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A cost-effectiveness analysis of adding a human papillomavirus vaccine to the Australian National Cervical Cancer Screening Program

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Abstract. ***Background:*** The cost-effectiveness of adding a human papillomavirus (HPV) vaccine to the Australian National Cervical Screening Program compared to screening alone was examined. ***Methods:*** A Markov model of the natural history of HPV infection that incorporates screening and vaccination was developed. A vaccine that prevents 100% of HPV 16/18-associated disease, with a lifetime duration of efficacy and 80% coverage offered through a school program to girls aged 12 years, in conjunction with current screening was compared with screening alone using cost (in Australian dollars) per life-year (LY) saved and quality-adjusted life-year (QALY) saved. Sensitivity analyses included determining the cost-effectiveness of offering a catch-up vaccination program to 14–26-year-olds and accounting for the benefits of herd immunity. ***Results:*** Vaccination with screening compared with screening alone was associated with an incremental cost-effectiveness ratio (ICER) of $51 103 per LY and $18 735 per QALY, assuming a cost per vaccine dose of $115. Results were sensitive to assumptions about the duration of vaccine efficacy, including the need for a booster ($68 158 per LY and $24 988 per QALY) to produce lifetime immunity. Accounting for herd immunity resulted in a more attractive ICER ($36 343 per LY and $13 316 per QALY) for girls only. The cost per LY of vaccinating boys and girls was $92 052 and the cost per QALY was $33 644. The cost per LY of implementing a catch-up vaccination program ranged from $45 652 ($16 727 per QALY) for extending vaccination to 14-year-olds to $78 702 ($34 536 per QALY) for 26-year-olds. ***Conclusions:*** These results suggest that adding an HPV vaccine to Australia's current screening regimen is a potentially cost-effective way to reduce cervical cancer and the clinical interventions that are currently associated with its prevention via screening alone.

Introduction

Since the introduction of the National Cervical Screening Program (NSCP) in Australia in 1991, the incidence of cervical cancer has continued to decline. There were 1091 cases of cancer reported in 1991 compared with 689 cases reported in 2002.[1] The program uses cytology-based screening to detect and treat cervical intraepithelial neoplasia (CIN), the cervical cancer pre-cursor lesion, and is offered to women beginning in their late teens. Currently, over 3 million women are screened every 2 years; of these ~3.6% are diagnosed with CIN.[2] The costs of the screening program are high. Based on the most recent (1995) estimate the annual cost of the screening program to government was estimated to be $198 million.[3]

Cervical cancer is caused by infection with oncogenic human papillomavirus (HPV).[4,5] Two HPV types, HPV 16 and 18, account for ~70% of cancers worldwide.[6] Data from ongoing vaccine trials suggest that vaccines to prevent infection with these two types are highly effective in preventing CIN 2–3 (>90% efficacy).[7–10] As a result, one vaccine, Gardasil (Merck & Co Inc, West Point, PA, USA), has already been approved for use in Australia and will be funded under a national immunisation program for females 12–26 years starting in 2007.[11] However, since the trials have only followed women for 5 years it will be some time before we know if these vaccines prevent cervical cancer.

In the absence of such data, decision modelling can be used to project the potential benefits of an HPV vaccine on

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cervical cancer. Decision models combine data on the natural history of HPV infection, CIN and cancer, the effectiveness of screening and vaccination, as well as costs. The model can then be used to compare different strategies for preventing cervical cancer, such as a strategy of vaccination and screening to determine the costs and life-expectancy gains for a cohort of girls.

A cost-effectiveness analysis was conducted from a government perspective for the reference year 2006, using a Markov decision model, to determine the incremental cost-effectiveness ratio of adding vaccination to the NCSP in Australia.

Methods

Overview

A Markov model was developed, of HPV infection and cervical cancer that simulates a cohort of women beginning at age 12 and follows them until age 85 using TreeAge Pro 2005 (Treeage, Williamstown, MA, USA). Movement through the health states of the model (i.e. HPV infection, CIN 1, CIN 2, CIN 3, International Federation of Gynaecology and Obstetrics Cancer Stages I–IV) over time was based on yearly transition probabilities derived from published reports and stratified by HPV type (low-risk HPV (LR HPV), non-16/18 high-risk HPV (HR HPV), and HPV 16/18). Selected transition probabilities are summarised in Table 1; further details are available upon request from the authors.

Women infected with LR HPV types only could progress to CIN 1 or have their infection clear.[5] Women with LR HPV CIN 1 could have their disease regress or persist. Women infected with HR HPV types or HPV 16/18 could have their infection progress to CIN 1 or CIN 2 and a minority, to CIN 3.[5,6,12,13] Women infected with HR HPV (including 16 and 18) who developed CIN 1, CIN 2 or CIN 3 could have their disease progress (to CIN 2, 3 or Stage 1 cancer respectively), regress, or persist. Women with cancer (Stages I–IV) could have their cancer detected based on symptoms in the absence of screening. Women who did not have their disease detected could progress to the next stage or remain in the same stage. Each year women faced an age-specific risk of dying from other causes. Women also faced an age-specific risk of undergoing hysterectomy for benign reasons.

Natural history

Age-specific HPV incidence was based on the model originally developed by Myers *et al*.,[14,15] but revised to include recent evidence that shows a high incidence of HPV in young women aged <20 years.[16–18] Stratification of incidence by HPV types (LR HPV, HR HPV and HPV 16/18) was based on a study of the distribution of HPV types among women with normal Pap smears[19] and a study by Peto *et al*. that provided information on the age-specific prevalence of HPV 16, low- and high-risk types.[20]

Transition probabilities between the different states were derived from recent studies[21–29] that provided information on type-specific progression and regression rates that matched the states in the Markov model (Table 1). In the absence of data, we used a plausible range in conjunction with data on the distribution of specific HPV types within CIN (1–3) and cancer to inform the choice of a given transition probability.

The proportion of CIN 1 attributable to HPV 16/18 was estimated to be 35%.[12] The proportion of CIN 2–3 attributable to HPV 16/18 was estimated to be ~55%.[13] We assumed that all cancers were attributable to high-risk HPV types, including HPV 16/18. The proportion of cancers attributable to infection with HPV 16/18 was estimated to be ~70%; this value is consistent with several published Australian studies.[6,13,30–33]

Non-cervical cancer deaths were estimated from the 2003 Australian Institute Health Welfare (AIHW) mortality database.[34] Benign hysterectomy rates were estimated from the AIHW National Hospital Morbidity database.[35] Cancer progression rates and the probability of symptoms were taken from Myers *et al*.[15] Survival probabilities by stage were based on estimates from the New South Wales and South Australian Cancer Registries.[36,37]

Screening

Current screening recommendations state that women should begin screening between the ages of 18 and 21, that screening should be conducted every 2 years, and that, for women who have a history of normal Pap smears, screening can end around age 70.[2] Although previous cost-effectiveness analyses of cervical cancer have assumed that women adhere to screening at set intervals and that this is constant across age, there is evidence to suggest otherwise. To account for this, data from the New South Wales Pap Test Register (S. Morrell, pers. comm., 2006) were combined with published studies of screening behaviour in Australia, as well as assumptions regarding screening used in an unpublished report on the cost-effectiveness of cervical cancer screening in Australia (M. Haas, pers. comm., 2006) to develop estimates of actual screening behaviour that better reflect current screening practices in Australia. These estimates are presented in Table 2.

In the model, the sensitivity of the Pap test (using a cytology cut point of ≥ atypical squamous cells of unknown significance) for detection of ≥CIN 1 was assumed to be 80% and the specificity was assumed to be 95%. We chose these estimates, although they are higher than those reported from studies that adjust for verification bias,[38] because they are consistent with a previous report that evaluated the cost-effectiveness of screening in Australia (M. Haas, pers. comm., 2006).[39] This approach is also conservative with respect to the cost-effectiveness of the interventions of interest: greater incremental cost-effectiveness ratios (ICER) for vaccination interventions are likely because the residual disease prevented by the vaccine is lower, the higher are the assumed sensitivity and specificity rates associated with screening.

Conditional probabilities for an abnormal Pap test based on underlying histology were estimated from data presented in the Medical Services Advisory Committee Assessment Report of HPV testing (data not shown).[40] Colposcopy and biopsy was assumed to have a sensitivity and specificity of 100%. Management of abnormal Pap smear results was based on 2005 National Health and Medical Research Council (NHMRC) Guidelines.[41] Stage-specific cancer treatments were assumed to be prescribed according to standardised protocols.[42,43]

Table 1. Natural history model parameters
CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus

Parameters	Age (years)	Value	Time period
Natural history			
Normal			
Uninfected to cervical HPV infection (HPV incidence)[14−18]	10–12	0	1 year
	13	0.01	1 year
	14	0.05	1 year
	15–19	0.2	1 year
	20–24	0.25	1 year
	25–29	0.25	1 year
	30–34	0.15	1 year
	35–49	0.03	1 year
	50+	0.02	1 year
Proportion of incident HPV infections attributable to low-risk (LR), high-risk (HR) or HPV 16/18 infection[19,20]			
LR HPV	12–24	0.1–0.17	1 year
	25–34	0.1–0.2	1 year
	35+	0.1	1 year
HR HPV	12–24	0.33–0.4	1 year
	25–34	0.3–0.6	1 year
	35+	0.6	1 year
HPV 16/18	12–24	0.5	1 year
	25–34	0.3–0.5	1 year
	35+	0.3	1 year
Progression and regression rates[21−33]			
Regression rate, HPV to Normal			
LR HPV		0.5	0.35 years
HR HPV		0.5	0.71 years
HPV 16/18		0.5	0.71 years
Progression rate, HPV to CIN			
LR HPV to CIN 1 LR		0.25	2 years
HR HPV to CIN 1 HR		0.13	1 year
HPV 16/18 to CIN 1 HPV 16/18		0.08	1 year
HR HPV to CIN 2 HR		0.17	3 years
HPV 16/18 to CIN 2 HPV 16/18		0.20	3 years
HPV 16/18 to CIN 3 HPV 16/18		0.067	3 years
Regression rate, CIN to HPV or Normal			
CIN 1 LR to LR HPV (10%) or Normal (90%)	12–24	0.27	1 year
	25+	0.22	1 year
CIN 1 HR to HR HPV (10%) or Normal (90%)	12–29	0.39	1 year
	30+	0.599	2 years
CIN 1 HPV 16/18 to HPV 16/18 (10%) or Normal (90%)	12–29	0.25	1 year
	30+	0.347	2 years
CIN 1 HR to CIN 2 HR		0.13	1 year
CIN 1 HR to CIN 3 HR		0.03	1 year
CIN 2 HR to CIN 3 HR		0.13	1 year
CIN 1 HPV 16/18 to CIN 2 HPV 16/18		0.13	1 year
CIN 1 HPV 16/18 to CIN 3 HPV 16/18		0.03	1 year
CIN 2 HPV 16/18 to CIN 3 HPV 16/18		0.14	1 year
CIN 1 HR to CIN 2 HR		0.13	1 year
CIN 1 HR to CIN 3 HR		0.03	1 year
Regression rates, CIN 2+			
CIN 3 HR to CIN 2 HR		0.06	1 year
CIN 3 HR to HR HPV (50%) or Normal (50%)		0.20	1 year
CIN 2 HR to CIN 1 HR		0.133	1 year
CIN 2 HR to HR HPV (10%) or Normal (90%)		0.19	1 year
CIN 3 HPV 16/18 to CIN 2 HPV 16/18		0.0135	1 year
CIN 3 HPV 16/18 to HPV 16/18 (50%) or Normal (50%)		0.20	1 year
CIN 2 HPV 16/18 to CIN 1 HPV 16/18		0.133	1 year
CIN 2 HPV 16/18 to HPV 16/18 (10%) or Normal (90%)		0.21	1 year

(*Continued next page*)

Table 1. (continued)

Parameters	Age (years)	Value	Time period
Progression rate, CIN 3 to undetected Stage I			
CIN 3 HR to undetected cancer Stage 1	15–36	0.00076	1 year
	37–42	0.02–0.043	1 year
	43+	0.047	1 year
CIN 3 HPV 16/18 to undetected cancer Stage 1	15–36	0.0008	1 year
	37–42	0.03–0.057	1 year
	43+	0.085	1 year
Overall 5-year survival with cancer by stage[36,37]			
Stage I		0.84	5 years
Stage II		0.66	5 years
Stage III		0.36	5 years
Stage IV		0.11	5 years

Vaccination

Vaccination was assumed to be given to 12-year-old girls as part of a school-based program. Vaccination coverage of 80% was assumed, consistent with other school-based adolescent vaccination programs in Australia.[44] Vaccine efficacy was estimated to be 100% (95% CI: 93–100) against HPV 16/18 related CIN 1, CIN 2–3 and cancer based on published clinical trial data.[8] The duration of protection was assumed to be lifelong for the base case, based on data that suggests an amnnestic response to vaccination and sustained high titres of neutralising antibodies that are at least as high as those observed with natural immunity.[45] In sensitivity analyses the cost-effectiveness of a catch-up program offered to 14–26-year-olds was determined. For these analyses the vaccine was assumed to be effective only in girls and women who had never been infected with HPV 16 or 18.

Herd immunity

The pre- and post-vaccination cumulative incidence of HPV predicted by the transmission model (described in a companion paper[46]) was used to calculate the relative risk of HPV infection. The relative risk of infection was used to determine the cost-effectiveness implications of accounting for the impact of reduced HPV transmission due to herd immunity for girls only as well as boys and girls in a sensitivity analysis.

Costs

The costs (Table 2) for cytology-based screening, follow-up and treatment were derived from Medicare Australia Schedule Fees and are based on procedures outlined in 2005 NHMRC Guidelines.[41,43,47,48] All costs were measured in 2005 Australian dollars. The cost of the vaccine was $115 per dose for three doses.[11] Administration was assumed to be through school-based programs for cohorts up to 18 years, and through primary care general practitioners for cohorts 18–26 years. The cost for a school delivery program was based on the Municipal Association of Victoria's Cost of Victorian Local Government Immunisation Service.[49] The cost for the general practitioner program was based on the Schedule Fee.[47]

Utilities

For the model, the utility estimates reported by Myers *et al*. for different health states associated with HPV were used; these estimates were assumed to be constant by age.[50] The duration of the health states was determined from a survey of 16 gynaecological oncologists (response rate of 67%) attending the May, 2006 Australian Society of Gynaecological Oncology meeting and are presented in Table 2.

Discount rate

We used a discount rate of 5% for the base case as required for health technology assessment in Australia, but examined a lower rate of 3% in sensitivity analyses.[51]

Analytic strategy

Results are presented as average lifetime costs, average life-expectancy, QALY and ICER. Strategies that were more costly and less effective, or less cost-effective than adjacent strategies were considered 'dominated'. Sensitivity analyses were conducted on key inputs to the model as shown in Table 2. Ranges for the analyses were based on the available literature, or in the absence of data, based on a plausible range.

Results

Fig. 1 shows the model predicted CIN 1, CIN 2–3 and cancer compared with the observed rates of disease in the population. The model predicts a lifetime risk of cancer of 2.4% without screening and a risk of 0.77% with screening. Vaccination of a cohort of 12-year-old girls reduces the lifetime risk of cancer to 0.37% with vaccination. Fig. 2 shows the average discounted life-time costs and life-expectancy comparing the current screening program to the current screening program and vaccination. The incremental cost per LY gained for adding vaccination is $51 103 ($18 735 per QALY).

Table 3 summarises key sensitivity analyses using cost per LY and cost per QALY comparing a strategy of current screening and vaccination to current screening only. As shown, the ICER increases with a shorter duration of vaccine efficacy (10 years), the need for a booster (at age 22) to maintain a lifelong duration, lowered vaccine coverage and reduced vaccine efficacy (from 100% to 93%). If the sensitivity of screening for detection of CIN 1 and CIN 2–3 were lower than that assumed for the base case, the lifetime risk of cancer would increase to close to 0.9% and the ICER for screening and vaccination compared

Table 2. Screening, vaccination, costs and utilities: baseline values and ranges

ASCUS, atypical squamous cells of unknown significance; CIN, cervical intraepithelial neoplasia; FIGO, International Federation of Gynaecology and Obstetrics; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion

Parameters	Base case		Ranges		
Screening characteristics					
Coverage rates of target groups by age[38,A,B]	No screening	q5	q3	q2	q1
20–24	5%	15%	65%	10%	10%
25–29	5%	15%	65%	10%	10%
30–34	5%	15%	65%	10%	10%
35–39	15%	15%	65%	10%	10%
40–44	15%	15%	65%	10%	10%
45–49	15%	15%	55%	20%	10%
50–54	20%	15%	55%	20%	10%
55–59	25%	15%	55%	20%	10%
60–64	30%	15%	55%	20%	10%
Pap sensitivity for CIN[39,B]	80%		48–80%		
Pap specificity for <CIN[39,B]	95%		90–99%		
Colposcopy/biopsy sensitivity	100%		95–100%		
Vaccine characteristics					
Vaccine efficacy for HPV 16/18[8]	100%		93–100%		
Duration of efficacy[45]	Lifetime		10 years–lifetime		
Vaccine coverage[44]	80%		70–90%		
Booster coverage[44]	Not applicable		80%		
Costs[47–49]					
Pap smear	$58		$29–$86		
Colposcopy (with or without biopsy)	$277		$138–$415		
Treatment of CIN 1	$899		$450–$1349		
Treatment of CIN 2/CIN 3	$905		$453–$1358		
Treatment of FIGO I	$10 617		$5308–$15 924		
Treatment of FIGO II	$15 673		$7837–$23 510		
Treatment of FIGO III	$15 731		$7865–$23 596		
Treatment of FIGO IV	$14 158		$7079–$21 237		
Terminal care	$6307		$3153–$9460		
Vaccine costs/dose	$115		$100–$150		
Administration costs/dose – school	$12		$6–$24		
Administration cost/dose – general practitioner	$31		$15–$62		
Booster cost/dose	Not applicable		$115		
Discount rates[51]					
Costs	5%		3–5%		
Benefits	5%		3–5%		
Parameters	Utility[50]		Range[52]	Time with disease	
Possible LSIL (ASCUS) pap	0.94		0.94–1	7 days	
LSIL pap	0.91		0.91–1	7 days	
HSIL or cancer pap	0.91		0.91–1	1 month	
CIN–1	0.91		0.91–1	6 months	
CIN 2/CIN 3	0.87		0.91–1	6 months	
FIGO I detected cancer	0.76		0.65–0.76	5 years	
Survivor	1		0.97–1	Lifetime	
FIGO II detected cancer	0.67		0.56–0.67	5 years	
Survivor	1		0.90–1	Lifetime	
FIGO III detected cancer	0.67		0.56–0.67	5 years	
Survivor	1		0.90–1	Lifetime	
FIGO IV detected cancer	0.67		0.48–0.67	5 years	
Survivor	1		0.62–1	Lifetime	

[A] S. Morrell, pers. comm., 2006.
[B] M. Haas, pers. comm., 2006.

with screening only would decrease to $48 278 per LY ($21 707 per QALY). The ICER were relatively insensitive to assumptions about the specificity of the Pap smear, but were sensitive to assumptions about the utilities for cancer, including those for survivors. If the cost of the vaccine were reduced to $100 per dose, the ICER would decrease to $42 567 per LY ($15 606 per QALY). If a discount rate of 3% was assumed, the ICER decreases to $16 448 per LY and $8 419 per QALY. Under a

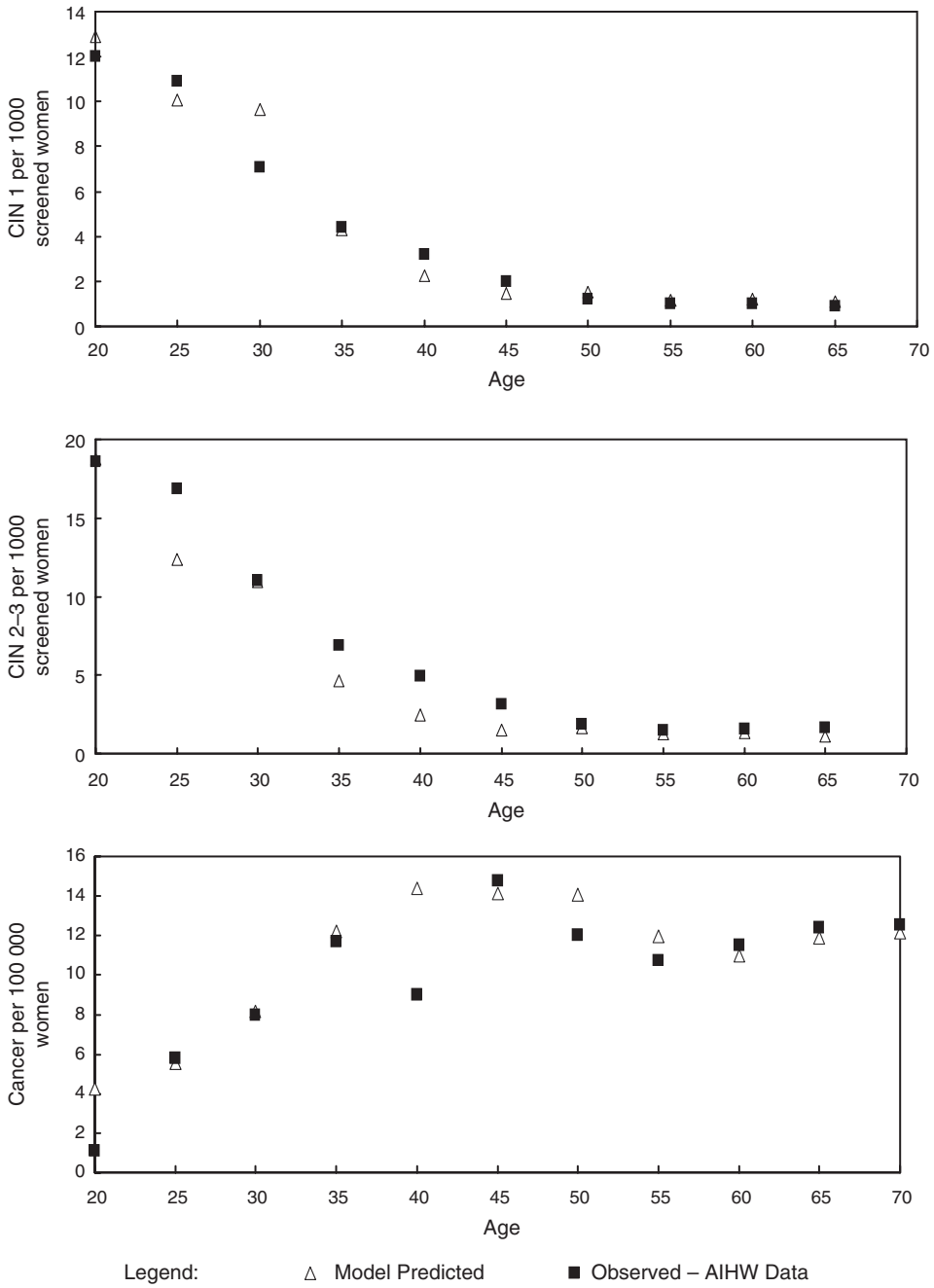


Fig. 1. Observed (based on Australian Institute of Health and Welfare 2002–2003) and predicted age-specific estimates of cervical intraepithelial neoplasia (CIN) 1, CIN 2–3 and cancer in Australia.

worst case scenario, if the cost per dose of the vaccine was high, the duration of efficacy was only 10 years, coverage was 70% and efficacy was 93%, then the ICER for vaccination and screening compared with screening only would increase to $255 580 per LY ($77 845 per QALY).

If vaccination allows for the screening interval to be changed (Fig. 3) to 3 years, the lifetime risk of cancer would still be lower than that for screening only (0.41%) and the ICER for screening and vaccination compared to screening only would be $16 664 per LY gained. As shown, if the age that screening starts can be delayed until age 25 in addition to using a 3-year screening interval, screening and vaccination would still be more effective than screening only at preventing cancer, and less costly. Expressed differently, a combined screening and vaccination program of this kind dominates a ‘screening-only’ approach to the prevention of cervical cancer in Australia.

Table 4 summarises the cost per LY and per QALY, comparing screening only (from the Markov model) with screening and vaccination for girls only, and for boys and girls, when accounting for potential herd immunity effects. Of the different scenarios presented here, varying the duration of vaccine down to 10 years with no further benefit has the largest impact on the

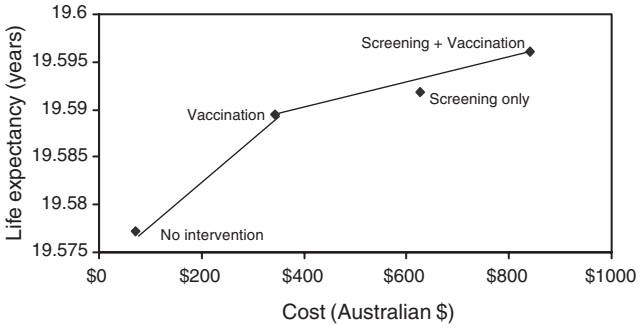


Fig. 2. Efficiency curve comparing the average (discounted) costs and average life-expectancy for the current cervical cancer screening program to vaccination, either alone or in addition to the current screening program.

cost-effectiveness ratios, with the cost per LY increasing to over $150 000. Use of age-specific estimates of relative risk when there was an increase in the age-specific incidence but a decrease in cumulative incidence as reported by Regan *et al*. (companion manuscript[46]) for the scenarios with 10 years duration did not change the results to any appreciable extent. Across a range of assumptions, extending vaccination to boys had an ICER in excess of $80 000 using cost per LY ($29 278 to $107 776 per QALY).

The cost per LY and per QALY of vaccinating girls aged 14–26 is presented in Table 5 comparing screening only to screening and vaccination. As shown, the ICER associated with offering vaccination to girls aged 14 to 18 is lower than that for vaccinating girls aged 12 years only, but then increases with increasing age. The lowest ICER is associated with vaccinating girls aged 16 ($43 445 per LY and $15 891 per QALY). The highest ICER is associated with vaccinating women aged 26 ($78 702 per LY and $34 536 per QALY).

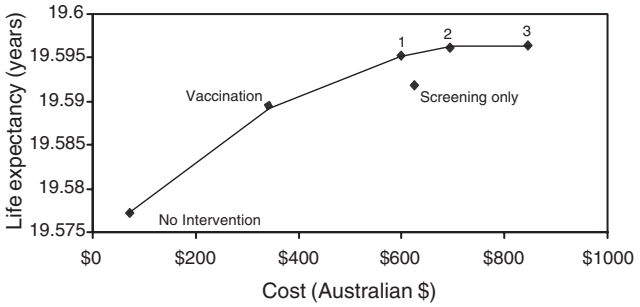
Discussion

The Australian NCSP has been successful in reducing the incidence of cervical cancer.[1] However, this is achieved by screening women on a frequent basis starting at a relatively

Table 3. Incremental cost-effectiveness ratios (ICER) for the base case and sensitivity analyses comparing current screening-only to current screening and vaccination

Results presented per life-year and per quality-adjusted life year (QALY). CIN, cervical intraepithelial neoplasia

Parameters	ICER ($/LY)	ICER ($/QALY)
Base case	$51 103	$18 735
Vaccine duration		
10 years	$175 333	$52 600
10 years + booster to achieve lifetime protection	$68 158	$24 988
Multiple infections		
10%	$60 411	$22 296
Vaccine efficacy		
93%	$57 534	$21 098
Vaccine coverage		
70%	$52 391	$19 215
90%	$49 810	$18 255
Pap sensitivity for detection of CIN 1, CIN 2+		
48% for CIN 2+; 20% for CIN 1	$42 237	$23 478
69% for CIN 2+; 45% for CIN 1	$48 278	$21 707
Pap specificity for <CIN		
90%	$51 848	$18 800
99%	$50 588	$18 690
Colposcopy sensitivity		
95%	$51 120	$18 861
Compliance with follow-up and treatment		
90%	$46 421	$19 310
Screening, diagnosis and treatment costs		
−50%	$62 470	$22 903
+50%	$39 736	$14 568
Vaccine costs		
$100 per dose	$42 567	$15 606
$150 per dose	$71 021	$26 038
Utilities		
Cancer only	Not applicable	$42 680
Lower estimates for cancer and cancer survivor	Not applicable	$7979
Upper estimates for cancer and cancer survivor	Not applicable	$18 850
Discount rates		
3% costs; 3% benefit	$16 448	$8419
Best case scenario for vaccination: vaccine is 100% effective, duration is for a lifetime, cost per dose is $100, coverage is 90%	$41 633	$16 325
Worst case scenario for vaccination: vaccines is 93% effective, duration is 10 years, cost per dose is $150, coverage is 70%	$255 580	$77 845



Legend
1. Vaccination and screening every 3 years beginning at age 25
2. Vaccination and screening every 3 years
3. Vaccination and current screening

Fig. 3. Efficiency curve comparing the average (discounted) costs and average life-expectancy for the current cervical cancer screening program to vaccination combined with the current screening program, screening at a less frequent screening interval or screening at a less frequent interval starting at a later age.

young age and diagnosing and treating a large number of women with lesions presumed to have malignant potential. An advantage of an effective vaccine is that it has the potential to prevent disease from occurring in the first place and thereby eliminates this whole spectrum of medical intervention. We developed a Markov model to predict the impact of adding vaccination to the current screening program. Strengths of model used for this analysis are that it was calibrated to population-based estimates from the NCSP of histologically confirmed CIN, in addition to cancer, and that it accounted for variability in screening behaviour among women by age. Compared to screening only, offering vaccination to 12-year-old girls in addition to screening reduces the lifetime risk of cancer by nearly 50% at a cost of $51 103 per LY and $18 735 per QALY.

Consistent with other published analyses, our results were sensitive to assumptions about the duration of vaccine efficacy.[52–54] We assumed initially that the duration of vaccine efficacy would be lifelong. Evidence to support this assumption includes a recently published study that shows that the geometric mean titres for the anti-HPV response to the quadrivalent vaccine are at least as high as natural immunity-induced titres, as well as data that suggests that the vaccine might produce an anamnestic response in women who are HPV seropositive.[45] In sensitivity analyses, we varied the duration of vaccine efficacy; a short duration of vaccine efficacy (10 years) with no opportunity for a booster would increase the costs of a vaccination and screening program considerably. Long-term follow-up studies are currently being conducted to provide information on waning immunity and the potential need for booster.[55] Implementation of the vaccination program in Australia will incorporate a registry so that women can be recalled if a booster is subsequently shown to be necessary.[56]

The cost of the vaccine has been the focus of much debate. We used the commercial price for three doses of the vaccine; we included the costs for administering the vaccine to girls within a school-based program as well as at a general practitioner's office.[11] As would be expected, varying the cost per dose of the vaccine from $100 to $150 did have an impact on the ICER for vaccination and screening compared to vaccination only. The discount rate also had a large impact on the ICER, which is common for preventive programs. Such programs have large

Table 4. Incremental cost-effectiveness ratio (ICER) per life-year (LY) and quality-adjusted life year (QALY) comparing screening-only to screening and vaccination accounting for herd immunity and varying the duration of vaccine-induced immunity, vaccine coverage and the probability of transmitting human papillomavirus (HPV) during sex

The efficacy of the vaccine in preventing transmission is varied from 84% to 100%

Parameters	Women only[A]		Men and women[A]	
	ICER ($/LY)	ICER ($/QALY)	ICER ($/LY)	ICER ($/QALY)
Vaccine duration is lifelong				
Efficacy of 84%	$41 748	$15 300	$100 988	$36 920
Efficacy of 100%	$36 343	$13 316	$92 052	$33 644
Vaccine duration is 10 years				
Efficacy of 84%	$166 765	$49 873	$360 426	$107 776
Efficacy of 100%	$162 244	$48 510	$347 416	$104 669
Vaccine coverage is 70%				
Efficacy of 84%	$39 137	$14 314	$94 016	$34 380
Efficacy of 100%	$31 591	$11 549	$80 092	$29 278
Vaccine coverage is 90%				
Efficacy of 84%	$44 852	$16 386	$109 481	$40 018
Efficacy of 100%	$41 672	$15 231	$106 398	$38 503
Transmission probability of 0.4				
Efficacy of 84%	$39 894	$15 605	$97 294	$35 566
Efficacy of 100%	$35 660	$13 034	$91 727	$33 525
Transmission probability of 0.8				
Efficacy of 84%	$43 135	$15 773	$104 996	$38 466
Efficacy of 100%	$32 268	$13 527	$92 242	$33 714

[A]Compared to lifetime costs, life-expectancy and quality-adjusted life-expectancy estimated from the Markov model for girls only.

Table 5. Incremental cost-effectiveness ratios (ICER) per life-year (LY) and quality-adjusted life year (QALY) comparing screening-only to screening and vaccination for catch-up vaccination offered to 14- to 26-year-old women

Parameters	ICER ($/LY)	ICER ($/QALY)
Base case (age 12)	$51 103	$18 735
School-based administration		
14 years (70% coverage)	$45 652	$16 727
16 years (70% coverage)	$43 445	$15 891
18 years (70% coverage)	$44 020	$16 552
General practitioner-based administration		
18 years (50% coverage)	$54 750	$20 591
20 years (50% coverage)	$56 752	$22 323
22 years (50% coverage)	$60 484	$24 752
24 years (50% coverage)	$66 664	$28 333
26 years (50% coverage)	$78 702	$34 536

up-front costs, but their benefits are often not realised for several years. For example, the costs of administering the HPV vaccine to a cohort of 12-year-old girls is incurred entirely in the first year of the program but its benefits (in the form of pre-cancerous lesions and cancers prevented) are largely realised several years into the future. Decreasing the discount rate will increase the estimated benefits, leaving the costs (which are already in present values) unchanged, thus resulting in more favourable cost-effectiveness ratios. The 5% discount rate mandated for health technology assessments in Australia is not universal. Of note, the USA uses 3% and the National Institute for Health and Clinical Excellence in the UK uses 3.5%.[57,58]

The utilities for pre-cancer and cancer used in this analysis are from a sample of women in the USA.[50] To date, these are the only published data available and although the psychosocial impact of cervical abnormalities are well documented, the data quantifying this impact are limited. Our study highlights the importance of accurately quantifying the stress and anxiety associated with the detection and treatment of pre-cancerous abnormalities. When we used QALY as an outcome instead of LY, all vaccination strategies had much lower incremental cost-effectiveness ratios.

If a successful vaccination program achieves the reduction in cervical disease predicted by this model, there will be a need to consider how best to screen women in a vaccinated population. Screening will continue to be important, because the current generation of vaccines are only targeted at two of the ~15 high-risk HPV types and, thus, disease can be expected to occur in vaccinated women caused by these other types. In this analysis, we have shown that changing the screening interval and/or age of first screening would reduce costs considerably, and would still be more effective than the current screening program at reducing cancer incidence and mortality. Although the present study is consistent with other analyses,[52,53] its results are sensitive to the behaviour of policy-makers, clinicians and consumers: any changes to the screening program must give consideration to the population coverage that will be achieved, the duration of vaccine efficacy and the degree to which any changes in screening interval or age might affect compliance with the recommended vaccination and screening protocols.

In a review, Dasbach *et al*.[59] noted the limitations of using a Markov model structure to quantify the impact of an HPV vaccine. Although such models tend to be more transparent and better understood, transmission models can more accurately quantify the impact of a vaccine at a population level and, importantly, determine herd immunity effects. In a companion paper, Regan *et al*.[46] have examined the impact on HPV transmission of vaccinating girls only, as well as boys and girls. We used the relative reduction in incidence predicted by the transmission model to determine how accounting for transmission of the virus within a population would affect the cost-effectiveness of the vaccine program. Studies to quantify the potential benefits of vaccinating boys are currently being conducted. In the meantime, our study suggests that in a setting like Australia, which already has an effective screening program, vaccinating boys in addition to girls is likely to be cost-effective when the morbidity of the screening program is taken into account (QALY) but not when only mortality associated with cervical cancer is considered (LY).[60,61]

We examined the cost-effectiveness of offering a catch-up program to girls aged 14 to 26 years. The higher ICER associated with vaccinating women in their late teens and early 20s is due, in part, to the assumption that an increasing percentage of these women will have already been exposed to the virus and will therefore not benefit from vaccination. The results of this analysis are limited by a lack of population-based data on the prevalence of HPV 16 and HPV 18 by age in Australian women as well as definitive data on the performance of the vaccine in women who are already exposed to HPV. As these become available, there will need to be additional analyses conducted to confirm our findings.

In conclusion, our results suggest that adding a program of vaccination to 12-year-old girls is a potentially cost-effective method for achieving further reductions in pre-cancer and cancer compared to screening only.

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