Cost-effectiveness of the next generation nonavalent human papillomavirus vaccine in the context of primary human papillomavirus screening in Australia: a comparative modelling analysis

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Summary

Background First generation bivalent and quadrivalent human papillomavirus (HPV) vaccines have been introduced in most developed countries. A next generation nonavalent vaccine (HPV9) has become available, just as many countries are considering transitioning from cytology-based to HPV-based cervical screening. A key driver for the cost-effectiveness of HPV9 will be a reduction in screen-detected abnormalities and surveillance tests. We aimed to evaluate the cost-effectiveness of HPV9 in Australia, a country with HPV vaccination of both sexes that is transitioning to 5-yearly HPV-based screening.

Methods We used Policy1-Cervix and HPV-ADVISE—two dynamic models of HPV transmission, vaccination, and cervical screening—to estimate the cost-effectiveness of HPV9 versus quadrivalent vaccine (HPV4), assuming lifelong vaccine protection, two vaccine doses, and that additional costs were incurred in girls only. Policy1-Cervix was used to estimate the lifetime risk of cervical cancer diagnosis and death. Probabilistic sensitivity analysis of the cost-effectiveness outcomes was done with both models, and results are presented as the median and 10th to 90th percentiles of simulation runs (referred to as 80% uncertainty intervals [UIs]).

Findings Compared with cytology-based screening, HPV screening is predicted to reduce lifetime risk of cervical cancer diagnosis by 18% and of death by 20%, even in unvaccinated cohorts. Under base-case assumptions (lifelong protection, full efficacy at two doses), HPV4 will provide a further reduction in diagnosis of 54% and in death of 53% and HPV9 will provide a further reduction in both diagnosis and death of 11%, compared with cytology-based screening in unvaccinated cohorts. For HPV9 to remain a cost-effective alternative to HPV4, the incremental cost per dose in girls should not exceed a median of AUS$35·99 (80% UI 28·47–41·18) with Policy1-Cervix or AUS$22·74 (15·49–34·45) with HPV-ADVISE, at a willingness-to-pay threshold of AUS$30 000 per quality-adjusted life-year.

Interpretation Differing methods and assumptions led to some differences in the estimates produced by the two models. However, on the basis of median results, HPV9 will be a cost-effective alternative to HPV4 if the additional cost per dose is AUS$23–36 (US$18–28). These results will be important when determining the optimum price of the vaccine in Australia.

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Introduction

Vaccination with first generation bivalent and quadrivalent human papillomavirus (HPV) vaccines has been implemented in many developed countries in the past decade. These vaccines protect against HPV types 16 and 18, which are implicated in 70% of cervical cancers worldwide and, in varying proportions, in other anogenital[1,2] and oropharyngeal cancers.[3–5] The quadrivalent vaccine (HPV4) also protects against HPV types 6 and 11, which are implicated in approximately 90% of cases of anogenital warts.[5] A second generation nonavalent HPV vaccine (HPV9) has been shown to protect against infection and disease associated with HPV types 16, 18, 31, 33, 45, 52, and 58, which together account for about 90% of cervical cancers worldwide,[6] and against types 6 and 11.

Australia was the first country to initiate a national publicly funded HPV vaccination programme in 2007. Three doses of HPV4 are funded for female and male adolescents aged 12–13 years, with more than 70% coverage in girls and more than 65% coverage in boys.[7] Two-dose schedules for HPV4 and bivalent vaccines (HPV2) have been recommended by WHO[8] and the European Medicines Agency,[9] and have been implemented in the UK[10] and Canada.[11] New vaccination schedules involving HPV9 are expected to also be two dose, on the basis of non-inferiority of geometric mean titres at 1 month after the last dose in adolescents aged 9–14 years who received two doses of HPV9 versus young women aged 16–26 years who received a three-dose regimen.[12]

The cost-effectiveness of HPV9 has been evaluated in various settings.[13–16] In Canada, HPV9 was a cost-effective

Research in context

Evidence before this study

Several cost-effectiveness studies have evaluated the optimum pricing of the human papillomavirus (HPV) nonavalent vaccine (HPV9) in cytology-based screening settings, and have shown that a key driver of cost-effectiveness is the reduction in screen-detected abnormalities and post-treatment surveillance tests. Many countries are considering a transition from cytology-based screening to primary HPV-based screening programmes, and modelling studies have shown that extended-interval HPV-based screening can reduce population-level cancer rates and impact precancer treatment rates and numbers of surveillance tests, all of which could affect the predicted cost-effectiveness of the nonavalent vaccine. We searched PubMed between Jan 1, 1990, and Sept 20, 2016, with no language restrictions, with the terms "nonavalent", "cost", and "nine-valent". Our search identified no studies of the cost-effectiveness of HPV9 in a primary HPV setting. We therefore used two independently developed modelling platforms (HPV-ADVISE and Policy1-Cervix) to evaluate the maximum additional cost per dose of HPV9 to remain a cost-effective alternative to quadrivalent vaccine (HPV4) in Australia, a country transitioning to 5-yearly HPV-based screening.

Added value of this study

This is the first study to evaluate the effect of HPV9 in a primary HPV screening setting. Our findings show that a further 11% reduction in diagnosis and death is expected in cohorts offered HPV9 compared with cohorts offered HPV4. This reduction is in the context of an expected reduction in the risk of diagnosis and death of more than 18% after the transition from the current cytology-based programme to primary HPV-based screening, even in the absence of vaccination. For HPV9 to remain a cost-effective alternative to HPV4, the additional cost per dose should not exceed a median of AUS$35·99 (80% uncertainty interval 28·47–41·18) with Policy1-Cervix, or AUS$22·74 (15·49–34·45) with HPV-ADVISE.

Implications of all the available evidence

Differing methods and assumptions led to some differences in the estimates produced by the two model platforms. However, on the basis of median results, HPV9 will remain a cost-effective alternative to HPV4 in the context of HPV-based screening if the additional cost per dose is AUS$23–36, equivalent to US$18–28. These results will be important when determining the optimum price of the vaccine in Australia.

alternative to HPV4 if the additional cost per dose remained less than CAN$24 (80% uncertainty interval [UI] 6–36).[16] In the USA, HPV9 was cost effective compared with HPV4 if the additional cost per dose was US$13.[15] A major finding of these analyses was that the health gains in terms of quality adjusted life-years (QALYs) and the cost savings of HPV9 are largely derived from the prevention of treatment and surveillance associated with cervical intraepithelial neoplasia grades 2 and 3.[13,15] Therefore, the cost-effectiveness of HPV9 is highly reliant on the screening process in place. However, previous cost-effectiveness analyses have focused on traditional, cytology-based screening approaches, or co-testing in the case of the USA,[15] and none have evaluated the effect of HPV9 in a primary HPV screening setting.

For **HPV-ADVISE** see http://www.marc-brisson.net/HPVadviseCEA.pdf

See Online for appendix

Several countries, including England, New Zealand, Australia, Italy, and The Netherlands, are now considering or implementing a transition from cytology to primary HPV screening. Introduction of a more sensitive test, in addition to extended-interval screening, will have a substantial effect on rates of cancer and cervical intraepithelial neoplasia grades 2 and 3.[17,18] In 2017, Australia will transition from 2-yearly cytology in women aged 18–69 years to 5-yearly primary HPV screening with genotyping for HPV types 16 and 18 for women aged 25–74 years. This decision was informed by an initial 2013 evaluation[18] that predicted an 18% reduction in the risk of cervical cancer diagnosis and a 20% reduction in cervical cancer death compared with the current programme. However, a more recent analysis, which incorporated detailed surveillance and post-colposcopy recommendations based on the final 2016 clinical guidelines for HPV screening, updated these predictions to a 31% reduction in the age-standardised rate of diagnosis and a 36% reduction in the age-standardised rate of cervical cancer diagnosis and death compared with the current programme.[19] Therefore, we did the present study to evaluate the effect of HPV9, and to estimate the maximum additional cost per dose for HPV9 to remain cost effective compared with HPV4, in the context of primary HPV screening.

Methods

Models

We used the Policy1-Cervix[20] and HPV-ADVISE[21] models to evaluate the effect of switching from HPV4 to HPV9 in the context of 5-yearly primary HPV screening in Australia (appendix). Both models contain various components, including dynamic HPV transmission, vaccination, cervical precancer and cancer, screening, diagnosis, and treatment (appendix). HPV-ADVISE also models other HPV-associated cancers.

Vaccine assumptions

Both models incorporated national uptake rates for HPV4 in girls[22] and boys,[7] in addition to vaccination of older cohorts included in the initial catch-up programme. For the base case, we assumed 95% efficacy in girls and 85% efficacy in boys naive for the relevant type at

two doses (no efficacy at one dose), lifelong duration of protection, and short-lasting HPV4 cross-protection. In Policy1-Cervix, the baseline set of HPV type-specific attributable fractions in cancer were based on preliminary results from the Australian Cervical Cancer Typing Study (ACCTS),[23] which found that 76·6% of cervical cancers in Australia were attributable to HPV types 16 and 18 and 15·8% were attributable to types 31, 33, 45, 52, and 58 (AF1). In sensitivity analysis, the Policy1-Cervix platform also explored the effect of a second set of attributable fractions (AF2) based on an international meta-analysis.[6] The appendix describes in detail the vaccine assumptions and the HPV attributable fractions in cervical intraepithelial neoplasia grades 2 and 3 and cancer for both models.

Screening assumptions

Policy1-Cervix simulated outcomes in a cohort of girls born in 2005, until they turn 85 years old. This cohort will turn 12 years old in 2017, and will therefore be the first cohort to receive HPV9 if it were released in 2017, and they will also be offered the new 5-yearly HPV screening programme for their lifetime. We explicitly modelled HPV testing for women aged 25–74 years with genotyping for HPV types 16 and 18 and direct referral to colposcopy for this group (as will occur in the new programme). Women positive for other high-risk types will be triaged by use of liquid-based cytology, with high-grade cytology cases referred for immediate colposcopy and other cases recalled for 12 month surveillance. Detailed downstream management was informed by the initial 2013 evaluation (primary HPV screening: initial evaluation),[18] but the effect of the final 2016 guidelines on the cost effectiveness of HPV9 was also assessed in sensitivity analysis (primary HPV screening: final guidelines).[19] In both models, screening attendance rates were based on data from the Victorian Cervical Cytology Register.

HPV-ADVISE modelled 5-yearly primary HPV screening from ages 25–74 years, with cytology triage of any HPV-positive women (rather than direct colposcopy for women testing positive for HPV types 16 and 18) and did not incorporate detailed downstream management of the 2016 clinical guidelines. Although the assumed management of HPV types 16 and 18 women by HPV-ADVISE does not exactly reproduce management pathways in the new screening programme, the relative effect of HPV9 versus HPV4 was expected to be affected by the management of women testing positive for HPV types 31, 33, 45, 52, and 58, and minimally affected by the management of women testing positive for HPV types 16 and 18.

Cost and health-economic assumptions

Both models took a health services perspective and considered costs for screening, diagnostic, and treatment procedures in 2013 (detailed methods have been described previously).[18] A discount rate of 5% was used for both costs and effects, consistent with Australian practice.[24] Previous reports have shown that use of different utility sets to calculate QALYs for HPV screening produces substantially different conclusions;[17,18] therefore, two QALY weight sets were used for screening-related disutilities to evaluate the cost-effectiveness outcomes—one based on an Australian study[25] and the second on a Canadian study.[26] We used the Canadian set for the base-case analysis because the sample size in that study was larger than that in the Australian study. Disutilities related to cervical cancer diagnosis were also used for each set (appendix).

Main outcomes

Both models assumed that only HPV4 was delivered before 2017, and from 2017 onwards, 12–13-year-old girls and boys would receive either HPV9 or HPV4. For both strategies, we used Policy1-Cervix to estimate the lifetime risk of cervical cancer diagnosis and death, and the lifetime risk of cervical precancer treatment as a measure of screening-associated harms. Policy1-Cervix and HPV-ADVISE were then used to identify the maximum additional cost per dose of HPV9 over HPV4 in girls, so that the incremental cost-effectiveness ratio of switching to HPV9 was less than AUS$30 000/QALY, consistent with willingness to pay for previous vaccine applications in Australia.[27] We assumed that HPV9 would not cost more than HPV4 for boys for the base case because the health gains of HPV9 over HPV4 are expected to be small in boys.

We used Policy1-Cervix to investigate the effect of changing one key parameter at a time whilst keeping all other variables unchanged (one-way sensitivity analysis). Key parameters assessed were vaccine efficacy, number of doses, cross-protective efficacy, whether additional costs for HPV9 are incurred in boys, willingness-to-pay threshold, and duration of vaccine protection. HPV-ADVISE was also used for one-way sensitivity analysis of some of these parameters, and to examine the effect of HPV9 on other HPV-associated cancers in men and women (appendix).

For the **Victorian Cervical Cytology Register** see http://www.vccr.org/

Statistical analysis

All models must incorporate assumptions. Therefore, probabilistic approaches should also be used to provide information about the uncertainty ranges around these predictions.[28] Probabilistic sensitivity analysis of the cost-effectiveness outcomes was done in both models, and results are presented as the median and 10th to 90th percentiles of simulation runs (referred to as 80% UIs). Policy1-Cervix assessed uncertainty in screening attendance rates, test accuracy rates, and cost assumptions for all scenarios (appendix). HPV-ADVISE assessed uncertainty due to natural history parameters, using ten parameter sets identified through calibration, as previously described.[29]

Throughout this article, conversion between AUS$, US$, and CAN$ was AUS$1=US$0·78, AUS$1=CAN$1·00 (conversion date based on the Reserve Bank April 21, 2016).[30]

Role of the funding source

The funders had no role in study design, data analysis, data collection, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In the absence of vaccination, the primary HPV screening programme (under the assumptions used for the 2013 evaluation) is predicted to reduce the lifetime risk of cervical cancer diagnosis by 18% (figure 1) and the lifetime risk of cervical cancer death by 20% (figure 2), compared with the current cytology-based programme. Cohorts offered HPV4 are predicted to have an additional reduction in diagnosis of 54% and in death of 53%, and those offered HPV9 are predicted to have a further reduction in both diagnosis and death of 11% compared with the current cytology-based programme (figures 1, 2). If full vaccine efficacy requires three doses instead of two, then because of lower effective vaccine coverage achieved, risk reduction is also somewhat lower: an additional reduction in the lifetime risk of both diagnosis and death of 51% for cohorts offered HPV4, and a further reduction in diagnosis of 11% and in death of 10% in cohorts offered HPV9 (figures 1, 2). Risk reduction is

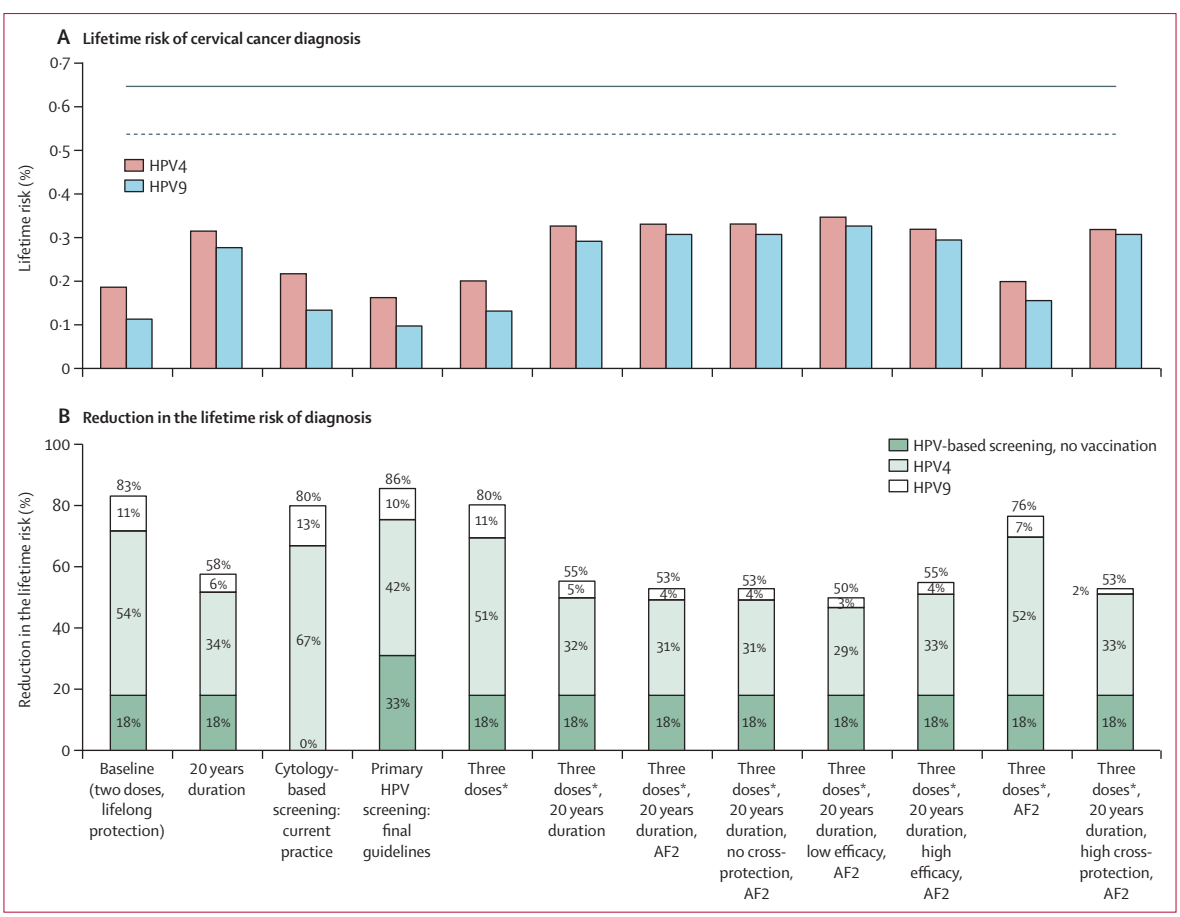

Figure 1: **Predicted lifetime risk of cervical cancer diagnosis and death for cohorts offered HPV4 or HPV9 for a range of vaccine assumptions, using Policy1-Cervix**
(A) Lifetime risk of cervical cancer diagnosis. The solid horizontal line shows lifetime risk in unvaccinated cohorts under the current cytology-based programme (0·65%), as obtained from the Australian Institute of Health and Welfare, 2014.[31] The dashed line shows lifetime risk in unvaccinated cohorts under primary HPV-based screening (primary HPV screening: initial evaluation; 0·53%), as obtained from published predictions.[18] (B) Reduction in the lifetime risk of cervical cancer diagnosis in cohorts offered HPV9 compared with current rates (ie, compared with rates in unvaccinated cohorts managed under the current cytology-based programme). Shading denotes the incremental reduction achieved after the change to HPV-based screening (dark region), the addition of HPV4 (light region), and the addition of HPV9 (unshaded region). If not specified in the axis label, vaccine duration of protection is lifelong, two doses are required to achieve efficacy, and attributable fractions are based on the Australian Cervical Cancer Typing study (ACCTS) study.[23] The sum of the incremental effects might not be equivalent to the final percentage reduction reported because of rounding. HPV=human papillomavirus. HPV4=quadrivalent vaccine. HPV9=nonavalent vaccine. AF2=attributable fractions based on a meta-analysis.[6] *Full efficacy at three doses (no efficacy at two doses). Note that three-dose scenarios result in higher cancer rates than two-dose scenarios because of the lower effective vaccine coverage at three doses.

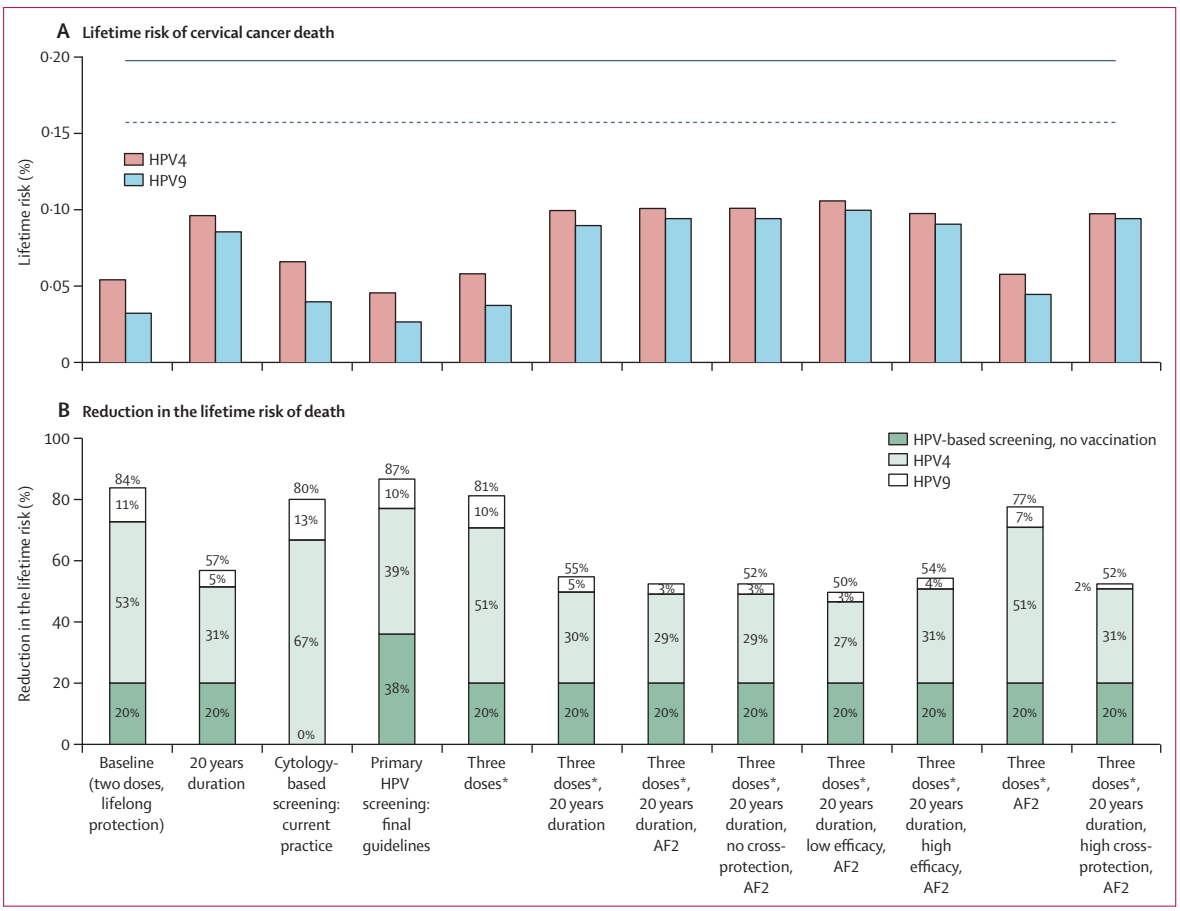

Figure 2: **Predicted lifetime risk of cervical cancer death for cohorts offered HPV4 or HPV9 for a range of vaccine assumptions, using Policy1-Cervix**
(A) Lifetime risk of cervical cancer death. The solid horizontal line shows lifetime risk in unvaccinated cohorts under the current cytology programme (0·2%), as obtained from the Australian Institute of Health and Welfare, 2014.[31] The dashed line shows lifetime risk in unvaccinated cohorts under primary HPV-based screening (primary HPV Screening: initial evaluation; 0·16%), as obtained from published predictions.[18] (B) Reduction in the lifetime risk of cervical cancer death in cohorts offered HPV9 compared with current rates (ie, compared with rates in unvaccinated cohorts managed under the current cytology-based programme). Shading denotes the incremental reduction achieved after the change to HPV-based screening (dark region), the addition of HPV4 (light region), and the addition of HPV9 (unshaded region). If not specified in the axis label, vaccine duration of protection is lifelong, two doses are required to achieve efficacy, and attributable fractions are based on the Australian Cervical Cancer Typing study (ACCTS) study.[23] The sum of the incremental effects might not be equivalent to the final percentage reduction reported because of rounding. HPV=human papillomavirus. HPV4=quadrivalent vaccine. HPV9=nonavalent vaccine. AF2=attributable fractions based on a meta-analysis.[6] *Full efficacy at three doses (no efficacy at two doses). Note that three-dose scenarios result in higher cancer rates than two-dose scenarios because of the lower effective vaccine coverage at three doses.

likewise lower if vaccine protection is 20 years rather than lifelong: an additional reduction in the risk of diagnosis of 34% and in the risk of death of 31% for cohorts offered HPV4, and a further percentage point reduction of 6% and 5%, respectively, for cohorts offered HPV9 (figures 1, 2).

The reduction in lifetime risk in cohorts offered HPV4 would have been higher if cytology-based screening had been retained in Australia than if it were replaced by a primary screening programme: HPV4 would have reduced the lifetime risk of both diagnosis and death by 67%, and HPV9 would have further reduced the risk of both diagnosis and death by 13% (figures 1, 2). When the final 2016 clinical management guidelines are incorporated, a 33% reduction in the risk of diagnosis and a 38% reduction in the risk of death is predicted in unvaccinated cohorts; HPV4 will provide an additional 42% and 39% reduction, respectively, and HPV9 a further reduction of 10% and 10%, respectively, compared with the current cytology-based programme (figures 1, 2). Vaccination has a larger effect on cancer in the cytology-based programme because the programme is predicted to be less effective than primary HPV screening and therefore more disease is available for prevention by vaccination; conversely, the final 2016 guidelines are more effective than the initial 2013 guidelines and therefore the relative effect of vaccination is lower (figures 1, 2).

In the absence of vaccination, the primary HPV screening programme is predicted to reduce the lifetime risk of precancer treatment by 10% compared with the

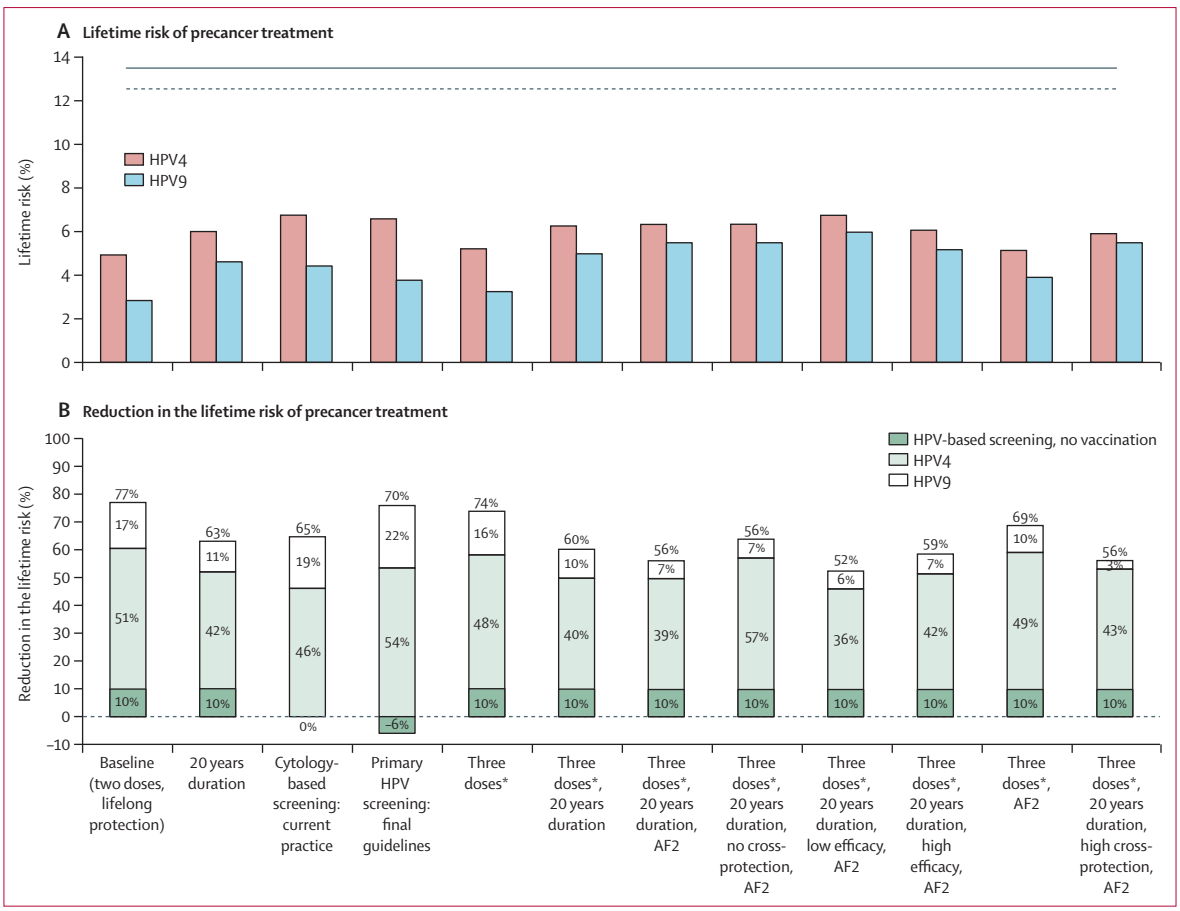

Figure 3: **Predicted lifetime risk of cervical precancer treatment for cohorts offered HPV4 or HPV9 for a range of vaccine assumptions, using Policy1-Cervix**
(A) Lifetime risk of cervical precancer treatment. The solid horizontal line shows lifetime risk in unvaccinated cohorts under the current cytology programme (13·5%), as obtained from published predictions.[18] The dashed line shows lifetime risk in unvaccinated cohorts under primary HPV-based screening (primary HPV screening: initial evaluation; 12·55%), as obtained from published predictions.[18] (B) Reduction in the lifetime risk of precancer treatment in cohorts offered HPV9 compared to current rates (ie, compared with rates in unvaccinated cohorts managed under the current cytology-based programme). Shading denotes the incremental reduction achieved after the change to HPV-based screening (dark region), the addition of HPV4 (light region) and the addition of HPV9 (unshaded region). If not specified in the axis label, vaccine duration of protection is lifelong, two doses are required to achieve efficacy, and attributable fractions are based on the Australian Cervical Cancer Typing study (ACCTS) study.[23] The sum of the incremental effects might not be equivalent to the final percentage reduction reported because of rounding. HPV=human papillomavirus. HPV4=quadrivalent vaccine. HPV9=nonavalent vaccine. AF2=attributable fractions based on a meta-analysis.[6] *Full efficacy at three doses (no efficacy at two doses).

current cytology-based programme (figure 3). Cohorts managed under the primary HPV screening programme and offered HPV4 are predicted to have an additional reduction in the lifetime risk of precancer treatment of 51%, and cohorts offered HPV9 a further reduction of 17% compared with the current cytology-based programme (figure 3).

Under baseline assumptions (two-dose efficacy, lifelong duration of protection, additional costs incurred in girls only, Canadian QALYs), the maximum additional cost per dose of HPV9 over HPV4 is AUS$35·99 (80% UI 28·47–41·18) with Policy1-Cervix and AUS$22·74 (15·49–34·45) with HPV-ADVISE, representing an overall range (based on median results) of AUS$22·74–35·99 (as specified, the methods for assessing uncertainty in the two models differ; figure 4). The maximum additional cost per dose would be lower if three doses rather than two are required to attain full efficacy for both vaccines (no efficacy at less than three doses; AUS$24·46 [80% UI 21·18–27·10] with Policy1-Cervix; AUS$13·09 (7·32–20·43) with HPV-ADVISE) and also if vaccine protection is 20 years rather than lifelong (AUS$26·26 [24·14–30·47] with Policy1-Cervix; AUS$13·27 [5·76–21·20] with HPV-ADVISE; figure 4). The maximum additional cost per dose is halved compared with baseline results if the incremental cost of HPV9 is applied to both girls and boys (AUS$17·99 [80% UI 14·24–20·59] with Policy1-Cervix; AUS$11·37 [7·75–17·24] with HPV-ADVISE; figure 4). The maximum additional cost per dose was likewise lower when Australian rather than Canadian disutilities were used (AUS$31·47 [80% UI 24·93–36·02] with Policy1-Cervix; AUS$22·37 [12·99–31·86] with

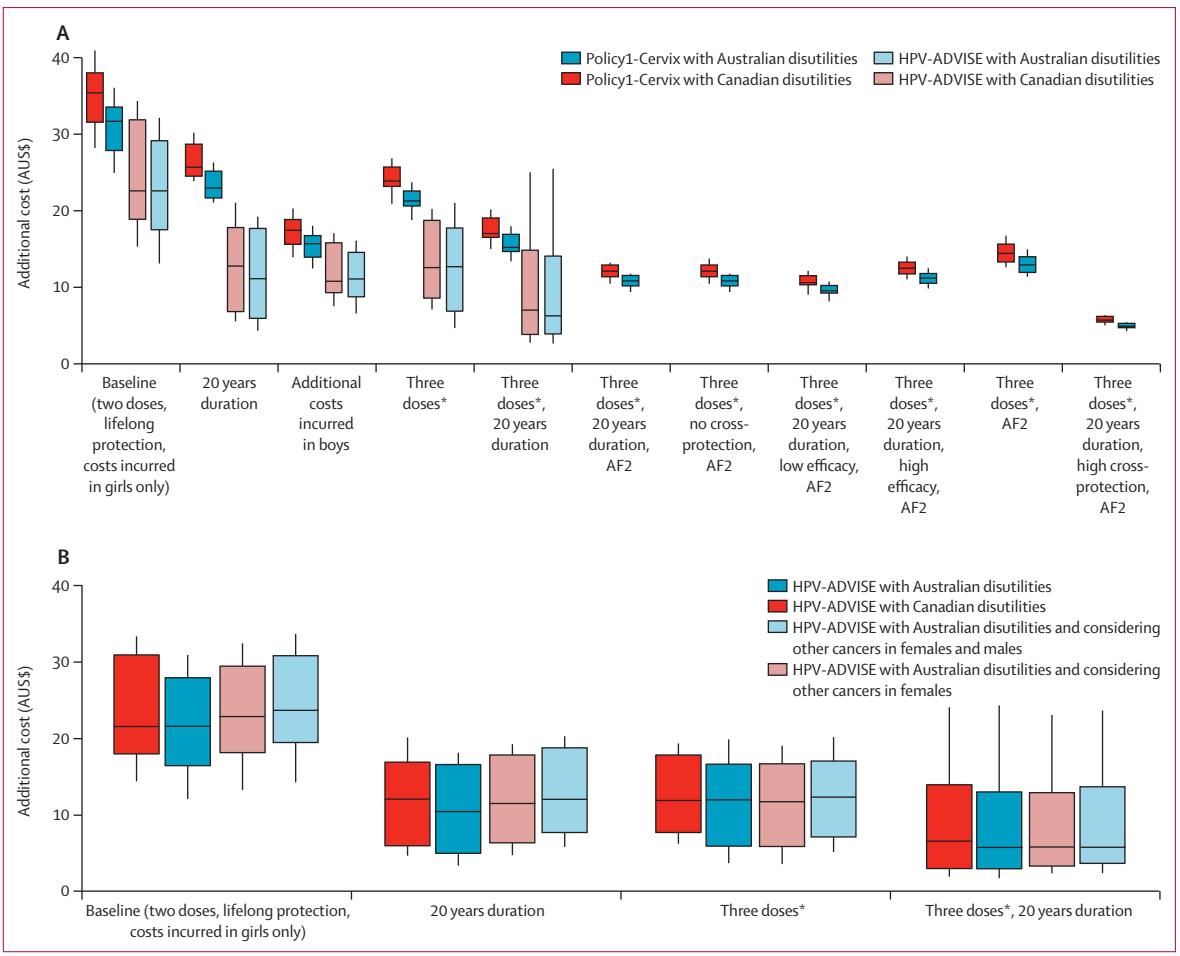

***Figure 4*: Predicted maximum additional cost per dose of nonavalent vaccine (HPV9) to remain a cost-effective alternative to quadrivalent vaccine (HPV4)**
The predicted maximum additional cost per dose of HPV9, considering (A) cervical cancer only and (B) other HPV-attributable cancers, based on a willingness-to-pay threshold of AUS$30 000 per quality adjusted life-year gained. Boundaries of each box represent the 25th and 75th percentiles, horizontal lines represent the 50th percentile, and vertical lines represent 10th to 90th percentiles. If not specified in the axis label, vaccine duration of protection is lifelong, two doses are required to achieve efficacy, costs were incurred in girls only, and attributable fractions are based on the Australian Cervical Cancer Typing study (ACCTS) study.[23] AF2=attributable fractions based on a meta-analysis.[6] *Full efficacy at three doses (no efficacy at two doses).

HPV-ADVISE), because disutilities for cervical screening are lower in the Australian set compared with Canadian disutilities (figure 4).

In sensitivity analysis, we used Policy1-Cervix to identify what the maximum additional cost per dose of HPV9 would be in the context of the current 2-yearly cytology-based programme, and found that the maximum additional cost per dose of HPV9 would be roughly AUS$1 greater than in the base case with use of Canadian disutilities, but roughly AUS$5 lower with use of Australian disutilities (appendix). We found only minor differences in the maximum additional cost per dose from Policy1-Cervix when assuming primary HPV screening according to the primary HPV screening: final guidelines rather than primary HPV screening: initial evaluation (<AUS$1 for both disutility sets; appendix). With HPV-ADVISE, we found that inclusion of other HPV-related cancers in men and women increased the maximum additional cost per dose by less than AUS$2 (appendix).

Discussion

Our findings show that, compared with the current cytology-based programme, cohorts managed under 5-yearly primary HPV screening (initial evaluation) would have an 18% reduction in lifetime risk of cervical cancer diagnosis and a 20% reduction in lifetime risk of cervical cancer death, even in the absence of vaccination. We predict a further reduction in diagnosis of 54% and in death of 53% if these cohorts are offered HPV4, or 65% and 64%, respectively, if they are offered HPV9 compared with the current cytology-based programme in unvaccinated cohorts. Therefore, the incremental effect of HPV9 (11%) will be smaller than the predicted effect of transitioning from the current 2-yearly cytology programme to the new 5-yearly primary HPV screening programme (>18%).

HPV9 will remain a cost-effective alternative to HPV4, provided the additional cost per dose remains less than AUS$23–36 and applies to girls only (or roughly half this amount if it applies to both girls and boys). The maximum additional cost per dose with HPV-ADVISE was somewhat lower than with Policy1-Cervix; however, uncertainty intervals from the two models overlapped and similar associations were observed, such as high sensitivity to assumptions around vaccine duration of protection and a higher predicted maximum additional cost per dose with Canadian versus Australian disutilities. This difference in maximum additional cost per dose under the two disutility sets is probably because there is a higher disutility associated with screening (and therefore a larger increase in QALYs gained after the switch from HPV4 to HPV9) in the Canadian set than in the Australian set. The inclusion of cancers at sites other than the cervix did not substantially affect cost-effectiveness outcomes from HPV-ADVISE, consistent with results from evaluations in other settings,[16] and is probably because a small proportion of these less common cancers are attributable to HPV types 31, 33, 45, 52, and 58.

Previous cost-effectiveness evaluations using HPV-ADVISE have found that HPV9 will remain a cost-effective alternative to HPV4 if the additional cost per dose remains less than CAN$24 in Canada (assuming HPV9 offered to girls only and vaccine protection of 20 years),[16] which is equivalent to US$19 with 2016 conversion rates, and would be cost effective in the USA if the additional cost per dose is US$13, even when assuming a gender-neutral programme.[15] The US-based study[15] also predicted that HPV4 would reduce rates of cancer diagnosis by 65% after 70 years, and that HPV9 would provide an additional reduction of 13% (when assuming lifelong vaccine protection and full efficacy at three doses), which is similar to the currently predicted reduction in a cytology-based setting (67% after HPV4 and 13% after HPV9).

The present study shows that HPV9 will remain a cost-effective alternative to HPV4 if the additional cost per dose remains less than AUS$23–36 (US$18–28), under assumptions of lifelong vaccine protection, full efficacy at two doses, and that additional costs of HPV9 would be incurred in girls only. We found that predicted health and cost-effectiveness outcomes for HPV9 are dependent on the cervical-screening background, in which the factors include age range, screening interval, technology for primary screening (cytology, HPV, or co-testing), and the management and surveillance pathways for screen-positive women. Our results are important for settings considering a change to primary HPV screening, because the cost-effectiveness of HPV9 might be dependent on the screening programme. However, because the details of primary HPV implementation are likely to vary by setting, our findings imply that a careful cost-effectiveness evaluation of HPV9 in the context of the screening protocols specific to each country should be considered; furthermore, settings that currently use HPV2 will also require careful evaluation to identify optimum pricing if switching to HPV9.

Our analysis has various strengths. Both Policy1-Cervix and HPV-ADVISE are comprehensive dynamic models of HPV transmission and cervical screening, capturing the effects of herd protection, and both models have been validated across a range of settings.[15–18,20] By necessity, we made several assumptions about future vaccine uptake and screening attendance rates; however, our assumptions are grounded in currently observed uptake data, and lower screening attendance rates were explored in probabilistic sensitivity analysis. Some differences were noted in the findings for Policy1-Cervix and HPV-ADVISE. These differences could be due to a number of factors, including differences in methods for estimating uncertainties in outcomes, the incorporation of detailed downstream management of the 2016 clinical guidelines by Policy1-Cervix, and potential differences in other previously fitted natural history parameters (eg, naturally acquired immunity to HPV infection). However, Australian-specific parameters were incorporated into both models, and HPV-ADVISE was recalibrated to match Australian cervical cancer rates in view of the current cytology-based screening programme. Furthermore, a wide range of vaccine assumptions were considered by both models, providing a thorough exploration of the potential effect of HPV9 in this setting.

Our study has some caveats. First, we assumed that cohorts previously offered HPV4 vaccination would not be revaccinated with HPV9, and that HPV9 would simply be integrated into routine vaccination of 12–13 year olds from 2017 onwards. Second, we assumed that HPV9 would be given to both boys and girls, but that incremental costs would be applied only to girls, because the direct health gains for HPV9 versus HPV4 are expected to be small in boys. This approach means that our findings are likely to be broadly relevant to countries with girls-only vaccination programmes that are also implementing or considering the implementation of primary HPV screening—eg, Italy, the Netherlands, and England.

The nonavalent vaccine has now received regulatory approval from the US Food and Drug Administration and the European Union, and some cost-effectiveness evaluations for HPV9 have been previously done.[15,17,18] However, these evaluations have all assumed that screening recommendations will remain unchanged. This study, for the first time, provides a cost-effectiveness evaluation of HPV9 in a primary HPV setting. Our results show the effect of the vaccine compared with other cervical cancer prevention changes currently underway in Australia and many other countries, and will be important when establishing the optimum price of the vaccine.

Contributors

KTS contributed to the design of the project, ran the simulation model (Policy1-Cervix), interpreted, graphed, and tabulated the results, and was responsible for write up of the document. MAS contributed to the design of the project, interpretation of the results, and critically revised the manuscript. J-BL participated in the design of the project and interpretation of results. MC contributed to configuration of the simulation model and provided technical and modelling advice throughout the project. KC conceived and oversaw the project, contributed to the study design, interpretation of results, and critically revised the manuscript. MB and J-FL did HPV-ADVISE analyses. MB and J-FL contributed to interpretation of results, critically revised the manuscript. All authors reviewed the manuscript and approved the final version.

Declaration of interests

KTS, MAS, J-BL, MC, and KC have received grants from the National Health and Medical Research Council, during the conduct of the study. KC is co-Principal Investigator of an investigator-initiated trial of cytology and primary HPV screening in Australia (Compass; ACTRN12613001207707 and NCT02328872), which is conducted and funded by the Victorian Cytology Service. The Victorian Cytology Service has received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana. KC is also a Principal Investigator of Compass in New Zealand (Compass NZ; ACTRN12614000714684), which is conducted and funded by Diagnostic Medlab, now Auckland District Health Board. Diagnostic Medlab received equipment and a funding contribution for the Compass trial from Roche Molecular Systems. Neither KC nor her institution on her behalf (Cancer Council NSW) receive direct or indirect funding from industry for Compass Australia or NZ, or any other project. MB has received unrestricted grant from Merck (for herpes zoster [project completed]). J-FL declares no competing interests.

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References

1 De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. *Int J Cancer* 2009; **124:** 1626–36.

2 Moscicki AB, Schiffman M, Burchell A, et al. Updating the natural history of human papillomavirus and anogenital cancers. *Vaccine* 2012; **30** (suppl 5)**:** F24–33.

3 Viens LJ, Hensley SJ, Watson M, et al. Human papillomavirus–associated cancers—United States, 2008–2012. *MMWR Morb Mortal Wkly Rep* 2016; **65:** 661–66.

4 Forman D, de Martel C, Lacey CJ, et al. Global burden of human papillomavirus and related diseases. *Vaccine* 2012; **30** (suppl 5)**:** F12–23.

5 Garland SM, Steben M, Sings HL, et al. Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine. *J Infect Dis* 2009; **199:** 805–14.

6 Serrano B, Alemany L, Tous S, et al. Potential impact of a nine-valent vaccine in human papillomavirus related cervical disease. *Infect Agent Cancer* 2012; **7:** 38.

7 National HPV Vaccination Program Regesiter. Coverage data. 2015. http://www.hpvregister.org.au/research/coverage-data (accessed Aug 7, 2015).

8 WHO. Comprehensive cervical cancer control—a guide to essential practice, 2nd edn. Geneva: World Health Organization, 2014.

9 European Medicines Agency. Public assessment report: Gardasil. 2014. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000703/human_med_000805.jsp (accessed May 5, 2014).

10 Public Health England, Department of Health. Human papillomavirus (HPV). In: Salisbury D, Ramsay M, eds. Immunisation against infectious diseases: the Green Book. London: Public Health England, 2014: chapter 18a. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/317821/Green_Book_Chapter_18a.pdf (accessed March 10, 2016).

11 Public Health Agency of Canada. Update on the recommended human papillomavirus (HPV) vaccine immunization schedule. Feb, 2015. http://www.phac-aspc.gc.ca/naci-ccni/acs-dcc/2015/hpv-vph_0215-eng.php (accessed Nov 7, 2016).

12 Dobson SR, McNeil S, Dionne M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents *vs* 3 doses in young women: a randomized clinical trial. *JAMA* 2013; **309:** 1793–802.

13 Weiss T, Pillsbury M, Dasbach E. Potential health and economic impact of the 9-valent HPV vaccine in the United States. International Human Papillomavirus Conference; Seattle, WA, USA; Aug 20–25, 2014. PH.OA06.04 (abstr).

14 Kiatpongsan S, Kim JJ. Costs and cost-effectiveness of 9-valent human papillomavirus (HPV) vaccination in two East African countries. *PLoS One* 2014; **9:** e106836.

15 Brisson M, Laprise J-F, Chesson HW, et al. Health and economic impact of switching from a 4-valent to a 9-valent HPV vaccination program in the United States. *J Natl Cancer Inst* 2016; **108:** djv282.

16 Drolet M, Laprise JF, Boily MC, Franco EL, Brisson M. Potential cost-effectiveness of the nonavalent human papillomavirus (HPV) vaccine. *Int J Cancer* 2014; **134:** 2264–68.

17 Kitchener HC, Canfell K, Gilham C, et al. The clinical effectiveness and cost-effectiveness of primary human papillomavirus cervical screening in England: extended follow-up of the ARTISTIC randomised trial cohort through three screening rounds. *Health Technol Assess* 2014; **18:** 1–196.

18 Lew JB, Simms K, Smith MA, et al. National cervical screening program renewal: effectiveness modelling and economic evaluation in the Australian setting (assessment report). MSAC application number 1276. Canberra: Department of Health, 2014.

19 Cancer Council Australia. Draft clinical management guidelines for the prevention of cervical cancer. 2016. http://wiki.cancer.org.au/australia/Guidelines:Cervical_cancer/Prevention (accessed Feb 18, 2016).

20 Simms KT, Smith MA, Lew JB, Kitchener HC, Castle PE, Canfell K. Will cervical screening remain cost-effective in women offered the next generation nonavalent HPV vaccine? Results for four developed countries. *Int J Cancer* 2016; **139:** 2771–80.

21 Laprise J-F, Drolet M, Boily M-C, et al. Comparing the cost-effectiveness of two- and three-dose schedules of human papillomavirus vaccination: a transmission-dynamic modelling study. *Vaccine* 2014; **32:** 5845–53.

22 National HPV Vaccination Program Regesiter. Coverage data. 2014. http://www.hpvregister.org.au/research/coverage-data (accessed May 19, 2013).

23 Tabrizi SN, Brotherton JM, Saville M, et al. The Australian cervical cancer typing study. International Human Papillomavirus Conference; Lisbon; Sept 17–21, 2015.

24 Department of Health and Ageing and enHealth Council. Guidelines for economic evaluation of environmental health planning and assessment. Canberra: Australian Government Department of Health and Ageing, 2003.

25 Simonella L, Howard K, Canfell K. A survey of population-based utility scores for cervical cancer prevention. *BMC Res Notes* 2014; **7:** 899.

26 Drolet M, Brisson M, Maunsell E, et al. The psychosocial impact of an abnormal cervical smear result. *Psychooncology* 2012; **21:** 1071–81.

27 The Pharmaceutical Benefits Scheme. Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine, injection, 0.5 mL, Gardasil. November, 2006. http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2006-11/pbac-psd-gardasil-nov06 (accessed April 26, 2016).

28 Metcalf CJE, Edmunds WJ, Lessler J. Six challenges in modelling for public health policy. *Epidemics* 2015; **10:** 93–96.

29 Chesson HW, Laprise J-F, Brisson M, Markowitz LE. The impact and cost-effectiveness of 3 doses of 9-Valent human papillomavirus (HPV) vaccine among US females previously vaccinated with 4-valent HPV vaccine. *J Infect Dis* 2016: **213:** 1694–700.

30 Reserve Bank of Australia. Historical data. http://www.rba.gov.au/statistics/historical-data.html (accessed Oct 27, 2016).

31 Australian Institute of Health and Welfare. Australian Cancer Incidence and Mortality (ACIM) books. http://www.aihw.gov.au/acim-books/ (accessed July 27, 2016).