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The cost-utility of integrated cervical cancer prevention strategies in the Ontario setting – Can we do better?

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ABSTRACT

Introduction: A universal, publicly funded, school-based human papillomavirus (HPV) vaccination program in grade eight girls was initiated in Ontario in 2007. We present a cost-utility analysis of integrated cervical cancer prevention programs from the healthcare payer perspective.
Methods: Our analysis was based on linked HPV transmission and disease history models. We obtained data from the literature, provincial surveys and Ontario population-based linked health administrative datasets. We modeled combinations of vaccination and screening strategies. We considered vaccination based on the Ontario experience, as well as conservative and optimistic scenarios, varying coverage, vaccine effectiveness and duration of protection. We considered 900 screening scenarios (screening start age: 21–70 years, screening interval: 3–20 years; 1-year time steps). The current schedule screens every 3 years starting at age 21 years. We examined (1) first vaccinated cohort (low herd-immunity), and (2) steady state, i.e. all cohorts were vaccinated (high herd-immunity).
Results: Adding vaccination to the current screening schedule was cost-effective (<C$10,000/quality-adjusted life year (QALY)) across all scenarios. Delaying screening start and/or extending screening intervals increased both expected QALYs and cost, and increased overall NHB for screening schedules with a start age of 25–35 years and 3–10-year intervals for most scenarios.
Conclusion: Delaying screening start age and/or extending screening intervals in vaccinated cohorts is likely to be cost-effective. Consideration should be given to both the short- and long-term implications of health policy decisions, particularly for infectious disease interventions that require long time intervals to reach steady state.

1. Introduction

Worldwide, cervical cancer is the second most common type Q4 of cancer in women. Routine cervical cancer screening programs have significantly reduced cervical cancer incidence. In Ontario, Canada's largest province (population of ~13 million), the incidence of cervical cancer has decreased by 2.1% annually since 1981, with mortality rates falling 3% annually for women aged 35 and over [1]. Provincial guidelines recommend screening every 3 years for all women who are or ever have been sexually active starting at age 21 [2].

Cervical cancer is caused by persistent infection with high-risk (HR) human papillomavirus (HPV), where types 16 and 18 are responsible for approximately 70% of cases prior to routine HPV

Abbreviations: Pap, Papanicolaou; HR, high-risk; HPV, human papillomavirus; LR, low risk; PHU, public health unit; MOHLTC, Ontario Ministry of Health and Long-Term Care; QALY, quality-adjusted life years; HSIL, high-grade cervical squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; OHR, other high risk; SIRS, susceptible-infectious-recovered-susceptible; NHANES, National Health and Nutrition Examination Survey; ASCCP, American Society for Colposcopy and Cervical Pathology; LBC, liquid based cytology.

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vaccinations [3]. HPV types 16 and 18 are also prevalent in anogenital and oropharyngeal cancers [3]. Low risk (LR) HPV types 6 and 11 are associated with anogenital warts and recurrent respiratory papillomatosis [4,5]. A bivalent vaccine (against types 16 and 18) and a quadrivalent vaccine (against types 6, 11, 16 and 18) are licensed in Canada. Both are highly efficacious against persistent infection with HR HPV types 16 and 18 and precancerous lesions. Ontario implemented a publicly-funded, school-based HPV vaccination program in 2007, targeting grade eight girls (~13 years of age). While falling short of the Canadian Immunization Committee benchmark of 90% of girls aged 14 years [6], vaccination program coverage has increased from 51% (2007/2008) to 80% (2012/2013) [7,8].

Many studies have shown the cost-effectiveness of HPV vaccination plus screening compared to screening only. Despite differences in methodology and setting, studies consistently conclude that HPV vaccination in girls is cost-effective from the health care payer perspective [9]. With the first vaccinated cohort approaching screening age, an assessment of the cost-utility of integrated cervical cancer prevention programs is imperative.

2. Methods

A cost-utility analysis evaluating integrated primary (HPV vaccination, assuming the bivalent and quadrivalent vaccines to have a similar profile in all important aspects) and secondary (screening) cervical cancer prevention strategies in Ontario was performed from the health care payer perspective (Ontario Ministry of Health and Long-Term Care (MOHLTC)). Health outcomes included HPV infection by age over time, cervical cancer cases, deaths and quality-adjusted life years (QALYs). Health care costs included intervention costs for immunization and screening programs and treatment costs for high-grade cervical squamous intraepithelial lesion (HSIL), cervical intraepithelial neoplasia (CIN 2–3), and invasive cervical cancer.

Primary outcomes were QALYs, costs in 2012 Canadian dollars, incremental cost-effectiveness ratio (ICER), and net health benefit (NHB), calculated as QALYs – (cost/λ), where λ was the cost-effectiveness threshold of $50,000 per QALY. NHB represents the difference between incremental effectiveness (in QALYs) and the health equivalent of the costs using a specific cost-effectiveness threshold (in QALYs). Hence, NHB greater than zero QALYs is considered cost-effective. NHB allows for strategies to be ranked from least to most cost-effective [10]. Multiple cohorts were simulated over 100 years. At the individual level, a lifetime time horizon was adopted. Future costs and QALYs were discounted at 5% [11].

2.1. Model

The analysis was based on linked HPV transmission and disease history models. The heterosexual network model of HPV transmission predicted age-specific incidence of infection over time by HPV type. The disease history model simulated the cervical cancer disease pathway from HPV infection to invasive cervical cancer and predicted HPV-related health outcomes.

2.2. HPV transmission model

The dynamic HPV transmission model was a pair model [12] that simulated sexual partnerships within a sexual network of 50,000 people. Multiple cohorts were simulated in 1 month time steps, accounting for overlapping partnerships, multiple age and sexual risk groups, partnership type (casual versus steady) and safe sex practices (condom usage). Males and females entered the population at age 15 years and exited upon death.

Infection with types 16, 18, other high risk (OHR), or LR types was transmitted in a partnership at a constant rate per unit time that varied according to infection type and age of the partners. The model assumed a Susceptible-Infectious-Recovered-Susceptible (SIRS) natural history (i.e. infection often clears spontaneously and the individual is susceptible to reinfection). Infections persisted for 1 year on average before clearing. Natural immunity lasted a few years on average. The duration of partnerships, infection, natural immunity, and vaccine immunity were sampled from an Erlang distribution for each individual, varying by age.

The sexual behavior parameters were calibrated with US National Health and Nutrition Examination Survey (NHANES) 2009–2010 data on number of lifetime partners by age and number of partners in the last 12 months by age [13]. The natural history parameters were calibrated with Canadian data on prevalence of type 16, type 18, OHR and LR infections by age [11,12].

2.3. Disease history model

The Ontario-specific cervical cancer model is an extension and update of the validated Canadian Cervical Cancer model [14] which only accounted for HR or LR persistent HPV infection. The pathway was restructured to accommodate the specific HPV types 16, 18, OHR and LR types, describing lifetime events of the Ontario

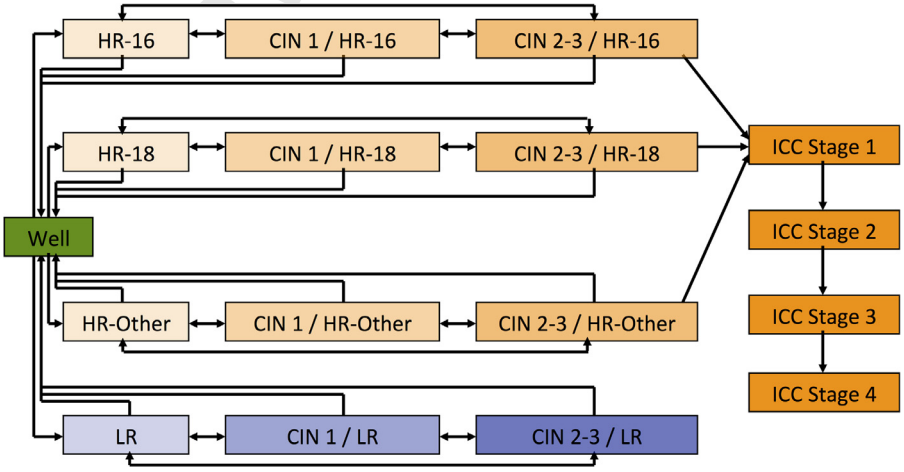

Fig. 1. Disease history model for cervical outcomes.
CIN 1, CIN 2, CIN 3, cervical intraepithelial neoplasia, stage 1, stage 2, stage 3; LR, low risk; HR, high risk; ICC, invasive cervical cancer.

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Table 1
Key input data to cost-utility model and costing data.

Parameter	Estimate*	Range for sensitivity analysis	Data sources
Cervical cancer screening			
Screening coverage by age		n/a	Cancer Care Ontario [1]
20–29 years	0.74		
30–39 years	0.73		
40–49 years	0.73		
50–59 years	0.72		
60–69 years	0.66		
Compliance to follow-up visit for potential Pap abnormalities (%)	0.85	0.50–0.90 [a]	Wagner and Duggan [35]
Cytology			
Probability of ASCUS and LSIL given			
Well	0.92	0.316–1[a]	Ronco et al. [36] Taylor et al. [37] Coste et al. [38] Kim et al. [39]
CIN 1	0.82	0.231–0.862[a]	
CIN 2/3	0.42	0.0293–0.836[a]	
Sensitivity in follow-up			
	0.82	0.735–0.843[a]	Arbyn et al. [40]
Specificity in follow-up	0.95	0.935–0.954[a]	Wright et al. [41] Burger et al. [42] Ronco et al. [36] Taylor et al. [37] Coste et al. [38]
Probability test negative (normal cytology) given			
Well	0.950	0–0.965[a]	Burger et al. [42] Coste et al. [38] Ronco et al. [36] Taylor et al. [37] Wright et al. [41]
CIN 1	0.184	0–0.712[a]	
CIN 2/3	0.176	0–0.862[a]	
Sensitivity for invasive cervical cancer	0.71	0.15–0.92[a]	Nanda et al. [43] Katki et al. [44]
Colposcopy			
Sensitivity	0.983	0.39–0.983[a]	Cantor et al. [45] Massad et al. [46] Stoler et al. [47]
Specificity	0.451	0.409–0.493[a]	Cantor et al. [45]
Utilities			
Healthy Canadian females	0.69–0.92	0.33–1[b]	Statistics Canada [48] for ages ≥20 Statistics Canada 1996/7 [49] for ages 15–19
CIN 1	0.91	0.37–1[b]	Myers et al. [26]
CIN 2/3	0.87	0.40–1[b]	Myers et al. [26]
Cervical cancer – untreated			
Stage I	0.65	0.49–0.81[a]	Goldie [27]
Stage II	0.56	0.42–0.70[a]	
Stage III	0.56	0.42–0.70[a]	
Stage IV	0.48	0.36–0.60[a]	
Cervical cancer – treated			
Stage I	0.97	0.73–0.99[a]	Stratton et al. [28]
Stage II	0.90	0.68–0.98[a]	
Stage III	0.90	0.68–0.98[a]	
Stage IV	0.62	0.47–0.78[a]	
Cost			
Vaccination (per dose)			
Vaccine	$90	$67.5–$112.50[c]	Hirschler 2012 [29]
Vaccine administration	$9	$6.75–$11.25[c]	MOHLTC, personal communication
Screening			
Colposcopy	$457.80	$343.35–$572.25[c]	Krahn et al. [14], adjusted by CPI 2012: 108.8 [50]

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Table 1 (*Continued*)

Parameter	Estimate*	Range for sensitivity analysis	Data sources
Cytology (including lab fee and office visit)	$112.92	$84.69–$141.15[c]	Krahn et al. [14], adjusted by CPI 2012: 108.8 [50]
CIN 2–3	$388.38–$1,198.51	$291.29–$1,498.14[c]	Lawrence Paszat, personal communication
Cervical cancer			
Initial cost			
Months 1–6	$13,375.94–$16,862.06	$10,031.96–$21,077.58[c]	
Months 7–12	$569.79–$1,373.64	$427.34–$1,717.05[c]	
Continuing cost (6 months)	$274.28–$510.66	$205.71–$638.33[c]	
Terminal cost (6 months prior to death)	$22,696	$17,022–$28,370[c]	

ASCUS, atypical squamous cells of undetermined significance; CIN 1, CIN 2, CIN 3, cervical intraepithelial neoplasia, stage 1, stage 2, stage 3; CPI, consumer price index.
[a] Range for sensitivity analysis taken from data sources.
[b] Range for sensitivity analysis derived from 95% confidence interval of beta distribution generated.
[c] Range for sensitivity analysis derived from varying estimate by ±25%.
* Six-month probability estimates unless specified otherwise.

female birth cohort (approximately 70,000) starting at age 13. At 6 months intervals, individuals may progress from HPV infection (as predicted by the dynamic transmission model and balanced by viral clearance) to precancer lesions CIN 1 or CIN 2/CIN 3 (balanced by natural regression), invasive cervical cancer (stage I–IV), and disease-related death (Fig. 1). Death can also occur at any time from unrelated (background) mortality.

Women infected with LR HPV continued to be at risk for HR infection. Most infections cleared spontaneously. Treated cases of cervical cancer were tracked for 5 years after treatment, since related mortality could occur within this period.

The disease history model incorporated cervical cancer screening and management of cytology abnormalities that may modify natural disease history. Cervical cancer screening followed current Ontario guidelines: starting age 21 years and a 3-year screening interval using cytology [15]. HPV DNA testing for triage was excluded because it is not currently publicly funded (i.e., for first vaccinated cohorts) [1]. Cytology results were classified based on the 2001 Bethesda System [16]. Colposcopy findings were classified as defined by the American Society for Colposcopy and Cervical Pathology (ASCCP) [17].

The Canadian Cervical Cancer model was calibrated along key segments of the disease pathway, including HPV prevalence, incidence of cervical cancer and deaths [14]. Output from the updated model was qualitatively verified against observed data [18,19]. The predicted number of cervical cancer cases and deaths were similar to age-specific data from the Ontario Cancer Registry [20] and to overall data (all ages) from the Canadian Cancer Registry (Appendix).

3. Model inputs and assumptions

Data on sexual behavior, disease history, quality of life, screening test performance, cervical screening uptake and HPV vaccine effectiveness were obtained from the literature. Vaccination coverage was obtained from an Ontario HPV coverage survey conducted within schools [8]. Direct medical costs attributable to cervical cancer screening, HPV infection, CIN and invasive cervical cancer were estimated using Ontario population-based health administrative datasets. Parameter values used are presented in Table 1 and the Appendix. Parameters from the literature were chosen to approximate our study population. The model was then calibrated to the number of cervical cancer cases and deaths in Ontario.

3.1. Epidemiology of HPV infection

Parameter values were from the sexual behavior literature and other data sources, or estimated via calibration. Targeted literature searches captured sexual behaviour data from (a) individual-level survey data (number of partners, rate of new partner acquisition, use of condoms, socioeconomic variables, etc.), and (b) contact tracing data, establishing the population's global sexual network structure. HPV transmission probabilities were obtained from studies that estimated the per-act or per-partnership probability of transmission. Parameter values are presented in the Appendix.

3.2. Disease history

Clinical parameters governing disease history were from targeted literature searches. The distribution of cervical abnormalities among Ontario women was based on data covering 8.7 million samples between 1996 and 2003 from the Ontario cytology screening registry (Cytobase) [21]. Cervical cancer distribution by stage was from Ontario (1971–1996) [22]. Cervical cancer-related mortality was from the United States from 2014 [23].

3.3. Interventions

Primary prevention, i.e. vaccination, modifies HPV transmission. We modeled vaccination with coverage based on the Ontario experience. Conservative and optimistic scenarios were also considered to address uncertainty around long-term vaccine effectiveness, duration of effectiveness, cross protection and variation in vaccine coverage.

The *Ontario coverage scenario* used: vaccine coverage from 48% to 90% over time [8], vaccine effectiveness 98% (HR16/18) [24], 37% (OHR) [24], lifetime duration of protection. The *conservative scenario* used: vaccine coverage 60% [7], vaccine effectiveness of 90% for HR16/18 (assumption based on the lower confidence bound for both licensed vaccines [24]), 22% for OHR (assumption based on Brown (2009)), 10 years duration of protection (Erlang distribution minimum 5 years, maximum lifelong; assumption based on Rowhani-Rahbar (2011) showing evidence of immune memory 8.5 years post-vaccination) [25]. The *optimistic scenario* used the same values as the *Ontario scenario* except coverage was 90% (assumption based on Canadian target [12]).

Secondary prevention, i.e. cervical cancer screening, modifies the disease pathway through prevention or early detection of cervical

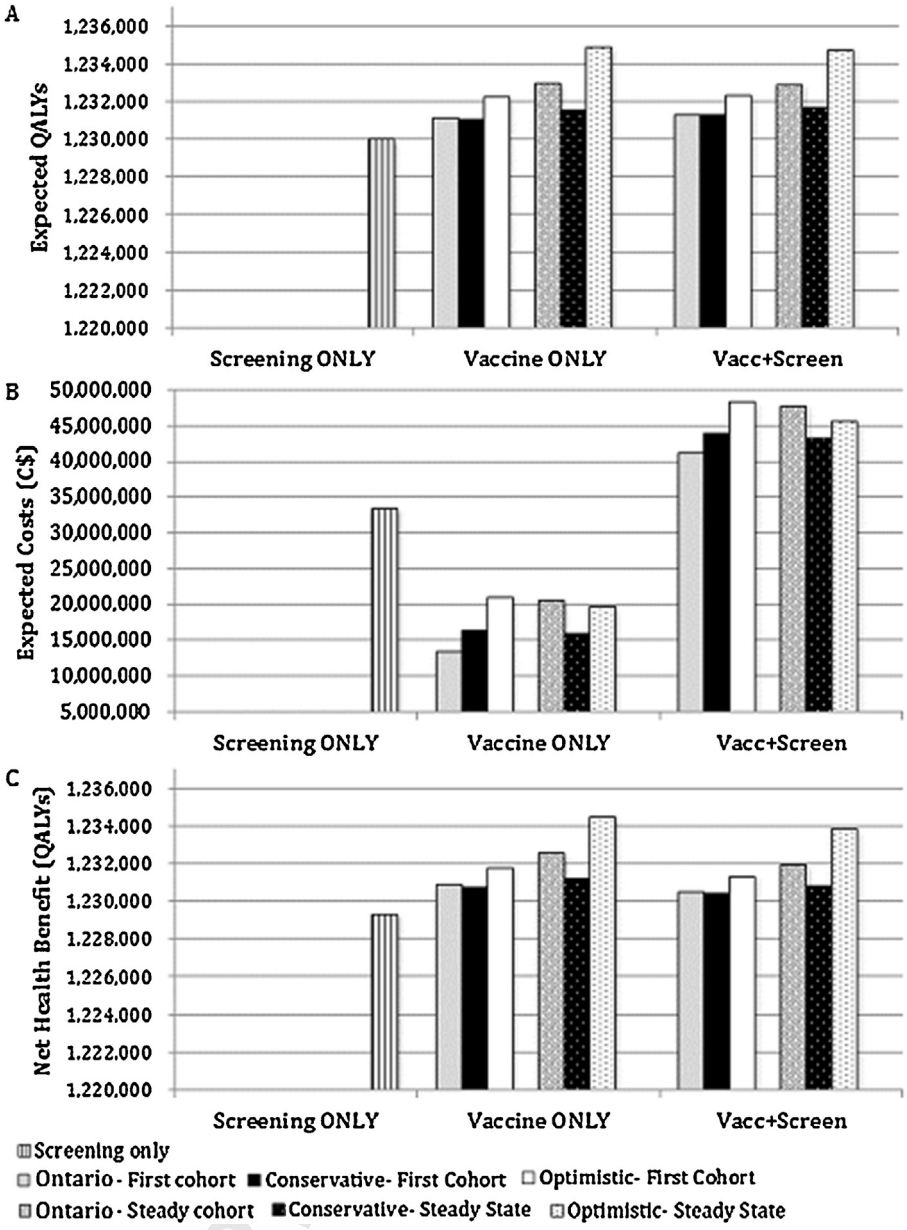

Fig. 2. Health and economics outcomes for the Ontario, conservative and optimistic vaccination and screening scenarios.
(A) Expected utility. (B) Expected cost. (C) Net health benefit (NHB). V1, conservative vaccination scenario; V2, optimistic vaccination scenario; QALYs, quality-adjusted life years.

cancer. Screening participation by age was obtained from Cancer Care Ontario for ages 20+ years, ranging from 66% to 74% [1].

3.4. Utilities

Utility values were derived from a published study using the time trade-off method in a study of 150 volunteers for CIN 1, CIN 2/3 and cervical cancer stage I [26] and published cervical cancer models for cervical cancer stages II–IV [27,28] described previously [14].

3.5. Healthcare cost

Direct healthcare costs attributable to CIN 2–3 and invasive cervical cancer were estimated based on Ontario health administrative data using a cohort design. Exposed subjects were identified through the Canadian Institute for Health Information's same-day surgery dataset (CIN 2–3) and the Ontario Cancer Registry (invasive cervical cancer) and matched to unexposed subjects to determine attributable cost for health states, including initial, continuing and terminal cancer cost by age group [personal communication Lawrence Paszat].

Direct healthcare costs related to screening, including cytology (conventional liquid based cytology, LBC) and colposcopy (with or without biopsy), were also from health administrative databases.

Costs of the HPV vaccination program consisted of the 3-dose vaccine series and program delivery by public health. A 2-dose schedule was considered in sensitivity analysis. Vaccine prices for publicly delivered programs are confidential in Canada. A vaccine price of C$90 per dose was assumed based on the Canadian list price for Cervarix [29]. The program delivery cost was obtained from the MOHLTC for the period 2008–2009 and was approximately C$9 per dose (MOHLTC, personal communication).

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3.6. Analyses

To account for the differential impact of herd immunity effects across cohorts, analyses were performed for (1) the first vaccinated cohort (low herd-immunity), and (2) the steady state, i.e. all cohorts were vaccinated (high herd-immunity). Higher herd-immunity offers indirect protection given the lower likelihood a susceptible person will come into contact with an infected individual. The time to reach steady state for HPV may be considerable, which impacts the choice of optimal screening schedules.

The base case analysis was defined as the Ontario vaccination scenario with the current screening schedule. Scenario analysis explored all possible combinations of the three vaccination scenarios (Ontario, conservative and optimistic), and screening scenarios (screening start age: 21–70 years, screening interval: 3–20 years; 1-year time steps).

Deterministic sensitivity analysis and threshold analysis were conducted for the base case to assess parameter uncertainty. One-way sensitivity analysis was performed on key parameters including vaccine price, screening coverage, compliance to follow-up visits, screening-related costs (cytology, colposcopy), sensitivity and specificity of cytology, and treatment cost for cervical cancer.

4. Results

4.1. Base case analysis

Vaccination combined with screening resulted in greater NHB compared with screening only but not compared to vaccination only. The combined strategies (under the current screening schedule) had a higher NHB compared to screening only (additional 1180 QALYs) versus a lower NHB compared to vaccination only (340 fewer QALYs) (Fig. 2).

Our analysis confirmed the cost-utility of vaccinating grade eight girls, resulting in ICERs of $5879.06 per QALY gained for the first cohort and $4948.19 per QALY gained for the steady state cohort, compared with screening only. There were 1337 more QALYs and 31 fewer cervical cancer deaths at an additional overall cost of approximately $8 million (Fig. 2).

Sensitivity analysis showed that the favorability of the combined vaccination and screening program over the screening

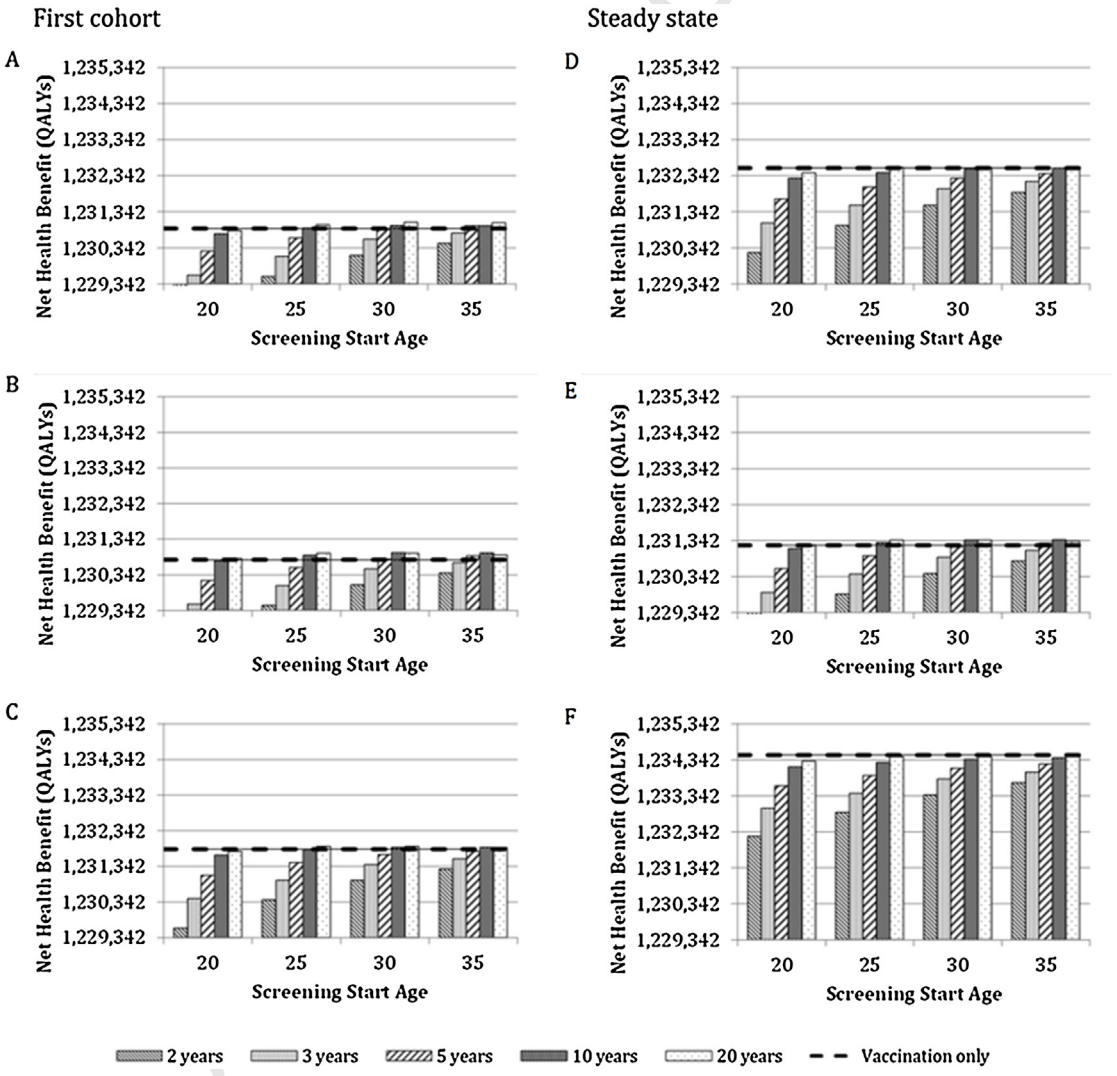

Fig. 3. Expected NHB (QALYs) given select screening start age and screening interval length.
The figure shows the expected NHB for a given combination of starting age of screening and screening interval length for the first cohort and steady state under conservative and optimistic vaccination scenarios. (A) First cohort Ontario vaccination scenario. (B) First cohort conservative vaccination scenario. (C) First cohort optimistic vaccination scenario. (D) Steady state Ontario vaccination scenario. (E) Steady state conservative vaccination scenario. (F) Steady state optimistic vaccination scenario. Vaccination only NHB: (A) 1,230,543 QALYs; (B) 1,231,681 QALYs; (C) 1,231,022 QALYS; (D) 1,234,412 QALYs. (A) 1,231,153 QALYs; (B) 1,231,090 QALYs; (C) 1,232,245 QALYS; and (D) 1,232,966 QALYs; (E) 1,231,531 QALYs; (F) 1,234,870 QALYs

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Table 2
Cost utility of HPV screening scenarios.

Strategy	Expected effective-ness (QALYs)	Incremental effective-ness (QALYs)	Expected cost ($)	Incremental cost ($)	ICER ($/QALY)	NHB (QALY)
Discounted (5%):						
Screening only	17.5716	–	$478.40	–	–	17.56
First cohort						
ON + Screening	17.5907	0.0191	$590.69	$112.29	$5,879.06	17.58
V1 + Screening	17.5903	0.0187	$629.47	$151.07	$8,078.61	17.58
V2 + Screening	17.6046	0.033	$690.35	$211.95	$6,422.73	17.59
Steady state						
ON + Screening	17.6131	0.0415	$683.75	$205.35	$4,948.19	17.60
V1 + Screening	17.5956	0.024	$621.04	$142.64	$5,943.33	17.58
V2 + Screening	17.6395	0.0679	$652.09	$173.69	$2,558.03	17.63
Undiscounted:						
Screening only	59.6522	–	$1,724.88	–	–	59.62
First cohort						
ON + Screening	59.7166	42.145	$1,742.80	$1,264.40	$30.00	59.68
V1 + Screening	59.7087	0.0565	$1,803.91	$79.03	$1,398.76	59.67
V2 + Screening	59.7837	0.1315	$1,734.10	$9.22	$70.11	59.75
Steady state						
ON + Screening	59.7861	42.215	$1,742.19	$1,263.79	$29.94	59.75
V1 + Screening	59.7249	0.0727	$1,769.06	$44.18	$607.70	59.69
V2 + Screening	59.864	0.2118	$1,615.98	-$108.90	−$514.16	59.83

ON, Ontario vaccination scenario; V1, conservative vaccination scenario; V2, optimistic vaccination scenario; QALYs, quality-adjusted life years; NHB, net health benefit.
ICER compares against 'Screening Only'.
Net health benefit used threshold of $50,000 per QALY.

only program was not sensitive to changes in key parameters (Appendix). The cost-effectiveness of the vaccination program can be improved using a 2-dose schedule with an expected ICER of $3722.73 per QALY gained for the first cohort (Appendix).

4.2. Scenario analysis

Even under conservative assumptions, vaccination and screening are cost-effective with an associated ICER of $8078.61 per QALY gained (Table 2). Under optimistic assumptions, this is even more so (ICER: $6422.73 per QALY gained). The results of the base case analysis using Ontario vaccine coverage fall in between the two scenarios.

Supplementary Figs. S3 and S4 show the expected effects and costs, respectively, for combined vaccination and screening strategies by screening start age and screening interval. In the base case of the first cohort, the highest QALYs were achieved at screening start age of 30 years and screening interval of 3–10 years. Costs were highest at a screening start age of 20 years and screening interval of 2 years in the first and steady cohorts for all three scenarios.

Fig. 3 shows that all strategies that combined vaccination and screening had a greater NHB than screening alone (1,229,342 QALYs) but not all had greater NHB compared to vaccination alone.

Overall, a greater NHB was observed for scenarios with greater herd immunity effects: optimistic vaccination assumptions compared to the Ontario vaccination compared to conservative assumptions, and steady state cohort compared to the first vaccinated cohort.

For scenarios other than steady state with optimistic vaccination assumptions, some of the greatest NHB was achieved for a screening start age of 30 years while maintaining a 3-year screening interval. However, because differences were small, screening schedules that combined a screening start age between 25 and 35 years, and intervals of 3–10 years may be acceptable, especially under steady state and optimistic vaccination assumptions. The increasing similarity in NHB across all strategies in Fig. 3f demonstrates that with optimistic assumptions of vaccine coverage, efficacy and duration, the specifics of cervical cancer screening schedules become less relevant.

5. Discussion

The results of our study suggest that a vaccination program for grade-eight girls is a cost-effective addition to the current screening schedule. Results were not sensitive to changes in parameters including cytology sensitivity, which is consistent with other studies [30–32]. Vaccination combined with screening results in greater NHB compared with screening only but not compared to vaccination only. However, delaying screening start age and increasing screening intervals can improve NHB for the combined strategy and exceed that of vaccination only. Further, we demonstrate that as herd immunity levels increase, the optimal design of screening schedules (e.g., such as cervical cancer screening intervals and screening start age) changes, highlighting the importance of jointly optimizing both primary and secondary prevention strategies when evaluating cervical cancer prevention.

Our model has several limitations. Firstly, we focus solely on cervical cancer, underestimating the cost-effectiveness of vaccination, as it prevents multiple HPV outcomes including genital warts, other anogenital cancers and possibly oropharyngeal cancers (although neither HPV vaccine are licensed for this use).

We do not consider catch-up vaccinations, underestimating the cost-utility of vaccination if a sufficient proportion of older females have also received the HPV vaccination, increasing herd immunity effects. We assume a vaccine price of $90 per dose. Since the introduction of HPV vaccine at $150 per dose in 2007, the price has been declining and the price paid by governments may now be lower than the $90 per dose assumed in our analysis, underestimating the cost-utility of vaccination.

Further, the screening test landscape in Canada has changed rapidly over the past decade. Liquid-based cytology [14] was introduced as an alternative to the conventional pap smear. HPV DNA test, while recommended by Cancer Care Ontario for women over age 30 and implemented in European jurisdictions, is not currently funded in Ontario [15]. This and additional diagnostic tests currently in the pipeline could improve the sensitivity and specificity of cervical cancer screening and change the cost-utility of screening.

As the models are Ontario-specific wherever possible, caution is necessary in generalizing these results to other jurisdictions, particularly due to differences in HPV immunization coverage, current

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screening schedules and uptake. In Canada, provincial guidelines recommend screening either every 2 or every 3 years. Approximately, 64–80% of women receive at least one pap smear within 3 years [33].

It should be noted that behavioral changes in response to the HPV vaccination program may alter our results and were not considered in the model. For example, vaccinated women may change the frequency at which they are screened for cervical cancer. There is also a potential selection bias in women who choose to be both vaccinated and screened. Social determinants of health may systematically affect the likelihood of participating in prevention programs, leaving some women more vulnerable to developing invasive cervical cancer. School-based immunization may improve health equity. The convenience of the program in a school-setting allows for increased coverage among adolescents as they are mandated to attend school and do not need to go off site to a health clinic, especially among those of lower socioeconomic status [34]. Completion of all scheduled doses, however, remains an issue. Low income is associated with school absenteeism, so needing to follow-up on missed doses at a general physician's or elsewhere may prove to be more difficult [34].

To our knowledge, this is the first modeling study to investigate optimal cervical screening policies in the HPV vaccination era in Canada. Our results provide both timely and relevant evidence to healthcare decision-makers on screening guidelines.

6. Conclusion

Our study suggests that screening schedules that combine a screening start age between 25 and 30 years, and screening intervals of 3–10 years improve the cost-utility of integrated primary and secondary cervical cancer prevention. Consideration should be given to short- and long-term implications of infectious disease interventions that have long time intervals before reaching steady state.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2016.02.016.

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