

Appendix 19: Cervical cancer: evidence review for newly arriving immigrants and refugees

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ABSTRACT

Background: Each year 250 000 deaths worldwide are related to cervical cancer. In developed countries, women who have not been adequately screened account for 60%–90% of cases involving invasive cervical cancer. We conducted an evidence review to determine the burden of cervical cancer among immigrant women, to evaluate the effectiveness of vaccination against human papillomavirus (HPV) and cervical cytology screening, and to identify barriers and facilitators to implementation in primary care.

Methods: We systematically assessed evidence on vaccination against HPV and screening for cervical abnormalities: benefits and harms, applicability, clinical considerations and implementation. We assessed quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation approach.

Results: Subgroups of immigrant and refugee women have a higher risk of cervical cancer because of lower screening rates (e.g. women from Asia) and higher rates of HPV infection (e.g. women from Africa and Latin America). Vaccination against HPV is effective for reducing morbidity from cervical cancer. Evidence shows that cervical cytology screening reduces morbidity and mortality. Limited knowledge of cancer prevention, language barriers, culture and sex preferences, and (particularly with refugees) a possible history of sexual assault can decrease acceptance of gynecologic examination. Understanding the benefits of screening, dedicated appointments and availability of female practitioners improve cervical screening rates.

Interpretation: Immigrant and refugee women are at risk of cervical cancer primarily owing to lower cervical screening rates. Efforts to vaccinate against HPV and improve cervical screening rates could reduce the incidence of cervical cancer.

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The case

Pa Mae is a 26-year-old non-English-speaking Karen woman who spent the last 12 years in a refugee camp on the Thai-Myanmar border. She has two daughters and a son and visits your clinic to have their TdP and MMR vaccines so they can attend school. She also expresses interest in discussing preventive care for herself.

How would you approach this patient?

Introduction

Cervical cancer is one of the most preventable forms of cancer, yet high mortality from cervical cancer persists among socially disadvantaged groups.¹⁻³ The introduction of cervical cancer screening programs is associated with dramatic decreases in morbidity and mortality from cervical cancer in developed countries.⁴⁻⁶

In Canada, more than 50% of immigrant women over the past three decades have originated from developing countries⁷ where cervical screening and vaccination against HPV are often unavailable. Several Canadian studies have documented lower rates of screening among immigrants and refugees.⁸⁻¹¹ Recent data from the Canadian Human Mortality Database (2000–2002)¹² suggest a high mortality rate from cervical cancer in foreign-born women. We reviewed the evidence to identify the burden of cervical cancer among immigrant and refugee women and to search for evidence that vaccination against HPV and cervical cytology screening for sexually active adolescents and women is effective. We also examined implementation issues related to cervical screening in immigrant and refugee women. Recommendations on screening for cervical cancer from the Canadian Collaboration for Immigrant and Refugee Health (CCIRH) are found in Box 1.

Methods

We used the 14-step method developed by the CCIRH.¹³ We constructed a clinician summary table to highlight the epidemiology relevant for immigrants and refugees, and potential clinical actions (Appendix 3). We then constructed a logic model to define the clinical preventive action, outcomes and key questions.

Search strategy for systematic reviews, guidelines and population-specific literature

We designed a search strategy in consultation with a librarian-scientist to identify relevant English-language systematic reviews and guidelines from electronic

Box 1: Recommendations on cervical cancer from Canadian Collaboration for Immigrant and Refugee Health

Vaccination against human papillomavirus (HPV):

Recommend vaccination against HPV to 9- to 26-year-old female patients.

Basis of recommendation

- **Balance of benefits and harms:** Vaccination against HPV prevented invasive changes related to cervical cancer (number needed to vaccinate [NNV] 139; 95% confidence interval [CI] 117–180) in studies with a duration of 15–48 months. Access to cytology screening is often limited among immigrant women and prevalence of HPV infection is higher in developing countries. Potential harms include anaphylaxis which is amendable to treatment, which occurs in fewer than one in 100 000 doses.
- **Quality of evidence:** Moderate
- **Values and preferences:** The Guideline Committee attributed more value to preventing cervical cancer and less value to current uncertainty of long-term effect on cancer deaths.

Cervical cytology screening:

Screen sexually active women for cervical abnormalities (Papanicolaou test) to detect and treat invasive changes.

Basis of recommendation

- **Balance of benefits and harms:** Identifying and treating early cervical cancer reduces mortality. The number needed to screen (NNS) to prevent one death from cervical cancer is 3497 (95% CI 2361–90 909). The rate of cytology screening is lower in immigrant women (40%–60%) than in Canadian-born women (60%–80%). Harms are minimal and depend on the course of treatment.
- **Quality of evidence:** Low
- **Values and preferences:** The Guideline Committee attributed more value to preventing cervical cancer and less value to uncertainty of size of effect and burden of screening on health services.

databases (MEDLINE, CINAHL, Embase and Cochrane Database of Systematic Reviews) and from hand-searching the website of the National Guideline Clearinghouse (www.guideline.gov/), the Public Health Agency of Canada (www.phac-aspc.gc.ca, including the National Advisory Committee on Immunization: www.phac-aspc.gc.ca/naci-ccni), the Canadian Cancer Society (www.cancer.ca), the United States Preventive Services Task Force (www.ahrq.gov/clinic/USpstfix.htm), the Canadian Task Force on Preventive Health Care

(www.canadiantaskforce.ca/), and the World Health Organization (www.who.int/en/) from January 1996 to September 2007. Two reviewers screened eligible systematic reviews for relevance to the benefits and harms of HPV vaccination and cervical cytology screening and treatment approaches. We appraised eligible systematic reviews using the critical appraisal tool of the United Kingdom's National Institute for Health and Clinical Evidence (NICE) to assess systematicity (the review must apply a consistent and comprehensive approach), transparency, quality of methods and relevant guidelines using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument. Using the same electronic databases, we conducted a second literature search to identify relevant and up-to-date clinical trials and cohort studies to supplement and verify consistency of evidence from the systematic reviews from 1980 to January 2008. Studies were included if the study design was a controlled clinical trial or cohort study that was relevant to our questions.

Using the same databases, we conducted a third literature search for cervical cancer and immigrant and refugee populations from 1996 to September 2007, categorized as baseline risk or prevalence; risk of clinically important outcomes; genetic and cultural factors (e.g., preferences, values, knowledge); and compliance variation. An updating search, focusing on randomized controlled trials and systematic reviews during the period of Jan. 1, 2007 to Jan. 1, 2010, was conducted to determine whether any recent publications would change the position of the recommendation.

Synthesis of evidence and values

We compiled evidence from systematic reviews and pertinent cohort and clinical trials using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) summary of findings table. We also appraised quality of evidence for each outcome using the GRADE quality-assessment tool, which assesses study limitations, directness, precision, consistency, and publication bias across all studies (Box 2). In the synthesis of data on clinical considerations, we identified both clinically relevant considerations and implementation issues. Finally, we identified gaps in the evidence base.

Results

The initial search found no systematic reviews or guidelines specifically focused on immigrants or refugees. However, the search for reviews for the general population and cervical cancer prevention identified 934

titles. We identified 13 relevant systematic reviews and, after critical appraisal, retained a pool of eight key systematic reviews and guidelines (Appendix 2).^{15–22} We selected the McLachlin and colleagues¹⁶ and US Preventive Services Task Force (2002)¹⁵ systematic reviews as the most up-to-date systematic reviews providing evidence for cervical cancer screening and the Rambout and coauthors¹⁸ systematic review on vaccination against HPV. Our supplementary search for new and pertinent cohort studies identified four cohort studies relating to cervical cytology screening.^{23–26} A related study⁵ provided historical time trend mortality data related to cervical cancer screening programs in Nordic countries. Finally, we identified one additional study reporting on the adverse events from HPV vaccination in Australia²⁷ and one meta-analysis reporting adverse pregnancy outcomes associated with treatment of cervical dysplasia²² (Appendix 1).

We retrieved 104 articles from the general immigrant and cervical cancer search that addressed several areas: epidemiology, screening, knowledge and compliance, treatment, or vaccination in the migrant population.

What is the burden of cervical cancer in immigrant populations?

Recent data from the Canadian Human Mortality Database¹² (non-age-standardized) showed foreign-born women had 1.4 times higher cervical cancer mortality rates than Canadian-born women (2000–2002). In the US, the incidence of cervical cancer in Vietnamese-American women has been estimated at five times the incidence in white American women (incidence rate 43/100 000 v. 8.7/100 000).^{28,29} A study of cervical mortality from the US Center for Disease Control and Prevention found foreign-born Hispanic women had 4 times higher mortality from cervical cancer compared with white women living in California between 1985 and 1996.³⁰ The Public Health Agency of Canada linked a sample of immigrants arriving to Canada (1980–1990) with cancer incidence data for the period (1980–1998) to compare incidence rates to the general Canadian population using indirectly age-standardized rate ratios. This study, in contrast to studies discussed above, found that foreign-born women had lower incidence rates of cervical cancer relative to Canadian-born women. Rates among refugee women and Canadian-born women were similar; however, older refugee women had higher rates of cervical cancer than Canadian-born women.³¹ The limitation of this study is that it does not capture cancer rates from recent immigrants.

Women who have never had cervical screening, or have not had cervical screening in the previous five years,

account for 60%–90% of invasive cervical cancers overall.²¹ Also, several cross-sectional Canadian studies have documented lower rates of screening among immigrant populations.^{8-11,32} Foreign-born women aged 25–64, especially those born in Asia, are at higher risk of having never had a Papanicolaou test (odds ratio 10.8).^{8,33} Data showed 25%–38% of foreign-born women in Canada report never having had a Pap test¹¹ and other data confirm immigrant women with Asian backgrounds have the lowest screening rates.³⁴ Once in Canada, language barriers, competing demands, and cultural and sex preferences are associated with decreased screening rates.^{35,36}

Many immigrant women have a higher fertility rate³⁷ relating to cultural norms, a risk factor for cervical cancer. Subgroups of immigrant and refugee women face higher prevalence of HIV (another risk factor).³⁷ It has been estimated that HIV-seropositive women are five times as likely to be infected with HPV and have a five-fold risk of cervical intraepithelial neoplasia.³⁸

Infection with HPV is strongly associated with cervical cancer.³⁹ Infection with HPV is common (75% lifetime prevalence) and can be acquired even if it is the first relationship involving sexual intercourse for both partners.⁴⁰ Prevalence is highest in developing countries; prevalence estimates are particularly high for Africa

Table 1: Summary of findings table on prophylactic HPV vaccination against cervical cancer in women

Patient or population: Women 15–25 yr not previously infected with HPV (diverse ethnic backgrounds)

Setting: multinational, primarily North America, Latin America, Asia Pacific and Europe

Intervention: HPV vaccination

Comparison: Placebo or “no HPV vaccination”

Source: Rabout L, Hopkins L, Hutton B, et al. Prophylactic vaccination against human papillomavirus infection and disease in women: a systematic review of randomized controlled trials. *CMAJ* 2007;177:469-79.

Outcomes	Absolute effect		Relative effect (95% CI)	No. of participants (studies)	GRADE quality of evidence	Comments
	Risk for placebo or no vaccination group	Risk for vaccination group (95% CI)				
High-grade cervical lesion	15 per 1000	7 fewer per 1000 (8.5 fewer per 1000 to 5.5 fewer per 1000)	0.52 (0.43–0.63)	36 266 (5)	Moderate	NNT 139 (95% CI 117–180)
Persistent HPV infection, 12 mo	16 per 1000	12 fewer per 1000 0.0041 (From 14 fewer per 1000 to 10 fewer per 1000)	0.26 (0.16–0.41)	7774 (2)	Moderate	NNT 84 (95% CI 74–106)
≥ 1 serious adverse event*	22 per 1000	0 more per 1000 (2 fewer per 1000 to 4 more per 1000)	1.00 (0.87–1.14)	39 609 (6)	Moderate	Two trials did not report allocation concealment
Death from adverse events	60 per 100 000	6 fewer per 100 000 (37 fewer per 100 000 to 70 more per 100 000)	0.91 (0.39–2.14)	36 783 (4)	Moderate	Two trials did not report allocation concealment
Death from cervical cancer	No data	No data	No data	No data	N/A	No data available for this outcome

Note: CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HPV = human papillomavirus; N/A = not applicable; NNT = number needed to treat; RR = relative risk.

*Serious adverse events: bronchospasm, gastroenteritis, headache, hypertension, pain at injection site or impaired joint movement in injected limb.

(22.1%; 95% CI 20.9%–23.4%) and Central America (20.4%; 95% CI 19.3%–21.4%).^{41,42} Human papillomavirus genotype 16 is the main contributor to infections worldwide, while genotype 52 predominates in eastern Africa. The second most common genotype in western Africa is 58, in South America is 31, and in southeastern Asia is 18.

Does vaccination against HPV decrease morbidity and mortality?

Relative benefits and harms of vaccination

A recent systematic review (six randomized controlled trials), showed reduction of high-grade cervical cancer lesions (relative effect 0.52; 95% CI 0.43–0.63), with no serious adverse events: bronchospasm, gastroenteritis, headache, hypertension, pain at injection site or impaired joint movement in injected limb).¹⁸ We downgraded the quality of this evidence to moderate due to indirectness,

since high-grade cervical lesions are considered surrogate outcomes for cervical cancer mortality.^{43,44} We found no data for cervical cancer mortality. We found no published data for anaphylactic shock from these randomized controlled trials, but there were fewer than 15 anaphylactic events in a longitudinal study of more than one million doses of HPV among women in Australia²⁷; this adverse reaction occurred within 15 minutes of vaccination and was amenable to treatment. We summarize these findings in Table 1.

Does cervical cancer cytology screening and treatment decrease morbidity and mortality?

Screening

Cytologic changes at the transformation zone of the cervix can detect cervical precancer as well as cancer in an early state. Ninety-two per cent of women will survive five years when cervical cancer is localized, but only 13%

Table 2: Summary of findings table on organized screening program compared with opportunistic screening for preventing cervical cancer

Patient or population: Sexually active women, target group for preventing cervical cancer Setting: UK primary care ²⁴ ; Wales primary care ²⁵ Intervention: Organized screening program (invitation letters, practice-based incentives to improve screening rates) Comparison: Opportunistic screening (screening recommended by practitioner without additional program aids) Sources: Quinn M, Babb P, Jones J, et al. Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. <i>BMJ</i> 1999;318:904-8. Rieck GC, Tristram A, Hauke A, et al. Cervical screening in 20–24 year olds. <i>J Med Screen</i> 2006;13:64-71.						
	Absolute effect in medium-risk population					
Outcomes	Before implementing cytology	Screening + recall	Relative effect(95% CI)	No. of participants (studies)	GRADE quality of evidence	Comments
Cervical cancer rates table 5, cervical cancer ²⁵			RR 0.48 (0.23–0.98)	400 000 (1)	Low	NNT 17 483 (95% CI 11 806–454 545)
	11 per 100 000	5 fewer per 100 000(8.5 fewer per 100 000 – 0 fewer per 100 000)				
Invasive cancer invasive cervical cancer ²⁴			RR 0.67 (0.30–1.48)	200 000 (1)	Very low	NNT 20 202 (NS)
	15 per 100 000	5 fewer per 100 000(11.5 fewer per 100 000– to 7 more per 100 000)				
Death from cervical cancer (surveillance) table 6, mortality ²⁵			RR 0.38 (0.10–1.41)	400 000 (1)	Very low	NNT 40 323 (NS)
	4 per 100 000	3 fewer per 100 000(3,6 fewer per 100 000 to 1.6 more per 100 000)				

Note: CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; NNT = number needed to treat; NS = not statistically significant; RR = relative risk.

will survive distant disease;^{15,45} overall age-standardized mortality ratio in North America for 2002 was 2.3/100 000.⁴⁶ Cervical cytology testing (liquid-based or conventional) is 60%–80% sensitive for high-grade lesions and 98% specific.¹⁶ Identifying cervical cancer using testing for HPV DNA is more sensitive but less specific than cervical cytology⁴⁷; however, several randomized controlled trials continue to investigate the effectiveness of this new technology for identifying cervical precancer. Introduction of screening programs to populations naïve to screening reduces cervical cancer rates by 60%–90% within three years of implementation.^{48,49} No randomized controlled trials of cervical screening programs have ever been conducted; however, correlational studies from the Nordic countries^{5,50} and British Columbia⁵¹ have demonstrated 55%–80% reductions in cervical cancer incidence with screening programs, and greater reductions associated with higher screening coverage.^{5,52} Key factors that improve the effectiveness of programs include high participation rate, quality control in smear interpretation, reliable follow-up for abnormal results and facilities for adequate treatment.⁵³

Relative benefits and harms of screening and treatment programs

For cervical cancer screening and treatment programs, we found two large-scale observational studies^{24,25} and two systematic reviews.^{15,16} Two studies considered data from England and Wales before and after implementing organized cervical screening programs.^{24,25} These screening programs used invitation and reminder letters and practitioner incentives to increase screening rates from 61% to 83% of the population. In Canada, comparable organized program initiatives are being implemented in several provinces. Data from Rieck and coworkers²⁵ showed a reduction in cervical cancer (RR 0.48; 95% CI 0.23–0.98) (Table 2). Adverse effects resulting from referral for colposcopy include anxiety over pain and discomfort,⁵⁴ difficulties with life insurance and worries about reproduction and psychosocial trauma. However, no data quantifying these adverse effects was found. Perinatal mortality and adverse pregnancy outcomes have also emerged as a rare though important harm in treatment of cervical intraepithelial neoplasia; however, the quality of this evidence remains very low.²² These harms are most relevant in relation to women younger than 25 whose early cervical changes can regress to normal.⁵⁵ In conclusion, we found low-quality but consistent evidence that cervical cancer screening programs can reduce morbidity and mortality and summarize this evidence in Table 2.

Clinical considerations

Are immigrants screened for cervical cancer or vaccinated against HPV during migration?

All immigrants arriving in Canada undergo the Citizenship and Immigration Canada Immigration Medical Examination.⁵⁶ Screening for cervical cancer is not routinely included in the examination, and vaccination against HPV is not offered.

How can we facilitate cervical screening and vaccination against HPV?

Preventive health care and screening programs will be a new concept for many immigrant women. In addition, structural barriers often limit access to preventive care for women new to Canada. Language proficiency, housing, employment and educational needs, transportation difficulties, child care and knowledge of preventative health care are important determinants of screening rates in immigrant and refugee women.⁵⁷⁻⁵⁹ Also, male physicians might be disinclined to provide cervical screening out of respect for a patient's modesty⁶⁰ or reluctant to refer women to female physicians out of fear of losing patients.⁶¹ Yet initiating a pelvic examination can build rapport, increase comfort, respect patients' modesty and empower patients with simple nonmedical language.⁶²

Acceptance of the HPV vaccine has been associated with personal beliefs and attitudes about the vaccine, perceived risk of HPV infection, knowledge about cervical cancer and knowledge about the vaccine. Women who perceive their risk of HPV infection as high are more accepting of HPV vaccination.⁶³ Other factors influencing acceptance of HPV vaccine include perceived efficacy of the vaccine and physicians' recommendation of vaccination. The most common barrier to vaccine acceptance is cost. Evidence demonstrating the acceptability of vaccination to those at highest risk for cervical cancer (including ethnic minorities) is limited.⁶³ In most provinces and territories in Canada, the HPV vaccine is publicly funded only for girls through a school-based immunization program with no catch-up vaccination provision for newly arriving older immigrant girls.

Women who have been victims of sexual trauma are at higher risk for HPV infection and cervical cancer.¹⁷ Refugee women in particular are disproportionately victims of sexual and sex-based violence,⁶⁴ which can include rape, domestic violence and female genital mutilation. Exposure to sexual violence often goes unreported because of shame or stigma associated with

loss of virginity,⁶⁴ fear of retaliation (especially if the offender is someone from the same community or culture), and fear of being shunned by family members.⁶⁵ These assertions are supported by a case-control study of an ethnically diverse group of American women demonstrating a much lower rate of cervical screening in women who were victims of childhood abuse.⁶⁶

Before screening for cervical cancer, practitioners should develop rapport with women who have been victims of sexual violence. This can take several visits. Abuse can continue or increase after arriving in Canada because of additional stresses related to moving to a new country,⁶⁷ so it is important to take time to listen to patients' stories to develop trust.

Initiation and cessation of screening: McLachlin and colleagues¹⁶ present evidence from an observation study that supports initiation of cervical cytology screening within three years of first vaginal sexual activity and supports discontinued screening after age 70 if a woman has received three or more normal cytology tests in the previous 10 years, as long as she has no new sexual partners.

Screening interval: The review by McLachlin and coauthors¹⁶ presents cross-sectional and case-control evidence for annual screening until a woman has received negative results from three consecutive Pap tests and for continued screening every two to three years after negative results from three annual Pap tests, as long as she and her partner have no new sexual partners.

Women who have undergone hysterectomy: McLachlin and coworkers¹⁶ conclude that women who have undergone subtotal hysterectomy (with an intact cervix) should continue screening according to the routine guidelines. Screening can be discontinued in women who have undergone total hysterectomy for benign causes with no history of cervical dysplasia or HPV infection.

Pregnant women: The review by McLachlin and colleagues¹⁶ provides observational evidence and concludes that screening frequency for pregnant women should be the same as for women who are not pregnant. We find no evidence to suggest modifications for immigrant and refugee women.

What are potential implementation issues?

Immigrant women often have little knowledge and many misconceptions of the benefits of screening and early detection of cervical cancer.⁶⁰ Women might fear the test itself or fear a diagnosis of cervical cancer, which could result in painful treatments and an increased burden to families.^{60,68}

Immigrant women often hold strong cultural and religious values related to sexuality and sexual health practices. Many cultures are very private regarding sexuality,⁶⁹ leaving women reluctant to ask for cervical screening.^{58,61,69,70} In addition, some women feel uncomfortable undressing in front of a stranger.^{58,60} Several studies conducted in immigrant populations in Canada and the US have documented that patients prefer female practitioners, especially female Muslim patients,^{58,60,71} and some also prefer a caregiver from the same culture.⁵⁹

Family sex roles can limit a women's decision-making power. Women can be reluctant to disclose private information or undergo pelvic examination if a male family member is present.⁵⁸ Women who hold strong values and attitudes of their country of origin are less likely to go for screening, regardless of length of residence.^{59,69,72} Inability to communicate because of language barriers^{73,74} and poor access to educational materials⁷⁰ further limit health-seeking behaviour. Immigrant and refugee women sometimes have little or no formal education, with limited capacity to understand even very simple health information required to make informed health decisions.^{61,70,75} Newcomers are also unfamiliar with society's health care structure⁷⁶ and often prefer to seek and share reproductive health information through their own social networks. Mainstream risk communication messages might be insufficient to increase immigrant women's uptake of cervical screening. Evidence suggests a potential role for immigrant community health workers and other community interventions relaying relevant information and offering transport, female physicians and interpreters in informal clinic settings.²⁹

Recommendations from other groups

The Canadian Immunization Committee has recommended vaccination of Canadian female patients against HPV types 16 and 18.⁷⁷ To increase immunization coverage to 80%–90%, the committee recommends school vaccination with programmatic options commencing in grade 4, 5, 6, 7 or 8. The Society of Obstetricians and Gynaecologists of Canada⁷⁸ and the Ontario cervical screening program,¹⁶ US Preventive Services Task Force,⁴ Canadian Task Force for Preventive Care,⁷⁹ and the American College of Obstetricians and Gynecologists⁸⁰ all recommend cervical cytology screening programs for sexually active adolescents and women. The International Agency for Research on Cancer recommends cervical screening for

women 25–65 years and suggests a three-year screening interval can be considered in countries with adequate resources.¹ The European recommendations⁸¹ suggest screening commence between 20–30 years of age until at least 60 years of age and discourage opportunistic screening, citing low screening rates with this method for women with low socio-economic status.

The case revisited

Pa Mae has never had a Pap test. Given the language barrier, it will be important to involve a qualified interpreter, provide the option of a female practitioner, use visual teaching aids and normalize the Pap; for example, explain that this examination is for all women, that there is no cost to her, that it is for prevention, that it is quick, that she does not need to be afraid. It will be important to obtain an address for follow-up. She is still in the ideal age group for HPV vaccination, which should be offered with explanation of benefits and risks. Her children will also be candidates for HPV immunization in the near future.

Conclusion and research needs

Benefits of cervical screening are most pronounced in women who have never been screened before, which is often the case with newly arriving immigrants and refugees. Future morbidity and mortality rate analysis should consider ethnic and immigrant characteristics and immunization against HPV to allow monitoring of the burden of cervical cancer and provide a better indication of baseline risks for immigrant subgroups. Cervical cytology screening in immigrant and refugee women could be improved with organized screening programs that address language, sex preferences and knowledge limitations. Community mediators have been effective in diabetes programs⁸² and in observational studies of cervical cytology screening programs, but more research is needed to implement and evaluate such special strategies in the context of local screening programs.

Key points

- Vaccination against HPV is recommended for 9- to 26-year-old female patients to reduce invasive changes related to cervical cancer.
- All sexually active women should be screened for cervical abnormalities (with Papanicolaou smear) to detect and treat invasive changes.
- Providing clear information about cervical screening, building rapport and offering access to a female practitioner improves acceptance of Pap tests.

- Immigrant girls might miss out on school vaccination programs depending on their age upon arrival in Canada.

Box 2: Grading of Recommendations Assessment, Development and Evaluation Working Group grades of evidence (www.gradeworkinggroup.org)

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and could change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

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Clinical preventive guidelines for newly arrived immigrants and refugees

This document provides the review details for the CMAJ CCIHR Cervical Cancer paper. The series was developed by the Canadian Collaboration for Immigrant and Refugee Health and published at www.cmaj.ca.

Appendix 1: Figure 1

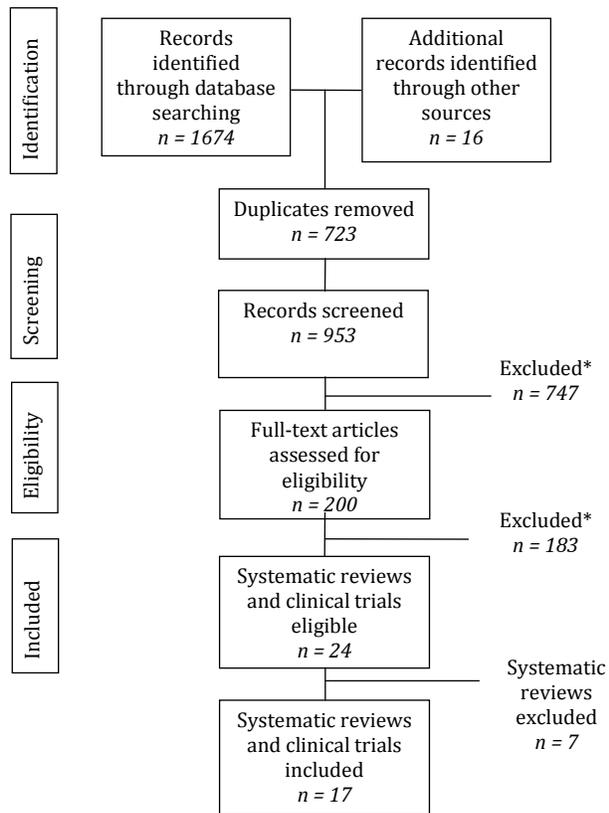


Figure 1: Search and selection of data on screening for cervical cancer. *Low quality or lack of national sample, availability of more recent data or lack of relevance to immigrant health status

Appendix 2: Characteristics of systematic reviews or guidelines related to screening for cervical cancer or vaccination against HPV virus

Author and Year	Objective	Number and Type of studies included	Participants	Intervention	Findings
Agency for Healthcare Research and Quality, 2002 ¹⁴	A systematic evidence review of benefits and harms of screening among older women (age 65 and older) and those who have had hysterectomies, and to examine the diagnostic performance of new technologies and human papillomavirus (HPV) testing for detecting cervical lesions.	12 studies included in review of benefits and harms of screening among older women (age 65 and older) and those who have had hysterectomies. Study designs included retrospective cohorts, prospective cohorts, one population-based cross-sectional study, one nested case control study, and one case series study. Inclusion criteria: participants were women over age 50, data presented stratified by age or in sub-analyses that compared older to younger women, and denominators for outcomes known. Databases searched from December 1999.	Women age 50 and older or who have had a hysterectomy	Screening programs, including: annual advised screening, spontaneous screening program with centralized follow-up of abnormal Paps, advised screening every 2 years after a negative pap, call and recall system for screening recommended every 3 years	Risk of high-grade cervical lesions falls with age, especially among those with prior normal screening results. Recommends against routine Pap smear screening in women who have had a total hysterectomy for benign disease. Results should be interpreted with caution as none of the studies evaluate outcomes in women who did not receive screening after a designated age, and none are experimental in design.
McLachlin et al, 2005 ¹⁵	To develop clinical practice guidelines for cervical screening and the primary management of abnormal cytology in Ontario, using an established methodological process.	Seven practice guidelines, six technology assessments, one meeting press release, one systematic review, three randomized controlled trials, one meta-analysis, eight cross-sectional studies, one prospective cohort study, four case-control studies, seven retrospective studies, and one conference report form.	Women who are, or ever have been, sexually active	Screening programs, including organized and spontaneous screening programs.	Recommendations: Initiation of cervical cytology screening within three years of first vaginal sexual activity. Screening should be done annually until there are three consecutive negative Pap tests, and should continue every two to three years thereafter. Women who have not been screened in more than five years should be screened annually until there are three consecutive negative Pap tests. Discontinue screening at age 70 if adequate negative screening history in past 10 years Immuno-compromised women should received annual screening Screening can be discontinued in women who have undergone total hysterectomy for benign causes with no history of cervical dysplasia or HPV. Women who have undergone subtotal

					hysterectomy (with an intact cervix) should continue screening according to the guidelines.
Saslow et al, 2002 ¹⁶	To update the American Cancer Society guideline regarding screening for the early detection of cervical neoplasia and cancer	Not specified	Girls, aged 10-19 years. Women 19 and older, including immunosuppressed and/or HIV positive women, women who have undergone total and subtotal hysterectomy	Cervical Cytologic screening	50-80% low –grade squamous intraepithelial lesions in adult women regress (21 years and older), 90% of LSIL in young women (13-21) will regress. Low efficiency of cytological screening in women over 50 Very low prevalence of abnormal cytologic smears in women who had a hysterectomy for benign disease, and low incidence of abnormal cytologic smears at two years after hysterectomy for CIN (0.7 per 1000). Compared to annual screening relative risks with a two year or three year screening interval range from 1-2 and 2-3, respectively.
Rambout et al, 2007 ¹⁷	To determine whether women who receive prophylactic HPV vaccination have a lower incidence of persistent HPV infection and precancerous cervical lesions than women who are not vaccinated.	Six studies, randomized control trials	40323 women were enrolled in the 6 studies. Ages ranged from 15 to 25 years	Prophylactic HPV vaccination against at least one oncogenic strain of the virus.	Prophylactic HPV vaccination associated with reduction in the frequency of high-grade cervical lesions caused by vaccine-type HPV strains compared with control groups.
Markowitz et al, 2007 ¹⁸	To provide recommendations for the use of a quadrivalent HPV vaccine among females aged 9-26 in the United States	A total of ten efficacy studies	Females aged 9-26 years.	Prophylactic HPV vaccination against at least one oncogenic strain of the virus.	Quadrivalent HPV vaccine has a high efficacy in preventing persistent HPV infection, cervical cancer precursor lesions, vaginal and vulvar cancer precursor lesions, and genital warts caused by HPV types 6, 11, 16, or 18 among females who not already been infected with the respective HPV type.
Barr and Tamms,	Reviews the efficacy of prophylactic	4 randomized, double-blind, placebo-controlled studies	Females from developed and	Prophylactic HPV vaccination against at least	Prophylactic vaccination of women was 96-100% effective HPV6/11/16/18-related cervical cancer

2007 ¹⁹ (N.B.: This review was funded entirely by MERCK)	vaccination of young women in preventing HPV 6/11/16/18-related cervical and anogenital precancers and genital warts.		developing countries, ages 16-26	one oncogenic strain of the virus.	and anogenital precancers and genital warts Efficacy remained high for at least 5 years following vaccination
Saslow et al, 2007 American Cancer Society ²⁰	To develop recommendations on the use of prophylactic HPV vaccines, including who should be vaccinated and at what age.	Not specified	Girls and women ages 9-26	Prophylactic PHV vaccination against at least one oncogenic strain of the virus.	Recommends routine HPV vaccination for females aged 11 to 12 years, females as young as 9 may receive HPV vaccination HPV vaccination is also recommended for females aged 13 to 18 years to catch up missed vaccine or complete the vaccination series. Insufficient data to recommend for or against universal vaccination for females aged 19 to 26 years in general population Vaccination not recommended for women over the age of 26 and males Screening for CIN and cervical cancer should continue for vaccinated and unvaccinated women.
Arbyn et al 2008 ²²	To assess the relative risk of perinatal mortality, severe preterm delivery, and low birthweight associated with previous treatment for precursors of cervical cancer.	19 retrospective cohort studies and one prospective cohort study	Women whom became pregnant after treatment for cervical intraepithelial neoplasia	Previous treatment for CIN (Cold knife conisation, laser conisation, large loop excision, cryotherapy, diathermy, laser ablation)	Cold knife conisation and radical diathermy are associated with increase risk of perinatal mortality, severe preterm delivery, and extreme low birthweight infants. Loop excision is associated with mild obstetric morbidity.

Appendix 3: Cervical Cancer Evidence Based Clinician Summary Table

Vaccination Against Human Papillomavirus (HPV)

Recommend vaccination to 9-26 year old females against HPV.

Cervical Cytology Screening

Screen sexually active women for cervical abnormalities (Pap test) to detect and treat invasive changes.

Prevalence: Cervical cancer is one of the most common cancers in underdeveloped countries. Women who have never had cervical screening, or have not had cervical screening in the previous 5 years, account for 60-90% of invasive cervical cancers.

Burden: Immigrant women who have higher cervical cancer mortality rates than Canadian born women: mortality rate ratio 1.4 (2000-2002). Cervical cancer is the most frequent cause of death from cancer in women in underdeveloped countries.

Access to Care: School immunization programs vary by province; immigrant girls and women may miss out on school vaccination programs depending on age upon arrival. There is evidence that language proficiency, housing, employment, and educational needs, as well transportation difficulties and childcare are important determinants of screening rates in immigrant and refugee women. These challenges faced by patients can be exacerbated by physician non-adherence to screening guidelines.

Key Risk Factors for Cervical Cancer: HPV infection is strongly associated with cervical cancer. HPV is common (66% lifetime prevalence of oncogenic strain of HPV) and can be acquired even if it is the first relationship involving sexual intercourse for both individuals. Risk factors for cervical cancer include high parity, genetic predisposition, and immuno-compromised conditions such as HIV. Women who have been victims of sexual trauma are at a higher risk for HPV infection and cervical cancer.

Screening Test: Cervical cytology testing (liquid based or conventional) is 60-80% sensitive for high-grade lesions and 98% specific. Screening for cervical cancer using testing for HPV DNA is more sensitive but less specific than cervical cytology, however, several Randomized Controlled Trials continue to investigate the effectiveness of this new technology.

Treatment: For vaccination against HPV infection, trials showed statistically significant reduction of high-grade cervical cancer lesions with no effects on adverse events.

Special Considerations:

- HPV prevalence is highest in developing countries; prevalence estimates are particularly high for Africa (22.1, 95% CI: 20.9-23.4) and Central America (20.4, 95% CI: 19.3-21.4).
- Providing information to patients, building rapport and offering access to female practitioners can improve acceptance of Pap tests.
- Organized screening systems, including call/recall, improve screening rates and may be possible to implement at clinic and provincial level.