



Technical Meeting

Challenges in the HPV Screening Landscape, Triage of Screening Positive Samples, and Screening in the Era of Vaccination

27 – 28 August 2020
Antwerp, Belgium

BACKGROUND DOCUMENT

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Background document, Technical Meeting 'Challenges in the HPV Screening Landscape, Triage of Screening positive sample, and Screening in the Era of Vaccination' – 27 – 28 August, Antwerp, Belgium

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Introduction

Meeting objectives:

- Landscape of HPV Screening
 - Discuss barriers to adoption and implementation of HPV testing
 - Review quality, validation and availability of HPV tests
 - Provide country examples of successful implementation of HPV testing
 - Discuss if we have enough options and supply needed for the global cervical cancer elimination
 - Review HPV screening and treatment challenges in different regions
 - Review challenges and opportunities to offer a complete system, from screening to treatment, in LMIC
 - Discuss the existing networks that support implementation of cervical cancer screening programs in LMICs.
- Triage: what are the best options.
 - Review current available triage, treatment and management algorithms
 - Discuss what are the best options for different situations
 - Review challenges and future opportunities
- Integration of Vaccination and Screening
 - How to organize cervical cancer screening in the era of vaccination (Keynote Lecture)
- Impact of COVID-19 on cervical cancer screening programs

Target audience:

- Projects and organisation representatives involved in HPV control and prevention
- Representatives of health organisations involved in the prevention and control of HPV and/or other health issues
- HPV prevention and control Board advisors

Purpose of the background document

This background document provides an overview of articles related to the meeting and a concise bibliography of speakers. The main purpose of the document is to frame the topics of the meeting on 'Challenges in the HPV Screening Landscape, Triage of Screening Positive Samples, and Screening in the Era of Vaccination'

The document should not be considered as an an exhaustive report of scientific articles related to the themes of the meeting.

Inclusion of references in this document does not indicate that the Executive Secretariat agrees with the content or correctness of the content. The first objective of this list is to give an overview of what has been published on this topic.

Part 1: References based on a Pubmed search, by session

Session 2 *Title: The Landscape of HPV Screening; Where do we stand today*

A Pubmed search was performed with the following selection criteria: [HPV] AND [Screening] AND [Implementation]; [HPV] AND [Screening] AND [Implementation] AND [Elimination]; [HPV testing] AND [Validation] AND [Cancer prevention] [title/abstract]; published in the last 5 years: 293, 18, and 125 items were retrieved respectively. Few of the articles retrieved were out of scope of the session or were relevant to other sessions. Herein, a relevant manual selection of 29 publications between 2015-2020 based on title and abstract was made, and imported into Endnote

Maver, P. J. and M. Poljak (2020). **"Primary HPV-based cervical cancer screening in Europe: implementation status, challenges, and future plans."** *Clin Microbiol Infect* **26**(5): 579-583.

BACKGROUND: Cytology-based screening has been a cornerstone of cervical cancer prevention for decades. Following extensive evidence demonstrating higher sensitivity and accuracy, lower variability and better reproducibility of human papillomavirus (HPV)-based screening compared with conventional or liquid-based cytology, recent European guidelines strongly recommend primary HPV-based screening over standard cytology-based screening. In addition, HPV-based screening offers the possibility of self-sampling and makes possible longer screening intervals in women with negative screening results. **OBJECTIVES:** We summarize the current status of implementation of HPV-based screening in Europe, describe the real-life experience and challenges from countries already performing HPV-based screening, and briefly review immediate and long-term plans for screening implementation in selected European countries. **SOURCES:** Data were obtained from peer-reviewed literature, personal communication with experts and authorities involved in formulating national recommendations and practical guidelines, and relevant national websites. **CONTENT:** As of July 2019, the Netherlands and Turkey are the only European countries with fully implemented national HPV-based cervical cancer screening. Italy, Sweden and Finland have already implemented HPV-based screening in several regions, and several other countries are at various stages of implementation. Some countries are considering transitioning from cytology-based to HPV-based screening, but are struggling with the suboptimal performance of current population-based programmes. Implementation of HPV-based screening has resulted in higher colposcopy referral rates, but also higher detection rates of CIN3+ lesions and cervical cancers requiring immediate treatment. Cytology is mostly used as a triage test, although other strategies are under consideration in some countries. **IMPLICATIONS:** HPV-based screening is best suited in organized population-based screening settings. In 2019, cervical cancer screening policies across Europe vary greatly. Experience in countries with national and regional HPV-based screening already implemented is generally very positive. Urgent action is needed in many European countries, especially those with suboptimal opportunistic cytology-based cervical cancer screening.

Thomsen, L. T., S. K. Kjær, C. Munk, K. Frederiksen, D. Ørnskov and M. Waldstrøm (2020). **"Clinical Performance of Human Papillomavirus (HPV) Testing versus Cytology for Cervical Cancer Screening: Results of a Large Danish Implementation Study."** *Clin Epidemiol* **12**: 203-213.

BACKGROUND: Human papillomavirus (HPV) testing is increasingly used as the primary cervical cancer screening test. In a large pilot implementation, we compared participation, referrals and detection of high-grade cervical intraepithelial neoplasia (CIN) in HPV- versus cytology-based cervical cancer screening. **METHODS:** The implementation was embedded into the routine screening program at Lillebaelt Hospital, Department of Pathology, Vejle, Denmark. Based on the area of residence, women aged 30-59 years were screened by either HPV testing (with HPV16/18

genotyping and cytology triage) or cytology (with HPV triage for minor abnormalities). Our analysis includes women invited or screened during May 2017-May 2018 (invited: n=35,081; screened: n=28,352) with 6 months of follow-up. Information on screening results and sociodemographic characteristics were obtained from registers. Using logistic regression, we estimated odds ratios (ORs) with 95% confidence intervals (CIs) of participation, referral and CIN3+-detection in HPV- versus cytology-based screening, adjusting for sociodemographic characteristics. RESULTS: Participation was virtually identical in the HPV- and cytology group (58.4% vs 58.8%; OR(adjusted)=0.97, 95% CI, 0.93-1.01). Referral to colposcopy was more common in the HPV- than cytology group (3.8% vs 2.1%; OR(adjusted)=1.88, 95% CI, 1.63-2.17). More cases of CIN3+ were detected in the HPV- than cytology group (1.0% vs 0.7%, OR(adjusted)=1.47; 95% CI, 1.13-1.91). CONCLUSION: Participation did not differ between HPV- and cytology-based screening. HPV-based screening detected more cases of CIN3+, but in this initial screening round also led to more colposcopies than cytology-based screening.

Kyrgiou, M., M. Arbyn, C. Bergeron, F. X. Bosch, J. Dillner, M. Jit, J. Kim, M. Poljak, P. Nieminen, P. Sasieni, V. Kesic, J. Cuzick and M. Gultekin (2020). "**Cervical screening: ESGO-EFC position paper of the European Society of Gynaecologic Oncology (ESGO) and the European Federation of Colposcopy (EFC).**" Br J Cancer.

This paper summarises the position of ESGO and EFC on cervical screening based on existing guidelines and opinions of a team of lead experts. HPV test is replacing cytology as this offers greater protection against cervical cancer and allows longer screening intervals. Only a dozen of HPV tests are considered as clinically validated for screening. The lower specificity of HPV test dictates the use of triage tests that can select women for colposcopy. Reflex cytology is currently the only well validated triage test; HPV genotyping and p16 immunostaining may be used in the future, although methylation assays and viral load also look promising. A summary of quality assurance benchmarks is provided, and the importance to audit the screening histories of women who developed cancer is noted as a key objective. HPV-based screening is more cost-effective than cytology or cotesting. HPV-based screening should continue in the post-vaccination era. Only a fraction of the female population is vaccinated, and this varies across countries. A major challenge will be to personalise screening frequency according to vaccination status. Still the most important factor for successful prevention by screening is high population coverage and organised screening. Screening with self-sampling to reach under-screened women is promising.

Bhatla, N. and S. Singhal (2020). "**Primary HPV screening for cervical cancer.**" Best Pract Res Clin Obstet Gynaecol **65**: 98-108.

Cytology-based cervical screening had unequivocal success in reducing the incidence and mortality of cervical cancer in the last century. The recognition of the role of human papillomavirus (HPV) as a necessary cause of cervical cancer led to the development of HPV testing. Gradually, there has been a shift from reflex HPV testing for mild cytological abnormalities, to co-testing with cytology and HPV, and lately to primary HPV screening, based on evidence from well-designed large randomized controlled trials and meta-analyses. Advantages of primary HPV screening include higher sensitivity to detect pre-neoplastic lesions, better re-assurance with a negative test, and safe prolongation of screening intervals. However, clinicians and policy makers must ensure the availability of clinically validated HPV assays and triage protocols of screen positive cases prior to implementation of primary HPV screening. This is likely to reduce potential harm from over-treatment as well as extra burden on the health care system.

Poljak, M., A. Oštrbenk Valenčak, G. Gimpelj Domjanič, L. Xu and M. Arbyn (2020). "**Commercially available molecular tests for human papillomaviruses: a global overview.**" Clin Microbiol Infect.

BACKGROUND: Molecular tests for detection of human papillomaviruses (HPVs) play a crucial role in the prevention of cervical cancer, including recently announced elimination efforts. HPV testing is a recommended approach for cervical cancer screening of women over 30 and for management of those with precancerous cervical lesions. In addition, they are widely used in epidemiological studies, HPV surveillance and vaccination impact monitoring. OBJECTIVES: The aim was to provide an updated 2020 inventory of commercial molecular HPV tests available on the market. SOURCES: Data were retrieved from internal files, and a detailed search using Medline/Pubmed, Web of Science, Scopus, Google Scholar, Google and Bing, without language or period restrictions, was performed in September 2019 and again in January 2020. CONTENT: We identified 254 distinct commercial HPV tests and at least 425 test variants available on the global market in 2020, which represents a 31% and 235% increase in the number of distinct tests and variants, respectively, compared with the previous inventory performed in 2015. Although the proportion of commercially available HPV tests with at least one peer-reviewed publication has increased over the past decade, 60% of the HPV tests on the global market are still without a single peer-reviewed publication. Furthermore, 82% of tests lack any published analytical and/or clinical evaluation, and over 90% are not evaluated in line with consensus requirements that ensure safe use in clinical settings. IMPLICATIONS: Significant challenges and scope for improvement still exist for both the HPV scientific community and the manufacturers of HPV tests. The latter must put more effort into validating their products, in agreement with standardized procedures, including all steps of HPV testing and various clinical specimens. High throughput capacity and point-of-care HPV tests are needed, both with affordable prices.

Chao, Y. S., M. Clark, E. Carson, L. Weeks, K. Moulton, S. McFaul, C. M. McLauchlin, B. Tsoi, U. Majid, S. Kandasamy, N. Arora, M. Vanstone, L. Reid, T. Krahn, K. Kaluzny, K. Farrah and C. Ford (2019). CADTH Optimal Use Reports. **HPV Testing for Primary Cervical Cancer Screening: A Health Technology Assessment.** Ottawa (ON), Canadian Agency for Drugs and Technologies in Health
Copyright © 2019 Canadian Agency for Drugs and Technologies in Health.

The objective of this health technology assessment (HTA) is to address the policy question by assessing the diagnostic test accuracy, clinical utility, safety, cost-effectiveness, patients' experiences and perspectives, ethical issues, and implementation issues of HPV testing as a primary screening tool for cervical cancer screening. This HTA was conducted to inform decision-making, policy development, capacity planning, and recommendations around primary HPV-based testing for cervical cancer screening.

Salazar, K. L., D. J. Duhon, R. Olsen and M. Thrall (2019). "**A review of the FDA-approved molecular testing platforms for human papillomavirus.**" J Am Soc Cytopathol **8**(5): 284-292.

The advent of US Food and Drug Administration (FDA)-approved molecular testing for human papillomavirus (HPV) has resulted in a dramatic shift from cytological testing alone to a combination of cytology and molecular testing for primary HPV screening. HPV testing has quickly become an essential component of daily practice in most laboratories and clinical practices. Although the principle of HPV testing is now familiar, it is important to understand the mechanisms behind these platforms in order to properly interpret the results and understand the limits of each method. HPV tests are more automated and reproducible than cytology, but are by no means perfect. None of these platforms will identify every HSIL/CIN2+ or cancer. This fact must be kept in mind when correlating the results of HPV testing with cytology or biopsy findings. The goal of this paper is to review the FDA- approved molecular testing platforms for HPV, including

methodology, limitations, and specifications. The concordance between the platforms will also be discussed. Package inserts of the 5 FDA- approved molecular testing platforms for HPV, as well as a literature review of the platforms, were reviewed and assimilated into the article. Due to the multiple modalities available for detection of hrHPV, the concordance between these assays becomes important. Prior publications have compared HC2, Cervista, cobas, and Aptima, with most studies comparing to HC2 because it is considered the reference standard. With the newly approved BD platform, concordance studies were reviewed as well.

Hall, M. T., K. T. Simms, J. B. Lew, M. A. Smith, J. M. Brotherton, M. Saville, I. H. Frazer and K. Canfell (2019). **"The projected timeframe until cervical cancer elimination in Australia: a modelling study."** *Lancet Public Health* 4(1): e19-e27.

BACKGROUND: In 2007, Australia was one of the first countries to introduce a national human papillomavirus (HPV) vaccination programme, and it has since achieved high vaccination coverage across both sexes. In December, 2017, organised cervical screening in Australia transitioned from cytology-based screening every 2 years for women aged from 18-20 years to 69 years, to primary HPV testing every 5 years for women aged 25-69 years and exit testing for women aged 70-74 years. We aimed to identify the earliest years in which the annual age-standardised incidence of cervical cancer in Australia (which is currently seven cases per 100 000 women) could decrease below two annual thresholds that could be considered to be potential elimination thresholds: a rare cancer threshold (six new cases per 100 000 women) or a lower threshold (four new cases per 100 000 women), since Australia is likely to be one of the first countries to reach these benchmarks. **METHODS:** In this modelling study, we used Policy1-Cervix-an extensively validated dynamic model of HPV vaccination, natural history, and cervical screening-to estimate the age-standardised incidence of cervical cancer in Australia from 2015 to 2100. We incorporated age-specific coverage of the Australian National HPV Vaccination Program in girls, including the catch-up programme, and the inclusion of boys into the vaccine programme from 2013, and a change from the quadrivalent to the nonavalent vaccine from 2018. We also modelled the effects of the transition to primary HPV screening. We considered two scenarios for future screening recommendations regarding the cohorts who will be and who have been offered the nonavalent vaccine: either that HPV screening every 5 years continues, or that no screening would be offered to these women. **FINDINGS:** We estimate that, in Australia, the age-standardised annual incidence of cervical cancer will decrease to fewer than six new cases per 100 000 women by 2020 (range 2018-22), and to fewer than four new cases per 100 000 women by 2028 (2021-35). The precise year of attaining these rates is dependent on the population used for age-standardisation, HPV screening behaviour and test characteristics, the incremental effects of vaccination of men on herd immunity in women, and assumptions about the future frequency of benign hysterectomies. By 2066 (2054-77), the annual incidence of cervical cancer will decrease and remain at fewer than one case per 100 000 women if screening for HPV every 5 years continues for cohorts who have been offered the nonavalent vaccine, or fewer than three cases per 100 000 women if these cohorts are not screened. Cervical cancer mortality is estimated to decrease to less than an age-standardised annual rate of one death per 100 000 women by 2034 (2025-47), even if future screening is only offered to older cohorts that were not offered the nonavalent vaccine. **INTERPRETATION:** If high-coverage vaccination and screening is maintained, at an elimination threshold of four new cases per 100 000 women annually, cervical cancer could be considered to be eliminated as a public health problem in Australia within the next 20 years. However, screening and vaccination initiatives would need to be maintained thereafter to maintain very low cervical

cancer incidence and mortality rates. FUNDING: National Health and Medical Research Council (Australia).

Simms, K. T., J. Steinberg, M. Caruana, M. A. Smith, J. B. Lew, I. Soerjomataram, P. E. Castle, F. Bray and K. Canfell (2019). "**Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020-99: a modelling study.**" Lancet Oncol **20**(3): 394-407.

BACKGROUND: Cervical screening and human papillomavirus (HPV) vaccination have been implemented in most high-income countries; however, coverage is low in low-income and middle-income countries (LMICs). In 2018, the Director-General of WHO announced a call to action for the elimination of cervical cancer as a public health problem. WHO has called for global action to scale-up vaccination, screening, and treatment of precancer, early detection and prompt treatment of early invasive cancers, and palliative care. An elimination threshold in terms of cervical cancer incidence has not yet been defined, but an absolute rate of cervical cancer incidence could be chosen for such a threshold. In this study, we aimed to quantify the potential cumulative effect of scaled up global vaccination and screening coverage on the number of cervical cancer cases averted over the 50 years from 2020 to 2069, and to predict outcomes beyond 2070 to identify the earliest years by which cervical cancer rates could drop below two absolute levels that could be considered as possible elimination thresholds—the rare cancer threshold (six new cases per 100 000 women per year, which has been observed in only a few countries), and a lower threshold of four new cases per 100 000 women per year. METHODS: In this statistical trends analysis and modelling study, we did a statistical analysis of existing trends in cervical cancer worldwide using high-quality cancer registry data included in the Cancer Incidence in Five Continents series published by the International Agency for Research on Cancer. We then used a comprehensive and extensively validated simulation platform, Policy1-Cervix, to do a dynamic multicohort modelled analysis of the impact of potential scale-up scenarios for cervical cancer prevention, in order to predict the future incidence rates and burden of cervical cancer. Data are presented globally, by Human Development Index (HDI) category, and at the individual country level. FINDINGS: In the absence of further intervention, there would be 44.4 million cervical cancer cases diagnosed globally over the period 2020-69, with almost two-thirds of cases occurring in low-HDI or medium-HDI countries. Rapid vaccination scale-up to 80-100% coverage globally by 2020 with a broad-spectrum HPV vaccine could avert 6.7-7.7 million cases in this period, but more than half of these cases will be averted after 2060. Implementation of HPV-based screening twice per lifetime at age 35 years and 45 years in all LMICs with 70% coverage globally will bring forward the effects of prevention and avert a total of 12.5-13.4 million cases in the next 50 years. Rapid scale-up of combined high-coverage screening and vaccination from 2020 onwards would result in average annual cervical cancer incidence declining to less than six new cases per 100 000 individuals by 2045-49 for very-high-HDI countries, 2055-59 for high-HDI countries, 2065-69 for medium-HDI countries, and 2085-89 for low-HDI countries, and to less than four cases per 100 000 by 2055-59 for very-high-HDI countries, 2065-69 for high-HDI countries, 2070-79 for medium-HDI countries, and 2090-2100 or beyond for low-HDI countries. However, rates of less than four new cases per 100 000 would not be achieved in all individual low-HDI countries by the end of the century. If delivery of vaccination and screening is more gradually scaled up over the period 2020-50 (eg, 20-45% vaccination coverage and 25-70% once-per-lifetime screening coverage by 2030, increasing to 40-90% vaccination coverage and 90% once-per-lifetime screening coverage by 2050, when considered as average coverage rates across HDI categories), end of the century incidence rates will be reduced by a lesser amount. In this scenario,

average cervical cancer incidence rates will decline to 0.8 cases per 100 000 for very-high-HDI countries, 1.3 per 100 000 for high-HDI countries, 4.4 per 100 000 for medium-HDI countries, and 14 per 100 000 for low-HDI countries, by the end of the century. INTERPRETATION: More than 44 million women will be diagnosed with cervical cancer in the next 50 years if primary and secondary prevention programmes are not implemented in LMICs. If high coverage vaccination can be implemented quickly, a substantial effect on the burden of disease will be seen after three to four decades, but nearer-term impact will require delivery of cervical screening to older cohorts who will not benefit from HPV vaccination. Widespread coverage of both HPV vaccination and cervical screening from 2020 onwards has the potential to avert up to 12.5-13.4 million cervical cancer cases by 2069, and could achieve average cervical cancer incidence of around four per 100 000 women per year or less, for all country HDI categories, by the end of the century. A draft global strategy to accelerate cervical cancer elimination, with goals and targets for the period 2020-30, will be considered at the World Health Assembly in 2020. The findings presented here have helped inform initial discussions of elimination targets, and ongoing comparative modelling with other groups is supporting the development of the final goals and targets for cervical cancer elimination. FUNDING: National Health and Medical Research Council (NHMRC) Australia, part-funded via the NHMRC Centre of Excellence for Cervical Cancer Control (C4; APP1135172).

Smith, M., I. Hammond and M. Saville (2019). "**Lessons from the renewal of the National Cervical Screening Program in Australia.**" Public Health Res Pract **29**(2).

OBJECTIVES: Australia was one of the first countries to make the transition from cytology-based to HPV-based cervical screening. This analysis of the national program's transition to a new model looks at the lessons learnt that can provide valuable insights to other settings. Type of program: Australia's National Cervical Screening Program (NCSP). METHODS: Following an extensive policy review, in December 2017 the NCSP transitioned from 2-yearly cytology-based screening in women from age 18, to 5-yearly primary HPV screening from age 25. RESULTS: Some changes were more complex than initially anticipated. Building and implementing the National Cancer Screening Register was a more demanding and specialised project than expected. Regulatory requirements for self-collection were unexpectedly onerous, because self-collection was not formally included as an intended use by HPV test manufacturers. This delayed the rollout of a key measure to improve participation and equity. Colposcopy demand was expected to increase substantially but exceeded expectations. Uncertainty about appropriate clinical management or testing outside guideline recommendations may have contributed to the excess demand, highlighting the importance of training providers in the rationale for guidelines as well as the content. LESSONS LEARNED: Although the changes were evidence based, there were nevertheless some concerns among women and healthcare providers, especially about the longer interval and later starting age for screening. These could have been reduced through earlier and more extensively delivered information to healthcare providers, who play a key role in addressing community concerns. Improved coordination of stakeholder support between government and nongovernment organisations may also have extended both the reach and credibility of communication about the program changes. Transitioning a well-established program is challenging, not only because of the changes required, but also because the existing program must continue to function until the transition. Delays may be hard to avoid, but early communication will enable better forward planning, especially by service providers. Since delays can reduce wider confidence in the changes, proactive communication is critical. Achieving high and equitable screening coverage is a key element if Australia and other countries are to succeed in eliminating cervical cancer as a public health problem. Improving screening program confidence

and participation remain important ongoing work. Lessons from Australia will provide valuable insights for other countries making similar changes.

Rebolj, M., J. Rimmer, K. Denton, J. Tidy, C. Mathews, K. Ellis, J. Smith, C. Evans, T. Giles, V. Frew, X. Tyler, A. Sargent, J. Parker, M. Holbrook, K. Hunt, P. Tidbury, T. Levine, D. Smith, J. Patnick, R. Stubbs, S. Moss and H. Kitchener (2019). **"Primary cervical screening with high risk human papillomavirus testing: observational study."** *Bmj* **364**: l240.

OBJECTIVE: To provide the first report on the main outcomes from the prevalence and incidence rounds of a large pilot of routine primary high risk human papillomavirus (hrHPV) testing in England, compared with contemporaneous primary liquid based cytology screening. **DESIGN:** Observational study. **SETTING:** The English Cervical Screening Programme. **PARTICIPANTS:** 578 547 women undergoing cervical screening in primary care between May 2013 and December 2014, with follow-up until May 2017; 183 970 (32%) were screened with hrHPV testing. **INTERVENTIONS:** Routine cervical screening with hrHPV testing with liquid based cytology triage and two early recalls for women who were hrHPV positive and cytology negative, following the national screening age and interval recommendations. **MAIN OUTCOME MEASURES:** Frequency of referral for a colposcopy; adherence to early recall; and relative detection of cervical intraepithelial neoplasia grade 2 or worse from hrHPV testing compared with liquid based cytology in two consecutive screening rounds. **RESULTS:** Baseline hrHPV testing and early recall required approximately 80% more colposcopies, (adjusted odds ratio 1.77, 95% confidence interval 1.73 to 1.82), but detected substantially more cervical intraepithelial neoplasia than liquid based cytology (1.49 for cervical intraepithelial neoplasia grade 2 or worse, 1.43 to 1.55; 1.44 for cervical intraepithelial neoplasia grade 3 or worse, 1.36 to 1.51) and for cervical cancer (1.27, 0.99 to 1.63). Attendance at early recall and colposcopy referral were 80% and 95%, respectively. At the incidence screen, the 33 506 women screened with hrHPV testing had substantially less cervical intraepithelial neoplasia grade 3 or worse than the 77 017 women screened with liquid based cytology (0.14, 0.09 to 0.23). **CONCLUSIONS:** In England, routine primary hrHPV screening increased the detection of cervical intraepithelial neoplasia grade 3 or worse and cervical cancer by approximately 40% and 30%, respectively, compared with liquid based cytology. The very low incidence of cervical intraepithelial neoplasia grade 3 or worse after three years supports extending the screening interval.

Malagón, T., S. Kulasingam, M. H. Mayrand, G. Ogilvie, L. Smith, C. Bouchard, W. Gotlieb and E. L. Franco (2018). **"Age at last screening and remaining lifetime risk of cervical cancer in older, unvaccinated, HPV-negative women: a modelling study."** *Lancet Oncol* **19**(12): 1569-1578.

BACKGROUND: There is a paucity of empirical evidence to inform the age at which to stop cervical cancer screening. The recommended age to stop screening generally varies between age 50-70 years worldwide. However, cervical cancer incidence and mortality remain high in older women. We used a Markov model of cervical cancer screening to estimate the remaining lifetime risk of cervical cancer at different ages and with different exit screening tests, with the aim of informing recommendations of the age at which to stop cervical cancer screening in developed countries. **METHODS:** For this modelling study, we developed a state transition (Markov) model of cervical cancer natural history and screening. We developed, calibrated, and validated our model using Canadian provincial registries and survey data. To simulate an age-structured population in the model, a new cohort of 236 564 women (one fifth of the population of Canadian women aged 20-24 years in 2012) entered the model every year and were successively modelled in parallel. Successive cohorts entered the model at age 10 years, creating an age-structured population of

women aged 10-100 years. Women who had a total hysterectomy were excluded from the analyses. We calibrated our model to human papillomavirus (HPV) infection and cancer incidence with data from Statistics Canada, which compiles the data from 13 individual provincial registries. We chose a three-stage progressive cervical intraepithelial neoplasia model to include differences in management and treatment decisions depending on lesion severity. We modelled infections with four high-risk HPV groups: HPV16 and HPV18; HPV31, HPV33, HPV45, HPV52, and HPV58; HPV35, HPV39, HPV51, HPV56, HPV59, HPV66, and HPV68; and a generic group of other potentially oncogenic HPVs. We estimated 5-year, 10-year, and remaining lifetime risk of cervical cancer for older, unvaccinated women who stopped screening at different ages and underwent different screening tests. FINDINGS: Cervical cancer incidence excluding women with hysterectomies underestimated the incidence of cervical cancer in women with a cervix by up to 71% in women aged 80-84 years. Our model predicted that women without HPV vaccination who have been never screened have a 1 in 45 (95% percentile interval 1 in 32 to 1 in 64) lifetime risk of cervical cancer. Perfect adherence (100% of women screened) to cytology screening every 3 years between the ages of 25 years and 69 years could reduce the lifetime risk of cervical cancer to 1 in 532 women (95% percentile interval 1 in 375 to 1 in 820) without HPV vaccination. Increasing the age at which women stopped cytology screening from 55 years to 75 years led to incremental decreases in cancer risk later in life. A 70-year old woman whose screening history was unknown had an average remaining lifetime risk of 1 in 588 (<1%; 95% percentile interval 1 in 451 to 1 in 873) if she stopped screening. Her remaining lifetime risk at age 70 years was reduced to 1 in 1206 (2.0 times reduction; 95% percentile interval 1 in 942 to 1 in 1748) if she had a negative cytology test, 1 in 6525 (12.9 times reduction; 95% percentile interval 1 in 3167 to 1 in 18 664) if she had a negative HPV test, and 1 in 9550 (18.1 times reduction; 95% percentile interval 1 in 4928 to 1 in 23 228) if she had a negative co-test for cytology and HPV. INTERPRETATION: Cervical cancer risk reductions might be achieved by screening with cytology up to age 75 years, although with diminishing returns. A negative exit oncogenic HPV test or negative HPV test plus cytology correlates with a low remaining lifetime cervical cancer risk for unvaccinated women with a cervix after the age of 55 years. FUNDING: Canadian Institutes of Health Research.

Hawkes, D. (2018). "**Human papillomavirus testing as part of the renewed National Cervical Screening Program.**" *Aust J Gen Pract* **47**(7): 412-414.

BACKGROUND: On 1 December 2017, Australia moved to a new National Cervical Screening Program (NCSP), which uses primary human papillomavirus (HPV) nucleic acid testing (NAT) followed by reflex liquid-based cytology for women aged between 25 and 74 years. OBJECTIVE: The aim of this article is to provide an overview of the different HPV NAT assays that satisfy the requirements for use in the renewed NCSP. DISCUSSION: Australia has adopted innovative, evidence-based criteria for the inclusion of HPV NAT assays in the renewed NCSP. These include the requirements for detection of all 12 designated oncogenic HPV types, including separate detection and reporting of HPV 16 and 18; validation against reference assays showing sufficient sensitivity and specificity for the detection of underlying high-grade cervical disease; reproducibility; and the presence of cellularity and inhibition controls. Practitioners can feel assured that HPV NAT undertaken as part of the renewed NCSP will produce high-quality results irrespective of location or pathology provider.

Esber, A., A. Norris, E. Jumbe, J. Kandodo, P. Nampondeni, P. C. Reese and A. N. Turner (2018). "**Feasibility, validity and acceptability of self-collected samples for human papillomavirus (HPV) testing in rural Malawi.**" *Malawi Med J* **30**(2): 61-66.

AIM: The World Health Organization (WHO) recently endorsed human papillomavirus (HPV) testing as a cervical cancer screening method in countries without established programs. Self-collection for HPV testing may be an effective way to expand screening. Our objective was to assess the feasibility, validity, and acceptability of self-collection for HPV testing in a population of care-seeking, unscreened women in rural Malawi. **METHODS:** We enrolled women reporting to a rural Malawian clinic from January to August 2015. Participants were offered the option to self-collect a vaginal sample and the study clinician collected a cervical sample for HPV testing. Using the clinician-collected sample as the reference standard, we calculated a kappa statistic, sensitivity, and specificity by hr-HPV type. Participants also received a brief survey assessing acceptability of the procedure. **RESULTS:** Among the 199 enrolled women, 22% had any high risk-HPV. Comparing self- and clinician-collected samples for HPV testing, we found generally high agreement ($\kappa = 0.66-0.90$) and high specificity (98%-100%), but varied sensitivity (50%-91%) for different types of hr-HPV. We also found that self-collection was acceptable, with 98% of women reporting it was easy to do and 99% reporting willingness to do so again. **CONCLUSIONS:** WHO guidelines recommend that treatment is available immediately after a positive screening test for clinic-based cervical cancer screening programs. Our findings demonstrate that self-collection of samples for HPV testing is a feasible and acceptable method of cervical cancer screening in this rural Malawian population. High agreement between the self- and clinician-collected samples and high levels of acceptability among women in the study suggest that self-collection of vaginal samples for HPV testing may be effectively incorporated into screening programs among rural, largely unscreened populations.

Pankaj, S., S. Nazneen, S. Kumari, A. Kumari, A. Kumari, J. Kumari, V. Choudhary and S. Kumar (2018). **"Comparison of conventional Pap smear and liquid-based cytology: A study of cervical cancer screening at a tertiary care center in Bihar."** *Indian J Cancer* 55(1): 80-83.

BACKGROUND: Cervical cancer is the fourth leading cause of cancer in women in the world and it is the second most common cancer in women 15-44 years of age. Strict implementation of screening programs has led to a large decrease in cervical cancer incidence and mortality in the developed countries. In contrast, cervical cancer remains largely uncontrolled in high-risk developing countries because of ineffective or no screening programs. Conventional Pap smear method has been the mainstay of most of the screening programs for many decades. However, this technique is not without limitations, and the sensitivity and specificity of cervical cytology are relatively low. To overcome the limitations of conventional Pap smear (CPS), liquid-based cytology (LBC) was introduced in 1990s as a better tool for processing cervical samples. **OBJECTIVES:** This study was undertaken to compare CPS with liquid-based methods, to assess the effectiveness and feasibility of LBC over CPS in our setting, and also to evaluate the prevalence of human papillomavirus (HPV) in our population. **MATERIALS AND METHODS:** This study was conducted in Gynecological Oncology Unit of Regional Cancer Center at Indira Gandhi Institute of Medical Sciences, Patna, Bihar. About 310 women were enrolled in this study and the sample was taken for both conventional cytology and LBC. The smears were studied in detail and were interpreted as per the Bethesda system of reporting Pap smears. The results were compared and analyzed statistically. **RESULTS:** Unsatisfactory smears were more commonly reported by conventional method (7.1%) than with liquid-based method (1.61%), and this difference is statistically significant. There was no difference in the detection of epithelial cell abnormalities using both the methods. HPV DNA for high-risk oncogenic strains (16 and 18) was detected in 6.45% of women in this study. **CONCLUSION:** LBC has been found to be more superior to conventional smears only with respect to lesser number of unsatisfactory smears, but considering the economic implications of LBC, conventional Pap is more feasible in our setting.

Silver, M. I., A. F. Rositch, D. F. Phelan-Emrick and P. E. Gravitt (2018). **"Uptake of HPV testing and extended cervical cancer screening intervals following cytology alone and Pap/HPV cotesting in women aged 30-65 years."** *Cancer Causes Control* **29**(1): 43-50.

OBJECTIVE: To evaluate the adoption of HPV testing and recommended extended cervical cancer screening intervals in clinical practice, we described yearly uptake of Pap/HPV cotesting and estimated length of time between normal screens by patient characteristics. **METHODS:** We examined 55,575 Pap/HPV records from 27,035 women aged 30-65 years from the Johns Hopkins Hospital Pathology Data System between 2006 and 2013. Cotest uptake and median times to next screening test for cotests and cytology only were calculated. Adjusted hazard ratios were estimated using Cox proportional hazards models, with random effects adjustment for clustering within clinic. **RESULTS:** Cotest usage increased from < 10% in 2006 to 78% in 2013. The median time to next screening test following normal cytology alone remained constant around 1.5 years. Screening intervals following a dual-negative cotest increased from 1.5 years in 2006/2007 to 2.5 years in 2010, coincident with increases in the proportion of women cotested. Intervals following a dual negative cotest were longer among Medicare patients (3 years) compared with privately insured women (2.5 years), and shorter among black (2 years) compared with white women (2.8 years). **CONCLUSION:** By mid-2013 we observed broad adoption of Pap/HPV cotesting in routine screening in a large academic medical center. Increased screening intervals were observed only among cotested women, while those screened by cytology alone continued to be screened almost annually. The influence of different combinations of race and insurance on screening intervals should be further evaluated to ensure balance of screening risks and benefits in the U.S.

Tatar, O., E. Thompson, A. Naz, S. Perez, G. K. Shapiro, K. Wade, G. Zimet, V. Gilca, M. Janda, J. Kahn, E. Daley and Z. Rosberger (2018). **"Factors associated with human papillomavirus (HPV) test acceptability in primary screening for cervical cancer: A mixed methods research synthesis."** *Prev Med* **116**: 40-50.

Primary screening for cervical cancer is transitioning from the longstanding Pap smear towards implementation of an HPV-DNA test, which is more sensitive than Pap cytology in detecting high-risk lesions and offers greater protection against invasive cervical carcinomas. Based on these results, many countries are recommending and implementing HPV testing-based screening programs. Understanding what factors (e.g., knowledge, attitudes) will impact on HPV test acceptability by women is crucial for ensuring adequate public health practices to optimize cervical screening uptake. We used mixed methods research synthesis to provide a categorization of the relevant factors related to HPV primary screening for cervical cancer and describe their influence on women's acceptability of HPV testing. We searched Medline, Embase, PsycINFO, CINAHL, Global Health and Web of Science for journal articles between January 1, 1980 and October 31, 2017 and retained 22 empirical articles. Our results show that while most factors associated with HPV test acceptability are included in the Health Belief Model and/or Theory of Planned Behavior (e.g., attitudes, knowledge), other important factors are not encompassed by these theoretical frameworks (e.g., health behaviors, negative emotional reactions related to HPV testing). The direction of influence of psychosocial factors on HPV test acceptability was synthesized based on 14 quantitative studies as: facilitators (e.g., high perceived HPV test benefits), barriers (e.g., negative attitudes towards increased screening intervals), contradictory evidence (e.g., sexual history) and no impact (e.g., high perceived severity of HPV infection). Further population-based studies are needed to confirm the impact of these factors on HPV-based screening acceptability.

Tota, J. E., J. Bentley, J. Blake, F. Coutlée, M. A. Duggan, A. Ferenczy, E. L. Franco, M. Fung-Kee-Fung, W. Gotlieb, M. H. Mayrand, M. McLachlin, J. Murphy, G. Ogilvie and S. Ratnam (2017). **"Introduction of molecular HPV testing as the primary technology in cervical cancer screening: Acting on evidence to change the current paradigm."** *Prev Med* **98**: 5-14.

Since being introduced in the 1940s, cervical cytology - despite its limitations - has had unequivocal success in reducing cervical cancer burden in many countries. However, we now know that infection with human papillomavirus (HPV) is a necessary cause of cervical cancer and there is overwhelming evidence from large-scale clinical trials, feasibility studies and real-world experience that supports the introduction of molecular testing for HPV as the primary technology in cervical cancer screening (i.e., "HPV primary screening"). While questions remain about the most appropriate age groups for screening, screening interval and triage approach, these should not be considered barriers to implementation. Many countries are in various stages of adopting HPV primary screening, whereas others have not taken any major steps towards introduction of this approach. As a group of clinical experts and researchers in cervical cancer prevention from across Canada, we have jointly authored this comprehensive examination of the evidence to implement HPV primary screening. Our intention is to create a common understanding among policy makers, agencies, clinicians, researchers and other stakeholders about the evidence concerning HPV primary screening to catalyze the adoption of this improved approach to cervical cancer prevention. With the first cohort of vaccinated girls now turning 21, the age when routine screening typically begins, there is increased urgency to introduce HPV primary screening, whose performance may be less adversely affected compared with cervical cytology as a consequence of reduced lesion prevalence post-vaccination.

Wentzensen, N. and M. Arbyn (2017). **"HPV-based cervical cancer screening- facts, fiction, and misperceptions."** *Prev Med* **98**: 33-35.

Several randomized trials have demonstrated that HPV-based cervical cancer screening is more effective than cytology-based screening. A pooled analysis of long-term follow-up data from these trials has shown reduced cervical cancer mortality in women screened with HPV compared to cytology. As a consequence, many health systems are currently transitioning to HPV-based screening programs. However, there are several controversies that influence whether and how HPV-based cervical cancer screening is implemented in different settings. Here, we discuss the most important controversies surrounding cervical cancer screening using primary HPV testing in light of published data from clinical trials and large observational studies. Overall, there is strong and uniform evidence for the efficacy of HPV-based screening, and little evidence for the usefulness of adding cytology to primary screening. However, there is currently limited data on optimal triage strategies for HPV-positive women, a critical component of an HPV-based screening program. There will likely be multiple choices for integrated screening programs and implementation may differ depending on risk perception, healthcare funds, assay costs, and available infrastructure, among other factors, in different settings. A particular challenge is the integration of screening and vaccination programs, since increasingly vaccinated populations will have a continuous decrease of cervical cancer risk.

Mariani, L., S. Igidbashian, M. T. Sandri, P. Vici and F. Landoni (2017). **"The clinical implementation of primary HPV screening."** *Int J Gynaecol Obstet* **136**(3): 266-271.

OBJECTIVE: To evaluate, from a gynecology perspective, the transition from cytology-based HPV screening to primary HPV screening. METHODS: Studies examining switching from cytology-based screening to primary HPV-DNA testing with triaging of patients with positive test results were retrieved and reviewed, with a particular focus on screening in an Italian setting. RESULTS: The

increased complexity of patient-management decisions when implementing HPV-based screening was a critical issue discussed in the literature. The change in strategy represents a paradigm shift in moving from a medical perspective of identifying the disease in individual patients, to a public-healthcare perspective of excluding HPV from the healthy population and identifying a small sub-group of individuals at increased risk of HPV. CONCLUSION: With knowledge about HPV screening evolving rapidly, new programs and related algorithms need to be sufficiently flexible to be adjusted according to ongoing research and the validation of new assays. The establishment of a national working group (including epidemiologists, gynecologists, pathologists, and healthcare providers) will be necessary to properly implement and govern this important technical and cultural transition.

Adsul, P., N. Manjunath, V. Srinivas, A. Arun and P. Madhivanan (2017). "**Implementing community-based cervical cancer screening programs using visual inspection with acetic acid in India: A systematic review.**" *Cancer Epidemiol* 49: 161-174.

The objective of this review was to systematically appraise the existing published literature about community-based cervical cancer screening programs that have used visual inspection methods using acetic acid (VIA) in India. All peer reviewed journal articles till December 2015 were searched per PRISMA guidelines. Articles reporting results from cervical cancer screening programs in community-based settings, conducted in India, and using VIA were included in this review. The search resulted in 20 articles to be included in the review with a total of 313,553 women at 12 unique urban and rural sites across India. Seventeen (85%) studies were cross-sectional and three studies were randomized controlled trials; most studies compared accuracy of VIA with other screening tests such as visual inspection using Lugol's Iodine (VILI), HPV DNA, and cytology. Of studies that reported test accuracy for CIN Grade 2+, the VIA sensitivity values ranged from 16.6-82.6% and specificity ranged from 82.1-96.8%. Women between age groups of 30-59 years were recruited using motivational one-on-one counseling and local support staff. All studies conducted diagnostic follow-up using colposcopy and guided biopsies, when necessary. Three major themes were identified that facilitated implementation of screening programs in a community-based setting: standardized training that maintained competency of test providers; collaborations with community-based organizations that used health education for recruitment of participants; and employing the screen-and-treat method to reduce loss to follow-up. Summarized evidence presented in this review could substantially influence future implementation and sustainment of cervical cancer screening programs at a national level.

Koliopoulos, G., V. N. Nyaga, N. Santesso, A. Bryant, P. P. Martin-Hirsch, R. A. Mustafa, H. Schünemann, E. Paraskevidis and M. Arbyn (2017). "**Cytology versus HPV testing for cervical cancer screening in the general population.**" *Cochrane Database Syst Rev* 8(8): Cd008587.

BACKGROUND: Cervical cancer screening has traditionally been based on cervical cytology. Given the aetiological relationship between human papillomavirus (HPV) infection and cervical carcinogenesis, HPV testing has been proposed as an alternative screening test. OBJECTIVES: To determine the diagnostic accuracy of HPV testing for detecting histologically confirmed cervical intraepithelial neoplasias (CIN) of grade 2 or worse (CIN 2+), including adenocarcinoma in situ, in women participating in primary cervical cancer screening; and how it compares to the accuracy of cytological testing (liquid-based and conventional) at various thresholds. SEARCH METHODS: We performed a systematic literature search of articles in MEDLINE and Embase (1992 to November 2015) containing quantitative data and handsearched the reference lists of retrieved articles. SELECTION CRITERIA: We included comparative test accuracy studies if all women received both HPV testing and cervical cytology followed by verification of the disease status with

the reference standard, if positive for at least one screening test. The studies had to include women participating in a cervical cancer screening programme who were not being followed up for previous cytological abnormalities. DATA COLLECTION AND ANALYSIS: We completed a 2 x 2 table with the number of true positives (TP), false positives (FP), true negatives (TN), and false negatives for each screening test (HPV test and cytology) used in each study. We calculated the absolute and relative sensitivities and the specificities of the tests for the detection of CIN 2+ and CIN 3+ at various thresholds and computed sensitivity ($TP/(TP + FN)$) and specificity ($TN/(TN + FP)$) for each test separately. Relative sensitivity and specificity of one test compared to another test were defined as sensitivity of test-1 over sensitivity of test-2 and specificity of test-1 over specificity of test-2, respectively. To assess bias in the studies, we used the Quality Assessment of Diagnostic test Accuracy Studies (QUADAS) tool. We used a bivariate random-effects model for computing pooled accuracy estimates. This model takes into account the within- and between-study variability and the intrinsic correlation between sensitivity and specificity. MAIN RESULTS: We included a total of 40 studies in the review, with more than 140,000 women aged between 20 and 70 years old. Many studies were at low risk of bias. There were a sufficient number of included studies with adequate methodology to perform the following test comparisons: hybrid capture 2 (HC2) (1 pg/mL threshold) versus conventional cytology (CC) (atypical squamous cells of undetermined significance (ASCUS)+ and low-grade squamous intraepithelial lesions (LSIL)+ thresholds) or liquid-based cytology (LBC) (ASCUS+ and LSIL+ thresholds), other high-risk HPV tests versus conventional cytology (ASCUS+ and LSIL+ thresholds) or LBC (ASCUS+ and LSIL+ thresholds). For CIN 2+, pooled sensitivity estimates for HC2, CC and LBC (ASCUS+) were 89.9%, 62.5% and 72.9%, respectively, and pooled specificity estimates were 89.9%, 96.6%, and 90.3%, respectively. The results did not differ by age of women (less than or greater than 30 years old), or in studies with verification bias. Accuracy of HC2 was, however, greater in European countries compared to other countries. The results for the sensitivity of the tests were heterogeneous ranging from 52% to 94% for LBC, and 61% to 100% for HC2. Overall, the quality of the evidence for the sensitivity of the tests was moderate, and high for the specificity. The relative sensitivity of HC2 versus CC for CIN 2+ was 1.52 (95% CI: 1.24 to 1.86) and the relative specificity 0.94 (95% CI: 0.92 to 0.96), and versus LBC for CIN 2+ was 1.18 (95% CI: 1.10 to 1.26) and the relative specificity 0.96 (95% CI: 0.95 to 0.97). The relative sensitivity of HC2 versus CC for CIN 3+ was 1.46 (95% CI: 1.12 to 1.91) and the relative specificity 0.95 (95% CI: 0.93 to 0.97). The relative sensitivity of HC2 versus LBC for CIN 3+ was 1.17 (95% CI: 1.07 to 1.28) and the relative specificity 0.96 (95% CI: 0.95 to 0.97). AUTHORS' CONCLUSIONS: Whilst HPV tests are less likely to miss cases of CIN 2+ and CIN 3+, these tests do lead to more unnecessary referrals. However, a negative HPV test is more reassuring than a negative cytological test, as the cytological test has a greater chance of being falsely negative, which could lead to delays in receiving the appropriate treatment. Evidence from prospective longitudinal studies is needed to establish the relative clinical implications of these tests.

Carozzi, F. M., A. Del Mistro, K. Cuschieri, H. Frayle, C. Sani and E. Burroni (2016). "HPV testing for primary cervical screening: Laboratory issues and evolving requirements for robust quality assurance." *J Clin Virol* **76 Suppl 1**: S22-s28.

This review aims to highlight the importance of Quality Assurance for Laboratories performing HPV test for Cervical Cancer Screening. An HPV test, to be used as primary screening test, must be validated according to international criteria, based on comparison of its clinical accuracy to HC2 or GP5+/6+ PCR-EIA tests. The number of validated platforms is increasing and appropriate Quality Assurance Programs (QAPs) which can interrogate longitudinal robustness and quality are paramount. This document describes the following topics: (1) the characteristics of an HPV

laboratory and the personnel training needs, to ensure an elevated quality of the entire process and the optimal use of the resources; (2) the Quality Assurance, as both internal (IQA) and external quality assessment (EQA) systems, to be implemented and performed, and the description of the existing EQAs, including limitations; (3) general considerations for an optimal EQA program for hrHPV primary screening Due to the importance of Quality Assurance for this field, international efforts are necessary to improve QA International Collaboration.

Engesæter, B., B. van Diermen Hidle, M. Hansen, P. Moltu, K. M. Staby, S. Borchgrevink-Persen, O. K. Vintermyr, S. Lönnberg, M. Nygård, E. A. Janssen, P. E. Castle and I. K. Christiansen (2016). "**Quality assurance of human papillomavirus (HPV) testing in the implementation of HPV primary screening in Norway: an inter-laboratory reproducibility study.**" *BMC Infect Dis* **16**(1): 698.

BACKGROUND: Human papillomavirus (HPV) testing as primary screening for cervical cancer is currently being implemented in Norway in a randomized controlled fashion, involving three laboratories. As part of the quality assurance programme of the implementation, an evaluation of the inter-laboratory reproducibility of the HPV test was initiated, to ensure satisfactory HPV test reliability in all three laboratories. METHODS: The HPV test used is the cobas 4800 HPV Test, detecting 14 high-risk types with individual HPV genotype results for HPV16 and HPV18. In addition to the three laboratories involved in the implementation, the Norwegian HPV reference laboratory was included as a fourth comparative laboratory. A stratified sample of 500 cervical liquid based cytology (LBC) samples was used in the evaluation, with an aim towards a high-risk HPV positivity of ~25%. Samples were collected at one laboratory, anonymized, aliquoted, and distributed to the other laboratories. RESULTS: Comparison of the test results of all four laboratories revealed a 95.6% agreement, an 86.3% positive agreement and a kappa value of 0.94 (95% CI 0.92-0.97). For negative cytology specimens, there was a 95.8% overall agreement, a 67.4% positive agreement, and a kappa value of 0.88 (95% CI 0.80-0.93). For abnormal cytology specimens, there was a 95.8% overall agreement, a 95.5% positive agreement, and a kappa value of 0.86 (95% CI 0.71-0.97). CONCLUSIONS: The study showed a high inter-laboratory reproducibility of HPV testing, implying satisfactory user performance and reliability in the laboratories involved in the implementation project. This is important knowledge and we recommend similar studies always to be performed prior to the introduction of new screening routines.

Smith, M. A., D. Gertig, M. Hall, K. Simms, J. B. Lew, M. Malloy, M. Saville and K. Canfell (2016). "**Transitioning from cytology-based screening to HPV-based screening at longer intervals: implications for resource use.**" *BMC Health Serv Res* **16**: 147.

BACKGROUND: Following a recent major review of cervical screening, from 2017 Australia will transition from two-yearly cytology-based screening to five-yearly primary HPV screening, with partial genotyping and direct referral for HPV 16/18 and LBC triage for other oncogenic types. Switching to a longer screening interval will result in transitional fluctuations for volumes of tests before a 'steady state' is reached for the new test volumes. This study aimed to quantify the impact of this transition on year-to-year volumes of screening and follow-up tests and procedures. METHODS: Number of women screened and test volumes from 2015 to 2032 were estimated via a detailed simulation model which explicitly modelled varying screening and HPV vaccination exposure in individual birth cohorts, and fully incorporated how a relatively rapid screening program switch in 2017 would affect both women attending for routine screening and those in surveillance following an abnormality. RESULTS: Numbers of women screened and HPV tests are predicted to fluctuate in the first screening rounds as a result of the transition to a longer screening interval (mean women screened and HPV tests 1.4 million in the first 5-year period,

year-to-year fluctuation > +/-50%; mean 1.5 million women/HPV tests in third 5-year period, fluctuation approximately +/-25%). The extent to which this fluctuation was predicted to carry through to secondary tests/procedures was less (fluctuations of +25%/-31% in first 5-year period; decreasing to +8%/-10% by third round). HPV vaccination is predicted to counteract increases in high grade cytology results, colposcopies and precancer treatments which would otherwise occur due to population increases. Precancer treatments are predicted to drop below 2015 levels within the first few years of program switchover. Mean colposcopy volumes are predicted to be similar to 2015 levels by the third round of HPV-based screening, and also be 25-40% lower than would have occurred in the absence of HPV vaccination. CONCLUSIONS: While numbers of women attending for screening and HPV tests are anticipated to initially fluctuate as a result of the transition to a longer recommended interval, there is expected to be less fluctuation in follow-up tests and procedures; however these will still have a significant impact on operational aspects of the screening program. Detailed modelling of the switchover process gave important insights into how volumes would be affected.

Schiffman, M. and N. Wentzensen (2016). "**A Suggested Approach to Simplify and Improve Cervical Screening in the United States.**" J Low Genit Tract Dis 20(1): 1-7.

Cervical cancer prevention strategies in the United States have become complicated and even controversial, despite advanced understanding of carcinogenic human papillomavirus (HPV) infection as the necessary causal agent. Twenty years ago, etiologic and methodologic studies had already yielded 2 powerful preventive approaches. There are excellent vaccines to prevent the most carcinogenic types of HPV infection; reduced HPV endemicity will ultimately prevent a large fraction of cervical precancer and cancers. For prevention of cervical cancer in the interim, sensitive HPV tests that target women at risk of cancer, by detection of the DNA/RNA of approximately a dozen carcinogenic HPV types, permit early diagnosis and treatment of precancers. Although HPV vaccines and tests have continued to improve, implementation of these new HPV-based prevention methods has been relatively slow in the United States and in most places worldwide. Increasing vaccination rates is the clearest and most vital long-term priority. But, for decades to come, screening will also be important. To promote useful discussion, this commentary will raise some current critical issues in simplifying and speeding the rational introduction of HPV molecular methods into US cervical screening.

Stanczuk, G., G. Baxter, H. Currie, J. Lawrence, K. Cuschieri, A. Wilson and M. Arbyn (2016). "**Clinical validation of hrHPV testing on vaginal and urine self-samples in primary cervical screening (cross-sectional results from the Papillomavirus Dumfries and Galloway-PaVDaG study).**" BMJ Open 6(4): e010660.

OBJECTIVES: Papillomavirus Dumfries and Galloway (PaVDaG) assessed the performance of a high-risk human papillomavirus (hrHPV) PCR-based assay to detect high-grade cervical intraepithelial neoplasia (CIN2+) in self-collected vaginal and urine samples. SETTING: Women attending routine cervical screening in primary care. PARTICIPANTS: 5318 women aged 20-60 years provided self-collected random urine and vaginal samples for hrHPV testing and a clinician-collected liquid-based cytology (LBC) sample for cytology and hrHPV testing. INTERVENTIONS: HrHPV testing. All samples were tested for hrHPV using the PCR-based cobas 4800 assay. Colposcopy was offered to women with high-grade or repeated borderline/low-grade cytological abnormalities; also to those who were LBC negative but hrHPV 16/18 positive. PRIMARY AND SECONDARY OUTCOME MEASURES: The self-tests' absolute sensitivity and specificity for CIN2+ were assessed on all biospecimens; also, their relative sensitivity and specificity compared with clinician-taken samples. Interlaboratory and intralaboratory performance of the hrHPV assay in

self-collected samples was also established. RESULTS: HrHPV prevalence was 14.7%, 16.6% and 11.6% in cervical, vaginal and urine samples, respectively. Sensitivity for detecting CIN2+ was 97.7% (95% to 100%), 94.6% (90.7% to 98.5%) and 63.1% (54.6% to 71.7%) for cervical, vaginal and urine hrHPV detection, respectively. The corresponding specificities were 87.3% (86.4% to 88.2%), 85.4% (84.4% to 86.3%) and 89.8% (89.0% to 90.7%). There was a 38% (24% to 57%) higher HPV detection rate in vaginal self-samples from women over 50 years compared with those \leq 29 years. Relative sensitivity and specificity of hrHPV positivity for the detection of CIN2+ in vaginal versus cervical samples were 0.97 (0.94 to 1.00) and 0.98 (0.97 to 0.99); urine versus cervical comparisons were 0.53 (0.42 to 0.67) and 1.03 (1.02 to 1.04). The intralaboratory and interlaboratory agreement for hrHPV positivity in self-samples was high (κ values 0.98 (0.96 to 0.99) and 0.94 (0.92 to 0.97) for vaginal samples and 0.95 (0.93 to 0.98) and 0.90 (0.87 to 0.94) for urine samples). CONCLUSIONS: The sensitivity of self-collected vaginal samples for the detection of CIN2+ was similar to that of cervical samples and justifies consideration of this sample for primary screening.

Hanson, C. M., L. Eckert, P. Bloem and T. Cernuschi (2015). "**Gavi HPV Programs: Application to Implementation.**" *Vaccines (Basel)* **3**(2): 408-419.

Developing countries disproportionately suffer from the burden of cervical cancer yet lack the resources to establish systematic screening programs that have resulted in significant reductions in morbidity and mortality in developed countries. Human Papillomavirus (HPV) vaccination provides an opportunity for primary prevention of cervical cancer in low-resource settings through vaccine provision by Gavi The Vaccine Alliance. In addition to the traditional national introduction, countries can apply for a demonstration program to help them make informed decisions for subsequent national introduction. This article summarizes information from approved Gavi HPV demonstration program proposals and preliminary implementation findings. After two rounds of applications, 23 countries have been approved targeting approximately 400,000 girls for vaccination. All countries are proposing primarily school-based strategies with mixed strategies to locate and vaccinate girls not enrolled in school. Experiences to date include: Reaching marginalized girls has been challenging; Strong coordination with the education sector is key and overall acceptance has been high. Initial coverage reports are encouraging but will have to be confirmed in population based coverage surveys that will take place later this year. Experiences from these countries are consistent with existing literature describing other HPV vaccine pilots in low-income settings.

Cooper, C. P. and M. Saraiya (2015). "**Perceived effectiveness of HPV test as a primary screening modality among US providers.**" *Prev Med* **78**: 33-37.

BACKGROUND: The human papillomavirus (HPV) test, administered alone without the Papanicolaou (Pap) test, was recently recognized as a cervical cancer screening option in the United States by the Society of Gynecologic Oncology and the American Society for Colposcopy and Cervical Pathology, and the Food and Drug Administration has approved an HPV test for primary screening. METHODS: Surveys of US internists, family practitioners, nurse practitioners, and obstetrician-gynecologists were conducted in 2009 and 2012 to investigate providers' perceptions of the effectiveness of the HPV test administered alone as a population-based screening modality (2009: N=1040, 141-494 per provider group; 2012: N=1039, 155-435 per provider group). RESULTS: The majority in each provider group agreed that the HPV test administered alone is an effective screening modality in 2009 (75.3%-86.1%) and 2012 (79.5%-91.8%), and agreement rose significantly during this time period among family practitioners ($\chi^2=15.26$, $df=1$, $p<0.001$) and nurse practitioners ($\chi^2=4.53$, $df=1$, $p=0.033$). CONCLUSIONS:

Agreement that the HPV test administered alone is an effective cervical cancer screening modality was widespread among providers in both 2009 and 2012, however implementation of guidelines for screening with the HPV test may be influenced by many other factors including reimbursement and patient preferences.

Session 2a: Self Sampling

A Pubmed search was performed with the following selection criteria: [HPV AND Self Sampling] (review only) [title/abstract]; published in the last 5 years, 33 items were retrieved respectively .Few of the articles retrieved were out of scope of the session or were relevant to other sessions. Herein, a relevant manual selection of 10 publications between 2015-2020 based on title and abstract was made, and imported into Endnote

Hawkes, D., M. H. T. Keung, Y. Huang, T. L. McDermott, J. Romano, M. Saville and J. M. L. Brotherton (2020). **"Self-Collection for Cervical Screening Programs: From Research to Reality."** *Cancers (Basel)* **12**(4).

In 2018, there were an estimated 570,000 new cases of cervical cancer globally, with most of them occurring in women who either had no access to cervical screening, or had not participated in

screening in regions where programs are available. Where programs are in place, a major barrier for women across many cultures has been the requirement to undergo a speculum examination. With the emergence of HPV-based primary screening, the option of self-collection (where the woman takes the sample from the vagina herself) may overcome this barrier, given that such samples when tested using a PCR-based HPV assay have similar sensitivity for the detection of cervical pre-cancers as practitioner-collected cervical specimens. Other advantages of HPV-based screening using self-collection, beyond the increase in acceptability to women, include scalability, efficiency, and high negative predictive value, allowing for long intervals between negative tests. Self-collection will be a key strategy for the successful scale up of cervical screening programs globally in response to the WHO call for all countries to work towards the elimination of cervical cancer as a public health problem. This review will examine self-collection for HPV-based cervical screening including the collection devices, assays and possible routine laboratory processes considering how they can be utilized in cervical screening programs.

Agorastos, T., K. Chatzistamatiou, A. Tsertanidou, E. Mouchtaropoulou, K. Pasentsis, A. Kitsou, T. Moysiadis, V. Moschaki, A. Skenderi, E. Katsiki, S. Aggelidou, I. Venizelos, M. Ntoula, A. Daponte, P. Vanakara, A. Garas, T. Stefos, T. Vrekoussis, V. Lymberis, E. N. Kontomanolis, A. Makrigiannakis, G. Manidakis, E. Deligeoroglou, T. Panoskaltis, G. O. Decavalas, G. Michail, I. Kalogiannidis, G. Koukoulis, P. Zempili, D. Halatsi, T. Truva, V. Piha, G. Agelena, A. Chronopoulou, V. Vaitsi, E. Chatzaki, M. Paschopoulos, G. Adonakis, A. M. Kaufmann, A. Hadzidimitriou and K. Stamatopoulos (2019). "**Implementation of HPV-based Cervical Cancer Screening Combined with Self-sampling Using a Midwifery Network Across Rural Greece: The GRECOSELF Study.**" *Cancer Prev Res (Phila)* **12**(10): 701-710.

Self-sampling for human papillomavirus (HPV) testing is an alternative to physician sampling particularly for cervical cancer screening nonattenders. The GRECOSELF study is a nationwide observational cross-sectional study aiming to suggest a way to implement HPV-DNA testing in conjunction with self-sampling for cervical cancer screening in Greece, utilizing a midwifery network. Women residing in remote areas of Greece were approached by midwives, of a nationwide network, and were provided with a self-collection kit (dry swab) for cervicovaginal sampling and asked to answer a questionnaire about their cervical cancer screening history. Each sample was tested for high-risk (hr) HPV with the Cobas HPV test. HrHPV-Positive women were referred to undergo colposcopy and, if needed, treatment according to colposcopy/biopsy results. Between May 2016 and November 2018, 13,111 women were recruited. Of these, 12,787 women gave valid answers in the study questionnaire and had valid HPV-DNA results; hrHPV prevalence was 8.3%; high-grade cervical/vaginal disease or cancer prevalence was 0.6%. HrHPV positivity rate decreased with age from 20.7% for women aged 25-29 years to 5.1% for women aged 50-60 years. Positive predictive value for hrHPV testing and for HPV16/18 genotyping ranged from 5.0% to 11.6% and from 11.8% to 27.0%, respectively, in different age groups. Compliance to colposcopy referral rate ranged from 68.6% (for women 25-29) to 76.3% (for women 40-49). For women residing in remote areas of Greece, the detection of hrHPV DNA with the Cobas HPV test, on self-collected cervicovaginal samples using dry cotton swabs, which are provided by visiting midwives, is a promising method for cervical cancer secondary prevention.

Almeida-Lugo, L. Z., C. M. Bonin-Jacob, V. T. G. de Matos and I. A. Tozetti (2019). "**Self-Collection and Molecular Diagnosis for Detection of Human Papillomavirus: Why Incorporate It?**" *Curr Infect Dis Rep* **21**(4): 13.

PURPOSE OF REVIEW: Cervical cancer, the third cause of death by cancer among Brazil's women, is associated with human papillomavirus (HPV) infection. In some countries of South America, North America, Europe, and Oceania, initial screening for HPV DNA and subsequent follow-up

with HPV-positive patients using colposcopy and cytological testing are used as preventative measures. RECENT FINDINGS: For HPV DNA detection, it is necessary to obtain cervical cells by conventional clinical collection method or self-collection of the cells that flake off from the uterine cervix and vaginal canal. Self-collection has been shown to be a viable option for obtaining samples and is a less invasive method that is more accepted by women. Thus, it can potentially decrease the limitations of the conventional clinical collection methods. The efficiency of the self-collection method aligned with the implementation of HPV molecular testing, if adopted by public and private health care systems, may extend the reach of current cervical cancer prevention efforts. In addition, considering all phases from triage to treatment, this method may reduce health care costs and the time spent by patients and health care teams to conduct examinations and collect samples.

Chao, Y. S. and S. McCormack (2019). **CADTH Rapid Response Reports. HPV Self-Sampling for Primary Cervical Cancer Screening: A Review of Diagnostic Test Accuracy and Clinical Evidence – An Update. Ottawa (ON), Canadian Agency for Drugs and Technologies in Health**

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The introduction of cervical cancer screening and timely intervention is associated with the recent decrease in cervical cancer incidence. There are several options to screen cervical cancer. Two of the methods commonly used in Canada are cytology and human papillomavirus (HPV) tests. Cytology requires clinicians to obtain samples from the cervix for further examination. HPV tests that detect the infection of HPV also requires samples from the cervix. The HPV tests that detect certain types of carcinogenic HPV genotypes, especially genotypes 16 and 18, are called high-risk HPV tests. The samples can be obtained via brushes or swabs or other devices not only by clinicians, but also by screening participants. Clinician-sampled HPV tests are used in screening program in several countries, such as Italy and Denmark. Self-sampled HPV tests have been tested in the capital region in Denmark but have not replaced clinician-sampled tests. With feasibility to conduct at home and potentially better acceptability to participants, self-sampled HPV tests have been used to reach individuals that are unscreened or under-screened for cervical cancer. In a previous CADTH report, there was some evidence to show similar diagnostic test accuracy between self- and clinician-sampled HPV tests. For example, the diagnostic test accuracy of GP5+/6+ polymerase chain reaction (PCR) HPV tests using samples taken with brushes is similar for self- and clinician-collected samples. In several primary studies, fair to high agreement between self- and clinician-sampled HPV tests has been found. Since the previous CADTH review, there have been primary studies comparing self- and clinician-sampled HPV tests published(,) and a systematic review has been updated. This report updates the previous review on the difference in the diagnostic test accuracy of self-sampled HPV tests and the agreement between self- and clinician-sampled HPV tests.

Chao, Y. S., M. Clark and C. Ford (2018). CADTH Rapid Response Reports. **HPV Self-Sampling for Primary Cervical Cancer Screening: A Review of Diagnostic Test Accuracy and Clinical Evidence. Ottawa (ON), Canadian Agency for Drugs and Technologies in Health**

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To understand the comparability and agreement of diagnostic test accuracy (DTA) between self- and clinician- sampled human papillomavirus (HPV) tests, we aim to review the literature and compare the DTA between self- and clinician-sampled HPV tests or cytology.

Esber, A., A. Norris, E. Jumbe, J. Kandodo, P. Nampondeni, P. C. Reese and A. N. Turner (2018). "**Feasibility, validity and acceptability of self-collected samples for human papillomavirus (HPV) testing in rural Malawi.**" *Malawi Med J* **30**(2): 61-66.

AIM: The World Health Organization (WHO) recently endorsed human papillomavirus (HPV) testing as a cervical cancer screening method in countries without established programs. Self-collection for HPV testing may be an effective way to expand screening. Our objective was to assess the feasibility, validity, and acceptability of self-collection for HPV testing in a population of care-seeking, unscreened women in rural Malawi. METHODS: We enrolled women reporting to a rural Malawian clinic from January to August 2015. Participants were offered the option to self-collect a vaginal sample and the study clinician collected a cervical sample for HPV testing. Using the clinician-collected sample as the reference standard, we calculated a kappa statistic, sensitivity, and specificity by hr-HPV type. Participants also received a brief survey assessing acceptability of the procedure. RESULTS: Among the 199 enrolled women, 22% had any high risk-HPV. Comparing self- and clinician-collected samples for HPV testing, we found generally high agreement ($\kappa = 0.66-0.90$) and high specificity (98%-100%), but varied sensitivity (50%-91%) for different types of hr-HPV. We also found that self-collection was acceptable, with 98% of women reporting it was easy to do and 99% reporting willingness to do so again. CONCLUSIONS: WHO guidelines recommend that treatment is available immediately after a positive screening test for clinic-based cervical cancer screening programs. Our findings demonstrate that self-collection of samples for HPV testing is a feasible and acceptable method of cervical cancer screening in this rural Malawian population. High agreement between the self- and clinician-collected samples and high levels of acceptability among women in the study suggest that self-collection of vaginal samples for HPV testing may be effectively incorporated into screening programs among rural, largely unscreened populations.

Gupta, S., C. Palmer, E. M. Bik, J. P. Cardenas, H. Nuñez, L. Kraal, S. W. Bird, J. Bowers, A. Smith, N. A. Walton, A. D. Goddard, D. E. Almonacid, S. Zneimer, J. Richman and Z. S. Apte (2018). "**Self-Sampling for Human Papillomavirus Testing: Increased Cervical Cancer Screening Participation and Incorporation in International Screening Programs.**" *Front Public Health* **6**: 77.

In most industrialized countries, screening programs for cervical cancer have shifted from cytology (Pap smear or ThinPrep) alone on clinician-obtained samples to the addition of screening for human papillomavirus (HPV), its main causative agent. For HPV testing, self-sampling instead of clinician-sampling has proven to be equally accurate, in particular for assays that use nucleic acid amplification techniques. In addition, HPV testing of self-collected samples in combination with a follow-up Pap smear in case of a positive result is more effective in detecting precancerous lesions than a Pap smear alone. Self-sampling for HPV testing has already been adopted by some countries, while others have started trials to evaluate its incorporation into national cervical cancer screening programs. Self-sampling may result in more individuals willing to participate in cervical cancer screening, because it removes many of the barriers that prevent women, especially those in low socioeconomic and minority populations, from participating in regular screening programs. Several studies have shown that the majority of women who have been underscreened but who tested HPV-positive in a self-obtained sample will visit a clinic for follow-up diagnosis and management. In addition, a self-collected sample can also be used for vaginal microbiome analysis, which can provide additional information about HPV infection persistence as well as vaginal health in general.

Madzima, T. R., M. Vahabi and A. Lofters (2017). "**Emerging role of HPV self-sampling in cervical cancer screening for hard-to-reach women: Focused literature review.**" *Can Fam Physician* **63**(8): 597-601.

OBJECTIVE: To provide a focused critical review of the literature on the acceptability, feasibility, and uptake of human papillomavirus (HPV) self-sampling among hard-to-reach women. **QUALITY OF EVIDENCE:** A focused search to obtain relevant literature published in English between 1997 and 2015 was done using PubMed and EMBASE using search terms including HPV self-test or HPV self-sample or HPV kit in combination with acceptability or feasibility. Only studies that focused on never-screened or underscreened populations were included in this review. **MAIN MESSAGE:** Human papillomavirus self-sampling was found to be highly acceptable and feasible among these hard-to-reach women across most studies. Mailing of self-sampling kits has been shown to increase participation among hard-to reach women. Some concerns remain regarding adherence to further follow-up among high-risk women with positive test results for HPV after screening. **CONCLUSION:** There is a strong body of evidence to support the usefulness of HPV self-sampling in increasing participation of hard-to-reach women in screening programs (level I evidence). Convenience, privacy, ease of use, and, likely, cost-effectiveness of HPV self-sampling are driving forces in its emerging role in cervical cancer screening among hard-to-reach women. Key barriers to participation could be addressed by overcoming disparities in HPV-related knowledge and perceptions about cervical cancer screening.

Publisher: Abstract available from the publisher.

Stanczuk, G., G. Baxter, H. Currie, J. Lawrence, K. Cuschieri, A. Wilson and M. Arbyn (2016). "**Clinical validation of hrHPV testing on vaginal and urine self-samples in primary cervical screening (cross-sectional results from the Papillomavirus Dumfries and Galloway-PaVDaG study).**" *BMJ Open* 6(4): e010660.

OBJECTIVES: Papillomavirus Dumfries and Galloway (PaVDaG) assessed the performance of a high-risk human papillomavirus (hrHPV) PCR-based assay to detect high-grade cervical intraepithelial neoplasia (CIN2+) in self-collected vaginal and urine samples. **SETTING:** Women attending routine cervical screening in primary care. **PARTICIPANTS:** 5318 women aged 20-60 years provided self-collected random urine and vaginal samples for hrHPV testing and a clinician-collected liquid-based cytology (LBC) sample for cytology and hrHPV testing. **INTERVENTIONS:** HrHPV testing. All samples were tested for hrHPV using the PCR-based cobas 4800 assay. Colposcopy was offered to women with high-grade or repeated borderline/low-grade cytological abnormalities; also to those who were LBC negative but hrHPV 16/18 positive. **PRIMARY AND SECONDARY OUTCOME MEASURES:** The self-tests' absolute sensitivity and specificity for CIN2+ were assessed on all biospecimens; also, their relative sensitivity and specificity compared with clinician-taken samples. Interlaboratory and intralaboratory performance of the hrHPV assay in self-collected samples was also established. **RESULTS:** HrHPV prevalence was 14.7%, 16.6% and 11.6% in cervical, vaginal and urine samples, respectively. Sensitivity for detecting CIN2+ was 97.7% (95% to 100%), 94.6% (90.7% to 98.5%) and 63.1% (54.6% to 71.7%) for cervical, vaginal and urine hrHPV detection, respectively. The corresponding specificities were 87.3% (86.4% to 88.2%), 85.4% (84.4% to 86.3%) and 89.8% (89.0% to 90.7%). There was a 38% (24% to 57%) higher HPV detection rate in vaginal self-samples from women over 50 years compared with those ≤29 years. Relative sensitivity and specificity of hrHPV positivity for the detection of CIN2+ in vaginal versus cervical samples were 0.97 (0.94 to 1.00) and 0.98 (0.97 to 0.99); urine versus cervical comparisons were 0.53 (0.42 to 0.67) and 1.03 (1.02 to 1.04). The intralaboratory and interlaboratory agreement for hrHPV positivity in self-samples was high (κ values 0.98 (0.96 to 0.99) and 0.94 (0.92 to 0.97) for vaginal samples and 0.95 (0.93 to 0.98) and 0.90 (0.87 to 0.94) for urine samples). **CONCLUSIONS:** The sensitivity of self-collected vaginal samples for the

detection of CIN2+ was similar to that of cervical samples and justifies consideration of this sample for primary screening.

Ondryášová, H., V. Koudeláková, J. Drábek, P. Vaněk, R. Slavkovský and M. Hajdúch (2015). "[Utilization of self-sampling kits for HPV testing in cervical cancer screening - pilot study]." *Ceska Gynekol* 80(6): 436-443.

OBJECTIVE: To get initial experience with alternative sampling (self-sampling) for HPV testing as the means of cervical cancer screening program. DESIGN: Original work. SETTING: Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacky University in Olomouc. METHODS: Based on expression of interest, 215 self-sampling kits were posted to women. Evalyn(®) Brush Vaginal swabs obtained by self-sampling were analyzed for the presence of HPV infection by Cobas 4800 HPV (Roche) followed by genotyping using PapilloCheck(®) HPV-Screening (Greiner Bio-One). Sixty women randomly chosen from our sample were sent a questionnaire focused on their experience with self-sampling. RESULTS: One hundred seventy-four of 215 (81%) distributed self-sampling devices have been delivered to analysis. All cervicovaginal swabs were sampled correctly and it was possible to analyze them by Cobas 4800 HPV test. Similarly, 98% (171/174) samples were analyzable by PapilloCheck(®) HPV-Screening. One hundred twenty-five (72%) of 174 tested samples were HPV negative. Low risk HPV infection was detected only in 7 samples (4%), and high risk HPV (hrHPV) infection was present in 42 samples (24%). The most frequently detected hrHPV genotypes were HPV16 (11/42; 26%) and HPV53 (6/42; 14%). HrHPV co-infection was detected in 10 cases, in 5 of them hrHPV infection was found also. Of the 60 questionnaires, 48 (80%) were returned. From this group, 47 (98%) women rated their experience with self-sampling device as good to excellent. User manual of self-sampling device was considered good to excellent by all women (100%). All women also rated the convenience of self-sampling device using as good to excellent. As expected, most of the women (n = 42 [88%]) preferred self-sampling to physician sampling. CONCLUSION: Cervicovaginal self-sampling leads to valid results of HPV screening using two molecular genetics methods and was accepted by Czech women very well. The self-sampling as an opportunity to participate in cervical cancer screening could increase the attendance of the screening program and would help to reduce the incidence and mortality for this disease in the Czech population.

Session 3 Title: HPV Screening and Treatment; Opportunities and Challenges in different regions.

A Pubmed search was performed with the following selection criteria: [HPV] AND [Challenges] AND [Screening] AND [Treatment]; [HPV] AND [Screening] AND [Challenges] AND [Countries]; [Cervical cancer] AND [national screening programs] AND [Screening] AND [Treatment] title/abstract published in the last 5 years: 708 items were retrieved and 32 were manually selected focused on country examples and their respective national screening programs. Some of the articles in the search were either out of scope of the session or related to other sessions. Herein, a relevant manual selection of 34 publications between 2015-2020 based on title and abstract was made, and references were imported in EndNote.

Baldauf, J. J., M. Fender, C. Bergeron, E. Marrer, M. Velten, P. Pradat and M. Arbyn (2019). "**Cervical morbidity in Alsace, France: results from a regional organized cervical cancer screening program.**" Eur J Cancer Prev **28**(1): 33-39.

In 1994, a pilot program of cervical cancer screening was introduced in the Alsace region, France. Women aged 25-65 years were proposed to have one Pap smear every 3 years. The objective was to assess cervical morbidity in Alsace before the human papillomavirus vaccinated population reaches the age of screening. Data on cervical lesions and cancers were collected by EVE for the period September 2008 to August 2011 from existing medical services and cytopathology laboratories in Alsace. Cytological and histological data were completed with data from the two cancer registries covering the region (Bas-Rhin and Haut-Rhin). Cancer incidence rates were computed for the target population (truncated to 25-64 years) and were age standardized according to the world reference population. World standardized incidence rates for the whole female population were obtained from the two cancer registries. During 2008-2011, 565 153 smears were performed in 498 913 women aged 25-64 years, representing an average of 1.13 smears/woman and 1.62 smears/screened woman. The overall screening coverage was 70.1% over the 3-year period. Histologically confirmed high-grade lesions were found in 2303 women (0.5%). Moreover, 215 cervical cancers were reported among women aged 25-64 years (crude and standardized truncated incidence rate of 10.6 and 10.0/100 000 women-years, respectively). The overall screening coverage of 70% at 3 years is higher than the national rate (57%), and the overall cancer incidence of 5.5/100 000 is below the national French level. The EVE database will be useful to assess trends in cervical morbidity over time and to further assess the effect of screening as well as of human papillomavirus vaccination.

Selmouni, F., L. Belakhel, C. Sauvaget, L. Abousselham, E. Lucas, R. Muwonge, R. Sankaranarayanan, Y. C. Khazraji and P. Basu (2019). "**Evaluation of the national cervical cancer screening program in Morocco: achievements and challenges.**" J Med Screen **26**(3): 162-168.

Machalek, D. A., J. M. Roberts, S. M. Garland, J. Thurloe, A. Richards, I. Chambers, T. Sivertsen and A. Farnsworth (2019). "Routine cervical screening by primary HPV testing: early findings in the renewed National Cervical Screening Program." Med J Aust **211**(3): 113-119.

OBJECTIVES: To report human papillomavirus (HPV) testing patterns and rates of oncogenic HPV-positivity for specimens submitted during the first 6 months after the National Cervical Screening Program switched from cytology- to primary HPV-based screening. DESIGN, PARTICIPANTS: Retrospective cross-sectional review of 195 606 specimens submitted for HPV testing, 1 December 2017 - 31 May 2018. SETTING: Large community-based general pathology laboratory in metropolitan Sydney. MAIN OUTCOME MEASURES: Prevalence of oncogenic HPV types (all, HPV16/18, non-HPV16/18) by reason for HPV test (primary screening, non-screening); for oncogenic HPV-positive women in the age band recommended for primary HPV screening (25-74 years), prevalence of cytologic abnormality and rates of 12-month follow-up and colposcopy recommendations. RESULTS: 195 606 samples were received: 157 700 (80.6%) for primary screening, 37 906 (19.4%) for non-screening tests. Oncogenic HPV was detected in 8.1% of screening tests (95% CI, 7.9-8.2%) and 20.9% of non-screening tests (95% CI, 20.5-21.3%); 35.5% (95% CI, 34.7-36.4%) of women of recommended screening age with positive oncogenic HPV screening test results also had a cytologic abnormality. The proportion of HPV16/18-positive samples with high grade abnormality was 15.3% (95% CI, 14.2-16.6%); for samples positive for other oncogenic HPV types, the proportion was 6.3% (95% CI, 5.8-6.8%). Repeat HPV testing after 12 months was recommended for 5.4% (95% CI, 5.3-5.5%) and direct colposcopy for 2.6% (95% CI, 2.5-2.7%) of screened women aged 25-74 years. CONCLUSIONS: High grade cytologic

abnormalities were more common in women positive for HPV16/18, supporting their higher risk classification. Colposcopy referral rates were higher than during primary cytology-based testing, as predicted by clinical trial and modelling data. The prevalence of HPV was much higher in non-screening than in primary screening samples. Our findings indicate the renewed program is performing as expected during the initial HPV screening round.

Veijalainen, O., S. Kares, P. Kujala, R. Vuento, V. Osuala, M. Tirkkonen, T. Luukkaala, I. Kholová and J. Mäenpää (2019). "**Implementation of HPV-based cervical cancer screening in an organised regional screening programme: 3 years of experience.**" *Cytopathology* **30**(2): 150-156.

OBJECTIVE: The aim of this study was to evaluate the performance of human papillomavirus (HPV)-based screening in the framework of an organised cervical cancer screening programme. **METHODS:** A total of 46 708 women aged 35-60 years invited to the regional cervical cancer screening programme from 1 January 2012, to 31 December 2014, were enrolled. Overall, 17 770 women were screened by the Abbot RealTime hrHPV test with cytology triage and 15 605 were screened by conventional (Papanicolaou, Pap) cytology. In both groups, women with at least low-grade squamous intraepithelial lesions were referred directly for colposcopy, whereas HPV-positive women with borderline or normal cytology were invited to intensified screening in the following year. In the Pap group, the indication for intensified follow-up was borderline cytology. **RESULTS:** The attendance rate was similar in the HPV and Pap groups (72% and 71%, respectively). Overall, 6.0% of women in the HPV group vs 6.4% in the Pap group were referred to intensified follow-up (relative risk 0.94, 95% confidence interval [CI]: 0.87-1.03). At the index screening years, the relative sensitivity of the HPV test with cytology triage vs conventional screening was 1.64 (95% CI: 1.05-2.55) for CIN2+ and 2.06 (95% CI: 1.17-3.41) for CIN3+. The specificity of the hrHPV test with cytology triage for CIN2+ and CIN3+ was equal to that of the Pap screening (99.2% vs 99.2% for CIN2+ and 99.1% vs 99.1% for CIN3+). **CONCLUSIONS:** Due to its high sensitivity and specificity, primary hrHPV testing with cytology triage seems to be acceptable for cervical cancer screening in an organised setting.

Woronoff, A. S., F. Molinié and B. Trétarre (2019). "[**Implementation of National Cervical Cancer Screening Program in France**]." *Bull Cancer* **106**(3): 253-261.

In 2017 in France, cervical cancer (CC) was diagnosed in 2850 women and 1100 women died. The decline in incidence and mortality rates observed for several decades has slowed since the early 2000s. CC is due to the persistence of a sexually transmitted infection by human papillomaviruses (HPV). Currently CC prevention depends on HPV vaccination and Pap smear tests (PST) and up until 2018 diagnosis has been carried out on an individual basis in France. The 2014-2019 French Cancer Plan has planned to implement a nationally organized screening program of CC which proposes in the short term to continue screening by PST, according to the recommendations set by HAS in 2010, while creating the conditions for the transition to HPV-testing in primary screening. The objective of this program is to reduce the incidence and number of CC deaths by 30% within the next 10 years, by achieving an 80% coverage rate in the target population and making screening more accessible to vulnerable populations and/or those who have poor access to the healthcare system. CC is one of the rare cancers that could become exceptional. The combination of the two primary and secondary prevention methods, with high rates of vaccination and screening coverage, should make it possible to eliminate this cancer in countries with sufficient economic resources for the effective implementation of these prevention programs.

Ngo-Metzger, Q. and P. Adsul (2019). "Screening for Cervical Cancer." *Am Fam Physician* **99**(4): 253-254.

Belglaiaa, E. and C. Mougin (2019). "[**Cervical cancer: Current situation and management in Morocco**]." Bull Cancer **106**(11): 1008-1022.

With more than 3300 new cases and almost 2500 deaths each year, cervical cancer (CC) ranks second among female cancers in Moroccan women. The majority of cases occurs in women aged 50 and over. In absence of a national cancer registry, data published in Morocco are limited to the number of cases recorded in some oncology centers, so the incidence of this cancer is likely much higher than estimated. A Moroccan national program against CC based on the practice of visual inspection after application of acetic acid was set up in 2010, allowing both screening and possibly immediate treatment of (pre)cancerous lesions. However, this program has not been implemented in all regions of the country. The CC develops slowly and most often without any symptoms, and so it is diagnosed at an advanced stage of the disease. Virtually, all CC are associated with persistent infection of high risk human papillomavirus (HPV), particularly HPV16 and 18. For more than ten years, two prophylactic vaccines targeting these two HPV genotypes have been marketed. They have proved their excellent immunogenicity and efficacy and they are well tolerated. However, HPV vaccine is not yet recommended by health authorities in Morocco. In this literature review, we focused on the current situation of CC, the prevalence of HPV infection and the prevention strategies against CC in Morocco.

de Sanjose, S. and F. Holme (2019). "**What is needed now for successful scale-up of screening?**" Papillomavirus Res **7**: 173-175.

Effective screening for pre-cancerous lesions of the cervix is the only protective intervention that can be offered to women that have not had the opportunity to be vaccinated. Elimination goals are being developed so that by 2030, 70% of women aged 35-45 years should have been screened at least once in a lifetime and 90% of all detected lesions should have been treated. These goals focus on a substantial reduction of cervical cancer burden in low- and middle-income countries (LMICs). Scaling-up screening in these settings may be substantially improved by using self-sampling (SS), human papillomavirus (HPV) testing, and managing screened-positive women with accessible treatment. The implementation of these tools requires minimal health information data for traceability, provider training, community education, operational management and quality control. Cost-effective algorithms tailored to country needs can greatly impact the burden of disease in a limited number of years.

Lew, J. B., E. Feletto, S. Wade, M. Caruana, Y. J. Kang, C. Nickson, K. T. Simms, P. Procopio, N. Taylor, J. Worthington, D. Smith and K. Canfell (2019). "**Benefits, harms and cost-effectiveness of cancer screening in Australia: an overview of modelling estimates.**" Public Health Res Pract **29**(2).

INTRODUCTION: There are three government-funded population-based screening programs in Australia - the national breast cancer screening program (BreastScreen Australia), the National Cervical Screening Program (NCSP), and the National Bowel Cancer Screening Program (NBCSP). Options for early detection of other cancers (e.g. hepatocellular carcinoma and melanoma) are under investigation. This study provides an overview of the health benefits, harms and cost-effectiveness of population-level breast, cervical and colorectal cancer screening, targeted-risk screening for lung cancer and Lynch syndrome, and prostate specific antigen (PSA) testing in Australia. METHODS: The study reviewed and, where possible, updated the estimated health benefits, harms and cost-effectiveness of screening approaches from modelling studies for four cancer types, PSA testing and Lynch syndrome testing in Australia. Costs are presented in 2018

Australian dollars. RESULTS: The renewed NCSP (for women not HPV-vaccinated) and the NBCSP were estimated to be cost-effective versus no screening; the cost-effectiveness ratio (CER) was \$16 632 per life-year saved (LYS) for the NCSP, and \$3380/LYS for the NBCSP. BreastScreen Australia was predicted to have a CER of \$40 279/LYS-\$65 065/LYS. In 2017, the NCSP transitioned to 5-yearly primary HPV testing with partial genotyping for HPV types 16 and 18 for women aged 25-74 years. Alongside vaccination, this change is predicted to prevent a further 587 cervical cancer deaths in 2018-2035, and have a favourable benefit-to-harm balance versus prior practice (biennial cytology testing for women aged 18-69 years). On average, the NBCSP (biennial screening using an immunochemical faecal occult blood test for people aged 50-74 years) is estimated to prevent 2519 colorectal cancer deaths and result in 350 colonoscopy-related adverse events annually. The inaccuracy of PSA testing as a screening tool impedes the capacity to conduct meaningful cost-effectiveness analyses at a population level, based on current evidence. Three annual low-dose computed tomography screens for lung cancer using the US National Lung Screening Trial selection criteria would not be cost-effective in Australia. A comprehensive cost-effectiveness evaluation of systematic proband testing, cascade testing and subsequent surveillance for Lynch syndrome in Australia is currently underway. CONCLUSIONS: Current evidence supports a favourable cost-effectiveness and benefit-to-harm balance for the NCSP and NBCSP. An updated cost-effectiveness and benefits-to-harms analysis for BreastScreen Australia is required. Carefully founded quantitative estimates of health benefits, harms and cost-effectiveness provide an important aid to policy decision making, and form the basis for developing decision aids to guide individual screening decisions. Opportunities exist for lung cancer screening, systematic Lynch syndrome testing and informed decision making about PSA testing. However, more evidence is required on risk assessment, targeting of screening tests, optimal referral pathways, managing potential harms and delivering services in a cost-effective framework.

Donatus, L., F. K. Nina, D. J. Sama, C. N. Nkfusai, F. Bede, J. Shirinde and S. N. Cumber (2019). "Assessing the uptake of cervical cancer screening among women aged 25-65 years in Kumbo West Health District, Cameroon." *Pan Afr Med J* **33**: 106.

INTRODUCTION: Cervical cancer remains one of the leading health hazards affecting a majority women across the globe. The situation is even more, preoccupying particularly in areas where screening programmes and services are absent. The World Health Organization (WHO) says "cervical cancer is the fourth most frequent cancer in women, with an estimated 570,000 new cases diagnosed in 2018 which represents 6.6% of all female cancers. Approximately 90% of deaths from cervical cancer occurred in low- and middle-income countries". Despite the high mortality rate from cervical cancer globally, the trend could be reduced through a comprehensive approach that includes prevention, early diagnosis, effective screening and treatment programmes. In Cameroon, the prevalence of cervical cancer is 24% among women of reproductive age. An estimated 1,993 new cases are recorded annually in Cameroon with 1676 deaths. Despite this precarious situation, the uptake in cervical cancer screening service remains poor and stands at 19.6% in Cameroon. It is against this background that this paper evaluates the uptake of cervical cancer among women aged 25-65 years in the Kumbo West Health District (KWHD). Specifically, this study assesses the knowledge of women in this health district on cervical cancer and determines factors that affect the uptake of cervical cancer screening services. METHODS: This study is a cross-sectional study in the KWHD involving 253 consented women between the ages 25 to 65 years. The principal research instrument was a three-part questionnaire designed to collect information on socio-demographic profile, cervical cancer knowledge and associated factors for uptake in cervical cancer screening. Data was entered in MS

Excel and analysed using Excel. Results were presented in tables and figures. RESULTS: Our study reveals that a majority of the participants (74.70%) had heard of cervical cancer and 43.48% had undergone cervical cancer screening. Again, 24.51% and 29.25% of the participants respectively could not identify any risk factor and symptom of cervical cancer. CONCLUSION: The study revealed that the uptake of cervical cancer screening in KWHD is higher than the national uptake. The level of awareness on the risk factors and symptoms of cervical cancer is low, posing a need to put more emphasis on educating and creating awareness of cervical cancer among communities on risk factors, prevention measures and signs and symptoms in all the health areas of the KWHD.

Cappelli, M. G., F. Fortunato, S. Tafuri, S. Boccalini, P. Bonanni, R. Prato and D. Martinelli (2018). "**Cervical cancer prevention: An Italian scenario between organised screening and human papillomaviruses vaccination.**" *Eur J Cancer Care (Engl)* **27**(5): e12905.

We aimed to assess the cervical cancer burden and performance of screening programme over the last decade in Apulia, Italy. Data from Hospital Discharge, Causes of Death and of Outpatient Services registries were analysed to estimate the disease burden, and data collected by the screening information system were used to evaluate the performance of the programme. We computed annual hospitalisation, incidence and mortality rates and number of outpatient services prescriptions for the follow-up of preneoplastic/neoplastic lesions. Indicators as proposed by the National Centre for Screening Monitoring were computed to describe the screening performance. Hospitalisation rates declined from 47 in 2001 to 28 per 100,000 in 2014, incidence from 10.3 in 2004 to 6.0 per 100,000 in 2014 and mortality from 1.4 in 2001 to 1.0 per 100,000 in 2010. Prescriptions increased from 3,333 in 2006 to 4,968 in 2010, then decreased to 3,634/year in 2012-2014. Actual extension of screening increased from 10.8% in 2007 to 62% in 2014; compliance with the invitation was 32%/year. In the last decade, we observed a reduction in the cervical cancer burden as early effect of screening implementation.

Darquy, S., G. Moutel, O. Jullian, S. Barré and N. Duchange (2018). "**Towards equity in organised cancer screening: the case of cervical cancer screening in France.**" *BMC Womens Health* **18**(1): 192.

BACKGROUND: The French national cancer institute (INCa) conducted a series of studies to assist decision-making in view of the implementation of organised cervical cancer screening that will be launched in 2018. The programme will concern all women aged 25-65 and targeted interventions will be developed for underscreened populations. This is an evolution from an equality-based approach to a step-by-step strategy of equity aiming to tackle health cancer inequalities that are avoidable and represents unfair differences. Here we present the work of the expert-group in ethics drafted by INCa to review the ethical issues prior to the programme implementation. DISCUSSION: We discuss the value of such a strategy and presents reflections with regard to issues of stigmatization, respect for individual freedom and autonomy. Indeed, the balance has to be found between the search for beneficence and the potential occurrence of perverse effects, which should be considered with particular attention. CONCLUSION: Moving toward an equity-oriented policy under a strategy of proportionate universalism faces a number of challenges, thus an overview of ethics and social sciences must be an integral part of the process.

Devarapalli, P., S. Labani, N. Nagarjuna, P. Panchal and S. Asthana (2018). "**Barriers affecting uptake of cervical cancer screening in low and middle income countries: A systematic review.**" *Indian J Cancer* **55**(4): 318-326.

BACKGROUND: Cervical cancer is the second-most common cancer among women in the developing world and approximately 500,000 cases are diagnosed each year. In developed

countries, cervical cancer (CCa) accounts for only 3.6% of newly diagnosed cancers. **OBJECTIVE:** The present study aims to identify the most effective barriers associated with CCa screening uptake in low and middle-income countries (L and MICs) and aid to adopt effective measures to overcome prevailing barriers to the attainment of CCa uptake in the community. **MATERIALS AND METHODS:** Health sciences electronic databases like MEDLINE, PubMed, Cochrane library, and Google Scholar were searched for studies published until August 2017. Keywords used for the search were ("cervical cancer screening"), ("barriers"), AND ("low income countries" OR "Middle income countries"). Articles were reviewed and data were extracted by using Mendeley Desktop Software (V-1.17.10). Income-level classification of countries was done as per the World Bank 2017 report. Statistical software like SPSS-V.23 and Medical-V.14 were used for the statistical application. **RESULTS:** A total of 31 studies met the inclusion criteria with a total of 25,650 participants. The sample size of the included studies ranged from 97 to 5929 participants. Articles majorly reported data on participants from African region (51.6%) and minimally in the Western Pacific region (3.2%). Sampling methods among studies varied from convenience sampling-12 (39.7%) to consecutive sampling-1 (3.2%). Besides, two studies (6.5%) did not discuss their sampling procedures. It was observed that "Lack of information about CCa and its treatment" (Barrier of lack of knowledge and Awareness); "Embracement or shy" (Psychological Barrier); "Lack of time" (structural Barrier); and "Lack of family support" (Sociocultural and religious barrier) were the most commonly reported among all 22 barriers. **CONCLUSION:** There is a need of policies advancement of CCa screening programs by focusing on aspects of accessibility, affordability, CCa education, and the necessity of screening to improve screening uptake to control the CCa morbidity and mortality rate in L and MIC's.

Ferreccio, C. (2018). "[**New strategies for the prevention and control of cervical cancer in Chile.**]." Salud Publica Mex **60**(6): 713-721.

OBJECTIVE: To discuss cervical cancer (CC), Human PapillomaVirus (HPV), CC control program and propose alternatives for Chile. **MATERIALS AND METHODS:** We analyzed the national program of CC 1966-2015 and the clinical CC guideline 2015-2020; HPV prevalence in women and in cases of CC; HPV infection and serology; the self-vaginal sample; the accuracy and cost-effectiveness of screening with HPV versus Papanicolaou, and triage options among HPV-AR positives. **RESULTS:** 600 women die of CC each year in Chile, mainly from low resources. Papanicolaou coverage is <70%; Papanicolaou sensitivity is much lower than HPV test. Change from Papanicolaou to HPV test is cost-effective. Since 2015, girls under 13 have been vaccinated against HPV. **CONCLUSIONS:** .There are the technical and economic conditions for a substantial improvement of CC in Chile: replacement of the Papanicolaou by HPV; screening every five years, with the option of self-sampling, and triage based on HPV 16/18 or Papanicolaou typing.

Garland, S. M., W. Dimech, P. Collignon, L. Cooley, G. R. Nimmo, D. W. Smith, R. Baird, W. Rawlinson, A. M. Costa and G. Higgins (2018). "**The new screening program to prevent cervical cancer using HPV DNA: getting the balance right in maintaining quality.**" J Pathol Clin Res **4**(4): 207-212.

Along with the reduction in human papillomavirus (HPV) infection and cervical abnormalities as a result of the successful HPV vaccination program, Australia is adopting a new screening strategy. This involves a new paradigm moving from cervical cytological screening to molecular nucleic acid technology (NAT), using HPV DNA assays as primary screening methodology for cervical cancer prevention. These assays must strike a balance between sufficient clinical sensitivity to detect or predict high-grade cervical intraepithelial lesions, the precursor to cervical cancer, without being too sensitive and detecting transient infection not destined for disease. Ensuring the highest quality HPV NAT is thus a priority in order to reduce the possibility of falsely negative screens and

manage the risk associated with false positive HPV NAT test results. How to do this needs informed discussion and on-going refinement of the screening algorithm. This is of relevance as more countries move to more sensitive HPV NAT tests for secondary prevention of cervical cancer and as more HPV assays become available.

Hamers, F. F., N. Duport and N. Beltzer (2018). **"Population-based organized cervical cancer screening pilot program in France."** *Eur J Cancer Prev* **27**(5): 486-492.

In France, cervical cancer screening is recommended every 3 years for women aged 25-65 years. With the exception of a few local organized programs, screening is mainly opportunistic. In view of setting up a nationwide population-based organized screening program, a pilot intervention was implemented in nine geographic areas using a common protocol. Women aged 25-65 years who had not undergone a cytological screening in the past 3 years were invited for screening during 2010-2012 and reminded up to 1 year after the initial invitation. Cytological results and follow-up data were collected up to the end of 2014 for all women screened irrespective of whether spontaneously or following invitation. Aggregate data were centralized nationally. Among the 2.4 million women from the total target population aged 25-65 years, 1.3 million were invited for screening. The overall screening coverage during 2010-2012 was 62.3%, with wide variations across geographic areas, ranging from 41.6 to 72.5%. Initial invitations and reminders enabled nearly 280 000 women to be screened, corresponding to an estimated increase in coverage of 12% points. Overall, 4.2% of the women screened had an abnormal smear. A total of 5180 high-grade cervical precancers and 323 invasive cervical cancers were reported, corresponding to detection rates of, respectively, 623 and 39 per 100 000 women screened 3-yearly. This study indicates that such organized screening may markedly improve the uptake of cervical cancer screening. On the basis of this pilot program, nationwide organized cervical cancer screening is currently being rolled out in France.

Allen-Leigh, B., P. Uribe-Zúñiga, L. León-Maldonado, B. J. Brown, A. Lörcincz, J. Salmeron and E. Lazcano-Ponce (2017). **"Barriers to HPV self-sampling and cytology among low-income indigenous women in rural areas of a middle-income setting: a qualitative study."** *BMC Cancer* **17**(1): 734.

BACKGROUND: Data is needed about barriers to self-collection of Human Papillomavirus (HPV) samples and cytology among low-income, disadvantaged women living in rural areas of lower-income countries as these women are at increased risk of cervical cancer mortality. **METHODS:** Individual interviews (n = 29), focus groups (n = 7, 5-11 participants) and discussion groups (n = 2, 18-25 participants) were organized with women from three indigenous ethnic groups residing in rural areas in Mexico, after they were provided with free, self-sampled HPV tests. These groups are low-income, underserved by healthcare and have historically been on the receiving end of racism and social exclusion. Descriptive, qualitative content analysis was done, including two cycles of coding. **RESULTS:** Interview and focus/discussion group data indicate women had limited understanding of HPV's role in cervical cancer etiology. They identified HPV's existence, that cytology detects cervical cancer, the need for regular testing and that cervical cancer is sexually transmitted. Organizational barriers to clinic-based cytology included irregular supplies of disposable speculums, distance to clinics and lack of clear communication by healthcare personnel. Women considered self-collected HPV-testing easy, less embarrassing and less painful than cytology, an opportunity for self-care and most felt they understood how to take a self-sample after a 20-min explanation. Some women feared hurting themselves when taking the self-sample or that they would take the sample incorrectly, which they worried would make the test useless. Attending HPV-testing in groups facilitated use by allowing women to discuss their doubts

and fears before doing self-collection of the sample or to ask other women who were the first to do the self-sampling what the experience had been like (whether it hurt and how easy it was). Lack of indoor bathrooms was a barrier to doing HPV self-sampling at home, when those homes were resource-poor (one-room dwellings). CONCLUSIONS: Low-income, indigenous Mexican women residing in rural, underserved areas identified their need for cervical cancer screening but encountered multiple barriers to cytology-based screening. They found a number of advantages of HPV self-sampled tests. Employing self-collected HPV-testing instead of cytology could resolve some but not all gender-related, organizational or technical quality-of-care issues within cervical cancer detection and control programs.

Davies, P., D. Valuta, N. Cojohari and H. Sancho-Garnier (2017). "**Implementing an organised cervical screening programme in the Republic of Moldova-Stakeholder identification and engagement.**" Cancer Epidemiol **50**(Pt B): 272-277.

INTRODUCTION: Successfully implementing cervical screening programmes requires them to be adapted to the local context and have broad stakeholder support. This can be achieved by actively engaging local stakeholders in planning as well as implementing the programmes. The Moldovan government started implementing an organised cervical screening programme in 2010 with the first step being stakeholder identification and engagement. MATERIALS AND METHODS: This process started by contacting easily identified stakeholders with each asked to recommend others and the process continued until no new ones were identified. Stakeholders were then involved in a series of individual and group meetings over a 2-year period to build confidence and encourage progressively greater engagement. RESULTS: In total, 87 individuals from 46 organisations were identified. Over the 2-year process, the individual and group meetings facilitated a change in stakeholder attitudes from disinterest, to acceptance and finally to active cooperation in designing the screening programme and preparing an implementation plan that were both well adapted to the Moldovan context. DISCUSSION: Developing the broad support needed to implement cervical screening programmes required ongoing interaction with stakeholders over an extended period. This interaction allowed stakeholder concerns to be identified and addressed, progress to be demonstrated, and stakeholders to be educated about organised screening programmes so they had the knowledge to progressively take greater responsibility and ownership.

DeGregorio, G., S. Manga, E. Kiyang, F. Manjuh, L. Bradford, P. Cholli, R. Wamai, R. Ogembo, Z. Sando, Y. Liu, L. K. Sheldon, K. Nulah, T. Welty, E. Welty and J. G. Ogembo (2017). "**Implementing a Fee-for-Service Cervical Cancer Screening and Treatment Program in Cameroon: Challenges and Opportunities.**" Oncologist **22**(7): 850-859.

BACKGROUND: Cervical cancer screening is one of the most effective cancer prevention strategies, but most women in Africa have never been screened. In 2007, the Cameroon Baptist Convention Health Services, a large faith-based health care system in Cameroon, initiated the Women's Health Program (WHP) to address this disparity. The WHP provides fee-for-service cervical cancer screening using visual inspection with acetic acid enhanced by digital cervicography (VIA-DC), prioritizing care for women living with HIV/AIDS. They also provide clinical breast examination, family planning (FP) services, and treatment for reproductive tract infection (RTI). Here, we document the strengths and challenges of the WHP screening program and the unique aspects of the WHP model, including a fee-for-service payment system and the provision of other women's health services. METHODS: We retrospectively reviewed WHP medical records from women who presented for cervical cancer screening from 2007-2014. RESULTS: In 8 years, WHP nurses screened 44,979 women for cervical cancer. The number of women screened

increased nearly every year. The WHP is sustained primarily on fees-for-service, with external funding totaling about \$20,000 annually. In 2014, of 12,191 women screened for cervical cancer, 99% received clinical breast exams, 19% received FP services, and 4.7% received treatment for RTIs. We document successes, challenges, solutions implemented, and recommendations for optimizing this screening model. CONCLUSION: The WHP's experience using a fee-for-service model for cervical cancer screening demonstrates that in Cameroon VIA-DC is acceptable, feasible, and scalable and can be nearly self-sustaining. Integrating other women's health services enabled women to address additional health care needs. IMPLICATION FOR PRACTICE: The Cameroon Baptist Convention Health Services Women's Health Program successfully implemented a nurse-led, fee-for-service cervical cancer screening program using visual inspection with acetic acid-enhanced by digital cervicography in the setting of a large faith-based health care system in Cameroon. It is potentially replicable in many African countries, where faith-based organizations provide a large portion of health care. The cost-recovery model and concept of offering multiple services in a single clinic rather than stand-alone "silo" cervical cancer screening could provide a model for other low-and-middle-income countries planning to roll out a new, or make an existing, cervical cancer screening services accessible, comprehensive, and sustainable.

Nowakowski, A., U. Wojciechowska, P. Wieszczy, M. Cybulski, M. F. Kamiński and J. Didkowska (2017). **"Trends in cervical cancer incidence and mortality in Poland: is there an impact of the introduction of the organised screening?"** *Eur J Epidemiol* **32**(6): 529-532.

Aside from existing opportunistic screening, an organised screening programme (OSP) for cervical cancer (CC) was implemented in 2006/2007 in Poland. We applied joinpoint regression and age-period-cohort model to look for the impact of the OSP on CC incidence/mortality trends. Decline of age-standardised incidence rates (ASIRs) in the screening-age group (25-59 years) accelerated from -2.2% (95% CI -2.7 to -1.7%) between 1993 and 2008 to -6.1% (95% CI -7.7 to -4.4%) annually after 2008. In women aged 60+ years, ASIRs declined from 1986 until 2005 [annual percent change (APC) = -2.6%, 95% CI -2.9 to -2.4%] and stabilised thereafter. Decline of age-standardised mortality rates (ASMRs) in the screening-age group accelerated from -1.3% (95% CI -1.5 to -1.1%) between 1980 and 2005 to -4.7% (95% CI -5.6 to -3.8%) annually after 2005. In women aged 60+ ASMR declined between 1991 and 2004 (APC = -2.9%, 95% CI -3.5 to -2.3%) and stabilised thereafter. Relative risks of CC diagnosis and death were 0.63 (95% CI 0.62-0.65) and 0.61 (95% CI 0.59-0.63), respectively, for the most recent period compared to the reference around 1982. Implementation of the OSP possibly accelerated downward trends in the burden of CC in Polish women under the age of 60, but recent stabilisation of trends in older women requires actions.

Olver, I. N. and D. Roder (2017). **"History, development and future of cancer screening in Australia."** *Public Health Res Pract* **27**(3).

INTRODUCTION: The aim of screening an asymptomatic population for cancer is to achieve better health outcomes, particularly a population survival benefit. Australia has three population screening programs: the National Cervical Screening Program (NCSP), BreastScreen Australia and the National Bowel Cancer Screening Program (NBCSP). METHODS: We reviewed the history and development of the three programs. NCSP: Women have a Pap smear every 2 years from age 18-20, or 2 years after first becoming sexually active, until age 69. Since introduction of the NCSP, the cervical cancer incidence has halved, with an approximate 60% decrease in mortality. The screening participation rate approximates 57%, but is lower for Aboriginal and Torres Strait Islander women, women in remote areas, and women with lower socio-economic status. The National HPV (human papillomavirus) Vaccination Program, introduced in 2007, is expected to

reduce the incidence of cervical cancer by a further 70% and has already reduced the incidence of high-grade lesions in girls. In 2017, testing for HPV every 5 years starting at age 25 will replace the Pap smear as the principal screening test. BreastScreen Australia: This program targets women aged 50-74. Over 20 years, mortality from breast cancer has decreased by 32% in response to screening and treatment advances. The participation rate is 56%. The major adverse impact of breast screening is overdiagnosis, estimated in Australia to be as low as 8% of detected cancers, but with estimates of up to 30% from some research. Women should be made aware of both the potential benefits and harms from screening. Genetic testing for BRCA1 and BRCA2 mutations in high-risk women leads to earlier screening. NBCSP: The NBCSP uses immunochemical faecal occult blood test (iFOBT) kits on stool samples to detect bleeding from the bowel. When rollout is complete in 2020, test kits will be sent every 2 years to people aged 50-74. People who test positive are followed up with a colonoscopy. The participation rate is currently 37%. The positivity rate is 7%, and stage 1 bowel cancer presentations have tripled since the program began. CONCLUSIONS: Research needs to focus on reducing mortality through increased screening participation and, in the future, obtaining guidance for customised screening from genomic testing.

Al-Mandeel, H. M., E. SAGR, K. Sait, H. M. Latifah, A. Al-Obaid, I. A. Al-Badawi, A. O. Alkushi, H. Salem, N. S. Massoudi, H. Schunemann, R. A. Mustafa and R. Brignardello-Petersen (2016). "**Clinical Practice Guidelines on the Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention in Saudi Arabia.**" *Ann Saudi Med* **36**(5): 313-320.

BACKGROUND: Cervical cancer is the third most common gynecological malignancy in Saudi women with an estimated incidence rate of 1.9 cases per 100 000 women-years. More than 40% of cervical cancer cases are diagnosed at advanced stages due to lack of a routine screening program in Saudi Arabia. Thus, national guidelines for routine screening and treatment of precancerous cervical lesions are needed. METHODS: The Saudi Centre for Evidence-Based Healthcare invited a panel of local experts and partnered them with a team from McMaster University in Canada for methodological support, to develop national clinical practice guidelines on the screening and treatment of precancerous lesions for cervical cancer. After the panel identified key clinical questions, the McMaster University working group updated existing systematic reviews that had been used for the 2013 WHO Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. Recommendations were based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. Those recommendations took into account the available evidence, patient values and preferences, and resource use in the Saudi context. The panel provided recommendations on two major issues: screening for precancerous lesions (cervical intraepithelial neoplasia 2 & 3) and treatment of those lesions to prevent cervical cancer in women who tested positive after screening. CONCLUSIONS: The Saudi expert panel recommends using the HPV DNA test followed by colposcopy or cytology (Pap test) followed by colposcopy to screen for CIN2+ in women at risk of cervical cancer. The panel recommends cryotherapy or loop excision electrosurgery procedure (LEEP) over cold knife cone biopsy to treat women at risk of cervical cancer that tests positive for CIN2+. Universal screening for precancerous cervical dysplasia in women in Saudi Arabia is recommended using HPV testing and or cytology. Either cryotherapy or LEEP are preferred for treatment. LIMITATIONS: National studies on cervical cancer screening modalities and treatment of precancerous cervical lesions, including HPV prevalence and its association with cervical cancer, are scarce.

Msyamboza, K. P., T. Phiri, W. Sichali, W. Kwenda and F. Kachale (2016). "Cervical cancer screening uptake and challenges in Malawi from 2011 to 2015: retrospective cohort study." *BMC Public Health* 16(1): 806.

BACKGROUND: Malawi has the highest cervical cancer incidence and mortality in the world with age-standardized rate (ASR) of 75.9 and 49.8 per 100,000 population respectively. In response, Ministry of Health established a cervical cancer screening programme using visual inspection with acetic acid (VIA) and treatment of precancerous lesions with cryotherapy. This paper highlights the roll out, integration with family planning services and HIV ART Programme, uptake and challenges of VIA and Cryotherapy programme. **METHODS:** We analyzed program data, supportive supervision, quarterly and annual reports from the National Cervical Cancer Control Program. We evaluated the uptake and challenges of screening services by age, HIV serostatus and trends over a five year period (2011-2015). **RESULTS:** Between 2011 and 2015, number of cervical cancer screening sites, number of women screened and coverage per annum increased from 75 to 130, 15,331 to 49,301 and 9.3 % to 26.5 % respectively. In this five year period, a total of 145,015 women were screened. Of these, 7,349 (5.1 %) and 6,289 (4.3 %) were VIA positive and suspect cancer respectively. Overall 13,638 (9.4 %) were detected to be VIA positive or had suspect cancer. Of the 48,588 women with known age screened in 2015; 13,642 (28.1 %), 27,275 (56.1 %) and 7,671 (15.8 %) were aged 29 or less, 30-45, 46 years or more. Among 39,101 women with data on HIV serostatus; 21,546 (55.1 %) were HIV negative, 6,209 (15.9 %) were HIV positive and 11, 346 (29.0 %) status was unknown. VIA positivity rate and prevalence of suspect cancer were significantly higher in HIV positive than HIV negative women (8.8 % vs 5.0 %, 6.4 % vs 3.0 %); in women aged 30-45 years than women aged 29 years or less (5.6 % vs 2.3 %, 2.6 % vs 1.2 %) respectively, all $p < 0.05$). The main challenge of the programme was failure to treat VIA positive women eligible for cryotherapy. Over the five year period, the programme only treated 1,001 (43.3 %) out of 2,311 eligible women and only 266 (31.8 %) of the 836 women with large lesion or suspect cancer who were referred, received the health care at the referral centre. The reasons for failure to provide cryotherapy treatment were stock out of gas, faulty/broken cryotherapy machine (usually connectors or probes) or no cryotherapy machine at all in the whole district. For women with large lesion or suspect cancer; lack of loop electrosurgical excision procedure (LEEP) machine or inadequate gynaecologists at the referral centre, were the major reasons. Cancer radiotherapy services were not available in Malawi. **CONCLUSIONS:** This study provided data on VIA positivity rate, prevalence of suspect cancer, failure rate of cryotherapy and challenges in the provision of cryotherapy and LEEP treatment in Malawi. These data could be used as baseline for monitoring and evaluation of Human Papillomavirus (HPV) vaccination programme which the country introduced in 2013, the linkage of cervical cancer screening and women on HIV ART and the long term effect of ART, voluntary male medical circumcision on the prevalence and incidence of cervical cancer.

Smith, M. and K. Canfell (2016). "Impact of the Australian National Cervical Screening Program in women of different ages." *Med J Aust* 205(8): 359-364.

OBJECTIVES: The Australian National Cervical Screening Program (NCSP) will transition in 2017 from cytology-based screening every two years, starting from age 18-20 years, to HPV-based screening every 5 years, starting from age 25. To examine the impact of the program before this transition we analysed trends in the incidence of cervical cancer, by age and histological subtype. **DESIGN, SETTING AND PARTICIPANTS:** National cervical cancer incidence data, 1982-2010. **MAIN OUTCOME MEASURES:** Standardised rate ratios (SRR) for 3-yearly average cervical cancer incidence, relative to the rate during 1988-1990, by age group and histological type. **RESULTS:** Between 1988-1990 and 2008-2010, cervical cancer incidence fell substantially in women aged

25-49 (SRR, 0.55; 95% CI, 0.51-0.59), 50-69 (SRR, 0.46; 95% CI, 0.42-0.51) and 70 years or more (SRR, 0.50; 95% CI, 0.43-0.58), but not in women aged 20-24 years (SRR, 0.70; 95% CI, 0.46-1.05). These declines were primarily driven by drops in squamous cell carcinoma (SCC) in women aged 25-49 (SRR, 0.50; 95% CI, 0.46-0.55), 50-69 (SRR, 0.39; 95% CI, 0.35-0.45) and more than 70 years (SRR, 0.43; 95% CI, 0.36-0.51). However, rates have now plateaued in women aged 25-69 years. The incidence of adenocarcinoma did not consistently decline across the program period in any age group. The incidence of neither SCC (SRR, 0.91; 95% CI, 0.55-1.51) nor adenocarcinoma (SRR, 0.91; 95% CI, 0.35-2.40) declined in women aged 20-24 years. **CONCLUSION:** Although women aged 20-24 years have been included in the NCSP since its inception, no significant impact on cervical cancer incidence was observed in this age group. The NCSP has had a substantial impact on SCC and overall cervical cancer incidence in women aged 25 years and over. Its impact on the incidence of adenocarcinoma, in contrast, has been limited.

Jeronimo, J., F. Holme, R. Slavkovsky and C. Camel (2016). "**Implementation of HPV testing in Latin America.**" *J Clin Virol* **76 Suppl 1**: S69-s73.

Cervical cancer is one of the leading killers among women in Latin America, a region where most countries have not been successful in implementing population-level cytology-based screening programs. This disease is caused by persistent infection with oncogenic HPV; in recent years, more HPV tests have become available and prices have dropped significantly, making it possible for countries to adopt these technologies. Pilot programs that took place in Nicaragua, Mexico, and Argentina showed a high level of efficacy in detecting precancerous cervical lesions and good feasibility and acceptance of self-sampling. El Salvador, Guatemala, Honduras, and Nicaragua are beginning to institutionalize HPV testing at the population level. The experience from the different countries has created rich information about the barriers and requirements for implementing HPV screening at large scale in these resource-constrained countries. There are several challenges for implementation, including a need to update screening guidelines, strengthen treatment capacity, and develop a comprehensive quality assurance plan for the HPV testing. At the same time, there are several opportunities in Latin America that make the process more feasible and faster than in other regions of the world: most Latin American countries already have screening programs funded by their national governments, several countries in the region are already implementing HPV testing, and there is a regional pooled procurement mechanism that could facilitate the purchase of HPV tests at an accessible price. We envision that most countries in the region will include HPV testing in their national program within the next three to five years.

Shieh, Y., M. Eklund, G. F. Sawaya, W. C. Black, B. S. Kramer and L. J. Esserman (2016). "**Population-based screening for cancer: hope and hype.**" *Nat Rev Clin Oncol* **13**(9): 550-565.

Several important lessons have been learnt from our experiences in screening for various cancers. Screening programmes for cervical and colorectal cancers have had the greatest success, probably because these cancers are relatively homogenous, slow-growing, and have identifiable precursors that can be detected and removed; however, identifying the true obligate precursors of invasive disease remains a challenge. With regard to screening for breast cancer and for prostate cancer, which focus on early detection of invasive cancer, preferential detection of slower-growing, localized cancers has occurred, which has led to concerns about overdiagnosis and overtreatment; programmes for early detection of invasive lung cancers are emerging, and have faced similar challenges. A crucial consideration in screening for breast, prostate, and lung cancers is their remarkable phenotypic heterogeneity, ranging from indolent to highly aggressive. Efforts have been made to address the limitations of cancer-screening programmes, providing an opportunity for cross-disciplinary learning and further advancement of the science. Current innovations are

aimed at identifying the individuals who are most likely to benefit from screening, increasing the yield of consequential cancers on screening and biopsy, and using molecular tests to improve our understanding of disease biology and to tailor treatment. We discuss each of these concepts and outline a dynamic framework for continuous improvements in the field of cancer screening.

Hillemanns, P. (2016). "**The paradigm shift in cervical cancer screening in Germany.**" Arch Gynecol Obstet **293**(1): 3-4.

With the adoption of the Cancer Screening and Registration Law (KFRG, 2013) based on the National Cancer Plan, the so far opportunistic cervical cancer screening in Germany is to be converted to an organized screening program. This decision in Germany is consistent with the new EU Guidelines and, in anticipation of the upcoming German S3 guideline for cervical cancer screening.

Waxman, A. G., L. E. Buenconsejo-Lum, M. Cremer, S. Feldman, K. A. Ault, J. M. Cain and M. L. Diaz (2016). "**Cervical Cancer Screening in the United States-Affiliated Pacific Islands: Options and Opportunities.**" J Low Genit Tract Dis **20**(1): 97-104.

OBJECTIVE: Successful cervical cancer screening in the United States-Affiliated Pacific Islands (USAPI) is limited by geographic, political, economic, and logistic factors. An expert panel convened to examine screening in each of the 6 island jurisdictions and to explore options beyond cytology-based screening. MATERIALS AND METHODS: Forty-one representatives of American Congress of Obstetrics and Gynecology, American Society for Colposcopy and Cervical Pathology, government agencies, the World Health Organization, Pan American Health Organization, health representatives of the 6 Pacific island jurisdictions, Puerto Rico, and several academic institutions met in a 2-day meeting to explore options to improve access and coverage of cervical cancer screening in the USAPI. RESULTS: Cytology-based screening is less widely accessed and less successful in the USAPI than in the United States in general. Barriers include geographic isolation, cultural factors, and lack of resources. Cytology-based screening requires multiple visits to complete the process from screening to treatment. Screen-and-treat regimens based on visual inspection with acetic acid or human papillomavirus requiring 1 or 2 visits have the potential to improve cervical cancer prevention in the USAPI. CONCLUSIONS: The standard US algorithm of cytology screening followed by colposcopy and treatment is less effective in geographically and culturally isolated regions such as the USAPI. Alternate technologies, both high tech, such as primary human papillomavirus screening, and low tech, such as visual inspection with acetic acid, have shown promise in resource-poor countries and may have applicability in these US jurisdictions.

Georgalis, L., S. de Sanjosé, M. Esnaola, F. X. Bosch and M. Diaz (2016). "**Present and future of cervical cancer prevention in Spain: a cost-effectiveness analysis.**" Eur J Cancer Prev **25**(5): 430-439.

Human papillomavirus (HPV) vaccination within a nonorganized setting creates a poor cost-effectiveness scenario. However, framed within an organized screening including primary HPV DNA testing with lengthening intervals may provide the best health value for invested money. To compare the effectiveness and cost-effectiveness of different cervical cancer (CC) prevention strategies, including current status and new proposed screening practices, to inform health decision-makers in Spain, a Markov model was developed to simulate the natural history of HPV and CC. Outcomes included cases averted, life expectancy, reduction in the lifetime risk of CC, life years saved, quality-adjusted life years (QALYs), net health benefits, lifetime costs, and incremental cost-effectiveness ratios. The willingness-to-pay threshold is defined at 20 000€/QALY. Both costs and health outcomes were discounted at an annual rate of

3%. A strategy of 5-year organized HPV testing has similar effectiveness, but higher efficiency than 3-year cytology. Screening alone and vaccination combined with cytology are dominated by vaccination followed by 5-year HPV testing with cytology triage (12 214&OV0556;/QALY). The optimal age for both ending screening and switching age from cytology to HPV testing in older women is 5 years later for unvaccinated than for vaccinated women. Net health benefits decrease faster with diminishing vaccination coverage than screening coverage. Primary HPV DNA testing is more effective and cost-effective than current cytological screening. Vaccination uptake improvements and a gradual change toward an organized screening practice are critical components for achieving higher effectiveness and efficiency in the prevention of CC in Spain.

Anttila, A., S. Lönnberg, A. Ponti, E. Suonio, P. Villain, J. W. Coebergh and L. von Karsa (2015). "**Towards better implementation of cancer screening in Europe through improved monitoring and evaluation and greater engagement of cancer registries.**" *Eur J Cancer* **51**(2): 241-251.

Proposals to improve implementation, monitoring and evaluation of breast, cervical and colorectal cancer screening programmes have been developed in a European project involving scientists and professionals experienced in cancer registration (EUROCOURSE). They call for a clear and more active role for cancer registries through better interfaces with cancer screening programmes and adapting data contents of cancer registries for evaluation purposes. Cancer registries are recognised as essential for adequate evaluation of cancer screening programmes, but they are not involved in screening evaluation in several European countries. This is a key barrier to improving the effectiveness of programmes across Europe. The variation in Europe in the implementation of cancer screening offers a unique opportunity to learn from best practices in collaboration between cancer registries and screening programmes. Population-based cancer registries have experience and tools in collecting and analysing relevant data, e.g. for diagnostic and therapeutic determinants of mortality. In order to accelerate improvements in cancer control we argue that cancer registries should take co-responsibility in promoting effective screening evaluation in Europe. Additional investments are vital to further development of infrastructures and activities for screening evaluation and monitoring in the national settings and also at the pan-European level. The EUROCOURSE project also aimed to harmonise implementation of the European quality assurance guidelines for cancer screening programmes across Europe through standardising routine data collection and analysis, and definitions for key performance indicators for screening registers. Data linkage between cancer and screening registers and other repositories of demographic data and cause of death and where available clinical registers is key to implementing the European screening standards and thereby reducing the burden of disease through early detection. Greater engagement of cancer registries in this collaborative effort is also essential to develop adequate evaluation of innovations in cancer prevention and care.

Agapova, M., A. Duignan, A. Smith, C. O'Neill and A. Basu (2015). "**Long-term costs of introducing HPV-DNA post-treatment surveillance to national cervical cancer screening in Ireland.**" *Expert Rev Pharmacoecon Outcomes Res* **15**(6): 999-1005.

INTRODUCTION: Co-testing (cytology plus human papillomavirus DNA testing) as part of cervical cancer surveillance in Ireland increases one-time testing costs. Of interest to policy makers was the long-term impact of these costs accompanied by decreases in intensity of recalls for women with no detected abnormalities. METHODS: A cost analysis of cytology-only and co-testing strategy was implemented using decision analytic modeling, aggregating testing utilization and costs for each of the two strategies over 12 years. RESULTS: Aggregated incremental costs of the co-testing strategy were positive for the first 3 years but became negative thereafter, generating a cost savings of roughly €20 million in favor of the cytology-only strategy over a 12-year period.

Results were robust over a range of sensitivity analyses with respect to discount and attrition rates. DISCUSSION: This analysis provided valuable information to policy makers contributing to the introduction of co-testing for post-treatment surveillance (PTS) in Ireland.

Parham, G. P., M. H. Mwanahamuntu, S. Kapambwe, R. Muwonge, A. C. Bateman, M. Blevins, C. J. Chibwasha, K. S. Pfaendler, V. Mudenda, A. L. Shibemba, S. Chisele, G. Mkumba, B. Vwalika, M. L. Hicks, S. H. Vermund, B. H. Chi, J. S. Stringer, R. Sankaranarayanan and V. V. Sahasrabudhe (2015). "**Population-level scale-up of cervical cancer prevention services in a low-resource setting: development, implementation, and evaluation of the cervical cancer prevention program in Zambia.**" *PLoS One* **10**(4): e0122169.

BACKGROUND: Very few efforts have been undertaken to scale-up low-cost approaches to cervical cancer prevention in low-resource countries. METHODS: In a public sector cervical cancer prevention program in Zambia, nurses provided visual-inspection with acetic acid (VIA) and cryotherapy in clinics co-housed with HIV/AIDS programs, and referred women with complex lesions for histopathologic evaluation. Low-cost technological adaptations were deployed for improving VIA detection, facilitating expert physician opinion, and ensuring quality assurance. Key process and outcome indicators were derived by analyzing electronic medical records to evaluate program expansion efforts. FINDINGS: Between 2006-2013, screening services were expanded from 2 to 12 clinics in Lusaka, the most-populous province in Zambia, through which 102,942 women were screened. The majority (71.7%) were in the target age-range of 25-49 years; 28% were HIV-positive. Out of 101,867 with evaluable data, 20,419 (20%) were VIA positive, of whom 11,508 (56.4%) were treated with cryotherapy, and 8,911 (43.6%) were referred for histopathologic evaluation. Most women (87%, 86,301 of 98,961 evaluable) received same-day services (including 5% undergoing same-visit cryotherapy and 82% screening VIA-negative). The proportion of women with cervical intraepithelial neoplasia grade 2 and worse (CIN2+) among those referred for histopathologic evaluation was 44.1% (1,735/3,938 with histopathology results). Detection rates for CIN2+ and invasive cervical cancer were 17 and 7 per 1,000 women screened, respectively. Women with HIV were more likely to screen positive, to be referred for histopathologic evaluation, and to have cervical precancer and cancer than HIV-negative women. INTERPRETATION: We creatively disrupted the 'no screening' status quo prevailing in Zambia and addressed the heavy burden of cervical disease among previously unscreened women by establishing and scaling-up public-sector screening and treatment services at a population level. Key determinants for successful expansion included leveraging HIV/AIDS program investments, and context-specific information technology applications for quality assurance and filling human resource gaps.

Serraino, D., A. Gini, M. Tadorelli, G. Ronco, P. Giorgi-Rossi, M. Zappa, E. Crocetti, A. Franzo, F. Falcini, C. B. Visioli, F. Stracci, M. Zorzi, M. Federico, M. Michiara, M. Fusco, S. Ferretti, F. PannoZZo, F. Tisano, R. Zanetti and A. Zucchetto (2015). "**Changes in cervical cancer incidence following the introduction of organized screening in Italy.**" *Prev Med* **75**: 56-63.

OBJECTIVE: To quantify the impact of organized cervical screening programs (OCSPs) on the incidence of invasive cervical cancer (ICC), comparing rates before and after activation of OCSPs. METHODS: This population-based investigation, using individual data from cancer registries and OCSPs, included 3557 women diagnosed with ICC at age 25-74years in 1995-2008. The year of full-activation of each OCSP was defined as the year when at least 40% of target women had been invited. Incidence rate ratios (IRRs) with 95% confidence intervals (95% CIs) were calculated as the ratios between age-standardized incidence rates observed in periods after full-activation of OCSPs vs those observed in the preceding quinquennium. RESULTS: ICC incidence rates

diminished with time since OCSPs full-activation: after 6-8years, the IRR was 0.75 (95% CI: 0.67-0.85). The reduction was higher for stages IB-IV (IRR=0.68, 95% CI: 0.58-0.80), squamous cell ICCs (IRR=0.74, 95% CI: 0.64-0.84), and particularly evident among women aged 45-74years. Conversely, incidence rates of micro-invasive (stage IA) ICCs increased, though not significantly, among women aged 25-44years (IRR=1.34, 95% CI: 0.91-1.96). Following full-activation of OCSPs, micro-invasive ICCs were mainly and increasingly diagnosed within OCSPs (up to 72%). CONCLUSION(S): Within few years from activation, organized screening positively impacted the already low ICC incidence in Italy and favored down-staging.

Session 4 Triage : Currently available options, future opportunities and challenges

A Pubmed search was performed with the following selection criteria: [Cervical cancer] AND [Triage] AND [Management algorithm]; [Triage] AND [Cervical cancer screening] AND [HPV]; [HPV Testing] AND [Triage] AND [Cervical cancer screening] AND [Management algorithms] title/abstract published in the last 5 years: 22, 391 and 18 items were retrieved respectively. 23 items were carefully selected as some of the articles were either out of scope of the session or relevant to other sessions. References were imported in EndNote. Herein, a relevant manual selection of publications between 2015-2020 based on title and abstract was made.

Rezhake, R., F. Chen, S. Y. Hu, X. L. Zhao, X. Zhang, J. Cao, Y. L. Qiao, F. H. Zhao and M. Arbyn (2020). "**Triage options to manage high-risk human papillomavirus-positive women: A population-based cross-sectional study from rural China.**" *Int J Cancer*.

Improvement in managing HPV-positive women is urgently needed. Based on a population-based study which included 2112 women aged 49 to 69 from Shanxi, China, we aimed to evaluate the clinical performance of multiple triage strategies based on liquid-based cytology (LBC), p16(INK4a), viral load and partial genotyping, as a single or combined strategy for detecting cervical intraepithelial neoplasia grade 2/3 or higher (CIN2+/CIN3+) in women who tested positive by Hybrid Capture 2 (HC2). Among 452 HC2-positive women, the test positivity of LBC (ASC-US+), p16(INK4a), HPV16/18 and HPV16/18/31/33/45 were 39.6%, 38.5%, 18.0% and 40.0%, respectively. Compared to LBC (ASC-US+) triage, a single triage strategies using p16(INK4a) or extended genotyping (SureX HPV16/18/31/33/45) achieved comparable sensitivity (relative sensitivity: 1.08, 95% confidence interval [CI]: 0.93-1.26 and 0.96, 95% CI: 0.76-1.22) and specificity (relative specificity: 1.05, 95% CI: 0.96-1.14 and 1.02, 95% CI: 0.92-1.14) for CIN3+. Viral load triage using a ≥ 50 RLU/CO cut-point also yielded similar results with LBC (ASC-US+). Among combined triage strategies, HPV16/18 genotyping with reflex p16(INK4a) showed higher sensitivity and slightly lower specificity than LBC (ASC-US+) for CIN3+ detection, however, the differences were not statistically significant. Of note, after a negative result by p16(INK4a) or LBC among HPV16/18 negative women, the posttest probability of CIN3+ was lower than 1%. Our study suggested that p16(INK4a), extended genotyping and increased viral load cut-point could be promising alternatives to cytology triage. Combined triage algorithms of HPV16/18 with reflex

p16(INK4a) or cytology, if negative, are associated with the substantial low posttest risk sufficient to release women to next screening round.

Sroczyński, G., E. Esteban, A. Widschwendter, W. Oberaigner, W. Borena, D. von Laer, M. Hackl, G. Endel and U. Siebert (2020). **"Reducing overtreatment associated with overdiagnosis in cervical cancer screening-A model-based benefit-harm analysis for Austria."** *Int J Cancer* **147**(4): 1131-1142.

A general concern exists that cervical cancer screening using human papillomavirus (HPV) testing may lead to considerable overtreatment. We evaluated the trade-off between benefits and overtreatment among different screening strategies differing by primary tests (cytology, p16/Ki-67, HPV alone or in combinations), interval, age and diagnostic follow-up algorithms. A Markov state-transition model calibrated to the Austrian epidemiological context was used to predict cervical cancer cases, deaths, overtreatments and incremental harm-benefit ratios (IHBR) for each strategy. When considering the same screening interval, HPV-based screening strategies were more effective compared to cytology or p16/Ki-67 testing (e.g., relative reduction in cervical cancer with biennial screening: 67.7% for HPV + Pap cotesting, 57.3% for cytology and 65.5% for p16/Ki-67), but were associated with increased overtreatment (e.g., 19.8% more conizations with biennial HPV + Papcotesting vs. biennial cytology). The IHBRs measured in unnecessary conizations per additional prevented cancer-related death were 31 (quinquennial Pap + p16/Ki-67-triage), 49 (triennial Pap + p16/Ki-67-triage), 58 (triennial HPV + Pap cotesting), 66 (biennial HPV + Pap cotesting), 189 (annual Pap + p16/Ki-67-triage) and 401 (annual p16/Ki-67 testing alone). The IHBRs increased significantly with increasing screening adherence rates and slightly with lower age at screening initiation, with a reduction in HPV incidence or with lower Pap-test sensitivity. Depending on the accepted IHBR threshold, biennial or triennial HPV-based screening in women as of age 30 and biennial cytology in younger women may be considered in opportunistic screening settings with low or moderate adherence such as in Austria. In organized settings with high screening adherence and in postvaccination settings with lower HPV prevalence, the interval may be prolonged.

Benski, A. C., M. Viviano, J. Jinoro, M. Alec, R. Catarino, J. Herniainasolo, P. Vassilakos and P. Petignat (2019). **"HPV self-testing for primary cervical cancer screening in Madagascar: VIA/VILI triage compliance in HPV-positive women."** *PLoS One* **14**(8): e0220632.

OBJECTIVE: To assess triage compliance and the effect of the time from screening to triage on follow-up among HPV-positive women. **METHODS:** We recruited 1232 women in a screening campaign in Madagascar from February to October 2015. In the first period (February-May), HPV tests were performed remotely using the cobas test. In the second period (May-October), testing was performed on-site using the Xpert HPV assay. HPV-positive women were invited for triage with visual inspection with acetic acid (VIA) and Lugol's iodine (VILI). Systematic biopsy and endocervical brushing were performed on all HPV-positive women for quality control. Three groups were defined according to time from HPV testing to triage invitation for HPV-positive women-Group I: delayed (> 3 months), Group II: prompt (24-48 hours), and Group III: immediate (< 24 hours). **RESULTS:** A total 1232 self-sampled HPV tests were performed in the study period (496 in Group I, 512 in Group II, and 224 in Group III). Participants' mean age was 43.2 ± 9.3 years. Mean time from screening to VIA/VILI testing was 103.5 ± 43.6 days. Overall HPV prevalence was 28.0%. HPV prevalence was 27.2% in Group I (cobas test), 29.2% in Group 2 (Xpert test), and 26,7% in Group III (Xpert test). The VIA/VILI compliance rate was 77.8% for Group I, 82.7% for Group II, and 95.0% for Group III. Of women undergoing VIA/VILI, 56.3% in Group I and 43.5% in Groups II/III had positive results. Prevalence of cervical intraepithelial neoplasia grade 2 or worse among HPV-positive women was 9.8% for Group I and 6.8% for Groups II/III. Non-adherence was higher

among rural women, uneducated women, and women in Group I. **CONCLUSION:** HPV-positive women with immediate VIA/VILI triage invitation had the best triage compliance. A single-day test and triage strategy is preferred for low-resource settings.

Bergengren, L., G. Lillsunde-Larsson, G. Helenius and M. G. Karlsson (2019). "**HPV-based screening for cervical cancer among women 55-59 years of age.**" *PLoS One* **14**(6): e0217108.

AIM: Many cervical cancers occurs among women over 65 and prevalence of HPV genotypes in this age cohort is sparingly studied. One aim of this study was to study the prevalence and distribution of HPV genotypes in women 55-59 years, with normal cytology when exiting the screening program. Secondly, HPV clearance as well as the value of HPV genotyping and/or liquid based cytology as triage tests for identifying histological dysplasia among women with persistent HPV was studied. **METHODS:** Women that exited the screening program with normal cytology, between the years 2012-2014, in Örebro County, Sweden, were invited to this study. A total of 2946 samples were analyzed with a broad-spectrum assay to detect both hrHPV and IrHPV in order to investigate the distribution of genotypes. In the consent group, women with a positive hrHPV test were offered a follow-up test and a cone biopsy for histological confirmation, and a follow up sample 6 months post cone. **RESULTS:** The overall prevalence of hrHPV was 7.4% and 59% of them remained hrHPV positive in a follow-up test after 12 months. A total of 99 women had a cone biopsy done, where 19% showed histological dysplasia. HPV 53 was the most common genotype, and among women with histology confirmed LSIL or HSIL, HPV 31 was most common. A positive hrHPV result showed a PPV of 25% for LSIL+ and 12.5% for HSIL+. Using detection of HPV 16/18 genotypes as a triage test for hrHPV positive tests, indicated FNR for histological LSIL+ and HSIL+ of 94% and 87.5% respectively, whilst triage based on cervical cytology had a FNR of 69% for LSIL+ and 37.5% for HSIL+. **CONCLUSION:** The most common hrHPV genotypes among women 55-59 years of age were non HPV16/18 genotypes, and in this population, these genotypes represented most of the histological verified HSIL lesions. This result does not support the proposition of a HPV 16/18 triaging test after a positive hrHPV test as a marker of histological HSIL+ cervical lesions in women over 55 years of age. Similarly, cytological triage after a positive hrHPV showed no additional benefit in this population. Specific triaging tests should be validated to follow post-menopausal women with a positive hrHPV test.

Polman, N. J., N. J. Veldhuijzen, D. A. M. Heideman, P. J. F. Snijders, C. Meijer and J. Berkhof (2019). "**Management of HPV-positive women in cervical screening using results from two consecutive screening rounds.**" *Int J Cancer* **144**(9): 2339-2346.

We studied whether triage of human papillomavirus (HPV)-positive women participating in an HPV-based screening programme can be improved by including the HPV result at the previous screen in the triage algorithm. We analyzed data of a subgroup of 366 women from the POBASCAM trial, screened by cytology and HPV cotesting. Women were included if they tested HPV-positive in the second HPV-based screening round. We evaluated the clinical performance of 16 strategies, consisting of cytology, HPV genotyping, and/or previous screen HPV result. The clinical endpoint was cervical precancer or cancer (CIN3+). The current Dutch triage testing policy for HPV-positive women is to refer women for colposcopy if they have abnormal cytology at baseline or after 6-18 months. In the second HPV-based screening round, this strategy yielded a negative predictive value (NPV) of 95.8% (95% confidence interval: 91.9-98.2) and colposcopy referral rate of 37.6% (32.3-43.2%). Replacing repeat cytology by the previous screen HPV result yielded a similar NPV (96.9%, 93.3-98.9) and colposcopy referral rate (38.8%, 33.4-44.4). A higher NPV (99.2%, 96.3-100%) at the cost of a higher colposcopy referral rate (49.2%, 43.6-54.8) was achieved when cytology was combined with HPV16/18 genotyping. The other 13 triage strategies

yielded a lower NPV, a higher colposcopy referral rate or performed similarly but required additional testing. HPV-positive women in the second HPV-based screening round can be suitably managed by cytology, HPV16/18 genotyping and the HPV result at the previous screen, obviating the need for repeat testing of HPV-positive, cytology negative women.

Termrungruanglert, W., N. Khemapech, T. Tantitamit and P. Havanond (2019). "**Cost effectiveness analysis of HPV primary screening and dual stain cytology triage compared with cervical cytology.**" *J Gynecol Oncol* **30**(2): e17.

OBJECTIVES: To assess the clinical and cost-effectiveness of human papillomavirus (HPV) primary screening triage with p16/Ki-67 dual stain cytology compared to cytology. **METHODS:** We conducted an Excel®-based budget impact model to estimate the preinvasive and invasive cervical cancer cases identified, mortality rate, direct medical costs, quality-adjusted life years (QALYs) and the incremental cost-effectiveness analysis of two strategies from the healthcare payer perspective. The study population is a cohort of women 30-65 years of age presenting for cervical screening. **RESULTS:** HPV primary screening triage with p16/Ki-67 dual stain showed higher sensitivity without losing specificity compared to conventional Pap smear. The improving the screening performance leads to decrease the prevalence of precancerous lesion, annual incidence and mortality of cervical cancer. The incidence of cervical cancer case detected by new algorithm compared with conventional method were 31,607 and 38,927, respectively. In addition, the new algorithm was more effective and more costly (average QALY 24.03, annual cost \$13,262,693) than conventional cytology (average QALY 23.98, annual cost \$7,713,251). The incremental cost-effective ratio (ICER) per QALY gained was \$1,395. The sensitivity analysis showed if the cost of cytology and HPV test increased three times, the ICER would fall to \$303/QALY gained and increased to \$4,970/QALY gained, respectively. **CONCLUSION:** Our model results suggest that screening by use of HPV genotyping test as a primary screening test combined with dual stain cytology as the triage of HPV positive women in Thai population 30-65 years old is expected to be more cost-effective than conventional Pap cytology.

Torres-Ibarra, L., J. Cuzick, A. T. Lorincz, D. Spiegelman, E. Lazcano-Ponce, E. L. Franco, A. B. Moscicki, S. M. Mahmud, C. M. Wheeler, B. Rivera-Paredes, R. Hernández-López, L. León-Maldonado and J. Salmerón (2019). "**Comparison of HPV-16 and HPV-18 Genotyping and Cytological Testing as Triage Testing Within Human Papillomavirus-Based Screening in Mexico.**" *JAMA Netw Open* **2**(11): e1915781.

IMPORTANCE: Triage tests enhance the efficiency cervical cancer screening based on human papillomavirus (HPV), but the best approach for maximizing programmatic effectiveness is still uncertain, particularly in a real-world scenario. **OBJECTIVE:** To compare the clinical performance of 6 triage strategies based on liquid-based cytology (LBC) and HPV-16 and HPV-18 genotyping individually or in combination as sequential triage tests to detect cervical intraepithelial neoplasia (CIN) grade 2 or higher among women with high-risk HPV. **DESIGN, SETTING, AND PARTICIPANTS:** This diagnostic study of routine cervical cancer screening was conducted at 100 primary health centers in Tlaxcala, Mexico. Women aged 30 to 64 years were recruited from August 1, 2013, to February 24, 2016, as part of the Forwarding Research for Improved Detection and Access for Cervical Cancer Screening and Triage study. Six triage scenarios for referral to colposcopy were examined: (1) LBC testing that found atypical squamous cells of undetermined significance (ASC-US) or worse, (2) positive results in HPV-16 genotyping, (3) positive results in HPV-18 genotyping, (4) positive results in HPV-16/HPV-18 genotyping, (5) positive results in HPV-16 genotyping or, if genotyping results were negative, reflex LBC testing that found ASC-US or worse, and (6) positive results in HPV-16/HPV-18 genotyping or, if genotyping results were negative, reflex LBC testing that found ASC-US or worse. Data were analyzed from October 2017 to August 2018. **EXPOSURES:**

Liquid-based cytological testing with simultaneous HPV-16 and HPV-18 genotyping. Women whose HPV genotyping results were positive for HPV-16 or HPV-18 or whose LBC results found ASC-US or worse and a random set of negative and normal results were referred to colposcopy with histologic analysis used for disease confirmation. MAIN OUTCOMES AND MEASURES: Clinical performance of each test strategy for detection of CIN grade 2 or higher. Secondary outcomes included resource utilization of each triage scenario, measured by the number of tests performed, the referral rate for colposcopy, and the numbers of colposcopies per CIN grade 2 or higher detected. RESULTS: A total of 36 212 women (median [interquartile range] age, 40 [35-47] years) were screened, and 4051 women (11.2%) had high-risk HPV. Of these women, 1109 (24.6%) were found to have HPV-16, HPV-18, or ASC-US or worse. Further histologic testing detected CIN grade 2 or higher in 110 of 788 women (14.0%) who underwent follow-up colposcopy. Sensitivity and specificity for 3 main triage strategies were 42.9% and 74.0% for LBC; 58.3% and 54.4% for HPV-16/HPV-18 genotyping; and 86.6% and 34.0% for HPV-16/HPV-18 genotyping with reflex LBC. The referral rate to colposcopy was 29% for HPV-16/HPV-18 with reflex LBC, which was 2-fold higher than the referral rate of 12% for LBC. CONCLUSIONS AND RELEVANCE: Triage of women with high-risk HPV with HPV-16/HPV-18 genotyping with reflex LBC was significantly associated with improvement in detection of CIN grade 2 or higher compared with LBC alone. The benefit of disease prevented may outweigh the cost of increasing requirements for colposcopy services in settings with limited adherence to follow-up after a positive screening result.

Wentzensen, N., M. A. Clarke, R. Bremer, N. Poitras, D. Tokugawa, P. E. Goldhoff, P. E. Castle, M. Schiffman, J. D. Kingery, K. K. Grewal, A. Locke, W. Kinney and T. S. Lorey (2019). "**Clinical Evaluation of Human Papillomavirus Screening With p16/Ki-67 Dual Stain Triage in a Large Organized Cervical Cancer Screening Program.**" *JAMA Intern Med* **179**(7): 881-888.

IMPORTANCE: As cervical cancer screening transitions from Papanicolaou cytologic screening to primary human papillomavirus (HPV) testing worldwide, effective triage tests are needed to decide who among the HPV-positive women should receive further diagnostic evaluation to avoid unnecessary colposcopies and biopsies. OBJECTIVE: To evaluate the performance of the p16/Ki-67 dual stain (DS) and HPV16/18 genotyping for the triage of HPV-positive women. DESIGN, SETTING, AND PARTICIPANTS: A prospective observational study was conducted within the cervical cancer screening program at Kaiser Permanente Northern California of 3225 HPV-positive women undergoing HPV and Papanicolaou cytologic testing with a valid DS result from September 16 to October 31, 2015, with follow-up through December 31, 2018. EXPOSURES: Human papillomavirus screening with partial genotyping and cytologic triage compared with DS triage. MAIN OUTCOMES AND MEASURES: Cervical intraepithelial neoplasia grade 3 or more severe (CIN3+) and grade 2 or more severe (CIN2+), diagnosed within 3 years after sample collection. RESULTS: A total of 3225 women (mean [SD] age, 37.9 [11.3] years) participated in the study. For triage of HPV-positive women with partial genotyping, DS showed better risk stratification for CIN3+ than did Papanicolaou cytologic testing, with women with positive DS results having a higher risk than women with positive Papanicolaou test results for CIN3+ (218 of 1818 [12.0%; 95% CI, 10.5%-13.5%] vs 219 of 2128 [10.3%; 95% CI, 9.0%-11.6%]; P = .005). Similarly, DS showed better risk stratification for CIN3+ compared with Papanicolaou cytologic testing in HPV-positive women, irrespective of genotyping. The greatest reassurance against CIN3+ was observed in HPV16/18-negative women with negative DS results, with a risk low enough to extend retesting intervals. Dual stain triage strategies required substantially fewer colposcopies per detection of CIN3+ compared with Papanicolaou cytologic testing, with a 32.1% (859 of 2677) reduction of colposcopies compared with the currently recommended triage strategy of HPV screening with Papanicolaou cytologic testing. Results for CIN2+ were very similar. CONCLUSIONS AND

RELEVANCE: Triage of HPV-positive women with DS was superior to Papanicolaou cytologic testing in this study, demonstrating equal immediate detection of precancerous lesions and substantially reduced referral to colposcopy. These findings suggest that DS can safely replace Papanicolaou cytologic testing as a triage strategy for primary HPV screening, and that retesting intervals in HPV16/18-negative women with negative DS results can be safely extended to 3 years.

Babion, I., B. C. Snoek, P. W. Novianti, A. Jaspers, N. van Trommel, D. A. M. Heideman, C. Meijer, P. J. F. Snijders, R. D. M. Steenbergen and S. M. Wilting (2018). "**Triage of high-risk HPV-positive women in population-based screening by miRNA expression analysis in cervical scrapes; a feasibility study.**" *Clin Epigenetics* **10**: 76.

BACKGROUND: Primary testing for high-risk HPV (hrHPV) is increasingly implemented in cervical cancer screening programs. Many hrHPV-positive women, however, harbor clinically irrelevant infections, demanding additional disease markers to prevent over-referral and over-treatment. Most promising biomarkers reflect molecular events relevant to the disease process that can be measured objectively in small amounts of clinical material, such as miRNAs. We previously identified eight miRNAs with altered expression in cervical precancer and cancer due to either methylation-mediated silencing or chromosomal alterations. In this study, we evaluated the clinical value of these eight miRNAs on cervical scrapes to triage hrHPV-positive women in cervical screening. **RESULTS:** Expression levels of the eight candidate miRNAs in cervical tissue samples (n = 58) and hrHPV-positive cervical scrapes from a screening population (n = 187) and cancer patients (n = 38) were verified by quantitative RT-PCR. In tissue samples, all miRNAs were significantly differentially expressed (p < 0.05) between normal, high-grade precancerous lesions (CIN3), and/or cancer. Expression patterns detected in cervical tissue samples were reflected in cervical scrapes, with five miRNAs showing significantly differential expression between controls and women with CIN3 and cancer. Using logistic regression analysis, a miRNA classifier was built for optimal detection of CIN3 in hrHPV-positive cervical scrapes from the screening population and its performance was evaluated using leave-one-out cross-validation. This miRNA classifier consisted of miR-15b-5p and miR-375 and detected a major subset of CIN3 as well as all carcinomas at a specificity of 70%. The CIN3 detection rate was further improved by combining the two miRNAs with HPV16/18 genotyping. Interestingly, both miRNAs affected the viability of cervical cancer cells in vitro. **CONCLUSIONS:** This study shows that miRNA expression analysis in cervical scrapes is feasible and enables the early detection of cervical cancer, thus underlining the potential of miRNA expression analysis for triage of hrHPV-positive women in cervical cancer screening.

Campos, N. G., N. Lince-Deroche, C. J. Chibwesa, C. Firnhaber, J. S. Smith, P. Michelow, G. Meyer-Rath, L. Jamieson, S. Jordaan, M. Sharma, C. Regan, S. Sy, G. Liu, V. Tsu, J. Jeronimo and J. J. Kim (2018). "**Cost-Effectiveness of Cervical Cancer Screening in Women Living With HIV in South Africa: A Mathematical Modeling Study.**" *J Acquir Immune Defic Syndr* **79**(2): 195-205.

BACKGROUND: Women with HIV face an increased risk of human papillomavirus (HPV) acquisition and persistence, cervical intraepithelial neoplasia, and invasive cervical cancer. Our objective was to determine the cost-effectiveness of different cervical cancer screening strategies among women with HIV in South Africa. **METHODS:** We modified a mathematical model of HPV infection and cervical disease to reflect coinfection with HIV. The model was calibrated to epidemiologic data from HIV-infected women in South Africa. Clinical and economic data were drawn from in-country data sources. The model was used to project reductions in the lifetime risk of cervical cancer and incremental cost-effectiveness ratios (ICERs) of Pap and HPV DNA screening and management algorithms beginning at HIV diagnosis, at 1-, 2-, or 3-year intervals. Strategies with

an ICER below South Africa's 2016 per capita gross domestic product (US\$5270) were considered "cost-effective." RESULTS: HPV testing followed by treatment (test-and-treat) at 2-year intervals was the most effective strategy that was also cost-effective, reducing lifetime cancer risk by 56.6% with an ICER of US\$3010 per year of life saved. Other cost-effective strategies included Pap (referral threshold: HSIL+) at 1-, 2-, and 3-year intervals, and HPV test-and-treat at 3-year intervals. Pap (ASCUS+), HPV testing with 16/18 genotyping, and HPV testing with Pap or visual triage of HPV-positive women were less effective and more costly than alternatives. CONCLUSIONS: Considering per capita gross domestic product as the benchmark for cost-effectiveness, HPV test-and-treat is optimal in South Africa. At lower cost-effectiveness benchmarks, Pap (HSIL+) would be optimal.

Cuschieri, K., G. Ronco, A. Lorincz, L. Smith, G. Ogilvie, L. Mirabello, F. Carozzi, H. Cubie, N. Wentzensen, P. Snijders, M. Arbyn, J. Monsonego and S. Franceschi (2018). "**Eurogin roadmap 2017: Triage strategies for the management of HPV-positive women in cervical screening programs.**" *Int J Cancer* **143**(4): 735-745.

Cervical cancer screening will rely, increasingly, on HPV testing as a primary screen. The requirement for triage tests which can delineate clinically significant infection is thus prescient. In this EUROGIN 2017 roadmap, justification behind the most evidenced triages is outlined, as are challenges for implementation. Cytology is the triage with the most follow-up data; the existence of an HR-HPV-positive, cytology-negative group presents a challenge and retesting intervals for this group (and choice of retest) require careful consideration. Furthermore, cytology relies on subjective skills and while adjunctive dual-staining with p16/Ki67 can mitigate inter-operator/-site disparities, clinician-taken samples are required. Comparatively, genotyping and methylation markers are objective and are applicable to self-taken samples, offering logistical advantages including in low and middle income settings. However, genotyping may have diminishing returns in immunised populations and type(s) included must balance absolute risk for disease to avoid low specificity. While viral and cellular methylation markers show promise, more prospective data are needed in addition to refinements in automation. Looking forward, systems that detect multiple targets concurrently such as next generation sequencing platforms will inform the development of triage tools. Additionally, multistep triage strategies may be beneficial provided they do not create complex, unmanageable pathways. Inevitably, the balance of risk to cost(s) will be key in decision making, although defining an acceptable risk will likely differ between settings. Finally, given the significant changes to cervical screening and the variety of triage strategies, appropriate education of both health care providers and the public is essential.

Yu, K., N. Hyun, B. Fetterman, T. Lorey, T. R. Raine-Bennett, H. Zhang, R. E. Stamps, N. E. Poitras, W. Wheeler, B. Befano, J. C. Gage, P. E. Castle, N. Wentzensen and M. Schiffman (2018). "**Automated Cervical Screening and Triage, Based on HPV Testing and Computer-Interpreted Cytology.**" *J Natl Cancer Inst* **110**(11): 1222-1228.

BACKGROUND: State-of-the-art cervical cancer prevention includes human papillomavirus (HPV) vaccination among adolescents and screening/treatment of cervical precancer (CIN3/AIS and, less strictly, CIN2) among adults. HPV testing provides sensitive detection of precancer but, to reduce overtreatment, secondary "trriage" is needed to predict women at highest risk. Those with the highest-risk HPV types or abnormal cytology are commonly referred to colposcopy; however, expert cytology services are critically lacking in many regions. METHODS: To permit completely automatable cervical screening/triage, we designed and validated a novel triage method, a cytologic risk score algorithm based on computer-scanned liquid-based slide features (FocalPoint, BD, Burlington, NC). We compared it with abnormal cytology in predicting precancer among 1839

women testing HPV positive (HC2, Qiagen, Germantown, MD) in 2010 at Kaiser Permanente Northern California (KPNC). Precancer outcomes were ascertained by record linkage. As additional validation, we compared the algorithm prospectively with cytology results among 243 807 women screened at KPNC (2016-2017). All statistical tests were two-sided. RESULTS: Among HPV-positive women, the algorithm matched the triage performance of abnormal cytology. Combined with HPV16/18/45 typing (Onclarity, BD, Sparks, MD), the automatable strategy referred 91.7% of HPV-positive CIN3/AIS cases to immediate colposcopy while deferring 38.4% of all HPV-positive women to one-year retesting (compared with 89.1% and 37.4%, respectively, for typing and cytology triage). In the 2016-2017 validation, the predicted risk scores strongly correlated with cytology ($P < .001$). CONCLUSIONS: High-quality cervical screening and triage performance is achievable using this completely automated approach. Automated technology could permit extension of high-quality cervical screening/triage coverage to currently underserved regions.

Isidean, S. D., M. H. Mayrand, A. V. Ramanakumar, I. Rodrigues, A. Ferenczy, S. Ratnam, F. Coutlée and E. L. Franco (2017). "**Comparison of Triage Strategies for HPV-Positive Women: Canadian Cervical Cancer Screening Trial Results.**" *Cancer Epidemiol Biomarkers Prev* **26**(6): 923-929.

Background: High-risk human papillomavirus (HR-HPV) testing has become a preferred cervical cancer screening strategy in some countries due to its superior sensitivity over cytology-based methods for identifying cervical intraepithelial neoplasia of grade 2 or worse (CIN2(+)). Improved sensitivity has been accompanied by reductions in specificity and concerns regarding overscreening and overtreatment of women with transient or nonprogressing HR-HPV infections. Triage of HR-HPV(+) women to colposcopy is, thus, warranted for appropriate management and treatment. Methods: Using data from the Canadian Cervical Cancer Screening Trial (CCCaST), we compared the performance of cytology and HR-HPV strategies to detect CIN2(+) among HR-HPV(+) women (age, 30-69 years). Colposcopy referral rates and performance gains from adding other HR-HPV genotypes to HPV16/18(+) triage were also evaluated. Results: A strategy referring all women HPV16/18(+) and HPV16/18(-), but with atypical squamous cells of undetermined significance or worse cytology (ASC-US(+)) had the highest sensitivity [82.5%; 95% confidence interval (CI), 70.9%-91.0%] but yielded the highest colposcopy referral rate. HPV16/18(+) triage was the next most sensitive strategy (64.1%; 95% CI, 51.1%-75.7%). Low-grade squamous intraepithelial lesion or worse cytology (LSIL(+)) triage yielded a low sensitivity (32.8%; 95% CI, 21.9%-45.4%) but had the most favorable specificity (93.6%; 95% CI, 91.0%-95.6%), positive predictive value (41.5%; 95% CI, 28.1%-55.9%), and colposcopy referral rate of strategies examined. HPV viral load triage strategies did not perform optimally overall. Inclusion of HR-HPV genotypes 31 and 52 to HPV16/18(+) triage provided the highest sensitivities. Conclusion: Concerns surrounding HPV-based screening can be effectively mitigated via triage. Impact: Balancing the benefits of HPV-based primary cervical screening with informed management recommendations for HR-HPV(+) women may decide the success of its widening utilization. *Cancer Epidemiol Biomarkers Prev*; 26(6); 923-9. ©2017 AACR.

Luo, H., J. L. Belinson, H. Du, Z. Liu, L. Zhang, C. Wang, X. Qu, R. G. Pretorius and R. Wu (2017). "**Evaluation of Viral Load as a Triage Strategy With Primary High-Risk Human Papillomavirus Cervical Cancer Screening.**" *J Low Genit Tract Dis* **21**(1): 12-16.

OBJECTIVE: The aim of the study was to evaluate the human papillomavirus (HPV) viral load combined with cytology as a secondary screening strategy after primary HPV screening. MATERIALS AND METHODS: The data referring to direct Hybrid Capture 2 (HC2), cytology, and histology from Shenzhen Cervical Cancer Screening Trial II were re-analyzed to determine the

correlation between viral load and cervical lesions. In addition, algorithms using different viral loads as cut points for immediate colposcopy plus cytology triage were compared with several recommended or controversial primary screening methods. RESULTS: A total of 8,556 women with a mean age of 38.9 years were included in the analysis, of which 13.67% tested high-risk HPV positive with a prevalence of 2.72% for cervical intraepithelial neoplasia 2+ (CIN 2+) and 1.65% for CIN 3+. A significant correlation was observed between increasing relative light units/control (RLU/CO) values and worsening cervical lesions. The mean RLU/CO values for negative, CIN 1, CIN 2, CIN 3, and cancer were 6.86, 119.43, 410.90, 449.39, and 853.26, respectively. A larger proportion of HPV infections with relative high viral load (≥ 10 RLU/CO) were found in higher-grade lesions. The algorithm using 10 or greater RLU/CO as cut point for immediate colposcopy followed by triage cytology for the other positive ($\geq 1 < 10$ RLU/CO) had sensitivity of 93.13%/96.45% and specificity of 92.32%/91.44% for CIN 2+/3+, and the colposcopy referral rate was 10.00%. CONCLUSIONS: Human papillomavirus viral load level is positively associated with cervical lesion grade. Ten relative light units/control or greater is a viable threshold for immediate colposcopy whereas 1 or greater or less than 10 RLU/CO is advised to reflex cytology for optimizing sensitivity and specificity, as well as referral rates.

Tjalma, W. A. A., E. Kim and K. Vandeweyer (2017). "The impact on women's health and the cervical cancer screening budget of primary HPV screening with dual-stain cytology triage in Belgium." Eur J Obstet Gynecol Reprod Biol **212**: 171-181.

Dual stain cytology, or "diagnostic cytology", offers a significant increase in sensitivity compared to cytology, with a slight decrease in specificity. This can reduce additional investigations like colposcopies, biopsies, and follow-up visits. Cervical cancer screening for women between 25 and 65 years of age with diagnostic cytology is estimated to reduce the incidence of cervical cancer by 36% and reduce annual cervical cancer mortalities by 40%. The reduced number of screening visits and the decrease in incidence and mortality will improve quality of life. In this article, a model was created to evaluate the cost-effectiveness of diagnostic cytology for Belgium. In this approach, precancerous cells are more likely to be immediately identified during the first screening visit. This reduces both the number and frequency of follow-up visits required. After two cycles (6 years), the prevalence of CIN and cervical cancer is decreased significantly in the screened population. At a population level, these shifts can reduce the screening budget by 21%, resulting in savings of 5.3 million euro a year in Belgium. Diagnostic cytology benefits all stakeholders involved in cervical cancer screening.

Ebisch, R. M., A. G. Siebers, R. P. Bosgraaf, L. F. Massuger, R. L. Bekkers and W. J. Melchers (2016). "Triage of high-risk HPV positive women in cervical cancer screening." Expert Rev Anticancer Ther **16**(10): 1073-1085.

INTRODUCTION: High-risk human papillomavirus (hrHPV) testing is expected to replace cytology as primary screening method for cervical cancer screening in an increasing number of countries. The high sensitivity of hrHPV testing is combined with a limited specificity which makes triaging of hrHPV positive women necessary. As an ideal triage method does not yet exist, an optimal triage strategy for hrHPV positive women based on current knowledge should be obtained. The aim of this article is to present an overview of available options for triage of hrHPV positive women, with their strengths and limitations and possible future opportunities. AREAS COVERED: Current knowledge on morphological biomarkers, molecular biomarkers and combined triage strategies will be discussed to give an overview of the state-of-the-art on triaging hrHPV positive women. The literature search was limited to studies on triage strategies for hrHPV positive women. Expert commentary: Experience with morphology-based biomarkers makes these a

valuable triage method. However, they lack the ability of differentiating productive from transforming infections. Molecular biomarkers are objective, highly reproducible, can be used in high throughput testing, and show promising results. With more extensive knowledge on these molecular markers, cervical cancer screening may transform to a full molecular screening in the future.

Ronco, G., M. Zappa, S. Franceschi, S. Tunesi, A. Caprioglio, M. Confortini, A. Del Mistro, F. Carozzi, N. Segnan, M. Zorzi and P. Giorgi-Rossi (2016). "**Impact of variations in triage cytology interpretation on human papillomavirus-based cervical screening and implications for screening algorithms.**" Eur J Cancer **68**: 148-155.

BACKGROUND: Women positive to human papillomavirus (HPV+) testing at cervical screening need triage, typically cytology and immediate colposcopy in case of atypical squamous cells of undetermined significance (ASCUS) or worse (ASCUS+) or, in cytology-normal HPV+ women, HPV test repeat after 1 year and colposcopy referral if still HPV+. Our hypothesis was that substantial variations in triage positivity and sensitivity may produce little variation in overall referral to colposcopy and on sensitivity of the entire screening process. METHODS: Centre- and age-aggregated data from 72,869 women aged 35-64 years were derived from 10 organised screening programmes which have piloted HPV screening in Italy since 2012. Overall colposcopy referral was evaluated as a function of immediate colposcopy referral and overall CIN2+ detection as a function of the proportion of all CIN2+ detected by immediate referral (a proxy of cytology's sensitivity). We fitted additive regression models, adjusted for centre, age, compliance to HPV retesting and to colposcopy, by generalised estimation equations. RESULTS: The proportion of HPV+ women directly referred to colposcopy varied across programmes (20-57%; average 37%) and so did CIN2+ detection (49-94%; average 77%). Overall, 63% (range 41-75%) of HPV+ were referred to colposcopy either immediately or at HPV repeat. An absolute 10% increase in immediate colposcopy referral resulted in 4.2% (95% CI: 3.3-5.1%) increase in overall referral. An absolute 10% increase in cytology's sensitivity resulted in a 1.1% (95% CI: 0.1-2.0%) increase in overall CIN2+ detection. CONCLUSIONS: Repeat HPV testing limits the effect of subjectivity of cytology interpretation on overall referral and sensitivity. These will change only slightly when replacing cytology with another test if the interval to HPV repeat remains unchanged.

Torres-Ibarra, L., E. Lazcano-Ponce, E. L. Franco, J. Cuzick, M. Hernández-Ávila, A. Lorincz, B. Rivera, P. Ramírez, I. Mendiola-Pastrana, S. E. Rudolph, L. León-Maldonado, R. Hernández, E. Barrios, P. Gravitt, A. B. Moscicki, K. M. Schmeler, Y. N. Flores, P. Méndez-Hernández and J. Salmerón (2016). "**Triage strategies in cervical cancer detection in Mexico: methods of the FRIDA Study.**" Salud Publica Mex **58**(2): 197-210.

OBJECTIVE: This paper describes the study design and baseline characteristics of the study population, including the first 30 829 women who enrolled in the Forwarding Research for Improved Detection and Access for Cervical Cancer Screening and Triage (FRIDA Study). This is a large population based study that is evaluating the performance and cost-effectiveness of different triage strategies for high-risk HPV (hrHPV) positive women in Mexico. MATERIALS AND METHODS: The target population is more than 100 000 women aged 30 to 64 years who attend the Cervical Cancer Screening Program in 100 health centers in the state of Tlaxcala, Mexico. Since August 2013, all women in the region have been invited to enroll in the study. The study participants are evaluated to determine hrHPV infection using the Cobas 4800 HPV test. The HPV-16/18 genotyping and cytology triage strategies are performed as reflex tests in all hrHPV-positive participants. Women with a positive HPV-16/18 test and/or abnormal cytology (atypical squamous cells of undetermined significance or worse, ASCUS+) are referred for colposcopy evaluation, where a minimum of four biopsies and an endocervical sample are systematically

collected. Histologic confirmation is performed by a standardized panel of pathologists. RESULTS: Among the 30 829 women who have been screened, the overall prevalence of hrHPV is 11.0%. The overall prevalence of HPV16 and HPV18 are 1.5% and 0.7%, respectively. Cytological abnormalities (ASCUS+) were detected in 11.8% of the hrHPV-positive women. A total of 27.0% (920/3,401) of the hrHPV-positive women were referred to colposcopy because of a positive HPV16/18 test and/or abnormal reflex cytology, (31.6% had only ASCUS+, 53.6% were HPV16/18 positive with a normal cytology result, and 9.5% were positive to both triage tests). CONCLUSION: The results of this study will help policy makers and health service providers establish the best practices for triage in cervical cancer screening in Mexico and other countries.

Wentzensen, N., M. Schiffman, T. Palmer and M. Arbyn (2016). "**Triage of HPV positive women in cervical cancer screening.**" *J Clin Virol* **76 Suppl 1**(Suppl 1): S49-s55.

Despite HPV vaccines, screening will remain central for decades to control cervical cancer. Recently, HPV testing alone or with cytology was introduced as an alternative to cytology screening. However, most HPV infections are harmless and additional tests are required to identify women with progressing infections or precancer. With three options for primary screening, and without clear strategies for triage of screen-positive women, there is great confusion about the best approach. Also, increasing HPV vaccination coverage will lead to lower disease prevalence, and force new screening approaches. Currently recommended triage strategies for primary HPV screening include HPV genotyping for HPV16 and HPV18 and cytology. Other alternatives that are currently evaluated include p16/Ki-67 dual stain cytology, host methylation, and viral methylation testing. Clinical management of women with cervical cancer screening results is moving to use risk thresholds rather than individual test results. Specific risk thresholds have been defined for return to primary screening, repeat testing, referral to colposcopy, and immediate treatment. Choice of test algorithms is based on comparison of absolute risk estimates from triage tests with established clinical thresholds. Importantly, triage tests need to be evaluated together with the primary screening test and the downstream clinical management. An optimal integrated screening and triage strategy should reassure the vast majority of women that they are at very low risk of cervical cancer, send the women at highest risk to colposcopy at the right time, when disease can be colposcopically detected, and minimize the intermediate risk group that requires continued surveillance.

Bansil, P., J. Lim, J. Byamugisha, E. Kumakech, C. Nakisige and J. A. Jeronimo (2015). "**Performance of Cervical Cancer Screening Techniques in HIV-Infected Women in Uganda.**" *J Low Genit Tract Dis* **19**(3): 215-219.

OBJECTIVE: Women infected with human immunodeficiency virus (HIV) have a higher risk of HPV infections and developing cervical cancer, thus screening them is imperative. This study was aimed to evaluate and compare the performance of 3 cervical cancer screening options among HIV-infected women in Uganda. MATERIALS AND METHODS: Data from 2,337 Ugandan women who reported their HIV status were obtained from a population-based cervical cancer screening study. Women were offered 3 screening tests: vaginal and cervical careHPV and visual inspection with acetic acid (VIA), and the results were evaluated by HIV status. RESULTS: The prevalence of HIV infection was 16.5%. Women infected with HIV had a higher prevalence of cervical intraepithelial neoplasia grade 2+ (CIN2+) than uninfected women (12.9% vs 1.7%; $p < .001$). The sensitivity for cervical careHPV among the HIV-infected women was 94.3% compared to 81.3% among the uninfected women. Whereas the sensitivity for vaginal careHPV was also higher among the HIV-infected women, the sensitivity of VIA was higher among the uninfected women. The mean vaginal and cervical careHPV signal strength was higher in the HIV-infected women than in

the uninfected women ($p < .001$). **CONCLUSIONS:** CareHPV is very sensitive for detecting CIN2+ in HIV-infected women, even using a vaginal sample. The sensitivity of careHPV in HIV-infected women is higher than in HIV-uninfected women. However, additional research is needed to determine the best option for screening and triage of HPV-positive women that can be implemented in low-resource settings, especially among HIV- and HPV-positive women.

Haldorsen, T., G. B. Skare, G. Ursin and T. Bjørge (2015). "**Results of delayed triage by HPV testing and cytology in the Norwegian Cervical Cancer Screening Programme.**" *Acta Oncol* 54(2): 200-209.

BACKGROUND: High-risk human papilloma virus (hrHPV) testing was added to the cytology triage of women with equivocal screening smears in the Norwegian programme for cervical cancer screening in 2005. In this population-based observational before and after study we assessed the effect of changing the screening algorithm. **MATERIAL AND METHODS:** In periods before and after the change 75 852 and 66 616 women, respectively, were eligible for triage, i.e. they had smear results of unsatisfactory, atypical squamous cells of undetermined significance (ASC-US), or low-grade squamous intraepithelial lesion (LSIL) at routine screening. The triage was delayed as supplementary testing started six months after the initial screening. The groups were compared with respect to results of triage and later three-year cumulative incidence of cervical intraepithelial neoplasia grade 2 or worse (CIN2+). **RESULTS:** Before and after the change in the screening algorithm 5.2% (3964/75 852) and 8.1% (5417/66 616) of women, respectively, were referred to colposcopy. Among women referred to colposcopy cumulative incidence of CIN2+ (positive predictive value of referral) increased from 42.0% [95% confidence interval (CI): 40.3 - 43.7%] in the period with cytology only to 48.0% (95% CI 46.6 - 49.4%) after the start of HPV testing. For women recalled to ordinary screening the three-year cumulative incidence decreased from 2.7% (95% CI 2.5 - 2.9%) to 1.0% (95% CI 0.9 - 1.2%) during the same period. Among women with LSIL at routine screening and HPV testing in triage, 52.5% (1976/3766) were HPV positive. **CONCLUSION:** The new algorithm with HPV testing implemented in 2005 resulted in an increased rate of referral to colposcopy, but in a better risk stratification with respect to precancerous disease.

Uijterwaal, M. H., N. J. Polman, F. J. Van Kemenade, S. Van Den Haselkamp, B. I. Witte, D. Rijkaart, J. Berkhof, P. J. Snijders and C. J. Meijer (2015). "**Five-Year Cervical (Pre)Cancer Risk of Women Screened by HPV and Cytology Testing.**" *Cancer Prev Res (Phila)* 8(6): 502-508.

Primary human papillomavirus (HPV)-based cervical screening will be introduced in the Netherlands in 2016. We assessed the 5-year cervical (pre)cancer risk of women with different combinations of HPV and cytology test results. Special attention was paid to risks for cervical intraepithelial neoplasia grade 3 and 2 or more (CIN3+/2+) of HPV-positive women with a negative triage test, because this determines the safety of a 5-year screening interval for HPV-positive, triage test-negative women. In addition, age-related effects were studied. A total of 25,553 women were screened by HPV testing and cytology in a screening setting. Women were managed on the presence of HPV and/or abnormal cytology. Five-year cumulative incidences for CIN3+/2+ were calculated. Five-year CIN3+(2+) risk was 10.0% (17.7%) among HPV-positive women. When stratified by cytology, the CIN3+(CIN2+) risk was 7.9% (12.9%) for women with normal cytology and 22.2% (45.3%) for women with equivocal or mildly abnormal (i.e., BMD) cytology. For HPV-negative women, the 5-year CIN3+(2+) risk was 0.09% (0.21%). Additional triage of HPV-positive women with normal cytology by repeat cytology at 12 months showed a 5-year CIN3+(2+) risk of 4.1% (7.0%). HPV-non 16/18-positive women with normal cytology at baseline had comparable risks of 3.5% (7.9%). HPV-non 16/18-positive women with normal baseline cytology and normal repeat cytology had a 5-year CIN3+ risk of 0.42%. No age-related effects were detected. In

conclusion, HPV-positive women with normal cytology and a negative triage test, either repeat cytology after 12 months or baseline HPV 16/18 genotyping, develop a non-negligible CIN3+ risk over 5 years. Therefore, extension of the screening interval over 5 years only seems possible for HPV screen-negative women.

Session 6 Title: Screening in the Era of Vaccination

A Pubmed search was performed with the following selection criteria: [Cervical cancer] AND [Screening] AND [HPV Vaccination] title/abstracts published in the last 5 years: 996 items were retrieved and 24 were selected. The selection was based on the relevance of the article with aims, and scope of the session as cervical cancer as a general keyword retrieves many articles which didn't fit in the scope of the session. References were imported in EndNote. Herein, a relevant manual selection of publications between 2015-2020 based on title and abstract was made.

Athanasidou, A., S. Bowden, M. Paraskevaidi, C. Fotopoulou, P. Martin-Hirsch, E. Paraskevaidis and M. Kyrgiou (2020). "**HPV vaccination and cancer prevention.**" Best Pract Res Clin Obstet Gynaecol **65**: 109-124.

Prophylactic vaccines have been found to be highly effective in preventing infection and pre-invasive and invasive cervical, vulvovaginal and anal disease caused by the vaccine types. HPV vaccines contain virus-like particles that lack the viral genome and produce high titres of neutralising antibodies. Although the vaccines are highly effective in preventing infections, they do not enhance clearance of existing infections. Vaccination programmes target prepubertal girls and boys prior to sexual debut as efficacy is highest in HPV naïve individuals. School-based programmes achieve higher coverage, although implementation is country specific. Vaccination of older women may offer some protection and acceleration of impact, although this may not be

cost-effective. HPV-based screening will continue for vaccinated cohorts, although intervals may increase.

Bosch, F. X. and C. Robles (2018). "HPV-FASTER: Combined strategies of HPV vaccination and HPV screening towards a one visit for cervical cancer preventive campaigns." *Salud Publica Mex* **60**(6): 612-616.

Canfell, K. (2018). "Cervical screening in HPV-vaccinated populations." *Climacteric* **21**(3): 227-234.

Cervical screening with cytology has been the basis for substantial reductions in cervical cancer incidence and mortality in most high-income countries over the last few decades. More recently, there have been two key, parallel developments which have prompted a major re-consideration of cervical screening. The first is the emergence of evidence on the improved sensitivity of human papillomavirus (HPV) DNA testing compared to cytology, and the second is the large-scale deployment of prophylactic vaccination against HPV. A key challenge to be overcome before HPV screening could be introduced into national cervical screening programs was the specificity of an infection, for detection of precancerous lesions. This has been done in three ways: (1) by considering the appropriate age for starting HPV screening (30 years in unvaccinated populations and 25 years in populations with mature vaccination programs and high vaccine uptake) and the appropriate screening interval; (2) via development of clinical HPV tests, which are (by design) not as sensitive to low viral loads; and (3) by introducing effective triaging for HPV-positive women, which further risk-stratifies women before referral for diagnostic evaluation. This review discusses these major developments and describes how the benefits of HPV screening are being optimized in both unvaccinated and vaccinated populations.

Canfell, K., M. Saville, M. Caruana, V. GebSKI, J. Darlington-Brown, J. Brotherton, S. Heley and P. E. Castle (2018). "Protocol for Compass: a randomised controlled trial of primary HPV testing versus cytology screening for cervical cancer in HPV-unvaccinated and vaccinated women aged 25-69 years living in Australia." *BMJ Open* **8**(1): e016700.

INTRODUCTION: Australia's National Cervical Screening Program (NCSP) currently recommends 2-year cytology in women aged 18-69 years. Following a review of the NCSP prompted by the implementation of human papillomavirus (HPV) vaccination, the programme will transition in 2017 to 5-year primary HPV screening with partial genotyping for HPV16/18 in women aged 25-74 years. Compass is a sentinel experience for the renewed NCSP and the first prospectively randomised trial of primary HPV screening compared with cytology to be conducted in a population with high uptake of HPV vaccination. This protocol describes the main Compass trial, which commenced after a pilot study of ~5000 women completed recruitment. **METHODS AND ANALYSIS:** Women aged 25-69 years will be randomised at a 1:2 allocation to (1) 2.5-year image-read, liquid-based cytology (LBC) screening with HPV triage of low-grade smears (active control Arm A) or (2) 5-year HPV screening with partial genotyping and referral of HPV16/18-positive women to colposcopy (intervention Arm B). Women in Arm B positive for other oncogenic HPV (not 16/18) will undergo secondary randomisation at a 1:1 allocation to either LBC or dual-stained (p16(INK4a) and Ki-67) cytology testing (dual-stained cytology). The primary outcome is cumulative CIN3+ (CIN3, adenocarcinoma in situ and invasive cervical cancer) following a 5-year HPV exit testing round in both arms, in women randomised to the HPV arm versus women randomised to the LBC arm, based on an intention-to-treat analysis. The primary outcome will

first be tested for non-inferiority and if declared, the primary outcome will be tested for superiority. A total of 36 300 women in birth cohorts not offered vaccination and 84 700 women in cohorts offered vaccination will be recruited, bringing the final sample size to 121 000. The trial is powered for the secondary outcome of cumulative CIN3+ in screen-negative women, adjusted for censoring after CIN2+ treatment and hysterectomy. ETHICS AND DISSEMINATION: Approved by the Bellberry Ethics Committee (2014-11-592). Findings will be reported in peer-reviewed journals and presented at scientific meetings. TRIAL REGISTRATION NUMBER: NCT02328872; Pre-results.

Kreusch, T., J. Wang, P. Sparén and K. Sundström (2018). "**Opportunistic HPV vaccination at age 16-23 and cervical screening attendance in Sweden: a national register-based cohort study.**" *BMJ Open* 8(10): e024477.

OBJECTIVES: To investigate whether cervical screening attendance differs between human papillomavirus (HPV)-vaccinated and unvaccinated women and to investigate potential underlying socioeconomic factors. DESIGN: Prospective cohort using registry linkage of vaccinations, screening invitations, screening attendance and socioeconomic covariates. SETTING: Swedish national HPV vaccination and cervical screening programmes. PARTICIPANTS: All Swedish women born between 1988 and 1991 and invited to screening (n=261 434). OUTCOME MEASURES: All participants were followed for up to 3 years. Screening attendance was compared between HPV-vaccinated and unvaccinated women. HR and 95% CI were estimated using Cox regression. RESULTS: Vaccination age averaged 18.1 years and the coverage for ≥1 dose was 13.5%. In HPV-vaccinated women (n=35 460), screening attendance was higher than in unvaccinated women (n=225 974) (74%vs69%, p<0.001). The crude HR of attendance in HPV-vaccinated women was 1.32 (95% CI 1.30 to 1.34). A positive association remained after adjustment for education, income and migration history (HR=1.10, 95% CI 1.09 to 1.12). CONCLUSION: HPV-vaccinated women were more likely to attend screening than unvaccinated women. Yet, the question needs to be reassessed in routinely vaccinated cohorts, since the vaccinated women included here represent a selected group and may be prone to more health-conscious habits.

Pedersen, K., E. A. Burger, M. Nygård, I. S. Kristiansen and J. J. Kim (2018). "**Adapting cervical cancer screening for women vaccinated against human papillomavirus infections: The value of stratifying guidelines.**" *Eur J Cancer* 91: 68-75.

BACKGROUND: Several countries have implemented vaccination against human papillomavirus (HPV) for adolescent girls and must decide whether and how to adapt cervical cancer (CC) screening for these low-risk women. We aimed to identify the optimal screening strategies for women vaccinated against HPV infections and quantify the amount that could be spent to identify vaccination status among women and stratify CC screening guidelines accordingly. METHODS: We used a mathematical model reflecting HPV-induced CC in Norway to project the long-term health benefits, resources and costs associated with 74 candidate-screening strategies that varied by screening test, start age and frequency. Strategies were considered separately for women vaccinated with the bivalent/quadrivalent (2/4vHPV) and nonavalent (9vHPV) vaccines. We used a cost-effectiveness framework (i.e. incremental cost-effectiveness ratios and net monetary

benefit) and a commonly-cited Norwegian willingness-to-pay threshold of €75,000 per quality-adjusted life-year gained. RESULTS: The most cost-effective screening strategy for 9vHPV- and 2/4vHPV-vaccinated women involved HPV testing once and twice per lifetime, respectively. The value of stratifying guidelines by vaccination status was €599 (2/4vHPV) and €725 (9vHPV) per vaccinated woman. Consequently, for the first birth cohort of ~22,000 women who were vaccinated in adolescence in Norway, between €10.5-13.2 million over their lifetime could be spent on identifying individual vaccination status and stratify screening while remaining cost-effective. CONCLUSION: Less intensive strategies are required for CC screening to remain cost-effective in HPV-vaccinated women. Moreover, screening can remain cost-effective even if large investments are made to identify individual vaccination status and stratify screening guidelines accordingly.

Barroeta, J. E., D. Adhikari-Guragain and C. E. Grotkowski (2017). "**Cervical cancer screening in the era of HPV vaccination: A review of shifting paradigms in cytopathology.**" *Diagn Cytopathol* **45**(10): 903-914.

Significant changes in cervical cancer screening practice, guidelines, and prevention of cervical cancer have taken place in recent years including the raising of initial cervical cancer screening age, changes in frequency of cytology screening, and the adoption of high risk HPV and cytology co-testing for some patients; the introduction of the bivalent, quadrivalent, and 9-valent HPV vaccines; and the recent approval of high risk HPV testing as primary screening with the use of cytology as triage in positive cases. This review discusses the significance of primary HPV screening, the impact of HPV vaccination in the prevalence of cervical cancer and its precursors, the interplay between high risk HPV testing and vaccination, and the implications for clinical and cytological management. Future strategies for cervical screening in the post-vaccination era are also discussed.

Canfell, K., M. Caruana, V. GebSKI, J. Darlington-Brown, S. Heley, J. Brotherton, D. Gertig, C. J. Jennett, A. Farnsworth, J. Tan, C. D. Wrede, P. E. Castle and M. Saville (2017). "**Cervical screening with primary HPV testing or cytology in a population of women in which those aged 33 years or younger had previously been offered HPV vaccination: Results of the Compass pilot randomised trial.**" *PLoS Med* **14**(9): e1002388.

BACKGROUND: Using primary human papillomavirus (HPV) testing for cervical screening increases detection of high-grade cervical intraepithelial neoplastic lesions and invasive cancer (cervical intraepithelial neoplasia grade 2+ [CIN2+]) compared to cytology, but no evaluation has been conducted in a population previously offered HPV vaccination. We aimed to assess colposcopy referral and CIN2+ detection rates for HPV-screened versus cytology-screened women in Australia's HPV-vaccinated population (by 2014, resident women ≤33 years had been age-eligible for HPV vaccination, with 3-dose uptake across age cohorts being about 50%-77%). METHODS AND FINDINGS: Compass is an open-label randomised trial of 5-yearly HPV screening versus 2.5-yearly liquid-based cytology (LBC) screening. In the first phase, consenting women aged 25-64 years presenting for routine screening at 47 primary practices in Victoria, Australia, provided a cervical sample and were randomised at a central laboratory at a 1:2:2 allocation to (i) image-read LBC screening with HPV triage of low-grade cytology ('LBC screening'), (ii) HPV screening with those HPV16/18 positive referred to colposcopy and with LBC triage for other oncogenic (OHR) types ('HPV+LBC triage'), or (iii) HPV screening with those HPV16/18 positive referred to colposcopy and with dual-stained cytology triage for OHR types ('HPV+DS triage'). A total of 5,006

eligible women were recruited from 29 October 2013 to 7 November 2014 (recruitment rate 58%); of these, 22% were in the group age-eligible for vaccination. Data on 4,995 participants were analysed after 11 withdrawals; 998 were assigned to, and 995 analysed (99.7%) in, the LBC-screened group; 1,996 assigned to and 1,992 analysed (99.8%) in the HPV+LBC triage group; and 2,012 assigned to and 2,008 analysed (99.8%) in the HPV+DS triage group. No serious trial-related adverse events were reported. The main outcomes were colposcopy referral and detected CIN2+ rates at baseline screening, assessed on an intention-to-treat basis after follow-up of the subgroup of triage-negative women in each arm referred to 12 months of surveillance, and after a further 6 months of follow-up for histological outcomes (dataset closed 31 August 2016). Analysis was adjusted for whether women had been age-eligible for HPV vaccination or not. For the LBC-screened group, the overall referral and detected CIN2+ rates were 27/995 (2.7% [95% CI 1.8%-3.9%]) and 1/995 (0.1% [95% CI 0.0%-0.6%]), respectively; for HPV+LBC triage, these were 75/1,992 (3.8% [95% CI 3.0%-4.7%]) and 20/1,992 (1.0% [95% CI 0.6%-1.5%]); and for HPV+DS triage, these were 79/2,008 (3.9% [95% CI 3.1%-4.9%]) and 24/2,008 (1.2% [95% CI 0.8%-1.6%]) ($p = 0.09$ for difference in referral rate in LBC versus all HPV-screened women; $p = 0.003$ for difference in CIN2+ detection rate in LBC versus all HPV-screened women, with $p = 0.62$ between HPV screening groups). Limitations include that the study population involved a relatively low risk group in a previously well-screened and treated population, that individual women's vaccination status was unknown, and that long-term follow-up data on disease detection in screen-negative women are not yet available. CONCLUSIONS: In this study, primary HPV screening was associated with significantly increased detection of high-grade precancerous cervical lesions compared to cytology, in a population where high vaccine uptake was reported in women aged 33 years or younger who were offered vaccination. It had been predicted that increased disease detection might be associated with a transient increase in colposcopy referral rates in the first round of HPV screening, possibly dampened by HPV vaccine effect; in this study, although the point estimates for referral rates in women in each HPV-screened group were 41%-44% higher than in cytology-screened women, the difference in referral rate between cytology- and HPV-screened women was not significant. These findings provide initial support for the implementation of primary HPV screening in vaccinated populations. TRIAL REGISTRATION: Australian New Zealand Clinical Trials Registry ACTRN12613001207707.

Giorgi Rossi, P., F. Carozzi, A. Federici, G. Ronco, M. Zappa and S. Franceschi (2017). "**Cervical cancer screening in women vaccinated against human papillomavirus infection: Recommendations from a consensus conference.**" *Prev Med* **98**: 21-30.

In Italy, the cohorts of women who were offered Human papillomavirus (HPV) vaccination in 2007/08 will reach the age (25years) for cervical cancer (CC) screening from 2017. The simultaneous shift from cytology-based screening to HPV test-based screening gives the opportunity for unprecedented reorganisation of CC prevention. The ONS (National Screening Monitoring Centre) Directive and the GISCI (Italian Group for Cervical Screening) identified the consensus conference as the most suitable method for addressing this topic. A summary of consensus recommendations is reported here. The main objective was to define the best screening methods in girls vaccinated against HPV and the knowledge required for defining evidence-based screening strategies. A Jury made recommendations about questions and proposals formulated by a panel of experts representative of Italian scientific societies involved in CC prevention and based on systematic reviews of literature and evidence. The Jury considered changing the screening protocols for girls vaccinated in their twelfth year as appropriate. Tailored screening protocols based on vaccination status could be replaced by "one size fits all" protocols

only when a herd immunity effect has been reached. Vaccinated women should start screening at age 30, instead of 25, with HPV test. Furthermore, there is a strong rationale for applying longer intervals for re-screening HPV negative women than the currently recommended 5 years, but research is needed to determine the optimal screening time points. For non-vaccinated women and for women vaccinated in their fifteenth year or later, the current protocol should be kept.

Lew, J. B., K. T. Simms, M. A. Smith, M. Hall, Y. J. Kang, X. M. Xu, M. Caruana, L. S. Velentzis, T. Bessell, M. Saville, I. Hammond and K. Canfell (2017). "**Primary HPV testing versus cytology-based cervical screening in women in Australia vaccinated for HPV and unvaccinated: effectiveness and economic assessment for the National Cervical Screening Program.**" *Lancet Public Health* 2(2): e96-e107.

BACKGROUND: Australia's National Cervical Screening Program currently recommends cytological screening every 2 years for women aged 18-69 years. Human papillomavirus (HPV) vaccination was implemented in 2007 with high population coverage, and falls in high-grade lesions in young women have been reported extensively. This decline prompted a major review of the National Cervical Screening Program and new clinical management guidelines, for which we undertook this analysis. **METHODS:** We did effectiveness modelling and an economic assessment of potential new screening strategies, using a model of HPV transmission, vaccination, natural history, and cervical screening. First, we evaluated 132 screening strategies, including those based on cytology and primary HPV testing. Second, after a recommendation was made to adopt primary HPV screening with partial genotyping and direct referral to colposcopy of women positive for HPV16/18, we evaluated the final effect of HPV screening after incorporating new clinical guidelines for women positive for HPV. Both evaluations considered both unvaccinated and vaccinated cohorts. **FINDINGS:** Strategies entailing HPV testing every 5 years and either partial genotyping for HPV16/18 or cytological co-testing were the most effective. One of the most effective and cost-effective strategies comprised primary HPV screening with referral of women positive for oncogenic HPV16/18 direct to colposcopy, with reflex cytological triage for women with other oncogenic types and direct referral for those in this group with high-grade cytological findings. After incorporating detailed clinical guidelines recommendations, this strategy is predicted to reduce cervical cancer incidence and mortality by 31% and 36%, respectively, in unvaccinated cohorts, and by 24% and 29%, respectively, in cohorts offered vaccination. Furthermore, this strategy is predicted to reduce costs by up to 19% for unvaccinated cohorts and 26% for cohorts offered vaccination, compared with the current programme. **INTERPRETATION:** Primary HPV screening every 5 years with partial genotyping is predicted to be substantially more effective and potentially cost-saving compared with the current cytology-based screening programme undertaken every 2 years. These findings underpin the decision to transition to primary HPV screening with partial genotyping in the Australian National Cervical Screening Program, which will occur in May, 2017. **FUNDING:** Department of Health, Australia.

Vorstors, A., M. Arbyn, M. Baay, X. Bosch, S. de Sanjosé, S. Hanley, E. Karafillakis, P. L. Lopalco, K. G. Pollock, J. Yarwood and P. Van Damme (2017). "**Overcoming barriers in HPV vaccination and screening programs.**" *Papillomavirus Res* 4: 45-53.

The Human Papillomavirus Prevention and Control Board brought together experts to discuss optimizing HPV vaccination and screening programs. Board members reviewed the safety profile of licensed HPV vaccines based on clinical and post-marketing data, reaching a consensus that current safety data is reassuring. Successful vaccination programs used well-coordinated

communication campaigns, integrating (social) media to spread awareness. Communication of evidence supporting vaccine effectiveness had beneficial effects on the perception of the vaccine. However, anti-vaccination campaigns have threatened existing programs in many countries. Measurement and monitoring of HPV vaccine confidence over time could help understand the nature and scale of waning confidence, define issues and intervene appropriately using context-specific evidence-based strategies. Finally, a broad group of stakeholders, such as teachers, health care providers and the media should also be provided with accurate information and training to help support prevention efforts through enhanced understanding of the risks and benefits of vaccination. Similarly, while cervical cancer screening through population-based programs is highly effective, barriers to screening exist: awareness in countries with population-based screening programs, access for vulnerable populations, and access and affordability in low- and middle-income countries. Integration of primary and secondary prevention has the potential to accelerate the decrease in cervical cancer incidence.

Bhatia, R., K. Kavanagh, H. A. Cubie, I. Serrano, H. Wennington, M. Hopkins, J. Pan, K. G. Pollock, T. J. Palmer and K. Cuschieri (2016). "**Use of HPV testing for cervical screening in vaccinated women--Insights from the SHEVa (Scottish HPV Prevalence in Vaccinated Women) study.**" *Int J Cancer* **138**(12): 2922-2931.

The management of cervical disease is changing worldwide as a result of HPV vaccination and the increasing use of HPV testing for cervical screening. However, the impact of vaccination on the performance of HPV based screening strategies is unknown. The SHEVa (Scottish HPV Prevalence in Vaccinated women) projects are designed to gain insight into the impact of vaccination on the performance of clinically validated HPV assays. Samples collated from women attending for first cervical smear who had been vaccinated as part of a national "catch-up" programme were tested with three clinically validated HPV assays (2 DNA and 1 RNA). Overall HR-HPV and type specific positivity was assessed in total population and according to underlying cytology and compared to a demographically equivalent group of unvaccinated women. HPV prevalence was significantly lower in vaccinated women and was influenced by assay-type, reducing by 23-25% for the DNA based assays and 32% for the RNA assay ($p = 0.0008$). All assays showed over 75% reduction of HPV16 and/or 18 ($p < 0.0001$) whereas the prevalence of non 16/18 HR-HPV was not significantly different in vaccinated vs unvaccinated women. In women with low grade abnormalities, the proportion associated with non 16/18 HR-HPV was significantly higher in vaccinated women ($p < 0.0001$). Clinically validated HPV assays are affected differentially when applied to vaccinated women, dependent on assay chemistry. The increased proportion of non HPV16/18 infections may have implications for clinical performance, consequently, longitudinal studies linking HPV status to disease outcomes in vaccinated women are warranted.

Boone, S. D., C. M. Pinkston, K. B. Baumgartner, R. N. Baumgartner, S. M. Harper, A. J. Bonham, C. A. Paynter and D. M. Harper (2016). "**Associations between prior HPV4 vaccine doses and cervical cancer screening participation.**" *Cancer Epidemiol* **42**: 108-114.

BACKGROUND: Cervical cancer screening, regardless of HPV vaccination, is a cornerstone of cancer prevention. This study evaluated associations between prior HPV vaccine doses and initiation and continued participation of screening by age at vaccination. METHODS: Using electronic medical records for a safety net healthcare system (Truman Medical Center), women aged 14-26y vaccinated ($n=1123$) between 07/01/2006 and 10/1/2009 were randomly selected

and matched on birth year and health campus to unvaccinated (n=1123) women. Frequency of screening was determined through 07/01/2013. Hazard ratios (HR) for screening were estimated using Cox proportional hazards regression. RESULTS: Screening rates were higher after vaccination: unvaccinated (53%), first (62%), second (59%) or third (61%) doses. Women who initiated screening were less likely to complete the vaccine series, regardless of age. Women receiving one dose were more likely than unvaccinated women to initiate screening (HR=2.98 95% Confidence Interval (CI):2.45-3.61) and were more likely to screen than those receiving two (1 vs. 2, HR=2.94 95% CI:2.09-4.14) or three doses (1 vs. 3, HR=3.15 95% CI:2.21-4.48). Compared to unvaccinated women, women <21y who completed 3-doses were 1.8-times more likely to screen at ≥21y, whereas vaccinated women ≥21y were more likely to screen regardless of number of doses (p<0.0001). CONCLUSIONS: Women who were vaccinated were more likely to screen than unvaccinated women; screening rate was highest after and occurred closest to the first vaccine dose. Research evaluating the efficacy of a one-dose vaccine is warranted and may provide both higher vaccination and screening rates.

El-Zein, M., L. Richardson and E. L. Franco (2016). "**Cervical cancer screening of HPV vaccinated populations: Cytology, molecular testing, both or none.**" *J Clin Virol* **76 Suppl 1**(Suppl 1): S62-s68.

Cervical cancer control includes primary prevention through vaccination to prevent human papillomavirus (HPV) infection and secondary prevention through screening to detect and treat cervical precancerous lesions. This review summarizes the evidence for the population impact of vaccines against oncogenic HPV types in reducing the prevalence of cervical precancerous lesions. We examine the gradual shift in screening technology from cervical cytology alone to cytology and HPV cotesting, and finally to the recognition that HPV testing can serve alone as the new screening paradigm, particularly in the initial post-vaccination era. We should expect an impact on screening performance and practices, as cohorts of HPV-vaccinated girls and adolescents reach cervical cancer screening age. In preparation for changes in the screening paradigm for the vaccination era, we propose that policymaking on cervical cancer screening should mirror current practices with other cancers as benchmarks. Cervical precancerous lesions will become a very rare condition following the widespread implementation of HPV vaccines with broader coverage in the number of preventable oncogenic types. Irrespective of screening technology, the false positive results will far outnumber the true positive ones, a tipping point that will herald a new period when the harms from cervical cancer screening will outweigh its benefits. We present a conceptual framework to guide decision making when we reach this point within 25-30 years.

Kim, J., C. Bell, M. Sun, G. Kliewer, L. Xu, M. McInerney, L. W. Svenson and H. Yang (2016). "**Effect of human papillomavirus vaccination on cervical cancer screening in Alberta.**" *Cmaj* **188**(12): E281-e288.

BACKGROUND: A school-based program with quadrivalent human papillomavirus (HPV) vaccination was implemented in Alberta in 2008. We assessed the impact of this program on Pap test cytology results using databases of province-wide vaccination and cervical cancer screening. METHODS: We conducted a nested case-control study involving a cohort of women in Alberta born between 1994 and 1997 who had at least 1 Pap test between 2012 and 2015. Women with negative cytology results were controls. Women with low-grade (atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion) and high-grade (atypical squamous cells, cannot rule out a high-grade lesion; or high-grade squamous intraepithelial lesion) cervical abnormalities were cases. Exposure status was assigned according to records of

HPV vaccination. Odds ratios (ORs) for abnormal cytology results by vaccination status were adjusted for neighbourhood income, laboratory service, rural versus urban residency, and age. RESULTS: The total study population was 10 204. Adjusting for age, vaccinated women had a higher screening rate than unvaccinated women (13.0% v. 11.4%, $p < 0.001$). Among women who received full vaccination (≥ 3 doses), the adjusted OR for cervical abnormalities was 0.72 (95% confidence interval [CI] 0.63-0.82). For high-grade lesions, the adjusted OR was 0.50 (95% CI 0.30-0.85). With 2-dose HPV vaccination, the adjusted OR for cervical abnormalities was 1.08 (95% CI 0.84-1.38). INTERPRETATION: Quadrivalent HPV vaccination significantly reduced high-grade cervical abnormalities but required 3 doses. Vaccination against HPV was associated with screening uptake. Population-based vaccination and screening programs should work together to optimize cervical cancer prevention.

Naber, S. K., S. M. Matthijsse, K. Rozemeijer, C. Penning, I. M. de Kok and M. van Ballegooijen (2016). "**Cervical Cancer Screening in Partly HPV Vaccinated Cohorts - A Cost-Effectiveness Analysis.**" *PLoS One* **11**(1): e0145548.

BACKGROUND: Vaccination against the oncogenic human papillomavirus (HPV) types 16 and 18 will reduce the prevalence of these types, thereby also reducing cervical cancer risk in unvaccinated women. This (measurable) herd effect will be limited at first, but is expected to increase over time. At a certain herd immunity level, tailoring screening to vaccination status may no longer be worth the additional effort. Moreover, uniform screening may be the only viable option. We therefore investigated at what level of herd immunity it is cost-effective to also reduce screening intensity in unvaccinated women. METHODS: We used the MISCAN-Cervix model to determine the optimal screening strategy for a pre-vaccination population and for vaccinated women (~80% decreased risk), assuming a willingness-to-pay of €50,000 per quality-adjusted life year gained. We considered HPV testing, cytology testing and co-testing and varied the start age of screening, the screening interval and the number of lifetime screens. We then calculated the incremental cost-effectiveness ratio (ICER) of screening unvaccinated women with the strategy optimized to the pre-vaccination population as compared to with the strategy optimized to vaccinated women, assuming different herd immunity levels. RESULTS: Primary HPV screening with cytology triage was the optimal strategy, with 8 lifetime screens for the pre-vaccination population and 3 for vaccinated women. The ICER of screening unvaccinated women 8 times instead of 3 was €28,085 in the absence of herd immunity. At around 50% herd immunity, the ICER reached €50,000. CONCLUSION: From a herd immunity level of 50% onwards, screening intensity based on the pre-vaccination risk level becomes cost-ineffective for unvaccinated women. Reducing the screening intensity of uniform screening may then be considered.

Salmerón, J., L. Torres-Ibarra, F. X. Bosch, J. Cuzick, A. Lörincz, C. M. Wheeler, P. E. Castle, C. Robles and E. Lazcano-Ponce (2016). "**HPV vaccination impact on a cervical cancer screening program: methods of the FASTER-Tlalpan Study in Mexico.**" *Salud Publica Mex* **58**(2): 211-219.

OBJECTIVE: To outline the design of a clinical trial to evaluate the impact of HPV vaccination as part of a hrHPV-based primary screening program to extend screening intervals. MATERIALS AND METHODS: A total of 18,000 women aged 25-45 years, attending the regular cervical cancer-screening program in primary health care services in Tlalpan, Mexico City, will be invited to the study. Eligible participants will be assigned to one of three comparison groups: 1) HPV16/18 vaccine and hrHPV-based screening; 2) HPV6/11/16/18 vaccine and hrHPV-based screening; 3)

Control group who will receive only hrHPV-based screening. Strict surveillance of hrHPV persistent infection and occurrence of precancerous lesions will be conducted to estimate safety profiles at different screening intervals; participants will undergo diagnosis confirmation and treatment as necessary. CONCLUSION: The FASTER-Tlalpan Study will provide insights into new approaches of cervical cancer prevention programs. It will offer valuable information on potential benefits of combining HPV vaccination and hrHPV-based screening to safely extend screening intervals.

Guerrero, A. M., A. J. Genuino, M. Santillan, N. Praditsitthikorn, V. Chantarastapornchit, Y. Teerawattananon, M. Alejandria and J. A. Toral (2015). "**A cost-utility analysis of cervical cancer screening and human papillomavirus vaccination in the Philippines.**" *BMC Public Health* **15**: 730.

BACKGROUND: Cervical cancer is the second leading cause of cancer cases and deaths among Filipino women because of inadequate access to screening and treatment services. This study aims to evaluate the health and economic benefits of HPV vaccination and its combination with different screening strategies to find the most optimal preventive strategy in the Philippines. METHODS: A cost-utility analysis was conducted using an existing semi-Markov model to evaluate different screening (i.e., Pap smear, visual inspection with acetic acid) and vaccination strategies against HPV infection implemented alone or as part of a combination strategy at different coverage scenarios. The model was run using country-specific epidemiologic, cost and clinical parameters from a health system perspective. Sensitivity analysis was performed for vaccine efficacy, duration of protection and costs of vaccination, screening and treatment. RESULTS: Across all coverage scenarios, VIA has been shown to be a dominant and cost-saving screening strategy with incremental cost-effectiveness ratio (ICER) ranging from dominant to Php 61,059 (1443 USD) per QALY gained. VIA can reduce cervical cancer cases and deaths by 25%. Pap smear screening was found to be not cost-effective due to its high cost in the Philippines. Adding HPV vaccination at a cost of 54 USD per vaccinated girl on top of VIA screening was found to be potentially cost-effective using a threshold of 1 GDP per capita (i.e., Php 120,000 or 2835 USD/QALY) with the most favorable assumption of providing lifelong immunity against high-risk oncogenic HPV types 16/18. The highest incremental QALY gain was achieved with 80% coverage of the combined strategy of VIA at 35 to 45 years old done every five years following vaccination at 11 years of age with an ICER of Php 33,126 (783 USD). This strategy may result in a two-thirds reduction in cervical cancer burden. HPV vaccination is not cost-effective when vaccine protection lasts for less than 20 years. CONCLUSION: High VIA coverage targeting women aged 35-45 years old at five-year intervals is the most efficient and cost-saving strategy in reducing cervical cancer burden in the Philippines. Adding a vaccination program at high coverage among 11-year-old girls is potentially cost-effective in the Philippines assuming a life-long duration of vaccine efficacy.

Herweijer, E., A. L. Feldman, A. Ploner, L. Arnheim-Dahlström, I. Uhnoo, E. Netterlid, J. Dillner, P. Sparén and K. Sundström (2015). "**The Participation of HPV-Vaccinated Women in a National Cervical Screening Program: Population-Based Cohort Study.**" *PLoS One* **10**(7): e0134185.

BACKGROUND: Concerns have been raised that HPV-vaccination might affect women's cervical screening behavior. We therefore investigated the association between opportunistic HPV-vaccination and attendance after invitation to cervical screening. METHODS: A cohort of all women resident in Sweden, born 1977-1987 (N=629,703), and invited to cervical screening, was followed October 2006 - December 2012. Invitations to screening were identified via the National Quality Register for Cervical Cancer Prevention, as was the primary outcome of a registered

smear. Vaccination status was obtained from two nationwide health data registers. Hazard ratios (HR) were estimated using Cox regression adjusted for age, education level and income (HRadj). Women were individually followed for up to 6 years, of which the first and second screening rounds were analyzed separately. RESULTS: Screening attendance after three years of follow-up was 86% in vaccinated women (N=4,897) and 75% in unvaccinated women (N=625,804). The crude HR of screening attendance in vaccinated vs. unvaccinated women was 1.31 (95% CI 1.27-1.35) in the first screening round. Adjustment for education and income reduced but did not erase this difference (HRadj=1.09, 95% CI 1.05-1.13). In the second screening round, attendance was likewise higher in HPV-vaccinated women (crude HR=1.26, 95% CI 1.21-1.32; HRadj=1.15, 95% CI 1.10-1.20). CONCLUSIONS: HPV-vaccination is so far associated with equal or higher attendance to cervical screening in Sweden in a cohort of opportunistically vaccinated young women. Most but not all of the difference in attendance was explained by socioeconomic differences between vaccinated and unvaccinated women. HPV vaccine effectiveness studies should consider screening attendance of HPV-vaccinated women when assessing incidence of screen-detected cervical lesions.

Hestbech, M. S., E. Lynge, J. Kragstrup, V. Siersma, M. Vazquez-Prada Baillet and J. Brodersen (2015). "**The impact of HPV vaccination on future cervical screening: a simulation study of two birth cohorts in Denmark.**" *BMJ Open* 5(8): e007921.

OBJECTIVES: To explore the interplay between primary and secondary prevention of cervical cancer by estimating future screening outcomes in women offered human papillomavirus (HPV) vaccination when they were sexually naïve. DESIGN: Estimation of outcome of liquid-based cytology screening for a post-HPV vaccination cohort using pre-vaccination screening data combined with HPV vaccination efficacy data reported in the literature. SETTING: Denmark. DATA: The number of screening diagnoses at first screen in a pre-vaccination birth cohort was multiplied by reported risk reductions expected for women who were vaccinated for HPV before sexual debut. All identified studies were reviewed by two authors, and weighted pooled estimates of vaccine efficacies were used. MAIN OUTCOME MEASURES: Proportions of positive and false-positive cervical cytologies and positive predictive value (PPV) were calculated using cervical intraepithelial neoplasia (CIN) grade 2+ and 3+ as cut-off values. RESULTS: The proportion of positive screening tests was reduced from 8.7% before vaccination to 6.5% after vaccination, and the proportion of false-positive screening tests using CIN2+ as a cut-off was reduced from 5.5% pre-vaccination to 4.3% post-vaccination, and using CIN3+ as a cut-off from 6.2% to 4.7%. PPVs were reduced from 23% to 19% (cut-off CIN2+), and from 14% to 12% (cut-off CIN3+). CONCLUSIONS: In our calculations, the proportion of positive screening results with liquid-based cytology will be reduced as a consequence of HPV vaccination, but the reduction is small, and the expected decline in PPV is very limited. In this situation, the information general practitioners will have to provide to their patients will be largely unchanged.

Obel, J., J. McKenzie, L. E. Buenconsejo-Lum, A. M. Durand, A. Ekeroma, Y. Soares, D. Hoy, W. Baravilala, S. M. Garland, S. K. Kjaer and A. Roth (2015). "**Mapping HPV Vaccination and Cervical Cancer Screening Practice in the Pacific Region-Strengthening National and Regional Cervical Cancer Prevention.**" *Asian Pac J Cancer Prev* 16(8): 3435-3442.

OBJECTIVE: To provide background information for strengthening cervical cancer prevention in the Pacific by mapping current human papillomavirus (HPV) vaccination and cervical cancer

screening practices, as well as intent and barriers to the introduction and maintenance of national HPV vaccination programmes in the region. **MATERIALS AND METHODS:** A cross-sectional questionnaire-based survey among ministry of health officials from 21 Pacific Island countries and territories (n=21). **RESULTS:** Cervical cancer prevention was rated as highly important, but implementation of prevention programs were insufficient, with only two of 21 countries and territories having achieved coverage of cervical cancer screening above 40%. Ten of 21 countries and territories had included HPV vaccination in their immunization schedule, but only two countries reported coverage of HPV vaccination above 60% among the targeted population. Key barriers to the introduction and continuation of HPV vaccination were reported to be: (i) Lack of sustainable financing for HPV vaccine programs; (ii) Lack of visible government endorsement; (iii) Critical public perception of the value and safety of the HPV vaccine; and (iv) Lack of clear guidelines and policies for HPV vaccination. **CONCLUSION:** Current practices to prevent cervical cancer in the Pacific Region do not match the high burden of disease from cervical cancer. A regional approach, including reducing vaccine prices by bulk purchase of vaccine, technical support for implementation of prevention programs, operational research and advocacy could strengthen political momentum for cervical cancer prevention and avoid risking the lives of many women in the Pacific.

Poljak, M. (2015). **"Towards cervical cancer eradication: joint force of HPV vaccination and HPV-based cervical cancer screening."** *Clin Microbiol Infect* **21**(9): 806-807.

Setiawan, D., J. Luttjeboer, T. A. Westra, J. C. Wilschut, A. A. Suwantika, T. Daemen, J. Atthobari, B. Wilffert and M. J. Postma (2015). **"The cost-effectiveness of HPV vaccination in addition to screening: a Dutch perspective."** *Expert Rev Vaccines* **14**(4): 589-604.

Addition of the HPV vaccine to available cytological screening has been proposed to increase HPV-related cancer prevention. A comprehensive review on this combined strategy implemented in the Netherlands is lacking. For this review, we therefore analyzed all relevant studies on cost-effectiveness of HPV vaccines in combination with cervical screening in the Netherlands. Most of the studies agree that vaccination in pre-sexual-activity periods of life is cost-effective. Based on published sensitivity analyses, the incremental cost-effectiveness ratio was found to be mainly driven by vaccine cost and discount rates. Fewer vaccine doses, inclusion of additional benefits of these vaccines to prevent HPV-related non-cervical cancers and vaccination of males to further reduce the burden of HPV-induced cancers are three relevant options suggested to be investigated in upcoming economic evaluations.

Wang, L. D., W. W. Lam and R. Fielding (2015). **"Cervical cancer prevention practices through screening and vaccination: A cross-sectional study among Hong Kong Chinese women."** *Gynecol Oncol* **138**(2): 311-316.

OBJECTIVE: No published data are available that currently evaluate Chinese adult women's cervical cancer prevention practices through screening and vaccination using population-based samples. This study describes patterns and correlates of these behaviors among Hong Kong Chinese women aged 30-59 years. **METHODS:** From February to November 2014 a random sample of 1482 Hong Kong Chinese women having at least one 12-17 year-old daughter, who had heard of HPV vaccine before but had not sought HPV vaccination for daughter(s) completed structured telephone interviews. Multiple logistic regression analyses were conducted to examine factors

associated with participants' cervical screening attendance, HPV vaccination uptake and intention to uptake. RESULTS: Overall, 80.8% of the participants reported attending asymptomatic cervical screening and 73% had regular screening. Family income and attitudes to cervical smear testing were associated with asymptomatic cervical screening attendance. Only 3.0% (45/1482) of all participants had received HPV vaccination. Among those who had not received HPV vaccination, 12.3% (183/1437) indicated positive intentions. Age below 50, household income and encouragement from family/friends were significantly associated with women's intended and actual uptake of HPV vaccination. Trusting formal and informal HPV vaccination information was positively associated with vaccination intention, while lack of concrete recommendation from doctors was negatively associated with vaccination uptake. CONCLUSIONS: Information trust was associated with vaccination intention but not actual uptake whereas encouragement from family/friends facilitates women's HPV vaccination. Continued efforts are needed to ensure Chinese women adopting cervical cancer preventive behaviors, and must consider different specific needs of population subgroups.

Session 7 Title: HPV Prevention and Control Programs in Pandemic Situation

A Pubmed search was performed with the following selection criteria: [Cervical cancer] AND [Screening] AND [COVID-19] title/abstracts published in the last 1 year: 6 items were retrieved and 6 were selected. References were imported in EndNote. Herein, a relevant manual selection of publications between 2019-2020 based on title and abstract was made.

Arbyn, M., M. Gultekin, P. Morice, P. Nieminen, M. Cruickshank, P. Poortmans, D. Kelly, M. Poljak, C. Bergeron, D. Ritchie, D. Schmidt, M. Kyrgiou, A. Van den Bruel, L. Bruni, P. Basu, F. Bray and E. Weiderpass (2020). **"The European response to the WHO call to eliminate cervical cancer as a public health problem."** *Int J Cancer*.

The age-standardised incidence of cervical cancer in Europe varies widely (between 3 and 25/100000 women-years) in 2018. HPV vaccine coverage is low in countries with the highest incidence and screening performance is heterogeneous among European countries. A broad group of delegates of scientific professional societies and cancer organisations endorse the principles of the WHO call to eliminate cervical cancer as a public health problem, also in Europe. All European nations should, by 2030, reach at least 90% HPV vaccine coverage among girls by the age of 15 years and also boys, if cost-effective; they should introduce organised population-based HPV-based screening and achieve 70% of screening coverage in the target age group, providing also HPV testing on self-samples for non- or under-screened women; and to manage 90% of screen-positive women. To guide member states, a group of scientific professional societies and cancer organisations engage to assist in the roll-out of a series of concerted evidence-based actions. European health authorities are requested to mandate a group of experts to develop the third edition of European Guidelines for Quality Assurance of Cervical Cancer prevention based on integrated HPV vaccination and screening and to monitor the progress towards the elimination goal. The occurrence of the COVID-19 pandemic, having interrupted prevention activities temporarily, should not deviate stakeholders from this ambition. In the immediate post-epidemic

phase, health professionals should focus on high-risk women and adhere to cost-effective policies including self-sampling. This article is protected by copyright. All rights reserved.

Ciavattini, A., G. Delli Carpini, L. Giannella, R. De Vincenzo, A. Frega, P. Cattani, F. Boselli, F. Sopracordevole and M. Barbero (2020). **"Expert consensus from the Italian Society for Colposcopy and Cervico-Vaginal Pathology (SICPCV) for colposcopy and outpatient surgery of the lower genital tract during the COVID-19 pandemic."** *Int J Gynaecol Obstet* **149**(3): 269-272.

In the context of the COVID-19 pandemic, patients need to be evaluated within 2-4 weeks in the following cases: cytology result of "squamous cell carcinoma," "atypical glandular cells, favor neoplastic," "endocervical adenocarcinoma in situ," or "adenocarcinoma"; histopathological diagnosis of suspected invasion from cervical/vaginal biopsy, or invasive disease after a cervical excision procedure, vaginal excision, or vulvar biopsy/excision; sudden onset of strongly suggestive symptoms for malignancy. Digital imaging technologies represent an important opportunity during the COVID-19 pandemic to share colposcopic images with reference centers, with the aim of avoiding any concentration of patients. All patients must undergo screening for COVID-19 exposure and should wear a surgical mask. A high-efficiency filter smoke evacuation system is mandatory to remove surgical smoke. Electrosurgical instruments should be set at the lowest possible power and not be used for long continuous periods to reduce the amount of surgical smoke. The following personal protective equipment should be used: sterile fluid-repellant surgical gloves, an underlying pair of gloves, eye protection, FFP3 mask, surgical cap, and gown. The colposcope should be protected by a disposable transparent cover. A protective lens that must be disinfected after each use should be applied. The use of a video colposcope should be preferred.

Cohen, M. A., A. M. Powell, J. S. Coleman, J. M. Keller, A. Livingston and J. R. Anderson (2020). **"Special ambulatory gynecologic considerations in the era of coronavirus disease 2019 (COVID-19) and implications for future practice."** *Am J Obstet Gynecol*.

The coronavirus disease 2019 pandemic has altered medical practice in unprecedented ways. Although much of the emphasis in obstetrics and gynecology to date has been on the as yet uncertain effects of coronavirus disease 2019 in pregnancy and on changes to surgical management, the pandemic has broad implications for ambulatory gynecologic care. In this article, we review important ambulatory gynecologic topics such as safety and mental health, reproductive life planning, sexually transmitted infections, and routine screening for breast and cervical cancer. For each topic, we review how care may be modified during the pandemic, provide recommendations when possible on how to ensure continued access to comprehensive healthcare at this time, and discuss ways that future practice may change. Social distancing requirements may place patients at higher risk for intimate partner violence and mental health concerns, threaten continued access to contraception and abortion services, affect prepregnancy planning, interrupt routine screening for breast and cervical cancer, increase risk of sexually transmitted infection acquisition and decrease access to treatment, and exacerbate already underlying racial and minority disparities in care and health outcomes. We advocate for increased use of telemedicine services with increased screening for intimate partner violence and depression using validated questionnaires. Appointments for long-acting contraceptive insertions can be prioritized. Easier access to patient-controlled injectable contraception and pharmacist-provided hormonal contraception can be facilitated. Reproductive healthcare access can be ensured through reducing needs for ultrasonography and laboratory testing for certain eligible patients desiring abortion and conducting phone follow-up for medication abortions. Priority for

in-person appointments should be given to patients with sexually transmitted infection symptoms, particularly if at risk for complications, while also offering expedited partner therapy. Although routine mammography screening and cervical cancer screening may be safely delayed, we discuss society guideline recommendations for higher-risk populations. There may be an increasing role for patient-collected human papillomavirus self-samples using new cervical cancer screening guidelines that can be expanded considering the pandemic situation. Although the pandemic has strained our healthcare system, it also affords ambulatory clinicians with opportunities to expand care to vulnerable populations in ways that were previously underutilized to improve health equity.

de Pelsemaeker, M. C., Y. Guiot, J. Vanderveken, C. Galant and M. R. Van Bockstal (2020). "**The Impact of the COVID-19 Pandemic and the Associated Belgian Governmental Measures on Cancer Screening, Surgical Pathology and Cytopathology.**" *Pathobiology*: 1-10.

INTRODUCTION: The severe acute respiratory syndrome coronavirus 2 caused a pandemic of coronavirus disease 2019 (COVID-19). Unprecedented public health actions were introduced, including social distancing, travel restrictions and quarantine. The Belgian government announced a national emergency plan, thereby postponing all non-urgent medical consultations and operations. This report analyses the impact of these measures on cancer screening, through assessment of the workload of a laboratory for histopathology and cytopathology. METHODS: Data on monthly numbers of histological and cytological samples, immunohistochemistry and molecular tests were extracted from the laboratory information management system. RESULTS: The global histopathological and cytological workload was substantially reduced. The impact on oncology-related surgical procedures was rather limited. The anti-COVID-19 measures significantly diminished all screening-related samples, such as colon biopsies, breast biopsies and cervical cytology, and strongly reduced the number of samples related to "functional" pathology, such as thyroidectomies and gastric biopsies. CONCLUSIONS: Since many health care interventions are reflected in the workload of a pathology laboratory, this study enabled us to identify areas for "deconfinement" health care actions. Our findings indicate that various areas in medicine were affected, but the impact seemed largest for cancer screening. Health care professionals should assure that consultations related to cancer screening are postponed instead of cancelled.

Matsuo, K., H. Novatt, S. Matsuzaki, M. S. Hom, A. V. Castaneda, E. Licon, D. J. Nusbaum and L. D. Roman (2020). "**Wait-time for hysterectomy and survival of women with early-stage cervical cancer: A clinical implication during the coronavirus pandemic.**" *Gynecol Oncol* **158**(1): 37-43.

OBJECTIVE: A global pandemic caused by a novel coronavirus (Covid-19) has created unique challenges to providing timely care for cancer patients. In early-stage cervical cancer, postponing hysterectomy for 6-8 weeks is suggested as a possible option in the Covid-19 burdened hospitals. Yet, literature examining the impact of surgery wait-time on survival in early-stage cervical cancer remains scarce. This study examined the association between surgery wait-time of 8 weeks and oncologic outcome in women with early-stage cervical cancer. METHODS: This is a single institution retrospective observational study at a tertiary referral medical center examining women who underwent primary hysterectomy or trachelectomy for clinical stage IA-IIA invasive cervical cancer between 2000 and 2017 (N = 217). Wait-time from the diagnosis of invasive cervical cancer via biopsy to definitive surgery was categorized as: short wait-time (<8 weeks; n = 110) versus long wait-time (≥8 weeks; n = 107). Propensity score inverse probability of treatment weighting was used to balance the measured demographics between the two groups, and disease-free survival (DFS) and overall survival (OS) were assessed. A systematic literature

review with meta-analysis was additionally performed. RESULTS: In a weighted model (median follow-up, 4.6 years), women in the long wait-time group had DFS (4.5-year rates, 91.2% versus 90.7%, hazard ratio [HR] 1.11, 95% confidence interval [CI] 0.47-2.59, P = 0.818) and OS (95.0% versus 97.4%, HR 1.47, 95%CI 0.50-4.31, P = 0.487) similar to those in the short wait-time group. Three studies were examined for meta-analysis, and a pooled HR for surgery wait-time of ≥ 8 weeks on DFS was 0.96 (95%CI 0.59-1.55). CONCLUSION: Our study suggests that wait-time of 8 weeks for hysterectomy may not be associated with short-term disease recurrence in women with early-stage cervical cancer.

Part 2: Bibliography of Speakers

List obtained via speaker forms. The section also contains presentation related references of the speakers.

Nathalie Broutet, MD, PhD, Department of Reproductive Health and Research, World Health Organization

Marc Arbyn, Scientific Institute of Public Health (Belgium)

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The European response to the WHO call to eliminate cervical cancer as a public health problem. Arbyn M, Gultekin M, Morice P, Nieminen P, Cruickshank M, Poortmans P, Kelly D, Poljak M, Bergeron C, Ritchie D, Schmidt D, Kyrgiou M, Van den Bruel A, Bruni L, Basu P, Bray F, Weiderpass E. *Int J Cancer*. 2020 Jul 7. doi: 10.1002/ijc.33189. Online ahead of print.

The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): A systematic review and meta-analysis of 148 studies from 9 countries.. Grant MC, Geoghegan L, **Arbyn M**, Mohammed Z, McGuinness L, Clarke EL, Wade RG. *PLoS One*. 2020 Jun 23;15(6):e0234765. doi: 10.1371/journal.pone.0234765. eCollection 2020.

Cervical screening: ESGO-EFC position paper of the European Society of Gynaecologic Oncology (ESGO) and the European Federation of Colposcopy (EFC). Kyrgiou M, **Arbyn M**, Bergeron C, Bosch FX, Dillner J, Jit M, Kim J, Poljak M, Nieminen P, Sasieni P, Kesic V, Cuzick J, Gultekin M. *Br J Cancer*. 2020 Aug;123(4):510-517. doi: 10.1038/s41416-020-0920-9. Epub 2020 Jun 8

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Mario Poljak, Head of Laboratory for Molecular Microbiology, Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Slovenia

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Maver PJ, Seme K, Korać T, Dimitrov G, Döbrössy L, Engele L, Iljazović E, Kesić V, Kostova P, Laušević D, Maurina A, Nicula FA, Panayotova Y, Primic Žakelj M, Repše Fokter A, Romejko-Wolniewicz E, Smailytė G, Şuteu O, Świdarska-Kiec J, Tachezy R, Valerianova Z, Veerus P, Vīberga I, Znaor A, Zubor P, Poljak M. Cervical cancer screening practices in central and eastern Europe in 2012. Acta Dermatovenerol Alp Panonica Adriat 2013; 22: 7-19.

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Anne Laure Page, Scientist – Prequalification of In Vitro Diagnostics Team, World Health Organization

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Michael Chung, Professor at Agha Khan University Kenya, Affiliate Professor of Global Health and Medicine at the University of Washington in Seattle, USA and an Adjunct Professor of Medicine at Emory University in Atlanta, USA

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