How will transitioning from cytology to HPV testing change the balance between the benefits and harms of cervical cancer screening? Estimates of the impact on cervical cancer, treatment rates and adverse obstetric outcomes in Australia, a high vaccination coverage country. [a]

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Novelty and Impact: There is some evidence that excisional treatment increases the risk of adverse obstetric outcomes in women with cervical intraepithelial neoplasia. The authors conducted a modelled analysis which predicts that in HPV-unvaccinated women, primary HPV screening compared to cytology may increase the lifetime risk of excision and potentially the number of adverse obstetric events. However, HPV screening in the context of vaccination is predicted to decrease the lifetime risk of excisional treatment which may also reduce the number of pre-term delivery and low-birthweight events.

Abbreviations

ASC-US: atypical squamous cells of undetermined significance; ASC-H: atypical squamous cells of undetermined significance cannot exclude high grade squamous intraepithelial lesion; CIN: cervical intraepithelial neoplasia; CLR: cumulative lifetime risk; LBC: liquid based cytology; pHSIL: possible high grade squamous intraepithelial lesion; pLSIL: possible low grade squamous intraepithelial lesions; TZ: transformation zone.

ABSTRACT

Primary HPV screening enables earlier diagnosis of cervical lesions compared to cytology, however, its effect on the risk of treatment has not been investigated. We estimated the cumulative lifetime risk (CLR) of cervical cancer and excisional treatment; and change in adverse obstetric outcomes in HPV unvaccinated women and cohorts offered vaccination (>70% coverage in 12-13 years) for the Australian cervical screening program. 2-yearly cytology screening (ages 18-69 years) was compared to 5-yearly primary HPV screening with partial genotyping for HPV16/18 (ages 25-74 years). A dynamic model of HPV transmission, vaccination, cervical screening and treatment for precancerous lesions was coupled with an individual-based simulation of obstetric complications. For cytology screening, the CLR of cervical cancer diagnosis, death and treatment would be 0.65%, 0.20% and 13% without vaccination and 0.18%, 0.06% and 7%, in vaccinated cohorts, respectively. For HPV screening, relative reductions of 33% and 22% in cancer risk for

unvaccinated and vaccinated cohorts are predicted, respectively, compared to cytology. Without vaccination, a 4% increase in treatment risk for HPV versus cytology screening is predicted, implying a possible increase in pre-term delivery (PTD) and low birthweight (LBW) events of 19-35 and 14-37, respectively, per 100,000 unvaccinated women. However, in vaccinated cohorts treatment risk will decrease by 13%, potentially leading to 4-41 fewer PTD events and from 2 more to 52 fewer LBW events per 100,000 vaccinated women. HPV screening starting at age 25 in populations with high vaccination coverage, is therefore expected to decrease the risks of cervical cancer and excisional treatment.

Introduction

Cytology-based screening has been successful in substantially reducing invasive cervical cancer and mortality rates where screening programs have long been established.[1] Evidence from international randomised controlled trials, however, has demonstrated increased effectiveness of primary HPV DNA screening, which provides up to a 60-70% increase in protection against developing invasive cervical cancer.[2] At the same time, the implementation of prophylactic HPV vaccination is expected to reduce the prevalence of cervical precancerous lesions, resulting in a potential deterioration in cytology screening performance.[3] Therefore, a number of countries are considering a move towards primary HPV screening. In Australia, the National Cervical Screening Program (NCSP), established in 1991, recommends 2-yearly screening with conventional cytology from 18-20 years to 69 years in sexually active women. However, given the emerging evidence on HPV screening and the impact of HPV vaccination, a major review of the program, termed "renewal", was carried out from 2011-2014. In the initial evaluation stage of the renewal process, the Australian government's Medical Services Advisory Committee (MSAC) considered a large number of new screening strategies including several primary HPV screening scenarios,[4] and recommended the replacement of the current program with 5-yearly primary HPV testing with partial genotyping for women aged 25 to 69 years and an exit test at 70-74 years of age. Clinical management guidelines for the new program have subsequently been developed to support the new program,[5] and the renewed NCSP will be implemented in May 2017.

All screening programs involve the balancing of benefits and potential harms. The benefits of cervical screening include early diagnosis and excisional treatment of cervical precancerous abnormalities, leading to a reduction in the number of cancer cases and mortality. Potential harms are associated with the treatment of lesions that would have regressed. Particularly in young women, evidence suggests that up to ~70% of high grade cervical intraepithelial

lesions (CIN2/3) in women aged <25 years would have regressed spontaneously.[6-8] Excisional treatment has been associated with an increased risk of adverse obstetric outcomes in several studies. A 2006 meta-analysis of retrospective case control and cohort studies found a summary relative risk (RR) of 1.70 (95%CI: 1.24-2.35) of preterm delivery (PTD) at less than 37 weeks and an RR of 1.82 (95%CI: 1.09-3.06) for low birth weight (LBW) of the neonate (<2500g) in women treated with large loop excision of the transformation zone (LLETZ) versus untreated women.[9] A more recent meta-analysis found an increased risk in women who had excisional treatment compared with women who gave birth at the same time but had no precancerous abnormalities (RR 2.19, 95% CI 1.93–2.49), and when obstetric outcomes after treatment were compared with outcomes before treatment for the same women (RR 1.96, 95% CI 1.46–2.64).[10] However, the methods and findings from the primary observational studies conducted in different settings are not consistent, and RRs are smaller when the comparison group is women diagnosed with precancerous changes but not treated,[10] indicating that confounding by indication for treatment is possible. Differences in quality systems in colposcopy and the subsequent impact on treatment have also been proposed as one explanation for the observed heterogeneity in outcomes and, in particular, for findings of no increased risk of PTD in treated women in England.[11] The most recent meta-analysis found some evidence that the baseline risk of PTD in untreated women with precancerous lesions is higher than the risk in the general population, but also concluded that, regardless of the comparator used, excisional treatment of CIN further increases that risk, to a degree which is dependent on the depth and dimensions of the excision.[12]

The objectives of the current study were to predict both the benefits and harms of 5-yearly primary HPV screening in three separate groups, defined by HPV vaccination status, using Australia as an example. We estimated the cumulative lifetime risks (CLRs) of invasive cancer and of excisional treatment and the number of pre-term delivery events and low birthweight events in: (i) an unvaccinated cohort of women (Group I), (ii) unvaccinated

women in cohorts offered vaccination as 12-13 year olds, considering the effect of herd immunity (Group II), and; (iii) women vaccinated as 12-13 year olds (Group III). Modelling was conducted in the context of the Australian NCSP and the National HPV Vaccination Program which includes vaccination of 12-13 year old females since 2007 (catch-up to age 26 years until end of 2009) and vaccination of 12-13 year old males since 2013 (2-year catch-up to age 14-15 years). Two primary HPV screening strategies, both incorporating partial genotyping for HPV16/18, but differing in downstream management of HPV-positive women, were compared to conventional cytology (current practice).

Materials and Methods

Population model of cervical screening

To estimate the impact of primary HPV screening on cervical cancer incidence and mortality and on treatment rates, we used a dynamic model of sexual behaviour, HPV transmission, natural history, cervical screening and HPV vaccination in females and males in the Australian population. The model platform has been extensively validated against a range of screening outputs and other national/ nationally representative data sources.[13] A detailed description of its development, parameterisation and calibration has been described previously.[4,14] This model has been used for a number of HPV vaccination and cervical screening evaluations in Australia, New Zealand and England.[4,15-18]

Two primary HPV strategies were considered. Both strategies involved 5-yearly primary HPV screening with partial genotyping for women aged 25-69 years, immediate referral of women positive for HPV16/18 to colposcopy and reflex liquid based cytology (LBC) triage for women who test positive for HPV types other than 16/18, with a cytology referral threshold of ASC-H+ (atypical squamous cells cannot exclude high grade squamous intraepithelial lesion) in this group. However, the two strategies differed in the management of HPV-positive women at and after colposcopy and for surveillance protocols after treatment of CIN2/3. The first of

these, the “initial strategy” was simulated for the original MSAC evaluation; further details can be found elsewhere.[4] In the second strategy, clinical management recommendations,[5] drafted as part of the implementation process of the renewed NCSP, have been included in the primary HPV model (“final guidelines strategy”). Differences in clinical management between the “initial strategy” and “final guidelines strategy”, are presented in Table 1. Briefly, these include changes to the post-colposcopy management of women with a HPV positive test result and a cytology report of negative, atypical squamous cells of undetermined significance (ASC-US) [referred to as possible low grade squamous intraepithelial lesions (pLSIL) in Australia] or ASC-H [referred to as possible high grade squamous intraepithelial lesion (pHSIL) in Australia] who had (i) a colposcopy result of negative [normal transformation zone (TZ)], (ii) type 3 TZ (TZ not fully visible), or (iii) a biopsy-confirmed lesion <CIN2. Updates to the assumptions around management of women previously treated for CIN2/3 and under post-treatment surveillance, the inclusion of an HPV exit test at ages 70-74, and compliance with colposcopy referral in the new program were also included in the “final guidelines strategy”.

Compliance assumptions

The model used a distribution of ages of starting screening to simulate the screening initiation pattern in Australia. For current practice, the proportion of women who initiate screening under the age of 25 years was based on information extracted from the Victorian Cervical Cytology Registry (VCCR). From ≥25 years, the additional proportion starting screening each year was chosen to be consistent with the reported age-specific rate of women aged ≥20 years who are never screened.[19-21] For both HPV screening strategies, we assumed women who currently have had their first screening test ≤25 years will initially screen at age 25 in the renewed NCSP after being prompted by an invitation on their 25th birthday (transition to a call-and-recall system is a key aspect of the renewed program). Given the transition to a call-and-recall system, we assumed there is less early re-screening,

and that a higher proportion of women return on time for their next screening test than currently. In the renewed program it was assumed that no women will initiate cervical screening <25 years and that the overall proportion of women ever-screened by the age of 30 is unchanged from current practice. In all cases, we assumed that changing the routine screening interval will not alter screening behaviour in very under-screened women (defined here as having a last screen 7+ years previously) or in women under follow-up management.

The modelled colposcopy compliance for current practice was based on the analysis of a large colposcopy database collected at the Royal Women's Hospital, in Melbourne, Australia.[4] The modelled colposcopy compliance for the "initial strategy" was assumed to be the same as for current practice; however, for the "final guidelines strategy", we assumed colposcopy compliance was equivalent to compliance in women referred with ASC-H cytology under current practice, since this is more applicable to the new program which refers women designated as "higher risk" (either HPV16/18 positive or positive for other oncogenic types with ASC-H+ cytology). The new clinical management guidelines also recommend that women aged 70-74 years who are HPV-positive (regardless of HPV type) at their final screening test be referred directly to colposcopy, regardless of the reflex cytology result. Further details of the assumptions used for the "final guidelines strategy" can be found elsewhere.[13]

Vaccination assumptions

Modelling of HPV vaccination against oncogenic types 16/18 took into account data from the National HPV Vaccination Register on observed 3-dose coverage rates in 12-13 year old females in 2009 (~72% coverage).[22] We did not consider the effects of cross-protection against non-vaccine included HPV types as their quantitative impact has yet to be defined and the long-term duration of cross-protection has not been determined. Modelling also took into account the coverage achieved in the catch-up program in females aged 12-26 years (which took place from 2007-2009),[23-24] since this increases the level of herd protection

experienced and thus has an impact on risk of cervical cancer in later cohorts. We also modelled the inclusion from 2013 of 12-13 year old males into the ongoing component of the program, and catch-up in males (aged 14-15) over 2013-2014, since this will also incrementally increase ongoing herd protection in females. We assumed that vaccine efficacy was 100%, and that the duration of protection was lifelong. The HPV natural history model also accounted for an apparent 'unmasking' of lesions associated with non-vaccine-included types (an increase of 8% in prevalence) post-vaccination, due to removal of concomitant HPV16 or 18 infections, for lesions previously attributed to HPV 16 or 18.[25]

Model of obstetric complications

In order to estimate the number and rates of adverse obstetric outcomes, we developed a Monte Carlo individual-based simulation, which used national age-specific fertility[26] and death[27] rates to model pregnancy events; data on age-specific treatment rates from the population screening model; and data on the baseline probability of an adverse obstetric event[27-28] and the excisional treatment-associated relative risk[9] of the adverse outcome to simulate the impact of changing screening recommendations on obstetric outcomes. We used a range of assumed relative risks (RRs) for women who had excisional treatment (LLETZ) which was defined by the 95% confidence interval of the estimates for PTD [RR 1.7 (1.24-2.35)] and LBW [RR 1.82 (1.20-3.16)] from the 2006 meta-analysis.[9] These estimates are broadly consistent with those reported in the most recent meta-analysis,[12] with significant overlap observed in the respective confidence intervals. The simulation continued until 95%CI of estimated mean number of adverse events had resolution <10 per 100,000 (43-77 million simulated women per year). Pre-term delivery and low birthweight were included in the model as two separate outcomes in line with results from meta-analyses of studies on adverse obstetric outcomes associated with CIN treatment.[9,12] However, it should be noted that in many cases these outcomes are likely to be correlated (i.e. pre-term infants are also likely to be of lower birthweight).

Ethical approval for analysis of VCCR and colposcopic observational data to support modelling was obtained from the Cancer Council NSW Human Research Ethics Committee. Simulations were implemented in C (HPV vaccination and transmission model), TreeAge Pro 2014 (CIN, invasive cancer and screening model) and C++ (obstetric complications model). More details on the modelling methods are provided in the Appendix.

Results

Predicted cervical cancer rates

Table 2 shows the predicted cumulative lifetime risk (CLR) of cervical cancer diagnosis and death, in each group of women, for current practice and the two primary HPV screening strategies. Given current practice, the predicted CLR of cervical cancer diagnosis in Groups I (unvaccinated), II (unvaccinated women in a cohort of females vaccinated at 12-13 year olds) and III (vaccinated as 12-13 year olds) are 0.65%, 0.52% and 0.18% respectively and CLRs of associated death are 0.20%, 0.16%, and 0.06%, respectively. Given primary HPV screening from the age of 25 years, the risks of cancer diagnosis and death are predicted to decrease in all groups when compared to current practice. The greatest impact on cancer diagnosis and death is predicted by the "final guidelines" strategy for HPV screening; relative reductions in cancer diagnosis in Groups I, II and III were 33%, 31% and 22% and relative reductions in associated death were 38%, 36% and 28%, respectively. Decreases in incidence and mortality for primary HPV screening are observed from 30-34 years onwards particularly in Groups I and II, when compared to current practice (Figure 1). Broadly similar results are predicted by the "initial strategy" for all groups of women, although the magnitude reductions in cervical cancer rates are smaller.

Lifetime risk of excisional treatment and predicted treatment rates

Given current practice, the average risk of lifetime exposure to cervical excisional treatment in an unvaccinated population (Group I) is 13%, but in vaccinated women (Group III) this rate is approximately halved to 7% (Table 2). Unvaccinated women in a cohort offered vaccination (Group II) will experience a slight decrease in risk of treatment to 12% due to herd protection. In the "final guidelines strategy", the lifetime risk of treatment relative to current practice in Groups I, II and III is predicted to increase by 4%, 0% and -13% (i.e. decrease), respectively, whereas for the "initial strategy", the lifetime risk of treatment is predicted to reduce by 13%, 16% and 31%, respectively. The predicted age-specific first treatment rates demonstrate that most treatments would occur in the 25-29 year age group due to the later age of starting screening and consequent increase in treatment rate in 25-29 year olds, decreasing thereafter (Figure 1). Although this pattern is observed in all groups of women, in vaccinated women the absolute rates are lower.

Predicted adverse obstetric outcomes

Tables 3 and 4 show the impact of HPV vaccination on the predicted rate of potential adverse obstetric events in the context of primary HPV screening, expressed as the number of events in a cohort of 100,000 women. Vaccination is predicted to reduce the number of PTD and LBW, both in vaccinated women and in those unvaccinated women in a cohort offered vaccination. In the "final guidelines strategy" (Table 3), vaccinated women are expected to have 310 fewer PTD events per 100,000 (from 7.40% to 7.23% of all births) and 300 fewer LBW events per 100,000 (from 6.17% to 6.01% of all births), compared to unvaccinated women, due to falling rates of abnormalities and treatments in the vaccinated population. Similarly, fewer PTD and LBW events in vaccinated women compared to unvaccinated women, were also predicted in the "initial strategy" of primary HPV screening although numbers were smaller (Table 4). In both strategies, fewer PTD and LBW events are also anticipated for unvaccinated women in a cohort offered vaccination, compared to earlier cohorts of unvaccinated women, because of herd protection.

Figure 2 shows the potential changes in the expected number of adverse obstetric outcomes under primary HPV screening, compared to cytology-based screening. In the "final guidelines strategy", 4-41 fewer PTD events and a range from 2 additional to 52 fewer LBW events are estimated per 100,000 vaccinated women compared to current practice. In unvaccinated women in an unvaccinated population, 19-35 more PTD events and 14-37 more LBW events per 100,000 women would have been predicted over a lifetime (i.e. in the counter-factual situation that women received a lifetime of screening in the new program but had not had any exposure to vaccination effect). In unvaccinated women in a cohort offered vaccination, 2-10 more PTD events and 3-8 more LBW events per 100,000 women are predicted. In contrast, reductions in adverse obstetric outcomes for all groups of women were estimated in the "initial strategy". These ranged from 21-89 and 10-107 fewer PTD and LBW events, respectively, per 100,000 unvaccinated women; 26-115 and 11-139 fewer PTD and LBW events, respectively per 100,000 unvaccinated women in a cohort offered vaccination and 17-98 and 5-121 fewer PTD and LBW events, respectively, per 100,000 vaccinated women.

As a supplementary analysis we also considered the situation where primary HPV screening is initiated at the age of 30 years, as per the existing or planned recommendations for HPV-based screening in a number of countries, including the Netherlands, Italy and Sweden (for detailed analysis see supplementary material). Under this scenario, for the final guidelines strategy the CLRs for cervical cancer diagnosis in Group I (unvaccinated), II (unvaccinated in cohort offered vaccination) and III (vaccinated) are 0.48%, 0.40%, and 0.15% respectively and CLRs for cervical cancer death are 0.13%, 0.11%, and 0.04%, respectively (Supplementary Table 1). Compared to current cervical screening practice in Australia, the relative reductions in cancer diagnosis in Groups I, II and III for this scenario are 26%, 24% and 20%, respectively. Under this scenario, a decrease in incidence and mortality of cervical cancer under primary HPV screening would occur from the ages of 35-39 years onwards (Supplementary Figure 1). In terms of lifetime risk of excisional treatment, the CLR for Group

I, II and III are 11%, 10% and 5% with highest rate of first treatment predicted in the 30-34 year age group, decreasing rapidly thereafter. In the final guidelines strategy, 38-198 fewer PTD events, and 12-243 fewer LBW events are predicted per 100,000 vaccinated women, compared to current practice (Supplementary Figure 2). In unvaccinated women in an unvaccinated cohort, 94-418 fewer PTD and 39-505 fewer LBW events, per 100,000 are predicted over a lifetime. Results are similar for unvaccinated women in a cohort offered vaccination.

Discussion

To our knowledge, this is the first study to predict in detail the lifetime effects of either cytology or primary HPV screening on both the protective effect against invasive cervical cancer (i.e. the effect on the benefits of screening) and the risk of excisional treatment and potential adverse obstetric outcomes (i.e. the harms and potential harms of screening). This is also the first report on the effect of HPV vaccination on the potential for adverse obstetric outcomes. For a primary HPV screening program the lifetime risk of cervical cancer diagnosis and death is predicted to decrease compared to cytology screening, regardless of a women's vaccination status. The lifetime risk of excisional treatment in vaccinated women is also predicted to fall, and fewer adverse obstetric outcomes are expected when compared to current practice. Apart from these potentially positive health outcomes, this effect may also have a beneficial economic impact at the community level as PTD are associated with significant short and long-term costs.[29] In unvaccinated women, one of our key findings was that the lifetime risk of treatment and the change in number of adverse obstetric events is dependent on the clinical management strategies introduced in conjunction with HPV screening. An increase in treatment risk is predicted when HPV positive women have more intensive follow-up, since this tends to lead more women to colposcopy referrals and subsequent treatments. These additional excisional treatments may subsequently increase the risk of adverse obstetric outcomes resulting in potentially more PTD and LBW events

compared to current practice. In unvaccinated women in a cohort offered vaccination the overall impact of more intensive follow-up in post-colposcopy management is smaller when compared to unvaccinated women, due to herd protection effects.

The analysis does have some limitations. Our predictions for the lifetime risk of treatment and cervical cancer in vaccinated women assume that the diagnostic performance of cytology will be sustained at the current level even when the prevalence of disease in the population drops. However, this may not be the case as the positive predictive value of cytology could decrease[3] if there is a substantial fall in cervical lesion prevalence as a result of cytologist de-training effects.[30] It should be noted that a decrease in screening sensitivity from what we assumed will reduce the risk of potential adverse obstetric outcomes but will also reduce screening effectiveness; ongoing analysis data from trials such as Compass[13], which involves randomising some women to cytology-based screening in the context of substantial population uptake of HPV vaccination, will be able to inform whether the performance of cytology will decrease in heavily vaccinated populations. In order to reflect the uncertainties regarding behavioural assumptions used in the model, we have presented a range of pre-term deliveries and low birthweight events. Additionally, major uncertainties about the extent of treatment-associated risk, and modifiers of risk, exist and thus we did not attempt to explicitly model such modifiers. These might include, for example, the effect of parity and multiple births, the potential for cervical regeneration and subsequent 'waning' of the risk of adverse pregnancy effects over time, the extent or depth of treatment and the delivery of multiple treatments. In relation to this last factor, a recent meta-analysis of studies reported that the risk of PTD increases progressively with increasing cone depths ≥10-12mm or cone volumes >3cc.[12] Furthermore, our findings for unvaccinated women in a cohort offered vaccination are dependent on the level of herd protection attained in the population and thus are broadly applicable only to countries with similar (high) levels of vaccination coverage as Australia. We also modelled adverse obstetric outcomes based on the quantified risks associated with loop excision, which does not take into account a smaller

(not well characterised) proportion of other treatment modalities used in Australia, such as laser coagulation. We also could not take into account the potential effect of quality control of colposcopy and treatment, which might serve to minimise the adverse impacts of treatment.[11] In this respect, it should be noted that quality assurance in colposcopy will be a new feature of the renewed NCSP. Submission of colposcopy data to a central National Cancer Screening Register has been discussed extensively with the relevant stakeholders and there is broad agreement that legislated mandatory data submission is important for monitoring the quality of care in colposcopy and treatment.[31] Taking all these factors under consideration, our results should be interpreted as indicative of the potential changes in adverse obstetric outcomes after a transition to primary HPV screening.

The transition to primary HPV screening, in conjunction with new clinical management guidelines,[5] and successful implementation, is predicted to be associated with considerable benefits, including lifetime reductions in cervical cancer, in both unvaccinated cohorts and younger cohorts offered vaccination. Starting screening at the older age of 25 years is not expected to reduce the benefits of screening as a recent analysis of national cervical cancer incidence data between 1982 and 2010 has shown that despite screening women 20-24 years with conventional cytology, there has been no decline in the incidence of either squamous cell carcinoma or cervical cancer overall in the last 20 years.[32] On the contrary, starting primary HPV screening in women from the age of 25 years will delay treatment in young women and a large proportion of cervical abnormalities in women 20-24 years will be given time to regress. However, when compared to current cytology screening, a higher first treatment rate is predicted in the 25-29 year age-group, which stems from detecting prevalent high grade cervical abnormalities at a later age because screening is initiated at 25 years versus 18-20 years and from earlier detection of cervical lesions due to increased sensitivity of HPV testing compared to cytology. However, the rate of first treatment rapidly decreases with age and from 60-64 years onwards the risk falls below that estimated under current practice.

For completely unvaccinated populations, the impact of primary HPV screening would be more complex. Our analysis indicates that the follow-up management of women who are HPV positive and after referral to colposcopy is a critical determining factor for the treatment rates experienced after transitioning to HPV screening. When compared to the "initial strategy", the follow-up management included in the "final guidelines strategy" involves more colposcopies, resulting in more treatments, driving a discernible, if relatively limited, potential increase in the number of PTD and LBW events. However, in 2017, when primary HPV screening is implemented in Australia, women aged ≤36 years will have been offered vaccination, which will mitigate any increase in precancerous treatments and associated obstetric outcomes (around 87% of births in Australia are to mothers aged ≤36 years). Therefore, our model predictions for vaccinated women and unvaccinated women in a cohort offered vaccination are more applicable to the expected impact of primary HPV screening in Australia. Because of the effect of vaccination in reducing the number of treatments and potential PTD and LBW events, it will be particularly important to ensure vaccine uptake in rural/remote areas of Australia or low income countries where obstetric/neonatal care may be limited, as the impact of these events is more significant in these settings.

The impact of HPV screening on potential obstetric outcomes will also depend on the management of women positive for high risk types other than HPV16/18 (OHR). We have previously shown that for women who test OHR positive and have a liquid based cytology result of ASC-US/LSIL, referral to immediate colposcopy is predicted to increase pre-cancer treatments by 2-5% compared to current treatment levels associated with 12 month surveillance of women with ASC-US.[5,15] These findings supported the final decision in Australia to refer this group to 12 month surveillance, which minimizes the impact on potential adverse obstetric outcomes in this subgroup of women.

We also conducted a supplementary analysis, initiating primary HPV screening at the age of 30 years. Overall, a different balance of benefits and potential harms is predicted for this scenario. Even in completely unvaccinated populations, a lower CLR in excisional treatment would be predicted for all women compared to current practice and initiating primary HPV screening at the age 25 years, with a further shift in the detection and treatment of cervical abnormalities to older ages. Although this would potentially lead to a possible further reduction in the number of PTD and LBW events due to higher fertility rates in women under 30 years old, the lifetime risk of cervical cancer diagnosis and death would be higher compared to initiating screening at the age of 25 years. It should however be noted that HPV screening starting at age 30 years would still be more effective than the current cytological based screening program in Australia starting at age 18-20 years.

Overall, it should be noted that our current model predictions are applicable in the context of vaccination with the quadrivalent vaccine. The Pharmaceutical Benefits Advisory Committee in Australia has recommended that a 2-dose schedule of the nonavalent vaccine replace the current 3-dose schedule of the quadrivalent vaccine. If this next generation vaccine were to be offered to 12-13 year olds in 2018, then a further review of the impact on cervical screening is likely to be appropriate after a decade or so, when these cohorts reach 25 years, the age of starting cervical screening in Australia. In our recent analysis of the optimal cervical screening approach in cohorts offered the nonavalent vaccine in several countries[35], we found that in Australia the number of lifetime screens could potentially be reduced from 10 to between 2-4 screens. However, the current study estimates the impact of changes due to take place on December 1st, 2017 – thus our focus here is on much more proximal, near-term, impact.

Our findings are of direct relevance to the Australian context. In addition, as more countries consider implementing primary HPV screening, our findings will, for the first time, provide women, practitioners, and policy makers with relevant evidence-based estimates about the

comparative benefits and harms of longer-interval primary HPV screening compared to cytology-based screening. Our findings are broadly relevant not only to countries with established organised screening programs, but also to countries with high levels of opportunistic screening which have implemented HPV vaccination in younger cohorts of females.

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