Rapid Synthesis

Economic Analyses of Policies to Reduce Cervical Cancer

15 February 2019

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Rapid Synthesis:
Economic Analyses of Policies to Reduce Cervical Cancer
30-day response

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McMaster Health Forum

The McMaster Health Forum's goal is to generate action on the pressing health-system issues of our time, based on the best available research evidence and systematically elicited citizen values and stakeholder insights. We aim to strengthen health systems – locally, nationally, and internationally – and get the right programs, services and drugs to the people who need them.

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Timeline

Rapid syntheses can be requested in a three-, 10-, 30-, 60- or 90-business-day timeframe. This synthesis was prepared over a 30-business-day timeframe. An overview of what can be provided and what cannot be provided in each of the different timelines is provided on the McMaster Health Forum's Rapid Response program webpage (www.mcmasterforum.org/find-evidence/rapid-response).

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Conflict of interest

The authors declare that they have no professional or commercial interests relevant to the rapid synthesis. The funder played no role in the identification, selection, assessment, synthesis or presentation of the research evidence profiled in the rapid synthesis.

Merit review

The rapid synthesis was reviewed by a small number of policymakers, stakeholders and researchers in order to ensure its scientific rigour and system relevance.

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KEY MESSAGES

Questions

- What are the costs or cost-effectiveness of population-level programs and policies aimed at HPV vaccination?
- What are the costs or cost-effectiveness of population-level programs and policies aimed at cervical cancer screening?

Why the issue is important

- Cervical cancer is the fourth most frequently diagnosed cancer in women globally, which is caused by the human papillomavirus (HPV).
- Over the last few decades, cervical cancer incidence and mortality rates have declined in many countries, including Canada.
- The improvements have been attributed, in part, to higher rates of cervical cancer screening and the implementation of population-level HPV vaccine strategies.
- However, immunization does not yet protect against all cervical cancers, and HPV vaccine coverage and uptake vary across Canada.
- In addition, not all provinces and territories have organized cervical cancer screening programs in place.
- Given this, the Canadian Partnership Against Cancer has requested this rapid synthesis to collect evidence on the costs or cost-effectiveness of population-level programs and policies aimed at reducing cervical cancer.

What we found

- We identified a total of 25 relevant documents by searching five databases (Health Systems Evidence, Cochrane Library, Health Evidence, EconLit and PubMed) including eight systematic reviews, 16 primary studies and one draft report focused on the costs or cost-effectiveness of population-level programs and policies aimed at HPV vaccination and cervical cancer screening programs.
- Generally, the findings from the literature on the cost-effectiveness of population-level HPV vaccination programs focused on: 1) the type of vaccine; 2) target population for vaccine administration; and 3) the setting for the delivery of the HPV vaccine program.
- Overall, we found supportive evidence for the cost-effectiveness of quadrivalent HPV vaccine programs in high-income countries, as well as their delivery through school-based vaccination programs (e.g., Canada, U.K., Australia and New Zealand).
- Overall, the expansion of HPV vaccination programs to males was not found to be cost effective compared to no vaccination in four primary studies, and was found to be cost effective in one primary study only under certain conditions.
- Vaccine administration to girls at 13 or 14 years of age (instead of 12 years) was found to be more cost effective in one primary study due to delayed benefits and that women were protected during a higher-risk period in their lives.
- Two primary studies suggest that the value of vaccinating against HPV diminishes as recipients age (e.g., expanding the vaccination to women up to the age of 45 was not cost-effective).
- Three reviews (two recent medium quality and one older medium quality) and two primary studies found that HPV DNA testing compared to cytology-based screening methods was more cost effective.
- Three primary studies specific to the Canadian context compared cervical cancer screening strategies and collectively identified 21 strategies that were more cost effective than current practices (e.g., HPV testing with Pap triage for those with positive HPV test results and colposcopy for women with abnormal Pap test results beginning at age 25 and repeated every three years).

QUESTIONS

- What are the costs or cost-effectiveness of population-level programs and policies aimed at HPV vaccination?
- What are the costs or cost-effectiveness of population-level programs and policies aimed at cervical cancer screening?

WHY THE ISSUE IS IMPORTANT

Cervical cancer is the fourth most frequently diagnosed cancer in women globally, and is caused by the human papillomavirus (HPV), a common sexually transmitted infection.(1) In 2018, there were an estimated 570,000 cases and 311,000 deaths worldwide.(2) Over the last few decades, the cervical cancer incidence and mortality rates have declined in many countries, including Canada.(3) The improvements have been attributed, in part, to higher rates of cervical cancer screening and the implementation of population-level HPV vaccine strategies.(3-5)

The Canadian Partnership Against Cancer (hereafter referred to as the Partnership) completed an environmental scan in 2018 of cervical cancer screening in Canada.(6) The scan found that organized cervical cancer screening programs are available in most provinces, with the exception of Quebec.(6) Organized cervical cancer screening programs are also not available in the three territories (Yukon, Northwest Territories and Nunavut).(6) Recommendations for screening varies by jurisdiction and includes commencement from the ages 21 to 25, with administration every two-to-three years, until the age of 61 to 70.(6) While several jurisdictions (British Columbia, Ontario and Quebec) are piloting and considering the implementation of HPV testing, the cytology-based Papanicolaou (Pap) test is the primary screening test for cervical cancer in Canada.(6; 7)

Box 1: Background to the rapid synthesis

This rapid synthesis mobilizes both global and local research evidence about a question submitted to the McMaster Health Forum's Rapid Response program. Whenever possible, the rapid synthesis summarizes research evidence drawn from systematic reviews of the research literature and occasionally from single research studies. A systematic review is a summary of studies addressing a clearly formulated question that uses systematic and explicit methods to identify, select and appraise research studies, and to synthesize data from the included studies. The rapid synthesis does not contain recommendations, which would have required the authors to make judgments based on their personal values and preferences.

Rapid syntheses can be requested in a three-, 10-, 30-, 60- or 90-business-day timeframe. An overview of what can be provided and what cannot be provided in each of these timelines is provided on the McMaster Health Forum's Rapid Response program webpage (www.mcmasterforum.org/find-evidence/rapid-response).

This rapid synthesis was prepared over a 30-business-day timeframe and involved four steps:

1) submission of a question from a policymaker or stakeholder (in this case, the Canadian Partnership Against Cancer);
2) identifying, selecting, appraising and synthesizing relevant research evidence about the question;
3) drafting the rapid synthesis in such a way as to present concisely and in accessible language the research evidence; and
4) finalizing the rapid synthesis based on the input of at least two merit reviewers.

The HPV vaccine helps to prevent most, but not all, cervical cancers.(8) There are three HPV vaccines available (bivalent, quadrivalent and nonavalent), all of which have been shown to be effective in preventing infection with virus types 16 and 18.(1; 9) To maximize the effectiveness of HPV vaccines, it is best if they are administrated prior to exposure to HPV, and the World Health Organization recommends vaccination between nine and 14 years of age.(8) In Canada, the HPV vaccine is offered to all children across provinces and territories and is typically administered in grades four to seven.(6) The quadrivalent vaccine offered in school-based vaccination programs in Canada prevents infections from HPV types that are linked with 70% to 90% of all cervical cancer cases, and also prevents anogenital warts caused by infection with HPV types 6 and 11.(1; 10)

Given this, the Partnership has requested this rapid synthesis to collect evidence on costs or cost-effectiveness of population-level programs and policies aimed at reducing cervical cancer incidence.

WHAT WE FOUND

We identified a total of 25 relevant documents by searching five databases (Health Systems Evidence, Cochrane Library, Health Evidence, EconLit and PubMed), and the search strategy for these databases are detailed in Box 2. We applied the following inclusion criteria (as outlined by the requestor):

1) time period (2002 to present);
2) jurisdictional focus on Canada and other high-income countries with a similar socio-economic context (e.g., Group of Seven countries, Northwest Europe, Australia and New Zealand); and
3) economic evaluation of programs and policies focused on reducing cervical cancer incidence, including improving access to HPV vaccines and cervical cancer screening.

In addition, we searched key organizational websites in Canada that are involved in the provision of evidence and guidelines about drugs and technologies (e.g., Canadian Agency for Drugs and Technologies in Health) and relevant guidance documents of the World Health Organization.

While our search strategy focused on finding evidence on the costs and cost-effectiveness of population-level programs and policies aimed at HPV vaccination and cervical cancer screening, we have also included relevant findings about the effectiveness of these policies on health outcomes, and any unintended consequences or other implementation considerations.

What are the costs or cost-effectiveness of population-level programs and policies aimed at HPV vaccination?

We found seven systematic reviews and nine primary studies that evaluated the cost-effectiveness of HPV vaccination programs. Generally, findings from the included literature focused on: 1) the cost-effectiveness of bivalent (HPV 16 and 18), quadrivalent (HPV 6, 11, 16 and 18) and/or nonavalent (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58) vaccines; 2) target population for vaccine administration (e.g., age and program expansion to males); and 3) setting for the delivery of HPV vaccination (e.g., school-based or primary care). A short summary of these findings has been provided in the narrative below, with additional details provided in Table 1.

Box 2: Identification, selection and synthesis of research evidence

We identified research evidence (systematic reviews and primary studies) by searching (in January 2019) Health Systems Evidence (www.healthsystemsevidence.org), Health Evidence, EconLit and PubMed. In Health Systems Evidence, we used the following search strategies: 1) "cervical cancer" AND screen*; and 2) (hpv OR human papillomavirus OR human papilloma virus) AND vaccin*. We also applied the following filters: overviews of systematic reviews, systematic reviews of effects, and economic evaluations and costing studies. In the Cochrane Library we used the following search strategies: 1) "cervical cancer" AND screen*; and 2) (hpv OR human papillomavirus OR human papilloma virus) AND vaccin*. In Health Evidence we used the following search filters: date (2002 - 2019) and searched for: 1) "cervical cancer" AND screen*; and 2) (hpv OR human papillomavirus OR human papilloma virus) AND vaccin*. In EconLit we searched for 1) "cervical cancer" AND screen*; and 2) (hpv OR human papillomavirus OR human papilloma virus) AND vaccin* [limited to 2002 - present]. Finally, in PubMed we used the following search strategies: 1) "cervical cancer" AND screen* AND cost; and 2) (hpv OR human papillomavirus OR human papilloma virus) AND vaccin* AND cost [limited to 2002 - 2019].

In addition, we searched: 1) organizational websites in Canada that are involved in the provision of evidence and guidelines about drugs and technologies (e.g., Canadian Agency for Drugs and Technologies in Health; and 2) relevant publications of the World Health Organization.

The results from the searches were assessed by one reviewer for inclusion. A document was included if it fit within the scope of the questions posed for the rapid synthesis.

For each systematic review we included in the synthesis, we documented the focus of the review, key findings, last year the literature was searched (as an indicator of how recently it was conducted), methodological quality using the AMSTAR quality appraisal tool (see the Appendix for more detail), and the proportion of the included studies that were conducted in Canada. For primary research (if included), we documented the focus of the study, methods used, a description of the sample, the jurisdiction(s) studied, key features of the intervention, and key findings. We then used this extracted information to develop a synthesis of the key findings from the included reviews and primary studies.

Type of vaccine

We identified three reviews (two recent medium quality and one recent low quality) and five primary studies that compared the cost-effectiveness of bivalent, quadrivalent and nonavalent vaccines.(11-16) One recent low-quality review assessed the cost-effectiveness of adult vaccinations and found that when cost-effectiveness was assessed, the incremental cost-effectiveness ratios (ICER) compared to no vaccination were less than US$100,000/quality-adjusted life year (QALY) gained in 69% of the evaluations conducted in nine cost-effectiveness studies of HPV vaccination (all costs were adjusted to 2016 U.S. dollars).(15) Another recent medium-quality review focused on the cost-effectiveness of HPV vaccination programs in high-income countries.(14) The cost components of included studies were converted to International Dollars (I$).(14) The official exchange rate was used to convert to local currency when the ICER was calculated in U.S. dollars or in a currency other than the local one. The local currencies were then converted into I$ by applying the Purchasing Power Parity indicators provided by the World Bank. Lastly, data were adjusted to 2015 using the price index of medical services, which is a sub-category of the consumer price index.(14) Within the included studies, the comparison is the current screening program. ICERs varied from I$818/QALY gained to I$166,102/QALY gained, and the average ICER for vaccination against HPV types 6, 11, 16 and 18 was estimated at I$25,132/QALY gained.(14) In addition, when the benefits of prevention of HPV types 6 and 11 were removed, the analysis suggests that the vaccination against oncogenic HPV types 16 and 18 ranged from I$2,561/QALY gained to I$166,102/QALY gained, and the average ICER was estimated at I$38,253/QALY gained.(14) One recent medium-quality review showed that inclusion of non-cervical HPV associated diseases on the ICER of vaccination programs targeted both at girls only and at both girls and boys generally caused more favorable ICERs than those that only considered the effect on cervix carcinoma.(13) One primary study estimating the cost-effectiveness of HPV vaccination in the U.S. found that the cost per QALY in the model was lower if: 1) herd immunity was assumed; 2) if the vaccine covered a greater number of HPV type (specifically types 6 and 11, rather than just 16 and 18); and 3) when other cancer-prevention benefits were included in the model.(17) Another primary study found supportive evidence (e.g., screening and vaccination had an ICER of £21,059 pounds/QALY gained and £34,687 pounds per life-year saved, when compared to screening alone) for adding the quadrivalent HPV vaccine to the U.K. cervical cancer program.(16) Similarly another primary study found supportive evidence for adding the quadrivalent vaccine in France to existing screening practices (compared to screening alone), finding €8,408 euros/QALY gained.(18)

One primary study examined cost-effectiveness by comparing the quadrivalent and the bivalent vaccines (cohort of 100,000 girls aged 12 years), and the cost-utility ratio for the bivalent vaccine was $31,000/QALY gained and $21,000/QALY gained for the quadrivalent vaccine.(19) Another primary study used the published data from the previous study to re-evaluate the cost-effectiveness model.(20) The author found that the model is highly sensitive to several assumptions (e.g., when the time horizon of the intervention is extended far into the future).(20) An example provided in the study highlights that if one takes a relatively conservative approach to several key assumptions, the ICER can quickly change from a value of $20,512/QALY gained to $80,144/QALY gained.(20)

Lastly, one primary study examined the cost-effectiveness of a next generation nonavalent vaccine (HPV9) in Australia compared to the quadrivalent vaccine.(21) The two models predicted that, compared to the current regime of cytology testing every two years, primary HPV screening (with the 2013 guidelines) would reduce lifetime risk of cervical cancer diagnosis by 18% and lifetime risk of cervical cancer death by 20%.(21) Offering the quadrivalent vaccine was predicted to have an additional 54% reduction in diagnosis and a 53% reduction in death.(21) In addition, the cohorts offered the nonvalent vaccine were predicted to have a further 11% reduction in diagnosis and death.(21) The nonvalent vaccine was found to be a cost-effective alternative to the quadrivalent vaccine if the additional cost per dose was less than $23 to $36 Australian dollars (based on assumptions of lifetime protection with two doses and that the additional costs of the nonvalent vaccine would only apply to girls).(21)

Target population for HPV vaccination

In terms of the target population for vaccine administration, we identified two recent reviews (one high quality and one medium quality) (11; 22) and five primary studies.(23-27) The evidence focused on expansion of vaccination programs by extending it to males or increasing the age of vaccination among women. Overall, the expansion of HPV vaccination programs to males was not found to be cost effective compared to no vaccination in four primary studies and was found to be cost effective in one primary study only under certain conditions (e.g., when the combined cost of the vaccine and administration were $125 New Zealand dollars or less per dose).(23; 24; 26) The evidence from one primary study on the age of vaccination suggests that administration to girls at 13 or 14 years of age (instead of 12 years) increases cost-effectiveness of the program because benefits are delayed and women were protected during a higher-risk period in their lives.(26) In terms of HPV vaccination for older women, one primary study found the probability of HPV vaccination being cost effective for screened women ages 35 to 45 in the U.S. was found to be low (threshold of $100,000/QALY gained).(25) Herd effects were found in a recent high-quality review in countries with high HPV vaccination coverage (minimum of 50%) and associated with a significant decrease in pre-vaccination and post-vaccination periods of HPV types 16 and 18 (68% - RR 0·32, 95% CI 0·19–0·52) and anogenital warts (61% - 0·39, 0·22–0·71) in females 13-to-19 years of age.(22) Another recent medium-quality review found that herd effects can be expected from vaccinating girls only, including coverage rates as low as 20%.(11) Lastly, one primary study conducted in New Zealand found that HPV vaccination particularly benefited Māori and low socio-economic populations, due to higher rates of cervical cancer among these groups.(27)

Setting for the delivery of HPV vaccination

With regards to setting for the delivery of HPV vaccination programs we found one recent high-quality review and one primary study.(22; 27) The review found that the largest declines in HPV-related outcomes in both males and females were found in countries using school-based vaccination programs (e.g., U.K., Australia and New Zealand), suggesting that school-based vaccination strategies support higher vaccination coverage.(22) One primary study conducted a Markov macro-simulation to model the impact of three HPV vaccination interventions: 1) vaccination across schools and primary care (current approach), yielded an estimated cost-effectiveness of US$9,700/QALY gained when compared to no intervention; 2) school-only vaccination program was less cost effective at US$33,000/QALY gained; and 3) impact of a new law mandating immunization (with a requirement for potential recipients to opt-out from vaccination) was the least cost effective at US$117,000/QALY gained.(27)

Two main limitations were reported in the systematic reviews and primary studies included in the evidence synthesis. The first limitation was that some of the models did not consider the impacts of herd immunity for vaccination.(16) The second limitation was that some of the models did not examine strategies that included program expansion of the vaccination to males.(16; 17)

Table 1. Summary of key findings about the costs or cost-effectiveness of population-level programs and policies aimed at HPV vaccination

Features of population-level programs and policies aimed at HPV vaccination	Key findings
Type of vaccine	*Key findings related to costs or cost-effectiveness* • One recent medium-quality review examined the cost-effectiveness of HPV vaccination programs and found that bivalent costs varied from €147–402 and quadrivalent three-dose vaccine costs varied from and €264–360.(12) o Vaccine costs were found to have an effect on the ICER, significantly affecting the cost-effectiveness of vaccination strategies.(12) • One recent medium-quality review showed that inclusion of non-cervical HPV associated diseases on the ICER of vaccination programs targeted both at girls only and at both girls and boys generally caused more favorable ICERs than those that only considered the effect on cervix carcinoma. o The girls-only vaccination program, compared to no vaccination, was €15,216 euros/QALY gained when all HPV-associated diseases were taken into account, and €24,080 euros /QALY gained when only cervical cancer was considered.(13) • One recent medium-quality review examined the cost-effectiveness of HPV vaccination programs in high-income countries and found that ICERs varied from I$818/QALY gained to I$166,102/QALY gained, and the average ICER for vaccination against HPV types 6, 11, 16 and 18 was estimated at I$25,132/QALY gained.(14)* o When the benefits of prevention of HPV types 6 and 11 were removed, the analysis suggests that the vaccination against oncogenic HPV types 16 and 18 ranged from I$2,561/QALY gained to I$166,102/QALY gained, and the average ICER was estimated at I$38,253/QALY gained.(14)* • One recent low-quality review assessed the cost-effectiveness of adult vaccinations and found that when cost-effectiveness was assessed, the ICERs compared to no vaccination were less than US$100,000/QALY gained in 69% of the evaluations conducted in nine cost-effectiveness studies of HPV vaccination (100% for influenza, 100% for pneumococcal, 71% for herpes zoster, and 50% for tetanus-diphtheria-pertussis vaccinations) (adjusted to 2016 U.S. dollars using the consumer price index).(15) • One primary study used a simplified approach to estimating the cost-effectiveness of HPV vaccination in the U.S. and found that the cost per QALY in the model was lower if: 1) herd immunity was assumed; 2) if the vaccine covered a greater number of HPV type (specifically types 6 and 11, rather than just 16 and 18); and 3) when other cancer-prevention benefits were included in the model.(17) • One primary study found supportive evidence for the cost-effectiveness of adding the quadrivalent HPV vaccine to the U.K. cervical cancer program, finding that screening and vaccination had an ICER of £21,059 pounds/QALY gained and £34,687 pounds per life-year saved, when compared to screening alone. o Other considerations included vaccine efficacy, need for a booster and impacts of herd immunity.(16) • One primary study examined the cost-effectiveness of adding the quadrivalent vaccine in France to existing screening practices compared to screening alone. o The screening plus vaccination program was €8,408 euros/QALY gained and considered cost effective using a threshold of €50,000 euros/QALY gained.(18) • One primary study examined cost-effectiveness by comparing the quadrivalent and the bivalent vaccines to no vaccination, under current conventional cytology-based screening rates in Canada. o Under base-case assumptions (vaccinating a cohort of 100,000 girls aged 12 years) the results were 1,400 (1,800) discounted QALYs-saved over the

Features of population-level programs and policies aimed at HPV vaccination	Key findings
	lifetime, and the cost-utility ratios for the bivalent vaccine was $31,000/QALY gained and $21,000/QALY gained for the quadrivalent vaccine.(19) • One primary study used the published data from a previous study (see study directly above) to re-evaluate the cost-effectiveness model and found that the model is highly sensitive to several assumptions (e.g., when the time horizon of the intervention is extended far into the future).(20) • One primary study found that the nonvalent vaccine was found to be a cost-effective alternative to the quadrivalent vaccine in Australia if the additional cost per dose was less than $23 to $36 Australian dollars (based on assumptions of lifetime protection with two doses and that the additional costs of the nonvalent vaccine would only apply to girls).(21) *Additional key findings related to benefits and harms* • None identified
Target population for HPV vaccination	*Key findings related to costs or cost-effectiveness* • One primary study assessed the cost-effectiveness of including males in the publicly funded childhood vaccination program (quadrivalent) in Norway, finding only modest additional reductions if males were included in the program.(23) • One primary study assessed the cost-effectiveness of including males in the current HPV vaccination program in New Zealand through a Markov macro-simulation model, which found that the vaccination of males only became cost effective when the combined cost of the vaccine and administration were $125 New Zealand dollars or less per dose.(24) • One primary study compared the cost-effectiveness of expanding HPV vaccination to women up to the age of 45 compared to available screening tests and found that the value of vaccinating against HPV diminishes as recipients age (the probability of HPV vaccination being cost effective for screened women ages 35 to 45 was found to be low at a threshold of $100,000 per QALY gained.(25) • One economic evaluation examined a range of HPV vaccination strategies in the U.K. and found that the base-case scenario (vaccination of girls at the age of 12, with 80% vaccine coverage) was cost effective (at £60-£80 pounds per dose at a threshold of £20 000-£30 000 pounds/ QALY gained), as long as the vaccine protected for 10 years.(26) o Administering vaccination to girls at 13 or 14 years of age was found to be more cost effective because benefits are delayed and women were protected during a higher-risk period in their life.(26) o The strategies were not cost effective past the age of 25 and extending the vaccination program to boys was not found to be cost effective.(26) *Additional key findings related to benefits and harms* • One recent high-quality review examined short-term population-level consequences and herd effects of HPV vaccination programs finding that countries with high vaccination coverage (minimum of 50%) were associated with a significant decrease in pre-vaccination and post-vaccination periods of HPV types 16 and 18 (68% - RR 0·32, 95% CI 0·19–0·52) and anogenital warts (61% - 0·39, 0·22–0·71) in females 13-to-19 years of age.(22) o The same review found that HPV types 31, 33, and 45 were significantly reduced, suggesting cross-protection.(22) • One recent medium-quality review that examined the model predictions of long-term population-level effectiveness of vaccinations against HPV types 6, 11, 16 and 18 found that elimination of all four types is possible if there is 80% coverage in both girls and boys coupled with high vaccine efficacy.(11) o Herd effects can be expected from vaccinating girls only, including coverage rates as low as 20%.(11)

Features of population-level programs and policies aimed at HPV vaccination	Key findings
	• One primary study conducted in New Zealand found that HPV vaccination particularly benefited Māori and low socio-economic populations, due to higher rates of cervical cancer among these groups.(27)
Setting for delivery of HPV vaccination	*Key findings related to costs or cost-effectiveness* • One primary study conducted a Markov macro-simulation to model the impact of three HPV vaccination interventions: 1) vaccination across schools and primary care (current approach), with a US$9,700/QALY gained when compared to no intervention; 2) school-only vaccination program was less cost effective at US$33,000/QALY gained; and 3) impact of a new law mandating immunization (with a requirement for potential recipients to opt-out from vaccination) was the least cost effective at US$117,000/QALY gained.(27) *Additional key findings related to benefits and harms* • One recent high-quality review examined short-term population-level consequences and herd effects of HPV vaccination programs finding the largest declines in HPV-related outcomes in both males and females were in countries using school-based vaccination programs (e.g., U.K., Australia and New Zealand), suggesting that school-based vaccination strategies support higher vaccination coverage.(22)

***** Cost components were converted to International Dollars (I$) and the official exchange rate was used to convert to local currency when the ICER was calculated in U.S. dollars or in a currency other than the local one. The local currencies were then converted into I$ by applying the Purchasing Power Parity indicators provided by the World Bank. Data were adjusted to 2015 using the price index of medical services (a sub-category of the consumer price index).(14)

What are the costs or cost-effectiveness of population-level programs and policies aimed at cervical cancer screening?

We identified three systematic reviews, six primary studies and one draft report that related to the costs or cost-effectiveness of population-level programs and policies aimed at cervical cancer screening. Findings from the included literature focused on the type of cervical cancer screening strategy (e.g., HPV DNA testing compared to cytology based) and most included modelling of a range of strategies. We provide a short summary of these findings in Table 2 and an overview of key findings below.

We found one draft health technology assessment report by CADTH, which reviewed the clinical effectiveness, cost-effectiveness, patient perspectives and experiences, ethical issues, and implementation issues regarding the use of HPV DNA testing compared to cytology-based primary cervical cancer screening programs.(28) Recommendations made by the health technology expert review panel included:

- adoption of a population-based primary cervical cancer screening program, but no recommendation of a specific test type due to insufficient evidence;
- if a jurisdiction adopts an HPV-based primary cervical cancer screening program, there should be five-year testing intervals from the ages of 25 to 69, and the test should have genotyping capability (to increase the certainty of oncologic strain and reduce additional testing); and
- reassessment of the screening program within 10 years due to potential changes in testing and immunization rates.(28)

It is important to note that the recommendation of the draft report may be revised upon the release of the final report in March 2019.

We found three reviews (two recent medium quality and one older medium quality) and two primary studies that examined the cost-effectiveness of HPV DNA testing compared to current cytology-based screening methods, which found the following:

- in high-income countries, HPV DNA primary screening was more cost effective than cytology alone;(29)
- HPV DNA testing was the most cost-effective strategy (comparing at intervals of two, three, five and 10 years), and testing at 30 years of age or older at an interval of five years yielded the most cost-effective results;(30)
- the most cost-effective strategy was an HPV DNA test every four years, with colposcopy referral after three additional positive tests six months apart;(31)
- HPV DNA testing followed by cytological triage of HPV-positive women combined with HPV vaccination was the best strategy, and was comparable in cost to other strategies and had a greater QALY gain;(12) and
- compared to Australia's National Cervical Screening Program at the time (cytological screening every 2 years between the ages of 18 to 69 years), primary HPV screening with partial genotyping for women aged 25 to 64, and an exit HPV test between ages 70 and 74, was found to be more cost effective.(32)

The recommendations from the above study on Australia's National Cervical Screening Program were implemented on December 1, 2017, marking one of the first countries to transition to primary HPV screening within a national screening program.(33)

The remaining evidence, four primary studies, focused on model simulations to compare cervical cancer screening strategies. Three of the studies were specific to the Canadian context and findings included:

- eight strategies were identified as being cost effective and HPV testing with optimal strategy of Pap triage for those with positive HPV test results and colposcopy for women with abnormal Pap test results beginning at age 25 and repeated every three years was found to be better at preventing cancer and less costly than the currently employed strategy, up until age 70 (consistent across jurisdictions studied - Canada, Ontario, Alberta, and Newfoundland);(34)
- 12 cervical cancer screening strategies (out of 21 strategies) were identified that were more cost effective than the current method used in Alberta (annual PAP test screening for women between the ages of 18 and 69, which was the recommended strategy when the study was originally published) and the three-year PAP + HPV + PAP-age was the preferred strategy ($16,078/QALY gained);(35) and
- HPV testing is more cost effective than cytology screening alone and ICERs were less than the per capita gross domestic product of Quebec.(36)

The final study estimated the cost-effectiveness of adding the quadrivalent HPV vaccine to the U.K. cervical cancer program and found that screening alone was associated with an ICER £11,156 pounds/QALY gained when compared to no screening or vaccination.(16) Screening and vaccination had an ICER of £21,059 pounds/QALY gained and £34,687 pounds per life-year saved, when compared to screening alone.(16)

The main limitation found in the literature reviewed related to the cost-effectiveness of population-level programs and policies aimed at cervical cancer screening was that some models did not account for the impact of HPV vaccination.(36)

Table 2. Summary of key findings about the costs or cost-effectiveness of population-level programs and policies aimed at cervical cancer screening

Features of population-level programs and policies aimed at cervical cancer screening	Key findings
Type of cervical cancer screening strategy	*Key findings related to costs or cost-effectiveness* • One recent medium-quality review examined the cost-effectiveness of three cervical cancer screening strategies: 1) the introduction of a new screening program compared to no screening; 2) changes to an existing screening algorithm without the introduction of new technology; and 3) introduction of a new screening technology. o All studies unanimously supported the introduction of screening programs where none existed. o The majority of studies recommended either the continuation of screening following vaccination or the introduction of screening in a post-vaccination setting, and post-vaccination HPV DNA primary screening was more cost effective than cytology alone in high-income countries.(29) • One recent medium-quality review explored the cost-effectiveness of alternative HPV prevention strategies that combine screening with vaccination and found that HPV DNA testing followed by cytological triage of HPV-positive women combined with HPV vaccination was the best strategy, and was comparable in cost to other screening strategies and had a greater QALY gain compared to other strategies (e.g., cytology alone).(12) o The review also found that strategies with shorter screening intervals led to increased costs and offered limited benefits compared to longer screening intervals.(12) • One older medium-quality review assessed the cost-effectiveness of cervical cancer screenings globally and found that HPV DNA was the most cost-effective strategy (comparing at intervals of two, three, five and 10 years) and testing at 30 years of age or older at five years or more interval of screening yielded the most cost-effective results.(30) • One primary study examined the impact of adopting recent cervical cancer prevention strategies, which involve HPV DNA testing, to determine the most effective strategy for both vaccinated and unvaccinated populations in Norway, and found that the current cytology-based screening method was less effective and incurred greater costs when compared to other strategies.(31) o The most cost-effective strategy was an HPV DNA test every four years, with colposcopy referral after three additional positive tests six months apart.(31) o For vaccinated women, the most effective strategy was to extend the screening protocol to every six years, but to otherwise follow the same follow-up criteria as unvaccinated women.(31) o A secondary analysis found that the same primary screening interventions initiated at 31 years of age could further reduce lifetime costs.(31) • One primary study Markov model simulation compared 27 distinct cervical cancer screening strategies with a focus on Canada as a whole and Alberta, Ontario and Newfoundland.(34) o Eight strategies were identified as being cost effective, all of which fell on the efficiency frontier (created by selecting only the strategies that have the greatest net benefits per willingness-to-pay threshold). The strategies included: no intervention; HPV test with Pap triage every five years beginning at age 25; HPV test with Pap triage every three years beginning at age 25; HPV test with Pap triage every three years beginning at age 18; the Miller strategy beginning at age 18 then Pap with HPV triage every year from age 25; Pap test with HPV triage every year beginning at age 18; Pap tests

Features of population-level programs and policies aimed at cervical cancer screening	Key findings
	every year beginning at age 18; and combined Pap and HPV tests every two years beginning at age 18.(34) • A strategy of HPV testing with Pap triage for those with positive HPV test results and colposcopy for women with abnormal Pap test results beginning at age 25 and repeated every three years was found to be better at preventing cancer and less costly than the currently employed strategy (screening every year from age 18 until 21 and then every three years afterwards with conventional Pap).(34) • One primary study estimated the cost-effectiveness of adding the quadrivalent HPV vaccine to the U.K. cervical cancer program, and findings of the model included: o screenings accompanied by vaccination would lead to a decline in lifetime risk of cervical cancer (from 0.71% to 0.29%); o 418 cases of cervical cancer and 127 deaths could be avoided (cohort of 100,000); o screening alone is associated with an ICER £11,156 pounds/QALY gained when compared to no screening or vaccination; o screening and vaccination had an ICER of £21,059 pounds /QALY gained and £34,687 pounds per life-year saved, when compared to screening alone; and o when a 10-year vaccine efficacy was assumed, the ICER for the vaccine and screening combination was found to be £68,417 pounds /QALY gained and £116,743 pounds per life year saved, when compared to screening alone.(16) • One primary study evaluated the cost-effectiveness of cervical cancer screening strategies in Quebec and found that HPV testing is more cost effective than cytology screening alone, and ICERs were less than the per capita gross domestic product of the province.(36) • One primary study modelled the cost-effectiveness of 21 cervical cancer screening strategies using a health-system perspective with data from Alberta and found that 12 strategies were more effective than the currently used method (annual PAP test screening for women between the ages of 18 to 69, which was the recommended strategy when the study was originally published), including: o the three-year PAP + HPV + PAP-age strategy was more effective and saved $16,078/QALY gained and reduced overall costs by 4.2% (PAP-age refers to age restriction and only women 30 years of age or older who have atypical squamous cells of undetermined significance receive a HPV-DNA triage test); o the one-year PAP + HPV + PAP-age provided benefit at a cost of $58,512/QALY gained; o the one-year PAP + HPV + PAP was found to cost $82,266/QALY gained; o one-year LBC + HPV + LBC strategy was found to cost $127,076/QALY gained (LBC refers to liquid-based cytology and women are retested with LBC in six months instead of PAP).(35) • One primary study compared Australia's National Cervical Screening Program at the time (cytological screening every two years between the ages of 18 to 69 years) and found that primary HPV screening with partial genotyping for women aged 25 to 64, and an exit HPV test between ages 70 and 74, was more cost effective.(32) *Additional key findings related to benefits and harms* • None identified

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APPENDICES

The following tables provide detailed information about the systematic reviews and primary studies identified in the rapid synthesis. The ensuing information was extracted from the following sources:

- systematic reviews - the focus of the review, key findings, last year the literature was searched, and the proportion of studies conducted in Canada; and
- primary studies (in this case, economic evaluations and costing studies) - the focus of the study, methods used, study sample, jurisdiction studied, key features of the intervention and the study findings (based on the outcomes reported in the study).

For the appendix table providing details about the systematic reviews, the fourth column presents a rating of the overall quality of each review. The quality of each review has been assessed using AMSTAR (A MeaSurement Tool to Assess Reviews), which rates overall quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality. It is important to note that the AMSTAR tool was developed to assess reviews focused on clinical interventions, so not all criteria apply to systematic reviews pertaining to delivery, financial or governance arrangements within health systems. Where the denominator is not 11, an aspect of the tool was considered not relevant by the raters. In comparing ratings, it is therefore important to keep both parts of the score (i.e., the numerator and denominator) in mind. For example, a review that scores 8/8 is generally of comparable quality to a review scoring 11/11; both ratings are considered "high scores." A high score signals that readers of the review can have a high level of confidence in its findings. A low score, on the other hand, does not mean that the review should be discarded, merely that less confidence can be placed in its findings and that the review needs to be examined closely to identify its limitations. (Lewin S, Oxman AD, Lavis JN, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP): 8. Deciding how much confidence to place in a systematic review. *Health Research Policy and Systems* 2009; 7 (Suppl1):S8).

All of the information provided in the appendix tables was taken into account by the authors in describing the findings in the rapid synthesis.

Appendix 1: Summary of findings from systematic reviews about costs or cost-effectiveness of population-level programs and policies aimed at HPV vaccination and cervical cancer screening

Type of review	Focus of systematic review	Key findings	Year of last search/ publication date	AMSTAR (quality) rating	Proportion of studies that were conducted in Canada
Systematic review and meta-analysis	To examine the population-level impact and herd effects following HPV vaccination programs (22)	The review examined 20 studies to assess the short-term population-level consequences and herd effects of HPV vaccination programs. All the included studies were undertaken in one of nine high-income countries. The results between the pre- and post-vaccination periods were analyzed by age sub-groups: 13 to19, 20 to 24. In females aged from 13 to 19, the overall prevalence of HPV types 16 and 18 decreased significantly by 64%. There was a significant dose-response association with the coverage of vaccination (p=0.005). The overall prevalence of HPV types 31, 33, and 45 decreased significantly by 28% (RR 0·72 [95% CI 0·54–0·96]). However, the overall prevalence of HPV types 31, 33, 45, 52, 58, and non-vaccine high-risk type did not significantly change post-vaccination. In females aged 20 to 24, the overall prevalence of HPV types 16 and 18 decreased by 31% and was not significant; there was a dose-response association with vaccination coverage (p=0.01). No significant decreases in prevalence were found in any other HPV type. There was a slight, but not significant, increase in non-vaccine high-risk HPV type (RR 1·09, 95% CI 0·98– 1·22). It was determined that in countries with high vaccination coverage (minimum of 50% coverage) there was a significant decrease in HPV types 16 and 18 infections (68%; RR 0·32, 95% CI 0·19–0·52) between the pre-and post-vaccination periods. In the same population of girls aged 12 to 19, anogenital warts were found to decrease by 61% (RR 0·39, 95% CI 0·22–0·71) while HPV types 31, 33, and 45 were significantly reduced (RR 0·72. 95% CI 0·54–0·96), suggesting cross-protection. Similarly, significant reductions of anogenital warts in the post-vaccination period were also reported in males aged 20 or younger (0·66 [95% CI 0·47–0·91]) and females aged 20 to 39 (0·68 [95% CI 0·51–0·89]). In countries that covered less than 50% of the female vaccination, there were significant reductions in HPV types 16 and 18 (RR 0·50, 95% CI 0·34–0·74]) and anogenital warts (0·86 [95% CI 0·79–0·94]) in females under 20 years of age. There was no indication of cross-protection or herd effects. The steepest declines in HPV-related outcomes in both males and females were evident in countries using school-based vaccine delivery (e.g., U.K., Australia), suggesting this method is beneficial for faster rollout. The findings indicate that HPV vaccination is quite effective and can provide cross-protection in some cases.	2014	9/11 (AMSTAR rating from McMaster Health Forum)	1/20
Systematic review	To examine economic evaluations of HPV vaccination including non-cervical HPV-associated diseases (13)	A review of 18 economic evaluations examined the ICER of preadolescent HPV-vaccination programs under the influence of non-cervical HPV-associated diseases and only cervical HPV-associated diseases. HPV is commonly associated with the development of cancers (cervical, vaginal, vulvar, penile, anal and oropharyngeal), genital warts and recurrent respiratory papillomatosis. There are currently three vaccines available for HPV-associated diseases: bivalent, quadrivalent, and nonavalent.	2016	4/11 (AMSTAR rating from McMaster Health Forum)	3/18

		The ICERs of analyses that included all recognized HPV-associated diseases were substantially lower than the analyses including only cervix carcinoma. In comparison to no vaccination programs, the mean ICER in a girls-only vaccination program including all HPV-associated diseases was €15,216 euros/QALY gained, and €24,080 euros/QALY gained considering only cervical cancer. The mean ICER in a gender-neutral vaccination program versus a girls-only vaccination was €95,444 euros/QALY gained including all HPV-associated diseases and €180,823 euros/QALY gained considering only cervical cancer. Taking into account all HPV-associated diseases, the mean ICERs were 2.85 times more favourable (95% CI 1.35–4.36) for girls-only vaccinations and 3.89 times for gender-neutral vaccinations (95% CI −0.10–7.85). According to an analysis including all HPV-associated diseases, a gender-neutral vaccination strategy with the nonavalent vaccine was found to be more cost-saving (ICER of €129,814 euros/QALY gained) than a quadrivalent vaccine. In conclusion, the inclusion of non-cervical diseases in economic evaluations of HPV vaccination programs generally causes ICER values to fall below the accepted cost-effectiveness thresholds.			
Systematic review	To evaluate model-based cervical cancer screening strategies (29)	A review of 135 articles examined the effectiveness and/or cost-effectiveness of cervical cancer screening strategies. Most studies (n=129) performed a cost-effectiveness analysis. The included studies evaluated three types of interventions: 1) the introduction of a new screening program (n=34); 2) changes to an existing screening algorithm without the introduction of new technology (n=43); and 3) introduction of a new screening technology (n=72). Out of the studies that conducted a cost-effectiveness analysis, 72 studies evaluated a new screening technology and 47 evaluated already-adopted technologies. The technologies assessed included cytology, HPV DNA, and visual inspection with acetic acid, with comparisons primarily between alternative cytology-based strategies, HPV DNA versus cytology, and visual inspection with acetic acid versus cytology and/or HPV DNA. Most of the evaluations were based on models that simulated aggregate groups of women at risk of cervical cancer. All studies unanimously supported the introduction of screening programs where none existed before (34/34), and the majority of included studies were economic evaluations. Among alternative cytology-based strategies, liquid-based cytology was recommended over conventional cytology (18/27, 67%). Several studies found HPV DNA to be the most cost effective among other methods such as cytology (15/17, 88%) and VIA (1/1, 100%). In low- and middle-income countries, VIA was identified to be more cost effective than cytology (2/2, 100%). Additionally, self-sampled HPV DNA testing was found to be a more cost-effective primary screening technique in high-income countries than clinic-based HPV DNA or conventional cytology alone (2/2, 100%). An exception is in the case of upper-middle-income countries where it is not cost effective compared to other technologies (2/2, 100%). Co-testing was more cost effective than cytology in high-income countries (6/7, 86%). In regard to screening and vaccination, the majority of studies recommended either the continuation of screening following vaccination or the introduction of screening in a post-vaccination setting (10/12, 83%). Post-vaccination HPV DNA primary screening was more cost effective than cytology alone in high-income countries (5/5, 100%).	2013	4/9 (AMSTAR rating from McMaster Health Forum)	9/135
Systematic review and meta-analysis	To examine the population-level impact, herd immunity, and	A review of 19 studies examined the model predictions of long-term population-level effectiveness of vaccinations against HPV 16, 18, 6, and 11.	2015	6/11 (AMSTAR rating from	Not reported

	elimination about HPV vaccination (11)	Sixteen of the models provided predictions. Under 40% vaccination coverage and girls-only vaccination, the relative risk (RR) of HPV 16 among women and men was 0.53 (80% UI 0.46–0.68) and 0.36 (0.28–0.61), respectively, after 70 years. With an increase in 40% girls-only vaccination, the RR of HPV 16 among women and men was 0.93 (0.90–1.00) and 0.83 (0.75–1.00), respectively. It was predicted by most models that both female and male vaccinations would eliminate the four types of HPV at this level of 80% vaccination coverage. The RR for HPV 16 were smaller than HPV 6, 11, and 18 for all the cases. The additional step of vaccinating boys increased the RR of HPV 16 among women and men by 0.18 (0.13–0.32) and 0.35 (0.27–0.39) for 40% coverage, and 0.07 (0.00–0.10) and 0.16 (0.01–0.25) for 80% coverage, respectively. The incremental benefit of vaccinating girls was found to be larger than vaccinating boys due to the substantial herd effects of girls-only vaccinations when vaccination coverage is moderate to high. HPV models offer generally consistent results. Results suggest that herd effects are predicted in vaccination coverage as low as 20%.		McMaster Health Forum)	
Systematic review	To examine the cost-effectiveness of prevention strategies against HPV infection (12)	A review of 18 papers examined the cost-effectiveness of prevention strategies against HPV infection. The cost-effectiveness of vaccination programs varied largely depending on the age of vaccination, the number of doses received, and whether a booster was given. The majority of studies examined bivalent (HPV 16/18) or quadrivalent (HPV 6/11/ and 16/18) vaccines (17/18). In terms of vaccine efficacy, bivalent vaccines were found to be greater than 75% to 95%. The costs of the bivalent and quadrivalent three-dose vaccines typically ranged between €147.00–402.00 euros and €264.00–360.00 euros, respectively. Among the strategies modelled, HPV DNA testing was found to the optimal strategy due to its comparable costs and a greater gain in QALY. In regard to vaccine valence, an increase in the duration of screening interval was associated with lower costs but also lower benefits. However, shorter screening intervals increased the costs with limited added benefits. A five-valent vaccine was less costly but also was associated with fewer QALY gains compared to a 13-valent vaccine, which had the greatest benefits but at the greatest costs. Despite a slight increase in the screening interval, the combination of vaccination with screening was found to have a marginal impact on benefits, but a large reduction in costs. An increased vaccine valence was found to counterbalance the negative effects of delayed/less frequent screening. Overall, variations in screening practices and valence of HPV vaccination were found to have large implications on cost-effectiveness. However, there was a high degree of heterogeneity in how HPV prevention strategies were assessed in terms of their economic and epidemiological impact. Across studies, vaccination coverage ranged from 70% to 100%.	2014	5/11 (AMSTAR rating from McMaster Health Forum)	1/18
Systematic review	To examine the cost-effectiveness of adult vaccinations (15)	This review included 78 papers examining the cost-effectiveness of adult vaccinations, particularly those included on the adult immunization schedule. Among outcomes assessing age-based vaccinations, the per cent indicating cost savings was 56% for influenza, 31% for pneumococcal, and 23% for tetanus-diphtheria-pertussis vaccinations. Among age-based vaccination outcomes reporting $QALY gained, the per cent of outcomes indicating a cost per QALY of ≤$100,000 was 100% for influenza, 100% for pneumococcal, 69% for HPV, 71% for herpes zoster, and 50% for tetanus-diphtheria-pertussis vaccinations. The majority of published studies report favorable cost-effectiveness profiles for adult vaccinations, which supports efforts to improve the implementation of adult vaccination recommendations.	2016	3/9 (AMSTAR rating from McMaster Health Forum)	Not reported

		Due to the relatively broad scope of this review, authors were unable to assess the overall quality of the publications or to assess the quality and influence of any specific inputs.			
Systematic review	To examine the cost-effectiveness of the HPV vaccine for high-income countries (14)	This review included 42 articles which assessed the cost-effectiveness of the HPV vaccine for high-income countries. In order to compare cost-effectiveness between countries, the cost components of included studies were converted to International Dollars (I$). The official exchange rate was used to convert to local currency when the ICER was calculated in U.S. dollars or in a currency other than the local one. The local currencies were then converted into I$ by applying the Purchasing Power Parity indicators provided by the World Bank. Lastly, data were adjusted to 2015 using the price index of medical services, which is a sub-category of the consumer price index. Overall, it was found that the quadrivalent vaccine was used in 23 studies while the bivalent was used in 14 studies. Both vaccines were used in the remaining five studies to assess the cost-effectiveness of HPV vaccination. Within the included studies, the comparison is the current screening program. ICERs varied from I$818/QALY gained to I$166,102/QALY gained, and the average ICER for vaccination against HPV types 6, 11, 16 and 18 was estimated at I$25,132/QALY gained. In addition, when the benefits of prevention of HPV types 6 and 11 were removed, that analysis suggests that the vaccination against oncogenic HPV types 16 and 18 ranged from I$2,561/QALY gained to I$166,102/QALY gained, and the average ICER was estimated at I$38,253/QALY. In conclusion, this review presented HPV vaccination in combination with screening as a potentially cost-effective intervention in high-income countries. If implemented, this strategy could reduce the incidence of HPV-related diseases. Although the methodology between included studies differed, the authors conclude that the number of studies examined despite the different assumptions used is large enough to support its conclusion.	2018	4/11 (AMSTAR rating from McMaster Health Forum)	Not reported
Systematic review	To examine the economic aspects of cervical cancer screening strategies worldwide (30)	This review included 21 articles examining the economic aspects of cervical cancer screening strategies worldwide. Nineteen out of 21 studies showed that HPV DNA testing was the most cost-effective strategy of all, while 13 studies suggested testing at an age of 30 years or more for the most cost-effective results. The authors note that there is a lack of a standard threshold for the ICER in many countries, and many countries have selected a threshold for the ICER (e.g., Australia, Canada, New Zealand, England and Wales, the Netherlands, Scotland and Japan). The WHO has suggested GDP per capita in each region as a threshold for the ICER. In the articles selected, most ICERs of HPV DNA testing in the screening programs were below one–fold of GDP per capita and one included study reported the ICER as five-fold the GDP per capita. Only three studies suggested that screening is cost effective if started at an age less than 30 years. Ten papers concluded that the most cost effective strategy for testing was HVP DNA testing, starting cervical screening at age 30 years or older, and five years or more interval of screening. In some countries, the national guidelines were found not to match the recommendations of the cost-effectiveness studies. In conclusion, implementing HPV DNA testing was deemed to be the most appealing and cost-effective strategy for almost all populations and should be included in the screening program. Closer collaboration with health economists is required during the development of guidelines in order to achieve the most cost-effective program for cervical cancer prevention.	2012	6/11 (AMSTAR rating from McMaster Health Forum)	Not reported

Appendix 2: Summary of findings from primary studies about costs or cost-effectiveness of population-level programs and policies aimed at HPV vaccination and cervical cancer screening

Focus of study	Study characteristics	Sample description	Key features of the intervention(s)	Key findings
Examining the cost-effectiveness and health outcomes of three HPV vaccination programs in New Zealand (27)	*Publication date:* 2014 *Jurisdiction studied:* New Zealand *Methods used:* A Markov macro-simulation model was used to estimate the cost-effectiveness and health outcomes of three different HPV vaccination interventions	A Markov macro-simulation model including 12-year-old girls and boys in New Zealand	Disease modelling and economic evaluation of the HPV vaccine with a focus on examining: 1) the quantifiable impact of vaccination on health inequalities; and 2) the cost-effectiveness of vaccination interventions.	HPV infection and resulting disease has a significant impact on health inequalities, with rates of cervical cancer and other HPV-associated cancers being higher among marginalized groups, including lower socio-economic, minority, and indigenous populations. Social inequalities in HPV-related disease exists in New Zealand, but vaccination is higher among Māori and Pacific peoples. This study aimed to model the impact of three HPV-vaccination interventions, taking into account social group differences, health gains, and cost-effectiveness. In this study, a Markov macro-simulation model was used to estimate the population of disease-free participants, stratified based on sex, ethnicity, and socio-economic status. QALY, quantifying years of life lost from premature death and loss of quality of life through disease morbidity, were used to estimate the impact of disease. Health-system costs were assigned to participants based on health status, with additional costs for cancer patients estimated at each stage of care, and vaccination costs were calculated for each fully vaccinated participant. The first intervention of interest was the 2008 HPV vaccination program in New Zealand, which disperses vaccination across schools and primary care. When compared to no intervention, this program yielded an additional cost of $4.65 million New Zealand dollars, with a gain of 266 QALYs. The ICER for the intervention (compared to no HPV vaccine) was $18,800 per QALY gained ($7,300–$35,400 New Zealand dollars). The second intervention of interest was the modification to the vaccination program to a school-only program, as has been done in Australia. This intervention saw a gain in QALYs from 266 to 348, and had a high cost-effectiveness ratio (ICER $22,600 per QALY gained - $9,800–$40,200 New Zealand dollars). The third intervention examined the impact of a new law requiring potential recipients to opt out from the vaccination, as has been done in some U.S. states. Mandated immunization led to an increase in QALYs to 382 (ICER $31,100 per QALY gained - $15,400–$52,000 New Zealand dollars), suggesting the law would be cost ineffective. This study found that HPV vaccination particularly benefited Māori and low socio-economic populations, due to higher rates of cervical cancer among these groups. Taken together, while the current vaccination program

Focus of study	Study characteristics	Sample description	Key features of the intervention(s)	Key findings
				is cost effective and equitable, a school-only program may enhance health gains.
Evaluating the cost-effectiveness of expanding Norway's vaccination program to include males (23)	*Publication date: 2014* *Jurisdiction studied:* Norway *Methods used:* A dynamic model of HPV transmission was applied to the Norwegian population	12-year-old girls and boys in Norway	The health outcomes and costs of expanding HPV vaccination to include males in Norway were evaluated using a dynamic model of transmission.	HPV infection poses an important risk factor for disease among both women and men. While an increasing number of countries recommend HPV vaccination for males, there are few public funding opportunities. The current study assessed the cost-effectiveness of including males in the publicly funded childhood-vaccination program in Norway. The health and economic burden of HPV infection in Norway was estimated using a previously-published dynamic model of transmission. The current three-dose vaccination program for females was compared to an intervention targeting similar coverage for males. The female-only vaccination program was estimated to reduce future cancer incidence significantly, with modest additional reductions calculated if males were included in the intervention (adding 12-year-old boys to the current program may be considered 'good value for money' at a willingness-to-pay threshold of $83,000 per QALY gained). This study found that expanding the current vaccination program to males would not be considered good value for money at a lower willingness-to-pay threshold $36 per dose (2010 US dollars). At a price of $120 - $150 per dose, expanding the HPV vaccination program to include males was most likely not be cost effective even when considering the higher threshold value ($83,000/QALY gained). Vaccine price and willingness-to-pay were found to be a significant parameter when determining cost-effectiveness, and there may be a combination of these factors that yields positive outcomes when expanding vaccination to include males. However, the current cost of HPV vaccination in Norway suggests that expanding the program to include males would not be cost effective. Thus, the expansion of coverage to females was found to be a more cost-effective approach compared to expansion of vaccination to males.
Examining the cost-effectiveness of an expanded HPV vaccination program in New Zealand (24)	*Publication date: 2014* *Jurisdiction studied:* New Zealand *Methods used:* An adapted Markov model was used to estimate cost-effectiveness	Annual cohort of 12-year-olds in New Zealand	An adapted Markov model which focused on the cost-utility of girl-only HPV vaccination was used to estimate QALYs and health-system costs for different vaccination interventions.	This study examined the cost-effectiveness of adding boys to the current HPV vaccination program in New Zealand, which currently provides vaccination only to girls. A Markov macro-simulation model was used to account for future health states, health-sector costs, and QALYs. Four vaccination interventions were examined: 1) the girls-only program, running in New Zealand in 2011; 2) an intensified girls-only program with school-only delivery; 3) adding boys to (1); and 4) adding boys to (2). Adding boys to the current vaccination intervention in New Zealand resulted in an increase in QALYs, but at a greater cost. Compared to intensifying the girls-only vaccination program, adding boys to the

Focus of study	Study characteristics	Sample description	Key features of the intervention(s)	Key findings
				intervention was not cost effective. When boys were added into either vaccination model, the QALYs gained for each individual female outweighed those gained for males. The vaccination of males only became cost effective when the combined cost of the vaccine and administration were NZ$125 or less per dose. Taken together, the results of this study indicate that policymakers should focus on expanding vaccine efforts among females, rather than expanding vaccination to males. Public pressure to expand the vaccine to boys should focus on ways to reduce costs.
Examining the impact of recent cervical cancer prevention strategies among vaccinated and unvaccinated women in Norway (31)	*Publication date: 2012* *Jurisdiction studied:* Norway *Methods used:* A decision-analytic model was used to assess the impact of cervical cancer screening interventions	Women who have either been vaccinated or not vaccinated against HPV in Norway	A simulation model of HPV-induced cervical cancer compared the current approach to screening with primary HPV testing at older ages.	In 2009, Norway introduced an HPV vaccination program for pre-adolescent girls. However, cytology-based screening programs continue to be the primary method of cervical cancer prevention for Norwegian women who are past the age of vaccination. This study examined the impact of adopting recent cervical cancer prevention strategies, which involve HPV DNA testing, to determine the most effective strategy for both vaccinated and unvaccinated populations. This study found that the current cytology-based screening method was less effective and incurred greater costs when compared to other strategies. For unvaccinated women, the most cost-effective strategy was found to be an HPV DNA test every four years, with colposcopy referral after three additional positive tests six months apart. For vaccinated women, the most effective strategy was to extend the screening protocol to every six years, but to otherwise follow the same follow-up criteria as unvaccinated women. A secondary analysis found that the same primary screening interventions initiated at 31 years of age could further reduce lifetime costs. It is possible that this proposed method of cervical cancer screening may lose woman to follow-up. However, a responsive system that helps women to meet screening needs and monitors outcomes will aid in the effectiveness of this model.
Examining the effectiveness of expanding HPV vaccination to older women in the U.S. (25)	*Publication date: 2009* *Jurisdiction studied:* U.S. *Methods used:* Comparative cost analysis using an empirically calibrated model	Women up to the age of 45 in the U.S.	A cost-effectiveness analysis examined the impact of HPV vaccination on older women in the U.S in the context of existing screening protocols.	In the U.S., women over the age of 30 are primary targets for HPV DNA screening. This study compared the cost-effectiveness of expanding the HPV vaccination to women up to the age of 45 compared to available screening tests. The results of this study indicated that the value of vaccinating against HPV diminishes as recipients age, and that the absolute reduction of HPV risk among women in their 30s and 40s. Vaccinating older women does not result in "good value" for resources, pointing to the potential efficacy of other screening programs including those that may address unscreened

Focus of study	Study characteristics	Sample description	Key features of the intervention(s)	Key findings
				women. However, there may be individuals who would benefit from vaccination, and decisions should take into account a person's risk, screening history and preference. As more becomes known about HPV and the impact of vaccination on older women, it is important to revisit these findings.
Economic evaluation of HPV vaccination in the U.K. (26)	*Publication date: 2009* *Jurisdiction studied:* U.K. *Methods used:* Economic evaluation of HPV vaccination using a transmission dynamic model	School-aged girls in the U.K. aged 12 or older	A transmission dynamic model was used to predict the burden of HPV before and after vaccination.	The study conducted an economic evaluation of a range of HPV vaccination strategies in the U.K. The base-case scenario included the vaccination of girls at the age of 12, with 80% vaccine coverage. Alternative scenarios included expanding the vaccination program to boys, vaccinating girls at 13 or 14 years of age, and a catch-up program where females who were not vaccinated receive vaccination. The results of this study indicated that the base-case scenario of vaccinating 12-year-old female students through a school-based program with the quadrivalent vaccine priced at £60-£80 pounds per dose was likely to be cost effective at a threshold of £20 000-£30 000 pounds/QALY gained, as long as the vaccine protected for 10 years. Administering vaccination to girls at 13 or 14 years of age was found to be more cost effective because benefits are delayed, and women were protected during a higher-risk period. Further, catch-up vaccinations reduced the incidence of HPV in the first 30 years. These campaigns are not cost effective past the age of 25. Extending the vaccination program to boys was not found to be cost effective.
Estimating the cost-effectiveness of HPV vaccination in the U.S. using a simplified model (17)	*Publication date: 2008* *Jurisdiction studied:* U.S. *Methods used:* Simplified model of HPV vaccine cost-effectiveness, based on current, age-specific incidence rates of HPV-related outcomes	Population model of 12-year-old girls in the U.S.	A simplified model of cost-effectiveness was used to characterize the potential impact of HPV-vaccination on related outcomes.	The current study offered a simplified approach to estimating the cost-effectiveness of HPV vaccination, accounting for factors including vaccine duration, efficacy and cost. The results were in alignment with other more complex cost-effectiveness models, indicating cost-effectiveness and saved QALYs. The cost per QALY in this model was lower if herd immunity was assumed, if the vaccine covered a great number of HPV types (specifically types 6 and 11, rather than just 16 and 18), and when other cancer-prevention benefits were included in the model. This model of cost-effectiveness was limited, and did not examine strategies for the vaccination of males or address all potential costs and benefits. However, a number of key findings emerged that were consistent with the results of more complex models.
Estimating the cost-effectiveness of adding the quadrivalent HPV vaccine to the U.K. cervical cancer program (16)	*Publication date:* 2008 *Jurisdiction studied:* U.K.	The model follows women from age 12 to age 85. The model follows over time and predicts the probability of HPV infection, cervical intraepithelial	A 98% effective vaccine for HPV types 6, 11, 16, and 18 was modelled. It was assumed to be administered to girls aged 12. The baseline model assumed the vaccine has lifetime efficacy. The effects of a booster at age 22 were	The model's prediction for cervical cancer incidence, and the distribution of cancer stages, was comparable to observed data from the U.K., confirming its validity. When screenings were accompanied by vaccination in the model, there was a decline in lifetime risk of cervical cancer, falling from 0.71% to 0.29%. For a cohort of 100,000 U.K. women, the model estimated that 418 cases

Focus of study	Study characteristics	Sample description	Key features of the intervention(s)	Key findings
	Methods used: Markov model of HPV infection and cervical cancer	neoplasia, and cervical cancer. The model assumed women aged 25 to 49 were screened for cervical cancer every three years while women aged 50 to 64 were screened every five years. Differences in screening coverage and methods were also incorporated. The effects of treatment for cervical intraepithelial neoplasia were also incorporated.	also calculated. Based on school programs for hepatitis B vaccination, an 85% vaccine coverage rate was assumed. The model tested costs and cost-effectiveness for vaccine prices ranging from £75 to £80. The cost of administration varied between £3.40 and £12. Health outcomes and costs were discounted at a 3.5% annual rate.	of cervical cancer and 127 deaths could be avoided. Furthermore over 6,600 cases of cervical intraepithelial neoplasia 1-3 and 4,798 cases of genital warts could be avoided. Screening alone is associated with an ICER of £11,156 pounds/ QALY gained, when compared to no screening or vaccination. Screening and vaccination had an ICER of £21,059 pounds/QALY gained and £34,687 pounds per life-year saved, when compared to screening alone. When a 10-year vaccine efficacy was assumed the ICER for the vaccine and screening combination was found to be £68,417 pounds/QALY gained and £116,743 pounds per life year saved, when compared to screening alone. When a booster given at age 22 with 50% coverage was added to the model the ICER was £26,782 pounds/QALY gained and £44,114 pounds per life year saved. For the base case (screening alone, compared to no screening or vaccination) when the discount rate for medical benefits was lowered from 3.5% to 1.5%, the ICER fell to £9,653 pounds per QALY. The authors concluded that this model may provide evidence of cost-effectiveness depending on the vaccine efficacy and whether a booster is needed. It was noted that the later start and less frequent screening for cervical cancer in the U.K. (when compared to the U.S.) decreases some costs. The authors noted that if booster doses were needed and incorporated into screening visits this would increase coverage and likely improve cost-effectiveness. Furthermore, one unmeasured potential benefit of vaccination is that it could allow women to be screened less frequently. This model did not consider the impacts of herd immunity for vaccination, and it did not include the vaccination of boys in the model.
Cost-effectiveness of HPV testing with Pap triage in Canada (34)	*Publication date:* 2009 *Jurisdiction studied:* Canada *Methods used:* Markov model	The results of the Canadian Cervical Cancer Screening Trial were combined with previous Markov models to estimate the effectiveness and cost-effectiveness of HPV tests, Pap tests, and combination of the two tests. A model was developed for Canada as a whole, as well as for Ontario, Alberta, and Newfoundland.	The Markov model was used to compare 27 distinct screening strategies. The strategies varied based on the age when screening began, and the methods used for screening. The ages for commencing screening were 18 and 25. Single test strategies, HPV test or Pap test, were modelled. Furthermore, combined test strategies, using both HPV and Pap tests and referring to colposcopy if the HPV test was positive, or there were findings of atypical squamous cells	The model's predicted cancer incidence rates closely followed observed incidence rates. Eight strategies were identified as being cost effective, all of which fell on the efficiency frontier. These strategies included the following: no intervention; HPV test with Pap triage every five years beginning at age 25; HPV test with Pap triage every three years beginning at age 25; HPV test with Pap triage every three years beginning at age 18; the Miller strategy beginning at age 18 then Pap with HPV triage every year from age 25; Pap test with HPV triage every year beginning at age 18; Pap tests every year beginning at age 18; and combined Pap and HPV tests every two years beginning at age 18. The Miller strategy was found to be associated with the highest numbers of cancer. Strategies beginning at age 18 were associated with a higher number

Focus of study	Study characteristics	Sample description	Key features of the intervention(s)	Key findings
			or undetermined significance, or other severe abnormalities appeared in smears. Finally, two triaging strategies were tested. The first involved HPV testing followed by Pap testing only if there was a positive HPV test. The second involved Pap testing followed by HPV testing if severe abnormalities were found in the Pap test. Screening coverage was based on the findings of the 1998 Surveillance Report on Cervical Cancer Screening in Canada. It was assumed that all women who received an initial test would also receive the triage test if needed. Finally, women with cervical intraepithelial neoplasia or cancer were assumed to be receiving the appropriate treatment. The sensitivity and specificity of tests were estimated based on a recent randomized trial, with corrections for changes in sensitivity and specificity for women of different ages. The costs of Pap and HPV tests, as well as the professional costs of the procedures, were based on provincial fee schedules, direct communications, and the Ontario Case Costing Initiative. The provincial costs per weighted case were used to adjust Ontario data so as to be relevant for Alberta and Newfoundland. Cancer-care costs, for various stages, was based on a previous study. All estimates are in 2006 Canadian dollars.	of false-positives and slightly fewer cancers than equivalent strategies beginning at age 25. HPV tests with Pap triage every three or five years were found to have ICER of less than $50,000 per life year gained. Pap tests followed by HPV triage were found to have ICERs less than $100 000 per life year gained. The currently recommended strategy (the Miller strategy) was found to be costlier and less effective than a strategy of an HPV test with Pap triage conducted every three years and commencing at age 25. Sensitivity analysis found that the results were sensitive to the discount rate and the cost of the Pap test. Probabilistic sensitivity analysis showed that the optimal strategy depends on a decision-maker's willingness to pay. If the willingness to pay is between $20,000 and $50,000 per life year gained the optimal strategy is HPV testing with Pap triage every three years beginning at age 25. If willingness to pay is less than $20,000 per life year the optimal strategy is an HPV test with Pap triage every five years. The authors concluded that a strategy of HPV testing with Pap triage for those with positive HPV test results and colposcopy for women with abnormal Pap test results beginning at age 25 and repeated every three years is better at preventing cancer and less costly than the currently employed strategy. The results were found to be consistent across the four jurisdictions studied (Canada, Ontario, Alberta and Newfoundland).

Focus of study	Study characteristics	Sample description	Key features of the intervention(s)	Key findings
			The utility estimates for false positive Pap tests and cancer were based on previously published results and assumed to be constant by age.	
Examining the cost-effectiveness of alternative cancer screening strategies (35)	*Publication date:* 2010 *Jurisdiction studied:* Alberta, Canada *Methods used:* Cohort simulation Markov model	The model was built to determine the cost-effectiveness of 21 cervical cancer screening strategies from the health-system perspective. The model follows a cohort of women from age 12 to age 80 and follows them through normal health, low-risk HPV infection and high-risk ontogenetic HPV. Alberta-specific data for cervical cancer incidence, prevalence and aggregated mortality were used in the model. Canadian data were used for the incidence of HPV infection and the stage-specific cervical cancer mortality rates. Costs were reported in 2007 Canadian dollars and discounted at 5%. The fees for physician and laboratory services were gathered from sources in Alberta. QALYs were discounted at 3%. Costs for cervical cancer screening were divided into four categories: screening tests, physician	The 21 screening strategies emerged from seven distinct screening and testing algorithms being used on one-, two-, and three-year screening intervals. The first, and currently used method (PAP + PAP), is to annually screen women from age 18 to 69 with a PAP test. The PAP test can result in repeated tests, colposcopy and biopsy, and (depending on the results from the histological assessments) a conization procedure and hysterectomy. The second method (PAP + HPV + PAP) involved a process identical to the first, except in the case that the PAP test found atypical squamous cells of undetermined significance an HPV-DNA test is used to test for high-risk oncogenetic HPV. If the HPV-DNA test came back positive, women would be referred for colposcopy and biopsy. The third strategy (PAP + HPV + PAP-age) was identical to the second except that the HPV-DNA test was only administered to women aged 30 or older. The fourth strategy (LBC + HPV + LBC) was identical to the second expect that liquid-based	Twenty-one screening strategies, including the currently used one-year PAP + PAP method were analyzed in the model. Twelve strategies were found to be more effective than the currently used method. Some of the strategies came at a higher cost. Notably, the three-year PAP + HPV + PAP-age strategy was more effective and was found to save $16,078/ QALY gained. The one-year PAP + HPV + PAP-age provided benefit at a cost of $58,512/QALY gained. The one-year PAP + HPV + PAP was found to cost $82,266/QALY gained. The one-year LBC + HPV + LBC strategy was found to cost $127,076/QALY gained. The three-year PAP + HPV + PAP-age strategy was found to reduce overall costs by 4.2%. This reduction was due to reductions in physician and testing costs. The costs for inpatient and outpatient services rose for this strategy, but to a lesser extent than the other costs fell. This knowledge can help policymakers reallocate resources. The author suggested that based on their simulation four strategies are worthy of consideration. The PAP + HPV + PAP-age strategy was more effective and cost less than the current strategy. The following three strategies were more expensive than the current strategy, but deliver additional effectiveness: one-year PAP + HPV + PAP-age; one-year PAP + HPV + PAP; and one-year LBC + HPV + LBC. The three more expensive strategies may be desirable depending upon policymakers' threshold for the cost of improvements in QALYs. These three strategies exceeded the conventional cost-effectiveness threshold of $50,000/QALY gained.

Focus of study	Study characteristics	Sample description	Key features of the intervention(s)	Key findings
		consultations, outpatient procedures, and inpatient procedures.	cytology was used for routine screenings in place of PAP tests. The fifth strategy (LBC + HPV + LBC-age) was identical to the fourth except that the HPV-DNA test was only administered to women aged 30 or older. The sixth strategy (HPV + LBC + HPV/LBC) involved screening women with the HPV-DNA test. Those who are not found to have high-risk oncogenetic HPV are screened every three years unless results change. Those who test positive receive a liquid-based cytology triage test. If this test does not return a satisfactory specimen it is repeated every three months. If the results are negative women go back into the routine screening group. If atypical squamous cells, cannot exclude; atypical glandular cells; or high-grade squamous intraepithelial lesions are found, a colposcopy and biopsy are immediately ordered. If atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesions are found women are retested with the HPV-DNA and liquid-based cytology tests in six months. If both tests come back negative, women return to screening every three years. If high-risk oncogenetic HPV and a high-risk result from liquid-based cytology are found a colposcopy and biopsy are ordered. If high-risk oncogenetic HPV and a negative or lower-risk result from liquid-based cytology are found the	

Focus of study	Study characteristics	Sample description	Key features of the intervention(s)	Key findings
			HPV-DNA and liquid-based cytology tests are redone in six months (and this can be repeated up to three times). If the results are still unclear after repeating the tests three times a colposcopy and biopsy are ordered. The seventh strategy (HPV + LBC + HPV/LBC-age) is identical to the sixth except that only women aged 30 or older receive the HPV-DNA test as their primary screening. Younger women receive the liquid-based cytology test as their primary screening.	
Cost-effectiveness of high-risk HPV testing in Quebec (36)	*Publication date:* 2010 *Jurisdiction studied:* Quebec, Canada *Methods used:* Lifetime Markov Monte Carlo simulation model	The model followed group of 100,000 women beginning at age 13. The model was divided into monthly Markov cycles where transitions in health states could occur. The HPV prevalence rate was based off data from Quebec. The effectiveness of HPV and cytology tests is based off data from the Canadian Cervical Cancer Screening Trial. Costs were calculated from the perspective of a healthcare payer. Health utilities (in this case based on data from the WHO-CHOICE program) were used to calculate QALYs. Costs and health outcomes were	This model evaluated six distinct screening strategies. All strategies involved screening women with Pap smears until the age of 30. The first strategy involved no screenings of any kind after age 30. The second strategy (cytology) involved Pap smears every one-to-three years with follow-up screening for those with atypical squamous cells of undetermined significance. The third strategy (cytology + HPV triage) involved using conventional cytology every one to three years and employing high-risk HPV testing to triage cases of atypical squamous cells of undetermined significance. The fourth strategy (HPV only) involved using high-risk HPV testing every three years and employing colposcopy for any positive HPV results that emerge.	The model was validated by running simulations and comparing the results to values found in the literature. The model predicted that cytology screening would reduce the annual incidence of cervical cancer by 74% to 85% compared to no screening. HPV-based screening was predicted to reduce the annual incidence of cervical cancer by 87% to 89% when compared to no screening. The HPV-based primary screening strategies were found to dominate, and be less costly than, the cytology screening strategies. The HPV only strategy was found to be the most effective option. However, the HPV only strategy also resulted in the greatest colposcopy use rates. In sensitivity analysis, the ICERs were affected by changing the risk of progressing from HPV to cervical intraepithelial neoplasia, the progression rate of cervical cancer, and the cervical intraepithelial neoplasia 1 regression rate. The sensitivity of HPV and cytology testing also had an impact on the cost-effectiveness of the strategies. The authors concluded that strategies using HPV testing for primary screening are more effective than those using cytology for primary screening. However, the high false-positive rate for the HPV testing means that more women will be referred for colposcopy, increasing the costs for this resource. These costs are offset by savings elsewhere in the system. The HPV + cytology triage strategy was found to be more cost effective than the currently used cytology methods and required fewer colposcopies than the HPV only method.

Focus of study	Study characteristics	Sample description	Key features of the intervention(s)	Key findings
		discounted at 5% per year.	The fifth strategy (HPV + cytology triage) involved using high-risk HPV testing every three years and employing cytology for those with positive HPV results. The sixth strategy (co-screening) involved using both high-risk HPV testing and cytology every three years.	This model was limited because it did not incorporate the impact of HPV vaccination.
Assessing the cost-effectiveness of HPV vaccines in Canada (19)	*Publication date:* 2007 *Jurisdiction studied:* Canada *Methods used:* Cohort model	The model followed a cohort of 10-year-old girls through different cervical infection and disease states (susceptible, infected, immune, genital warts, CIN 1, CIN 2/3, cervical cancer) for four classes of HPV genotypes (HPV 16, HPV 18, Low Oncogenic Risk types and other High Oncogenic Risk types). Researchers assumed that there is no cross-protection between HPV type, that co-infection can occur, and that women can develop lifelong immunity following infection. The model also accounted for screening and treatment outcomes, meaning that women have an age-specific rate of screening and a lesion-specific test sensitivity of being detected. Researchers assumed that screening practice and compliance	Researchers conducted analyses from the perspectives of the ministry of health, which includes all direct medical costs. Future costs and outcomes were discounted at 3% per year over the lifetime of the target population. Researchers compared the quadrivalent (HPV types 6, 11, 16 and 18) and the bivalent (HPV types16 and18) vaccines to no vaccination, under conventional cytology-based screening rates in Canada. Base-case vaccine characteristics were assumed to be as follows: 1) the proportion of individuals protected following immunization (take) is 100%; 2) vaccine duration is lifelong; and 3) reduction in susceptibility to HPV types 6, 11, 16 and18 and HPV types 16 and 18 (vaccine efficacy) is 95%.	Under base-case assumptions, the model predicted that vaccinating a cohort of 100,000 girls aged 12 years against HPV types 6, 11, 16 and 18 would prevent 18,000 episodes of genital warts (0 without HPV types 6 and 11 in the vaccine), 20,000 CIN 1 (16,000 without HPV types 6 and 11), 13,000 CIN 2/3, 310 cervical cancer cases, and 140 cervical cancer deaths over their lifetime. This corresponded to lifetime risk reductions of 86% (0% without HPV types 6 and 11), 24% (19% without HPV types 6 and 11), 47%, and 62% for genital warts, CIN 1, CIN 2/3 and cervical cancer, respectively. The greatest gains in reduction of morbidity (as measured in terms of QALYs gained) were through the prevention of cervical cancer deaths and QALY life expectancy.

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		is unaffected by vaccination status.		
Examining the cost-effectiveness of introducing the quadrivalent HPV vaccine in France (18)	*Publication date:* 2008 *Jurisdiction studied:* France *Methods used:* Markov model	The model followed a group of females from 14 to 85 years of age through different health states, including the natural history of HPV infection, CIN, invasive cervical cancer, and genital warts. Movement between the health states was based on yearly transition probabilities. Women infected with HPV could return to a "well" state, suffer a persistent infection and progress to CIN 1, or in some cases, progress directly to CIN 2. They could also develop genital warts. It was assumed that the genital warts would be cured within the year and the woman would return to a "well" state. Women who developed CIN 1, CIN 2, or CIN 3 were at risk of developing cervical cancer. It was also assumed that women would return to the "well state" after treatment for their cervical lesions. As women with precancerous lesions are generally asymptomatic, the disease may not have	The model assumes a reduction of approximately 35% for CIN 1, 55% for CIN 2/3, 75% for cancer, and 90% for genital warts. This finding reflects the percentage of cervical cancer, CIN 1–3, and genital warts attributable to HPV types 6, 11, 16, and 18 based on data from the literature. This economic evaluation was done from two perspectives: 1) a direct healthcare cost perspective (DCP), which includes all direct medical costs linked to the vaccination and management of the diseases; and 2) a third-party payer perspective, which includes only direct costs reimbursed by the payers. Indirect costs such as loss of productivity are not considered in this model. The estimated costs associated with a screening program alone and a screening plus vaccination program were determined and presented as 2005 costs.	Results from this study showed that the predicted age-specific annual incidence of invasive cervical cancer in the French screened population was similar to the observed data in France. The model in this study predicted a lifetime cervical cancer risk of 0.94% and a lifetime cancer mortality risk of 0.22% for women undergoing cervical screening in France. With the introduction of a quadrivalent vaccine, that will protect against 75% of cervical cancers caused by HPV types 16 and 18, and 90% of genital wart cases. Alongside the screening program and assuming a vaccination coverage rate of 80%, these risks are decreased by approximately 65% to 0.33% and 0.08%, respectively.

Focus of study	Study characteristics	Sample description	Key features of the intervention(s)	Key findings
		been detected until the cancer became invasive.		
Examining the cost-effectiveness of HPV vaccine as a public-health intervention (20)	*Publication date:* 2008 *Jurisdiction studied:* Canada *Methods used:* Re-evaluation of a cost-effectiveness model using existing data	This study author chose to focus his analysis on the Brisson (2007) manuscript, a Canadian paper that is fairly representative of a common analysis for the HPV vaccine. The model compares a cohort of 100,000 12-year-old girls receiving the vaccine to a cohort of girls that do not receive the vaccine. Assumptions were made regarding the timing of expenditures and benefits and generally relied on a linear expenditure over time with some assumptions regarding the percentage of costs and benefits occurring early versus later in a subject's life cycle.	Using existing published data, this study author performed a re-evaluation of a cost-effectiveness model presented in a 2007 manuscript by Brisson et al. The analysis focused on model assumptions regarding time horizon, discount rate, and the disutility of genital warts.	Results from this study demonstrated the profound impact assumptions can have in economic modelling, particularly when the time horizon of the intervention is extended far into the future. The authors found that the Brisson (2007) manuscript was highly sensitive to several assumptions, in contrast to the majority of published papers that either choose not to report these analyses or to limit the range of values used. One of the findings of the paper, for example, highlights that if one takes a relatively conservative approach to several key assumptions, the ICER can quickly change from a value of $20,512 to $80,144 per QALY, and at the same time, from an attractive investment to one that is much lesser so. Policymakers should be cautious when making funding decisions that hinge on these key assumptions.
To evaluate the cost-effectiveness of a next generation nonvalent HPV vaccine in Australia (21)	*Publication date:* 2016 *Jurisdiction studied: Australia* *Methods used:* Policy1-Cervix and HPV-ADVISE dynamic models	The base case assumed a lifetime vaccine efficacy of 95% for girls and 85% for boys, when given two doses of the quadrivalent vaccine (HPV4). For Policy1-Cervix, the baseline set of cancers associated with HPV were based on the findings of the Australian Cervical Cancer Typing Study. This study found	The Policy1-Cervix model employed HPV testing for women aged 25-74. This included genotyping and direct referral to colposcopy for HPV types 16 and 18. Other high-risk HPV types were to be triaged with liquid-based cytology. This would be followed by immediate colposcopy for high-grade cytology cases and 12 months for other cases. Downstream management of cases	The models predicted that, compared to the current regime of two-yearly cytology testing, primary HPV screening (with the 2013 guidelines) will reduce lifetime risk of cervical cancer diagnosis by 18% and lifetime risk of cervical cancer death by 20%. Offering the quadrivalent vaccine were predicted to have an additional 54% reduction in diagnosis and a 53% reduction in death; the cohorts offered the nonvalent vaccine were predicted to have a further 11% reduction in diagnosis and death. If vaccine efficacy is predicted to be lower and three doses are required or if the efficacy last only 20 years (rather than for a lifetime), the risk reductions are slightly lowered. The effect of vaccines (both quadrivalent and nonvalent) was found to be greater when the cytology-based screening program is in place because this

Focus of study	Study characteristics	Sample description	Key features of the intervention(s)	Key findings
		that 76.6% of cervical cancers were due to HPV types 16 and 18, and 15.8% of cervical cancers were due to HPV types 31, 33, 45, 52, and 58. The Policy1-Cervix model, girls born in 2005 were followed to age 85. This cohort would be the first to receive the next generation nonvalent vaccine (HPV9), and they would be screened for HPV every five years. The model employed HPV testing for women aged 25-74. Screening attendance was based on findings from the Victorian Cervical Cytology Register. The HPV-ADVISE model also assumed five-yearly screening for HPV for women aged 25-74. Both models had a health services perspective and employed 2013 costs for screening, diagnostics, and treatment. A discount rate of 5% was employed. Two different QALY weight sets (one from an Australian study and one from a Canadian study) were used to evaluate cost-effectiveness. The	was based on the initial 2013 evaluation In the HPV-ADVISE model, the five-yearly HPV screening was followed by cytology triage for all HPV-positive women. The assumed management of HPV types 16 and 18 did not follow management pathways in the new screening program, but it was expected that the management of HPV types 31, 33, 45, 52, and 58 would have the more significant impact on cost-effectiveness.	program is less effective than HPV screening, so more disease exists to be prevented by vaccination. Furthermore, the 2016 clinical management guidelines are more effective than the 2013 clinical management guidelines, so the vaccines have more of an effect with the 2013 guidelines. When compared to cytology-based screening, primary HPV screening programme was found to reduce lifetime risk of precancer treatment by 10%. Adding a quadrivalent vaccine further reduces risk by 51% and offering cohorts the nonvalent vaccine further reduces risk of precancer treatment by 17%. The two models found that the maximum additional cost per dose of switching from the quadrivalent vaccine to the nonvalent vaccine ranged from $22.74 to $35.99 Australian dollars in the base-case (two-doses, lifelong efficacy, additional costs only for girls, and Canadian QALYs). The maximum cost per dose was found to be lower when three doses were required and when the vaccine only offered 20 years of protection. The maximum cost per dose was significantly lowered when the incremental cost of the nonvalent vaccine was applied to both boys and girls and when Australian QALYs were used. Sensitivity analysis found that the maximum additional cost per dose increased by $1 Australian dollar (for Canadian QALYs) and $5 Australian dollars (for Australian QALYs) when the nonvalent vaccine was evaluated in the current cytology-based screening regime. The maximum additional cost per dose was slightly increased when assuming 2016 clinical management guidelines instead of 2013 guidelines. The authors concluded that the nonvalent vaccine will be a cost-effective alternative to the quadrivalent vaccine if the additional cost per dose is less than $23 to $36 Australian dollars. This conclusion is based on assumptions of lifetime protection with two doses and that the additional costs of the nonvalent vaccine would only apply to girls.

Focus of study	Study characteristics	Sample description	Key features of the intervention(s)	Key findings
		Canadian set was used for the base-case. Policy1-Cervix was used to estimate lifetime risk of cancer, death, and the risk of cervical precancer treatment as a measure of screening-associated harms. Both models were used to calculate the maximum additional cost for switching from the quadrivalent vaccine to the nonvalent vaccine (in girls) so that the incremental cost-effectiveness ratio was less than $30,000 Australian dollars/QALY. It was assumed that the cost of both vaccines would be the same in boys in the base-case.		
To evaluate various cervical cancer screening strategies for effectiveness and cost-effectives with both vaccinated and unvaccinated cohorts (32)	*Publication date:* 2017 *Jurisdiction studied:* Australia *Methods used:* Combined dynamic model of HPV transmission and vaccination with a Markov model of cervical cancer progression	Australian data for demographics, health-economic factors, vaccine coverage, screening compliance, and costs were used in these models. The model worked with a simulated cohort of women from age 10 to age 84; there were cohorts with and without vaccination. All strategies were compared the National Cervical Screening Program standards at the time of publication (two-yearly	Six primary screening approaches were evaluated: 1) conventional cytology every three years for women aged 25 to 49 and every five years for those aged 50 to 64; 2) manually read liquid-based cytology every three years for women aged 25 to 49 and every five years for those aged 50 to 64; 3) image-read liquid-based cytology every three years for women aged 25 to 49 and every five years for those aged 50 to 64; 4) primary HPV testing every five years with liquid-based cytology triage for oncogenic HPV-positive women; 5) primary HPV screening every five years with partial genotyping for HPV types 16 and 18 and	Almost all of the modelled strategies were less costly, and many were more effective, than the comparator strategy. Conventional cytology-based strategies were cheaper but less effective than the comparator strategy. Strategies using liquid-based cytology may be more effective than the comparator strategy (depending on the assumptions of test characteristics) but often require HPV triage for some cases. Primary HPV screening strategies were found to be the most effective and least costly strategies. Some approaches were found to have an impact on the number of colposcopies performed. Without vaccination, primary HPV screening with partial genotyping and co-testing were found to result in the greatest rises in the number of colposcopies performed. Conversely, with vaccination, all strategies except co-testing were found to lower the number of colposcopies performed. All strategies were found to reduce the number of screening tests, follow-up tests, and precancer treatments (when compared to the base case). The most significant declines came from the HPV screening with partial genotyping (45-51% reduction in screening tests, 8-17% reduction in

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		conventional cytology for women aged 18 to 69 and no HPV triage testing). The strategies used in the model all commenced screening at age 25 and ended at age 64, but another trial was run modelling the impacts of ending screening at age 69. The outcomes of interest included health outcomes; costs; and resource use. The evaluation was conducted from a health services perspective, and a five percent discount rate was applied.	liquid-based cytology for other HPV types; and 6) testing with both liquid-based cytology and HPV screening every five years (co-testing). Several variations on standard clinical management algorithms were also evaluated. These variations included the following: 1) alternate management for women with HPV types other than 16 and 18 and cytology findings that found low-grade squamous cells of undetermined risk; 2) a call and recall invitation with a reminder system which was compared with a reminder system to assess the impact on screening adherence; 3) initiation of screening with fast uptake (invitation sent on 25th birthday) was compared to slower uptake (no invitation); and 4) the impact of an exit HPV test at the end of the screening age interval which would be followed with aggressive management for HPV-positive women. In total, 132 screening strategies were tested.	treatments for unvaccinated cohorts, 16-29% reduction is treatments for vaccinated cohorts). Several strategies were found to increase the relative distribution of treatments for cervical intraepithelial neoplasia grade 3, due to decreases in treatment for cervical intraepithelial neoplasia grade 2. Strategies that encouraged fast uptake by sending invitations at age 25 were found to reduce mortality by one to three percent compared to the same strategies without invitation. Immediate follow-up for women with positive triage results was found to be more effective than a 12-month follow-up, but this effect was smaller for primary HPV screening strategies with partial genotyping. Ending screening at age 69 was found to reduce cancer mortality by five to eight percent, when compared to ending screening at age 64. Extending screening to age 69 with a primary HPV testing and partial genotyping strategy was found to reduce incidence and mortality by 13-23% compared to the comparator strategy. A six-year screening interval for primary HPV screening strategies was found to increase incidence and mortality by approximately three to four percent compared to strategies with a five-year interval. The six-year interval was also found to reduce costs by eight to ten percent compared to a five-year interval. A five-yearly primary HPV screening strategy with partial genotyping for women aged 25 to 69, an exit test between ages 70 and 74, and liquid-based cytology for women with HPV other than type 16 and 18, along with updated clinical management, was found to reduce long-term incidence and mortality by 31 to 36% compared the comparator strategy for unvaccinated cohorts. The result was a 24 to 29% reduction in incidence and mortality for vaccinated cohorts. Overall, the authors found that primary HPV screening with partial genotyping for women aged 25 to 64, and an exit HPV test between ages 70 and 74, was a very effective strategy and less costly than the current strategy. The HPV screening with partial genotyping strategy was found to reduce cervical cancer mortality by 13-22% compared to the current strategy. The model's findings are sensitive to several assumptions about adherence, screening behaviour, and test characteristics, among other factors. Furthermore, the model did not account for cross-protection for HPV types not targeted by the vaccine. The predicted cost-savings may also be overestimated if the predicted fall in primary care visits is not realized.

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