The impact of alternate HPV vaccination and cervical screening strategies in Japan: a cost-effectiveness analysis

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Summary

Background The Japanese 2020 cervical screening guidelines recommend conventional cervical cytology screening every 2-years for women aged 20–69 years. The nonavalent human papillomavirus (HPV) vaccine has also recently been approved in Japan. We therefore evaluated the cost-effectiveness of cervical cancer screening strategies alongside universal nonavalent HPV vaccination of girls (12–16 years).

Methods A cost-effectiveness analysis was performed using an age-specific Markov microsimulation model for Japan to evaluate total costs, quality adjusted life-years (QALYs) gained, incremental cost-effectiveness ratios (ICER), colposcopies, biopsies, precancer and cervical cancer treatments for 29 combined vaccination and screening strategies (conventional cytology, liquid-based cytology (LBC), HPV testing, and HPV self-collection). A cohort of 100,000 girls (12–16 years old) over a lifetime offered the nonavalent HPV vaccine was used (current vaccination coverage = 0.08%, current screening coverage = 43.7%). A discount rate of 3% was applied to costs and QALYs. Univariate and probabilistic sensitivity analysis was performed to assess robustness of the findings. Costs were reported in US dollars (2023).

Findings Compared with conventional cytology, evaluated strategies would incur an additional cost of US$839,280–738,182,669 and gain 62,755–247,347 quality-adjusted-life-years. HPV testing distinguishing HPV16/18 with reflex LBC (3-yearly) would be most cost-effective (ICER = US$7511 per QALY gained). At a willingness-to-pay (WTP) of 1-times gross domestic product (GDP) per capita, the probability of it being cost-effective was 70%. At historically high vaccination coverage (70%) ICERs decreased overall but did not affect the ranking of the most cost-effective strategy. While a 5-yearly interval became more cost-effective than a 3-yearly interval. Including HPV self-collection for under-screened women made all strategies more cost-effective.

Interpretation At current cervical screening participation (43.7%) and low vaccination coverage (<1.0%), HPV testing distinguishing HPV16/18 with reflex LBC (3-yearly) would be the most cost-effective screening strategy compared to conventional cytology (2-yearly).

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Keywords: HPV; Cervical cancer; Vaccination; Cervical screening; Japan

Introduction

The momentum towards cervical cancer elimination in Japan faces significant challenges. In 2020, 12,785 new cases (age-standardized rate (ASR): 15.2 per 100,000 women) and 4213 deaths (ASR: 2.9 per 100,000 women) from cervical cancer were reported.[1] The World Health

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Research in context

Evidence before this study

Combined human papillomavirus (HPV) vaccination and cervical screening programmes are safe, effective, and cost-effective strategies for preventing cervical cancer. Current cervical screening coverage for eligible women (20–69 years) is 43.7%. Despite the HPV test being a more sensitive method than conventional cytology for the detection of cervical cancer, the current revision of the Japanese Cervical Screening Guidelines still recommends conventional cytology testing with limited consensus on implementation of HPV testing as the primary method of cervical screening. HPV vaccination is included in the Japanese national immunisation programme provided free of charge for girls aged 12–16 years old. Current HPV vaccination coverage is extremely low (<1%) largely due to the suspension of proactive recommendation in June 2013 due to unconfirmed reports of adverse events following vaccination in the media. In late 2021 the suspension of proactive recommendation was lifted; however, vaccination coverage has been slow to increase.

We searched PubMed, Embase, and Japanese policy documents between January 2007 and November 2022 with the search terms "Japan" or "Japanese," "HPV vaccine," "screening," and "cost-effectiveness" to identify published economic evaluations on HPV vaccination and cervical screening strategies. Only three studies were identified that evaluate the cost-effectiveness of cervical screening. All studies were performed before the introduction of the nonavalent vaccine, and *none* provided a comparative analysis of alternate vaccination and screening strategies. The recent resumption of HPV vaccination, and availability of highly sensitive detection methods highlight the urgency for the timely re-evaluation of cervical cancer prevention strategies in Japan.

Added value of this study

This study is supported by National Cancer Centre (NCC) internal grants. We performed a cost-effective analysis of *all* cervical screening strategies outlined in the 2020 Japanese cervical screening guidelines including conventional cytology, manual and image read liquid-based cytology (LBC), HPV testing, and adjunct HPV and LBC testing (co-testing). We also included self-collection of HPV cervical samples, not currently referenced in the guidelines, and the impact of 1 or 2-dose schedule on cost-effectiveness. A total of 29 intervention strategies were evaluated at different screening frequencies. In our study we found that HPV testing distinguishing HPV16/18 with reflex LBC (3-yearly) was the most cost-effective strategy. If vaccination coverage reached a previous historical high (70%), a 5-yearly interval would be more cost-effective than a 3-yearly screening interval. In a supplementary analysis we also found that a 1-or 2-dose schedule reduced ICERs overall. Finally, including HPV self-collection for under-screened women improved the cost-effectiveness of all strategies.

Implications of all the available evidence

Contrary to the current Japanese cervical screening guidelines HPV testing once every 3-years distinguishing HPV16/18 with reflex LBC with vaccination using the nonavalent vaccine is the most cost-effective strategy at current cervical screening coverage (43.7%) and low vaccination coverage (<1%). A 5-yearly screening interval should be considered as vaccination coverage increases to previous levels.

Organization (WHO) Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem aims to reduce cervical cancer incidence to <4 cases per 100,000 women.[2] It sets interim scale up targets for all countries to meet by 2030 to be on track to achieve cervical cancer elimination globally within 100 years where: 90% of girls are fully vaccinated by the age of 15, 70% of women are screened with a high-performance test by the age of 35 and 45 years of age, and 90% of women with cervical pre-cancer or cancer are treated. It has been predicted that Japan is unlikely to reach the elimination threshold of <4 cases of cervical cancer per 100,000 women by the end of the century using vaccination alone.[3]

Japan has a long history of using cytology-based cervical screening.[4,5] The most recent revision of the cervical cancer screening guidelines recommend 2-yearly cytology screening for women between 20 and 69 years of age, and current screening coverage is 43.7%.[4,6,7] Women with ASC-US cytology are followed up with reflex HPV testing and women who are ASC-US & HPV16/18 positive are referred to colposcopy, while those who are ASC-US & HPV16/18 negative return for retesting in 12 months.[8,9] Women with > LSIL cytology are referred to colposcopy, following which women with histologically confirmed high-grade cervical intra-epithelial neoplasia (CIN2/3) or adenocarcinoma in-situ (AIS) are recommended for further treatment.[7] When detected, CIN1 and CIN2 lesions may be observed, while it is recommended that CIN3 lesions should be treated with post-treatment follow-up.

Many countries recognise that transitioning to HPV primary cervical screening is safe, efficacious, and cost-effective for the detection of invasive cervical cancers and its precursor lesions.[10,11] Higher sensitivity and negative predictive value of HPV primary cervical screening allows for longer screening intervals.[12–16] Even though HPV testing is a superior screening method, the optimal triage strategy for HPV-positive women has been country specific.[10] For example, Australia has chosen a primary HPV strategy where all HPV16/18 positive women are sent directly to colposcopy, while

women positive for other oncogenic types have a reflex liquid-based cytology (LBC) test. Those with high-grade squamous intraepithelial lesions (HSIL) are sent to colposcopy and those with a low-grade squamous intraepithelial lesion (LSIL) or less are retested in 12-months.[17,18] The Netherlands sends all oncogenic positive women with atypical squamous cells of undetermined significance (ASC-US) or worse directly to colposcopy, regardless of oncogenic genotype, and women who are oncogenic HPV positive but cytology negative are retested in 12-months.[10]

First-generation HPV vaccines have both been available free-of-charge since 2007 in Japan. Initially, three-dose coverage for eligible adolescent girls in some prefectures was as high as 70–80%.[19] Given such success, the HPV vaccine was added to the national routine vaccination register in April 2013. It was also recommended under the Preventative Vaccination Law that the HPV vaccine should be made available to all girls between of 12 and 16 years of age. However, in response to a series of media reported adverse events, the active recommendation of the HPV immunisation programme was suspended by the Japanese Ministry of Health, Labour, and Welfare (MHLW) in June 2013.[20] Encouragingly, in June 2020, the nonavalent vaccine was approved for use. Since April 2022, active recommendation of the HPV vaccine has resumed and has been included in the national vaccination program in April 2023.[21]

With the recent resumption of active recommendation of the HPV vaccination programme in Japan, and the most recent revision of the cervical cancer screening guidelines in 2020, we aimed to evaluate the cost-effectiveness of all screening strategies outlined in the Japanese cervical screening guidelines, including self-collection of under-screened women.

Methods

Study design

An economic evaluation was used to assess the cost-effectiveness of combined HPV vaccination and cervical screening using a health-care systems perspective. The model was constructed using R Version 4.3.1, and TreeAge Pro 2022. Analysis was reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement and the HPV-FRAME reporting standards for HPV models.

Modelling

An age-specific Markov microsimulation model was constructed to simulate the disease progression of HPV infection with high-risk HPV to cervical cancer or regression in a designated initial cohort of 100,000 girls aged 12–16 years for a lifetime. The model consisted of 22 health states from susceptible to cervical cancer (Appendix 1). We assumed girls were infected at age-specific rates for HPV16, 18 and other high-risk HPV genotypes. Individuals infected with high-risk HPV can progress to CIN2, and CIN3 or regress to the susceptible state. Progression and regression rates were associated with the duration of infection. The cervical cancer stage consisted of local, regional, and distant cancer states. In the absence of screening, women with CIN2, CIN3 or cervical cancer would be diagnosed by self-initiated examinations according to state specific probabilities (Table 1). Women diagnosed with cancer would receive state specific treatments and undiagnosed women remained untreated. Age-specific natural background mortality rates were assumed. Women with cervical cancer experienced age-specific mortality due to cervical cancer in addition to background mortality. A model cycle-length of 1-year, with half-cycle correction was assumed.

Intervention strategies

Vaccination was performed when the cohort entered the model at 12–16 years of age, and screening was conducted when the cohort progressed to a designated age dependent on the screening interval modelled. The comparator for this analysis was cervical screening with conventional cytology according to the current guidelines with current very low vaccination coverage of 0.08%.[9,22] A total of 29 combined vaccination and primary screening interventions were evaluated in this study. This included a combination of eight screening strategies (Conventional cytology, LBC (image), LBC (manual), LBC with reflex HPV testing, HPV testing with LBC (any oncogenic HPV), HPV testing with LBC (HPV16/18), HPV self-collection, and HPV & LBC (co-testing)), and 5-screening intervals (once per lifetime, twice per lifetime, 2-yearly, 3-yearly, and 5-yearly). We assumed baseline participation of the base strategy, and 25% of women who would not otherwise attend for screening do using HPV self-collection from 20 or 30 years of age depending on primary screening method (Table 2, and detailed in Appendix 2).[16,23] Women diagnosed with cancer would receive state specific treatments.

The target population for cervical screening was women 20-years-and-over using conventional cytology, and 30 years-and-over for HPV based screening as per the current Japanese guidelines.[9] It was assumed that once-per-lifetime screening was performed at the age of 35, and twice-per-lifetime screening was performed at 35 and 45 years of age which coincides with the peak in pre-cancer lesions for the Japanese female population and as recommended by The Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem.[2,24] Japan specific test sensitivities and specificities were based on a large meta-analysis performed as part of the cervical screening evidence report performed by the National Cancer Center.[8]

Parameter	Base-case	Range	Distribution	Reference
Vaccine coverage	0.08%	0.04–70.0%	Beta (15.21, 190.12)	WHO HPV vaccination coverage[1]
Vaccine efficacy	100%	80–100%	Beta (313, 0.003)	Assumed
Screening coverage	43.7%	30–70%	Beta (8.17, 10.52)	National Cancer Center, Cancer Information Services[2]
Conventional cytology performance				
Sensitivity	63.5	49.2–76.0	Beta (58.24, 33.47)	MHLW cervical cancer screening evidence report[8]
Specificity	94.7	91.5–96.7	Beta (474.36, 26.55)	
Manually read LBC performance				
Sensitivity	65.4	61.6–69.2	Beta (58.54, 30.97)	Systematic review and meta-analysis[71]
Specificity	86.2	79.5–92.8	Beta (40.15, 6.43)	
Image read LBC performance				
Sensitivity	69.9	60.3–73.0	Beta (58.13, 25.03)	Cohort study[72]
Specificity	93.7	92.8–95.6	Beta (552.18, 37.13)	
Adjunctive cytology and HPV\testing				
Sensitivity	98.5	78.0–99.9	Beta (144.55, 2.20)	MHLW cervical cancer screening evidence report[8]
Specificity	84.4	68.4–93.2	Beta (43.61, 8.06)	
HPV test for primary screening performance				
Sensitivity	96.0	95.0–98.0	Beta (367.68, 15.32)	Systematic review and meta-analysis[73]
Specificity	91.0	88.6–99.3	Beta (118.34, 11.70)	
Test for primary screening performance (self-collection)				
Sensitivity	93.0	(87.0–98.0)	Beta (95.94, 7.22)	Two cohort studies[74,75]
Specificity	91.0	(88.6–93.3)	Beta (118.34, 11.70)	
Annual self-initiated examination				
CIN2 or CIN3	0.01	0.005–0.02	Beta (3.95, 391.05)	Campos et al. (2014)[76]
Local cancer	0.1899	0.15–0.20	Beta (3.05, 13.01)	
Regional cancer	0.5999	0.40–0.65	Beta (5.80, 3.87)	
Distant cancer	0.90	0.85–0.95	Beta (39.10, 4.34)	
Cost, US$				
Vaccination (3-doses)	586.0	146.5–586.0	Gamma (27.04, 0.05)	Manufacturer's market price Appendix 3
Conventional cytology test	83.5	29.0–87.0	Gamma (123.46, 1.49)	
Manually read LBC test	59.8	29.9–89.7	Gamma (24.99, 0.42)	
Image read LBC test	61.6	30.8–92.5	Gamma (13.71, 0.22)	
HPV-DNA and cytology test (co-test)	260.4	130.2–390.6	Gamma (17.36, 0.07)	
HPV-DNA test for primary screening	78.6	39.3–117.9	Gamma (17.36, 0.22)	Medical fee reimbursement schedule.[77] Appendix 3
HPV-DNA test for primary screening (self-collection)	78.6	39.3–117.9	Gamma (17.36, 0.22)	
Colposcopy (with biopsy)	115.7	57.9–173.6	Gamma (20.66, 0.18)	
Colposcopy (without biopsy)	80.4	40.2–120.6	Gamma (18.90, 0.24)	
Precancerous lesion treatment				
Ablation therapy	327.5	163.7–491.2	Gamma (16.65, 0.05)	Medical fee reimbursement schedule.[77] Appendix 3
Excision therapy	450.0	225.0–675.0	Gamma (15.02, 0.03)	
Hysterectomy	2765.7	1382.8–4148.5	Gamma (18.11, 0.006)	
Cancer work-up				
Local cancer	1309.5	654.8–1964.3	Gamma (18.57, 0.007)	Medical fee reimbursement schedule.[77] Appendix 3
Regional cancer	3780.9	1890.4–5671.3	Gamma (17.65, 0.004)	
Distant cancer	2011.7	1005.8–3017.5	Gamma (19.24, 0.009)	
Cancer treatment				
Local cancer	3193.8	1596.9–4790.7	Gamma (17.58, 0.006)	Medical fee reimbursement schedule.[77] Appendix 3
Regional cancer	3598.8	1799.4–5398.2	Gamma (13.72, 0.004)	
Distant cancer	11,860.8	5930.4–17,791.2	Gamma (19.30, 0.002)	
Utility score				
CIN1	0.89	0.80–0.98	Beta (138.52, 17.12)	Appendix 3. Insigna et al. (2007)[78] Elbasha et al. (2007),[79] Goldie et al. (2004)[80]
CIN2	0.88	0.79–0.97	Beta (36.29, 4.95)	
CIN3	0.89	0.80–0.98	Beta (33.96, 4.19)	
Local cancer	0.76	0.68–0.84	Beta (13.10, 4.13)	

(Table 1 continues on next page)

Parameter	Base-case	Range	Distribution	Reference
(Continued from previous page)				
Regional	0.67	0.60–0.74	Beta (14.14, 6.96)	
Distant	0.48	0.43–0.53	Beta (11.50, 12.46)	
Discount rate	0.03	0.00–0.08		Walker et al. (2010)[70]

Detailed definition of screening parameters and cost parameters are described in Appendix 3. Utility scores range from 0 (death) to 1 (perfect health). LBC: liquid based cytology. CIN: cervical intraepithelial neoplasia. All eligible studies assessed the performance of cervical screening methods at least based on the detection of CIN2+ on histology.

Table 1: **Summary of model parameters.**

It was assumed that the 3-dose nonavalent vaccine coverage was 0.08% (range 0.04–1.2%) in the base-case analysis.[19,22] The impact of increased vaccination coverage was assessed at 30, 50 and 70% coverage.[19,22] Vaccine efficacy against oncogenic vaccine types (HPV16/18) was assumed to be 100% (range 80–100%) based on previous findings.[25–27] For 1 and 2-dose vaccine schedules, equivalency to the 3-dose schedule was assumed.[28–37] We assumed that nonavalent vaccine would provide direct protection against HPV16 and 18 infections, and conservatively assumed direct protection against a proportion of other high-risk infections (including 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, 82, and their co-infections).[38] Any cross-protective effect on other high-risk genotypes was not considered. It was assumed that HPV vaccination provided lifetime protection for recipients.

Data analysis

A detailed description of model parameters is summarised in Appendix 3. Annual transition probabilities were derived from Japanese databases and published literature. Cancer mortality data was derived from Cancer Information Services, National Cancer Center, Japan.[24] Background mortality statistics were obtained from the Japanese Mortality Database collected by the National Institute of Population and Social Security Research in 2022.[39] The cost of cervical screening, diagnosis and treatment were summarised using the Japan Medical Database Claims (JMDC) data, an individual health insurance receipts database.[40] The cost of vaccination was derived from the manufacturer's market price. All costs were converted from Japanese Yen to US dollars ($1 = 0.0089 Japanese Yen in 2023).[41]

Utility weights for health states were obtained from two international studies which derived QALY weights for associated health states.[42,43] A discount rate of 0.03 (range 0.00–0.08) for all costs and QALYs was assumed. The distribution of parameters was chosen based on their respective properties and the natural distributions referenced in the literature. QALYs were evaluated as a primary outcome for the cost effectiveness of alternate strategies in this analysis.

The discounted incremental costs and incremental QALYs for a total of 29 intervention strategies were assessed in a designated cohort of 100,000 girls aged 12–16 years over their lifetime for each strategy were calculated. We calculated the cost-effectiveness ratio (ICER), the incremental cost per QALY gained for each strategy on the cost-effectiveness frontier compared with a lower cost and non-dominated strategy to identify the most cost-effective strategy. The WHO definition of

Strategy	Screening frequency	Included base strategy + 25% HPV self-collection for under screened women (Y/N)	Earliest screening age
Conventional cytology (comparator)	2-yearly	N	20
Liquid-based cytology (manual)	1-lifetime, 2-lifetime, 2-yearly, 3-yearly, 5-yearly	N	20
Liquid-based cytology (image)	1-lifetime, 2-lifetime, 2-yearly, 3-yearly, 5-yearly	N	20
Liquid-based cytology (image) with reflex HPV testing	1-lifetime, 2-lifetime, 2-yearly, 3-yearly, 5-yearly	Y	20
HPV with reflex LBC (any oncogenic)	1-lifetime, 2-lifetime, 3-yearly, 5-yearly	Y	30
Partial HPV with reflex LBC (HPV16/18)	1-lifetime, 2-lifetime, 3-yearly, 5-yearly	Y	30
Adjunctive HPV and LBC testing (co-testing)	1-lifetime, 2-lifetime, 3-yearly, 5-yearly	Y	20
HPV self-collection - Partial HPV with reflex LBC (HPV16/18)	1-lifetime, 2-lifetime, 3-yearly, 5-yearly	N	30

All strategies were modelled at baseline with the nonavalent vaccine at 0.08% coverage. Self-collection assumed participation as per the base cervical screening strategy and starting age, where 25% of women who would not otherwise attend for screening do attend due to self-collection. Detailed descriptions of modelled pathways are from the 2020 Japanese cervical screening guidelines and are detailed in Appendix 2.

Table 2: **Summary of modelled intervention strategies.**

cost-effectiveness was used, whereby: highly cost-effective, cost-effective, or not cost-effective with a corresponding ICER <1, 1–3, or >3 times the per capita gross domestic product (GDP). The Japanese GDP used was $US43,300 in 2021.[41] We also assessed the total consumption of colposcopies, histological examinations, and pre-cancer treatments for each combined vaccination and screening strategy.

The model was visually calibrated to observed data for age-specific cervical cancer incidence and mortality, by varying probabilities of annual transitions within their published 95% confidence intervals (Appendix 4),[24,44] The prevalence of high-risk HPV infections in CIN2, CIN3 or cervical cancer, the distribution of clinical stages of cervical cancer,[45] the 5-year survival of cervical cancer by clinical stage,[46] and the population survival of Japanese women were used to validate the reliability of the model.[47] Univariate sensitivity analyses were performed for all parameters within their respective ranges to identify the most sensitive (Appendix 5). In addition, a probabilistic sensitivity analysis was performed based on 10,000 simulations to determine the probability of being cost-effective at each willingness to pay threshold. We also explored the impact of increased vaccination coverage, screening participation, vaccine efficacy, and vaccine dosage (1 or 2-dose schedule) on the probability of being cost effective. The impact of increasing vaccination coverage on screening interval was also assessed.

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The funders of this study had no role in the study design, data collection, data analysis, data interpretation, drafting or writing of this manuscript. All authors had full access to the study data and MP, KK, JSH, JMLB, and JJO had final responsibility for the decision to submit the article for publication.

Results

All combined vaccination and screening strategies were below the highly cost-effective willingness-to-pay (WTP) threshold. The most cost-effective strategies from the 2020 cervical screening guidelines are shown in Table 3 and presented in Fig. 1a. On the cost effectiveness frontier, image-based LBC ($13 per QALY) performed 2-yearly according to the current screening strategy was more cost effective than the comparator (2-yearly conventional cytology). The next two strategies on the cost-effectiveness frontier were HPV testing distinguishing HPV16/18 with reflex LBC once per lifetime ($40 per QALY), and twice per lifetime screening ($206 per QALY). The final strategy on the cost-effectiveness frontier was HPV testing distinguishing HPV16/18 with reflex LBC every 3-years ($7511 per QALY). Including self-collection of under-screened women, the cost-effectiveness frontier changed (Fig. 1b). In this case, the final strategy on the cost-effectiveness frontier was LBC with reflex HPV testing performed 2-yearly with 25% of under-screened women having a self-collected sample ($3112 per QALY). Overall, the combined strategies incurred an additional cost between $839,280 and $738,182,669 compared with current vaccination and cervical conventional cytology screening (2-yearly) coverage. These strategies would result in 62,755–247,347 QALYs gained (Appendix 5).

The cost-effectiveness acceptability curves for all intervention strategies between zero and 3-times per capita GDP were shown in Fig. 2a. At 1-times per capita GDP, HPV testing with reflex LBC for HPV16/18 (3-yearly) showed a 70% probability of being cost effective and outperformed all other strategies at this threshold ($43,300). Between 1-times and 2-times GDP, and at 3-times GDP, the probability of HPV testing distinguishing HPV16/18 with reflex LBC testing being cost-effective increased. When self-collection was included, this conclusion did not change (Fig. 2b).

All other combined strategies resulted in QALYs gained and an increase in the number of colposcopies, biopsies, or precancer treatments, associated with an increase in the number of QALYs gained over a lifetime compared to conventional cytology (2-yearly). Strategies that include self-collection for under-screened women resulted in more QALYs gained with a relatively higher number of colposcopies, histological evaluations, and precancer treatments (Appendix 5).

Performing a univariate sensitivity analysis did not significantly impact the rankings of cost-effectiveness. Increasing vaccination coverage to 30%, 50%, or 70% also did not impact the rankings of cost-effectiveness. However, a 5-yearly interval became more cost-effective than a 3-yearly screening interval at historical high vaccination coverage (70%). Reducing vaccine efficacy to 80%, reducing vaccination cost by 75%, 50%, and 25% of market price, increasing screening coverage to 70%, or using a 1 or 2-dose schedule also decreased ICERs overall but did not affect the conclusion that HPV testing distinguishing HPV16/18 with reflex LBC would be the most cost-effective strategy compared to conventional cytology (Appendix 5).

Discussion

This study presents the most comprehensive economic modelling of combined cervical cancer screening and HPV vaccination strategies in Japan and coincides with the recent resumption of active recommendation supporting HPV vaccination for Japanese girls by the MHLW of Japan, after over 8.5-years of suspension of active recommendation.[19,48] It also considers the impact of the recent decision to reduce the number doses from a three to two-dose schedule in April 2023. The 2020 Japanese cervical screening guidelines recommend

Strategy	Screening interval	QALYs	Incremental QALYs	Cost (US$)	Incremental cost (US$)	ICER
Cervical screening guideline strategies[a]						
Conventional cytology (comparator)	2-yearly	5,890,335		15,105,298		
Liquid-based cytology (image)	2-yearly	5,953,090	62,755	15,944,579	839,280	13
Partial HPV with reflex LBC (HPV16/18)	Once per lifetime	6,047,108	94,017	19,707,191	3,762,612	40
	Twice per lifetime	6,056,395	9287	21,616,097	1,908,906	206
	3-yearly	6,089,425	33,031	269,694,651	248,078,554	7511
Cervical screening guidelines in addition to self-collection strategies[b]						
Conventional cytology (comparator)	2-yearly	5,890,335		15,105,298		
Liquid-based cytology (image)	2-yearly	5,953,090	62,755	15,944,579	839,280	13
Partial HPV with reflex LBC (HPV16/18)	Once per lifetime	6,047,108	94,017	19,707,191	3,762,612	40
	Twice per lifetime	6,056,395	9287	21,616,097	1,908,906	206
LBC with reflex HPV + 25% HPV self-collection	2-yearly	6,150,033	93,638	313,037,647	291,421,550	3112

All strategies were modelled at baseline with the nonavalent vaccine at 0.08% coverage. QALYs and costs are expressed as the value in 2023. LBC: liquid-based cytology. QALY: quality adjusted life year. ICER: incremental cost effectiveness ratio. Self-collection assumed participation as per the base cervical screening strategy and starting age, where 25% of women who would not otherwise attend for screening do attend due to self-collection. [a]Cost effectiveness frontier calculated for strategies reviewed in the cervical screening guidelines only. [b]Cost effectiveness frontier calculated for strategies reviewed in the cervical screening guidelines including primary self-collection and self-collection of under-screened screened women.

Table 3: **Incremental QALYs and costs of intervention strategies on the cost-effectiveness frontier (100,000 women).**

primary cervical screening with conventional cytology, with limited consensus on the implementation of HPV testing as the primary method of cervical screening.[9] We found that at current low screening participation (43.7%) and vaccination coverage (<1.0%) HPV testing distinguishing HPV16/18 with reflex LBC (3-yearly) would be more cost-effective compared to conventional cytology.

Notably, the very low level of HPV vaccination in Japan is of greatest concern. In our study, even when vaccination coverage reached a previous historical vaccination coverage plateau (30%) or the highest level reached in some municipalities (70–80%), all strategies remained cost-effective and would result in more QALYs gained.[19,22] However, if historically high vaccination coverage of 70% for Japanese women was reached, a 5-yearly interval would become more cost-effective than a 3-yearly screening interval. When vaccine efficacy was reduced to 80%, or with the use of a 1 or 2-dose schedule the conclusions regarding cost effectiveness did not change. Including HPV self-collection for under-screened women improved cost-effectiveness of all strategies and remained highly cost-effective at one-times per capita GDP.

Cancer screening guidelines are developed by the Japanese Advisory Committee on Cancer Screening and are implemented by local governments. Local government cancer screening programme participation (other than for cervical cancer) are much higher for men compared to women.[4] In 2019, 2-yearly gastric cancer screening participation reached 50.2% for men compared to 41.0% for women[4] and screening for colorectal cancer reached 45.2% for men compared to 37.6% for women.[4] The MHLW has previously funded gastric cancer and colorectal cancer screening programmes.[49,50] The most recent studies suggest that the cost per QALY for population based colorectal screening was between $2879–7660.[51] This compares to population based gastric cancer screening which costs $45,655 per QALY.[52] Our study suggests that for primary HPV testing, the cost per QALY would be significantly lower ($7511 per QALY) than either population-based colorectal or gastric cancer screening programmes, and will benefit women who are underrepresented in Japan's existing cancer screening programmes.

We demonstrated that HPV testing would be superior to conventional cytology in terms of cost and effectiveness in line with evidence in other high income countries.[53] There are several benefits to using an HPV test. Because of its high sensitivity and negative predictive value, it has the potential to prevent more cervical cancer cases by identifying high-grade lesions earlier and lower risk of CIN3 and cervical cancer.[12,13,54,55] Genotyping for oncogenic HPV16/18 would also improve risk stratification of women with a positive oncogenic HPV test results as seen in other settings.[38,53] The COMPACT study conducted in Japan also found that HPV testing with risk stratification of HPV16/18 positive women would be an effective strategy without over referral to colposcopy.[56] We confirmed that HPV testing distinguishing HPV16/18 from other oncogenic types with reflex LBC would be a more cost-effective strategy for the triage of HPV positive women than any oncogenic type, and both would be more cost-effective than current conventional cytology.

It has been estimated that 80% of cervical cancers occur in women who are under-screened or never participate in cervical screening in other settings.[57–59] Self-collection has been shown to overcome barriers to undergoing cervical screening test that women in Japan experience. Providing HPV self-collection to under-screened women has been shown to improve

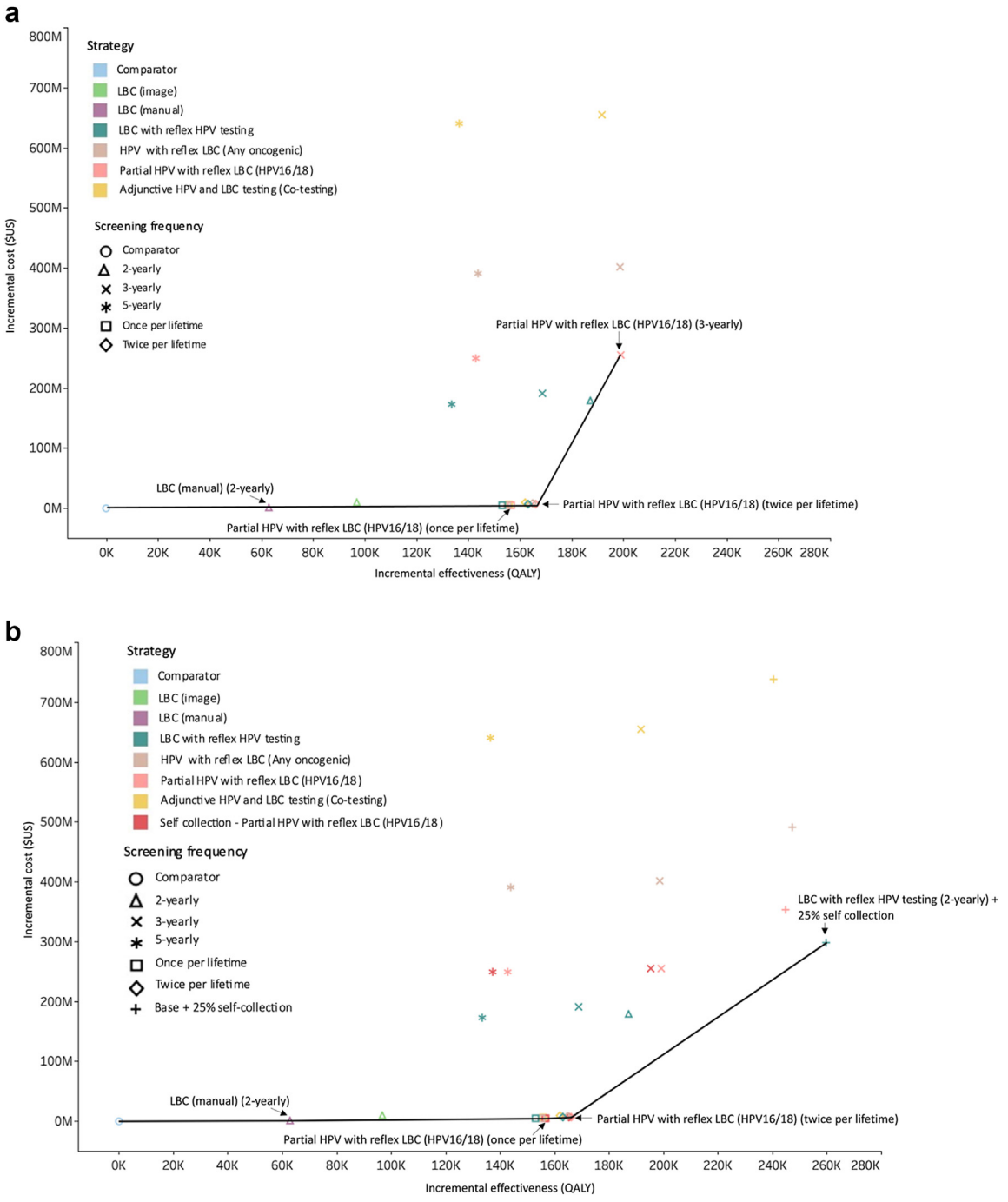

***Fig. 1*: Cost effectiveness frontier for intervention strategies (a) included in the 2020 Japanese cervical screening guidelines and (b) all intervention strategies including HPV self-collection strategies (100,000 cohort members).** Incremental QALYs and incremental costs of intervention strategies compared with current screening and vaccination coverage. Names of strategies located on the cost-effectiveness frontier and their incremental cost-effectiveness ratios compared with the lower-cost non-dominated strategy are shown. Self-collection assumed participation as per the base cervical screening strategy and starting age, where 25% of women who would not otherwise attend for screening do attend due to self-collection. LBC: liquid-based cytology. HPV: human papillomavirus.

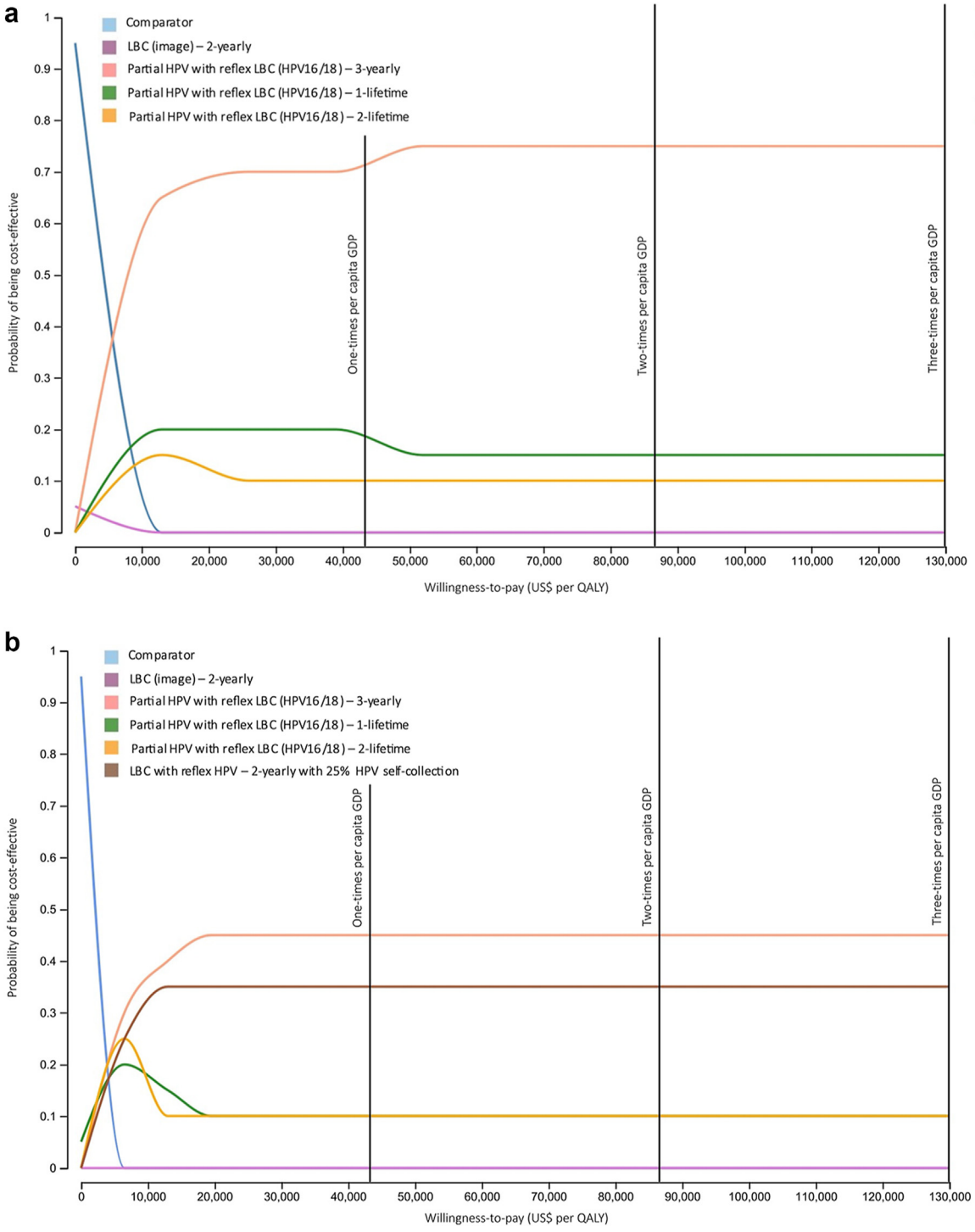

Fig. 2: **Cost effectiveness acceptability curves for (a) all strategies included in the 2020 Japanese cervical screening guidelines and (b) all intervention strategies including HPV self-collection strategies (100,000 cohort members).** The probability of intervention strategies being cost-effective at baseline vaccination and screening coverage within one-times, one-times and two-times GDP, and two-time and three-times Japanese per-capita GDP are represented. Self-collection assumed participation as per the base cervical screening strategy and starting age, where 25% of women who would not otherwise attend for screening do attend due to self-collection. The probability that each strategy is cost-effective represents the proportion of times each strategy offers the highest expected net benefit compared to other strategies at 1 to 3 times GDP. LBC: liquid-based cytology. HPV: human papillomavirus. QALY: quality-adjusted life-years. GDP: gross domestic product.

screening participation in other international studies.[16] A recent RCT (The ACCESS Trial) in Japan found self-collection to be a feasible option to increase screening for non-responders.[23] Another study found that mail-out HPV self-sampling kits may improve detection in under-screened women.[60] In the non-responding arm of the ACCESS trial, 16.3% ordered and returned a self-collection test. Our modelling indicates that offering HPV self-collection to 25.0% of non-responders would be a cost-effective strategy, as it increased participation of women who are not normally screened as part of an existing programme.

At present there remain substantial barriers to the implementation of HPV based primary screening in Japan, notwithstanding the lack of endorsement of its use as the preferred primary screening method in the current Japanese guidelines.[9] Although not documented clinician support for primary HPV screening or self-collection is currently low. Attention must also be given to the reasons why women opt-out of the current screening program, where lack-of-time, embarrassment, discomfort and personal barriers are commonly associated with physician collected conventional cervical screening.[61–64] Studies that have evaluated HPV self-collection suggest that women who receive instruction and support to self-collect report that it is easy, and women who do self-collect prefer to self-collect in the future.[61,65–68] In our study, offering self-collection as a screening method to under-screened women is a cost-effective strategy.

This study presents the most comprehensive economic modelling of all cervical cancer screening strategies in the Japanese cervical screening guidelines. Our study has several limitations: A Markov microsimulation model was used to assess cost-effectiveness of combined vaccination and screening strategies which does not consider the effects of herd immunity. Compared to using a dynamic model, this study is likely to underestimate the population effects of HPV vaccination and the cost-effectiveness of the strategies evaluated. Secondly, there is limited national representative epidemiological data in Japan for HPV infection status, cervical screening coverage, and loss to follow-up. These values were tested in the sensitivity analysis and did not impact the ICER values. Thirdly, combined vaccination and screening strategies for 12–16-year-old girls only was assessed. Finally, it did not assess the impact of implementing a female catch up program initially, as recommended by WHO to reduce time to impact on disease, or on vaccination of other at-risk populations such as older-women, boys and men who have sex with men (MSM).[69]

Conclusion

Contrary to the current Japanese cervical cancer screening guidelines, we found that at the current cervical screening participation (43.7%) and low vaccination coverage (<1.0%), HPV testing distinguishing HPV16/18 with LBC (3-yearly) would be the most cost-effective cervical screening strategy for Japanese women compared to conventional cytology. If historically high vaccination coverage is reached, a 5-yearly screening interval should be considered. Including self-collection of under-screened women improved the cost-effectiveness of all strategies. This study contributes much needed information as Japan recommences HPV vaccination and urgently addresses cervical cancer as a public health problem.

Contributors

MP was responsible for project administration, conceptualisation, methodology, conducting analysis, design of visualisations, and writing of the original manuscript draft. JO (University of Melbourne, Monash University & London School of Tropical Hygiene and Medicine) provided detailed supervision regarding analytical methods specific to this manuscript and review and editing of the original manuscript. JMLB provided detailed guidance as a subject matter expert on HPV vaccination and Cervical Screening and provided detailed input on conceptualisation, writing, review and editing of the original manuscript. JSH provided input regarding conceptualisation, supervision, writing review and editing of the manuscript. KK (National Cancer Center, Japan) and ES (National Center for Global Health & Medicine) provided guidance on conceptualisation, interpretation of findings, review and editing of final manuscript. HS provided detailed support of interpretation of the medical reimbursement data for Japan, and review and editing of the final manuscript.

Data sharing statement

The data used to generate the findings of this study were systematically collected from publicly available data and were cited in this manuscript or are included in the Supplementary Materials. Further details are available from the corresponding author after publication upon reasonable request.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101018.

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