 (DDL Diagnostic Laboratory, the Netherlands) from women enrolled in the Costa Rica HPV Vaccine Trial was used for validation including591 blinded replicates.

Results: The ACIB-Costa Rica lab showed that all batches passed sequencing metrics thresholds (had good chip loading and expected read length histogram), and all batches and plates passed PCR and lysis controls performance metrics (Figure 1, Tables 1-2). Proficiency Panel sample results (Table 3) are well within reproducibility expectations by overall sample and individual type concordance. Inter-lab variability is similar to intra-lab variability. We will present the results of the assay validation at EUROGIN.

Conclusions: Although technology transfer is a challenging and complex process, we demonstrated that TypeSeq2 run in ACIB-Costa Rica performs similarly to tests run in NCI.

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#6873

A COMPARATIVE ANALYSIS OF CYCLE THRESHOLD (CT) VALUES FROM COBAS4800 AND AMPFIRE HPV ASSAY FOR TRIAGE OF WOMEN WITH POSITIVE HRHPV RESULTS

09 - HPV testing

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Background/Objectives: This study aimed to evaluate the performance of Ct values from the AmpFire assay for triaging HPV-positive women. We compare AmpFire Ct values to those from the Cobas4800 assay and assess their utility as triage markers for women testing positive for hrHPV.

Methods: The study used data from a sub-study of the Chinese Multi-Center Screening Trial (CHIMUST), a cross-sectional cervical cancer screening study in China. The primary screening involved 10,885 women aged 30-59 years who provided both self-collected vaginal and clinician-collected endocervical samples. These samples were tested for HPV using the Cobas4800 assay and the SeqHPV assay. Women who tested positive for HPV on either or both assays were recalled for colposcopy. The sub-study focused on validating the effectiveness of the AmpFire assay for detecting CIN2+ and CIN3+. It tested residual samples from 6,619 participants. With the Ct values reported by both the Cobas4800 and AmpFire assays as the triage algorithms, we compare the two assays in identifying the cases of CIN2+ and CIN3+ by categorizing the cases into three groups: HPV16, HPV18, and pooled other HPV. Cases with matching HPV results and Ct values from both assays were included in the analysis.

Results: The sub-study of CHIMUS included 6,042 women with complete data on cytology and histology analysis. Among them, 560 women had matched HPV positive results from both Cobas and AmpFire tests and were eligible for analysis. of the 560 cases, 99 were positive for HPV16, 31 for HPV18, and 430 for other pooled HPV types, Among those, 165 were categorized into the A9 group, 90 into the A7 group, and 61 into the A5/A6 group. A total of 114 cases were excluded unidentifiable single-type CtV. 446 cases were included. The mean age of these women was 45.2 years (±7.42). Among them, 22.20% (99/446) were positive for HPV16, 6.95% (31/446) for HPV18, and 70.85% (316/446) for non-HPV16/18. The CtV of hrHPV tested by Cobas4800 and AmpFire showed significant linear correlations. Spearman's correlation coefficients were 0.664 for hrHPV, 0.818 for HPV16, 0.766 for HPV18, 0.749 for non-16/18 hrHPV, 0.660 for A5/A6 group, 0.815 for A7 group, and 0.775 for A9 group (all pinf0.001). Pathologically, 66.82% (298/446) of the hrHPV-positive cases were reported as non-CIN, 16.14% (72/446) as CIN1, 17.04% (76/446) as CIN2+ (including CIN2, CIN3, AIS, and cancers), and 7.26% (34/446) as CIN3+. Spearman's correlation coefficients were -0.278, -0.467, -0.23, and -0.327, respectively, between the CtV of hrHPV, HPV16, non-HPV16/18, and A9 group from Cobas4800 assay, and the severity of cervical lesions, with pinf0.001 significance. Similarly, Spearman's correlation coefficients were -0.34, -0.344, -0.209, and -0.307, respectively, between the CtV from AmpFire and cervical lesion grades, with pinf0.001 significance.

Conclusions: In conclusion, the AmpFire assay, in combination with Ct values and genotyping, provides a promising approach for more effective and efficient cervical cancer screening and triage, particularly in low-resource settings. Further research and implementation of such strategies have the potential to significantly reduce the burden of cervical cancer in LMICs.

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#6985

E6/E7 HOMOLOGY RELATIVE TO HPV PROTOTYPES AND PERFORMANCE OF HPV TESTING BY COBAS AND ANYPLEX ASSAYS

09 - HPV testing

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Background/Objectives: DNA sequence homology is the basis for classifying HPVs into different genotypes. HPV tests clinically validated for cervical cancer screening were designed based on European HPV prototypes. However, no previous studies assessed the impact of polymorphisms on performance of these HPV tests. We 1) compared the performance of Anyplex II HPV28 assay and cobas 4800 HPV tests with HPV detection by next-generation sequencing (NGS), 2) assessed the impact of cobas cycle threshold (Ct values are inversely correlated with viral load) and HPV DNA viral load-Anyplex on NGS detection, and 3) evaluated the lack of homology in E6/E7 relative to HPV prototypes (PapillomaVirus Episteme, PaVE) and test performance.

Methods: We used data from 990 women enrolled (2019-2022) from four countries (Belgium, Portugal, Brazil and Ecuador) in the ELEVATE study. Mocked self-samples (cervicovaginal) collected by gynecologists/nurses were tested by Cobas and Anyplex. The former provides separate results for HPV16 and HPV18, and a pooled result for 12 other high-risk HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). Anyplex separately identifies 28 HPV types (19 high-risk and 9 low-risk). Only the 14 high-risk HPV types considered by Cobas were included in the current analysis. NGS was designed to amplify E6/E7 of each of these 14 high-risk HPVs using Ampliseq and Ion Torrent technology. The sequence extraction was performed using a depth >100 and a mean quality >20 in each nucleotide base; otherwise the base was considered unknown (samples were considered HPV negative if >25% of the sequence was unknown). We assessed agreement between HPV E6/E7 detection and each of Cobas and Anyplex test results by calculating Cohen's kappa statistics. We compared Cobas-Ct values and Anyplex viral loads (low, moderate, and high) according to NGS detection results; the Mann-Whitney and Cochran-Armitage tests were used to test for significance, respectively. We calculated lack of homology (%) by dividing the number of single nucleotide polymorphisms by the length of E6/E7 for each HPV type and multiplying it by 100.

Results: Based on 934 samples with complete data on all tests, kappas for NGS-Cobas comparison were 0.75, 0.87, 0.85, and 0.74 for any HPV type, HPV16, HPV18, and 12 pooled HPVs, respectively. Corresponding values for NGS-Anyplex comparison were 0.73, 0.84, 0.81, and 0.71. For HPV-positive samples by Cobas, the median Ct values were significantly higher in NGS HPV-negative than positive samples (HPV16: 37.2 vs 29.1; HPV18: 37.3 vs 30.4; 12 pooled HPVs: 36.4 vs 30.2, all p-values <0.01). Likewise, we observed a significant dose-response pattern by Anyplex viral load tertiles in HPV-negative than -positive samples detected by NGS for all HPV types, except for HPV59 (p-value=0.0716). Lack of homology was, on average, higher in HPV-negative than -positive samples by Cobas for HPV16 (0.46% vs 0.13%) and HPV18 (0.44% vs 0.37%). Similar findings were observed by Anyplex for HPV16 (0.78% vs 0.13%), HPV33 (0.66% vs 0.40%), HPV58 (0.79% vs 0.53), and HPV66 (1.14% vs 0.25%). Conversely, lack of homology was, on average, higher in HPV-positive than -negative samples by Anyplex for HPV45 (0.87% vs 0.43%). For HPV types 31, 35, 39, 51, 52, 52, 56, 59 and 68, the average lack of homology was similar between HPV-negative and -positive samples by Anyplex.

Conclusions: Our findings show similar performance between HPV tests and NGS and that deviation from the prototypes may have an impact on test performance

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#6889

Clinical performance of Aptima and Onclarity HPV Assays indetection cervical precancer and cancer: A head-to-head comparison study in China

09 - HPV testing

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Background/Objectives: Persistent infection of human papillomavirus (HPV) is the major factor for cervical cancer, which has led to the derivation of various HPV-specific cervical cancer detection assays at the molecular level. Both Aptima and Onclarity achieved their detection aim from the critical regulatory role of the E6/E7 genes in cervical cancer development. However, Aptima targets E6/E7 mRNA, while Onclarity targets E6/E7 DNA. Compared to DNA-based assays, Aptima HPV Assay only targets transcriptionally active viruses, which might lead to a better specificity. Our head-to-head comparison study aims to assess the clinical performance of two HPV detection assays.

Methods: 911 eligible women attended the routine cervical cancer program, and 211 outpatients/inpatients with biopsy-confirmed cervical intraepithelial neoplasia grade 2 or worse (≥CIN2) from 5 tertiary hospitals across China.Cervical exfoliated cell samples were collected before colposcopy referral and treatment for liquid-based cytology (LBC), HPV E6/E7 DNA, and HPV E6/E7 mRNA detection. One exfoliated sample was transformed into PreservCyt® solution (Hologic, Inc. Marlborough, MA, USA) and stored at 4℃ for 6 months. Another sample for Aptima HPV Assay is validated for Pap smear specimens collected in ThinPrep vials containing PreservCyt transport solution (Cytyc Corporation, Boxborough, MA, USA) and specimens collected with the Aptima Cervical Specimen Collection and Transport Kit (Gen-Probe Incorporated, San Diego, CA, USA). Any positive results were referred for colposcopy, processed in concordance with the standard procedures.

Results: No significant differences were shown between Aptima and Onclarity HPV Assay in terms of overall positive rates and positive rates for each HPV type in the study population (N=1607). For patients with a pathologic diagnosis of SCC and a cytologic diagnosis of HSIL/Cancer, there was a statistically significant difference in the overall positive rate between the two Assays. The two assays met the highest concordance for HPV16 (Kappa value: 0.929). Among all, the Aptima HPV Assay has similar sensitivity and positive predictive values (PPV) as the Onclarity HPV Assay in detecting CIN2+ (93.66%, 90.73%; 78.09%, 77.14%). Aptima HPV assay also has a similar sensitivity to the LBC method in CIN2+ detection (93.07%, 91.77%). The Area under the curve (AUC) of both Assays is ideal (CIN2+: 0.895, 0.880; CIN3+: 0.881, 0.865). For CIN1 and below, Aptima HPV Assay had similar specificity with LBC and negative predictive values (NPV). Screening with Aptima and Onclarity HPV Assay reduced the number of referrals, with significantly lower colposcopy referral rates than LBC (4.4%, 4.8%, 18.0%) and a higher proportion of CIN2+ disease than LBC. Abnormal test results of either test had a higher PPV and AUC if used as a referral criterion.

Conclusions: The Aptima HPV assay and Onclarity HPV assay have similar sensitivity, specificity, NPV, and PPV. The two assays showed good agreement in the detection of specific types, especially in HPV16. Compared to LBC, both assays reduce the colposcopy referral rates, which can be used as an alternative to cervical cancer screening.

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#7105

PERFORMANCE OF ANYPLEX II HPV28 ASSAY AND COBAS 4800 HPV TEST FOR HIGH-RISK HPV DETECTION

09 - HPV testing

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Background/Objectives: Persistent infection with specific high-risk HPV types is the main risk factor for cervical cancer and its precancerous lesions. While numerous molecular tests are available to detect HPV, only 11 are clinically validated for cervical cancer screening. We 1) evaluated and compared the performance of two well-established commercial HPV tests (Cobas and Anyplex for short) for the detection of high-risk HPV types, 2) assessed the composition of HPV types (other than HPVs 16 and 18) that influenced Cobas performance, and 3) considered the impact of the cycle threshold, Ct, values-Cobas (inversely correlated with viral load) and HPV DNA viral load-Anyplex on test performance.

Methods: We used data from the ELEVATE study (2019-2022), which involved the collection of mocked self-samples (i.e., cervicovaginal samples collected by gynecologists/nurses) from 1042 women aged 21-74 years in four countries: Belgium (n=244), Portugal (n=309), Brazil (n=244), and Ecuador (n=245). Samples were tested by 1) Cobas, which provides individual results for HPV16 and HPV18 and a pooled result for 12 other high-risk HPVs (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) and 2) Anyplex which provides separate results for 19 high-risk and 9 low-risk HPVs. The current analysis considered only the 14 high-risk HPV types assessed by both tests. We calculated HPV positivity rates by each test and compared the performance between tests by calculating Cohen's kappa statistics. We described Ct values and compared differences by Anyplex HPV test results using the Mann-Whitney test. We classified Anyplex's high-risk HPV DNA viral load in tertiles as low, moderate, and high and compared the differences by Cobas HPV test results using the Cochran-Armitage's test. We conducted similar analyses considering the composition of individual HPV types detected by Anyplex relative to the pooled HPV Cobas results.

Results: Based on 938 samples with complete data from both tests, positivity by Cobas was 14.2%, 3.6%, 35.6%, and 47.5% for HPV16, HPV18, 12 pooled HPVs, and any HPV. Corresponding HPV positivity by Anyplex were 14.9%, 3.7%, 37.8%, and 50.0% for the same categories with high concordance; kappa statistics were 0.90, 0.87, 0.82, and 0.85, respectively. Based on 355 samples that tested positive for at least one of the 12 pooled HPVs, most types showed high agreement (80.9%-100%) between individual-Anyplex and pooled-Cobas HPV results, except for HPV68 (61.3% agreement). For HPV positive samples by Cobas, the average Ct values were significantly higher in Anyplex HPV negative than positive samples (HPV16: 37.8 vs 29.2, p-value=0.0002; HPV18: 37.4 vs 31.2, p-value=0.0059; 12 pooled HPVs: 37.6 vs 30.1, p-value=0.0000). Likewise, in HPV16 and HPV18 positive samples by Anyplex, we found a significant dose-response pattern by viral load tertiles between HPV16 positive and negative samples by Cobas. A similar trend was found when considering individual-Anyplex and pooled-Cobas HPV results, except for HPV68 where the proportion of samples that were Cobas negative and had low, moderate, and high viral loads-Anyplex were 35.7%, 42.9% and 33.3%, respectively.

Conclusions: Our findings suggest that the two commercial tests may have different performances depending on the specific HPV types being detected, emphasizing the need for continued research and assessment to enhance these tests, especially for less common or less studied HPV types.

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#6822

Comparison of high-risk HPV DNA detection using AnyplexTM II HPV28 and XpertTM HPV in clinician obtained cytological samples among women living with HIV in Lusaka, Zambia

10 - HPV screening

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Background/Objectives: The World Health Organization recommends testing for high-risk human papillomavirus (hrHPV) genotypes as the first test in cervical screening programs. Partial and extended hrHPV testing for triage may reduce overtreatment among screened women living with HIV (WLH). Numerous HPV tests are available, but few studies compare different detection systems among WLH who are at a higher risk for HPV infection and cervical cancer. We compared the detection of hrHPV genotypes on clinician-obtained cytological samples using Xpert HPV (Cepheid) and Anyplex II HPV28 (Seegene) with histological diagnosis among WLH in Zambia.

Methods: Women previously enrolled in a cervical screening test accuracy study (NCT03931083) were invited to another screening round at 30-36 months. Trained nurses obtained one cytology sample in ThinPrep medium and 2-4 colposcopy-directed cervical biopsies from all women. ThinPrep medium was divided and tested using, 1) Xpert HPV on-site within four hours of collection, and 2) Anyplex II,analysed within two weeks, at a laboratory in South Africa. Although, Anyplex II provides genotype information for 28 HPV types, we only considered HPV genotypes included in the Xpert HPV test: HPV16, HPV18/45, hrHPV other (any of genotypes 31, 33, 35, 39, 51, 52, 56, 58, 59, 66, or 68) for this analysis. Biopsies were assessed at a laboratory in South Africa using the WHO Classification of Tumours of Female Reproductive Organs and p16 immunostaining when indicated. We calculated type-specific hrHPV prevalence and used Cohen's kappa to assess agreement beyond chance between the two HPV detection systems.

Results: We included 238 WLH who had valid hrHPV results on both tests and valid cervical histology results at the 30-36 months follow-up visit. Between baseline and follow-up, 25% (60/238) of women received treatment. The prevalence of any hrHPV at follow-up was 26% (95% confidence interval [CI] 20-32%, n=62) using Xpert HPV and 36% (95% CI 30-42%, n=86) using Anyplex II (Figure panel A). Overall agreement between the two detection systems was 83.2% for any hrHPV with fair agreement beyond chance (Kappa=0.61; 95% CI 0.50 - 0.72). Agreement beyond chance was similar for HPV16 (Kappa=0.64; 95% CI 0.46-0.83) and other hrHPV (Kappa=0.65; 95% CI 0.54-0.76) but worse for HPV18/45 (Kappa=0.47; 95% CI 0.23-0.71). Agreement for any hrHPV was better among women with cervical intraepithelial neoplasia grade 2 or higher (CIN2+) (Kappa=0.83; 95% CI 0.51 - 1.00) than among women with infCIN2 (Kappa=0.54; 0.41-0.66). HPV16 was detected in 5% (95% CI 3-9%, n=13) using Xpert HPV and 10% (95% CI 6-14%, n=23) using Anyplex II. Among 21 women with histological CIN2+, three women tested negative for any hrHPV on both detection systems and one woman tested positive only on Anyplex II (Figure panel B). In 217 women without CIN2+, Xpert HPV detected fewer hrHPV positive samples than Anyplex II.

Conclusions: Both the Xpert HPV and Anyplex II are in the WHO 2021 list of HPV assays suitable for primary cervical cancer screening. While we found excellent agreement for hrHPV detection among WLH with CIN2+, agreement of any hrHPV detection among women with infCIN2 was limited. Consistency in detecting hrHPV genotypes across different detection systems is increasingly important if partial and extended hrHPV genotyping is to be considered feasible for triage.

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#6844

HPV type-specific viral load in CIN2+

09 - HPV testing

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Background/Objectives: HPV-based screening is a key component of the cervical cancer elimination efforts. However, different HPV tests vary greatly regarding which HPV types they detect and what the detection limit in amounts of virus is. When designing campaigns for cervical cancer elimination using HPV screening it would be an advantage to know the optimal type of composition and analytical detection limit of the tests. It is also essential to know how sensitivity and specificity are changing in HPV vaccinated birth cohorts.

Methods: A nested case control study consisting of 101 cases and 202 controls was conducted.The cases were a consecutive series of histopathology-verified CIN2+ identified among women resident in the capital region of Sweden and had had a cervical liquid-based cytology sample taken at most three months before the histopathology diagnosis. Controls were identified among women resident in the capital region of Sweden who were participating in the population-based cervical screening program. Only primary screening samples were eligible (not reflex samples or samples from disorganized screening). Two controls taken at the same time as the matched case and matched by years of age were identified. The HPV status of all samples were extracted from the laboratory database of the screening program, but not used for selection of cases or controls. The national reference laboratory (NRL) for Sweden tested the samples for virus types and amounts using QuantStudioTM 3 Real-Time PCR System (Thermo Fisher Scientific) for HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59. National reference laboratories (NRL) in the HPV LabNet were invited to participate and aliquots from all samples were sent to 9 laboratories from 9 different countries for analysis.

Results: NRL Sweden found that 99 cases (98%) and 34 controls (17%) were positive for HPV. The most important type was HPV16, found in 34% of cases and 2,5% of controls. The 7 oncogenic types HPV16/18/31/33/45/52/58 were jointly found in 78% of cases and 8,4% of controls. The median amount of viral DNA present of HPV16, 18 and 45 was 2833, 1905, 32375 and 11, 7527 and 47 IU among cases and controls, respectively. Ranking HPV types either according to the IARC cancer risk data or according to which HPV type was present with the highest amounts of virus found similar results. In the birth cohorts with substantial HPV vaccination (born between 1993-1999), the vaccine-targeted HPV types were less common (among both cases and controls).

Conclusions: As expected, the 7 most oncogenic HPV types were the most important for CIN2+ detection. The amounts of virus present in CIN2+ case women were, for viruses with substantial number of cases, higher among CIN2+ cases. Particularly after the comparison with results from other countries is ready, we expect the data to be useful for determining which HPV types need to be detected by HPV screening tests, and at what analytical sensitivity.

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#6802

PHOTODYNAMIC THERAPY WITH APL-1702 FOR HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS (HSIL): RESULTS FROM A RANDOMIZED PHASE 3 GLOBAL STUDY（YHGT-CEV-R1/APRICITY）

25 - Cervical neoplasia

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Background/Objectives: To evaluate the efficacy and safety of the investigational product APL-1702, which is an integrated combination of topical hexaminolevulinate (HAL) hydrochloride with photodynamic therapy (PDT), compared to placebo (PBO, PDT without HAL) in treatment of patients (pts) with cervical histologic HSIL.

Methods: The YHGT-CEV-R1/APRICITY study is a prospective, double blind, randomized, PBO controlled, multi-center global phase 3 study, which enrolled pts with cervical histologic HSIL from 8 countries (China, Hungary, Germany, Czech Republic, Slovakia, Poland and the Netherlands). Eligible pts were randomly (2:1) assigned to receive APL-1702 (5% HAL HCl ointment, PDT 125 J/cm2 over 4.6 hours) or PBO no more than twice in 6 months. The primary endpoint is response rate (RR], defined as normal histology or Low-grade squamous intraepithelial lesions (LSIL) histology and clearance of baseline HPV] at 6 months after first treatment. Secondary endpoints are proportion of HPV, HPV16, HPV16 and/or 18 positive patients with clearance of baseline HPV at 6 months after first treatment, and proportion of patients with histologic regression (LSIL or normal histology at 6 months after first treatment). All histologic samples were reviewed by an independent adjudication panel of three pathologists.

Results: Between Nov 10, 2020 and Jul 18, 2022, 402 eligible pts were randomized. Median age was 29.6 years (range 18.7-51.9). A total of 93.3% of pts were HPV positive, with 55.7% being HPV16+. The RR in the APL-1702 group nearly doubled that in the PBO group (41.1% vs. 21.7%, p = 0.0001). The clearance rate of high risk HPV16/18 was also significantly improved in the APL-1702 group (31.4% vs. 15.4%, p = 0.01). Treatment emergent adverse events (TEAEs) in the APL-1702 and PBO groups were 56.8% and 56.0%, respectively. The majority of TEAEs were mild, including vaginal discharge (10%), vaginal infection (9.3%), abdominal pain (6.5%), vaginal hemorrhage (5.5%). Treatment related AEs in the APL-1702 and PBO groups are 31.6% and 26.1%, respectively. The incidence of serious TEAEs was 1.5% in both groups.

Conclusions: Results from the APRICITY trial demonstrate robust efficacy and excellent safety of APL-1702 in cervical HSIL pts. This study provides evidence of an innovative, non-surgical treatment option for precancerous cervical lesions, and APL-1702 shows efficacy as early as 6 months after the first treatment.

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#6874

ADENOCARCINOMA IN SITU OF THE CERVIX: RISK FACTORS FOR RECURRENCE AFTER FERTILITY-SPARING TREATMENT.

23 - Risk management

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Background/Objectives: Adenocarcinoma in situ (AIS) of the cervix is a premalignant precursor to cervical adenocarcinoma. Although AIS is less common than its squamous counterpart, cervical intraepithelial neoplasia grade 3, its incidence has increased over the last 50 years. The mean age at diagnosis of AIS ranges from 32 to 40 years, with almost 68% of cases found in women younger than 35 years. International guidelines recommend total extra-fascial hysterectomy as the standard treatment for AIS. However, fertility preservation is crucial for women of childbearing age with desire of pregnancy. Cervical excision with negative margins may be a reasonable fertility-sparing treatment option, but this approach requires careful counseling and strict follow-up, due to a 3-5% risk of recurrence and a 1% risk of progression to invasive disease. Our study aims to investigate the risk factors for recurrence in women undergoing conization for AIS in order to evaluate the feasibility of fertility-sparing treatment.

Methods: We conducted a retrospective analysis of women who underwent excisional procedures for AIS at the European Institute of Oncology, Milan, from January 2000 to December 2022, with a minimum 6-months follow-up. We summarized HPV infection status at baseline and first follow-up, and margin status by counts and percentages, while age was summarized by mean and standard deviation. Relapse-free survival and hazard ratios were estimated by using the actuarial life table method and the Cox model, respectively.

Results: A total of 122 women with a mean age of 38.1±8.3 years (range: 22-70) were enrolled. Ninety-one percent of cases were High-Risk (HR) HPV related, with HPV 16 and 18 being the most prevalent genotypes (84.2%). Only 21.7% of women were still HR-HPV positive at the first follow-up. Overall, after a median follow-up time of 3.7 years, 6 patients developed recurrence, with a 2-year relapse-free survival of 99.0% (95% CI: 93.1-99.9) and a 5-year relapse-free survival of 92.6% (95% CI: 82.8-96.9). Positive endocervical and deep surgical margins on cone-biopsy specimens and persistent HR-HPV infection at the first follow-up were associated with a higher risk of relapse, with hazard ratios of 2.62 (95% CI:0.48-14.4), 4.76 (95% CI: 0.87-26.1), and 1.63 (95% CI: 0.30-9.0), respectively. Age at diagnosis was not related to recurrence (HR=0.96, 95% CI: 0.85-1.08).

Conclusions: Negative cervical excision margins are considered protective against AIS recurrence, confirming the need for reconization in cases of positive resection margins as recommended by recent guidelines. Additionally, the risk of AIS recurrence should not be underestimated when HR-HPV infection persists after treatment, even in women with negative surgical margins. Therefore, post-treatment surveillance with HPV genotyping helps identify women at increased risk of relapse. Considering the low risk of recurrence, conservative surgical treatment with careful long-term follow-up could be considered a valid therapeutic approach even for women no longer desiring pregnancy, as in the case of high-grade squamous intraepithelial lesions.

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#6856

REPRODUCTIVE OUTCOMES AFTER FERTILITY-SPARING SURGERY FOR CERVICAL CANCER - RESULTS OF THE MULTICENTER FERTISS STUDY

40 - Fertility and HPV

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Background/Objectives: The goal of fertility-sparing treatment (FST) for patients with cervical cancer is to achieve comparable oncologic outcomes to those after radical treatment while achieving the best reproductive outcomes, which include the ability to conceive and minimizing the risk of preterm birth.

Methods: Patients from the international multicentre retrospective FERTISS study, which included women treated with any type of FST, were analysed for information on timing of FST in relation to pregnancy, attempts to conceive, mode of conception, prophylactic procedures to reduce the risk of severe prematurity, rate of pregnancy failure, overall duration of pregnancy and mode of delivery.

Results: Of the 733 patients treated at 44 centres in 13 countries, only half (49.7%) attempted to become pregnant during median follow-up of 72 months. Successful pregnancy was achieved in 22.6% (166/733) patients from the whole cohort. Of these patients, 63.2% (122/193) underwent non-radical surgery and 25.7% (44/171) radical trachelectomy (p inf 0.001). Data from 124 pregnant patients (74.7%) were available for detailed analysis. A total of 89.5% (111/124) patients became pregnant naturally. The abortion rate in the first pregnancy did not differ between patients after radical and non-radical procedures. There was no difference in delivery success rates between patients after non-radical and radical procedures (86% vs. 83%, p=0.77). Preterm delivery (inf38 weeks gestation) occurred more frequently in patients after radical than non-radical procedures (76.5% vs. 57.7%, p=0.15). Almost all patients (97.3%; 73/75) who underwent regular ultrasound cervicometry in pregnancy with subsequent prophylactic procedures delivered a live fetus, in contrast to women without such management (30.6%; 15/49), (OR 31.6 (7.74-216), pinf0.001).

Conclusions: Half of the patients did not attempt pregnancy at all after FST. Patients who underwent non-radical surgery had significantly higher pregnancy rates. Most women who became pregnant delivered a viable fetus, but women who underwent radical trachelectomy had a higher rate of preterm births in the severe prematurity range.

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#7095

RANDOMIZED TRIAL ON TREATMENT OF HIGH-GRADE VAGINAL INTRAEPITELIAL NEOPLASIA -SELF-ADMINISTERED VAGINAL IMIQUIMOD AND LASER VAPORIZATION

26 - Vulvar diseases and neoplasia

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Background/Objectives: Vaginal high grade squamous intraepithelial lesions (HSIL) may progress to invasive cancer if untreated. Despite treatment method, vaginal HSIL has a high recurrence rate associated with human papillomavirus (HPV) persistence. Repeated surgical or destructive treatments may cause loss of anatomy and function. The aim of this study was to assess the efficacy and tolerability of self-administered vaginal immunomodulator imiquimod compared to laser vaporization in treatment of vaginal HSIL in a randomized controlled setting.

Methods: Patients with histological vaginal HSIL were randomized in a 1:1 ratio to either imiquimod treatment or laser vaporization at a single tertiary center. Follow-up for 32 weeks consisted of regular colposcopy visits and histological sampling. At enrolment and end of study a sample for HPV genotyping was obtained. Laser vaporization was performed according to clinical guidelines. In the imiquimod arm patients applied 14 vaginal suppositories 12.5 mg of imiquimod over a period of 8 weeks. The main outcome measure was histological regression and secondary outcome measures were HPV clearance and tolerability of imiquimod.

Results: 53 patients with vaginal HSIL were available for final analyses; 26 in the laser arm and 27 in the imiquimod arm. At baseline 91.7% of patients were HPV positive and high-risk genotypes were found 62.5%, with HPV16 being to most common genotype (35.4%). There were no statistically significant differences between baseline characteristics of the study arms. No progressions to invasive carcinoma occurred during the study period. At the end of study, histological regression to low-grade lesions or normal occurred in 57.7% in laser arm compared to 84.6% in imiquimod arm (p=0.03). HPV clearance was 25.0% in laser arm and 55.0% in the imiquimod arm (p=0.07). Local irritation was reported by ten patients in the imiquimod arm, eight reported a subsiding fever, and four reported abdominal pain. One patient in the imiquimod arm discontinued treatment and was treated with laser and was excluded from the data before analyses.

Conclusions: Self-administered imiquimod was found to be effective and relatively tolerable in treatment of vaginal HSIL. A medical option for commonly used surgical and destructive methods especially in relapsed cased could be well welcomed. Imiquimod also presents a feasible treatment option in light of increased HPV clearance which could decrease recurrence rates if proven long-lasting.

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#8027

THE DELVIN TRIAL: INTERIM RESULTS FROM A MULTICENTER CLINICAL PHASE I TRIAL EVALUATING THE SAFETY AND PRELIMINARY EFFICACY OF LOCAL DECITABINE TREATMENT OF HUMAN PAPILLOMAVIRUS-INDUCED VIN GRADE 2/3

08 - Immunotherapy - Immuno-oncology - New treatments

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Background/Objectives: Aberrant host cell and HPV genome methylation has functional relevance for HPV-induced carcinogenesis by promoting HPV E6/E7 oncogene expression and down-regulating tumor suppressor genes. Treatment with demethylating agents, such as the DNA methyltransferase (DNMT) 1 inhibitor decitabine, holds potential as a novel and causally effective treatment for HPV-transformed lesions. To demonstrate safety and preliminary efficacy of VTD-101 ointment, a newly developed topical dosage form of decitabine, in patients with HPV-induced vulvar intraepithelial neoplasia (VIN) grade 2/3, we are conducting the clinical study "The DelVIN Trial" (NCT05717621).

Methods: DelVIN is a prospective, multicenter, single-arm, open-label phase I study. The study enrolls twenty-nine patients with high-risk HPV DNA-positive, p16INK4a-positive VIN 2/3 who self-administer VTD-101 ointment to their uni- or multi-focal lesions. The primary study objective is to determine the recommended phase 2 dose (RP2D) of VTD-101 ointment for the topical treatment of HPV-induced VIN grade 2/3. The RP2D is defined as the dose that is safe, tolerable, and effective. Corresponding endpoints comprise the rate of patients experiencing at least one dose limiting toxicity (DLT) and the rate of patients with clinical complete or partial response (cCR/cPR) according to adapted RECIST criteria. Clinical response is determined by computation of the sum of longest diameter (SLD) among all lesions per patient. A protocol-defined interim analysis was performed after the first ten enrolled patients had completed study treatment.

Results: Twenty-nine patients at five different trial centers were found to be eligible for study participation resulting in complete recruitment of the study. Fifty percent of the ten patients included in the interim analysis showed a clinical response (n=4 with cPR and n=1 with cCR) upon study treatment completion substantiating continuation of the DelVIN trial. None of the ten patients included in the interim analysis experienced any DLTs. In addition, none of these patients experienced any serious adverse events (SAEs), serious adverse reactions (SARs) or suspected unexpected serious adverse reactions (SUSARs) during the study treatment with VTD-101 ointment.

Conclusions: Interim data from the clinical phase I study DelVIN demonstrate first evidence for clinical efficacy of VTD-101 ointment and a favorable safety profile in patients with HPV-induced VIN 2/3. These promising preliminary results substantiate advancing the development of VTD-101 ointment as a novel treatment concept for patients with VIN 2/3, a disease with a high unmet medical need. Considering the shared molecular biology of HPV-induced (pre-)cancerous lesions arising in different anatomical locations, our demethylating treatment approach holds potential for other HPV-induced precancerous lesions in the anogenital area.

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#7045

Assessment of Intra-observer Rating of Women with Warty Vulvar Lesions

01 - HPV disease and COVID-19

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Background/Objectives: Genital human papillomavirus (HPV) is a common sexually transmitted infection associated with genital warts and lower genital tract lesions. Data suggest that HPV vaccination may control lesion size and or recurrence after treatment. This study investigated the intra-rater agreement of assessing photographs of vulvovaginal lesions, taken at several visits before and after vaccination and treatment.

Methods: Women with large vulvovaginal warty lesions were recruited to an interventional study conducted in two Academic Hospitals in South Africa. At first visit, clinical assessment of lesions was done, digital photographs (using ruler as scale) were taken, and participants were randomised to receive either the quadrivalent HPV or hepatitis-B vaccine. Participants were prospectively followed up at weeks 8, 16, 24, 36, 48, 60 and 72 and photographs taken at each visit. Participants received treatment between weeks 25 and 30. Lesion size and response were assessed by comparisons of pictures and reassessed two months later by the same observer. Rating scale was as follows: complete response, partial response, uncertain, no response and progressive disease. Intra-rater agreement was determined using Cohen's Kappa (κ). Interpretation of κ value: 0.01-0.20 slight agreement, 0.21-0.40 fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 substantial agreement and 0.81-1.00 almost perfect agreement.

Results: The mean age of the 53 participants was 34.2 years, and the majority (91.8%) were women living with HIV. Overall, there was slight to fair intrarater agreement of lesion assessment of the vulva for weeks 8, 16 and 24 visit, $\kappa = 0.10\text{-}0.39$. At week 8 visit, there was fair intrarater agreement in the assessment of both the left and right vulva, $\kappa = 0.32$ & 0.33, p 0.003 & 0.002 respectively. There was moderate intrarater agreement of both right and left vulva at week 36, $\kappa = 0.59$ & 0.55, p 0.0001 & 0.0003 respectively. At the exit visit, the overall intrarater agreement of vulva lesion assessment was moderate, although with a relatively wide margin, $\kappa = 0.50$ and 0.43 for left and right vulva respectively.

Conclusions: Overall, there was moderate intrarater agreement in the assessment of the lower genital tract warty lesions after treatment intervention. The bias associated with memory recall of previous rating was significantly removed as the time interval between the ratings was longer than two weeks.

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#6811

IDENTIFICATION OF RISK FACTORS FOR TREATMENT STRATIFICATION FOR CERVICAL SQUAMOUS- AND GLANDULAR CELL LESIONS

22 - Diagnostic procedures / management

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Background/Objectives: In younger women, the incidence of adenocarcinomas and adenocarcinomas in situ (AIS) is increasing, despite the national cervical cancer (CC) screening program in Finland. The aim of this study was to evaluate how co-factors for squamous cell lesions differ from those for glandular lesions and how the treatment of glandular lesions could be optimized.

Methods: This study comprised of 1246 women who all underwent loop electrosurgical excision procedure (LEEP) at the colposcopy unit of the Tampere University Hospital, Finland between the years 2012-2022. The women had all participated in the national CC screening program and been referred to the colposcopy unit due to abnormal findings. Partial HPV genotyping of HPV16, 18 and 12 other high-risk genotypes was performed. Information on background factors and treatment follow-up was collected from hospital patient charts.

Results: Of the patients that underwent LEEP 4.9 % (n=61) had AIS and 41 % (n=512) had high grade squamous intraepithelial lesion (HSIL). The median age of the women in AIS and HSIL groups were 36 (Interquartile range 31-41) and 35.5 years (IQR 30-42). AIS was detected more often between the age 30-44 than HSIL, 72 % and 57 % respectively. None of the background factors such as BMI, pregnancies, parity, immunosuppression, HIV and other sexually transmitted diseases, smoking or used contraception varied between these two groups. Among the partial HPV genotypes 21 % (n=13) of AIS patients were HPV18 positive compared to only 1.8 % (n=9) of the HSIL patients (pinf0,001). Most of these were detected as single HPV18 infection. Among the HSIL women again the other high-risk HPV positivity was more common 19 % (n=95) compared to 7 % (n=4) in the AIS group (p=0,019). HPV16 prevalence showed no difference between these groups. Only 8.2 % (n= 5) women with AIS had a hysterectomy done, while others were treated with LEEP and extended follow-up. Further risk-evaluation will be done using the histological conization results and markers among the AIS and HSIL groups.

Conclusions: AIS lesions are predominantly associated with HPV18 genotype, and the prevalence is highest among women between 30 to 44 which is also the prime childbearing age. The current guideline for treatment of AIS is hysterectomy, however due to the young age and childbearing age of these women further evaluation of risk factors for treatment management is needed.

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#7021

TO COMPARE THE NEW SMART AND HANDY DEVICE DEVELOPED WITH STANDARD COLPOSCOPE FOR CANCER CERVIX SCREENING

25 - Cervical neoplasia

Background/Objectives: Cervical cancer annually in India, accounting for nearly one-fifth of the global cervical cancer burden[1]It is estimated that cervical cancer will occur in Indian women approximately 1 in 53 during their lifetime compared with 1 in 100 women in developed countries.[2] Several screening options are available. Patients with abnormal screening tests are evaluated by colposcopy and detection of high-risk Human papillomavirus DNA [3,4]. Visual methods are the low-cost alternatives for low- and middle-income countries like India.[5] there is a need for affordable device for detecting and screening abnormalities in the cervix (6). colposcopy needs to have a working distance of 300 mm. The New Smart and Handy device found to be easy to handle for cancer cervix screening and also cost-effective. The USB camera attached to android phone captures, saves pictures and video from a distance of 3cm to 4cm with good quality and clarity , with MScopes Application. Aim objectives of the research project: To compare the images of a standard Colposcope with those of images of a Smart and handy device to detect precancerous and cancer cervix. Objectives of the research project: 1. To determine whether smart and handy device can be utilized in low-resource centers to detect cancer cervix 2. To determine whether the quality of images captured is comparable with standard Colposcope 3. To determine the sensitivity & specificity of the smart and handy device diagnosis with that of standard Colposcope

Methods: Methodology & Research design: After informed, after ethical clearance 154 Women attending the Gynaec outpatient department were screened for detection of precancerous and cancerous lesions of the cervix using a standard Colposcope and with a Smart& Handy device. Inclusion criteria were women for routine cancer cervix screening, women with abnormal Pap Test, women with white discharge, and women with post coital bleeding and exclusion criteria were women with cervical growth.

Results: Results: Focus of the image at 91%, Sharpness of the image at 92% and zoom at 94% with a Smart & handy instrument and by colposcope Focus -at 94%, sharpness at 98% and Zoom at 100% In Smart & hand device evaluation done with Swede score without vessels Based on Aceto-white uptake, Margins, Lesion size, and Iodine uptake. Each was given two. score. Among -0 -3 score - 53.3%, 4-5 score -33.3%, 5-8 score - 13.3% In Colposcopy evaluation done with Swede score based on Aceto-white uptake, Margins, Lesion size, Iodine uptake,5. Vessels, Among 0-3 score -60% 4-7 score- 26.6 %.8-10score -13.4% Biopsy reports results in SMART AND HANDY DEVICE when score 0 -3 -Normal -72%, Score of 4-5 - LSIL - 15.8%, Score of 5-8- -HSIL-6.2% COLPOSCOPY biopsy results when score of 0-4 -Normal-78% , Score of 5-7 - LSIL- 14.8%, Score of 8-10-HSIL -7.2%. The sensitivity, Specificity, Positive likelihood Ratio, and Negative Likelihood Ratio of Smart and hand Device are as follows 93.10%,90.32%,9.62, 0.08. The sensitivity, Specificity, Positive likelihood Ratio, and Negative Likelihood Ratio of colposcopy are as follows 96.55 % 93.33%, 14.48, 0.04

Conclusions: Conclusion: SMART AND HANDY DEVICE gives high-quality images and video and an efficient method to store data,handy and portable,cost effective and can be incorporated into cervical screening methods in low-setting resources.

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5-AZA-2'-DEOXYCYTIDINE (DAC, DECITABINE) INDUCES BENEFICIAL TREATMENT EFFECTS IN A PRECLINICAL IN VIVO MODEL

17 - Methylation

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Background/Objectives: HPV-driven malignant transformation is functionally associated with a disturbance of the host cell's epigenetic profile including DNA hypermethylation in distinct regions of the viral and host genome, which contributes to aberrant expression of the HPV E6/E7 oncoproteins. Treatment with demethylating agents has emerged as a causal novel therapeutic concept against HPV-transformed lesions. In this project, we aimed to analyze effects of treatment with the DNA methyltransferase (DNMT) 1 inhibitor 5-aza-2'-deoxycytidine (DAC, decitabine) in a preclinical mouse model for HPV-induced cancer. As DAC is instable in aqueous environments and further is actively degraded by cytidine deaminases (CDAs) in vivo, we combined systemic DAC application with preceding administration of the CDA inhibitor tetrahydrouridine (THU). This combined DAC+THU application scheme has been shown to allow the generation of therapeutically relevant plasma levels, while avoiding high DAC dose-associated cytotoxicity in mice and non-human primates.

Methods: We inoculated NOD scid gamma (NSG) mice with human HPV-transformed cells (CaSki). Systemic treatment with either PBS (control group), low-dose DAC (0.1 mg/kg) alone (DAC only), or DAC (0.1 mg/kg) in combination with THU (10 mg/kg) (DAC+THU) was initiated, once all mice carried a palpable lesion. The treatment was conducted on three consecutive days per week and terminated as soon as pre-set stopping criteria were reached. The performed analyses comprise determination of overall survival and assessment of molecular and biological treatment effects including among others determination of the intact cell proportion within the tumor area and immunohistochemical staining for p16INK4a/Ki-67.

Results: Mice of the DAC+THU treated group survived significantly longer than mice of the PBS-treated control group and mice treated with DAC only. Tumor tissue analysis showed that the proportion of intact cells within the tumors decreased along with increasing duration of DAC-based treatments. Immunohistochemical co-staining for p16INK4a and Ki-67 indicated a reversal of the HPV-transformed phenotype as a consequence of DAC treatment in vivo. This effect could be maintained for the total duration of the experiment (up to 121 days) in DAC+THU-treated mice. None of the mice showed indications of toxicity upon any of the applied treatments.

Conclusions: The results indicate biologically relevant beneficial effects of DAC-based treatment approaches against HPV-transformed lesions.

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Prognostic impact and adjuvant treatment decision of poor differentiation on early-stage cervical cancer

34 - Conventional therapies

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Background/Objectives: Postoperative adjuvant therapy decisions for early-stage cervical cancer now depend on Sedlis criteria, which do not mention about the degree of differentiation. Some previous studies have shown that poor differentiation is an independent risk factor for higher recurrence for early-stage cervical cancer. In this study, we aimed to explore the benefit of adjuvant chemotherapy for early-stage cervical cancer patients with poor differentiation but without positive Sedlis criteria after radical hysterectomy, and develop a score to predict the recurrence risk in these patients, so as to further improve the indications of postoperative adjuvant therapy for early-stage cervical cancer.

Methods: Patients of early-stage cervical cancer with pathologically proven poor differentiation after radical hysterectomy were prospectively included. Univariate Cox proportional hazards regression were developed to evaluate the independent risk factors for recurrence. The log-rank test was performed to compare the PFS and OS of adjuvant chemotherapy (ACT) and no further treatment (NFT) groups. Selected variables were then analyzed in a multivariate Cox Regression Model and used to build a nomogram for early-stage cervical cancer to predict the survival probabilities.

Results: In total, 352 patients were randomly assigned to two groups, a training group and a validation group, at a ratio of 1:1 (176 patients: 176 patients). Patients in the training cohort who received adjuvant chemotherapy had longer progression-free survival (PFS, P =0.007) than those had no further treatment (NFT), but the differences of overall survival (OS, P=0.922) between the two groups was not statistically significant. In the multivariate analysis, ACT was proved an independent prognostic factor for the PFS (P=0.048), and the strongest predictor of PFS even analyzing with other potential independent prognostic factors (HR 0.116, 95%CI 0.014-0.981). Five factors, including ACT, histologic type, isthmus uteri involvement, FIGO stage, SCCA level, were included in the nomogram to predict survival probabilities in the training cohort and performed well in the validation cohorts. In the model, ACT is demonstrated the best performance for predicting PFS.

Conclusions: For the early-stage cervical cancer patients who doesn't meet to Sedlis criteria but with poor differentiation, ACT after radical hysterectomy can reduce the recurrence rate. Meanwhile, the model based on clinical and pathological information could help physician make clinical decision of personalized treatment by predicting the probability of recurrence in these population of patients.

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EFFECT OF A CORIOLUS VERSICOLOR-BASED VAGINAL GEL AS A CONSERVATIVE TREATMENT FOR HR-HPV-DEPENDENT HSIL IN PREGNANT WOMEN

32 - HPV transmission

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Background/Objectives: Human papilloma virus (HPV) infection is the most common sexually transmitted infection and also the main causative agent of the 99% of cervical cancer cases. HPV persistence, particularly with genotype 16, may lead to different grade squamous intraepithelial lesions that can result in high-grade lesions (HSIL) and cervical cancer. Surgical excisional treatment of HSIL/CIN2 and 3 during pregnancy is contraindicated due to the high rate of complications, including probability of aborption and preterm birth. Thus, the management of an HSIL diagnose during pregnancy remains to be a challenge to both, the patient and the clinician. With these three clinical case reports, we aimed to evaluate the effect of a Coriolus versicolor-based vaginal gel in the conservative management of CIN2 lesions during pregnancy.

Methods: Here we present three clinical case reports involving pregnant women between 26 and 34 years old with high-risk HPV (HR-HPV) genotypes including 16, 18, 31, 39, and 45, and who were diagnosed with HSIL/CIN2-3 through colposcopy and biopsies. Patients were prescribed with Coriolus versicolor-based vaginal gel (1 cannula/day for 1 month + 1 cannula/alternate days for 2 months) gel as a conservative treatment. Follow-up colposcopy, cytology and HPV tests were performed over time for monitoring patients.

Results: All patients showed a regression of CIN2/3 lesions to CIN1 lesions. Two of them, achieved the regression after 3 months of conservative treatment with Coriolus versicolor-based vaginal gel and one the other patient after 6 months of conservative treatment with Coriolus versicolor-based vaginal gel. None of the patients reported any negative effect associated with the use of Coriolus versicolor-based vaginal gel. The patients gave birth to healthy babies.

Conclusions: A Coriolus versicolor-based vaginal gel treatment leads to regression of HSIL/CIN2 in pregnant women with HR-HPV. This conservative treatment approach represents a clinical advantage in patients during their "wait and see" period who are not candidates for an excisional surgery.