Cervical screening in HPV-vaccinated populations

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ABSTRACT

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 its specificity 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 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 stratify women before referral for diagnostic evaluation. This review discusses these major developments and describes how the benefits of HPV screening are being optimised in both unvaccinated and vaccinated populations.

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INTRODUCTION

HPV is a common sexually transmitted virus, which can cause cancer of the cervix, vulvar, vagina, anus, penis and oropharynx. There are over 100 types of HPV, with 15 anogenital types commonly considered ‘oncogenic’. Almost all cervical cancers are caused by HPV; of these approximately 70% are caused by HPV16/18. HPV is also implicated in the development of anogenital warts with HPV6/11 likely responsible for around 90% of warts. However, risks associated with specific types vary and HPV 16 is uniquely oncogenic, responsible for around half of cervical cancers and the majority of other HPV-related cancers at other sites in both females and males.

There is a now well-established direct causal relationship between HPV infection, the development of high grade cervical precancerous lesions (known as Cervical Intraepithelial Neoplasia grades 2/3; CIN2/3), and the development of cervical cancer from a small proportion of CIN2/3 cases. This fundamental insight is the basis for the most effective mechanisms of primary prevention (prophylactic vaccination against HPV) and secondary prevention (HPV DNA based cervical screening). Both approaches are, in different ways, usurping the long-established “Pap smear” (cervical cytology), which has been the basis for very successful organised screening programs in many high-income countries over the last few decades.

This review considers the impact of HPV vaccination on cervical screening, the evidence base for primary HPV screening, and the current global status of HPV-based cervical screening programs. In doing so, Australia is used as a key example setting, since Australia was the first country to introduce a national publicly-funded HPV vaccination program and has been the first country to introduce primary HPV screening in cohorts who have received vaccination.

HPV VACCINATION

Vaccine experience

HPV vaccines were developed and trialled in the 1990s/2000s and involve synthetic empty viral capsids designed to provoke an immune response to the included HPV types. First generation vaccines were either bivalent (GlaxoSmithKline), protecting against HPV16/18 infections, or quadrivalent (Merck, Whitehouse Station, NJ, USA), protecting against HPV16/18 and HPV6/11. Prophylactic vaccination of young pre-adolescent females provides effective protection against persistent HPV infection and thus protects against future development of anogenital warts (quadrivalent vaccine) and high grade cervical precancerous lesions. Both vaccines are associated with ~98% efficacy against HPV16/18-related CIN2+ in HPV-naïve women, substantially reducing future risk of cervical cancer. Vaccination of young girls has consistently found to be highly cost-effective in high income countries and has also been found to be cost-effective in low and middle income country (LMIC) settings.

Australia was the first country in the world to introduce a national publicly-funded HPV vaccination program for young girls and women in 2007, but most high-income countries followed suit shortly afterwards. The coverage rates achieved have differed, as have recommendations for the age target group for initial catch-up vaccination, which varied between countries from 16-18 years up to 26 years. Following the initial catch-up phase, almost all high-income countries recommend ongoing HPV vaccination for young 12-13-year-old girls.

HPV vaccination is also effective in protecting against HPV-associated precancers in males. The cost-effectiveness of universal male vaccination of pre-adolescents is contingent on a number of factors, including the burden of HPV-related disease in males, vaccine price and delivery costs, and
the coverage achieved in females (since males receive herd protection from female-only vaccination, the incremental benefits of both-sex vaccination are more limited if high coverage is achieved in females).\textsuperscript{8,9} So far, universal male vaccination has been implemented in a few jurisdictions. The first priority in unvaccinated populations should be achieving high coverage vaccination in young females, since cervical cancer comprises the major burden of HPV-attributable cancers, and because males also benefits from female vaccination via herd immunity.\textsuperscript{9} Men who have sex with men (MSM) also have a higher burden of HPV-related cancers, especially anal cancer, and therefore targeted vaccination of this group in a sexual health or primary practice setting is another possibility and has now been found to be cost-effective in UK context.\textsuperscript{10} Vaccination of MSM has been recommended by the UK'S Joint Committee on Vaccination and Immunisation.

\textbf{Vaccine impact}

The first decade of experience with female HPV vaccination has been associated with a dramatic impact on several health outcomes in several countries.\textsuperscript{11} For example, in Australia, routine quadrivalent vaccination of 12-13 year females commenced in conjunction with a school and GP-based catch-up for females 12-26 years; coverage rates achieved for routine vaccination were over 70\%.\textsuperscript{12} Within a few years of program rollout, the prevalence of infection with vaccine-included types rapidly fell,\textsuperscript{13,14} as did incidence of anogenital warts in both young females,\textsuperscript{15-17} and males (due to herd immunity protection).\textsuperscript{16,18} A fall in cervical precancerous lesions has also been observed, first in young women <18 years,\textsuperscript{19} and eventually, as vaccinated cohorts have aged, in women in both their early and late twenties.\textsuperscript{20}

\textbf{Next generation vaccines and reduced dose schedules}

A major recent development has been the introduction of next generation polyvalent vaccines. The nonavalent vaccine (Merck), protects against nine HPV types, with the newly added 5 types (31,33,45,52 and 58) protecting against ~20\% of cervical cancers, bringing the total protection against cervical cancer in effectively vaccinated girls (i.e. vaccinated before exposure to the included types) to 90\%. IN HPV-naïve females, vaccine efficacy is >96\% against high-grade cervical, vulvar, or vaginal disease related to the newly included types with antibody responses to HPV 6, 11, 16, and 18 non-inferior to quadrivalent vaccine.\textsuperscript{21} Next generation vaccines can be cost-effective compared to first generation vaccines in high income countries, if the per-dose cost is contained at about a maximum price of 10\% higher than that for first generation vaccines.\textsuperscript{22-24} A major driver of cost savings for next generation vaccines is a further reduction in cervical screening and diagnostic costs generated via a reduction in screen-detected abnormalities and subsequent surveillance tests.\textsuperscript{22}

Of note is the emergence of recent data from the first few years of the Scottish HPV vaccination program, which initially used the bivalent vaccine, suggesting that substantial cross-protection against several non-vaccine-included types is provided by the bivalent vaccine. This suggests that the bivalent vaccine is capable of supplying broad spectrum protection, of a degree perhaps approaching that from the nonavalent vaccine.\textsuperscript{25}

HPV vaccines were initially delivered with 3-dose schedules, but 2-dose vaccination for pre-adolescents (both first and second-generation vaccines) have now been approved by the US Food and Drug Administration (FDA), the European Medicines Agency, and the World Health Organisation (WHO). Among pre-adolescent and young adolescent girls and boys receiving 2 doses of nonavalent vaccine separated by 6 or 12 months, immunogenicity has been shown to be non-inferior to a 3-dose regime in a cohort of adolescent girls and young women.\textsuperscript{26} Reduced-dose vaccination schedules
increase the potential for higher coverage vaccination, although it is important to achieve optimal spacing between the two doses for effective protection.

THE EVIDENCE BASE FOR PRIMARY HPV SCREENING

Cervical screening with cytology - ‘the Pap smear’ - has been the basis for substantial reductions in cervical cancer incidence and mortality in most high-income countries over the last few decades.\textsuperscript{27,28} Despite this success, the evidence base supporting a transition from cytology to primary HPV screening has been building for many years. This evidence base now consists of several elements, including (i) observational data on cross-sectional information on comparative test sensitivity and specificity and long-term outcomes from longitudinal cohort studies; (ii) randomised controlled trials (RCTs) of HPV screening vs. cytology screening in unvaccinated populations and emergent evidence from a RCT in a vaccinated population in Australia (‘Compass’); and (iii) structured syntheses of these data including meta-analyses, pooled information from RCTs, and modelled evidence which utilises evidence from primary sources to predict long term outcomes.

Observational data

Several meta-analyses on the cross-sectional test sensitivity and specificity for HPV vs. cytology testing have now been published. The results have demonstrated increased sensitivity for histologically-confirmed CIN2+ and CIN3+ for HPV testing even with a low test threshold of ASCUS (Atypical Squamous Abnormalities of Undetermined Significance; which is an equivocal result often caused by reactive changes) or LSIL (Low grade Squamous Intraepithelial Lesion).\textsuperscript{29} However, the specificity of HPV testing is lower than cytology, and this has been a challenge that needed to be overcome before HPV testing could routinely be introduced into screening programs. Longitudinal cohort studies provide information on intermediate and long-term outcomes after a negative HPV test, for women testing positive for any oncogenic HPV type, or according to baseline status for specific HPV types. This study design also provides comparative results for cytology vs. primary HPV testing, and according to joint HPV and cytology status (i.e. after ‘co-testing’). Such studies consistently demonstrate comparatively lower rates of CIN3+ in HPV-negative women, with follow-up periods of up to 18 years. Examples include the Joint European Cohort Study,\textsuperscript{30} which found that the cumulative incidence rate of CIN3+ after six years was lower among women negative for HPV at baseline (0.27%, 95%CI:0.12%-0.45%) than for cytology-negative women (0.97%, 95%CI:0.53%-1.34%). The lower risk in HPV-negative women is related to the necessary causal role of the virus in the development of invasive cervical cancer; a woman who does not have an HPV infection at baseline must acquire infection, which must persist and then progress to precancer and then invasive cervical cancer – a process that takes a decade or more in most cases. It has been estimated that the median age at which women who develop invasive cervical cancer acquire the causal HPV infection is in the early twenties,\textsuperscript{31} whereas rates of invasive cancer peak in women in their forties and above.

Another important source is the Portland Kaiser and Kaiser Permanente Northern California (KPNC) cohorts, from which many analyses have been published. A recent example concerns the recent screening history in co-tested women who do develop invasive cervical cancer, which was driven by concerns, which have surfaced mainly in the USA context, about HPV testing potentially missing a proportion of invasive cancers, despite the greater sensitivity of HPV compared to cytology testing. The KPNC analysis of outcomes in 1.2 million women found that HPV-negative test results associated with an abnormal cytology result proceeded only a small proportion of cases of invasive cancer (5.6%) and concluded that the “contribution of cytology to screening translated to earlier detection of at
most five cases per million women per year.” This provides ongoing support for using HPV as the sole primary screening test, and accords with previous findings from other cohorts that using cytology in conjunction with HPV testing for screening in all women provides only incremental benefits compared to using HPV testing alone.

Randomised controlled trials

Several RCTs of HPV screening (or co-testing) vs. cytology in unvaccinated populations have now been performed, many of which have reported outcomes from two or more rounds of screening. The first tranche of trials involved first generation HPV screening technology with a pooled test for all oncogenic types. Examples include the CCAST trial and HPV FOCAL trials (Canada), the POBASCAM trial (The Netherlands), the NTCC trial (Italy), the ARTISTIC trial (UK), a Finnish trial, and the Swedescreen trial (Sweden). More recent trials, including ATHENA in the USA, have involved second generation clinical HPV tests which include partial genotyping for the highest risk HPV types, HPV16/18 (some new technologies also include extended partial genotyping for other types). The general pattern is for increased sensitivity for confirmed CIN2+ for HPV compared to cytology in the first round of screening; detected CIN2+ can be treated and this leads to downstream protection against the development of CIN3 or invasive cancer, observed in subsequent rounds of screening.

There is now also emerging evidence on the relative performance of cytology and primary HPV screening in HPV-vaccinated populations from Australia’s Compass trial. Compass is a large scale RCT of 5-yearly HPV vs. 2.5 yearly liquid-based cytology (LBC) screening involving 121,000 women aged 25-69 years. HPV testing is conducted with partial genotyping for HPV16/18 and direct referral of this group to colposcopy; women with other oncogenic types receive triage testing, and are secondarily randomised to either reflex cytology triage or to triage with a new technology, cytology with dual-staining for the markers p16 and Ki67. Initial results from the first round of screening in the Compass pilot (for which the subgroup of women aged 33 years and younger had been offered HPV vaccination) are consistent with findings in unvaccinated women with significantly increased detection of CIN2+ in HPV-screened women compared to cytology-screened women. Compass is acting as a sentinel experience for the Australian National Cervical Screening Program transition and will continue to provide further evidence including on the long-term protection of HPV screening against CIN3+, and the relative effectiveness of alternate triaging strategies for HPV positive women.

Structured syntheses of data

Observational studies and RCTs have been conducted in different populations, with differences in HPV exposure, cytology quality, and the existing screening ‘background’. Thus, although there is broad consistency in the findings, there are some differences in the magnitude of relative effects of HPV and cytology screening. A structured synthesis is very helpful and a number of systematic review and meta-analyses of the cross-sectional test performance of HPV and cytology screening have been performed. More recently, an analysis of pooled individual-level data for four of the European RCTs (NTCC, Swedescreen, ARTISTIC and POBASCAM) was performed; by pooling data this was able to look at long term invasive cervical cancer outcomes. The pooled analysis demonstrated a lower rate of cumulative detection of invasive cervical cancer for HPV-screened women compared to cytology-screened women. The analysis showed a similar detection rate ratio for invasive cancer in the first 2.5 years of follow-up but the rate ratio for invasive cancer in the HPV-screened women was significantly lower thereafter. In screen-negative women the rate ratio in the HPV-screened group was 0.30 (95%CI:0.15-0.60), reflecting up to 70% improved protection against developing invasive cervical cancer at longer intervals. Notably, the protective effect for adenocarcinoma was higher than for
squamous cell cancer, an important outcome given that cytology-based screening programs have generally not succeeded in reducing rates of adenocarcinoma.46,47

Modelling is another mechanism to synthesise information. Because there is limited direct experience of screening in HPV-vaccinated women, modelling has been an important means of projecting long term precancer and cancer rates for new screening strategies in vaccinated populations. Comprehensively calibrated and validated platforms synthesise the evidence from cross-sectional studies of test accuracy, and are ideally validated against longitudinal outcomes from RCTs and cohort studies.38 To project outcomes in a particular country, the evidence on test performance is combined with local information on screening and vaccination coverage, burden of disease and the existing cervical screening recommendations.5,48,49

Australia is one example where modelling was used to guide decision-making in cervical screening. Prompted by the impact of HPV vaccination and the emergent evidence on primary HPV screening, the Renewal (review) of Australia’s National Cervical Screening Program was announced in 2011. Supported by systematic review of the evidence, the health impact and cost-effectiveness analysis of 132 potential screening strategies were evaluated considering the impact of vaccination49 and the resulting recommendation was that the program transition from 2-yearly cytology in women aged 18-20 to 69 years, to 5-yearly HPV screening in women aged 25 to 74 years. This is predicted to reduce rates of cervical cancer incidence and mortality in the population by a further 20-30% over the long term.49 The renewed cervical screening program commenced in December 2017.

Modelling also has a key role in predicting the transitional implications of switching to primary HPV screening, allowing health services to prepare for changes in demand. For example, modelling of the screening program transition in Australia suggests that initial rates of colposcopy referral will increase by up to 40-50% as the more sensitive test initially detects more prevalent precancerous lesions;50 this prediction accords with early evidence with the Compass trial.43 Over the longer term, modelling can assist in understanding the complex interacting effect of changes induced by both vaccination and screening. For example, the combined future impact of vaccination and HPV screening on cervical cancer is expected to result in a reduction in invasive cancer rates of approximately 50% (compared to 2015 rates) by 2035 in Australia.51

**HPV SCREENING – OPTIMISING THE BENEFITS**

All population screening programs involve balancing the benefits against the harms. For cervical screening the obvious health benefits include protection against the development of cervical cancer, avoidance of cancer treatment, and the avoidance of death from cervical cancer. Potential harms include psychological distress associated with the screening test, colposcopy referral to investigate a possible abnormality, and undergoing treatment for precancer. Treatment for cervical precancer involves the ablative removal of a small portion of the cervix, with the primary modalities in high-income countries being either Loop Electrosurgical Excision (LEEP) (also known as Large Loop Excision of the Transformation Zone [LLETZ]) or cone excision. Several meta-analyses have found an association between treatment for cervical precancerous lesions and subsequent obstetric complications, including premature rupture of the membranes and premature delivery;52-54 this might result from the possible induction of cervical incompetency after treatment. However, interpreting these data are complex, since there is a possibility of the association being confounded by patient-level variables including the number of prior full-term births, as well as treatment variables including prior treatment history and the depth of the excision.55 It has even been suggested that HPV infection itself might play...
a direct biological role in causing obstetric harms (as opposed to that role being mediated via development of precancerous lesions and subsequent treatment). The most recent meta-analysis on the topic concluded that even after taking into account confounding factors, there is evidence to support an association between treatment for cervical precancerous lesions and adverse obstetric outcomes.

HPV infection in the pre-vaccination era was very common in young women, and most infections in women <25 years regress. A barrier to the introduction of HPV screening has been related to valid concerns that it might lead to over-detection and over-treatment. Because of the potential harms, the major challenge was to ensure that HPV screening was implemented in a way that did not result in large numbers of young women with active infections (destined to regress naturally) being referred to colposcopy and potentially being unnecessarily treated.

This challenge is being overcome via the deployment of three separate strategies to optimise the trade-off between the effective sensitivity and specificity for HPV testing, including (i) carefully choosing both the appropriate age at which to start screening and the screening interval; (ii) via technology developments which have enable careful setting of thresholds used for clinical HPV tests before the results are considered ‘positive’; and (iii) selection of appropriate triage strategies for managing HPV positive women and for determining which subgroup of these should be referred to colposcopy.

Since HPV-based screening allows for safe lengthening of the screening interval, screening-related harms can be reduced over a woman’s lifetime simply by reducing the number of screening tests. In terms of the age of starting screening, HPV-based screening in unvaccinated populations has mostly been confined to women aged over 30 years, for which HPV prevalence rates are lower and in whom detected HPV is more likely to represent persisting infection with the potential to progress. Although many countries initiate screening starting at age 30 years, confining screening to this age group has proven a challenge for countries which have traditionally initiated screening at younger ages, and for which starting screening even at age 25 years (rather than a younger age) has been controversial.

One suggested solution is to use cytology screening in younger women, switching to HPV screening for women aged over 30 years. However, in vaccinated populations overall HPV detection rates will decline as vaccinated cohorts reach screening age, and this opens up practical possibilities for HPV screening in women in their late twenties. For example, the Australian National Cervical Screening Program, which switched to primary HPV screening in December 2017, recommends HPV testing starting at age 25 years, in a context in which vaccination had been offered to all women aged 37 years or younger at the time of the switchover.

Another method for increasing the specificity of clinical HPV testing for detection of high grade precancerous lesions is to increase the test threshold. HPV tests used for studies of HPV prevalence often involve PCR testing with very low thresholds for HPV positivity – such tests have a key role in understanding the epidemiology of HPV infection. By contrast, clinical HPV tests, for use in screening programs, have been designed such that they do not read ‘positive’ for very small viral copy numbers. There have also been efforts to develop minimum performance standards for both sensitivity and specificity for clinical HPV tests.

Finally, triaging HPV positive women is an important means of performing further risk stratification for HPV-positive women. The initial tranche of clinical trials of primary HPV screening involved using liquid-based cytology as a reflex triage test in HPV positive women; only women who have a cytological abnormality are then referred directly to colposcopy, other HPV positive women are generally referred for follow-up HPV testing to check for persisting HPV infection after 12 months (or longer).
Several newer clinical HPV test systems incorporate partial genotyping for HPV 16/18 and/or for other HPV types; this allows women with the highest risk infections to be immediately referred to colposcopy whereas women with other oncogenic HPV infections can be managed via cytological triage, potentially with a high cytological threshold for referral in this group.\textsuperscript{59} ATHENA and Compass are two trials which incorporated partial genotyping, and this strategy is being used in the renewed Australian National Cervical Screening Program.

Taking all of these measures into account (age, impact of HPV vaccination, screening interval, clinical test performance, and triaging strategies) it is predicted that switching HPV-based screening can actually reduce the harms associated with cervical screening at the same time as providing increased health benefits.\textsuperscript{60}

**HPV SELF-COLLECTION**

A further potential benefit of moving to HPV as the primary screening test is the option of introducing HPV self-collection using a vaginal swab or other sampling instrument. Although this has slightly reduced sensitivity compared to using a cervical practitioner-collected sample,\textsuperscript{61} it has been shown to increase uptake in underscreened and unscreened women in several settings. It is likely that self-collection is effective in overcoming cultural and other barriers to participating in cervical screening. The practical implementation of self-collection strategies, however, is non-trivial. Delivery models that are being proposed for use in screening programs include sending kits in the mail (as in the Netherlands HPV screening program)\textsuperscript{62} or having the sample taken under the supervision of a practitioner (as in the new Australian program).\textsuperscript{63}

**SCREENING IN THE ERA OF NEXT GENERATION HPV VACCINES**

An area of future research is the role of cervical screening in cohorts vaccinated as pre-adolescents with next generation broad-spectrum vaccines. These vaccines have major implications for future cervical screening programs since these young cohorts will be at very low lifetime risk of ever developing cervical cancer. Two modelling studies have recently investigated whether screening will continue to be cost-effective in this situation. The first examined screening in women who had been effectively vaccinated with nonvalent vaccine in the USA, finding that such women would only need to be screened every ten years starting at age 30 or 35 (i.e. around four cervical screens in a lifetime).\textsuperscript{64} A second study addressed the question at a population level in four countries (USA, UK, Australia and NZ)\textsuperscript{65} and concluded that, although there were some differences between countries in the optimal recommendations (generated via differences in vaccine coverage and health economic conventions), only 2-5 screens in a lifetime were likely to remain cost-effective. These initial studies, therefore, suggest that further revision of cervical screening recommendations is likely to become necessary when nonavalent-vaccinated cohorts reach the age of starting screening, but this will be a decade or more into the future in most countries.

**PRIMARY HPV SCREENING: CURRENT STATUS**

Several high-income countries are in the process of transitioning to primary HPV screening. The Netherlands, Italy, and Australia have already implemented the transition, and a number of other countries are piloting HPV screening or imminently planning to transition.\textsuperscript{66} In the USA, the situation
is complex, with the American Society for Colposcopy and Cervical Pathology and the American Cancer Society currently recommending 3-yearly cytology in women aged 21-30 years and in older women either 3-yearly cytology or 5-yearly co-testing.\(^6^7\) Recently, the US Preventative Services Taskforce published draft revised guidelines for cervical screening which include a recommendation to use HPV as the sole primary screening test in women aged over 30 years; this is currently in the consultation phase but is likely to prove controversial in the US, a country which has widely adopted co-testing.

Several logistical challenges have limited the large-scale implementation of cytology in LMIC. Although HPV vaccination will provide a long term mechanism for reducing cervical cancer incidence rates in LMIC, unfortunately current coverage rates are low (with <3% of females in less developed regions receiving the full vaccine course\(^6^8\)). Furthermore, some form of secondary protection will be required for adult women already potentially exposed to HPV. Recently the American Society for Clinical Oncology published resource-stratified guidelines\(^6^9\) which recommend (at least) once or twice lifetime screening with HPV even in the poorest countries. There are considerable challenges to be overcome in the delivery of HPV screening in LMIC (as there are for vaccination), but the availability of affordable point-of-care HPV tests is likely to be key to the success of such initiatives.

**CONCLUSIONS**

Cervical screening using cytology has been the basis for the successful reduction in cervical cancer incidence and mortality rates in high-income countries. However, two key, parallel developments have prompted a major re-consideration of cervical screening. The first is the emergence of evidence from cohort studies and randomised controlled trials on the improved performance of human papillomavirus (HPV) DNA testing compared to cytology for cervical screening. The second has involved the large-scale deployment of prophylactic vaccination against HPV. One of the key challenges that needed to be overcome before HPV screening could be introduced into national cervical screening programs was its specificity for precancerous lesions. This has now been overcome, by considering the appropriate age and interval for HPV screening, via development of higher specificity clinical HPV tests and by introducing effective triaging tests for HPV positive women. In this way, the benefits of HPV screening are being optimised in both unvaccinated and vaccinated populations.

**REFERENCES**

28. Iarc. Chapters 5 - 8: Effectiveness of screening in populations; Summary; Evaluation; Recommendations; Glossary. IARC Handbooks of Cancer Prevention Volume 10: Cervix Cancer Screening; 2005: 201; 93-43; 98.
43. Canfell K, Caruana M, Gebski V, et al. 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 2017; 14(9): e1002388.


