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The value of male human papillomavirus vaccination in preventing cervical cancer and genital warts in a low-resource setting

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Objective To estimate health benefits and incremental cost-effectiveness of human papillomavirus (HPV) vaccination of pre-adolescent boys and girls compared with girls alone for preventing cervical cancer and genital warts.

Design Model-based economic evaluation.

Setting Southern Vietnam.

Population Males and females aged ≥9 years.

Methods We simulated dynamic HPV transmission to estimate cervical cancer and genital warts cases. Models were calibrated to epidemiological data from south Vietnam.

Main outcome measures Incremental cost-effectiveness ratios (ICERs): cost per quality-adjusted life-year (QALY).

Results Vaccinating girls alone was associated with reductions in lifetime cervical cancer risk ranging from 20 to 56.9% as coverage varied from 25 to 90%. Adding boys to the vaccination programme yielded marginal incremental benefits (≤3.6% higher absolute cervical cancer risk reduction), compared with vaccinating girls alone at all coverages. At ≤25 international dollars (I$) per vaccinated adolescent (I$5 per dose), HPV vaccination of boys was below the threshold of Vietnam's per-capita GDP (I$2800), with ICERs ranging from I$734 per QALY at 25% coverage to I$2064 per QALY for 90% coverage. Including health benefits from averting genital warts yielded more favourable ICERs, and vaccination of boys at I$10/dose became cost-effective at or below 75% coverage. Using a lower cost-effectiveness threshold of 50% of Vietnam's GDP (I$1400), vaccinating boys was no longer attractive at costs above I$5 per dose regardless of coverage.

Conclusion Vaccination of boys may be cost-effective at low vaccine costs, but provides little benefit over vaccinating girls only. Focusing on achieving high vaccine coverage of girls may be more efficient for southern Vietnam and similar low-resource settings.

Keywords Boys, cervical cancer, cost-effectiveness, human papillomavirus, vaccination, Vietnam.

Tweetable abstract Limited cervical cancer reduction from including boys in HPV vaccination of girls in low-resource settings.

Linked article This article has journal club questions by EYL Leung. To view these visit http://dx.doi.org/10.1111/1471-0528.13562.

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Introduction

In Vietnam, age-standardised cervical cancer incidence is 10.6/100 000 woman-years.[1] However, there is striking variation in cervical cancer incidence within the country, with high rates in south Vietnam, where it is the most common cancer in women. Ho Chi Minh City in south Vietnam reports an age-standardised rate of 26.0/100 000 woman-years, four-times higher than the northern city, Hanoi.[2] Similarly, human papillomavirus (HPV) prevalence estimates are five times higher in Ho Chi Minh City than in Hanoi. These disparities are likely the result of historical differences between regions. North Vietnam, formerly communist, is more socially conservative, whereas south Vietnam has adopted more liberal sexual attitudes. Historically, rates of premarital sex were higher in south Vietnam compared with north Vietnam. Additionally, during the war with the USA, commercial

sex outlets catering to US soldiers were common in the south.[2] A study found that women whose husbands served in the military during the war and were stationed in south Vietnam had an increased risk of cervical cancer.[3] More recently, urbanisation and higher disposable incomes have led to more sex outside marriage, particularly in southern Vietnam.[4]

Cervical cancer screening coverage in Vietnam remains low; only 4.9% of women have ever had a Papanicolaou smear.[5] Screening is opportunistic and faces challenges such as insufficient follow up for screen-positives, inadequate laboratories to process results, and lack of political will to improve coverage. Population-based screening was established in ten districts of southern/central Vietnam, yet coverage has not exceeded 40%.[6]

Because of the challenges of implementing cervical cancer screening in Vietnam, HPV vaccination is a promising primary prevention strategy. Two currently available vaccines are highly effective against HPV types 16 and 18 (HPV-16/18) infections, which cause 70% of cervical cancers.[7] Both HPV vaccines are licensed in Vietnam and have high acceptability.[8,9] Merck (Kenilworth, NJ, USA), makers of Gardasil which also targets HPV types 6 and 11 (responsible for most genital warts), recently offered the vaccine at a reduced price of US$4.50/dose to the GAVI Alliance.[10] Since 2013, 20 countries have been approved to receive GAVI support to introduce HPV vaccination through demonstration projects and national programmes.[11] Vietnam is GAVI-eligible, and therefore could apply to receive the vaccine at the lower price.[12] However, policymakers will need to decide whether HPV vaccination is a good health investment and if so, determine the target population. If Vietnam does not receive GAVI funding for Gardasil, policymakers may consider implementing Cervarix, which may have a lower market price but only provides protection against HPV-16/18. Therefore, we separately assessed the cost-effectiveness of a vaccine targeted towards HPV-16/18 cervical cancer and one that also provides protection against HPV-6/11-associated genital warts.

Previous modelling has shown that HPV vaccination of girls is cost-effective for Vietnam at low vaccine costs.[13,14] However, these models could not evaluate the added value of vaccinating boys, which provides greater cervical cancer reduction through herd immunity. The long-term impact of HPV vaccination cannot be observed for many years, so mathematical models that synthesise available data and project the impact of prevention strategies provide policymakers with valuable insight. Because of the heterogeneity of HPV prevalence and the high cervical cancer burden in the south of the country, we focus our analysis on southern Vietnam, since a composite model may not accurately reflect regional differences in cost-effectiveness.

Methods

We used a previously developed dynamic model of HPV-16/18 sexual transmission between men and women.[15,16] We linked this model to a previously developed stochastic model that includes other high-risk and low-risk HPV types.

Models

We used both a dynamic model that simulates transmission of HPV-16/18 between men and women through heterosexual mixing and an individual-based first-order Monte Carlo simulation model that mimics HPV-induced cervical carcinogenesis associated with all HPV types. The models have been described previously.[13,15,17] Briefly, the dynamic model is an open cohort, age-structured model in which men and women form sexual partnerships. Girls and boys enter the susceptible pool at age 9 and as they become sexually active, they face a risk of HPV-16/18 acquisition with each sexual partnership; their risk varies over time and depends on their number of partners, HPV prevalence in the opposite sex, and probability of HPV-16/18 transmission from a sexual partner. Individuals develop partial type-specific immunity after clearing their first HPV infection, which reduces their susceptibility to future infections of the same type. Once infected with HPV-16 or HPV-18, women can develop grade 1 cervical intraepithelial neoplasia or grade 2 or 3 cervical intraepithelial neoplasia, and subsequently invasive cancer.

To simulate sexual mixing, we adapted a previously published mixing algorithm[18] to reflect sexual behaviour in south Vietnam, characterised through a comprehensive literature review. More details on sexual mixing are available in the Supplementary material (Appendix S1). Briefly, we assigned males and females to one of four sexual mixing categories (none, low, moderate and high). An individual's mixing category determines his/her age of sexual initiation and number of new partners per year. Incidence of HPV-16 and HPV-18 varies per year according to number of new partners, HPV prevalence, and transmission probability of type-specific HPV given an infected partner. Because of the changing risk of acquiring HPV infection, the dynamic model can estimate age-specific reductions in HPV-16 and HPV-18 incidence associated directly with vaccination, and indirect effects (herd immunity). Estimated HPV-16 and HPV-18 incidence reductions after vaccination served as inputs to the stochastic model, which represents females only, simulates all HPV types (HPV-16, HPV-18, high risk other, and low risk), accommodates costs, and tracks each woman's history (screening, treatment and past cervical abnormalities). HPV incidence in the stochastic model is a function of age and individual-level characteristics, and does not change over time with sexual activity.

Reductions in age-specific cancer incidence in the vaccinated cohorts were applied in two separate stochastic model

analyses: one representing direct benefits to vaccinated girls, and the second representing herd immunity to unvaccinated girls. This process was performed to accommodate heterogeneity in risks associated with both segments of the population. A weighted average of relevant outputs (lifetime cancer costs, life expectancy, and lifetime cancer incidence) was calculated and combined with estimated benefits to older unvaccinated cohorts to create composite health and economic outputs for cost-effectiveness analyses.

Before projecting benefits of vaccination, both models were calibrated to epidemiological data from south Vietnam using a likelihood-based approach. Data used for calibration included age-specific cervical cancer incidence rates, HPV-16/18 type distribution in cervical cancer, and age-specific prevalence of HPV-16/18 in women with normal cytology.[19] Our calibration approach has been described elsewhere,[15,17] and details of calibration for the current analysis, including data ranges, target data and calibration results, are provided in the Supplementary material (Appendix S1).

We modelled HPV-16 and HPV-18 incidence reductions over time associated with vaccination strategies of pre-adolescent girls alone and those including boys. Vaccine coverage varied from 0 to 90%. We assumed that vaccination occurs before age 12 years, and individuals receive all three doses. Vaccine efficacy against HPV-16 and HPV-18 infections was assumed to be 100% for girls and 85% for boys based on published clinical trials[20,21] and extended over the lifetime.

To assess the additional benefits of the quadrivalent vaccine against HPV-6/11-associated genital warts, we parameterised previously a described incidence-based model that simulates genital warts in boys and girls and allows for recurrence.[16,22] Details on this approach are found in the Supplementary material (Appendix S1).

Cost-effectiveness analysis

We estimated the lifetime costs and health benefits of preventing cervical cancer and genital warts, and associated quality-adjusted life expectancy experienced by ten consecutive birth cohorts vaccinated at age 11 years in an ongoing vaccination programme (out to 100 years). We included birth cohorts of women who were aged 12–50 years in the first year of the vaccination programme in the analysis so as to capture herd immunity to older cohorts. We compared strategies of vaccinating girls only, vaccinating both sexes, and a baseline scenario of no vaccination or screening, using incremental cost-effectiveness ratios (ICERs). The ICER is calculated as the additional cost of a strategy divided by its additional health benefit when compared with the next least costly strategy. Strategies that were more costly and less effective ('strongly dominated') or less costly and less cost-effective ('weakly dominated') than an alternative were considered inefficient, and following standard practice, were excluded from calculations in that analysis. For cost-saving scenarios, the ICER for the next most costly strategy was compared with the cost-saving scenario and not with natural history.

Consistent with published guidelines on cost-effectiveness analyses, we adopted a societal perspective and discounted future costs and benefits by 3% annually.[23–25] The approach used to estimate costs has been described previously.[13,26,27] Costs were expressed in 2008 international dollars (I$), a currency that provides a means of translating and comparing costs among countries, taking into account differences in purchasing power.[28] Costs include both direct medical costs (such as screening, treatment of cancer or lesions, hospitalisation, vaccine, administration and programmatic) and indirect costs (including transportation and patient time). Sources for cost estimates include a previously published analysis in Vietnam[13] and WHO CHOICE.[29] Costs of nontradable goods were converted to I$ using purchasing power parity conversion rates to go to and from local currency units. As both the price of the HPV vaccine and cost of delivery have not yet been determined for Vietnam, we used a composite cost per vaccinated adolescent, which we assumed to include vaccine, wastage, freight and supplies, administration, immunisation support, and programme costs. We varied the composite cost from I$10 (I$2 per dose) to I$200 (I$40 per dose). For example, for a cost of I$25 per vaccinated adolescent, we assumed three doses of vaccine at I$5 each, with the remaining I$10 allocated to the other component costs. Additional assumptions about costs are supplied in the Supplementary material (Appendix S1). As cervical cancer screening coverage in Vietnam is low and of variable quality, we assumed no screening in the base-case analysis but assessed the impact of screening in sensitivity analyses, varying coverage from 25 to 100%. For analyses that included cervical cancer screening, we assumed screening with cytology once per lifetime at age 45 years. Screening was assumed to occur in three visits including initial screen (visit 1), colposcopy and possibly biopsy for screen-positive women (visit 2) and treatment for precancerous lesions or cancer using either cryosurgery, loop electrosurgical excision procedure, cold-knife conisation, or simple hysterectomy depending on lesion size or cancer stage (visit 3). Loss to follow up was assumed to be 15% for each subsequent visit. Screening assumptions have been detailed previously.[13,26,30] As there is no universally agreed-upon threshold below which interventions are considered cost-effective (i.e. good value for money relative to other health investments that Vietnam could adopt), we used the commonly cited threshold of per-capita GDP (I$2800),[31–33] but also explored the implications of using a lower, more stringent threshold of 50% GDP per capita (I$1400). We present separate ICERs for cervical cancer only and cervical

cancer and genital warts combined, (1) to assess the relative effect of each health benefit on the ICERs; (2) to allow for a relevant ICER estimate for both the bivalent and quadrivalent vaccines; and (3) because the epidemiological data on genital warts are more limited than those of cervical cancer in Vietnam.

Results

Base-case analysis

Table 1 shows mean reductions in lifetime risk of cervical cancer and ICERs associated with vaccination of girls alone or both sexes. Vaccination coverage varied from 25 to 90%, and cost per vaccinated adolescent varied from I$10 to I$200 (i.e. I$2 to I$40 per dose). For cohorts directly benefiting from the vaccination programme, vaccinating girls alone was associated with a 20% reduction in lifetime cervical cancer risk with 25% coverage and a 56.9% reduction with 90% coverage. In contrast, inclusion of boys in vaccination yielded marginal incremental benefits (≤3.6% higher absolute cervical cancer risk reduction), compared with vaccinating girls alone; this result was consistent at all coverage levels. In addition, scaling up vaccination coverage of girls yielded more benefits in cancer reduction than including boys. For example, increasing coverage of girls from 25 to 50% yielded an additional 16.5% reduction in cervical cancer but expanding coverage to include boys at 25% only provided a 2.7% greater benefit over vaccinating girls alone at 25%.

At a cost of I$25 per vaccinated adolescent (I$5 per dose) or less, HPV vaccination of boys fell below the threshold of Vietnam's per capita GDP (I$2800), with ICERs ranging from I$734 per quality-adjusted life-year (QALY) for vaccine costs of I$5 per dose at 25% coverage to I$2064 per QALY at 90% vaccine coverage (Table 1). The ICERs for inclusion of boys increased as vaccination coverage and cost increased, and exceeded the per-capita GDP when vaccine costs were higher than I$10 per dose at 75% coverage or I$15 per dose at 50% coverage. Using a lower cost-effectiveness threshold of 50% of Vietnam's GDP (I$1400), including boys in a vaccination programme was no longer attractive at costs above I$5 per dose regardless of coverage. Under this threshold, vaccinating boys at coverages above 75% was no longer cost-effective at I$5 per dose. In contrast, HPV vaccination of girls only was highly attractive across all ranges of costs and coverages.

Table 2 shows the ICERs associated with HPV vaccination when the health benefits from reductions in cervical cancer in females and genital warts in both sexes are considered. Inclusion of protection against HPV-6/11-related genital warts reduced the cost per QALY for vaccination of girls only and girls and boys by an average of 12% and 15%, respectively. Relative reductions became smaller with increasing vaccine cost. Similar to ICERs associated with cervical cancer benefits only, HPV vaccination of boys and girls fell below the threshold of Vietnam's per-capita GDP at a cost per dose of I$5 or less, with ICERs ranging from I$572 per QALY at 25% coverage to I$1751 per QALY at 90% coverage. With the inclusion of reductions in genital warts, vaccinating boys at 75% coverage at a cost of I$10 per dose fell just below the cost-effectiveness threshold. The ICERs for inclusion of boys exceeded the per-capita GDP when vaccine costs were higher than I$15 per dose at 50% coverage. Using a threshold of 50% of Vietnam's GDP yielded results similar to those when considering cervical cancer benefits only; vaccination of boys was not cost-effective at vaccine costs above I$5 per dose. With the inclusion of genital warts reduction, HPV vaccination of girls alone was now cost saving at I$5 per dose at all coverage levels.

In addition to mean cancer reductions presented for the vaccinated cohorts, we explored the herd immunity benefits to the older, unvaccinated cohorts (Figure 1). Cancer reductions were highest in younger cohorts and declined substantially with age. For example, we assumed that girls aged 15 years or older at the start of the vaccination programme were beyond the age of receiving the vaccine (which is targeted to age 12 and younger). However, they would experience indirect, herd immunity benefits of 2% reduction in lifetime risk of cervical cancer with a vaccination programme covering 25% of 12-year-old girls; adding boys to this programme would increase their cancer reduction to 4.4%. Increasing coverage to 90% of girls only would yield a cancer reduction of 15% and the inclusion of boys would further increase benefits to 20.5%. Unlike the herd immunity benefits of including boys in the vaccination programme to the vaccinated cohorts, which peaked when coverage was 50% (Table 1), the relative benefits of vaccinating boys to older cohorts continued to increase up to 90% vaccination coverage of boys.

Sensitivity analyses

To explore the effect of key assumptions on our findings, we varied screening costs and coverage, cancer costs, and sexual behaviour. Full results of sensitivity analyses including effects on reduction in lifetime cancer risk and ICERs for vaccine costs I$10–200 are available in the Supplementary material (Appendix S1). Figure 2 displays the results of our varied assumptions on ICERs for vaccinating boys at HPV vaccine costs of I$5 (Figure 2, top) and I$10 per dose (Figure 2, bottom). Overall, results were consistent with the base case across the range of analyses. Inclusion of boys in the vaccination programme fell below Vietnam's GDP per capita at a vaccine cost of I$5 per dose at all coverage levels and exceeded the threshold when cost per dose increased to I$10 75% coverage; the exception was in the case of doubled cancer costs, which resulted in an ICER just below the threshold

Table 1. Cervical cancer only: mean cancer reductions and ICERs by cost per vaccinated adolescent and vaccination coverage*

	Mean cancer reduction**	Cost per vaccinated individual***						
		I$10 (I$2 per dose)	I$25 (I$5 per dose)	I$50 (I$10 per dose)	I$75 (I$15 per dose)	I$100 (I$20 per dose)	I$150 (I$30 per dose)	I$200 (I$40 per dose)
25% coverage								
Natural history (no screening or vaccination)	–	–	–	–	–	–	–	–
Vaccination, girls only	20.0%	CS	$9	$276	$543	$809	$1343	$1877
Vaccination, girls and boys	22.7%	**$127**	**$734**	**$1746**	**$2758**	$3770	$5795	$7819
50% coverage								
Natural history (no screening or vaccination)	–	–	–	–	–	–	–	–
Vaccination, girls only	36.5%	CS	$22	$300	$579	$858	$1415	$1972
Vaccination, girls and boys	40.1%	**$208**	**$930**	**$2133**	$3337	$4541	$6948	$9355
75% coverage								
Natural history (no screening or vaccination)	–	–	–	–	–	–	–	–
Vaccination, girls only	50.2%	CS	$28	$313	$599	$884	$1456	$2027
Vaccination, girls and boys	52.9%	**$376**	**$1364**	$3012	$4659	$6307	$9601	$12 896
90% coverage								
Natural history (no screening or vaccination)	–	–	–	–	–	–	–	–
Vaccination, girls only	56.9%	CS	$26	$311	$597	$883	$1454	$2025
Vaccination, girls and boys	58.2%	**$655**	**$2064**	$4411	$6758	$9105	$13 799	$18 493

*Values represent ICERs expressed as cost (in I$) per QALY; values in bold type indicate scenarios in which HPV vaccination of boys falls below the per capita GDP of Vietnam; shaded values indicate strategies in which HPV vaccination of boys falls below 50% of the per capita GDP of Vietnam; strategies listed in order of increasing effectiveness; 'CS' denotes strategies that were cost-saving compared to no intervention, because the future costs averted by preventing cancer were greater than the cost of the intervention. For each coverage level and cost scenario, the ICERs are calculated as the additional cost of a strategy divided by its additional benefit when compared with the next least costly strategy. However, in scenarios in which vaccination of girls only was cost-saving, the ICER for vaccination of girls and boys was calculated in comparison to vaccination of girls only and not natural history. All strategies assume no cervical cancer screening coverage.

**Reductions in lifetime cancer risk were calculated against no intervention and values for the ten cohorts of vaccinated girls were averaged. Herd immunity benefits to older unvaccinated cohorts are not included in this estimate.

***Cost per vaccinated adolescent includes three doses of vaccine, wastage, freight and supplies, administration, immunisation support, and programmatic costs. Costs are expressed in 2008 international dollars.

Table 2. Cervical cancer and genital warts: ICERs by cost per vaccinated adolescent and vaccination coverage*

	Cost per vaccinated individual**						
	I$10 (I$2 per dose)	**I$25 (I$5 per dose)**	**I$50 (I$10 per dose)**	**I$75 (I$15 per dose)**	**I$100 (I$20 per dose)**	**I$150 (I$30 per dose)**	**I$200 (I$40 per dose)**
Vaccination at 25%							
Natural history (no screening or vaccination)	–	–	–	–	–	–	–
Vaccination, girls only	CS	CS	$211	$454	$697	$1182	$1667
Vaccination, girls and boys	**$49**	**$572**	**$1445**	**$2317**	$3190	$4935	$6680
Vaccination at 50%							
Natural history (no screening or vaccination)	–	–	–	–	–	–	–
Vaccination, girls only	CS	CS	$264	$529	$794	$1323	$1853
Vaccination, girls and boys	**$151**	**$811**	**$1910**	$3009	$4108	$6306	$8504
Vaccination at 75%							
Natural history (no screening or vaccination)	–	–	–	–	–	–	–
Vaccination, girls only	CS	CS	$252	$515	$777	$1302	$1827
Vaccination, girls and boys	**$280**	**$1153**	**$2608**	$4062	$5517	$8426	$11 335
Vaccination at 90%							
Natural history (no screening or vaccination)	–	–	–	–	–	–	–
Vaccination, girls only	CS	CS	$253	$517	$781	$1308	$1835
Vaccination, girls and boys	**$519**	**$1751**	$3806	$5860	$7914	$12 023	$16 131

*Values represent ICERs expressed as cost (in I$) per QALY; values in bold type indicate scenarios in which HPV vaccination of boys falls below the per capita GDP of Vietnam; shaded values indicate strategies in which HPV vaccination of boys falls below 50% of the per capita GDP of Vietnam; strategies listed in order of increasing effectiveness; 'CS' denotes strategies that were cost-saving compared with no intervention, because the future costs averted by preventing cancer were greater than the cost of the intervention. For each coverage level and cost scenario, the ICERs are calculated as the additional cost of a strategy divided by its additional benefit when compared to the next less costly strategy. However, in scenarios in which vaccination of girls only was cost-saving, the ICER for vaccination of girls and boys was calculated in comparison to vaccination of girls only and not natural history. All strategies assume no cervical cancer screening coverage.

**Cost per vaccinated adolescent (2008 international dollars) includes three vaccine doses, wastage, freight and supplies, administration, immunisation support, and programmatic costs.

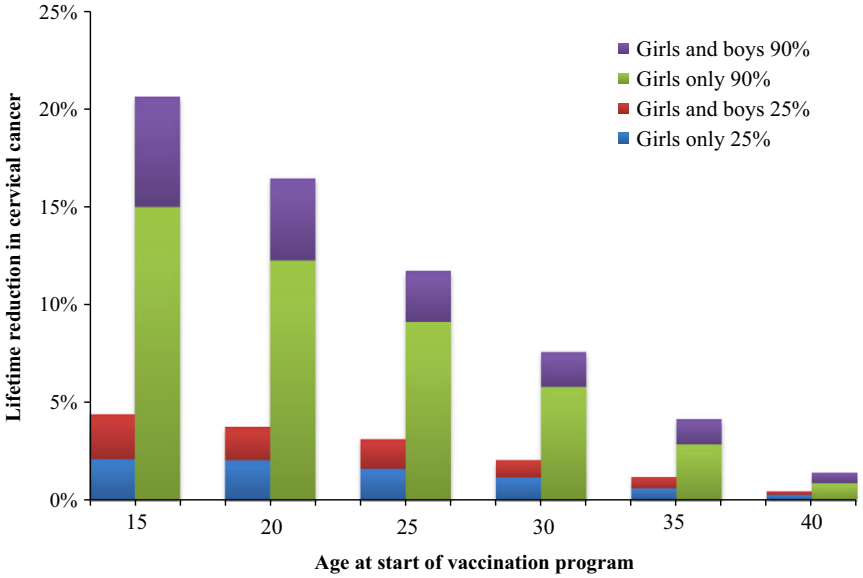

Figure 1. Herd immunity benefits to older unvaccinated cohorts. Lifetime reductions in cervical cancer for females aged from 15 to 40 years at the start of the vaccination programme. Benefits are shown for 25 and 90% coverage for girls alone and girls and boys.

(ICER = I$2730 per QALY). Using the lower threshold (50% of Vietnam's GDP per capita), vaccinating boys was cost-effective up to 50% coverage at I$5 per dose under all assumptions and exceeded the threshold at 75% coverage, with the exceptions of doubling of partners and doubling of cancer costs, which yielded ICERs of I$1800 and I$1330 per QALY, respectively. At a cost of I$10 per dose, no analyses yielded ICERs below the 50% GDP threshold. Assuming 25% of women received cytology screening once per lifetime at age 45 years decreased the cost-effectiveness of vaccinating boys relative to the base case of no screening. Further increasing screening coverage to 100% yielded the highest ICERs. Doubling cancer costs had the greatest beneficial impact on the ICERs, decreasing the cost per QALY by I$280 compared with the base case regardless of vaccine cost or coverage. Varying the number of sexual partners had a non-linear impact on base-case ICERs: doubling number of partners generated higher ICERs at lower vaccine coverage and lower ICERs at higher vaccine coverage. Conversely, halving the number of partners yielded more attractive ICERs than the base case at lower vaccine coverage but less attractive ICERs at higher coverage.

Discussion

Main findings

Despite the high cervical cancer burden in south Vietnam, our results suggest that including boys in the HPV vaccination programme provides a marginal reduction in cancer risk compared with vaccinating girls alone. Although herd immunity benefits to older cohorts increased with greater coverage of boys, ICERs for vaccination strategies of both sexes were far higher than those for girls alone at the same coverage even when considering the reduction of genital warts. Consistent with previous analyses, we found that increasing coverage of girls provided greater health benefits than extending coverage to boys.[15,34,35] For example, at a cost of I$10 per dose, increasing coverage of girls from 25 to 50% has an incremental cost of I$102 per vaccinated girl and achieves a two-fold increase in QALYs compared with vaccination of girls only at 25%; by comparison, expanding coverage to boys at 25% costs I$139 per vaccinated adolescent and provides only a 28% increase in QALYs (Appendix Table S1). Using a threshold of Vietnam's GDP (I$2800), we found that including boys in an HPV vaccination programme of girls may not be a good health investment for cervical cancer prevention unless vaccine costs are low (≤I$5 per dose) and/or vaccine coverage is low (Table 1). Inclusion of HPV-6/11-associated genital warts made ICERs more attractive by 12–15%, but had little impact on our conclusions. Vaccination of both sexes at 75% coverage at a cost of I$10 per dose fell just below the cost-effectiveness threshold (Table 2). Realistically, GDP per capita may be a high threshold for a developing country so we explored the implications of a lower threshold (50% of GDP per capita). Under this threshold, vaccination of boys is cost-effective only at a cost per dose of I$2 or I$5 if coverage is 75% or lower even with the inclusion of genital warts reduction. Results were robust to a number of sensitivity analyses including 100% screening coverage for one-time screening with cytology, reduced cancer costs, and changes in sexual mixing patterns (Figure 2).

In light of the GAVI Alliance's decision to prioritise funds for HPV vaccination in eligible countries,[10] policy-

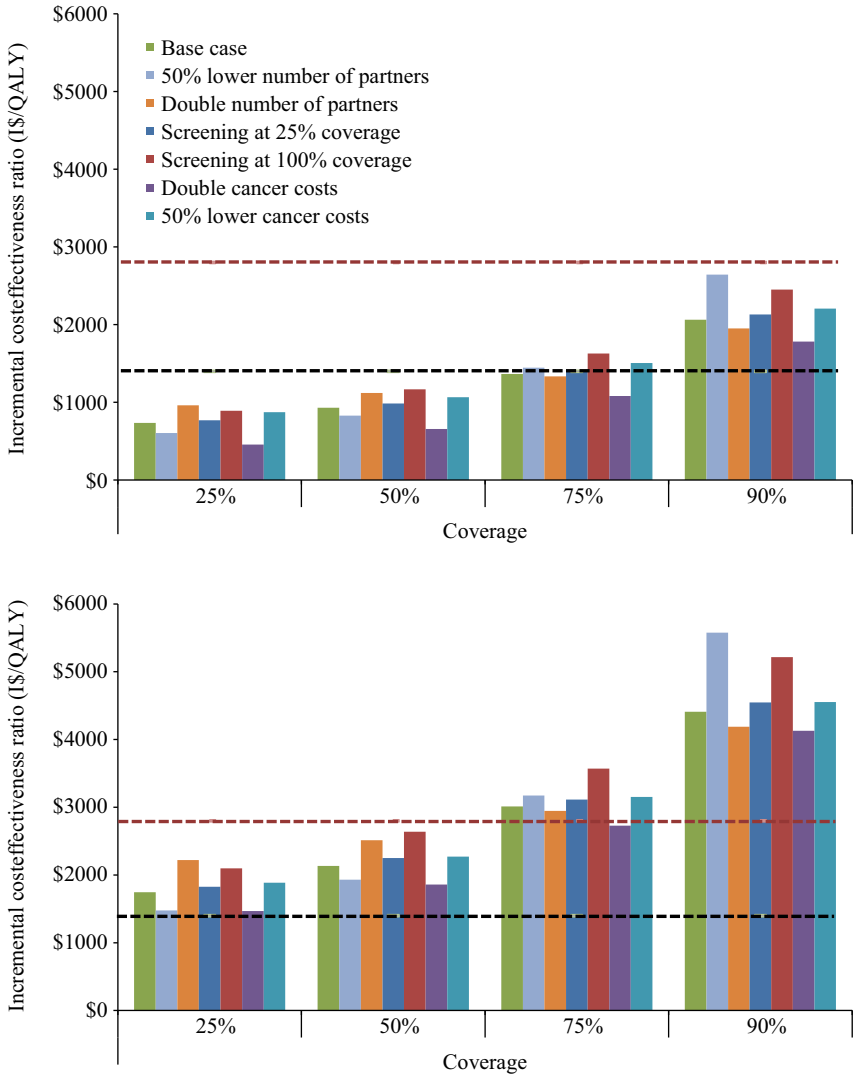

Figure 2. Sensitivity analyses. Impact of varying assumptions on the incremental cost-effectiveness ratios of vaccinating girls and boys versus vaccinating girls alone in south Vietnam at different coverage levels for vaccine costs of I$5 per vaccinated adolescent (top panel) and I$10 per vaccinated adolescent (bottom panel). Red dashed lines depict the ICER threshold of Vietnam's GDP per capita. Black dashed lines depict 50% of Vietnam's GDP per capita.

makers in Vietnam may consider applying for support to implement large-scale vaccination. We aimed to provide evidence-based insight to inform discussions about resource allocation. Consistent with previous analyses,[13,14] we found that HPV vaccination of girls alone was highly cost-effective, particularly at costs ≥I$20 per dose. Vaccinating boys may be cost-effective if Vietnam obtains the GAVI price of I$5 per dose, but provides little incremental benefit over vaccinating girls only, particularly at high coverage of girls. Indeed, recent HPV vaccine demonstration projects in Vietnam have achieved 83–96% coverage of girls for all three doses administered through school and health centre-based programmes, indicating that high coverage of girls is feasible.[36] The results of our analysis are relevant to policy-makers in other developing settings who are considering the implementation of Cervarix or Gardasil. Although absolute costs and cancer reductions will vary by setting, the relative benefit of adding boys to a vaccination programme of girls is likely similar. Additionally, although we focused our analysis on south Vietnam, our results can be useful for north Vietnam, where cervical cancer burden is far lower and HPV vaccination of boys is likely to be less cost-effective.

Strengths and limitations

Our analysis employed a long-time horizon that incorporates immediate costs of a vaccination programme as well as future costs averted by preventing cervical cancers and

genital warts. We used a well-known model of cervical cancer pathogenesis calibrated to primary epidemiological data from south Vietnam, including sexual behaviour characterised from a thorough literature review. This analysis is the first to examine the benefits of male HPV vaccination in Vietnam, as well as the first to include health benefits from reductions in genital warts in a developing setting.

Although cost-effectiveness analyses can identify interventions providing good 'value for money', they do not provide information on affordability given fixed budgets or competing health priorities. In addition to cost-effectiveness, factors including feasibility, cultural acceptability, political will and equity will probably be incorporated into policymakers' decisions about implementing HPV vaccination and determining the target population.

Similar to all model-based approaches, our analysis is subject to several limitations. Certain progressions in the natural history of HPV to cervical cancer are unobservable so we estimated them indirectly through our calibration procedure; we estimated HPV-16/18 transmission per partnership in a similar fashion. As the focus of our analysis was cervical cancer prevention, we did not incorporate the potential of vaccination to avert other HPV-related cancers (i.e. oropharyngeal, anal, penile and vulvar cancer). However, these cancers are very rare in Vietnam. For example, anal cancer incidence is estimated to be 0.1–0.4 per 100 000 person-years, and vulvar and vaginal cancer incidences are 0.4 and 0.2 per 100 000 person-years, respectively.[5] Their inclusion would make vaccination strategies more cost-effective but would be unlikely to change our conclusions. Our findings are in consensus with the published literature, with most analyses finding that including boys in an HPV vaccination programme is not cost-effective, particularly in developing countries and increasing vaccination coverage of girls provides greater health benefits than extending coverage to boys.[15,37] In addition, we assumed complete, lifelong vaccine efficacy. As additional data on duration of vaccine protection become available, this analysis should be re-visited.

Although we characterised sexual mixing patterns through a comprehensive literature review, sexual behaviours are based on self-report and are subject to underreporting and measurement error. We did not model homosexual or bisexual partnerships explicitly. We assumed random vaccination uptake within the population. If a subgroup of adolescents was more likely to receive the vaccine and more likely to form sexual partnerships with each other, herd immunity benefits of vaccinating boys might decrease and inclusion of boys in the vaccination programme would become less cost-effective. However, this pattern is less likely to impact our results at high vaccination coverage.

Interpretation

Similar to previous modelling analyses, our results suggest that the added benefit of cervical cancer and genital warts prevention from including boys in an HPV vaccination programme of girls is relatively small. Vaccination of boys is not cost-effective at vaccine costs greater than I$5 per dose if high vaccination coverage is achieved in girls. Our results are likely to be generalisable to other low-resource settings. The reductions afforded by including boys in an HPV vaccination programme are likely to be small relative to high coverage of girls only.

Conclusion

Focusing on attaining high HPV vaccination coverage of girls, rather than including boys in a vaccination programme, may be a more efficient strategy to reduce cervical cancer and genital warts in southern Vietnam and similar low-resource settings.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

MS and JK conceived of the analysis and wrote the manuscript. MS and SS conducted the analysis.

Details of ethics approval

None required.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Analytic overview, model calibration, and sensitivity analyses.

Table S1 is in the appendix S1.

Data S1. Powerpoint slides summarising the study. ■

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