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# Optimization of primary and secondary cervical cancer prevention strategies in an era of cervical cancer vaccination: A multi-regional health economic analysis

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ABSTRACT

With the recent advent of cervical cancer vaccines, many questions relating to the best overall prevention methods for cervical disease are beginning to arise. A Markov model was used across five geographic regions (Canada, The Netherlands, Taiwan, UK, US) to examine the clinical benefits and cost-effectiveness of: (1) vaccination combined with screening, considering changes to screening-related parameters and (2) vaccination combined with screening, considering changes to screening policy. Given the assumptions used in this analysis, adding vaccination to current screening is likely to be cost-effective in the regions studied. When considering vaccination with several plausible changes to screening programmes, locations with the most frequent Papanicolaou smear testing may achieve the most efficiency gains by adopting a less frequent screening interval or incorporating HPV testing into their screening practices. Although it may be beneficial to change screening to maximize efficiency, the most cost-effective strategies for vaccination and screening combinations may not lead to the greatest reductions in cervical cancer; therefore such policy decisions may vary depending on region-specific goals. Finally, new screening paradigms such as primary HPV testing should be considered in future analyses.



## Introduction

With the implementation of cytology-based screening programmes, cervical cancer incidence and mortality have decreased substantially over the last few decades, approaching reductions of approximately three quarters in developed countries that were successful in adopting such programmes [1]. Screening technologies have evolved considerably since the 1950s with several technical advancements, including liquid-based cytology, computer-assisted smear-reading, and human papillomavirus (HPV) DNA testing [2]. Several modelling studies of cervical cancer screening have been completed, mainly for developed countries, to inform specific policy questions related to these continuing advancements, addressing issues such as the choice of screening interval, ages for screening initiation and cessation, enhancements to conventional cytology, and integrating HPV testing into cytology-based programmes [3]. These studies have been very useful in providing information that advances the understanding of the most cost-effective approaches to cervical cancer screening.

Despite these advances, cervical screening remains a secondary prevention approach, targeting disease treatment rather than eliminating the cause, which is HPV infection [4]. Cervical cancer incidence rates and the associated economic burden still remain unacceptably high due to pitfalls of programme implementation and compliance, especially in developing nations [5]. Prophylactic vaccination against cervical cancer represents a primary prevention strategy, with two recently approved vaccines targeted against oncogenic HPV types 16 and 18 that are responsible for the majority (~70–80%) [6] of cervical cancers (i.e., *Gardasil*™, *Cervarix*™) [7,8]. Together, if adopted in synergy, screening and vaccination

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have the potential to significantly reduce cervical cancer globally; however, in an era of strained health care budgets, much consideration needs to be given to how to best optimize the use of limited resources while maximizing reduction in disease burden. Even for resource-rich countries, it will be difficult to absorb the extra costs of vaccination without some level of re-structuring of their screening programmes [9].

Given that vaccination against cervical cancer is becoming accepted as the primary prevention strategy, it will be essential to examine how screening practices (secondary prevention) could change to permit the synergy between the two prevention strategies [10]. It is likely that screening modifications may only be implemented several years post-vaccine implementation, and that vaccination strategies may vary widely between regions depending on perceptions of the cost-effectiveness of vaccination. Therefore, modifications of screening programmes will need to be made on a country- or region-specific basis [9–13]. In some locations, implementation of cost-effective policies including vaccination with changes to screening programmes may only be acceptable to policy makers if it results in comparable or greater effectiveness than screening alone or vaccination with no change in current screening practice [9]. The cost of vaccination might then be partially offset by savings achieved to alterations of the screening programme. Modelling studies in the United States (US) have begun to address policy-specific questions about whether screening programme recommendations need to change in a world with vaccination. Two of these studies identified that the most cost-effective approaches, integrating both vaccination and screening, were those that incorporated less frequent screening with initiation of screening at older ages [14,15]. Thus, alterations to screening programme recommendations in combination with vaccination result in strategies that remain cost-effective according to common decision thresholds of cost-effectiveness in the US.

In the presence of vaccination, screening parameters such as compliance, costs, and perceptions about susceptibility to cervical disease, may naturally evolve even without changes to screening policy. Compliance to screening guidelines may change as women may undergo screening more frequently due to increased awareness of disease, or alternatively, may not feel the need to be screened as frequently due to misconceptions that the vaccine will be fully protective against cervical cancer. The quality of cytology-based screening programmes may change in the presence of vaccination because cytological abnormalities will become less frequent over time with reduced HPV prevalence [9,16]. The latter will reduce the positive predictive value of cytology even at today's performance standards of sensitivity and specificity for this test. It is possible that cyto-technicians, who are responsible for determining if a cytological smear is abnormal, may become more likely to flag any apparent abnormality and increase the number of false positives. On the other hand, cyto-technicians may become more likely to overlook actual abnormalities if lesions become less frequent, leading to an increase in the number of false negatives. On balance, these situations would lead to an overall decrease in screening specificity, sensitivity or both, with further detrimental impact on the positive predictive value of cytology [9,16]. Finally, other health economic factors related to screening programmes (e.g., costs and quality of life associated with screening) may naturally change as a result of introducing vaccination programmes. All of these changes may impact the effectiveness of screening programmes, and ultimately the cost-effectiveness of a combined screening and vaccination programme.

Many questions therefore exist about how the introduction of a vaccination programme will impact screening. To address these uncertainties, one objective of our study was to understand how predicted changes to screening parameters, in the absence of policy change, would impact the cost-effectiveness of a combined screening and vaccination programme. Given that screening policies may change once vaccination is implemented, a second objective was to determine the most cost-effective hypothetical screening and vaccination policy. We conducted multiple analyses in several regions of the world with established, yet unique, screening programmes including Canada, the Netherlands, Taiwan, the United Kingdom (UK), and the US. It should be noted that variation in parameters associated with vaccination strategies were modelled in another manuscript in this issue [17].

## Methods

### *Natural history parameters and model calibration*

Technical details pertaining to the model structure have previously been published [18,19]. In brief, the natural history of HPV infection (due to seven HPV strata: 16, 18, 31, 45, 52, other high risk, low risk) may progress or regress from a normal cervical state to one of the seven HPV strata, and then through three stages of cervical intraepithelial neoplasia (CIN1, CIN2, CIN3). From the CIN 3 state, women may progress through four stages of cervical cancer (Federation of Gynecology & Obstetrics Stages 1, 2, 3, 4) (Fig. 1). The model was calibrated to regional data for each of the five regions using methods described elsewhere [18,19]. Table 1 describes transition probability inputs used and selected location-specific epidemiological results predicted by the model. Transition probabilities are based on ranges of globally derived estimates taken from studies that have observed women transitioning from one health state to another. During calibration these probabilities were allowed to vary within the established ranges to allow for region-specific model prediction of observed age- and HPV type-specific epidemiology.

### *Screening parameters*

A complex screening algorithm in the model allowed for adaptation to country- or region-specific screening programmes. Specifically, for each primary screening test, an outcome is assigned. Screening trees capture these outcomes (Fig. 2), and probabilities are assigned for moving to future tests or treatments within one model cycle. For simplicity, the Bethesda classification

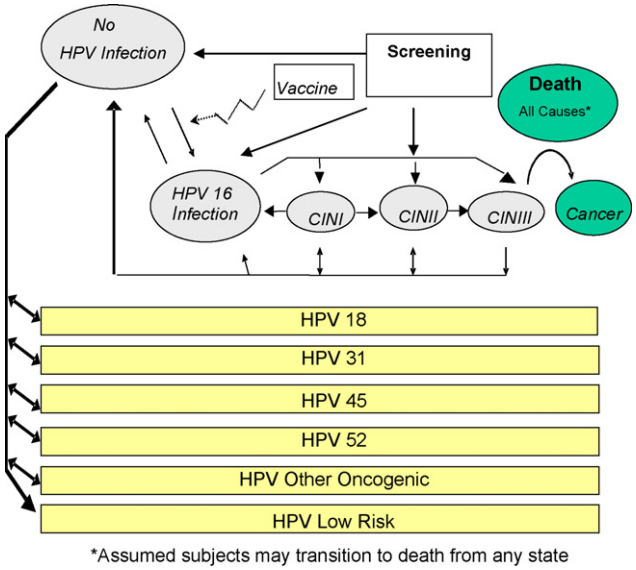


**Figure 1.** Schematic structure of the Markov model.

**Table 1**
Regional natural history 6-month transition probability inputs and selected model-predicted disease outcomes in the presence of current screening practices

| | Canada | Netherlands | Taiwan | UK | USA |
|---|---|---|---|---|---|
| Natural history transition probabilities[a] [15,71–79] | | | | | |
| Normal to HPV | 0.0–0.05 | 0.0–0.05 | 0.03–0.08 | 0.0–0.08 | 0.0–0.10 |
| HPV to CIN 1 | 0.05–0.08 | 0.03–0.05 | 0.014–0.035 | 0.05 | 0.02–0.14 |
| CIN 1 to CIN 2 | 0.004–0.15 | 0.001–0.05 | 0.03–0.31 | 0.01–0.32 | 0.03–0.18 |
| CIN 2 to CIN 3 | 0.07–0.11 | 0.03–0.10 | 0.10–0.20 | 0.10–0.20 | 0.03–0.17 |
| CIN 3 to cancer | 0.001–0.02 | 0.002–0.069 | 0.002–0.05 | 0.002–0.017 | 0.003–0.15 |
| HPV clearance | 0.40–0.48 | 0.38 | 0.44 | 0.38 | 0.38–0.46 |
| CIN 1 clearance | 0.02–0.26 | 0.31–0.54 | 0.31–0.54 | 0.31–0.44 | 0.11–0.44 |
| CIN 2/3 clearance | 0.01–0.21 | 0.046 | 0.02–0.10 | 0.033 | 0.026 |
| Model predicted disease outcomes in women[b] [6,18,22,80–105] | | | | | |
| HPV prevalence (%) | 10.5% | 9.4% | 20.7% | 11.5% | 14.5% |
| CIN2/3 prevalence (%) | 0.51% | 0.34% | 0.77% | 0.54% | 0.60% |
| CC incidence, per 100,000 | 12.0 | 8.2 | 24.4 | 10.5 | 11.3 |
| CC mortality, per 100,000 | 4.2 | 2.8 | 10.9 | 5.1 | 3.0 |

[a] Ranges reflect the lowest and highest transition probability values used across age groups and seven HPV categories.
[b] Model predicted prevalence and incidence rates differ from crude or age-adjusted rates reported in the literature. In the model, HPV and CIN2/3 prevalence reflects the average prevalence over all 5-year age groupings between ages 15 and 75+ (ages 75–100 are grouped together). Cervical cancer (CC) incidence rates per 100,000 women are averaged over ages 15–100 in the model.

nomenclature for Papanicolaou (Pap) test outcomes was applied for all regions, since this is the most common system used around the world [20,21].

In the model, a certain percentage of women in each location will never be screened for cervical cancer. For this percentage, the benefits of screening and follow-up tests, as well as the costs associated with screening do not apply. For the rest of the cohort, actual age-specific screening coverage rates based on observed regional data were modelled. This may differ from official cervical cancer screening recommendations in some locations. Since screening is a diagnostic test with imperfections, the model accounts for test sensitivity and specificity of Pap smears, HPV tests, colposcopies and biopsies. Screening practices for each region are described in Table 2.

*Vaccination parameters*

For the purpose of these analyses, we assumed that 100% of women would be covered by a full dosage (three injections) of vaccine against HPV at the age of 12 years, that the vaccine does not wane over the lifetime of vaccinated women, and that no booster vaccination is given. Vaccine efficacy of 95% against persistent HPV 16/18 infections was assumed from previous modelling studies [22] and was also in agreement with clinical trial data [8,23–31].

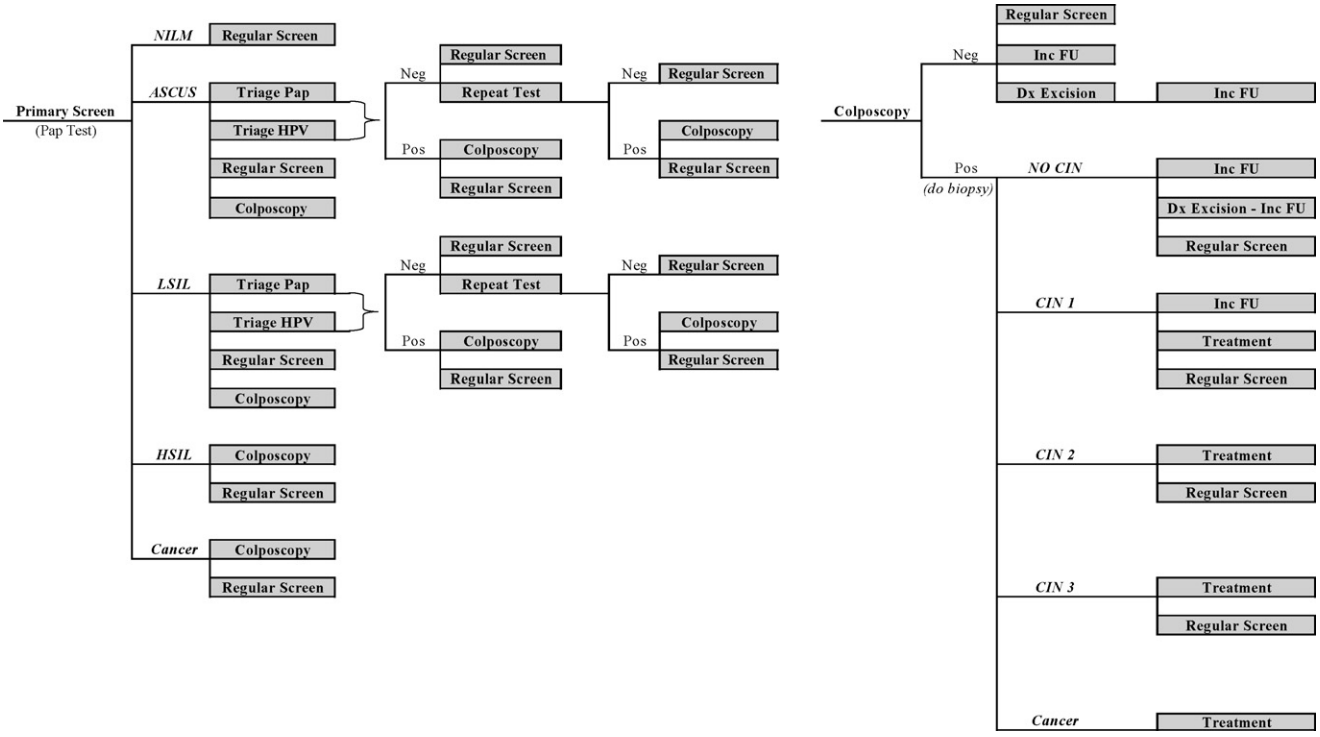


**Figure 2.** Screening decision trees for the Markov model. After primary screen with cytology, numerous management options exist after abnormal results. Where colposcopy is noted (left side), the entire colposcopy tree (right side) is applied as options. NILM: negative for intraepithelial lesion or malignancy; ASCUS: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; Neg: negative test result; Pos: positive test result; regular screen: patients transition back to routine screening practices; CIN: cervical intraepithelial neoplasia; Inc FU: increased follow-up (women transition to annual screening for their lifetime); Dx Excision: diagnostic excision; Dx Excision – Inc FU: Dx excision followed by transition to Inc FU.

**Table 2**
Regional base-case model inputs

| | Canada | Netherlands | Taiwan | UK | USA |
|---|---|---|---|---|---|
| Screening parameters [106–123] | | | | | |
| Screening interval (years) | 1 | 5 | 1 | 3 | 1 |
| Screening age range[a] (years) | 18–69 | 30–60 | 30–100 | 20–75 | 15–89 |
| Screening coverage rate (%) | 21–48 | 80 | 17–34 | 1–73 | 3–60 |
| Percentage never screened (%) | 12 | 10 | 31 | 7 | 7 |
| Cytology sensitivity (specificity) (%) | 68–81 (96.6)[b] | 40–80 (98.5) | 41–67 (96.6) | 41–67 (96.6) | 41–67 (96.6) |
| Colposcopy sensitivity (specificity) (%) | 96 (48) | 96 (48) | 96 (48) | 96 (48) | 96 (48) |
| Accurate biopsy diagnosis (%) | 54 | 54 | 54 | 54 | 54 |
| Screening practices [2,22,86,109,114,124–127,102] | | | | | |
| Triage cytology after ASCUS (%) | 100 | 84.2 | 50 | 80 | 69 |
| Triage cytology after LSIL (%) | 100 | 84.2 | 0 | 58 | 38 |
| Negative triage[c] test to repeat test (%) | 0 | 40 | 100 | 16 | 50 |
| Negative triage[c] to regular screen (%) | 100 | 60 | 0 | 84 | 50 |
| Colposcopy after ASCUS (%) | 0 | 0 | 0.5 | 20 | 31 |
| Colposcopy after LSIL (%) | 0 | 0 | 100 | 42 | 62 |
| Colposcopy after HSIL (%) | 100 | 100 | 100 | 100 | 100 |
| Positive triage[c] test to colposcopy (%) | 100 | 100 | 100 | 100 | 100 |
| Negative biopsy to regular screen (%) | 50 | 100 | 50 | 50 | 50 |
| Negative biopsy to increase screen (%) | 50 | 0 | 50 | 50 | 50 |
| Compliance to CIN 1 treatment (%) | 50 | 41 | 0 | 50 | 50 |
| Compliance to CIN 2/3 treatment (%) | 100 | 82–100 | 100 | 100 | 100 |
| Economic parameters [15,18,22,36,40,42,117,119,128–134] | | | | | |
| Currency | CAD ($) | EUR (€) | NTD ($) | GBP (£) | USD ($) |
| Vaccine cost (per dose) | 135 | 105 | 4000 | 84 | 158 |
| Cytology test cost | 57 | 52 | 530 | 23 | 96 |
| Colposcopy/biopsy cost | 144 | 198 | 2183 | 236 | 515 |
| CIN 1–3 treatment cost | 858–1000 | 1523–1919 | 3124–9639 | 667 | 1493–3346 |
| Cancer stage 1–4 treatment cost | 11,915–25,759 | 19,630–27,244 | 175,822–386,937 | 11,435–19,916 | 25,430–43,593 |
| Discount rate costs, outcomes (%) | 3%, 3% | 4%, 1.5% | 3%, 3% | 3.5%, 3.5% | 3%, 3% |
| Utility for CIN lesion (6-month duration) | 0.92–0.99 | 0.92–0.99 | 0.92–0.99 | 0.92–0.99 | 0.92–0.99 |
| Utility for treated cancer (6-month duration) | 0.73 | 0.73 | 0.73 | 0.73 | 0.73 |
| Utility for follow-up cancer (6-month duration) | 0.62–0.97 | 0.62–0.97 | 0.62–0.97 | 0.62–0.97 | 0.62–0.97 |

[a] Screening age ranges presented in the table were those that were modelled. Ages in the table may differ from ages recommended by regional guidelines. In the UK recommended ages are 25–64, but ages 20–24 had modelled screening coverage rates of <50%, and ages 65+ had modelled screening coverage rates of <33% based on actual practice data. In the US, 21+ is the recommended age, yet ages <20 and >70 had modelled screening coverage rates of <20% based on actual practice data.

[b] Values used for the sensitivity of cytology in Canada were based on an older meta-analysis rather than recently published CCCaST data [70].

[c] Triage tests in the base-case refer to cytological triage (i.e. Pap tests) tests that exist as a means to follow an abnormal test result. "Negative" refers to a negative (normal) result on a follow-up test, and "positive triage" refers to a positive (abnormal) result. HPV triage tests following abnormal Pap results are explored only in additional analysis (Table 5).

Supplemental cross-protection of 53% efficacy against HPV 31 and 88% efficacy against HPV 45 were based on a trial after 5.5 years of follow-up [32]. Vaccine efficacy was modelled as a reduction in transitions from normal to HPV infection according to the specified values.

*Economic parameters*

Costs, utilities and discounting of events associated with cervical screening and treatment by region are presented in Table 2. Costs are expressed in location-specific currencies, and discounting (costs, effects) is applied according to regional guidelines. The perspective was typically that of a health care payer (i.e. direct), except for in the US and the Netherlands where a societal perspective (i.e. indirect) was adopted since these countries had a stronger preference for indirect costs listed in their health economic guidelines [33]. Values associated with quality of life decrements due to treatments for CIN lesions and cancer stages were the same for all regions and are provided in Table 2. Costs were adjusted to 2006 values using location-specific consumer price indices [34–36]. For more details on discounting methods and cost perspectives, readers are encouraged to consult the appendix in the first paper of this supplement [37].

*Analysis*

For the base-case analysis, we compared a scenario of no vaccination (with current screening) with a scenario of vaccination (added to current screening). Therefore we assumed that there are no changes to cervical cancer screening in a world with vaccination, as this would likely be the situation at the start of a vaccination programme. The models were run for the lifetime of a cohort of 100,000 12 year old females in Canada, the Netherlands, Taiwan, the UK, and the US, with economic inputs and cost-effectiveness outcomes specified in region-specific currencies. In addition, absolute numbers of screening events, pre-cancer and cancer outcomes were calculated for vaccinated and non-vaccinated cohorts.

First, we conducted exploratory analyses on predicted changes to screening parameters with the implementation of vaccination, assuming no changes to screening policy. The ranges for analyses were based on expert opinion given lack of specific estimates on how screening programmes could change in the presence of vaccination. The following analyses were conducted with the vaccinated arm and compared with a non-vaccinated arm with unchanged screening:

(1) **Costs** were increased and decreased by 50% for all screening and diagnostic tests (including Pap tests, colposcopies, and biopsies).
(2) **Screening compliance** was increased and decreased by 20% by altering age- and region-specific coverage rates accordingly.
(3) **Disutilities** (i.e. quality of life decrements) associated with CIN lesions and cancer were increased and decreased by 20%.

(4) **Screening sensitivity** was decreased by 20% **and specificity** was decreased by 10% in order to examine how adding vaccination might cause changes to screening quality [38].

Second, given that screening policy changes may be planned in the presence of vaccination, we conducted several analyses to determine the most cost-effective hypothetical vaccination and screening strategy from a list of plausible strategies. These strategies reflect alternative screening policies that could be considered that may reduce the overall cost of screening compared with the status quo of current screening. The following screening policy changes were considered:

(1) **Reduction in recommended screening frequency**. We assumed that one policy of interest may be that the recommended screening frequencies be reduced in locations with vaccination (e.g., change frequency from every year to every 3 or 5 years in US). With these analyses, we applied the same observed coverage statistics by age, but with a reduced frequency of screening.
(2) **Reduction in recommended age interval for screening**. We assumed another potential policy change may focus on reducing the recommended age interval for screening. We chose age ranges of 25–60 years and 30–60 years, as these ranges were typically smaller than current observed recommendations for all regions, except the Netherlands which starts their screening programme at the age of 30 years.
(3) **Introduction of HPV triage for atypical squamous cells of undetermined significance (ASCUS) smears**. Last, we incorporated HPV triage testing for ASCUS smears, as this technology and practice has become more common in some Western countries. In these analyses, for all regions we assumed that an HPV test would be performed after detection of an ASCUS smear; however, LSIL or clinically higher risk results would be assessed immediately through colposcopy. HPV test costs were estimated to be Canadian (CA) $100 [39], €33 [15], New Taiwan (NT) $1300 [40], GB£ 22.29 [41] and US$ 117.70 [15,42] respectively in Canada, the Netherlands, Taiwan, the UK and the USA. Ranges used for oncogenic HPV test sensitivity and specificity were 0.95–0.97 and 0.95–1.0, respectively [43,44].

For each region, we ordered hypothetical strategies by the total cost and then we calculated incremental cost-effectiveness ratios, which is defined as the additional cost of a specific strategy divided by the additional clinical benefit compared with the next most expensive strategy. Strategies that were dominated were considered to be those that were more costly and less effective than other options and were excluded from the final incremental comparisons; those that were weakly dominated were those with higher incremental cost-effectiveness ratios than more effective options; these were also excluded. The concept of weak dominance is also known as extended dominance [45]. For all strategies, we assume that vaccination has already been adopted and thus we do not consider a scenario of no vaccination. To determine the cost-effectiveness of a specific vaccination and screening strategy, we used common region-specific incremental cost-effectiveness ratio (ICER) thresholds for interpretation [46,47]: CA$ 20,000–100,000/QALY for Canada [48], €20,000/QALY for the Netherlands [49,50], NT$ 966,000/QALY[1] for Taiwan [51,52], GB£ 20,000–30,000/QALY for the United Kingdom [53], and US$ 50,000–$100,000/QALY for the United States [54–56].

## Results

### *Base-case analysis*

Adding vaccination to current screening for a cohort of 12 year old females was predicted to reduce the lifetime number of abnormal cytology test results by 15–24%, treated CIN lesions by 24–56%, and cervical cancer cases and deaths by 71–77% (Fig. 3). Absolute numbers of screening events (i.e., abnormal cytology, treated CIN lesions) were observed to be highest in regions with the most frequent screening intervals (i.e., US, Canada), and lowest in the locations with the least frequent screening interval of 5 years (i.e., the Netherlands). Percentage reductions in screening outcomes tended to be lowest for Taiwan. Predicted percentage reductions in cancer cases and deaths were found to be comparable across regions.

The total lifetime discounted costs, QALYs, and cost-effectiveness ratios associated with a strategy that incorporated vaccination with current screening in the different regions is provided in Table 3. In all locations, vaccination of 12 year olds, combined with current cervical screening programmes, was likely to be cost-effective according to region-specific decision thresholds. Discounted cost-effectiveness results ranged from a low of US$ 7828 (US) to a high of GB£ 18,037 (UK) per QALY across locations. Non-discounted analyses demonstrated that a combined vaccination and cervical screening programme would either approach cost-savings, or be cost-saving in all regions when compared with the status quo of cervical screening alone (no vaccination).

### *Exploratory analyses: changes to screening parameters*

Several exploratory analyses were conducted to assess the potential impact that vaccination may have on screening-related parameters (Table 4). Increasing screening and diagnostic test costs, and increasing screening compliance (% covered by screening in each age group) resulted in the highest change in cost-effectiveness ratios in both Canada and the US, with not much change seen in the other regions. For all locations, a reduction in screening test performance (i.e., reduced sensitivity and specificity) in the presence of vaccination was predicted to result in higher cost-effectiveness ratios, although the majority of the ratios remained below region-specific decision thresholds. Results were not sensitive to assumed changes in the impact of cervical outcomes, such as pre-cancerous lesions and cancer, on quality of life. Quality of life was also characterized as utility.

### *Exploratory analyses: changes to screening policies*

Several hypothetical policy analyses were conducted for each region assuming that vaccination has already been implemented and that policy changes to screening programmes would need to be considered. Table 5 outlines the hypothetical strategies considered for each location and the results of the incremental cost-effectiveness calculations. Strategies were generally ordered by cost, with the exception that those which were either strongly dominated (more costly and less effective than the next least expensive strategy) or weakly dominated (more costly and less cost-effective than the next least expensive strategy) were removed from the incremental analysis [45].

Results demonstrate that all hypothetical screening and vaccination strategies are predicted to result in greater reductions in

[1] The threshold for Taiwan is based on recommendations from the World Health Organization that interventions of less than three times the GDP (per capita) of the nation may be considered cost-effective while interventions that are less than one time the GDP are very cost-effective. The GDP of Taiwan is approximately NT $966,000 (=US $29,600).

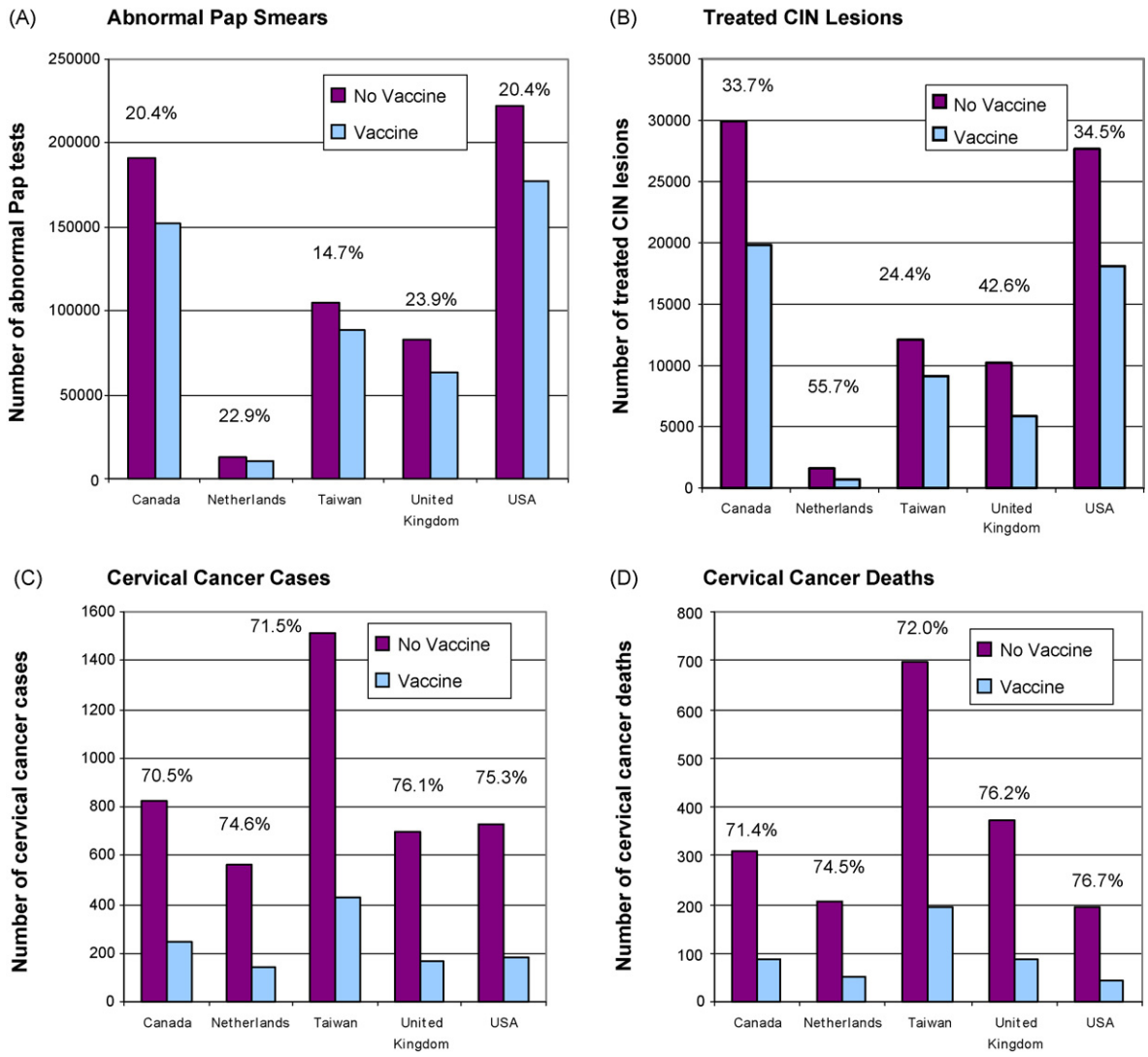


**Figure 3.** Total number of abnormal Pap tests (a), treated CIN lesions (b), cervical cancer cases (c), and cervical cancer deaths (d) predicted in a non-vaccinated and vaccinated cohort of 100,000 12 year old girls over their lifetime. Percentages indicated above the bars represent the percent reduction in cervical events achieved with vaccination (compared with no vaccination). Results were not discounted.

cervical cancer compared with a screening-only situation (no vaccination). However, for most hypothetical screening and vaccination strategies, the model predicts that making changes to the screening programme compared with the status quo of vaccination and current screening will result in additional cancer cases but lower costs.

To interpret Table 5, we begin by examining the most favorable cost scenario, and then move through the subsequent next most-expensive scenarios examining cancer cases and incremental cost-effectiveness ratios, noting those that were more costly, yet less effective. For example, when considering several plausible vaccination and screening strategies in Canada, the least expensive hypothetical strategy was a 5-yearly screening programme combined with vaccination. If this strategy were adopted, there would be 30% fewer cancer cases when compared with 3-yearly current screening (no vaccination), and the cost would be CA$ 657 per woman. When comparing this with current screening (plus vaccination) at a cost of CA$ 1163 per woman, this would represent a cost savings of CA$ 506 per woman. It would, however, also mean that cancer cases expected over the lifetime of that cohort of 100,000 12 year olds would increase from 242 to 572 cases. Both of these strategies would result in fewer cancer cases than with screening alone (i.e., 821 cases for the same cohort). From an efficiency perspective, the next most favorable strategy for Canada after the 5-yearly strategy is a 3-yearly screening programme with vaccination. When these strategies were compared, the ICER was CA$ 40,740/QALY, and an additional 159 cancers were prevented. One additional strategy for Canada was under the cost-effectiveness threshold of CA$ 100,000/QALY. Changing the ages of women screened to 25–60 years, was cost-effective at CA$ 77,434 compared with 3-yearly screening. Further increasing screening coverage by widening the age interval to 18–69, as is currently practiced in Canada, increases cancer detection but is not economically attractive compared with the alternatives in this analysis. Changing ages screened to 30–60 years costs more, but only had a slight improvement in QALYs, making it subject to the principles of extended dominance and thereby precluding it from further consideration from an economic perspective [45]. A strategy of HPV triage combined with vaccination was more costly and less effective than the existing strategy of current screening and vaccination and was therefore not considered in the final incremental comparisons.

**Table 3**
Per woman discounted total lifetime costs, QALYs, and LYs, with discounted and non-discounted[a] cost-effectiveness ratios for current screening and vaccination compared with current screening in five regions[b]

| | Canada | Netherlands | Taiwan | United Kingdom | United States |
|---|---|---|---|---|---|
| Costs | | | | | |
| Discounted cost (no vaccine) | CA$ 906 | €123 | NT$ 4112 | £ 216 | US$ 2144 |
| Discounted cost (vaccine) | CA$ 1163 | €403 | NT$ 14,911 | £ 409 | US$ 2232 |
| Discounted incremental costs | CA$ 258 | €280 | NT$ 10,879 | £ 193 | US$ 87 |
| Quality-adjusted life years (QALYs) | | | | | |
| Discounted QALYs (no vaccine) | 28.68901 | 42.34406 | 27.75853 | 25.51839 | 28.35851 |
| Discounted QALYs (vaccine) | 28.70045 | 42.35923 | 27.77573 | 25.52906 | 28.36964 |
| Discounted incremental QALYs | 0.01143 | 0.01517 | 0.01720 | 0.01067 | 0.01112 |
| Life years (LYs) | | | | | |
| Discounted LYs (no vaccine) | 28.69553 | 42.34790 | 27.76260 | 25.52135 | 28.36466 |
| Discounted LYs (vaccine) | 28.70362 | 42.36026 | 27.77732 | 25.53012 | 28.37247 |
| Discounted incremental LYs | 0.00810 | 0.01236 | 0.01472 | 0.00876 | 0.00781 |
| Cost per QALY | | | | | |
| Discounted cost per QALY | CA$ 22,532 | €18,472 | NT$ 632,559 | £18,037 | US$ 7828 |
| Non-discounted cost per QALY | CA$ 1249 | €5679 | NT$ 93,508 | £1449 | Dominates[c] |
| Cost per LY | | | | | |
| Discounted cost per LY | CA$ 31,817 | €22,672 | NT$ 738,972 | £21,962 | US$ 11,156 |
| Non-discounted cost per LY | CA$ 1554 | €6785 | NT$ 105,267 | £1627 | Dominates[c] |

[a] Costs and QALYs are discounted according to region-specific guidelines (Table 2) from the end of the first year in the model.
[b] Results are specified in country- or region-specific currencies.
[c] The new intervention of vaccination and current screening is cost savings (i.e. both less costly and more effective) compared with the previous intervention of current screening alone.

**Table 4**
Exploratory analysis results (expressed as cost per QALY) of the comparison between vaccination with changed screening, and no vaccination with current screening[a]

| | Canada | Netherlands | Taiwan | UK | USA |
|---|---|---|---|---|---|
| Base-case (current screening and no vaccination) | CA$ 22,532 | €18,472 | NT$ 632,559 | £18,037 | US$ 7828 |
| Increase Screening & Diagnostic Test Costs[b] by 50% | CA$ 51,092 | €21,159 | NT$ 710,562 | £24,445 | US$ 74,358 |
| Decrease Screening & Diagnostic Test Costs[b] by 50% | Dominates[c] | €15,786 | NT$ 554,556 | £11,629 | Dominates[c] |
| Increase Screening Compliance by 20% | CA$ 31,510 | €18,680 | NT$ 651,409 | £19,787 | US$ 51,639 |
| Decrease Screening Compliance by 20% | CA$ 12,999 | €18,490 | NT$ 615,271 | £16,386 | Dominates[c] |
| Increase Cervical CIN/Cancer Disutility by 20% | CA$ 23,562 | €18,529 | NT$ 639,756 | £18,278 | US$ 8171 |
| Decrease Cervical CIN/Cancer Disutility by 20% | CA$ 21,588 | €18,416 | NT$ 625,521 | £17,804 | US$ 7514 |
| Decrease screening test quality | CA$ 40,545 | €21,344 | NT$ 764,114 | £28,808 | US$ 79,581 |

[a] Results are specified in country- or region-specific currencies, and have been discounted according to regional guidelines (Table 2).
[b] Screening & diagnostic tests include Pap smears, colposcopies and biopsies.
[c] The new intervention of vaccination with changed screening is cost-savings (i.e. both less costly and more effective) compared with current screening alone.

Similar to Canada, reducing the recommended frequency to the widest interval between screens was also the least costly strategy in the Netherlands (7-yearly), Taiwan (5-yearly) and the US (5-yearly), at an average cost of €383, NT$ 13,007, and US$ 1037 respectively per woman. In the UK, restricting the ages screened (to age 30–60 years) represented the least costly strategy at GB£ 351 per woman. In the Netherlands, the next most efficient strategies were including HPV triage (€20,491/QALY compared with the 7-yearly strategy) and then expanding the age range to include 25-year olds (€71,381/QALY when compared with HPV triage strategy). Although neither of these strategies would be considered cost-effective compared with 7-yearly screening given the threshold of €20,000/QALY, they would be more efficient than current screening (with vaccination) since this scenario was less efficient than, and therefore dominated by the other strategies in the Netherlands.

In both the UK and the US, the next most efficient strategy after widening the screening frequency interval would be narrowing the age range for screening to 25–60 years. A comparison to the least costly strategies in each of these regions yielded cost-effectiveness ratios of GB£ 39,025/QALY and US$ 87,197/QALY, respectively. Further strategies involving vaccination and screening in the US and UK were either outside the cost-per-QALY gained deemed acceptable for these regions or were dominated by other strategies. Several options would be less costly than current screening (with vaccination). For Taiwan, the results were similar to Canada, with the exception that vaccination and HPV triage were also more efficient strategies than vaccination added to current screening.

## Discussion

Decisions are currently being made at the national level regarding the implementation of two efficacious vaccines (i.e., *Gardasil*™, *Cervarix*™) against cervical cancer. As part of these decisions, the efficiency associated with current cervical screening programmes needs to be evaluated alongside vaccination for the purpose of maximizing cost-effectiveness results achieved from a combination of vaccination and screening [57]. To facilitate these decisions, we developed a detailed mathematical model capable of evaluating the long-term impact and cost-effectiveness of both types of prevention strategies combined.

Our results demonstrate that vaccination targeted towards 12 year old girls combined with the current screening practices is likely to be cost-effective across a majority of locations when results are interpreted according to acceptable decision thresholds for each region. Assuming that screening programmes remain the same in the presence of vaccination, the incremental cost-effectiveness ratios varied across regions from US$ 7800 to GB£ 18,000 (=US$ 35,000 = €24,000) per QALY [58]. These results are comparable to

**Table 5**
Hypothetical incremental policy analysis results (expressed as discounted cost per QALY) for changes to screening programme with vaccination

| Scenario | Total discounted cost (per woman) | Total discounted QALYs (per woman) | Incremental cost (per woman) | Incremental QALYs (per woman) | Discounted cost/QALY | Cervical cancer cases[a] | % Change cancer relative to current screen + vaccine[b] | % Change cancer relative to current screening only |
|---|---|---|---|---|---|---|---|---|
| **Canada** (age range) {# lifetime screens} | (CA) | | | | (CA) | (821)[c] | | |
| Vaccine + **5-year**[d] screen (18–68) {11} | $657.40 | 28.69553 | – | – | – | 572 | 136% | −30% |
| Vaccine + **3-year** screen (18–69) {18} | $763.06 | 28.69812 | $105.66 | 0.00259 | $40,740 | 413 | 70% | −50% |
| Vaccine + 1-year screen (**25–60**) {36} | $925.98 | 28.70023 | $123.55 | 0.00170 | $77,434 | 295 | 22% | −64% |
| Vaccine + current (1-year screen, 18–69) {52} | $1163.43 | 28.70045 | $237.45 | 0.00022 | $1,075,935 | 242 | Baseline [e] | −70% |
| Vaccine + 1-year screen (**30–60**) {31} | $802.43 | 28.69853 | | | Dominated[g] | 234 | 47% | −57% |
| Vaccine + 1-year screen (18–69), **HPV triage** {52} | $1248.40 | 28.69983 | | | Dominated[f] | 356 | −4% | −72% |
| **Netherlands** | | | | | | (565)[c] | | |
| Vaccine + **7-year** screen (30–58) {5} | €382.50 | 42.35833 | – | – | – | 166 | 16% | −71% |
| Vaccine + 5-year screen (30–60), **HPV triage** {7} | €407.75 | 42.35956 | €4.90 | 0.00033 | €20,491 | 131 | −9% | −77% |
| Vaccination + 5-year screen (**25–60**) {8} | €427.44 | 42.35984 | €19.68 | 0.00028 | €71,381 | 135 | −6% | −76% |
| Vaccine + current (5-year screen, 30–60) {7} | €402.85 | 42.35923 | | | Dominated[f] | 144 | Baseline [e] | −75% |
| **Taiwan** | (NT) | | | | (NT) | (1,511)[c] | | |
| Vaccine + **5-year** screen (30–100) {15} | $13,007.58 | 27.77337 | – | – | – | 687 | 60% | −55% |
| Vaccine + **3-year** screen (30–99) {24} | $13,371.59 | 27.77419 | NT$ 364.01 | 0.00081 | $447,225 | 602 | 40% | −60% |
| Vaccine + 1-year screen (**30–60**) {31} | $14,343.70 | 27.77535 | NT$ 972.11 | 0.00117 | $833,586 | 568 | 32% | −62% |
| Vaccine + 1-year screen (30–100) **HPV triage** {71} | $14,995.91 | 27.77581 | NT$ 4.58 | 0.00008 | $1,433,084 | 433 | 1% | −71% |
| Vaccine + current (1-year screen, 30–100) {71} | $14,991.33 | 27.77573 | | | Dominated[f] | 430 | Baseline [e] | −72% |
| Vaccine + 1-year screen (**25–60**) {36} | $15,004.22 | 27.77562 | | | Dominated[g] | 555 | 29% | −63% |
| **United Kingdom** | | | | | | (700)[c] | | |
| Vaccine + 3-year screen (**30–60**) {11} | £351.49 | 25.52816 | – | – | | 210 | 25% | −70% |
| Vaccine + 3-year screen (**25–58**) {11} | £376.44 | 25.52880 | £16.64 | 0.00081 | £39,025 | 193 | 16% | −72% |
| Vaccine + current (3-year screen, 20–68) {17} | £408.81 | 25.52906 | £32.38 | 0.00026 | £124,290 | 167 | Baseline [e] | −76% |
| Vaccine + **5-year** screen (20–70) {11} | £359.79 | 25.52800 | | | Dominated[g] | 233 | 39% | −67% |
| Vaccine + 3-year screen (20–68), **HPV triage** {17} | £429.40 | 25.52905 | | | Dominated[g] | 157 | −6% | −78% |
| **United States** | (US) | | | | (US) | (725)[c] | | |
| Vaccine + **5-year** screen (15–85) {15} | $1037.05 | 28.36334 | – | – | | 610 | 241% | −16% |
| Vaccine + 1-year screen (**25–60**) {36} | $1575.71 | 28.36952 | $332.33 | 0.00292 | $87,197 | 262 | 46% | −64% |
| Vaccine + 1-year screen (15–89), **HPV triage** {75} | $2287.86 | 28.36965 | $56.33 | 0.00002 | $5,449,765 | 171 | −5% | −76% |
| Vaccine + 1-year screen (**30–60**) {31} | $1242.61 | 28.36765 | | | Dominated[f] | 403 | 125% | −44% |
| Vaccine + **3-year** screen (15–87) {25} | $1243.38 | 28.36660 | | | Dominated[g] | 339 | 89% | −53% |
| Vaccine + current (1-year screen, 15–89) {75} | $2231.53 | 28.36964 | | | Dominated[f] | 179 | Baseline [e] | −75% |

[a] Lifetime cases per 100,000 women in a cohort of 12 year olds.
[b] Percent (%) change was calculated as follows: (number of cancer cases in hypothetical scenario minus the number of cancer cases in current screening)/number of cancer cases in current screening.
[c] Number of cancer cases predicted over lifetime of a cohort of 100,000 12 year olds in an environment with current screening only (no vaccine).
[d] Parameters in this column that have been altered from the current screening scenario are displayed in bold font.
[e] "Baseline" refers to the current screening programme with vaccine implementation.
[f] Strategy cost more but was less cost-effective than next strategy and therefore weakly dominated.
[g] Strategy cost more but was less effective than next strategy and therefore strongly dominated.

published results from North America and the Netherlands using similarly constructed models that compared vaccination and current screening with current screening alone [15,22,59–62]. While region-specific modelled results are similar between studies, any differences in results between our study and others are most likely explained by variation in assumptions about model structure and inputs. Our study also provides cost-effectiveness results for Taiwan and the UK, which have not been previously reported on in the literature. When vaccination was added to current screening, some of the variation in results between locations can be explained by differences in screening programmes and HPV epidemiology. For example, of the locations analyzed here, Canada and the US invest the most money in screening as a result of the high frequency, high coverage and wide age range covered. Therefore, the absolute numbers of screening events and associated costs are very large, and these regions are expected to experience the largest downstream cost-savings from vaccination (Fig. 3a and b). On the other hand, in the Netherlands not many Pap smears or CIN treatments will be averted with vaccination due to the low levels already observed (Fig. 3a and b). It should be noted, however, that the number of treated CIN lesions projected by the Netherlands model may be lower than is observed [63]. If more CIN treatments were modelled in non-vaccinated women, more could be prevented with vaccination. On the other hand, Taiwan has the smallest percentage reduction in Pap tests and treated CIN lesions with vaccination because they have the least percentage of women screened at approximately 30% population coverage. However, we also see the greatest absolute reductions in cervical cancer cases and deaths with vaccination in Taiwan, since Taiwan has the lowest screening coverage and the highest cancer rates of all the regions studied here. Interestingly, proportional reductions in cancers and related mortalities are lower in Taiwan when compared with other locations, mainly due to the fact that Asian regions have a lower overall type distribution of HPV 16 and 18 in cervical cancers [6].

*Impact of changes to screening parameters*

Given the uncertainty associated with how screening parameters may change when vaccination is introduced, we conducted exploratory analyses to test the health-economic implications associated with changes to screening. When changes to the costs of screening and diagnostic tests were examined, the largest variations in ICERs were observed in the US and Canada. This finding is due to the large number of screening events, and the current high costs of screening in the US. It is also supported by the observation that these two countries also had the largest difference in ICERs when screening compliance rates were varied (Table 4). Interestingly, little variation is seen in the ICERs when screening cost and compliance parameters are varied in regions having a wider screening interval (Table 4). Our exploratory analyses also demonstrated that a loss in quality of cytology testing would influence cost-effectiveness results. Vaccination with reduced screening quality is less cost-effective compared with a vaccination programme where the screening quality is maintained at the same level. This result is expected, given that additional cancer cases (sensitivity loss) and higher screening costs (due to losses in both specificity and sensitivity) would occur in this situation. It will therefore be important to consider alternative screening strategies when vaccination is introduced. For example, it has been suggested that a programme of primary HPV testing combined with cytological triage may be cost-effective when combined with vaccination. HPV testing has, on average, 20–40% greater sensitivity than cytology. It is not prone to subjective interpretation and will thus maintain its performance characteristics even under low lesion prevalence conditions [9,64]. As results from effectiveness studies of primary HPV testing become more readily available, it will be important to determine the cost-effectiveness of combined primary HPV testing and cytology triage with vaccination [65–67].

*Impact of changes to screening policies*

Once vaccination has been implemented, policy-makers may consider making changes to screening programmes. In our study, we analyzed some hypothetical policy changes to demonstrate how alterations to screening programme recommendations in the presence of vaccination could impact both costs and outcomes within regions.

A previously published cost-effectiveness analysis of nearly 500 different screening policies concluded that increasing the frequency of screening became progressively inefficient because the costs of cytological testing generally increased more rapidly than the benefits gained [68]. Our study found that the same trend existed post-vaccination, but also demonstrated that the least costly combination strategy in four locations was the one with the widest tested screening interval. In accordance with our study, both Goldie et al. [15] and Kulasingam et al. [14] showed that the least costly combination strategies in the US were those that included a reduced frequency of screening (i.e. 5-yearly). Our US analyses revealed that the most efficient strategies to combine with vaccination would be 5-yearly screening or altered ages of screening (25–60 years). Goldie et al. determined that the best strategy with an ICER <US$ 100,000 would be combining vaccination at age 12 with cytological screening every 3 years beginning at age 21 [15]. Kulasingam et al. found that vaccination and biennial screening was the most attractive option at US$ 44,889 per life year gained compared with biennial screening with vaccination beginning at age 24 [14]. Although we did not alter more than one screening parameter simultaneously in our study, these other studies have demonstrated that modelling combinations of screening factors in order to generate an ideal prevention approach alongside vaccination are of value and should be pursued in further analyses.

From a clinical perspective, inclusion of HPV triage testing for ASCUS smears is better than current screening practices in the Netherlands, the UK, and the US because it averts more cases of cancer. In Taiwan, HPV triage and current screening practices produce essentially the same benefit. From an economic perspective, this approach is more efficient than current screening practices in the Netherlands, the US, and Taiwan. In the UK and Canada, HPV triage was not an economically attractive option compared with current screening practices. Additional analyses are required to determine if HPV triage testing would become more efficient if it were implemented with other policy changes such as increasing the screening interval or changing the age range of women screened. Furthermore, the cost of HPV testing will likely decrease over time, improving the relative economic attractiveness of this strategy.

A comparison between the US and the Netherlands provides a nice example of how it becomes more difficult to make minimal investments in further prevention and still achieve better efficiency if good prevention programmes are already in place. Changes that focus on optimizing the efficiency of the prevention strategy for locations currently investing large amounts of money into inefficient programmes have the potential to be very cost effective.

Keeping in mind that the baseline strategy of current screening (with vaccination) was considered cost-effective compared with current screening alone (no vaccination) in nearly all regions it was interesting to observe that current screening (with vaccination) was dominated by other more efficient strategies in the Netherlands, Taiwan and US. This finding lends credence to an argument for reconsidering what the most efficient screening strategies would be in a world with vaccination. The most efficient combination of

vaccination and screening for a region will not necessarily prevent the most cervical cancers, so policy makers will have to decide if they prefer to maximize the efficiency or the benefit of their prevention programmes. Further to this, since screening will remain the main means of prevention for generations of unvaccinated women, policy makers will be called to remain cognizant of these cohort effects.

*Study limitations*

Our study has a number of limitations. First, our analyses did not consider the effects of herd immunity. Given results of past studies, we anticipate that cost-effectiveness ratios of screening with vaccination would improve in all situations where herd immunity is considered [60]. Second, other types of HPV-related diseases or cancers may be prevented with vaccination. This would have added additional complexity to the interpretation of results, and data would have been either non-existent or limited across regions. Third, we did not explore primary HPV testing as a screening strategy in our analyses. Recent evidence indicates that this may be a feasible and cost-effective option in various locations due to the anticipated reduced performance of conventional cytology-based screening programmes in the presence of vaccination, and further study using available algorithms [69] or based on policies already being adopted by decision makers should be considered [9,66]. Fourth, our incremental comparisons of hypothetical screening and vaccination strategies are based on varying only one parameter at a time (e.g., screening frequency only), rather than multiple parameters simultaneously. Given that we completed analyses for multiple locations, we chose to limit the number of combinations to reduce the complexity in interpretation of the results and make more general conclusions regarding key changes to the existing screening programmes. Future analyses should expand the number and type of screening strategies compared. Fifth, it is important to note that if vaccination coverage is incomplete, screening will be more valuable, and possibly vice versa. This will be especially true if there is a strong correlation between women receiving neither screening nor vaccination, and will be an important caveat to explore in future work. Sixth, we did not conduct sensitivity analyses around assumptions related to the vaccine itself, nor to vaccinating older cohorts of women who have already been exposed to HPV infection; however, these analyses have been done in other papers in this supplement [17]. Seventh, in the Netherlands, levels of treated precancerous CIN lesions were lower than levels observed in the POBASCAM study [63]. Although the calibration matched well to other outcomes including Pap tests and cancer, levels of treated CIN in the Netherlands may have been under-predicted. Eighth, the Canadian values for sensitivity of cytology reflected older meta-analysis data. More recent data with lower values are now available from a Canadian study [70]. Given these values were used in calibration to generate estimates of costs and effectiveness of current interventions it is unclear how this impacts the comparison of these current interventions with new interventions. Finally, we do not make a distinction between the time of vaccination implementation and the delay in discounting for when screening policy changes would take place.

*Conclusions*

In conclusion, our analyses show that vaccination added to current screening is likely to be cost-effective in the regions studied. Once vaccination is well established, countries or locations with the least efficient screening programmes may benefit the most from making changes to their screening programmes. Countries and specific regions within countries should conduct their own analyses to determine the best strategies for future screening and should be cautious not to implement changes without first realizing the benefits of vaccination and carefully weighing the advantages of maximizing efficiency against maximizing cervical cancer protection [66].

Gardasil is a registered trademark of Merck & Co., Inc. Cervarix is a registered trademark of the GlaxoSmithKline group of companies.

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