RESEARCH COMMUNICATION

Comparative Cost-Effectiveness of HPV Vaccines in the Prevention of Cervical Cancer in Malaysia

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Abstract

Objectives: Cervical cancer(CC) had the second highest incidence of female cancers in Malaysia in 2003-2006. Prevention is possible by both Pap smear screening and HPV vaccination with either the bivalent vaccine (BV) or the quadrivalent vaccine (QV). In the present study, cost effectiveness options were compared for three programs i.e. screening via Pap smear; modeling of HPV vaccination (QV and BV) and combined strategy (screening plus vaccination). A scenario based sensitivity analysis was conducted using screening population coverages (40-80%) and costs of vaccines (RM 100-200/dose) were calculated. Methods: This was an economic burden, cross sectional study in 2006-2009 respondents were interviewed from six public Gynecology-Oncology hospitals. Methods included expert panel discussions to estimate treatment costs of CC, Genital warts and Vulva Vagina Cancers by severity and direct interviews with respondents using costing and SF-36 quality of life questionnaires. Results: A total of 502 cervical cancer patients participated with a mean age at 53.3±11.2 years and a mean marriage length of 27.7±12.1 years, Malays accounting for 44.2%. Cost/quality adjusted life year (QALY) for Pap smear in the base case was RM 1,215 and RM 1,100 at increased screening coverage. With QV only, in base case it was RM 15,662 and RM 24,203 when the vaccination price was increased. With BV only, the respective figures were RM 1,359,057 and RM 2,530,018. For QV combined strategy cost/QALY in the base case it was RM 4,937, reducing to RM 3,395 in the best case and rising to RM 7,992 in the worst case scenario. With the BV combined strategy, these three cost/QALYs were RM 6,624, RM 4,033 and RM 10,543. Incremental cost-effectiveness ratio (ICER) showed that screening at 70% coverage or higher was highly cost effective at RM 946.74 per QALYs saved but this was preceded by best case combined strategy with QV at RM 515.29 per QALYs saved. Conclusions: QV is more cost effective than BV. The QV combined strategy was more CE than any method including Pap smear screening at high population coverage.

Keywords: HPV vaccinations - pap smear screening - cost-effectiveness - quality of life - cervical cancer

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Introduction

Cervical cancer (CC) was the second most common cancer after breast cancer in women globally until 1985, and ranked as the second most common cancer among women in Malaysia in 2006 (National Cancer Registry MOH 2006). The age standardized rate has declined from 19.7/100,000 (year 2003) to 12.2 per 100,000 (year 2006), reflecting better screening, detection and early cancer management in this country. Not without setbacks in achieving national screening targets in coverage, the country has set an exemplary vision to reduce cancer among women in this country. This is done through proposing the publicly funded mass national country HPV vaccination among 13 year old girls announced in September 2009; and is on the verge of implementation through the Ministry of Education and Ministry of Health (MOH) collaborative efforts.

The human papillomaviruss (HPV) is one of the most common sexually transmitted infections worldwide (Ault 2006) that can further divided into high risks oncogenic HPVs and low risk HPVs. HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 are considered to be of oncogenic risk. The remaining genital types 6, 11, 42, 43 and 44 are considered of low oncogenic risk (Franco et al., 2001).

Invasive cervical cancer (ICC) and its dysplasia are strongly related to incident infection and prevalence of oncogenic genital HPVs. Genital HPV infections among women are predominantly acquired in adolescence, but its prevalence decreased in middle-aged women during to clearing by immune system of infected women. In a study by Smith et al., (2008), results indicated that among middle-aged women of between 35-50 years old; maximum HPV prevalence differed across geographical regions: Africa (~20%), Asia/Australia (~15%), Central and South America (~20%), North America (~20%), Southern Europe/Middle East (~15%), and Northern Europe (~15%). The worldwide variations in HPV prevalence across age appear to largely reflecting differences secondary to sexual behavior across geographical regions (Smith et al., 2008). High risk HPV

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genotypes were detected in 95% of the abnormal cervical smears in a Malaysia study by Sharifah et al., 2009. Eight high-risk oncogenic types were identified i.e. types 16, 18, 31, 51, 52, 56, 58 and 66. There is no study till now that evaluates HPV infection among normal cervical smears in this country as its cost effectiveness is debatable.

Two vaccine types are under scrutiny to achieve these visions with each having developed first generation prophylactic vaccines, now currently in Phase 3 trials (Koutsky et al., 2002; Harper et al., 2006; Joura et al., 2007) with successfully registering it for use in 2006. They are Gardasil (the name Merck & Co's has given its quadrivalent vaccine (QV)) and Cervarix (the name GlaxoSmithKline or GSK has given to its' bivalent vaccine (BV)). QV are known to cover against HPV genotypes 6, 11, 16 and 18. While BV covers against HPV types 16 and 18 only. Given the added value of cross protection from these vaccines, the final protections provided by both vaccines are expected to be higher than originally predicted, but this depend on the antigens used for immunization (Rousseau et al., 2001). However, both vaccines only work against women who are not already infected with HPV (Luntz 2006; Moss et al., 2006). The mass public vaccination program has not started in Malaysia's public sectors yet, although both HPV vaccinations have been on the private market since QV approval in 2006 subsequent to US Food and Drug Administration (FDA) and Malaysia's MOH approvals. The BV FDA approval came later in October 2009. Gardasil was licenced by the Australian Therapeutic Goods Administration in June 2006 for use in women and girls aged 9-25 years and boys aged 10-15 years (Skinner et al., 2008). Cervarix was licensed more recently for use in females 10-45 years. It is likely that Gardasil will also be approved for older women in the near future.

Merck's L1 virus like particle (VLP) QV is based on recombinant yeast technology designed to protect both males and females against HPV types 16 and 18 as well as 6 and 11. The former pair are associated with cervical cancer while the latter causing genital warts. Although most HPV infections are benign, persistent infection (repeated detection of an oncogenic type of HPV) is associated with the development of cervical cancer (Joura et al., 2007). Merck & Co started the third phase human clinical trials of 25,000 women in 33 countries in an effort to develop an anti HPV vaccination program. It was found that the vaccine was 100% effective against two strains of HPV responsible for 70% of cervical cancer, vulva and vaginal cancers (Ault, 2006; Harper et al., 2006). The low-risk HPV types are associated with genital warts and low-grade intraepithelial lesions of the cervix, vagina, and vulva (Clifford et al., 2005; Markowitz 2007). Participants in QV trial were given a three-stage dose of either Gardasil, or a placebo. QV prevented all cases of pre-cancer and non-invasive cervical, vulva and vaginal cancers in the women administered to it. QV also reputed no side-effects more serious than local discomfort and pain at the injection site (Joura et al., 2007; Koutsky, 2007).

Vaccine efficacy was defined as (1-relative risk) x 100%, where the relative risk is the ratio of the incidence rate in the vaccine group over the incidence rate in the placebo group (Joura et al., 2007). The sustained high efficacy of QV against clinical disease was found whereby 98% protection against high grade intra-epithelial disease and external genital warts. There is no immune correlation or a peak serum antibody titer that actually correlates with an immune protection. Robust immune memory (B cells and plasma cells) i.e. strong anamnestic or recall response was found in the QV (Koutsky et al., 2002; Villa et al., 2006; Koutsky, 2007).

GSK's BV is based on recombinant baculovirus technology and formulated with the proprietary adjuvant efficacy enhancer AS04. ASO4 is formulated with aluminium hydroxide combined with a novel substance (alum plus monophosphoryl lipid A [MPL]). It induced sustained efficacy up to 5.5 years of antibody levels against the two most common cancer-causing HPV types i.e. types 16 and 18, although the end point in this study was against precancerous and cervical cancer per say and not examining incidence of vulva and vaginal cancers. The BV is currently undergoing Phase III clinical trials involving more than 30,000 women worldwide. Both vaccines are considered safe and effective in producing response greater than natural infection, with no serious side effects and with the evidence of cross protection (Ault 2006; Harper et al., 2006).

Joura et al., (2007) and Garland et al., (2007) concluded that the QV was 100% effective against ano genital diseases; VIN (Vulva intra epithelial neoplasi) stage 2-3 or VaIN (Vagina intra epithelial neoplasia) stage 2-3 irrespective of whether the HPV DNA was detected in the lesion or not as much as 49% (95% CI: 18-69). This climbed to as high as 100% (95% CI: 72-100) in the women population naive for HPV at the start of the study. In a vaccinated cohort of 12-year-old girls, impact of vaccination on cervical cancer and deaths; precancerous lesions and screening were estimated. Results indicated a reduction of 66% in the prevalence of high grade precancerous lesions and a 76% reduction in cervical cancer deaths (Kohli et al., 2007) and thus reducing the number of cervical cancer incidence and deaths.

The long and short term effects post vaccinations are multiple. Sanders and Taira (2003) showed that a vaccine with a 75% probability of immunity against high-risk HPV infection resulted in a life-expectancy gain of 2.8 days or 4.0 quality-adjusted life days at a cost of $246 relative to current practice (i.e. an incremental cost effectiveness of $22,755/ quality-adjusted life year). Koutsky et al., (2002), showed that vaccination three times with the HPV 16 L1 VLPs provided 100% protection (95% CI: 90-100 at $p<0.001$) over 17.4 months but reduced to 91.2% (95% CI: 80-97) when women with pre-existing transient infections were included. Joura et al., (2007) also supported similar findings of highly efficacious vaccine property. A study by Taira et al., (2004) predicted that HPV vaccine would reduce the new developments of cervical cancer associated with HPV 16 and 18 by 95%. Elbasha et al., (2007) predicted that reduction would be 91% and Taira et al., (2004) predicted at 61.8% based on different assumptions as well. However these studies agreed it would take at least a decade for the effect to be seen in a mass organized screening scenario. Assuming the

same trend would happen in Malaysia once the adoption of HPV vaccination into the country's immunization programs, this would lead to lower incidence of cervical cancer for Malaysia; to plunge to as low as 3.5/100,000 in the next decade as well

Materials and Methods

This was a cross sectional study from November 2006 till December 2008 done in five tertiary hospitals based in West Malaysia and a teaching hospital in Klang Valley that provided gynae oncology services to public patients in Malaysia. Patients with cervical cancers and pre invasive diseases were universally selected in gynaecological and oncological inpatients wards and specialists out patients' clinics. Selection criteria's include aged 18 and above; diagnosed with cervical changes i.e. Atypical Squamous Cells of Undetermined Significance (ASCUS), pre invasive diseases such as LSIL (CIN 1) and HSIL (collectively for CIN 2 and CIN 3) or invasive squamous cell carcinoma (ICC) for at least six months prior seen at hospitals and agreed to give written consent and participated. Patients that have been admitted or seen at these tertiary hospitals were patients referred by primary or secondary districts hospitals, primary health centres or private general practitioners throughout the country.

Cost Effectiveness Analysis and Assumptions with the Two Vaccines

The need to study local scenario between these two HPV vaccines and impact on cost per QALYs saved was the main objective in this study. Specifically, this study aims to undertake comparative cost effective analysis of management of cervical cancer in Malaysia by publicly funded health care providers.

Proportions of vaccine wastage per dose were expected to be around 0.05% only or 15 cents each (Hanizah 2004). The prices of vaccinations differed by cost per dose ranging from RM 100-200. Vaccine efficacy was assumed to be at 95% efficacy and efficacy would last a life time with no necessary booster needed. The side effects of vaccinations were assumed to be minimal and did not incur deaths or admissions to hospitals. Staffs costs of three administrations of vaccines were from secondary data at RM 16.21 per shot (Hanizah, 2004). An expected 70% fraction of women's CC can be avoided if HPV vaccinations against types 16 and 18 were administered. Each woman will save 13 years per person saved if CC could be avoided (Ezat and Aljunid, 2010). Obtaining input from the private sectors was not done as permission for costing data are not readily available from the private sectors. As method for national financing does not come from national health insurance or other form of national health coverage, data on costing was not easy to retrievable and subjected to confidentiality. Assumptions on society's cost (providers and patients costs) and QALYs were published elsewhere (Ezat and Aljunid, 2010). Assumptions also included population vaccination coverage at 96% of all 15 years old and a constant 70% of populations catch up period of 9-26 years old adolescents and women. All inputs and outcomes were discounted at 3% for 10 years.

Management Of Vulva, Vagina Cancers And Genital Warts

In the parameters used, the incidence rate of vulva and vagina cancers (VV CA), were based from the National Cancer Registry MOH year 2006. They were for vulva cancer 0.03/100,000 and vulva cancer at 0.06/100,000. As Malaysia does not have a central collection of genital warts (GW) incidence rate, secondary data was imputed from the US incidence rate of 100/100,000 (Centers for Disease Control and Prevention 1999). The QALYs saved per person was taken from secondary data of QALYs saved from cervical cancer (Sharifa Ezat and Aljunid 2010) that was 24.40.

The cost of management of VV CA and GW were obtained through combinations of clinical pathways and case mix costings (Amrizal et al., 2005), treatment algorithm and their activities based costing of the activities involved in the management of vulva, vagina cancers and genital warts. The following Tables 1 and 2, showed the cost of managing a case of vulva, vagina cancer and genital wart by stage or site per case per annum. Outcomes of cost per QALYs saved were shown in this following Table.

Sensitivity Analysis

The assumptions used in calculating the costs of vaccinations were multiple. These included 95% coverage of 15 years old girls adolescents across the country (taken from the trend of national data of vaccination coverage of 3rd dose Tetanus among 15 years old adolescent girls in schools 2006, Annual Health Report, MOH Malaysia). Plus an expected catch up program of either BV or QV HPV vaccination for 9-26 years old women at only 70% coverage of this population within the next 5 years. Sensitivity analysis was calculated through the scenario based scenario analyses. Sensitivity analysis of base case and its ranges (minimum to maximum cost) were also calculated for all cost components. Three alternative strategies options were compared i.e. the base case, the best case and the worst case scenario. However, these scenarios were dependent on the following parameters.

a) Population coverage of Pap smear screenings, using different population coverage i.e. at 40% for base case and worst case scenarios and 70% in best case scenario.

b) HPV vaccination cost (either BV or QV). Both were analyzed using RM 100 per dose in base case and best case; while RM 200 per dose for worst case.

c) Combined strategy (Pap smear screening together with either QV or BV vaccination). In the combined strategy, HPV vaccinations program is foreseen to run concurrently with screening of women population based on current clinical CPG recommendations in Malaysia. The combined strategy best case will involve high screening coverage at 70% and low cost at RM 100 vaccination cost per dose; the base case is at 70% screening coverage and cost of RM 100 per dose and in the worst case is when the screening was maintained at 40% but the cost of vaccination had increased to RM 200 per dose.

Results

Socio Demographic Profiles of Respondents

Five hundred and two respondents participated in this study. Respondents came from Kuala Lumpur Hospital (30.9%), Seremban Hospital (25.7%), Alor Star Hospital (23.9%), UKMMC (13.1%), Kangar Hospital (4.0%) and Kuantan Hospital (2.4%) as in Table 3. Mean age of respondents were 53.0±11.23 years i.e. respondents are slightly older women.

The combined ASCUS, HSIL and LSIL (generally grouped as pre invasive diseases) made up for a large proportion seen but ICC was by far the highest proportion by various stages in this study. From 502 respondents, majority of cases seen (in decreasing order) were from the pre invasive stages (33.0%), stage 2B-4A at 31.1%, followed by stage 1B-2A (29.0%), stage 1A1 (3.4%), stage 1A2 (2.2%) and lastly stage 4B (1.4%).

Majority of the respondents obtained education up till secondary school level (40.6%). This was followed by primary schools (36.9%), never schooled (20.5%) and tertiary level education (2%). By ethnicity most of the respondents were Malays (45.8%), followed by Chinese (37.3%), Indians (15.1%) and others (1.8%). These was a reflection the the normal distribution of the Malaysian population where Malays was the majority ethnic group, followed by Chinese and Indians that seeks health services from the public sectors. Most of the respondents at 73.3% was currently married; 21.3% was widowed; 4.2% was divorced; 1.0% was single and unmarried while remaining 0.2% cohabited with a partner.

The mean ages by stages were as follows. In the pre-invasive stages, the mean age for ASCUS was 44.67 years±11.08 years, 46.37±12.02 years for LSIL and 47.85±10.82 years for HSIL. For stage 1A1 mean age was 53.64±9.56 years, stage 1A2 the mean age was 58.20 years±8.94, stage 1B-2A the mean age was 54.98 years±10.56, stage 2B-4A the mean age was 56.01years±10.16 and stage 4B the mean age was 55.60 years±7.91. These mean difference was calculated using ANOVA and was statistically significant with F=10.56 and p<0.0001.

The mean length of marriage was 20.06±16.07 years. Most of the respondents were no longer working, retired or were full time housewives (73.9%). Thus formal income from work was not normally distributed. Their income came from own self wages or supported by spouse or other family members. Only 11.6% were employed full time, 9.2% were employed on a part time basis, 4.8% were self employed and 0.6% were working on and off basis when health permits. The median income per month for 502 respondents was RM 300 per person (IQR RM 0.0-700).

By distribution of patients monthly income (in decreasing order), 62% of respondents received an income of between RM 0-499. As much as 20.3% earned a monthly income of between RM 500-999. 10% received a monthly income of RM 1,000-1,499; 2.8% received RM 1,500-1,999, 2.6% received income of RM 2,000-2,499; 2% received a monthly income of RM 3000 and above and 0.4% receive income of RM 2,500-2,999.

Most of the respondents were still in marriage and were provided by their spouses. The median income of spouses was RM 500 per month (IQR RM 0-1,150). As high as 48.6% of respondents' spouses earned an income of less than RM 500 per month. 18.5% earned an income of between RM 500-999 per month; 11.4% earned between RM 1,000-1,499 per month; 7.2% earned between RM 1,500-1,999; 6.4% earned between RM 2,000-2,499; 1.8% earned between RM 2,500-2,999 and 6.2% earned at least RM 3,000 and above per month.

Household income per month is contribution from both, i.e. patients, their partners and members in the household that contributed to the house income. Median household's income per month was RM 800 (IQR RM 400-1,525). Majority at 49.4% earned a monthly income of less than RM 500. In decreasing order, as much as 16.7% earned RM 500-999, 9.6% earned between RM 1,000-1,499; 7.8% earned RM 3,000 and above; 7.2% earned between RM 2,000-2,499, 7.0% earned between RM 1,500-1,999 and 2.4% earned between RM 2,500-2,999.

Health care expenditure showed that majority of respondents i.e. 86.5% did not spend any amount on

Table 1. Stages by Cancer Type and Annual Cost (RM) per Case

Stages	Vagina Carcinoma (RM)			Vulva Carcinoma (RM)		
	Base	Min	Max	Base	Min	Max
VaIN/VIN	24,336.81	6,084.20	42,589.42	48,692.53	24,346.26	73,038.79
Stage 1	58,472.65	51,163.57	73,090.81	56,123.51	46,769.59	65,477.43
Stage 2	56,271	46,892.50	65,649.51	110,096.80	97,863.82	122,329.78
Stage 3	56,271	46,892.50	65,649.51	84,281.96	67,425.57	117,994.74
Stage 4	56,271	46,892.50	65,649.51	84,281.96	67,425.57	117,994.74
Mean cost (RM)	50,893.80	39,665.36	65,948.76	76,695.35	60,766.16	99,367.10

Table 2. Stages of Genital Warts and Annual Cost (RM) per Case

Types of Genital Warts (by site)	Cost (RM)		
	Base	Min	Max
External genitalia	6,696.41	3,348.20	10,044.61
Peri anal/ Anal	899.27	359.71	2,158.26
Urethral	292.15	116.86	701.15
Cervical	317.81	127.12	762.75
Vaginal	105.94	42.37	254.25
Mean Cost (RM)	1,662.32	1,331.42	4,640.34

Table 3. Socio-Demographic Profiles of Respondents

Socio demographic Profiles of Respondents		Percent (%)/ Mean
Hospitals	Kuala Lumpur Hospital	30.9
	Seremban Hospital	25.7
	Alor Star Hospital	23.9
	UKMMC	13.1
	Kangar Hospital	4.0
	Kuantan Hospital	2.4
Age	Mean age	53.0 ± 11.23 years
	Less than 25 years old	0.6
	25-34	4.6
	35-44	18.3
	45-54	32.1
	55-64	27.5
	=>65 years and above	16.9
Stages of Pre invasive and ICC	Pre-Invasive Cancers	33.0
	Stage 1A1	3.4
	Stage IA2	2.2
	Stage 1B till 2A	29.0
	Stage 2 B-4A	31.1
	Stage 4B	1.4
Education	Never Schooled	20.5
	Primary	36.9
	Secondary	40.6
	Tertiary	2.0
Ethnicity	Malays	45.8
	Chinese	37.3
	Indians	15.1
	Others	1.8
Marriage Status	Mean length of marriage	20.06 ± 16.07 years
	Married	73.3
	Widowed	21.3
	Divorced	4.2
	Single	1.0
	Cohabiting	0.2
Employment Status	Unemployed	73.9
	Employed Full Time	11.6
	Employed Part Time	9.2
	Self Employed	5.4
Patient's Income (RM)	Median Income, IQR (RM)	RM 300 (IQR 0-700)
	0-499	62.0
	500-999	20.3
	1000-1499	10.0
	1500-1999	2.8
	2000-2499	2.6
	2500-2999	0.4
	=>3000	2.0
Partners' Income (RM)	Median Income and IQR	RM 500 (IQR 0-1,150)
	0-499	48.6
	500-999	18.5
	1000-1499	11.4
	1500-1999	7.2
	2000-2499	6.4
	2500-2999	1.8
	=>3000	6.2
Household's Income (RM)	Median Income and IQR	RM 800 (400-1,525)
	0-499	49.4
	500-999	16.7
	1000-1499	9.6
	1500-1999	7.0
	2000-2499	7.2
	2500-2999	2.4
	=>3000	7.8

health care such as buying vitamins, procuring preventive healthcare services or other health needs that were considered non critical. These patients largely depended on free public provided health care facilities and services. 11.8% spent less than RM 250 per month. 1% spent between RM 250-499; 0.4% spent between RM 500-749

and the remaining 0.4% spent at least RM 750 and above per month on health care expenses.

Based on percentages spent on health care from total expenditure, the majority 90% of respondents spent less than 10% of their total expenditure on health care. The remaining 5% of respondents spent between 10-19%; 2.6% respondents spent between 20-29%; 0.6% spent between 30-39%; 0.2% respondents spent between 40-49% and 1.6% respondents also spent the maximum percentage on health care i.e. 50-59%.

Cost/ QALYs saved for three options

Three program options defined in this study included women that had undergone Pap smear screening only, HPV vaccinations only (either with BV or QV types) and combined strategy of HPV vaccinations; either with BV or QV together with Pap smear screening but at different level of population coverage. The costs calculated were based on annual costs using year 2006 as the reference year.

Three scenarios cases were included in the sensitivity analysis based on screening coverage's of women populations ranging from 40-70% and cost of HPV vaccination per dose ranging from RM 100-200 per dose. They were base case, worst case and best case scenarios. In the Pap smear screening program the base and worst cases were assumed to be of similar screening coverage at 40% but increased to 70% coverage in best case scenario. In the combined strategy, the base case scenario assumed was to be at status quo of screening at 40% screening coverage and when the cost of HPV vaccination (either BV or QV) but the cost of vaccination was at RM 100/dose only. The best case scenario was when the screening coverage was increased to 70% and cost of HPV vaccination was maintained at RM100/dose. While the worst case scenarios was when the screening was still at status quo at 40% but the price of HPV vaccination was increased to RM 200/ dose.

Costs of Pap smear was taken from secondary data (Nik Shamsidah 2005) and adjusted for inflation rates thorough CPI calculations. The amount of women age 20-65 expected to perform and undergo Pap smear screening was from the Statistics Dept Malaysia year 2006.

Cost of Pap Smear Program

In Pap smear screening program of whole women population; the costs of negative tests detection was RM 21,187,988 (min-max: RM 14,907,836-36,286,436), abnormal tests base cost was RM 496,946 (min-max: RM 349,651-851,068) and inadequate tests base costs was RM 903,539 (min-max: RM 349,651-851,068) (Nik Shamsidah 2005). 20.8% of women seen through screenings programs were expected to display LSIL changes, 11.2% LSIL and 2% ICC changes. Costs were imputed for percentage of women population assumed to be screened and later will present with cervical abnormalities (intention to treat group) and assumed everyone with disease will receive treatment. The rests of unscreened women population based on the national incidence of CC in this country, the number of women expected to develop cervical cancer will be 464 women only.

Table 4. CEA of Three Programs Strategies at Different Coverage and Sensitivity Analysis

Program Cost	Pap smear by Coverage ($x10^3$)		HPV Vaccination Only ($x10^3$)				Combined Strategy ($x10^3$)					
			BV Vaccination		QV Vaccination		BV Vaccination & Pap smear			QV Vaccination & Pap smear		
	Base, Worst Caseat 40%	Best Case at 70%	Base & Best Case at RM 100/ dose	Worst Case at RM 200 /dose	Base & Best Case at RM 100/ Dose	Worst Case at RM 200/ Dose	Base Case	Best Case	Worst Case	Base Case	Best Case	Worst Case
Pap smear	41,573.9	72,754.3	-	-	-	-	126,732.9	208,097.8	126,732.9	126,732.9	208,097.9	126,732.9
Intentionto treat group	85,159.0	135,343.4										
HPV Vaccination	-	-	597,102.9	854,333.9	597,102.9	854,333.9	597,102.9	597,102.9	854,333.9	597,102.9	597,102.9	854,333.9
Avoided Cost to manage CC	18,246.5	5,473.9	7,658.3	7,658.3	7,658.3	7,658.3	18,246.5	5,473.9	30,107.5	5,473.9	10,947.9	5,473.9
Avoided cost to manage VV CA & GW	-	-	4,202.7	4,202.7	4,202.7	4,202.7	11,861.0	11,861.0	30,107.5	11,861.0	11,861.0	11,861.0
Total Avoided Cost (RM)	18,246.5	5,473.9	11,861.0	11,861.0	11,861.0	11,861.0	30,107.5	17,334.9	30,107.5	17,334.9	22,808.9	17,334.9
Total Cost (RM)	126,732.9	208,097.8	597,102.9	854,333.9	597,102.9	854,333.9	723,835.8	805,200.6	981,066.9	723,835.8	805,200.6	981,066.9
QALYs saved avoidance of CC	109.8	192.2	0.4	0.4	38.2	38.2	109.8	192.2	109.8	109.8	192.2	109.8
QALYs saved avoidance of VV CA & GW	-	-	-	-	37.8	37.8	0.4	0.4	0.4	75.9	75.9	75.9
Total QALYs saved	109.8	192.2	0.4	0.4	75.9	75.9	110.3	192.7	110.3	185.8	268.2	185.8
Cost (RM) /QALYs saved	1.2	1.1	1.4	1.9	7.9	11.2	6.6	4.2	8.9	3.9	3.0	5.3

Table 5. ICER of Dominated Options between the Three Main Strategies

Strategy	Cost (RM x10^3)	Effectiveness (QALYs saved x 10^3)	Incremental Cost (RM)	Incremental QALYs saved	ICER (per QALYs saved)
QV Combined Strategy Best Case	805,200.60	268.20	-81,364.80	-157.90	515.29
QV Combined Strategy Base Case	723,835.80	185.80	-126,732.90	-185.40	683.57
QV Combined strategy worst Case	981,066.90	185.8	-126,733.00	-185.40	683.57
Pap smear program 70% Coverage	208,097.80	192.20	-81,364.90	-82.40	987.44

Total populations QALYs saved in screening program are for the whole women population. This is calculated based on average QALYs/woman with CC multiplied the expected number of women population available in the country.

Cost for HPV Vaccination Program

Although catch up programs were utilized in the calculations, the coverage of catch up vaccinations was only 70% of women and adolescents populations. From the total of 9-26 years old women of 3,292,394 women; HPV vaccination would have avoided 649 CC incident cases. The unvaccinated 987,699 women would still be at risk of developing new incidences of CC or pre invasive diseases but at a lower incidence rate. This lower incidence of CC at only 3.5/100,000 i.e. only 35 women developed ICC from 9-26 years old cohort that had not received the vaccinations.

The populations' vaccinations' cost involved multiplying the cost of vaccination per schedule of between RM 100 to 200 per dose to the total number of 15 years old girls and the targeted number of women population in the catch up groups. This cost differed according to the vaccines' cost per dose. Total population QALYs saved were QALYs saved per person at 24.4 multiplied by number of women ICC and pre invasive cervical diseases that could be avoided. The total QALYs saved for the different programs interventions were based on the number of women populations expected to benefit from those specific interventions.

Cost for Combined Strategy Program

The combined strategy was targeted towards both 15 years old adolescents' girls and the catch up with only 70% coverage of 9-26 years old girls and women. The combined strategy also combined the cost and QALYs saved from routine Pap smear screenings for women till the age of 65 years old according to Malaysia's national CPG guidelines. As above, three scenarios (base, best and worst scenarios) were incorporated into the three programs. Hereafter, screening does not provide any extra benefit against ICC or its pre invasive diseases. The costs of three different programs and effects of QALYs saved were as in the following table 4. The BV vaccinations did not take into account the protection against vulva, vagina cancers and genital warts as these were not end point of BV efficacy study. This modeling also did not take into account the benefit to older women incurred by BV.

Table 4 shows the cost involved in program implementation including cost of cancer management in the intention to treat groups; cost of HPV vaccinations (both BV and QV but with different cost of RM 100 and RM 200) and avoided cost of managing cancers (may it be cervical, vagina or vulva cancers) and genital warts.

Incremental Cost Effectiveness Ratio (ICER)

For ICER calculations, twelve different outcomes for different scenarios were compared from the most to the least cost effective option. The Pap smear screening at status quo i.e. 40% population coverage was taken as reference base situation. Dominated consequences were eliminated from this table as it was not a cost effective option. Once these strategies were eliminated from the table, the ICER were arranged again and recalculated. From the ICER table, only four options were left.

They were Pap smear coverage at 70%, QV combined strategy for base, best and worst case scenarios. However, the ICER showed that the most cost effective strategy was QV combined strategy at best cases scenario of RM 515.3 per QALYs saved. This was followed by QV combined strategy at base and worst case scenarios as assumption on screening coverage were similar even though the cost per dose was different with worst case scenario having higher cost per dose of vaccination. The least cost effective strategy was Pap smear screening at 70% coverage of RM 987.4 per QALYs saved although all ICER were not relatively different much from one another. However, by definition of outcomes costing less than national GDP as to be cost effective then these options in the following table were still condidered as cost effective.

Discussion

Immunization, suitable with WHO recommendations are intended to reduce sufferings against disabilities, disease complications and even initiations of intended diseases such as seen in the HPV vaccinations programs (Preparing for the introduction of HPV vaccines UNFPA WHO 2006). The mean life expectancy saved if women could avoid cancers was 13.0 years. Futher information can be optained from Sharifa Ezat and Aljunid (2010).

Sensitivity analysis were based on the three scenarios which were the base case, best case and worst scenario. All costs and outcomes were discounted for 3% for the next 10 years. In the base and worst case scenario, cost/QALYs saved are the same at RM 1,215 for Pap smear program since in both cases, the coverage is assumed to be the same at 40% population coverage. The cost/QALYs saved for best case scenario showed lower cost/QALYs saved (more cost effective), since the screening coverage was higher at 70%, thus making it more cost effective to screen at higher population coverage.

Under the HPV vaccination program, cost/QALYs saved showed that both base and best case scenarios were

lower (more cost effective) since the cost per vaccine dose was at RM 100. The worst case scenarios that used RM 200/dose showed higher cost/QALYs saved that was less cost effective than in the above scenarios.

QV combined strategy program at best case scenario was definitely more cost effective since this strategy covered higher population coverage of screening but at a lower cost of HPV vaccination per dose. With the added effects of QALYs saved from genital warts QV protects; the increased QALYs saved were higher than the BV. This is in accordance with Jit et al., (2008) that concluded vaccinating 12 year old schoolgirls with a QV at 80% coverage is likely to be cost effective at a willingness to pay threshold of £30 000 (€37,700; $59,163) per QALY gained. However this was highly dependent on the average duration of protection from the vaccine, if the vaccines protection is more than 10 years or even better if lifelong efficacy is achieved. Implementing a catch-up campaign of girls up to age 18 is likely to be cost effective. A BV with the same efficacy will cost £13-£21 less per dose (depending on the duration of vaccine protection) may be as cost effective as the QV although it will be less effective as it does not prevent anogenital warts.

Ensuring Vaccine Programs Sustainability

Since this is an expansive vaccine, establishing a comprehensive vaccination program in Malaysia (considered a high-middle income country with high Human Development Index value), a program that encompasses catch up vaccinations of 9-26 years old women are highly unlikely. The funding among these age 9-26 years old group would be too substantial and can't be handled alone by the public sector. Since voluntary private and social health insurance are not establised in this country and health financing relies heavily on tax funded universal access to health care, government financing will be extremely stretched if universal mandatory vaccinations of 9-26 years old will be provided by the government.

The most likely less costly strategy would be establishing vaccinations among 13 years old for next 10 years as evidenced from a few other literatures (Goldie et al., 2004; 2005). A specific vaccination target in this age group ensure that long term sustainability and managibility among health providers. The public school health team in Malaysia, mostly attended by nurses, has a long and successful immunization program. However it has been stretched to the limit and providing three doses in schools set ups among 13 years old will be another substantial challenge.

Malaysia consist of a dichotomy of both private and private health providers, thus public and private primary care doctors in schools vicnicity can be incorporated as vaccinations centres that students, with their parents, could come for vaccinations on their own time. Payment for these vaccinations should always come fron the government as to ensure public goods will be delivered in a standard and orderly form. This approach encourages attendances by parents that may need to enquire related informations that could be provided by physicians. They could not obtain these precious informations and discussions had these vaccinations be done at schools' basis only because of the restricted attentions and time apportioned to students. Selecting which clinic to provide vaccinations services must come from governments' pre determined selections criterias and standards. A centrally defined guideline from a central committee must be in place for these mechanisms to run in order. Queries on culture conflicts, resistance and implementation issues must be dealt by advocacy groups from both private and public sectors. Even though existing mechanisms are already in place and incorporated in both public and private vaccinations services, these valuable resouces only reach a small proportions of the community and does not reach the ground level and the high at risks groups including men.

A strong support by the male fraternity that may comprise of political figures and health advocaters are not well established in this country. This looks as if the women community are left to fend on their own of this disease that affects mainly women of elderly age groups (Othman et al., 2009).

Im conclusion, from the ICER, the most cost effective strategy of cost/QALYs saved was from QV through the best case strategy approach. Incorporating the Pap smear programs; however must be done with high screening coverages of women population. Achievement of high coverages are an imposible feat to achieve even after nearly 30 years of women advocacy and free screening services at public sectors. Thus vaccinating young women with QV is a more reachable target measure for long term protection. However, government roles in maintaining costs by mass supply and competitiveness of products, advocating vaccines among the community leaders and the public must be encouraged.

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