Primary HPV testing versus cytology-based cervical screening in women in Australia vaccinated for HPV and unvaccinated: effectiveness and economic assessment for the National Cervical Screening Program

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Summary

Background **Australia's National Cervical Screening Program currently recommends cytological screening every 2 years for women aged 18–69 years. Human papillomavirus (HPV) vaccination was implemented in 2007 with high population coverage, and falls in high-grade lesions in young women have been reported extensively. This decline prompted a major review of the National Cervical Screening Program and new clinical management guidelines, for which we undertook this analysis.**

Methods **We did effectiveness modelling and an economic assessment of potential new screening strategies, using a model of HPV transmission, vaccination, natural history, and cervical screening. First, we evaluated 132 screening strategies, including those based on cytology and primary HPV testing. Second, after a recommendation was made to adopt primary HPV screening with partial genotyping and direct referral to colposcopy of women positive for HPV16/18, we evaluated the final effect of HPV screening after incorporating new clinical guidelines for women positive for HPV. Both evaluations considered both unvaccinated and vaccinated cohorts.**

Findings **Strategies entailing HPV testing every 5 years and either partial genotyping for HPV16/18 or cytological co-testing were the most effective. One of the most effective and cost-effective strategies comprised primary HPV screening with referral of women positive for oncogenic HPV16/18 direct to colposcopy, with reflex cytological triage for women with other oncogenic types and direct referral for those in this group with high-grade cytological findings. After incorporating detailed clinical guidelines recommendations, this strategy is predicted to reduce cervical cancer incidence and mortality by 31% and 36%, respectively, in unvaccinated cohorts, and by 24% and 29%, respectively, in cohorts offered vaccination. Furthermore, this strategy is predicted to reduce costs by up to 19% for unvaccinated cohorts and 26% for cohorts offered vaccination, compared with the current programme.**

Interpretation **Primary HPV screening every 5 years with partial genotyping is predicted to be substantially more effective and potentially cost-saving compared with the current cytology-based screening programme undertaken every 2 years. These findings underpin the decision to transition to primary HPV screening with partial genotyping in the Australian National Cervical Screening Program, which will occur in May, 2017.**

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Introduction

Australia was one of the first countries to implement a national, publicly funded, human papillomavirus (HPV) vaccination programme. Administration of the quadrivalent vaccine (Gardasil; CSL, Parkville, VIC, Australia) commenced in April, 2007, and entailed a catch-up programme for adolescent girls and young women aged 12–26 years until the end of 2009. Three-dose coverage of girls aged 12–13 years in 2013 was 79%,[1] and coverage in the catch-up cohorts reached 53–70%.[2,3] By 2016, women aged 35 years or younger had been offered the HPV vaccine. In 2013, HPV vaccination was extended to boys aged 12–13 years, with a 2-year catch-up until age 14–15 years. A rapid fall in HPV prevalence in vaccinated females has been reported, and a decline has also been noted in unvaccinated females (due to herd immunity).[4] Reductions have also been observed in anogenital warts[5] and high-grade histological findings[6] in younger females.

The Australian National Cervical Screening Program currently recommends conventional cytology every 2 years for sexually active women aged between 18–20 years and 69 years. The proportion of women participating in the screening programme is 58% over 2 years and 83% over 5 years.[7] The annual cost of the National Cervical Screening Program was estimated to

Research in context

Evidence before this study

We did a literature search of the UK National Health Service Economic Evaluation Database (NHS EED), Medline, and Embase between January, 2008, and June–July, 2013, to identify published economic evaluations of cervical screening strategies. The search terms we used are listed in the appendix (p 65). With our literature review, we identified a few modelling or health economic studies in which human papillomavirus (HPV) DNA testing was evaluated as the primary method of cervical screening, in both vaccinated and unvaccinated women. However, assessment of a range of approaches to primary HPV screening, including partial genotyping versus triaging all oncogenic types with cytology, or co-testing all women with cytology and HPV testing, has not been done previously.

Added value of this study

We evaluated the effectiveness, resource utilisation, and cost-effectiveness of 132 screening strategies and did a detailed model simulation of management pathways including primary screening, triage testing, surveillance, colposcopy referral, and management, treatment, and post-treatment surveillance. In our initial evaluation, we found that primary HPV testing strategies are more effective than cytology-based screening. Specifically, a strategy of primary HPV screening every 5 years, with partial genotyping and direct referral to colposcopy for women positive for HPV16/18, and liquid-based cytology triage for women who test positive for oncogenic HPV other than HPV16/18, aged 25–69 years with an exit test at age 70–74 years, is highly effective for cervical screening in unvaccinated and vaccinated cohorts. Based on this initial evaluation, we recommended that Australia transition to primary HPV screening. After development of detailed clinical management guidelines for HPV screening and management of women in the screening programme, these final management pathways were incorporated into the modelling platform and we obtained updated model predictions. We found that the renewed Australian National Cervical Screening Program will reduce cervical cancer incidence and mortality and is cost-saving when compared with the current programme.

Implications of all the available evidence

The findings of our study have underpinned the decision to transition in Australia from conventional cytology screening every 2 years to primary HPV screening every 5 years, in May, 2017. Taken together with evidence from international studies, including findings of a subsequent reanalysis of four European trials, published after we began our study, in which better protection was shown against invasive cervical cancer in women who underwent HPV screening versus those who had cytological analysis, our findings support the upcoming national implementation of primary HPV DNA screening in both unvaccinated women and in those who have been offered HPV vaccination.

be AUS$194·8 million in 2010 (roughly $23 per woman).[8] After implementation of the National Cervical Screening Program in 1991, incidence of cervical cancer declined by 36%, and mortality by 44%, by the mid-2000s.[9] Since then, incidence and mortality in Australia seem to have stabilised,[7] most likely because of difficulties with screening all eligible women and limitations in the performance of cytology, particularly in relation to the detection of glandular lesions.

In recent years, primary HPV testing has been evaluated extensively as a cervical screening approach. Evidence from randomised controlled trials[10–13] has shown the increased effectiveness of HPV DNA testing compared with cytology-based screening. Furthermore, findings of several longitudinal observational studies[13–16] have shown a lower risk of subsequent high-grade cervical intraepithelial neoplasia in women testing negative for HPV oncotypes, compared with those negative for cytology. In a pooled analysis of four randomised controlled trials,[10] HPV-based screening was reported to increase protection significantly against the development of invasive cervical cancer, compared with cytology-based screening.

On the basis of this mounting evidence, several countries are considering HPV testing as the primary method of population-based screening for cervical cancer. In Australia, the emergent evidence on HPV screening in conjunction with the introduction of HPV vaccination, and the comparatively longer screening intervals and narrower age range for screening recommended by the International Agency for Research on Cancer (IARC),[17] prompted a major review of the National Cervical Screening Program (referred to as "Renewal"). The aim of the renewal process was to ensure that Australia continues to have a successful screening programme that is acceptable, effective, efficient, and based on current evidence, for all women, whether vaccinated against HPV or not.

As an initial evaluation of screening options, the Australian Government's Medical Services Advisory Committee (MSAC) commissioned a systematic review of the international evidence[18] and a modelled assessment of health outcomes, resource utilisation, and costs for various screening strategies, both in unvaccinated cohorts and in cohorts offered vaccination.[19] Based on this evaluation and literature review, MSAC recommended in 2014 a new screening approach for the renewed National Cervical Screening Program. This initial recommendation outlined the suggested primary test technology, immediate follow-up recommendations for women testing positive, and the screening interval and age range, but made no further

recommendations about surveillance, colposcopy, and post-colposcopy management. Therefore, a subsequent evaluation, which incorporated newly developed detailed clinical management guidelines for the HPV-based screening programme, was conducted in 2015.

Here, we aim to first present the initial evaluation of screening options, in which screening technology (conventional cytology, liquid-based cytology, HPV testing), screening interval, and age range were considered. Second, we aim to present the updated evaluation of outcomes and cost-effectiveness of the selected screening approach recommended by MSAC in 2014, after incorporating new clinical management guidelines based on HPV screening with partial genotyping.

Methods

Model platform and data sources

For this study, we used a dynamic model of HPV transmission and vaccination (implemented in Microsoft Visual Studio C++ Community 2013), coupled with a deterministic multi-cohort Markov model (implemented using TreeAge Pro 2014; TreeAge Software, Williamstown, MA, USA) of the natural history of cervical intraepithelial neoplasia, cervical screening, and invasive cervical cancer survival (appendix p 4). The model incorporates Australian-specific demographic and health-economic factors as well as test accuracy, screening compliance, vaccination coverage and screening, and diagnosis and treatment-related costs. We did an extensive validation of the model against many screening outputs. A detailed description of the model used in this study, its development, parameterisation, data sources, calibration, and validation outcomes, has been described elsewhere (appendix pp 1, 5–11, 20, 64, 65).[19,20] This model platform has been used previously for several HPV vaccination and cervical screening evaluations in Australia, New Zealand, England, and the USA.[19–23]

Evaluation of screening options

We did the initial evaluation of screening options under the overarching guidance of an expert committee—the Renewal Steering Committee—according to a Decision Analytic Protocol prespecified by the Protocol Advisory Subcommittee of MSAC. A summary of the broad approaches specified in the protocol are detailed in the appendix (pp 1–3).[24] MSAC considered the findings of this evaluation together with evidence from a systematic review of the literature and provided subsequent recommendations to the Australian Minister of Health.

For each strategy, the model simulated a cohort of women from age 10 years to age 84 years, who were 12 years old in 2009, with and without vaccination. The comparator was the current National Cervical Screening Program in Australia (every 2 years, conventional cytology, in women aged 18–69 years, no HPV triage testing). All alternative strategies initially entailed an evaluation of screening in women aged 25–64 years, as specified in the Decision Analytic Protocol, taking into account evidence that screening in women younger than 25 years does not substantially reduce cervical cancer rates in women younger than 30 years.[25] However, we did a subsequent evaluation of retaining a screening end-age of 69 years after interim results became available and were considered by the Renewal Steering Committee. We evaluated six primary screening approaches (appendix pp 14–17). First, we looked at conventional cytology at IARC intervals—ie, every 3 years for ages 25–49 years and every 5 years for ages 50–64 years.[17] Second, we evaluated manually read liquid-based cytology at IARC intervals, with or without HPV triage of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion cases. Third, we assessed image-read liquid-based cytology at IARC intervals, with or without HPV triage of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion. Fourth, we investigated primary HPV testing at intervals every 5 years and liquid-based cytology triaging of all oncogenic HPV-positive women. Fifth, we evaluated primary HPV testing, at intervals every 5 years, with partial genotyping for HPV types 16/18 and liquid-based cytology triage of other HPV types. Finally, we looked at co-testing of all screened women with both liquid-based cytology and HPV testing, at intervals every 5 years.

See Online for appendix

The Renewal Steering Committee established preliminary clinical management algorithms for each screening approach. We considered several variations for each approach. First, we looked at alternate management options for women infected with HPV oncotypes other than 16/18 and cytological findings of low-grade squamous intraepithelial lesions or atypical squamous cells of undetermined significance (women at intermediate risk). Second, we considered the behavioural (screening adherence) effect of a call-and-recall invitation combined with a reminder system versus a reminder-based system. Third, we considered initiation with faster uptake (the invitation for screening initiation sent on the woman's 25th birthday) versus slower uptake (no active invitation sent). Finally, we looked at whether an HPV test was offered specifically as an exit test at the end of the recommended screening age (exit HPV test), in which case a more aggressive management for this last test was assumed, in that all HPV-positive women would be referred to colposcopy (and HPV-negative women were assumed to be discharged from screening). For our evaluation, we assumed that no screening occurs in women younger than 25 years. We did each cost and effectiveness calculation for each possible variation within each of the six primary screening approaches. We then did additional analyses for all screening strategies to ascertain the effect of retaining an end-age of 69 years and of extending HPV testing intervals from every 5 years to every 6 years. We assessed 132 specific screening strategies, in unvaccinated women and in those offered vaccination.

For the **Decision Analytic Protocol** see http://www.msac.gov.au/internet/msac/publishing.nsf/Content/D924E2F768B13C4BCA25801000123B9E/$File/1276-NCSP-FinalDAP.pdf

For each screening strategy, we considered several outcomes: health outcomes; costs; use of resources, including HPV DNA tests, cytology tests, colposcopies, treatment for precancerous lesions, and the proportion of treatments for cervical intraepithelial neoplasia grade 3 (CIN3) compared with cervical intraepithelial neoplasia grade 2 (CIN2), which is a measure of more targeted treatment (CIN2 is known to be histologically heterogeneous, with some cases more comparable with CIN3, and others with cervical intraepithelial neoplasia grade 1 [CIN1]); and the relation between health outcomes and resource utilisation. We calculated annual cross-sectional estimates for these outcomes based on outcomes from the cohort model, age-weighted to the female population in 2015. We did the evaluation from a health services perspective. We calculated costs and life-years over a woman's lifetime with a 5% discount rate, as per the standard approach for health technology assessment in Australia.

A brief summary of modelled screening participation rates, test accuracy rates, natural history, vaccination coverage, and cost assumptions are provided in the appendix (pp 6–13).[19,21,26,27] We did one-way and probabilistic sensitivity analyses on selected strategies to assess the effect of changes in selected model assumptions on the findings (appendix pp 7–10, 64, 65).

Evaluation of management options for the new clinical management guidelines

Based on assessment of the evaluation described above, MSAC recommended one primary screening approach for the National Cervical Screening Program (figure 1) but did not specify the detailed clinical management of HPV-positive women nor detailed colposcopy or post-colposcopy management strategies for the new screening programme. Therefore, detailed clinical management guidelines were developed in 2015–16 to support the new HPV programme. An expert working party was convened to assess current evidence (and results from modelling in the absence of sufficient evidence in published literature) for different management options. The overall methodology for guidelines development is described elsewhere.[28] Based on the evidence, the working party developed new clinical management guidelines,[28] which were incorporated into the modelling platform. Using this updated model, we made revised predictions for health outcomes, resource utilisation, and the cost-effectiveness of the renewed National Cervical Screening Program. Details of changes incorporated in the final modelled guidelines evaluation are in the appendix (pp 18, 19).

Data sources and consent

Our study was a modelled evaluation. We used data from the Victorian Cervical Cytology Register and the Royal Women's Hospital to inform model parameters. All datasets used in this modelled evaluation were de-identified and, therefore, we did not obtain direct consent from participants. The Cancer Council NSW human research ethics committee (EC00345) approved the transfer of these data to the researchers. Ethics approval for the use and analysis of these datasets to inform the model was provided by the Cancer Council NSW ethics committee (references 232, 236) and by the University of New South Wales human research ethics committee (references HC13270, HC13349).

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

Role of the funding source

The funder had no role in study design, data collection, or data analysis. The Australian Government's MSAC's Protocol Advisory Subcommittee (on which KC sits)—developed the Decision Analytic Protocol for the original analysis. The funder was an observer at meetings of advisory committees (eg, meetings of the MSAC, the Renewal Steering Committee, and the Cancer Council Australia cervical cancer screening guidelines working party). TB represents the funder and contributed to writing of the final report. J-BL, KTS, MAS, KC, MC, XMX, LSV, and Y-JK had access to raw data. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Predicted age-specific cancer incidence and mortality for selected strategies, which were among the most effective for each primary screening approach, are shown in figure 2. If screening ends at age 64 years (figure 2A, 2B), strategies entailing conventional cytology at IARC intervals result in increased incidence of cervical cancer in women of all ages compared with current practice. Strategies including liquid-based cytology with HPV triage testing generally decrease incidence in women aged 30–69 years. Primary HPV screening approaches were the most effective. These relative relations between the effectiveness of the different primary screening approaches were similar for incidence and mortality, and for unvaccinated cohorts and cohorts offered vaccination.

The estimated cost of the existing National Cervical Screening Program in 2015 was $215 million. Almost all screening strategies were less costly than current practice and many were also more effective, in both unvaccinated and vaccinated cohorts (figure 3). Conventional cytology-based strategies were less costly than current practice but were also less effective. Strategies including liquid-based cytology could be more effective than current practice (given favourable assumptions for test characteristics),[19] although this possibility generally required HPV triage of atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesions. Primary HPV screening approaches with or without partial genotyping were among the most effective and least costly strategies.

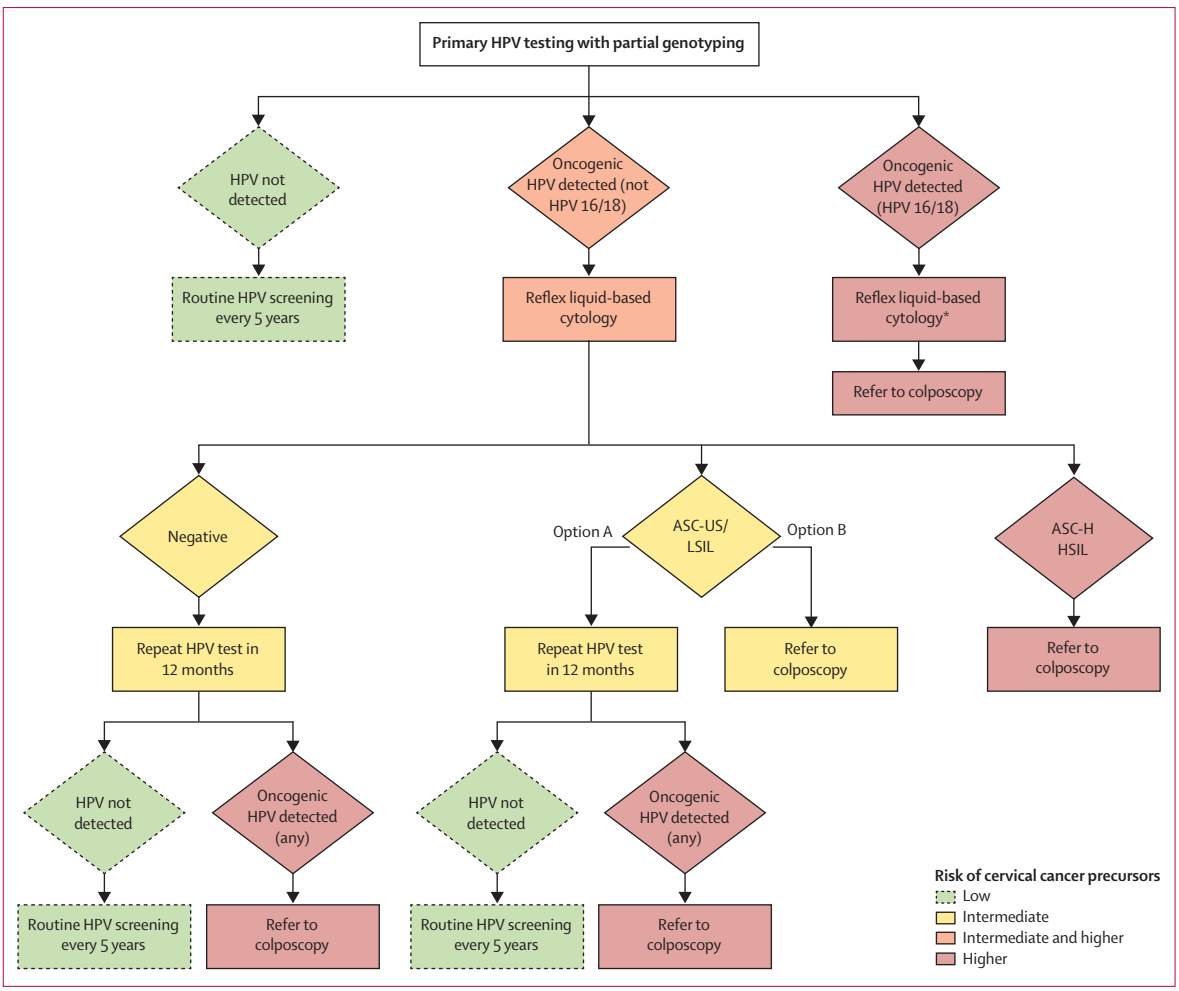


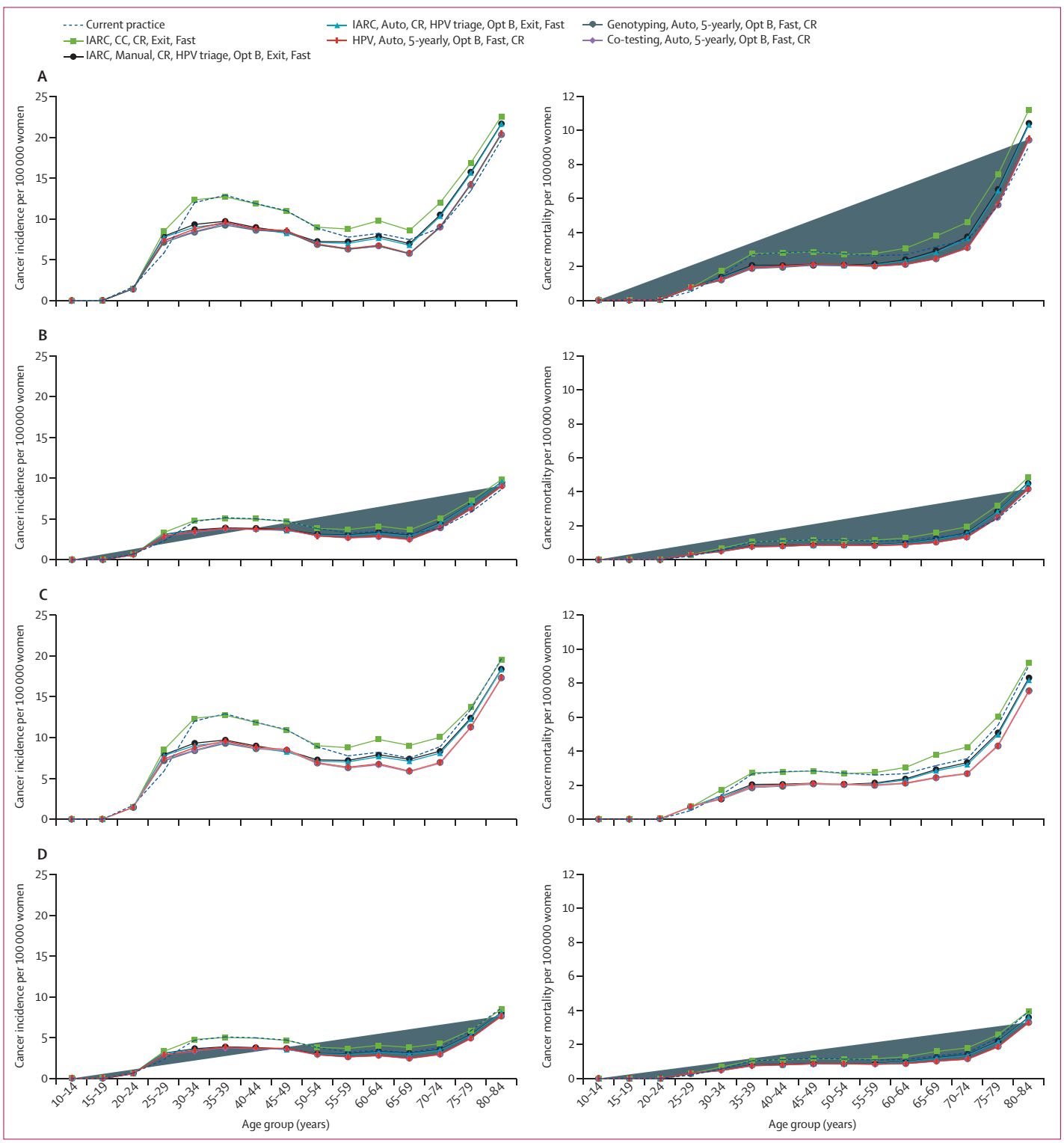
Figure 1: **Schematic diagram of primary screening approach**
ASC-H=atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion. ASC-US=atypical squamous cells of undetermined significance. HPV=human papillomavirus. HSIL=high-grade squamous intraepithelial lesion as predicted by cytology. LSIL=low-grade squamous intraepithelial lesion as predicted by cytology. *To assist with management decisions at colposcopy, not to determine whether to refer to colposcopy.

Several approaches were predicted to increase the number of colposcopies compared with current practice. Figure 4 shows the annual number of colposcopies corresponding to each of the primary screening approaches. In unvaccinated cohorts, HPV strategies with partial genotyping and co-testing were associated with the largest increase in colposcopies. By contrast, in the cohorts offered vaccination, the number of colposcopies in the long term is predicted to be lower than current practice for all liquid-based cytology and HPV strategies (except co-testing).

All strategies were associated with further reductions in screening tests, follow-up tests, and precancer treatments compared with current practice (appendix pp 21, 22). The largest declines were noted for strategies entailing primary HPV screening with partial genotyping, resulting in decreases of 45–51% in the average lifetime number of screening tests (predicted seven or eight screening tests per lifetime compared with a predicted 15 tests per lifetime under current practice) and reductions of 8–17% and 16–29% in treatments in unvaccinated cohorts and cohorts offered vaccination, respectively. For several of the strategies evaluated, a substantial increase was also seen in the relative proportion of treatments that were for CIN3 versus treatments for CIN2 when compared with current practice (appendix pp 23, 24). For HPV screening strategies, the CIN2 proportion was predicted to decrease to 30–36% (unvaccinated) and 31–39% (vaccinated). The CIN2 proportion under current practice was 40% (unvaccinated) and 44% (vaccinated).

Some other strategy variations affected results. Those in which an invitation was sent at age 25 years further reduced overall mortality by an additional 1–3% relative to the same strategy without an active invitation at age 25 years (appendix p 25). Immediate follow-up of women

who were triage-positive was more effective than follow-up at 12 months (appendix pp 27, 28). However, for the HPV-based strategies entailing partial genotyping, this difference was very small, with about 1–4% difference in incidence and mortality between immediate colposcopy versus 12-month follow-up strategies entailing partial genotyping, compared with a difference of 3–10% for other strategy types (appendix pp 27, 28).



This finding suggests that, within the group of women who are HPV-positive and with low-grade cytology, gains in effectiveness from immediate colposcopy are being driven by the subgroup of women who are positive for HPV16/18, and if these women are already referred for colposcopy (as in the strategies entailing partial genotyping), those with low-grade cytology and other oncogenic HPV types can be managed via surveillance.

Further analyses were done to assess the effect of retaining a screening end-age of 69 years, for all strategies (appendix pp 34, 63). The predicted age-specific incidence and mortality for selected strategies, which were among the most effective for each primary approach, are shown in figure 2 (C, D). Overall, screening until age 69 years was associated with a 5–8% reduction in cancer mortality (age-standardised rate) when compared with screening until age 64 years. For strategies entailing HPV testing with partial genotyping, screening until age 69 years was predicted to result in an overall decrease in incidence and mortality of 13–23% compared with current practice, considering both unvaccinated cohorts and cohorts offered vaccination.

Extending the screening interval to 6 years for HPV screening strategies is predicted to increase incidence by 3–4% for both unvaccinated and vaccinated cohorts, relative to the same strategy with screening every 5 years. Results were similar for mortality. A further 8–10% decrease in programme costs was predicted for an interval every 6 years compared with every 5 years (appendix pp 29, 30).

A one-way sensitivity analysis of key variables was done (appendix pp 56–60). The relative effectiveness of the new strategies compared with current practice was most sensitive to assumptions around adherence to the recommended screening interval and follow-up recommendations, test characteristics, natural history of cervical intraepithelial neoplasia, and discount rate (as used for calculating discounted life-years and discounted costs for cost-effectiveness). Relative costs were also sensitive to these assumptions, and to test costs. Probabilistic sensitivity analysis showed that all new extended-interval strategies entailing conventional cytology remained less effective than current practice under a broad range of assumptions (appendix pp 31–33, 62). Selected strategies including manually read and image-read liquid-based cytology, which were more effective than current practice in the base case, remained more effective on probabilistic sensitivity analysis, although several model runs entailing sets of plausible assumptions for these approaches resulted in an increase in cost compared with current practice. The selected HPV strategies examined also remained more effective than current practice on probabilistic sensitivity analysis; however, some model runs for these strategies also showed a rise in costs compared with current practice (appendix p 62). Detailed discounted cost and life-years outcomes are provided in the appendix (pp 36–55) for all scenarios.

Based on the initial evaluation, the strategy recommended by MSAC for the renewed National Cervical

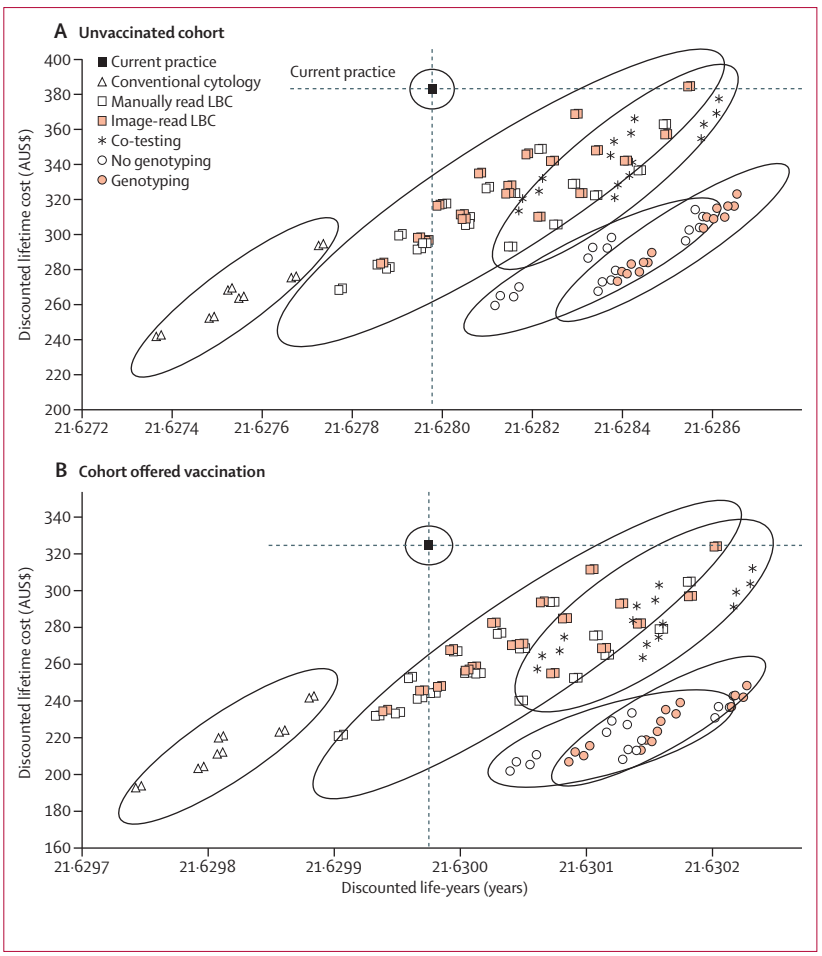


Figure 3: **Cost-effectiveness of screening strategies compared with current practice with screening ending at age 64 years**
The ovals represent clusters of strategies with the same, or very similar, primary screening approaches. LBC=liquid-based cytology.

Figure 2: **Predicted age-specific cancer incidence and mortality for selected strategies**
Each square represents the mean incidence or mortality for a particular 5-year age range. (A) An unvaccinated cohort, all except current practice ending screening at age 64 years. (B) A cohort offered vaccination, all except current practice ending screening at age 64 years. (C) An unvaccinated cohort, ending screening at age 69 years. (D) A cohort offered vaccination, ending screening at age 69 years. Auto=image-read liquid-based cytology. CC=conventional cytology. CR=set of screening adherence assumptions assuming a call-and-recall programme (proactive invitation). Alternative assumptions were also assessed for the effect of call-and-recall on screening adherence for each primary screening approach (appendix pp 9, 21, 29–33). Exit=HPV exit testing for women leaving the programme. Fast=women receive an invitation to attend their first cervical screen. HPV=human papillomavirus. IARC=IARC recommended screening age and interval. Manual=manually read liquid-based cytology. Opt B=direct colposcopy referral for women with low-grade cytology and testing HPV-positive with reflex HPV triage or under primary HPV screening, women testing HPV-positive and reflex cytology low-grade (or HPV-positive for types other than 16/18 and reflex cytology low-grade under primary HPV screening strategies utilising partial genotyping).

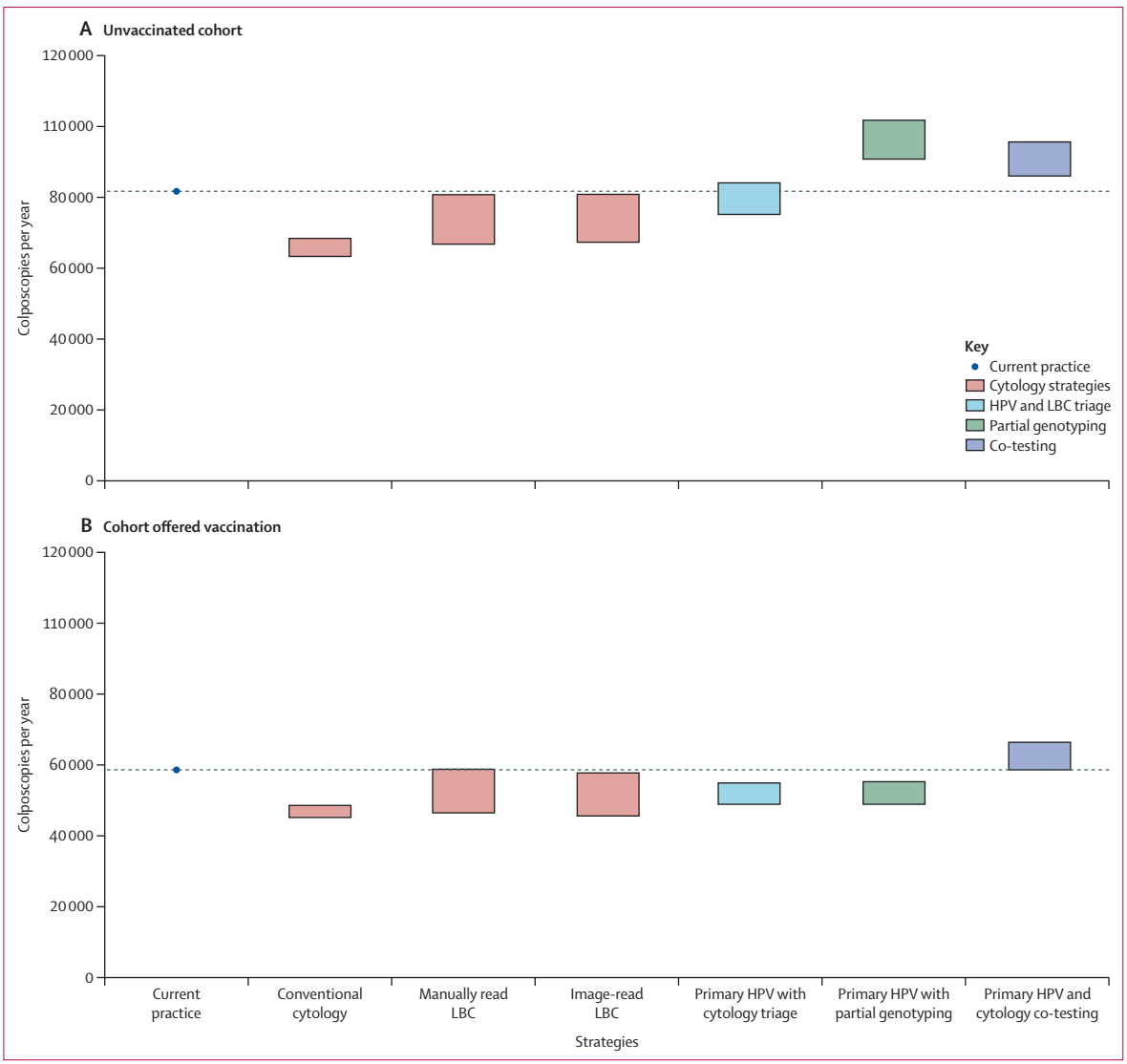


Figure 4: **Annual number of colposcopies for each primary screening approach with screening ending at age 64 years**
Bars represent the range between minimum value and maximum value estimated for variants of each primary screening approach. The number of colposcopies per year was calculated by applying the steady-state rates to the projected female Australian population in 2015. HPV=human papillomavirus. LBC=liquid-based cytology.

Screening Program was primary HPV screening with partial genotyping every 5 years for women aged 25–69 years, an exit test at age 70–74 years, and liquid-based cytology triage for women who test positive for oncogenic HPV types other than 16/18 (figure 1). As a result of recommendations made for clinical management guidelines to support the new programme, several updates were needed to the model platform. One key area in which changes were made was the assumed management for women positive for oncogenic HPV types other than 16/18 and low-grade cytology. A separate modelled evaluation focused on this specific issue.[29] The recommendation for guidelines was that these women should be referred for 12-month surveillance; if they were HPV-positive at 12 months they should be referred to colposcopy and if they were HPV-negative at 12 months they should be discharged to routine screening (figure 1). However, many other changes to existing management recommendations were made as part of the guidelines process. The incremental effect of each of these changes to the predicted outcomes is summarised in the appendix (p 35). Changes in post-colposcopy management, extension of screening end-age, and colposcopy compliance assumptions (ie, how many women would attend colposcopy follow-up) contributed to the overall difference in predictions between the initial evaluation and the final guidelines evaluation.

After incorporating the new clinical management guidelines, a 31–36% long-term reduction in incidence and mortality compared with current practice was

	Current practice		HPV: final guidelines*	
	If HPV vaccination had not been introduced	Cohort offered vaccination at age 12 years	If HPV vaccination had not been introduced	Cohort offered vaccination at age 12 years
Cervical cancer incidence†	6·92	2·87	4·73 (–31%)	2·17 (–24%)
Cervical cancer mortality†	1·80	0·74	1·15 (–36%)	0·53 (–29%)
Cervical cancer cases (n)‡	850	353	584 (–265; –31%)	267 (–85; –24%)
Cervical cancer deaths (n)‡	227	94	145 (–82;–36%)	66 (–28;–29%)
Colposcopies (n)‡	85 795	60 995	116 889 (31 094; 36%)	56 479 (–4516; –7%)
Treatments (n)‡	22 661	13 899	23 963 (1302; 6%)	13 240 (–659; –5%)
Annual cost† of screening programme (AUS$)	$223 million	$192 million	$182 million (–41 million; –19%)	$142 million (–50 million; –26%)
Average discounted cost per woman‡ (AUS$)	$383	$325	$304	$227
Average discounted life-year per woman§	21·6219	21·6239	21·6229	21·6242

Effects predicted from the initial evaluation model and the final guidelines model (differences compared with current practice shown in parentheses). Presented case numbers are rounded to the nearest integer; the difference in case numbers between current practice and final guidelines are calculated using unrounded values and, therefore, might not match calculations using the rounded values presented here. HPV=human papillomavirus. *Case numbers for the strategy "HPV: final guidelines" were calculated by applying the steady-state rates to the 2017 population and, therefore, assumes that women have been managed under the HPV-based programme for their entire lives. When the transition from cytology every 2 years to HPV screening every 5 years occurs in 2017, fluctuations in outcomes are likely to occur for several years before reaching steady-state. Therefore, predictions shown for the year 2017 are illustrative only, and do not represent actual predictions for this year. †Age-standardised rate (0–84 years), standardised to the 2001 Australian population and represented per 100 000 women. ‡Using the female Australian population as predicted for 2017. §Discounting at 5%.

Table: **Predicted incidence of cervical cancer and mortality, number of colposcopies and treatments for cervical intraepithelial neoplasia grades 2 and 3, and annual and discounted costs of the programme**

predicted in unvaccinated cohorts, corresponding to 265 fewer cases of cancer and 82 fewer deaths if steady-state rates are applied to the projected female Australian population in 2017 (table). Similarly, in cohorts offered vaccination, a 24–29% reduction in incidence and mortality was predicted (85 fewer cancer cases and 28 fewer deaths if steady-state rates are applied to the projected female Australian population in 2017).

When compared with current practice, for the renewed National Cervical Screening Program, a 36% long-term increase in the number of colposcopies would have occurred in unvaccinated women (after a transition period), by contrast with a 7% decrease for cohorts offered vaccination (table). In terms of treatments, over the longer term, a 6% increase would be predicted in unvaccinated cohorts but a 5% decrease in treatments is predicted in cohorts offered vaccination.

In the absence of HPV vaccination, the renewed National Cervical Screening Program was predicted to result in a 19% reduction in costs, equivalent to annual cost-savings of $41 million if steady-state rates are applied to the projected female Australian population in 2017 (table). For cohorts offered vaccination, this cost-saving was estimated at $50 million, and a 26% reduction compared with the current programme.

Discussion

We report a comprehensive modelled assessment of the effectiveness, resource utilisation, and cost-effectiveness of several cervical screening approaches in the context of the National HPV Vaccination Program in Australia. We implemented a detailed simulation of all management pathways, from primary screening and triage, surveillance, colposcopy referral, and management, treatment, and post-treatment surveillance. We found that primary HPV testing with partial genotyping was one of the most effective strategies, and was less costly than the current programme entailing cytology screening every 2 years. Specifically, our initial findings indicated that primary HPV screening with partial genotyping for women aged 25–69 years, with an exit HPV test at age 70–74 years, would result in a 13–22% reduction in cervical cancer mortality compared with current practice. These findings underpinned the 2014 recommendation by MSAC to replace the current conventional cytology test every 2 years with primary HPV screening and partial genotyping every 5 years. In August, 2014, the Australian Health Ministers' Advisory Council endorsed the recommendation and, in March, 2015, they approved the draft policy for the renewal of the National Cervical Screening Program.[30] In June, 2015, the Department of Health commissioned the development of clinical management guidelines, which were used to undertake a more detailed evaluation of the renewed National Cervical Screening Program.[28] After incorporating management as specified in these guidelines, substantial improvements in incidence and mortality of at least 24% and up to 36% are predicted, compared with current screening practice, and a cost-saving of up to 26%.

Our analysis has some limitations. First, as with every modelled evaluation, our findings are sensitive to specific assumptions—eg, unknown future adherence to

screening behaviours, and test characteristics. However, our model has been calibrated extensively and data from a meta-analysis were used for test characteristics, which were also fitted to observed rates of cytology test outcomes at a population level in Australia. Furthermore, extensive one-way and probabilistic sensitivity analyses of a range of assumptions were done; findings of the sensitivity analysis indicated that strategies entailing partial genotyping, which were more effective than current practice, remained more effective. As previously reported, we used modelling to inform the management of women with low-grade cytology who are positive for oncogenic HPV other than 16/18,[29] but little evidence was available to validate our predicted outcomes in this group. No directly relevant data are available from randomised trials that compare the management of these women for immediate colposcopy referral with 12-month follow-up and re-testing for HPV, and little other evidence is available to inform the assessment of risk in this group.[29] The Compass trial (NCT02328872)—a randomised controlled trial of HPV-based screening every 5 years versus liquid-based cytology screening every 2·5 years—is currently underway in Australia and will provide relevant data for this group and more broadly for primary HPV screening. Compass is acting as a sentinel experience of the renewed National Cervical Screening Program in Australia.

The second limitation is that we did not account for cross-protection against non-vaccine targeted HPV types. Although some evidence shows that HPV vaccines provide a degree of cross-protection against HPV types 31, 33, 45, and 58, their quantitative effect has yet to be defined, and the long-term duration of cross-protection has not been determined.[31,32] A third limitation is that our predicted cost-savings might not be fully realised, because they are based on the assumption that the overall number of primary care visits will fall because of the reduced number of screening visits. In practice, these screening visits might be replaced by routine visits for other conditions, with no obvious reduction in visit costs to the health system.

Our evaluation has several strengths. We used an extensively calibrated modelling platform to assess cervical screening strategies in both vaccinated and unvaccinated cohorts, did an analysis of many screening strategies, and undertook an extensive sensitivity analysis. However, the outcomes presented here represent long-term predictions. After the switch from current screening practice to the renewed National Cervical Screening Program, there will be a transitional period (three or more screening cycles) during which fluctuations in resource utilisation will occur because of the transition to the longer screening interval. To complement the major evaluation reported here, and to provide practical information at the health services level, we previously modelled the transition in more detail to estimate the effect on volumes of women screened and resource utilisation during the initial screening rounds.[20] We found that the number of HPV tests, precancer treatment procedures, and colposcopies will fluctuate in the first few screening rounds but that HPV vaccination will reduce the fluctuations to some extent.[20]

Our aim was to identify a screening strategy that was effective and cost-effective in both unvaccinated women and in cohorts offered vaccination. We assumed that information about vaccination status and efficacy—ie, whether a woman had been vaccinated, vaccination age, whether all doses were received, and whether vaccination was done before sexual debut—was not available at the woman's screening visit; however, if this information could be available, which might be possible in a few settings, less intensive screening recommendations could be made for women who were vaccinated before sexual debut, since these women are at a lower lifetime risk of cervical cancer than unvaccinated women. Cervical screening will probably need further re-evaluation for future cohorts offered a next-generation nonavalent HPV vaccine, which protects against seven oncogenic subtypes of HPV that cause about 90% of invasive cervical cancers worldwide. In our evaluation of the cost-effectiveness of cervical screening in cohorts offered next-generation vaccine in four high-income countries (Australia, the USA, New Zealand, and England),[23] we found that only a few cervical screens per lifetime would remain cost-effective for these cohorts. Findings of another evaluation in the USA also concluded that reduced screening would be optimum for nonavalent vaccinated women.[33]

To date, few modelling or health economic studies have assessed HPV DNA testing as the primary method of screening in both vaccinated and unvaccinated women. In an Italian evaluation,[34] use of primary HPV testing every 5 years with cytology triage was more cost-effective than was cytology screening every 3 years for vaccinated and unvaccinated women. In two other studies in vaccinated and unvaccinated women,[35,36] retaining cytology-based screening in younger women but switching to primary HPV screening in older women was more effective and cost-saving than was screening with cytology only. None of these three studies, however, assessed the potential range of approaches to primary HPV screening, including partial genotyping versus triaging all oncogenic types with cytology.[34–36] We have previously done similar evaluations to those presented here in England[22] and New Zealand,[21] in which we also concluded that primary HPV screening is a highly effective strategy for cervical screening in unvaccinated and vaccinated women.

Our findings support the implementation of primary HPV DNA screening in both unvaccinated women and in the context of HPV vaccination. This evaluation has supported Australia's decision to transition to primary HPV screening, which will take place on May 1, 2017. Australia is, thus, expected to be one of the first countries in the world to transition to primary HPV screening within a national organised screening programme.

Contributors

J-BL, KTS, MAS, and KC designed the study. MS, IH, and TB provided and coordinated expert input into clinical parameters and pathways. J-BL, KTS, MAS, MH, XMX, MC, and KC contributed to model design and/or construction. J-BL, KTS, and MAS analysed or extracted data to inform model parameters. J-BL, KTS, MH, and XMX ran the modelled analyses. J-BL, KTS, MAS, MH, Y-JK, XMX, MC, LSV, and KC contributed to interpretation of data. LSV and KC wrote the report, with input from J-BL, MAS, and KTS. KC oversaw all aspects of study design and conduct. All authors critically reviewed the report and approved the final version.

Declaration of interests

KC and MS are co-principal investigators 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 (VCS), a government-funded health promotion charity. VCS has received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana USA. KC and MS are also investigators for Compass in New Zealand (Compass NZ; ACTRN12614000714684), which is conducted and funded by Diagnostic Medlab (DML), now Auckland District Health Board. DML received an equipment and funding contribution for the Compass trial from Roche Molecular Systems. However 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. KC's group at Cancer Council NSW has done modelling work to analyse the implications for resource use for the transition from cytology-based screening to HPV-based screening at longer intervals; this work was commissioned and funded by VCS to inform a response to the Australian Government's request for tender for the National Cancer Screening Register (RFT Health/124/1415).

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