RESEARCH COMMUNICATION

Burden of Disease Associated with Cervical Cancer in Malaysia and Potential Costs and Consequences of HPV Vaccination

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Abstract

Background: An estimated 70% of cervical cancers worldwide are attributable to persistent infection with human papillomaviruses (HPV) 16 and 18. Vaccination against HPV 16/18 has been shown to dramatically reduce the incidence of associated precancerous and cancerous lesions. The aims of the present analyses were, firstly, to estimate the clinical and economic burden of disease attributable to HPV in Malaysia and secondly, to estimate long-term outcomes associated with HPV vaccination using a prevalence-based modeling approach. Methods: In the first part of the analysis costs attributable to cervical cancer and precancerous lesions were estimated; epidemiologic data were sourced from the WHO GLOBOCAN database and Malaysian national data sources. In the second part, a prevalence-based model was used to estimate the potential annual number of cases of cervical cancer and precancerous lesions that could be prevented and subsequent HPV-related treatment costs averted with the bivalent (HPV 16/18) and the quadrivalent (HPV 16/18/6/11) vaccines, at the population level, at steady state. A vaccine efficacy of 98% was assumed against HPV types included in both vaccines. Effectiveness against other oncogenic HPV types was based on the latest results from each vaccine's respective clinical trials. Results: In Malaysia there are an estimated 4,696 prevalent cases of cervical cancer annually and 1,372 prevalent cases of precancerous lesions, which are associated with a total direct cost of RM 39.2 million with a further RM 12.4 million in indirect costs owing to lost productivity. At steady state, vaccination with the bivalent vaccine was estimated to prevent 4,199 cervical cancer cases per year versus 3,804 cases for the quadrivalent vaccine. Vaccination with the quadrivalent vaccine was projected to prevent 1,721 cases of genital warts annually, whereas the annual number of cases remained unchanged with the bivalent vaccine. Furthermore, vaccination with the bivalent vaccine was estimated to avert RM 45.4 million in annual HPV-related treatment costs (direct+indirect) compared with RM 42.9 million for the quadrivalent vaccine. Conclusion: This analysis showed that vaccination against HPV 16/18 can reduce the clinical and economic burden of cervical cancer and precancerous lesions in Malaysia. The greatest potential economic benefit was observed using the bivalent vaccine in preference to the quadrivalent vaccine.

Keywords: Cervical cancer burden - HPV vaccination - Malaysia

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Introduction

Human papillomaviruses (HPV) are common double-stranded DNA viruses that infect epithelial tissues and estimates suggest that, globally, HPV DNA is present in 10.4% of women with normal cervical cytology (de Sanjose et al., 2007). A number of types of HPV have been causally linked to cervical cancer (Bosch et al., 2002), which is the third most common cancer in women and accounts for 8.8% of all female cancers (Ferlay et al., 2010). In the Malaysian peninsula this figure is 9.1% with the age-standardized incidence rate being approximately 12.2 cases per 100,000 women in 2006 (Malaysian National Cancer Registry, 2006). This is reflective of the fact that the Asia-Pacific region bears a disproportionate amount of the global burden associated with cervical cancer. Indeed, Garland et al., (2008) estimate that 52% of all cervical cancer cases occur in the Asia-Pacific and Australasia region. Moreover, the same study estimates that if the current rate of cervical screening remains unchanged in this region there will be a 62% increase in the burden of disease associated with cervical cancer by 2025. Another noteworthy issue is the discrepancy between cervical cancer mortality rates in the Asia-Pacific region versus those in a number of European countries. The mortality rate in Malaysia is approximately 8.4 per 100,000 which is similar to that of other countries in the region, such as Indonesia, Singapore and Thailand, but more than two-fold higher in comparison with The Netherlands, the United Kingdom and Finland (Othman and Rebolj, 2009).

In Malaysia, despite the inception of freely available Papanicolaou (pap) screening in 1995 the uptake rate of screening remains low: approximately 43.7% of females

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above 18 years underwent at least one pap smear, but only 59.7% of those respondents who had undergone pap smear had it done less than 3 years ago (Third National Health and Morbidity Survey, 2006), which is considerably lower than in some European countries (e.g. The Netherlands and the UK; Canfell et al., 2006; Rebolj et al., 2007). Pap screening in Malaysia is largely opportunistic and barriers to screening include no national recall system, a lack of knowledge and resources as well as social and cultural barriers (Othman and Rebolj, 2009; Wong et al., 2009). The sub-optimal uptake of screening, despite its availability, therefore makes the evaluation of HPV vaccination programs, such as that performed in the present study, particularly salient. Although some studies raise the concern that barriers to HPV vaccination exist, particularly among conservative sectors of society (Chow et al., 2010), a recent study by Sam et al., (2009) suggests that maternal acceptance of HPV vaccination in Malaysia is high (approximately 66% acceptance for daughters, rising to approximately 98% if vaccination was routine and free of charge).

Two cervical cancer vaccines (a bivalent vaccine - Cervarix®(GSK) against HPV 16 and 18 and a quadrivalent vaccine - Gardasil® (Merck) against HPV 16,18, 6 and 11) have been developed and are currently available in the private healthcare sector in Malaysia. Evidence from large scale randomized controlled trials has shown that both vaccines significantly reduce the incidence of infection with HPV 16 and 18, which together are responsible for approximately 70% of cervical cancers worldwide. In particular, results of the PATRICIA trial on the bivalent vaccine, published by Paavonen et al., (2009) reported a vaccine efficacy against HPV 16/18 infection in CIN2+(cervical intraepithelial neoplasia) of 98.1% in a HPV-naïve population (i.e. pre-sexual debut of girls) with a mean follow up period of approximately 3 years. Similarly, in a phase III trial of >12,000 women aged 15-26 years the efficacy of the quadrivalent vaccine against high grade cervical lesions associated with HPV 16/18 was 98% in a HPV-naïve population (FUTURE II study group, 2007). Although both vaccines are specifically directed against the L1 viral capsid protein of HPV 16 and 18 (and HPV 6 and 11 in the quadrivalent vaccine), evidence of cross-protection against other HPV types has been observed with both vaccines. However, from their respective trials, the bivalent vaccine formulated with a proprietary AS04 adjuvant system has been reported to have higher efficacy against non-vaccine oncogenic HPV types compared with that reported by the quadrivalent vaccine (Brown et al., 2009; Skinner et al., 2009; Szarewski, 2010).

The cost-effectiveness of prophylactic cervical cancer vaccination has been extensively studied in a number of European and North American settings, the results of which have consistently shown cervical cancer vaccination, potentially, to be (highly) cost-effective in adolescent girls (Sanders et al., 2003; Goldie et al., 2004; Taira et al., 2004; Bergeron et al., 2008). However, there is a paucity of cost-effectiveness data from studies conducted in the Asia-Pacific region. The few studies that have been conducted in this region have largely concurred with the findings of European studies. For example, in a cost-effectiveness analysis in the Taiwanese setting (performed from a third party payer perspective) Liu et al., (2010) projected that the vaccination of 12 year-old females would reduce incident cervical cancer by 73%. They also reported a potential incremental cost-effectiveness ratio (ICER) of below USD 14,000 per quality-adjusted life (QALY) year gained versus no vaccination, which was considered to be a favorable ratio. A further analysis by Suarez et al., (2008), examined the cost-effectiveness of vaccination of 11 year-old females in five different settings including Taiwan. The authors reported an ICER of TWD 278,665 per QALY gained, indicating that HPV vaccination was considered to be cost-effective compared with screening alone. However, it was noted that the ICER was sensitive to changes in assumptions regarding discount rate used and age at vaccination.

Given the lack of data available for the Malaysian setting the current analysis was designed to examine the potential clinical and economic outcomes associated with the introduction of a cervical cancer vaccination program in the Malaysian setting. The current analysis was performed in two parts. Firstly, a burden of disease study was performed to determine the direct and indirect costs associated with the treatment of cervical cancer and precancerous lesions (abnormal pap smear, cervical intraepithelial neoplasia [CIN] 1 and CIN 2/3) and to determine the overall burden of disease attributable to cervical cancer in Malaysia (from both a societal and third party payer perspective). In the second part of the analysis data from the burden of disease study were used to inform a prevalence-based model used to estimate the potential number of cases of cervical cancer and precancerous lesions that could be prevented with vaccination using the bivalent vaccine directed against HPV 16/18 and the resultant treatment costs that could potentially be averted. Lastly, the clinical and economic impact of vaccination with the bivalent versus the quadrivalent vaccine were compared.

Materials and Methods

Burden of disease study

The burden of disease study was performed to estimate the direct, indirect and total annual costs associated with cervical cancer and precancerous lesions in Malaysia.

In Malaysia, cervical cancer cases are treated primarily within regional hospitals, whilst precancerous lesions are treated primarily within the ambulatory care set up. In order to assess the average direct costs per patient associated with cervical cancer, a retrospective review of patient records from four hospitals from the period January 2007 to December 2008 was performed to identify cervical cancer patients and to characterize resource use in these patients. The four hospitals chosen in this study (one teaching hospital in Kuala Lumpur and three government hospitals in Central, Northern and East Coast region of Malaysia) are geographically dispersed and were carefully selected to provide data representative of the whole country. A total of 444 hospital admissions attributable to cervical cancer were identified at the selected hospitals,

classified according to the ICD-10 code C53 for malignant neoplasm of the cervix uteri. Cervical cancer cases were categorized according to cancer stage.

The clinical treatment pathways and annual resource use (number of visits, medication use and procedures) of patients with precancerous lesions were estimated by an expert panel comprising obstetricians, pathologists, oncologists, radiotherapists, public health specialists and nurses. The number of leave days attributable to inpatient and outpatient visits associated with precancerous lesions and cervical cancer (16 leave days per hospitalization and 3 leave days per outpatient visit) was also estimated by the expert panel.

The direct costs of inpatient and outpatient treatment of cervical cancer were estimated using a top-down costing approach. Clinical Cost Modeling Software Version 2.1 (CCM Ver. 2.1) was used to distribute the cost from top level overhead cost centers to intermediate and patient cost center, with the final cost endpoint being cost per day of stay per patient with cervical cancer. Outpatient treatment costs for patients with precancerous lesions were estimated by multiplying annual outpatient resource use by unit costs (based on unit cost charges from a teaching hospital in Malaysia). The societal analysis accounted costs due to lost productivity due to absenteeism; however, lost productivity associated with presenteeism (compromised productivity in the workplace owing to illness) was not included due, in part, to the heterogeneity associated with defining presenteeism and the difficulty in quantifying it. Costs attributable to lost productivity (absenteeism) were calculated by multiplying the number of leave days, estimated by the expert panel, by the average gross domestic product per capita per day in 2008 (Malaysian Ringgit [RM] 65 per day). All costs in the analysis are presented in 2008 RM.

The total burden of precancerous lesions and cervical cancer, from a societal perspective, was calculated by multiplying the direct and indirect average annual cost per patient with the prevalent number of precancerous lesions and cervical cancer cases. The total burden from a provider's perspective was estimated similarly, but including direct medical costs only. The annual number of prevalent cervical cancer cases were retrieved from the WHO GLOBOCAN 2002 database, using 5-year prevalence data. The annual number of prevalent cases of precancerous lesions were calculated by multiplying the proportion of cases of precancerous lesions relative to the number of cervical cancer cases in Malaysia (based on an earlier study by Sharifah Ezat et al., 2009) by the 5-year prevalence of cervical cancer.

Prevalence-based model assessment

A prevalence-based model that used 1-year cross-sectional data was developed to estimate the number of events (cases of precancerous lesions, cervical cancer and genital warts) and costs (direct+indirect) that could be avoided by vaccination, at the population level, at steady state (i.e. many years after the introduction of vaccination) when the majority of the susceptible population have been vaccinated. Two healthcare outcomes were analyzed. Firstly, the number of lesions prevented by each vaccine was calculated by multiplying the number of cases observed in one year by the corresponding lesion-specific vaccine efficacy. Secondly, the total savings in HPV-related treatment costs (direct+indirect) per year were calculated by multiplying the difference in the number of cases for each vaccination scenario (net number of cases prevented) by the treatment cost for each lesion type.

The rationale for selecting this approach was that a prevalence-based model offers the advantages of being transparent, is relatively straightforward and easily understood by decision makers, and requires fewer assumptions to be made in comparison with more complex models.

In the analysis the outcomes associated with the introduction of the bivalent vaccine versus no vaccine and of the bivalent vaccine versus the quadrivalent vaccine were examined. The costs of vaccination, in terms of pharmacy and administration costs were not included in the current analysis as this analysis assumed both vaccines to be priced at parity, thereby resulting in a null incremental value.

A vaccine coverage of 100% of 12 year-old females was assumed for both vaccines. The efficacy against CIN, cervical cancer and GW lesions associated with vaccine HPV types (i.e. with HPV-type 16 and 18 for the bivalent vaccine and with HPV-type 16, 18, 6 and 11 for the quadrivalent vaccine) was set at 98% for both vaccines, based on results from their respective clinical trials showing efficacy levels ranging from 96 to 100% depending on the endpoint (Haper et al., 2006; FUTURE II Study group, 2007; Garland et al., 2007; Paavonen et al., 2009; Muñoz et al., 2010). Cross-protection against non-vaccine oncogenic HPV types (HPV 31,33,35,39,45,51,52,56,58 and 59) was also taken into account in the model based on data from Brown et al., 2009; Skinner et al., 2009; Tjalma et al., 2009; Szarewski et al., 2010 (Table 1). Overall vaccine efficacy for each type of lesion was calculated based on the proportion of cases caused by the different HPV types in each type of lesion multiplied by the vaccine efficacy for each HPV type observed in a HPV-naïve population. As the only Malaysian data available on the distribution of cases according to subtype were based on a small sample size, and not recent, data from the WHO for the Asia region (Castellsague et al., 2007; WHO, 2010) were used. No discounting was applied to either future costs or clinical outcomes owing to the 1-year time horizon.

The annual number of cervical cancer cases and precancerous lesions were based on the same sources as those used for the burden of disease study (see further burden of disease study). For the estimation of the number of cases of genital warts it was assumed that prevalence was equal to incidence and that annual incidence of genital warts in women in Malaysia was 2,304 cases. Owing to a paucity of Malaysian data, incidence was derived from a number of assumptions. Firstly it was assumed that incidence in Malaysia was comparable to that reported in other countries, notably the US, UK and France, where incidence among females aged 15-65 years is approximately 100 per 100,000 (Simms and Fairley, 1997; Lukasiewicz et al., 2002; Insinga et al., 2003). It

Table 1. Model Input Data and Assumptions

	HPV type distribution in Malaysia (%)[a]	Bivalent vaccine		Quadrivalent vaccine	
		Vaccine efficacy (%)	Reference	Vaccine efficacy (%)	Reference
ASCUS					
Overall efficacy		22.2	Tjalma et al., 2009	16.0	Huh 2009
CIN1					
HPV 16/18	30.1	98	Consensus	98	Consensus
Cross protection	32.5	48	Tjalma et al., 2009	23.4	Brown et al., 2009
HPV 6/11	7.3	0		98	
Overall efficacy CIN1		45.1		44.3	
CIN2/3					
HPV 16/18	40.3	98	Consensus	98	Consensus
Cross protection	47.3	68.4	Skinner et al., 2009/ Szarewski, 2010	32.5	Brown et al., 2009
Overall efficacy CIN2/3		71.8		54.9	
Genital warts					
HPV 6/11	76.2	0	-	98	Consensus
Overall efficacy genital warts		0	-	74.7	
Cervical cancer					
HPV 16/18	74.9	98	Consensus	98	Consensus
Cross protection	23.4	68.4	Skinner et al., 2009/ Szarewski, 2010	32.5	Brown et al., 2009
Overall efficacy cervical cancer		89.4		81.0	

[a]Data on HPV type and distribution were derived from Castellsague et al. 2007 and the WHO/ICO Information Centre on Human Papilloma Virus (HPV) and Cervical Cancer; ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; Cross protection refers to HPV 31/33/35/39/45/51/52/56/58/59

was also assumed that only approximately 30% of cases of genital warts are treated in the Malaysian setting (M Rushdan, personal communication). Consequently, as there are approximately 8 million females in Malaysia aged 15-65 years, the number of treated cases of genital warts per year was estimated to be 2,304 cases. In the absence of data relating to the cost of treating genital warts specific to Malaysia, data from an Italian-based study were used as a proxy for the direct costs of treating warts (Capri et al., 2009) (the cost of treating one case of genital warts was EUR 144.37, exchange rate = RM 5.07 (Capri et al., 2009)). Indirect costs were based on input from the expert panel. Unit costs relating to the treatment of cervical cancer and precancerous lesions were derived from the burden of disease study.

In order to explore the impact of changes in assumptions relating to unit treatment costs and cross protection a number of univariate sensitivity analyses were performed. Specifically, scenarios in which treatment unit costs were increased and decreased by 20% were investigated. Additionally, sensitivity analyses in which the degree of the bivalent vaccine cross-protection against non-vaccine oncogenic HPV subtypes was increased and decreased by 20% were also performed.

Results

Burden of disease study

The results of the retrospective data review showed that the occurrence of cervical cancer in Malaysia is strongly related to age, with a total of 34.5% of cases occurring in women aged 50-59 years and that cervical cancer cases are frequently detected in the early stages of disease, with 64.4% of cases being either stage I or stage II disease (Table 2). Additionally, the ethnicity of the 444 cervical cancer patients was broadly representative of Malaysia, 49.8% of patients were Malay, 34.2% were Chinese, 11.3% Indian and 4.7% other. Inpatient care costs for cervical cancer were dependent on disease stage

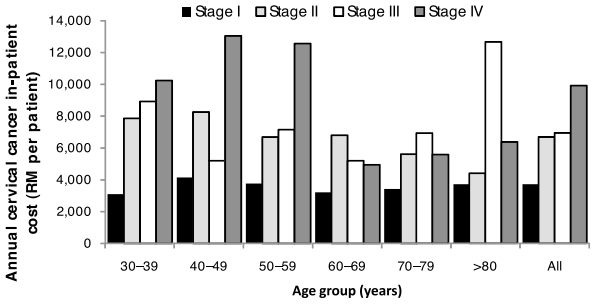

Figure 1. Annual Inpatient Cost of Treating Cervical Cancer According to Cancer Stage and Age Group in Malaysia

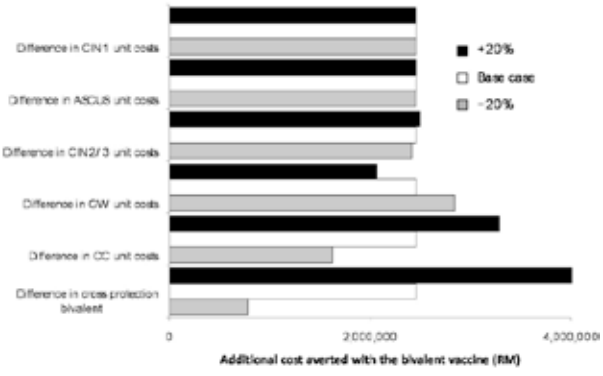

Figure 2. Results of Sensitivity Analysis, Additional Costs Averted with the Bivalent Vaccine Versus the Quadrivalent Vaccine

Table 2. Demographic Data of Cervical Cancer Patients Identified Via Patient Records in Four Hospitals in Malaysia

	Number of patients	Percent of total
By cancer stage		
Stage I	120	27.0
Stage II	166	37.4
Stage III	97	21.8
Stage IV	61	13.7
By age		
30-39 years	24	5.4
40-49 years	98	22.1
50-59 years	153	34.5
60-69 years	86	19.4
70-79 years	66	14.9
80+ years	17	3.8
Total	444	100

with patients with more advanced disease having higher annual costs, when considering all patients independent of age group (Figure 1). In some of the age groups other patterns were seen, but this might be partly explained by low sample sizes. From a societal perspective the average cost per patient per year of ASCUS (atypical squamous cells of undetermined significance), CIN1, CIN2/3 and cervical cancer in Malaysia were RM 898, RM 1,453, RM 1,948 and RM 10,540, respectively (Table 3). In terms of prevalence, data from the WHO GLOBOCAN estimated an annual prevalence of 4,696 cases of cervical cancer per year in Malaysia, and there were estimated to be a total of 1,372 cases of precancerous lesions (ASCUS, CIN1 and CIN2/3).

The total annual direct costs associated with the treatment of cervical cancer (both inpatient and

Table 3. Direct and Indirect Costs Associated with Cervical Cancer and Precancerous Lesions in Malaysia

	ASCUS	CIN1	CIN2/3	Cervical cancer	Total precancerous lesion and cervical cancer
Prevalence					
Total number of cases per year	451	329	592	4,696	
Average costs per patient per year					
Direct costs per patient per year					
Inpatient care	-	-	-	6,386	-
Outpatient care	508	1,063	1,558	1,632	-
Indirect cost per patient per year					-
Inpatient care	-	-	-	1,352	-
Outpatient care	390	390	390	1,170	-
Total cost per patient per year	898	1,453	1,948	10,540	-
Total annual burden in Malaysia (= prevalence * average costs per patient per year)					
Total annual direct cost	229,108	349,727	922,336	37,652,528	39,153,699
Inpatient care	-	-	-	29,988,656	29,988,656
Outpatient care	229,108	349,727	922,336	7,663,872	9,165,043
Total annual indirect cost	175,890	128,310	230,880	11,843,312	12,378,392
Inpatient care	-	-	-	6,348,992	6,348,992
Outpatient	175,890	128,310	230,880	5,494,320	6,029,400
Total annual cost	404,998	478,037	1,153,216	49,495,840	51,532,091

ASCUS, atypical squamous cells of undetermined significance; CIN cervical intraepithelial neoplasia

Table 4. Impact of HPV Vaccination in Malaysia

	ASCUS	CIN1	CIN2/3	Genital warts	Cervical cancer
Estimated annual number of cases (prevalence)	451	329	592	2,304[a]	4,696
Annual unit cost per case (direct and indirect)	898	1,453	1,948	1,120	10,540
Bivalent vaccine					
Overall efficacy	22.2	45.1	71.8	0	89.4
Estimated number of cases prevented (= prevalence * overall efficacy)	100	148	425	0	4,199
Treatment cost averted (= cases averted * annual unit costs per case)	89,910	215,585	828,553	0	44,253,043
Total treatment cost averted					45,387,091
Quadrivalent vaccine					
Overall efficacy	16.0	44.3	54.9	74.7	81.0
Estimated number of cases prevented	72	146	325	1,721	3,804
Treatment costs averted	64,800	211,565	632,729	1,926,999	40,095,095
Total treatment costs averted					42,931,188
Bivalent versus quadrivalent vaccine					
Additional cases prevented with the bivalent vaccine	28	3	101	-1,721	394
Additional treatment costs averted with the bivalent vaccine	25,110	4,020	195,824	-1,926,999	4,157,948
Total additional treatment costs averted with the bivalent vaccine					2,455,903

Numerical discrepancies are due to rounding of numbers; ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; [a]Expert opinion (prevalence of genital warts was assumed to be equal to incidence, and it was assumed that approximately 30% of genital warts cases in Malaysia are treated)

outpatient treatment) was RM 37,652,528 with a further RM 1,501,171 attributable to the outpatient treatment of precancerous lesions, leading to total direct costs of RM 39,153,699 (Table 3) for the management of HPV-related cervical lesions. The total indirect cost attributable to cervical cancer and precancerous lesions was RM 12,378,392. The results from the societal analysis show that total overall costs associated with cervical cancer are primarily driven by inpatient costs; however, 24% of overall costs were estimated to be attributable to lost productivity associated with absenteeism.

Prevalence-based model assessment

The results from the prevalence-based model assessment estimate that the introduction of a bivalent HPV vaccination program in 12 year-old females could potentially avert an estimated 4,199 cases of cervical cancer per year (Table 4). This in turn would avert an estimated RM 44,253,043 associated with direct treatment costs and lost productivity attributable to cervical cancer (assuming a mean cost of RM 10,540 per case). If the impact of vaccination on the prevention of precancerous lesions is also considered a total of 100, 148 and 425 cases of ASCUS, CIN1 and CIN2/3 could be prevented and a total of RM 1,134,048 per year in HPV-related treatment costs (direct + indirect) averted.

A second analysis was performed in which the outcomes associated with the introduction of the bivalent vaccine were compared with that of a vaccination program in which the quadrivalent vaccine was used. Both vaccines were assumed to have an efficacy of 98% against HPV 16 and 18; for the quadrivalent vaccine an efficacy of 98% against HPV 6 and 11 was also assumed. Despite equal efficacy against HPV 16 and 18 a greater reduction in the number of cases of cervical cancer cases (and cases of precancerous lesions) was predicted with the bivalent vaccine in comparison with the quadrivalent vaccine (Table 4). Indeed, an additional 394 cases of cervical cancer could potentially be prevented by vaccinating with the bivalent vaccine compared with the quadrivalent vaccine. The difference in the number of cases of cervical cancer and precancerous lesions observed with the two vaccines was attributable to differences in terms of the amount of cross-protection afforded against 10 non-vaccine oncogenic HPV types included in the model. Although the bivalent vaccine was projected to prevent a greater number of precancerous lesions and cervical cancer cases in comparison with the quadrivalent vaccine, the quadrivalent vaccine affords 98% protection against genital warts caused by HPV 6 and 11 whereas bivalent vaccine affords no protection against these HPV types (Table 4). Vaccination with the quadrivalent vaccine was projected to prevent 1,721 cases of genital warts annually, whereas the annual number of cases remained unchanged with the bivalent vaccine. The total HPV-related treatment costs (direct+indirect) averted by the bivalent vaccine were higher than by the quadrivalent vaccine (RM 45,4 million versus RM 42.9 million), as the costs saved by the prevention of additional lesions and cervical cancer cases (bivalent vaccine) outweighed the costs saved by the prevention of additional cases of warts (quadrivalent vaccine).

Sensitivity analysis

Results from the univariate sensitivity analyses (Figure 2) revealed that the overall cost difference between the two vaccines is most sensitive to the degree of cross protection offered by the vaccine, followed by the unit costs of cervical cancer and genital warts. Notably in a conservative scenario in which the degree of cross protection afforded by the bivalent vaccine was reduced by 20%, the bivalent vaccine remained superior to the quadrivalent vaccine, and was projected to prevent 244 more cases of cervical cancer and avert RM 781,946 in additional HPV-related treatment costs (direct + indirect) in comparison with the quadrivalent vaccine. If cross-protection was increased by 20% it was estimated that 545 more cases of cervical cancer and RM 4.1 million of additional HPV-related treatment costs would be prevented with the bivalent vaccine in comparison with the quadrivalent vaccine.

Discussion

The results of the present analysis have provided evidence that, at present, the clinical and economic burden of disease associated with cervical cancer in Malaysia is substantial, but that it could be considerably reduced by the introduction of a vaccination program targeted against HPV 16 and 18, the leading causes of cervical cancer. However, it may be many years before the full benefits of vaccination would be fully manifest. In the present analysis it was assumed that vaccination occurred in 12 year-old females; whereas data from the burden of disease study suggests that in excess of 70% of cervical cancer cases occur in women aged over 50 years.

In the burden of disease study the annual number of cervical cancer cases was estimated to be 4,696 with a further 1,372 cases of precancerous lesions (ASCUS, CIN1 and CIN2/3). In comparison to what is observed in most countries, the number of precancerous lesions are lower than the number of cervical cancer cases in Malaysia, which may be explained by the low screening coverage.

Together, the treatment of cervical cancer and precancerous lesions is currently associated with estimated annual direct costs of RM 39.1 million with indirect costs associated with lost productivity contributing a further RM 12.4 million to the overall economic burden. The results of the prevalence-based model assessment indicated that, at steady state, the incidence of cervical cancer in Malaysia could potentially be reduced by in excess of 89% by vaccinating all 12 year-old females with the bivalent HPV 16/18 vaccine. This in turn could avert an estimated RM 45.4 million in direct and indirect costs associated with the treatment of cervical cancer and precancerous lesions. Moreover, an analysis comparing the number of cases and associated treatment costs averted with the bivalent vaccine in comparison with the quadrivalent vaccine suggested that 394 more cases of cervical cancer could be prevented and additional RM 2.5 million of HPV-related treatment costs (direct+indirect)

averted, annually with the bivalent vaccine. Indeed, the introduction of a national vaccination program, using the bivalent vaccine, could potentially reduce the economic burden associated with precancerous lesions and cervical cancer treatment by in excess of 85%. To provide some context for these figures, in 2008 the operating budget for the Ministry of Health was RM 10.7 billion with overall expenditure on health in both the public and private sector totaling RM 30.2 billion (Ministry of Health, 2008). The magnitude of the clinical and economic benefits of HPV vaccination projected in this study is therefore considerable. Additionally, it is possible that the estimation of the clinical cancer burden averted may even be conservative as the current study does not take into account the potential prevention of other cancer types that have been etiologically linked to HPV 16/18 as for example head and neck cancer (Marur et al., 2010).

In the modeling analysis a vaccine efficacy against HPV 16/18 of 98% was assumed for both vaccines and efficacy of 98% was also assumed against HPV 6/11 for the quadrivalent vaccine. The difference in the projected number of cases averted with the two vaccines was therefore attributable to the higher degree of protection that has been observed in clinical trials with the bivalent vaccine against the ten non-vaccine HPV subtypes included in the analysis. Moreover, these findings remained robust in sensitivity analyses as even in a conservative scenario in which the degree of cross-protection afforded by the bivalent vaccine was reduced by 20% the bivalent vaccine was still associated with a greater reduction in the number of cervical cancer cases and additional costs averted in comparison with the quadrivalent vaccine.

The limitations of this study should also be noted, in particular the modeling methodology used was not that of a cost-effectiveness model evaluating future costs and clinical outcome for a cohort of patients over a time horizon of patient lifetimes, which might be preferred by some decision makers to judge the cost-effectiveness of HPV vaccination. However, the type of information derived from this study might be preferred by many other (financial) decision makers, as it gives annual budget forecasts substantiated by information on the difference in cases prevented. Another limitation of the current analysis was the use of non-Malaysian data relating to the direct costs associated with the treatment of genital warts, which is clearly sub-optimal. However, in the absence of Malaysian data the use of data from a similar study conducted in a different setting (in this instance Italian data published by Capri et al., 2009) represents the best available alternative.

The current analysis is also subject to a number of limitations inherent to modeling, in particular that the data used here have been used to project outcomes many years after the introduction of HPV vaccination, which has required a number of assumptions to be made. Notably, the modeling analysis assumed that the duration of vaccine efficacy was that of patient lifetimes. Whilst long-term data for both HPV vaccines are not yet available, ongoing studies have shown that antibody levels are maintained for up to 8.4 years for the bivalent vaccine (Rotelli-Martins et al., 2010). Additionally, a modeling study by David et al., (2009) projected the persistence of HPV 16 and 18 antibody levels using a number of different modeling methods. They consistently projected that antibody levels with the bivalent vaccine would persist at levels well above those induced by natural infection for at least 20 years (David et al., 2009). In light of this, it is reasonable to assume for purposes of this modeling exercise that the duration of vaccine protection for the bivalent vaccine would be that of patient lifetimes. A recent head-to-head comparison of the immunogenicity profile over time of the two vaccines demonstrated that the bivalent vaccine induced a significantly higher neutralizing antibody titre and more circulating memory B-cells specific to HPV 16 and 18, compared with the quadrivalent vaccine (Einstein et al., 2009). Even though the clinical significance of the difference in immune response is not known, this enhanced immune response may indicate that the bivalent vaccine provides longer duration of protection than the quadrivalent vaccine. By assuming lifetime protection for both of the vaccines in our modeling exercise, a conservative estimate of the additional health and economic gain of the bivalent versus the quadrivalent vaccines was obtained.

Although the current analysis only examines the cost-consequences of vaccination in relation to cervical cancer cases potentially averted, a number of previous health economic analyses have concluded that vaccination is cost-effective in comparison with the current standard of care in many settings, both in countries with and without established screening programs (Sanders and Taira, 2003; Goldie et al., 2004). A number of analyses have been conducted in the US setting where an established cervical screening program exists and which has contributed to a 74% reduction in mortality from cervical cancer in the period 1955-1992 (American Cancer Society, 2010). However, in many countries, there are inconsistencies in the availability and uptake of screening owing to a number of factors such as social and cultural barriers and the fact that rural areas are frequently underserved in terms of healthcare provision. In Malaysia, despite being freely available the uptake of screening is poor, furthermore, there is no national systematic recall, follow up and surveillance system. It is thought that in settings where cervical cancer screening is either unavailable or ineffective that vaccination represents a more practical approach to reducing the burden of cervical cancer (Stanley, 2008). However, even assuming a 100% vaccine efficacy, vaccination will not prevent all cases of cervical cancer, therefore screening is still necessary to detect cervical cancers.

In conclusions, the analysis has shown that the introduction of widespread vaccination of females against HPV 16/18 in Malaysia could potentially prevent 89% of cervical cancer cases at steady state. Furthermore, vaccination could potentially lead to annual savings of over RM 45 million in terms of HPV-related treatment costs (direct + indirect) averted. Vaccination with the bivalent vaccine is estimated to prevent more precancerous lesions, cervical cancer cases and HPV-related treatment costs compared with vaccination with the quadrivalent

vaccine but the quadrivalent vaccines prevents more genital warts.

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References

American Cancer Society. Detailed Guide: cervical cancer. Available at: http://www.cancer.org/docroot/cri/content/cri_2_4_1x_what_are_the_key_statistics_for_cervical_cancer_8.asp [Last accessed June 03, 2010]

Bergeron C, Largeron N, McAllister R, et al (2008). Cost-effectiveness analysis of the introduction of a quadrivalent human papillomavirus vaccine in France. *Int J Technol Assess Health Care*, **24**, 10-9.

Bosch FX, Lorincz A, Muñoz N, et al (2002). The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol*, **55**, 244-65.

Brown DR, Kjaer SK, Sigurdsson K, et al (2009). The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16-26 years. *J Infect Dis*, **199**, 926-35.

Canfell K, Sitas F, Beral V (2006). Cervical cancer in Australia and the United Kingdom: comparison of screening policy and uptake, and cancer incidence and mortality. *Med J Aust*, **185**, 482-6.

Capri S, Demarteau N, Standaert B (2009). Differences in cross-protection between bivalent and quadrivalent vaccines: cost-consequences evaluation in the Italian setting. Poster presentation at the 16th International Meeting of the European Society of Gynaecological Oncology, Belgrade, Serbia October 11-14.

Castellsague X, de Sanjose S, Aguado T, et al (2007). HPV and cervical cancer in the world: 2007 report. *Vaccine*, **25**, C1-26.

Chow SN, Soon R, Park JS, et al (2010). Knowledge, attitudes, and communication around human papillomavirus (HPV) vaccination amongst urban Asian mothers and physicians. Vaccine, Mar 25. [Epub ahead of print]

David MP, Van Herck K, Hardt K, et al (2009). Long-term persistence of anti-HPV-16 and -18 antibodies induced by vaccination with the AS04-adjuvanted cervical cancer vaccine: modeling of sustained antibody responses. *Gynecol Oncol*, **115**, S1-6.

de Sanjosé S, Diaz M, Castellsagué X, et al (2007). Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. *Lancet Infect Dis*, **7**, 453-9.

Dunne EF, Unger ER, Sternberg M, et al (2007). Prevalence of HPV infection among females in the United States. *JAMA*, **297**, 813-9.

Einstein MH, Baron M, Levin MJ, et al (2009). HPV-010 study group. Comparison of the immunogenicity and safety of cervarix and gardasil human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18-45 years. *Hum Vaccin*, **5**, 705-19.

Ferlay J, Shin HR, Bray F, et al (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*, [EPub ahead of print].

Fleury MJ, Touzé A, Alvarez E, et al (2006). Identification of type-specific and cross-reactive neutralizing conformational epitopes on the major capsid protein of human papillomavirus type 31. *Arch Virol*, **151**, 1511-23.

FUTURE II Study Group (2007). Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med*, **356**, 1915-27.

Garland SM, Cuzick J, Domingo EJ, et al (2008). Recommendations for cervical cancer prevention in Asia Pacific. *Vaccine*, **26**, M89-98.

Garland SM, Hernandez-Avila M, Wheeler CM, et al (2007). FUTURE I investigators. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med*, **356**, 1928-43.

Goldie SJ, Kohli M, Grima D, et al (2004). Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. *J Natl Cancer Inst*, **96**, 604-15.

Harper DM, Franco EL, Wheeler CM, et al (2006). HPV Vaccine Study group. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet*, **367**, 1247-55.

Health Facts (2008). Health Informatics Centre Planning and Development Division. Ministry of Health Malaysia (Published in May 2009) Available at: http://www.moh.gov.my/images/gallery/stats/heal_fact/health_fact_2008_page_by_page.pdf [Last accessed June 03, 2010]

Huh WK (2009). Impact of quadrivalent human papillomavirus (hpv) types 6/11/16/18 l1 virus-like particle vaccine on the incidence of abnormal pap tests and cervical procedures. (Abstract number 020 presented at the society of gynecologic oncologists (sgo) annual meeting on women's cancer, 9 -12 March, 2009, Tampa, U.S.A.)

Insinga RP, Dasbach EJ, Myers ER (2003). The health and economic burden of genital warts in a set of private health plans in the United States. *Clin Infect Dis*, **36**, 1397-403.

Lukasiewicz E, Aractingi S, Flahault A (2002). Incidence and management of condylomata accuminata by French general physicians. *Ann Dermatol Venereol*, **129**, 991-6.

Liu PH, Hu FC, Lee PI, et al (2010). Cost-effectiveness of human papillomavirus vaccination for prevention of cervical cancer in Taiwan. *BMC Health Serv Res*, **10**, 11.

Malaysian National Cancer Registry (2006). Malaysian cancer statistics data and figures Malaysian Peninsula.

Marur S, D'Souza G, Westra WH, et al (2010). HPV-associated head and neck cancer: a virus-related cancer epidemic. *Lancet Oncol*, **11**, 781-9.

Muñoz N, Kjaer SK, Sigurdsson K, et al (2010). Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. *J Natl Cancer Inst*, **102**, 325-39.

Othman NH, Rebolj M (2009). Challenges to cervical screening in a developing country: the case of Malaysia. *Asian Pac J Cancer Prev*, **10**, 747-52.

Paavonen J, Naud P, Salmerón J, et al (2009). HPV PATRICIA study group. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomized study in young women. *Lancet*, **374**, 301-14.

Rebolj M, van Ballegooijen M, Berkers LM, et al (2007). Monitoring a national cancer prevention program: successful changes in cervical cancer screening in the Netherlands. *Int J Cancer*, **120**, 806-12.

Roteli-Martins CM, Naud P, Borba P, et al (2010). Sustained immunogenicity and efficacy of the HPV 16/18 AS04 adjuvanted vaccine: follow up of up to 8.4 years. Abstract presented at European society for pediatric infectious diseases meeting May 2010, Nice, France.

Sam IC, Wong LP, Rampal S, et al (2009). Maternal acceptance of human papillomavirus vaccine in Malaysia. *J Adolesc Hlth*, **44**, 610-2.

Sanders GD, Taira AV (2003). Cost-effectiveness of a potential vaccine for human papillomavirus. *Emerg Infect Dis*, **9**, 37-48.

Sharifah Ezat WP, Aljunid SA, Ng P, et al (2009). Quality of life among preinvasive and invasive cervical cancer in Malaysia. *ASEAN J Psychiatry*, **10**, 1-11.

Simms I, Fairley CK (1997). Epidemiology of genital warts in England and Wales: 1971 to 1994. *Genitourin Med*, **73**, 365-7.

Skinner R, Apter D, Chow SN, Wheeler C, Dubin G, for the HPV PATRICIA Study Group(2009). Cross-protective efficacy of Cervarix™ against oncogenic HPV types beyond HPV-16/18. Abstract number O-29.01. presented at the 25th International Papillomavirus Conference, May 8-14, Malmö, Sweden

Smith JS, Lindsay L, Hoots B, et al (2007). Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int J Cancer*, **121**, 621-32.

Stanley M (2008). Human papillomavirus vaccines versus cervical cancer screening. *Clin Oncol (R Coll Radiol)*, **20**, 388-94.

Suarez E, Smith JS, Bosch XF, et al (2008). Cost-effectiveness of vaccination against cervical cancer: a multi-regional analysis assessing the impact of vaccine characteristics and alternative vaccination scenarios. *Vaccine*, **26S**, F29-45.

Szarewski A (2010). HPV vaccine: Cervarix. *Expert Opin Biol Ther*, **10**, 477-87.

Taira AV, Neukermans CP, Sanders GD (2004). Evaluating human papillomavirus vaccination programs. *Emerg Infect Dis*, **10**, 1915-23.

Tjalma W, Paavonen J, Naud P, et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against abnormal cytology and low-grade histopathological lesions in an oncogenic hpv-naïve population. (Abstract number A-171-0004-01446 presented at the 16th international meeting of the European society for gynaecological oncology (ESGO), 11-14 Oct, Belgrade, Serbia).

Third National Health and Morbidity Survey. Available at: www.nih.gov.my/NHMS.

Wheeler CM, Kjaer SK, Sigurdsson K, et al (2009). The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in sexually active women aged 16-26 years. *J Infect Dis*, **199**, 936-44.

WHO/ICO Information Centre on Human Papilloma Virus (HPV) and Cervical Cancer. Available at: http://www.who.int/hpvcentre/en/ [Last accessed July 02, 2010]

WHO GLOBOCAN 2002 database - summary table by population. Available at: http://globocan.iarc.fr/. [Last accessed: September 13, 2010]

Wong LP, Wong YL, Low WY, et al (2009). Knowledge and awareness of cervical cancer and screening among Malaysian women who have never had a Pap smear: a qualitative study. *Singapore Med J*, **50**, 49-53.