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Cost-effectiveness analysis for Pap smear screening and human papillomavirus DNA testing and vaccination

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Abstract

Introduction As the effectiveness of cytology-based screening programme for cervical cancer in mortality reduction has reached a plateau, various preventive strategies have been considered, including intensive Pap smear screening and the supplemental use of human papillomavirus (HPV) DNA test or HPV vaccination. Cost and effectiveness of these various preventive strategies are therefore of great concern for health policy makers.
Objective We intended to assess whether the combination of HPV DNA testing or HPV vaccination with Pap smear screening programme or the sole annual Pap smear screening is more effective and cost-effective in prevention of cervical cancer than the existing triennial Pap smear screening programme.
Methods A Markov decision model was constructed to compare total costs and effectiveness between different preventive strategies (including annual Pap smear, HPV DNA testing or HPV vaccination together with Pap smear screening programme) as opposed to the triennial Pap smear screening alone (the comparator). Probabilistic cost-effectiveness (C-E) analysis was adopted to plot a series of simulated incremental C-E ratios scattered over C-E plane and also to yield the acceptability curve for different comparisons of strategies. The threshold of vaccine cost and the influence of attendance rate were also investigated.
Results Compared with triennial Pap smear screening programme, most of preventive strategies cost more but gain additional life years (quadrant I of C-E plane) except HPV DNA testing with Pap smear every 5 years dominated by triennial Pap smear screening programme. The most cost-effective strategy was annual Pap smear (incremental C-E ratio = $31 698), followed by HPV DNA testing with Pap smear every 3 years ($36 627), and vaccination programme with triennial Pap smear screening ($44 688) with the corresponding cost-effective probabilities by the acceptability curve being 65.52%, 52.08% and 35.84% given the threshold of $40 000 of willingness to pay. Vaccination combined with triennial Pap smear would be as cost-effective as annual Pap smear provided the cost of vaccination was lowered to $250 per full course of injection.
Conclusions Among various preventive strategies annual Pap smear screening programme is still the most cost-effective and additional HPV DNA testing is a cost-effective choice under a reasonable threshold of willingness to pay. Vaccination programme in combination with triennial screening would be cost-effective if vaccine cost can be greatly reduced in a large economic scale.

Introduction

Pap smear screening for reducing incidence and mortality of cervical cancer has been well documented. However, the effectiveness of mortality reduction has reached a plateau in the countries where population-based Pap smear screening programme has been implemented. To achieve more benefit, human papillomavirus (HPV) DNA testing, HPV vaccination and the combination of any

of the two [1] together with Pap smear screening have been proposed in recent years. The balance between cost and effectiveness between these preventive strategies is of great concern for health policy makers.

There are several cost-effectiveness studies on HPV vaccination and HPV DNA testing. The studies conducted in developing countries focused on the comparison between HPV vaccination and various strategies of Pap smear screening, particularly on less frequent policy (three times during the lifetime or every 5 years or longer) [2–7] or the comparison between the strategies with HPV DNA testing and Pap smear screening [8–11]. In developed countries, the corresponding studies focused on subsidiary issues including age at start of vaccination and catch-up programmes, different inter-screening intervals, and age beginning and terminating screening [12–16]. Most of these cost-effectiveness studies on HPV vaccination compared the programmes of HPV vaccination combined with the existing Pap smear screening programme. Note that the coverage rate of screening programmes in these countries is considerably higher than those in the developing countries and the inter-screening intervals vary across countries [12,17–19]. It is still equivocal for HPV DNA testing related to the optimal screening interval, ages of starting and terminating screening and the role of HPV testing as primary screening, with or without Pap smear, or as a triage for those Pap results [8,20–28].

Few studies have been so far conducted to do economic appraisal of comparing cost and effectiveness of three preventive strategies, including Pap smear, HPV DNA testing and HPV vaccination, in one study because it is very rare to see the possibility of adopting three strategies worldwide. Taiwan is one of possible candidates for the implementation of three strategies for different age groups and target populations. Since 1995, the government has mandated that all women should undergo Pap smear at least every 3 years. Around 60–66% reduction in mortality of cervical cancer has been projected [29–31]. However, like Western countries, effectiveness has reached a plateau recently. Relatively poor sensitivity of cytology screening [32], low attendance rate (52%) and prevalent infection of HPV [33] may account for the ceiling limit of effectiveness [34]. Two potential preventive strategies, HPV DNA testing and vaccination, in combination with routine screening programme are therefore proposed for the future policy in Taiwan.

Hence, we conducted a probabilistic cost-effectiveness analysis to estimate cost and effectiveness of HPV vaccination or HPV DNA testing combined with routine Pap smear screening or intensive Pap screening programme in contrast to the existing triennial Pap smear programme.

Methods

Natural history model

For those without the uptake of preventive strategy, we developed a multi-state stochastic process to simulate the temporal natural course of cervical cancer from normal, cervical intraepithelial neoplasia (CIN) grade 1, CIN grade 2 or 3, local cancer and invasive cancer by the stratification of HPV infection (Fig. 1). The transition can only jump one state in one cycle (in year) whereas the regressions from HPV infection to no infection, CIN 1 without HPV infection to healthy, CIN 1 with HPV infection to HPV infection and from CIN 2 to CIN irrespective of HPV infection can be allowed. We assumed that those in CIN1 and CIN2/3 states would not change the status of HPV infection after one cycle because the occurrence of cervical cancer needs prolonged HPV infection and relevant parameters are still unavailable. The reinfection rate for those regressing from HPV infection to normal was also assumed to be similar to primary infection rate.

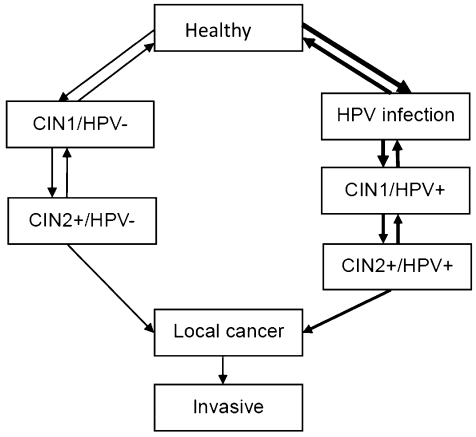

Figure 1 Simplified natural history of cervical cancer, the arrows direct transitions from one state to another. CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

Study cohort and intervention strategies

A cohort comprising of 150 000 women identical to demographic features of Taiwanese population in 1995 was simulated following the temporal natural course of cervical neoplasm as mentioned above. Five preventive strategies were compared, including annual Pap smear screening, triennal Pap smear screening, Pap smear combined with HPV DNA testing every 3 years, Pap smear combined with HPV DNA testing every 5 years and triennial Pap smear accompanied by vaccination offered for aldolescent girls.

Pap smear cytology categories were based on 2001 Bethesda system [35] and the cut-off of the HPV DNA test was set at 1.0 pg mL^{-1}. The simulated screening/prevention regimens were as follows. Periodical screening was performed for each woman allocated to each preventive strategy by predetermined inter-screening interval. For example, in the cohort of cytology-based screening in combination with HPV DNA testing every 5 years, each woman underwent routine screening every 5 years if the previous screening result was normal. Regarding HPV DNA testing in combination with Pap smear screening programme, if positive HPV DNA testing result was observed in women with normal cytology results then the interval of repeated Pap smear and HPV DNA testing was shortened to 1 year. The treatment policy was the same regardless of the screening strategy. If an abnormal cytology result was noted, colposcopy with biopsy was arranged for verification and further conization was offered for women whose biopsy results revealed CIN2 and CIN3 or severe lesions. The sensitivity and specificity of colposcopy with biopsy were 100%. For women diagnosed as CIN2 or 3 treated by conization, or biopsy-confirmed CIN1 lesions, repeated cervical Pap

smear and HPV DNA testing was performed by 6-month interval. A Markov cycle tree with a cycle in 1 year was adopted to simulate this complex disease process for woman aged 30–70 years.

Parameters

Annual transition parameters relating to the natural history of cervical cancer and HPV infection were derived from published medical literatures (Table 1). Time horizon for each cycle was 1 year. The attendance rate at cervical cytology was 52.2%, which represented the proportion of general women who had at least one Pap test between January 2001 and December 2003 in Taiwan [34]. The vaccination rate in adolescent who were offered with the HPV vaccination was close to 100%. The efficacy of the vaccine in terms of the number of cervical cancers prevented was estimated from the prevalence of type 16/18 HPV infection among the high-risk oncogenic HPV types. We assumed that the effect of the vaccination on the incidence of other subtypes of HPV infection would not influence rates of cervical cancers, namely no cross protection, partial protection or competition between HPV subtypes. Moreover, the duration of protection offered by the vaccine against type 16/18 HPV was assumed to be life-time. The sensitivity and specificity of each screening tool were defined as the ability to detect lesions of CIN2 or severe. As base-case estimates

Table 1 Base-case estimate and corresponding distributions of relevant parameters

Variable	Base-case estimate	Distribution	Reference
HPV infection			
Prevalence	Age-specific table		[1]
Infection rate	0.127	Gamma (652, 4782.3)	[41–45]
Regression rate	0.561	Gamma (115, 139.6)	[42]
16/18 type prevalence	0.692	Beta (385, 1250)	[46]
Attendance rate	0.522		[31,34]
Outcome of health			
Progression to CIN1	0.051	Gamma (109, 2064)	[41,44]
Outcome of HPV carrier			
Progression to CIN1	0.135	Gamma (157, 1086)	[41,44]
Outcome of CIN1			
With HPV infection			
Progression to CIN2+	0.087	Gamma (43, 474.2)	[44,47,48]
Regression	0.569	Gamma (89, 105.63)	[47,48]
Without HPV infection			
Progression to CIN2+	0.016	Gamma (11, 686.8)	[44,47,48]
Regression	0.716	Gamma (70, 55.6)	[47,48]
Outcome of CIN2+			
Progression to cancer	0.0408	Beta (6, 146)	[9,26,49]
Regression with HPV	0.584	Gamma (41, 46.7)	[47,50]
Regression without HPV	0.806	Gamma (18, 10.98)	[47,50]
Local cancer progress to advanced cancer	0.213	Beta (29, 106)	[49]
Local cancer cure rate after treatment	0.788	Beta (27, 161)	[51]
Death rate for local cancer	0.181	Gamma (3506, 17 532)	[52]
Death rate for advanced cancer	0.459	Gamma (7759, 12 639)	[52]
Pap smear			
Sensitivity	0.603	Beta (522, 865)	[37,53–55]
Specificity	0.963	Beta (53004, 55057)	[37,53–55]
HPV DNA test			
Sensitivity	0.942	Beta (877, 930)	[37,53,54,56–58]
Specificity	0.908	Beta (60 466, 67 010)	[37,53,54,56–58]
Benign hysterectomy rate	0.002	Gamma (111 287, 38 302 978)	[59,60]
Death rate from other causes	Age-specific table		[Vitalstatistics 2004]
Direct cost + indirect cost			
Pap smear	59.91	Triangular (33, 59.91, 81)	[14–16,24–28]
HPV DNA testing	36.51*	Triangular (29, 36.51, 49)	[14,24–28,61]
HPV vaccine	365.0*	Triangular (230, 365.0, 500)	[17]
Colposcopy and biopsy	305.66	Triangular (176, 305.66, 526.5)	[14,24–28,61]
Conization	686.33	Triangular (360, 686.33, 898)	[25,26,28,61]
Treatment for local cancer	15 549.22	Triangular (3082, 15 549.22, 31 485)	[15,16,25,28]
Treatment for advanced cancer	25 816	Triangular (5060, 25 816, 36 912)	[15,16,25,28]

*Only direct cost included.

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

were derived from the literatures, parameters from a series of successive studies were updated using Bayesian conjugate gamma or beta prior distributions [36] in chronological order.

The cost of each clinical outcome was determined by aggregating estimates from various studies (Table 1). The vaccination and health care costs were valued in currency units (in US dollars). Both direct and indirect costs were included except for cost of vaccination and HPV DNA testing, which merely included direct cost only. The direct cost of Pap smear covers the fee for sampling and cytology and additional fee for those with uncertain results. The direct cost of vaccination was composed of vaccine cost (three shots), fee for pre-injection evaluation and technique fee for injection. We assumed that the programme of vaccination could be performed with other vaccination programmes in high school and therefore no additional indirect cost was assigned. The indirect cost of Pap smear, colposcopic examination, conization and treatment for local or advanced cancer was related to production loss. Because the HPV DNA testing can be performed concomitantly with Pap smear, no additional indirect cost was included. Variation in costs was modelled by using a triangular distribution. All analyses were performed from a societal perspective. All costs were discounted at 3% annually.

Because the short-term efficacy of HPV vaccination in preventing further high-risk oncogenic HPV infection among adolescent girls was demonstrated in several randomized controlled clinical trials, it is therefore interesting to assess the threshold of vaccine cost. Moreover, attendance rate is one of the factors responsible for effectiveness of Pap smear screening programme; it is imperative to assess the impact of this parameter on cost-effectiveness analysis of the comparisons between Pap smear screening programme by various inter-screening intervals and the comparisons between Pap smear screening and the combined strategies of Pap smear screening with HPV DNA testing or HPV vaccination.

Cost-effectiveness analysis

The primary end point of this analysis was the number of life years gained discounted at 3% annually. Both average and incremental cost-effectiveness ratios (ICERs) were calculated in a probabilistic approach using Monte Carlo simulation to select values at random from specific distributions of model parameters.

To consider the influence of uncertainty of parameters, a series of estimates from Monte Carlo simulation are plotted in four quadrants of the C-E plane and the probability of being cost-effective by the reparameterization of each ICER point is also plotted with an acceptability curve. A total of 5000 simulations were implemented as suggested by Briggs *et al.* [36]. The threshold of willingness to pay (WTP) for assessing whether each ICER is cost-effective was set as $US40 000 per life year gained, which roughly amounts to EUR 30 000, and was slightly lower than the value of three times per capita Gross Domestic Product in Taiwan.

Result

Base-case estimates

Table 2 shows the results of cost and life years per screenee and average cost-effectiveness ratio for each strategy. In terms of expected life years, the most effective strategy was annual Pap smear alone, followed by triennial Pap smear combinded with vaccination, triennial Pap smear combinded with HPV DNA testing, triennial Pap smear only, and the least one, Pap smear combinded with HPV DNA testing every 5 years.

Table 2 also shows most of strategies compared with triennial Pap smear cost more but also yielded more life years. In terms of ICER, the most cost-effective was annual Pap smear that traded an excess of $31 698 for one additional lifer year gained. The second cost-effective strategy was Pap smear combined with HPV DNA testing every 3 years with the corresponding ICER estimate amounting to $36 448. To svae more life years, the current strategy of triennial Pap smear combined with vaccination was the most costly with an estimate of ICER equal to $44 688. Note that the strategy of Pap smear combinded with HPV DNA testing every 5 years was dominated by triennial Pap smear as life years gained was less but yet cost was higer.

Probability analysis

The Monte Carlo simulated results on the C-E plane given the threshold of $40 000 of WTP are plotted on Fig. 2. Compared with triennial Pap smear alone, the probability of being cost-effective was 65.52%, 52.08% and 35.84% for annual Pap smear (Fig. 2a), Pap smear combined with HPV DNA testing every 3 years (Fig. 2b) and vaccination combined with triennial Pap smear screening (Fig. 2c), respectively. The strategy of Pap smear combined with HPV DNA testing every 5 years had only 0.18% chance of being cost-effective (Fig. 2d).

Acceptability curve

The probability of being cost-effective for five alternative strategies by various WTP values is plotted by using acceptability curve (Fig. 3a). When the WTP value was below $33 000, the strategy of triennial Pap smear was still the most cost-effective. However, as the WTP value increased to $33 000, annual Pap smear dominated other strategies. The strategy of triennial Pap smear combined with

Table 2 Cost-effectiveness analysis for cervical cancer prevention

Strategy	Cost per person ($US)	Expected life years aged 30–70 years	C/E ($)	ICER
Triennial Pap smear	379.60	PY 21.8148	17	
Pap smear + 5-yearly HPV test	436.50	PY 21.8144	20	Dominated
Pap smear + HPV test triennially	625.00	PY 21.8215	29	$36 627
Pap smear triennially + vaccination	723.70	PY 21.8225	33	$44 688
Annual Pap smear	893.10	PY 21.8310	41	$31 698

C/E, cost per life year; HPV, human papillomavirus; ICER, incremental cost-effectiveness ratio.

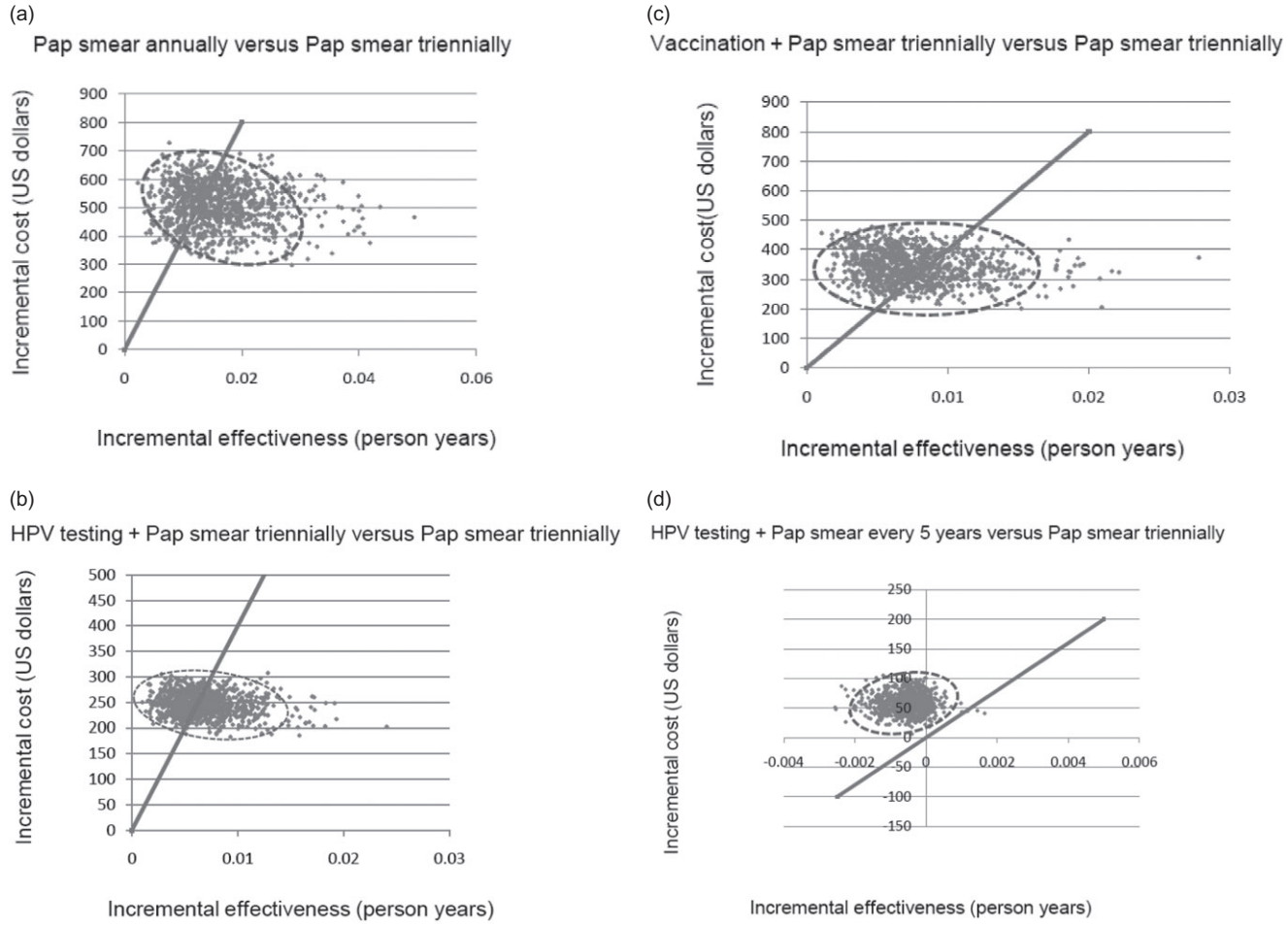

Figure 2 Simulated results of each strategy compared with triennial Pap smear only are shown on (a)–(d). The thick lines on (a)–(d) represent the ceiling ratio of willingness to pay = $US40 000. HPV, human papillomavirus.

HPV DNA testing had a low likelihood (1–2%) of being cost-effective when the WTP values ranged between $20 000 and $60 000.

Excluding the strategy of annual Pap smear, Pap smear combined with HPV DNA testing every 3 years was the most cost-effective and had 40–56% chance of being most cost-effective and dominated other strategies when the WTP value ranged between $40 000 and $100 000 (Fig. 3b). Given the current price of vaccine, vaccination combined with triennial Pap smear screening programme may become the most cost-effective when the WTP value reached more than $100 000.

Threshold of vaccine cost

Regarding the analysis of threshold on vaccine cost, vaccination combined with triennial Pap smear screening could be on the same frontier on the C-E plane with the strategy of annual Pap smear when the cost of vaccination was lowered to $250 and the probability of being cost-effective was 68% given $40 000 of WTP value (Fig. 4). This combined strategy would be as cost-effective as Pap smear combined with HPV DNA testing every 3 years if the cost was lowered to $300.

Influence of attendance rate

Regarding the impact of attendance rate, the strategies of Pap smear alone with various inter-screening intervals and attendance rates were almost on the same frontier with the similar ICER. The strategies with HPV testing or HPV vaccination combined with Pap smear were more costly than those with Pap smear alone given the same screening interval and attendance rate.

Discussion

Although Pap smear screening has demonstrated a substantial mortality reduction from cervical cancer, alternative policies for prevention of cervical cancer have been proposed for two main reasons. First, the trend in mortality reduction from cervical cancer in Western countries has become steady. The main reason for seeing this plateau may be due to false negative cases of Pap smear

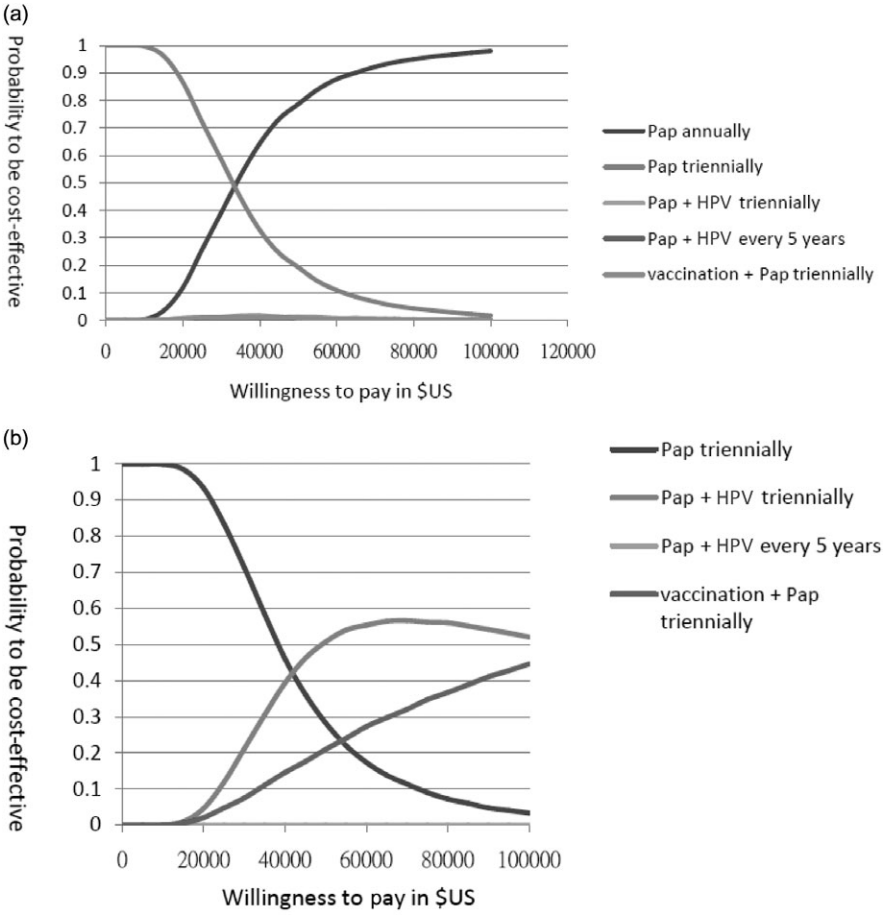

Figure 3 Acceptability curves of alternative strategies under different ceiling ratios. (a) Acceptability curves of all five strategies. (b) Acceptability curves excluding the strategy of annual Pap smear. HPV, human papillomavirus.

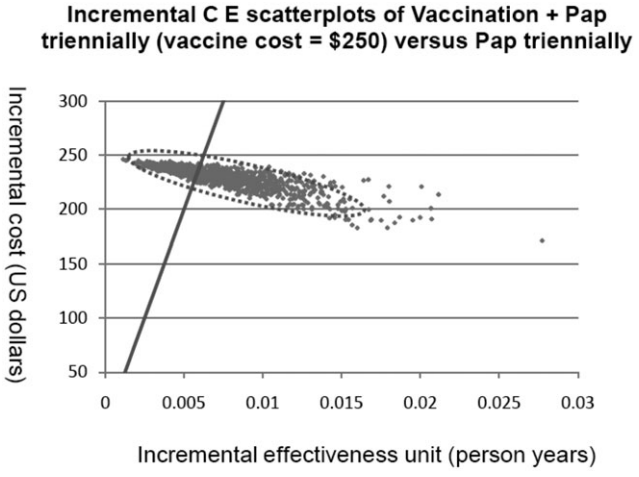

Figure 4 Simulated results of cost-effectiveness (C-E) plane of Vaccination + triennial Pap smear at vaccine cost = $250 compared with Pap smear screening triennially under willingness to pay = $40 000.

screening, particularly found in young women. Second, in other developing countries with nation-wide screening programmes, mortality reduction is modest partly because of poor quality of Pap smear screening and partly because of low attendance rate. The attendance rate of annual Pap smear screening programme in Taiwan is around 30%. The reason for the low annual attendance may be affected by cultural factors. For example, women do not like to undergo examination executed by male doctors.

To reduce false negative rates, a collaborative study on the comparison between HPV testing and Pap smear screening for young women suggests HPV testing may reduce the false negative rate and enhance the negative predictive value [37]. In addition, two randomized trials have demonstrated the efficacy of vaccination in reducing persistent HPV infections and pre-cursor lesions [38,39]. To achieve more benefit in mortality reduction, it is necessary to consider various screening strategies such as intensive Pap smear screening, the supplemental use of HPV DNA testing and HPV vaccination. The two latter approaches are particularly meaningful for certain Asian countries where the attendance rate and coverage rate of Pap smear are low as a result of cultural factors. The balance between cost and effectiveness is therefore a great concern for health policy maker given limited resources.

Cost-effectiveness analysis was therefore performed for the comparison of five preventive strategies for cervical cancer. Annual Pap smear is still the most effective and cost-effective. Triennial Pap smear combined with HPV DNA testing was cost-effective under a reasonable range of WTP values whereas vaccination with the combination of Pap smear was not cost-effective given the current vaccine cost.

From the aspect of temporal disease natural course, it would not be surprised to see the highest yield of life years gained from annual Pap smear screening programme because intensive screening may not only detect ealy invasive carcinoma of cerive but also arrest the malignant transformation of pre-cursor lesions of cervical neoplasm. Moreover, the cost of Pap smear is also low relative to two state-of-the-art screening tools, HPV DNA testing and HPV vaccination. Both features make other preventive strategies be eclipsed by the strategy of annual Pap smear screening. However, it should be noted that unlike Western countries low attendance and coverage rate of Pap smear often seen in Asian countries because of cultural factors may still make annual screening programme become less effective and cost-effective and may consider alternatives such as HPV DNA testing.

Triennial Pap smear combined with HPV DNA testing was cost-effective under the threshold $40 000 of WTP but still more costly than annual Pap smear. The reason comes from the low positive prediction value of HPV testing. It is possible that more costs were involved in substantial procedures and management in those with HPV infection but normal cervix after screening.

In our cost-effectiveness analysis, we may also underestimate the value of HPV DNA testing, particularly for young women, pertaining to high negative predictive value as suggested by the HART study [1], which may lengthen inter-screening interval for women with negative results of HPV DNA test or apply routine instead of intensive surveillance schedule to women with borderline cytological result (LSIL or ASCUS). However, in the current study we could not exactly model its negative predictive value as we used CIN2 and more as the cut-off of sensitivity and specificity and empirical data and result on this part were lacking. More detailed parameters on the cylogy results on different real states were required to tune relevant parameters of cost-effectiveness analysis in the future.

A vaccination programme in combination with triennial Pap smear screening give the highest yield of life years but the most costly compared with other strategies. The high yield of life years is mainly due to the reduction in HPV infection from adolescent onward. It would be as cost-effective as the strategy of annual Pap smear if the cost of vaccination was reduced to $250, and would be as cost-effective as the strategy of triennial Pap smear combined with HPV DNA testing when the price was lowered to $300. This suggests that universal vaccination in combination with Pap smear screening programme may be cost-effective in the future as vaccination in a large economic scale may greatly reduce the price of vaccine.

Apart from the main reason of expensive vaccine price, another possible reason for the failure of yielding cost-effective results for the vaccination with Pap smear screening is that other subtypes of HPV, such as type 31, 33, 45, 52, 58, account for 35% of cervical cancers in Taiwan [33]. Whether the current vaccination also play a role in partial immunization from these subtypes remains unclear. In addition, the lifelong protection assumption about the HPV vaccine may also overestimate the effectiveness of vaccination. Both the efficacy and duration of protection in HPV vaccination need further investigation.

To validate the credibility of results, we compared the projected incidence rate of cervical cancer with the underlying figure from Taiwanese women and compared HPV infection among women with cervical cancer with the previous similar study in Taiwan. The estimated incidence rate was 20.6×10^{-5} per women year, which was slightly lower than the underlying incidence of Taiwan (28.6×10^{-5} per person year) [40]. This is reasonable as base-case estimates derived from literatures to project the incidence rate tended to focus on young women. Those with oncogenic high-risk HPV infection in cervical cancer were about 85.6%, which is only slightly lower than the result reported by Lai CH *et al.* [33] because HPV testing and polymerase chain reaction method used in Lai *et al.* study were based on surgical specimen that may be more likely to get higher HPV infection rate compared with samples from general women.

Conclusion

By considering various preventive strategies related to cervical neoplasm, annual Pap smear alone was still the most cost-effective. We also demonstrated that the supplemental use of HPV testing in combination with Pap smear screening programme every 3 years was also cost-effective under a reasonable threshold of WTP. A vaccination programme in combination with triennial screening would be cost-effective if vaccine cost can be reduced substantially in a large economic scale.

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Conflicts of interest

All authors have no conflicts of interest.

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