

Maximising the cost-effectiveness of human papillomavirus testing for cervical screening in the context of routine HPV vaccination in Hong Kong: abridged secondary publication

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KEY MESSAGES

1. Among cohorts without a human papillomavirus (HPV) vaccination programme, use of the HPV test as a standalone primary test or as a screening test after receiving cytological analysis of atypical squamous cells of undetermined significance was considered a cost-effective cervical screening strategy to reduce deaths from cervical cancer when the willingness-to-pay threshold was one gross domestic product per capita (US\$46 615).
2. Reassessment of the comparative cost-effectiveness of strategies with longer routine screening intervals, a pre-defined fixed number of routine screenings per lifetime, or a later starting age is needed to identify optimal screening strategies for vaccinated cohorts, especially

when newer data about the duration of vaccine protection become available.

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Introduction

The second-generation nonavalent human papillomavirus (HPV) vaccine (9vHPV) is >90% effective against seven high-risk HPV (hrHPV) types, which collectively cause >90% of cervical cancers. As HPV prevalence drops (eg, when vaccine uptake is high in a vaccination programme), the positive predictive value of cytology for cervical precancerous lesions and cancer decreases, whereas the negative predictive value of the HPV test for the same clinical outcomes increases. Consequently, incorporation of the HPV test into cytology-based screening algorithms becomes more important in the context of routine 9vHPV vaccination.

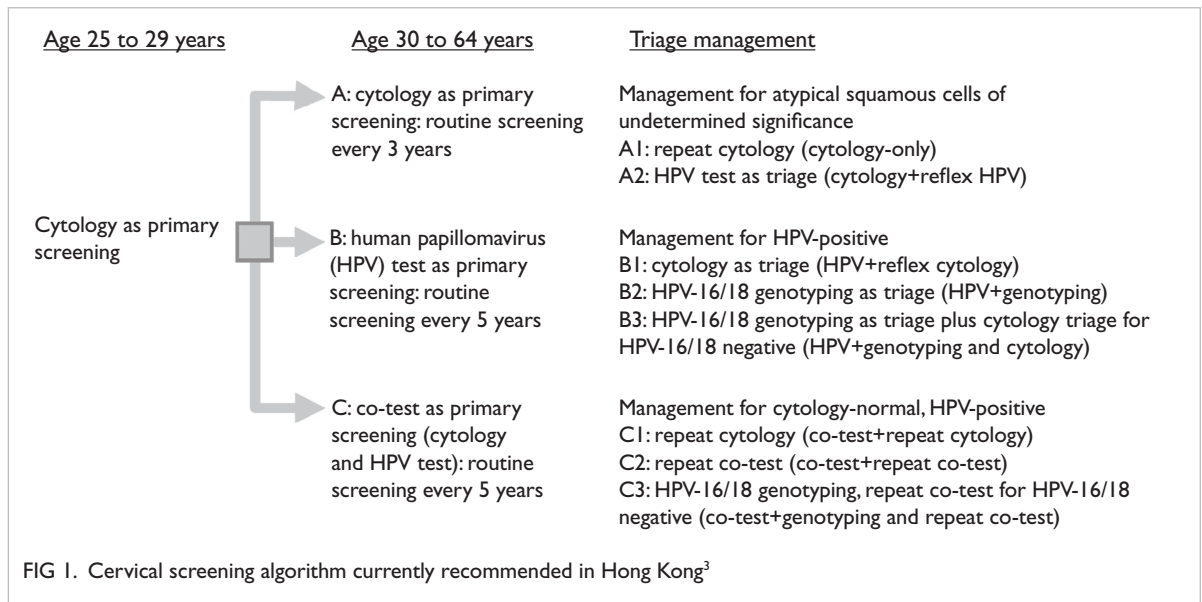
In Hong Kong, a population-based cervical screening programme was initiated in 2004, in which women aged 25 to 64 years are recommended to undergo cytology-based cervical screening every 3 years after two consecutive normal screening results.¹ Since June 2021, the updated recommendations include the use of high-risk HPV testing, either as a primary test or in combination with cytology, for women aged 30 to 64 years. Furthermore, the government recently implemented HPV vaccination for female adolescents. Beginning in the 2019-20 school year, schoolgirls in primary 5 and 6 (equivalent to age 11 to 12 years) could receive two doses of the 9vHPV vaccine at no cost. This

study evaluated the cost-effectiveness of different HPV testing applications in Hong Kong.

Methods

We extended our calibrated model for HPV vaccination and cervical screening² to compare the cost-effectiveness of various screening strategies. Our model consisted of a deterministic age-structured compartmental dynamic model that simulates heterosexual transmission of hrHPV and a stochastic individual-based cohort model that simulates the development of cervical cancer over the lifetime of each female. We grouped hrHPV into four classes: (1) HPV-16, (2) HPV-18, (3) HPV-OV (other vaccine type that comprises the other five hrHPV targeted by the 9vHPV vaccine, namely HPV-31, 33, 45, 52, and 58), and (4) HPV-NV that comprises all non-vaccine hrHPV.

Based on the latest screening recommendations from the Cancer Expert Working Group and guidelines from the Hong Kong College of Obstetricians and Gynaecologists (HKCOG),^{3,4} we considered the following screening strategies (FIG 1): A: cytology as primary screening, B: high-risk HPV DNA test (HPV test) as primary screening, and C: a combination of cytology and HPV test (co-test) as primary screening. In accordance with HKCOG guidelines, we assumed that the routine



screening interval was every 3 years for cytology and every 5 years for HPV test and co-test.³

The findings were analysed separately for (1) cohorts who were aged ≥12 years when the routine HPV vaccination programme began in 2019 (nVP cohorts) and (2) the first 10 cohorts eligible for HPV vaccination programme during their lifetime (VP cohorts). Thus, nVP cohorts included females aged 16 to 64 years in 2022; VP cohorts included females aged 6 to 15 years in 2022. We assumed that screening uptake would be similar among vaccinated and unvaccinated individuals. We also assumed that 70% of eligible females would undergo cervical screening with full compliance.

Regarding test performance, we assumed that the mean respective sensitivities for identifying CIN1 and CIN2/3 were 0.69 and 0.76 for cytology and 0.81 and 0.93 for the HPV test. The mean specificities were 0.97 for cytology and 0.91 for the HPV test. We also assumed that colposcopy-directed biopsy was 100% accurate.

We set vaccine uptake at 85%, in accordance with statistics regarding eligible primary 5 schoolgirls who received the first dose of the 9vHPV vaccine. The class-specific vaccine efficacies of the 9vHPV vaccine were based on data from the 9vHPV vaccine trials. We considered three scenarios for the duration of vaccine protection: lifelong, 30 years, and 20 years; we tested scenarios that assumed vaccine uptake decreasing to 75%, 50%, and 25%.

The costs of screening were based on charges for private patients in public hospitals, which represent >90% of inpatient care in Hong Kong. Treatments were based on expert opinions of oncologists and gynaecologists in Hong Kong. With reference to other cost-effectiveness analysis on cervical screening, we

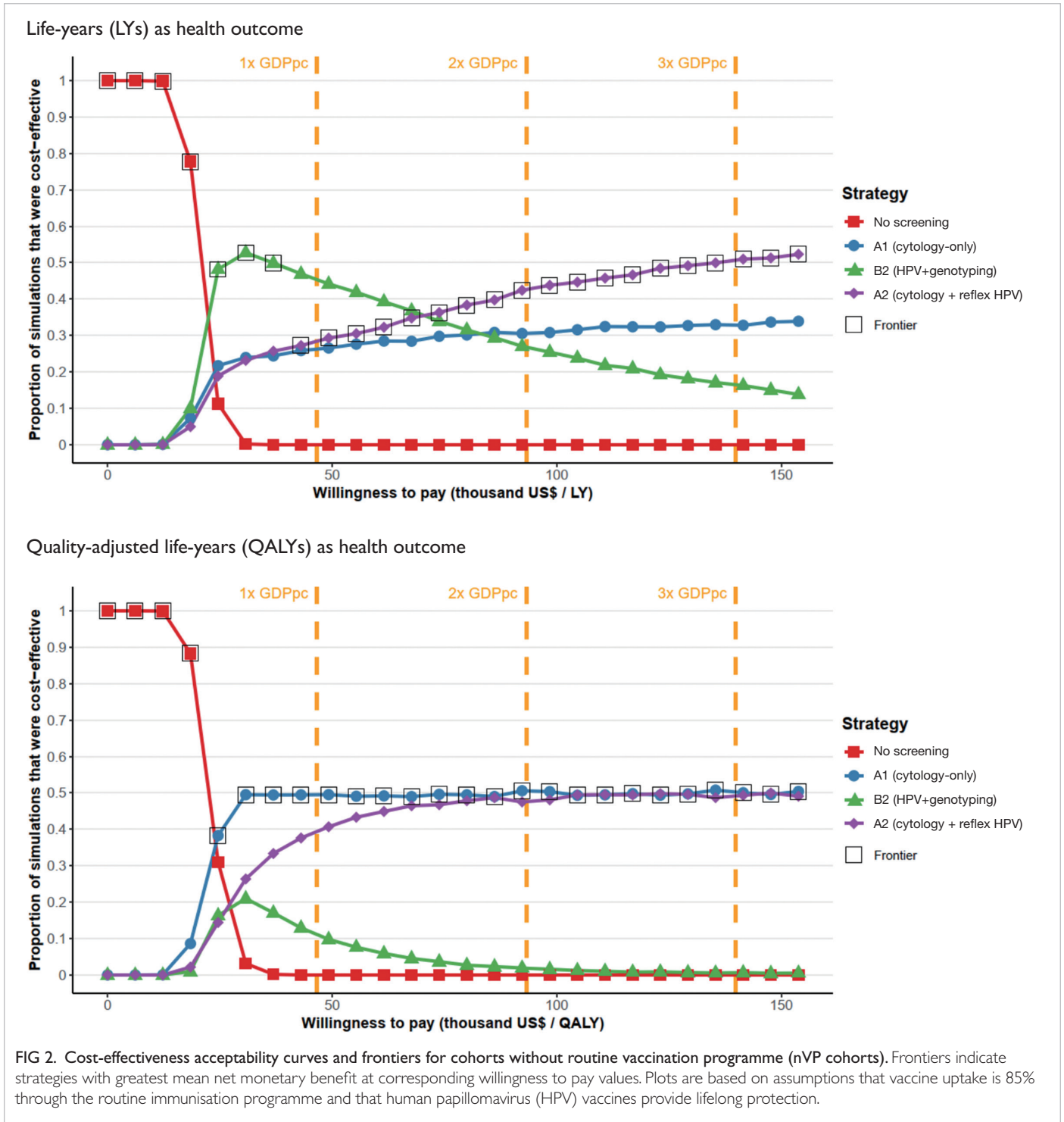
considered both life-years (LYs) and quality-adjusted life-years (QALYs) as metrics for quantifying health outcomes. When calculating QALYs, we adopted health utility parameters from studies in other countries because there were insufficient data from Hong Kong. Both costs and health benefits were discounted by 3% per year.

We conducted probabilistic sensitivity analysis to adjust for parameter uncertainty. The analysis included 100 parameter sets related to disease epidemiology (eg, natural history of HPV transmission, vaccine efficacy, and test performance) and 100 parameter sets related to costs and health utilities. In total, 10 000 parameter combinations were studied.

The incremental cost-effectiveness ratio (ICER) was defined as the additional mean cost divided by the additional mean health outcome. The willingness to pay (WTP) threshold was set at one Hong Kong gross domestic product per capita (GDPpc; US\$46 615 / HK\$363 596). We used net monetary benefit (NMB) to quantify the strategies in terms of monetary value. NMB is defined as "WTP × E - C", where C and E are the cost and health outcome of a particular strategy. We constructed cost-effectiveness acceptability curves and cost-effectiveness acceptability frontiers to allow simultaneous ranking of multiple strategies across a range of WTP values.

Results

For cohorts without the routine vaccination programme (nVP cohorts), the comparative cost-effectiveness of the evaluated strategies was not sensitive to vaccine uptake or duration of vaccine protection. When vaccine uptake was 85% and



vaccine protection was lifelong, if LYs were used as the metric for health outcomes, B2 (HPV+genotyping) was the most cost-effective strategy, with an ICER of US\$21 644 per LY gained. The next most cost-effective strategy was A2 (cytology+reflex HPV), with an ICER of US\$40 137 per LY gained. The remaining strategies were either dominated or associated with ICERs >3 times GDPpc. The comparative cost-

effectiveness of strategies B2 and A2 was sensitive to parameter uncertainty when the WTP threshold was near 1 GDPpc (FIG 2). However, as the WTP threshold increased, A2 (cytology+reflex HPV) was the most cost-effective strategy in more scenarios as the mean NMB increased. If QALYs were used as the metric for health outcomes, A1 (cytology-only) was the most cost-effective strategy, with an ICER

of US\$23 389 per QALY gained. The next most cost-effective strategy was A2 (cytology+reflex HPV), with an ICER of US\$181 297 per QALY gained. The remaining strategies were dominated. The comparative cost-effectiveness of A1 (cytology-only) and A2 (cytology+reflex HPV) was not sensitive to parameter uncertainty; thus, A1 was the most cost-effective strategy if the WTP threshold was <1 GDPpc (FIG 2). However, as the WTP threshold increased to >1.5 times GDPpc (US\$70 000), A1 and A2 were the most cost-effective strategies in a similar proportion of scenarios, with A1 consistently demonstrating a higher mean NMB.

For cohorts eligible to receive routine vaccination (VP cohorts), if LYs were used as the metric for health outcomes, B2 (HPV+genotyping) was the most cost-effective strategy—regardless of vaccine uptake and duration of vaccine protection—with ICERs ranging from US\$22 849 (for 25% uptake and 20 years of protection) to US\$59 836 (for 85% uptake and lifelong protection) [Table]. The remaining strategies were either dominated or associated with ICERs >10 times GDPpc. If the WTP threshold was 1 GDPpc, B2 was cost-effective only if vaccine uptake was <75% and vaccine protection was <20 years (Table). For screening to be cost-effective regardless of vaccine uptake and duration of protection, the WTP threshold would need to be >1.3 times GDPpc (US\$60 000). If QALYs were used as the metric for health outcomes, A1 (cytology-only) was the most cost-effective strategy regardless of vaccine uptake and duration of vaccine protection. The corresponding ICERs (compared with no screening) ranged from \$24 884 (for 25% uptake and 20 years of protection) to \$78 003 (for 85% uptake and lifelong protection). The remaining strategies were dominated by higher ICERs or associated with QALY loss. If the WTP threshold was 1 GDPpc, screening

would be cost-effective only if vaccine uptake was ≤50% or if duration of protection was 20 years and vaccine uptake was ≤75%. For screening to be cost-effective regardless of vaccine uptake and duration of protection, the WTP threshold would need to be >1.7 times GDPpc (US\$78 000). The comparative cost-effectiveness of the evaluated strategies for VP cohorts was not sensitive to parameter uncertainty.

Discussion

We compared the cost-effectiveness of different uses of HPV testing in cervical screening currently recommended by health authorities in Hong Kong.³ Among cohorts who could not enrol in the routine 9vHPV vaccination programme (ie, nVP cohorts), when the WTP threshold is 1 GDPpc, strategy A2 (cytology+reflex HPV) and strategy A1 (cytology-only) are the optimal strategies for achieving the greatest health benefit when health outcome metrics are LYs and QALYs, respectively.

For females eligible to receive 9vHPV vaccination through the routine immunisation programme (ie, VP cohorts), the comparative cost-effectiveness of each screening strategy depends on vaccine uptake and duration of vaccine protection. If the effect of the immunisation programme is high, the marginal benefit of screening decreases and the corresponding ICER increases. The vaccine effect is highest when vaccine uptake is 85% (consistent with the latest statistics) and vaccine protection is lifelong. In this scenario, none of the evaluated screening strategies is cost-effective if the WTP threshold is 1 GDPpc. If the WTP threshold is ≥1.7 times GDPpc, the optimal screening strategy for VP cohorts is strategy B2 (HPV+genotyping) and strategy A1 (cytology-only) when health outcome metrics are LYs and QALYs, respectively.

TABLE. Incremental cost-effectiveness ratios (ICERs) of the most cost-effective screening strategies across scenarios of human papillomavirus (HPV) vaccine uptake and duration of vaccine protection for cohorts in the routine vaccination programme (VP cohorts)

Strategy	Vaccine protection	Vaccine uptake among cohorts eligible to receive routine vaccination			
		85%	75%	50%	25%
ICER per life-year gained, US\$					
B2 (HPV+genotyping) vs no screening	Lifelong	59 836	49 218	32 600*	23 581*
B2 (HPV+genotyping) vs no screening	30 years	57 008	47 301	32 039*	23 491*
B2 (HPV+genotyping) vs no screening	20 years	48 509	41 511*	29 851*	22 849*
ICER per quality-adjusted life-year gained, US\$					
A1 (cytology-only) vs no screening	Lifelong	78 003	61 994	38 458*	26 289*
A1 (cytology-only) vs no screening	30 years	72 943	58 506	37 177*	25 921*
A1 (cytology-only) vs no screening	20 years	59 322	49 409	33 772*	24 884*

* ICERs that are below the willingness-to-pay threshold at 1 gross domestic product per capita (US\$46 615 / HK\$363 596)

The guidelines-based recommendation of routine screening every 5 years may be excessive for VP cohorts when vaccine effect is high. In a study of the role of the HPV test as the primary method for cervical screening in female adolescents who were offered the 9vHPV vaccine in four high-income countries (Australia, England, New Zealand, and the United States), the most cost-effective strategy involved only two to five screenings per lifetime. Current guidelines suggest that if the HPV test is used as the primary method for routine screening, females should begin with cytology-based screening (ie, strategy A1) at age 25 years and then switch to the HPV test at age 30 years. If vaccine uptake in the routine immunisation programme is high, cytology-only screening before age 30 years may be unnecessary. If the HPV test is used as the primary method, cervical screening at age 30 or 35 years would reduce costs, potentially without significant increases in precancerous lesions and cancer cases. Further comparative analyses of the cost-effectiveness of strategies (eg, with longer routine screening intervals, a pre-defined fixed number of routine screenings per lifetime, or a later age at initial screening) are needed to identify optimal screening strategies for vaccinated cohorts, particularly as newer data about the duration of vaccine protection become available.

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Disclosure

The results of this research have been previously published in:

1. Choi HCW, Leung K, Chan KKL, Bai Y, Jit M, Wu JT. Maximizing the cost-effectiveness of cervical screening in the context of routine HPV vaccination by optimizing screening strategies with respect to vaccine uptake: a modeling analysis. *BMC Med* 2023;21:48.

Acknowledgements

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