Canada's Role in Accelerating Global Elimination of Cervical Cancer

JULY 2019

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For more information on this document please contact:
Marc Steben, Chairperson
Canadian Network on HPV Prevention
drmarcsteben@gmail.com

George Wurtak, Executive Director
CIDC - Consortium for Infectious Disease Control, Inc.
GWurtak@CIDCgroup.org

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Executive Committee

(in alphabetical order)

- Ian Culbert, Canadian Public Health Association, Ottawa, Ontario
- Eduardo Franco, McGill University, Montreal, Quebec
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- Laurie Smith, BC Cancer & Women's Health Research Institute, Vancouver, British Columbia
- Marc Steben (Chair), Canadian Network on HPV Prevention, Montreal, Quebec
- George Wurtak (Project Lead), Consortium for Infectious Disease Control, Winnipeg, Manitoba

Authors,* contributors and reviewers

(in order of presentation)

- **Marc Steben**, MD, Chairperson, Canadian Network on HPV Prevention, Montreal
- **George Wurtak**, MED, Executive Director, Consortium for Infectious Disease Control (CIDC), Winnipeg
- **Silvia de Sanjosé**, MD, PhD, Director of Scale-up Project, Reproductive Health Global Program, PATH
  - Laia Bruni, MD,PhD, Catalan Institute of Oncology, Barcelona, Spain
  - Laia Alemany, MD,PhD, Catalan Institute of Oncology, Barcelona, Spain
  - Ann N. Burchell, PhD, St. Michael's Hospital, Toronto, Canada
- **Marina Salvadori**, MD, Division Head, Pediatric Infectious Diseases, London Health Sciences Center; Professor, University of Western Ontario, London
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  - Mel Krajden, MD, Medical Director, British Columbia Centre for Disease Control Public Health Laboratory, Vancouver
  - Alberto Severini, MD, Chief, Viral Exanthemata and STD Section, National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg
- **Alberto Severini**, MD, Chief, Viral Exanthemata and STD Section, National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg
- **Salah Mahmud**, MD, PhD, Professor of Community Health Sciences and Pharmacy, University of Manitoba, Winnipeg
- **Eduardo Franco**, DrPH, PhD (Hon.), James McGill Professor and Minda de Gunzburg Chair, Gerald Bronfman Department of Oncology; Director, Division of Cancer Epidemiology, McGill University, Montreal

* Lead/co-lead chapter author in bold

- **Ann N. Burchell**, PhD, Department of Family and Community Medicine and Centre for Urban Solutions, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Ontario
  - Aisha Lofters, Department of Family and Community Medicine and Centre for Urban Health Solutions, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto
  - C. Sarai Racey, School of Population and Public Health, University of British Columbia, Vancouver, British Columbia
  - Laurie W. Smith, Cancer Control Research, BC Cancer & Global Control HPV Related Diseases, Women's Health Research Institute, Vancouver, British Columbia
- **Hélène M. Gagné**, MD, Assistant Professor, Department of Obstetrics and Gynecology, The University of Ottawa, Ottawa
- **James Bentley**, MB ChB, Professor and Head, Department of Obstetrics and Gynaecology, Dalhousie University, Halifax Nova Scotia; President, Society of Gynaecologic Oncology of Canada; President, International Federation of Cervical Pathology and Colposcopy
- **Laurie Elit**, MD, MSc, Professor Department of Obstetrics and Gynecology, McMaster University; Division Head, Gynecologic Oncology, Juravinski Cancer Centre, Hamilton
- **Magali Lecavalier-Barsoum**, MD, MSc, Assistant Professor, Department of Oncology, McGill University, Division of Radiation Oncology
  - Michael Milosevic, MD, Vice Chair (Research) and Professor, Department of Radiation Oncology, University of Toronto; Director of Research, Radiation Medicine Program, Princess Margaret Cancer Centre/ University Health Network, Toronto
- **Deborah Dudgeon**, MD, Senior Scientific Lead, Person-Centred Perspective, Canadian Partnership Against Cancer, Toronto
- **Nitika Pant Pai**, MD, MPH, PhD, Associate Professor, Department of Medicine, Division of Clinical Epidemiology & Infectious Diseases, McGill University; Scientist, Research Institute of the McGill University Health Centre; Founder, President and CEO, Sympact X, Montreal
- **Angela Karellis**, MSc, PhD, Postdoctoral Fellow, McGill University and Research Institute of the McGill University Health Centre, Montreal
- **Catherine Popadiuk**, MD, MBA, MSL, Medical Director Cervical Screening Initiatives, Newfoundland and Labrador; Associate Professor, Division Gynecologic Oncology, Faculty of Medicine, Memorial University, St. John's, Newfoundland and Labrador
- **Laurie W. Smith**, RN(C), BN, MPH, Cancer Control Research, BC Cancer & Global Control HPV Related Diseases, Women's Health Research Institute. Vancouver
  - Ann N. Burchell, MSc, PhD, Dept of Family and Community Medicine and Centre for Urban Health Solutions, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto
  - Zeev Rosberger, MA, PhD, Lady Davis Institute for Medical Research and McGill University, Montreal
- **Teresa Norris**, Founding President, HPV Awareness, Montreal
- **Amelie McFadyen**, MA, Executive Director, HPV Awareness, Montreal
  - Marie Plante, MD, Full professor, Department of Obstetrics, Gynecology, and Reproduction, Faculty of Medicine, Université Laval; Gynecologic Oncologist, CHU de Québec
  - Therese Lethu, CEO, Global Health Objectives; Special Advisor Women's Health in Africa, Université Numérique Francophone Mondiale
  - Zeev Rosberger, MA, PhD, Lady Davis Institute for Medical Research and McGill University, Montreal
- **Jennifer Blake**, MD, MSc, FRCSC, Adjunct Professor of Obstetrics and Gynecology, University of Toronto and University of Ottawa; CEO, Society of Obstetricians and Gynaecologists of Canada
- **Roger Simard**, B. Pharm, Montreal, Quebec

List of abbreviations

- AI – Artificial intelligence
- AIDS – Acquired immune deficiency syndrome
- ASIR, ASR – Age Standardized Incidence Rate
- BCCDC – British Columbia Centre for Disease Control
- BD – Becton Dickinson
- BMI – Body Mass Index
- C or CT – Chemotherapy
- CanMEDS – Canadian Medical Education Directives for Specialists
- CCCaST – Canadian Cervical Cancer Screening Trial
- CIDA – Canadian International Development Agency
- CIN – Cervical intraepithelial neoplasia
- CIN2+ – high-grade squamous intraepithelial lesion (HSIL) encompassing: moderate and severe dysplasia, carcinoma in situ, CIN 2 and CIN 3
- CO2 – Carbon dioxide
- CoP – Communities of Practice
- CPAC – Canadian Partnership Against Cancer
- CRT – Chemo-radiation therapy/treatment
- CxCa – Cervical cancer
- DALY – Disability adjusted life years
- DNA – Deoxyribonucleic Acid
- DSS – Disease specific survival
- ECHO – Extension for Community Healthcare Outcomes
- EDL – Essential Diagnostics List
- EQAP – External quality assurance programs
- FOCAL – HPV FOr CervicAL cancer screening trial
- FN – First Nations
- GAVI – GAVI, the Vaccine Alliance (formerly Global Alliance for Vaccines and Immunisation)
- HC-2 – Hybrid capture-2
- HCP – Healthcare professional
- HDI – Human development index
- HICs – High income countries
- HIV – Human immunodeficiency virus
- HPV – Human papillomavirus
- HPV Test / hrHPV Test – Screening test for HPV viruses
- hrHPV – High risk Human papillomavirus
- HR – Hazard ratio
- H+N – Head and neck
- IARC – International Agency for Research on Cancer
- IFCPC – International Federation of Cervical Pathology and Colposcopy
- INESSS – Institut national d'excellence en santé et en services sociaux
- LEEP – Large loop electrosurgical excisional procedure
- LIC – Low income countries
- LLETZ – Large loop excision of the transformation zone
- LMI(Cs) – Low- and medium-income (countries)
- MDALL – Medical Devices Active License Listing
- MIC – Middle Income Countries
- mRNA – Messenger ribonucleic acid
- MSM – Men who have sex with men
- NAATs – Nucleic acid amplification tests
- NCD – Non-communicable disease
- NGOs – Non-governmental organizations
- OPC – Oropharyngeal cancer
- OS – Overall survival
- Pap – Papanicolaou
- PCR – Polymerase chain reaction
- PCR-EIA – Polymerase chain reaction-enzyme immunoassay
- POC – Point of care
- RR – Relative risk
- RRprev – Relative risk prevalence
- RT – Radiation therapy
- SDGs – Sustainable Development Goals
- SEC – Socio-economic class
- SCC – Squamous cell cancer
- SOP – Standard operating procedures
- UN – United Nations
- UK – United Kingdom
- US – United States
- Valgent – Validation of HPV Genotyping Tests
- VIA – Visual inspection with acetic acid
- VILI – Visual inspection with Lugol's iodine
- WHO – World Health Organization
- YLL – Years of Life Lost
- Yo – Years old
- Yr – Year

Introduction

- **Marc Steben**, MD, Chairperson, Canadian Network on HPV Prevention, Montreal
- **George Wurtak**, MED, Executive Director, Consortium for Infectious Disease Control (CIDC), Winnipeg

Elimination of cervical cancer by 2030 is a key global objective that the World Health Organization (WHO) has proposed. Canadian experts have determined that, to achieve this goal, the Montréal Global Human Papillomavirus (HPV) prevention objectives need to be met in the targeted population:

- **90% of girls fully vaccinated with the HPV vaccine by 15 years of age;**
- **90% of women are screened with an HPV test;* and**
- **90% of women identified with cervical disease receive treatment and care.**

The incidence rate of cervical cancer in Canada was 8.3/100,000 in 2017.[1] These rates, and the rates of the three major HPV endpoints (HPV infections, genital warts, and cervical lesions) certainly can be greatly reduced if HPV prevention efforts are accelerated immediately.

HPV vaccine coverage in most Canadian provinces and territories still falls below the targeted uptake rates. Those who are not covered sufficiently include children of hesitant parents, hesitant adults, people experiencing extreme poverty and/or homelessness, men who have sex with men, immigrants and refugees, immuno-compromised persons, and Indigenous Peoples. Individuals in those groups are harder to reach and immunize than people who are typically immunized against a variety of other diseases. Consequently, reaching those individuals will need special outreach strategies. Most people in these categories are also less-frequently screened for cervical cancer or other diseases and have limited access to health care. With the use of a traditional Pap smear in vaccinated populations now being perceived to be less valuable, screening strategies must change to HPV molecular testing. This in turn will present new possibilities of reaching more of the population at higher risk of cervical cancer and not having been screened through self-sampling at home or in a community setting (e.g., a walk-in clinic). These self-sampling kits could be acquired at an established clinic, a pharmacy, a temporary community clinic or another venue and then sent back by mail. In order to reach females with higher risk of cervical cancer, consideration should be given to the combination of HPV vaccination and cervical cancer screening during the same visit.

While most people in Canada believe that vaccines are both safe and effective,[2] efforts should be made to emphasize the fact that the HPV vaccine is effective, safe and efficient, and that cervical cancer screening can be lifesaving.

The situation is different in many lower- and middle-income countries (LMIC) where health care structures are insufficient and budgetary issues make delivery of vaccines and screening for cervical cancer difficult or impossible. In order to be successful in reducing HPV-related diseases, different outreach strategies are required in LMIC.

Canadian experts are available to help accelerate cervical cancer elimination here in Canada and around the globe. Recommendations are provided within this document for consideration of the Government of Canada (specifically the Health Portfolio and Global Affairs Canada) so that Canadians can be major contributors – both at home and around the world – to achieving the goal set by the World Health Organization of eliminating cervical cancer by 2030.

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1. Canadian Cancer Society.
2. Public Health Agency of Canada and Statistics Canada.

* The WHO has changed their objective to 70% screening rate with a high-precision test at 35 and 45 years of age; the authors of this document feel that this is reasonable for low- and middle-income countries.

Chapter 1
HPV: The World's Burden

- **Silvia de Sanjose**, MD, PhD, PATH, Seattle, USA
  - Laia Bruni MD, PhD, Catalan Institute of Oncology, Barcelona, Spain
  - Laia Alemany MD, PhD, Catalan Institute of Oncology, Barcelona, Spain
  - Ann N. Burchell PhD, St. Michael's Hospital, Toronto, Canada

OVERVIEW

The chapter aims to provide an overview of the worldwide burden of human papillomavirus (HPV) related cancers and in particular on cervical cancer and to inform on the burden of cervical cancer in Canada today and in the years to come.

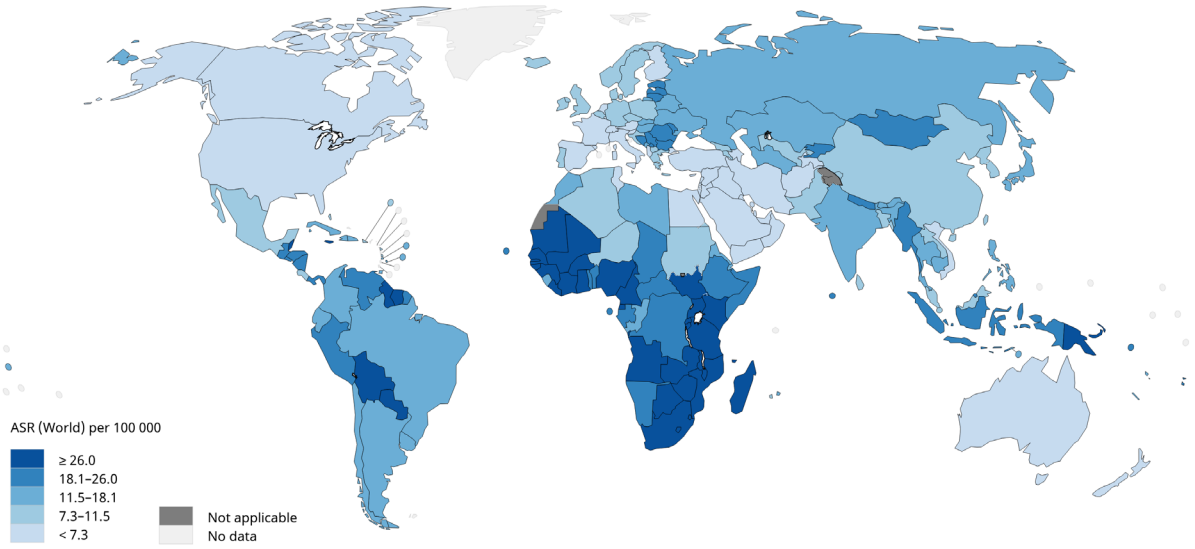
DATA AND DESCRIPTION

Global Burden of oncogenic HPV infection

Infection with high risk (HR) HPV is recognized as one of the major causes of infection-related cancer worldwide. Approximately 1 in 2 cancers associated to an infection will be related to HPV. HPV infection is now a well-established necessary cause of cervical cancer and of a certain proportion of cancers of the anus, vulva, vagina and penis and head and neck cancers, particularly the oropharynx including base of tongue and tonsils. Cancers of anus, vulva, vagina and penis are much less frequent compared to cancer of the cervix. Head and neck tumors can be, in some settings as common as cervical cancer, although causative factors include smoking and alcohol exposures and HPV. Noticeable increases in HPV associated head and neck tumors have been reported in the last decade including Northern America and Northern Europe.

Because of the bigger burden of cervical cancer amongst all HPV related cancers, the rest of the chapter will be focusing on this tumor site. Most genital HPV infections (70%–90%) are asymptomatic and resolve spontaneously in 1–2 years. In some instances, persistent infection with HR types may ultimately progress to invasive carcinoma unless the preceding lesion is detected and treated.[1] The vast majority of female HPV-related cancers are cervical cancer cases (more than 85%) with around 85% of the cases diagnosed in resource limited settings. Cervical cancer is the fourth most common female malignancy worldwide in incidence and in mortality, with an estimated 569,000 new cases and 313,365 new deaths in 2018, more than 95% attributable to HPV infection.[2]

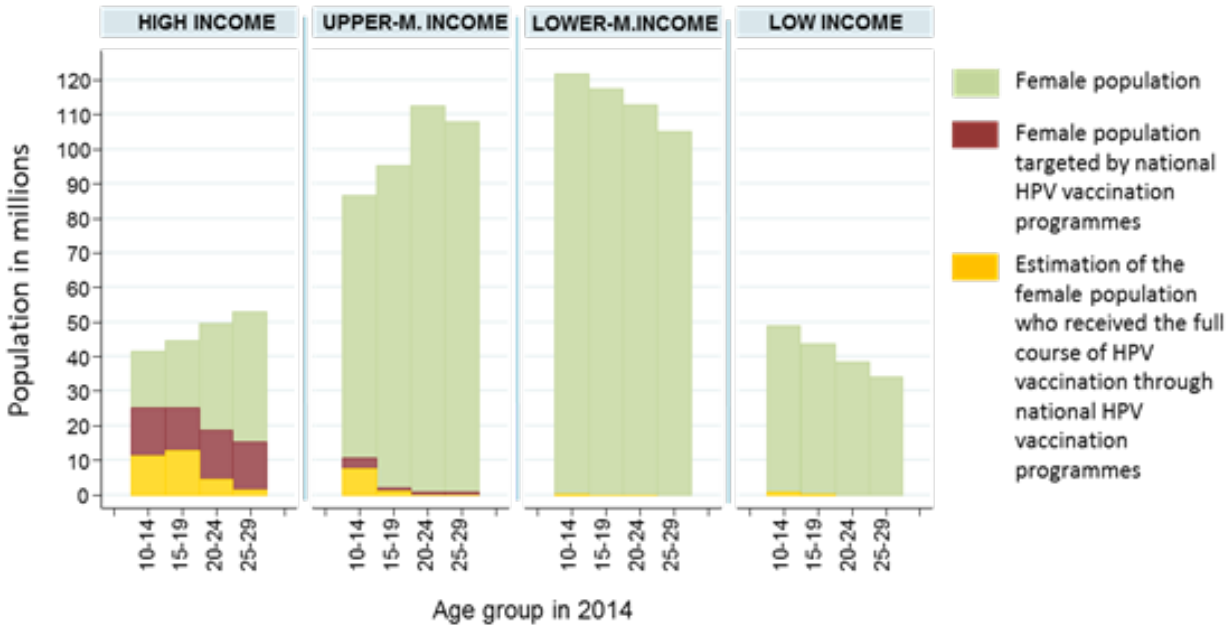
FIGURE 1. ESTIMATED AGE-STANDARDIZED INCIDENCE RATES (WORLD) IN 2018, CERVIX UTERI, FEMALES, ALL AGES



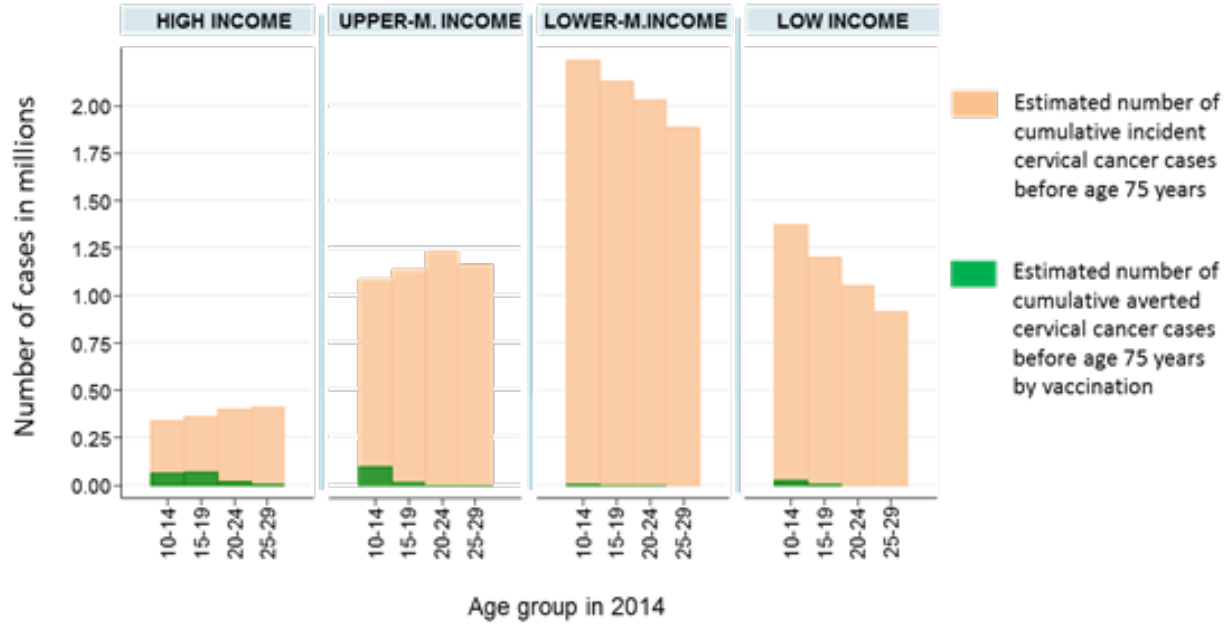
Data source: GLOBOCAN 2018
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization

FIGURE 2. VACCINATED FEMALE POPULATION AND CERVICAL CANCER CASES AVERTED BEFORE AGE 75 YEARS BY INCOME AND AGE GROUP IN WOMEN TARGETED BY HPV VACCINATION PROGRAMS BY THE END OF 2014

A) Vaccinated and unvaccinated female population



B) Cumulative number of expected cervical cancer cases up to age 75 years, assuming 70% vaccine effectiveness



Source: Bruni L. *HPV World* Year 1 No. 24
https://www.hpvworld.com/media/29/media_section/4/1/441/18.pdf

The map in Figure 1 shades the countries by the level of the diagnosis of new appearing cases, so called "incidence", of cervical cancer. The depicted data have been weighted by the age structure of the population so that all countries can be compared one to another. The level of incidence increases with increasing the intensity of blue. As shown in the map, sub-Saharan Africa, Latin America and some countries in the Pacific experience higher age-standardized incidence rates (ASR), while Australia, Northern America, Western Europe and Middle East all have ASR values lower than 10 per 100,000. A similar pattern is observed for mortality.

The disproportionate distribution of cervical cancer is largely explained by the wide introduction of screening in the different world regions using the Papanicolau test that allows identification of early pre-neoplastic lesions in cervico-vaginal cells. The test has been effective in reducing incidence and mortality if applied repeatedly over time to a large number of women at risk. Countries that, in 2018, are reported to be at the lower end of incidence, did have very high incidence rates 60-80 years ago. Clear examples are Canada, The Netherlands and Nordic European countries. The exception are the countries in the Middle-East that have always had a very low burden of disease due probably to low spread of HPV infection within the population.

High resource settings have invested in cervical cancer screening and are now largely investing in HPV vaccination of cohorts of susceptible girls, and also boys in some jurisdictions.[3] The global scenario is that, given estimates of screening and vaccine coverage in 2016, many women alive today will still develop invasive cervical cancer either because they are ineligible for HPV vaccine and/or because they will not be screened. These women, expected to live up to 50 years, will generate an enormous burden that is estimated to be over 35 million of new cervical cancers cases during their lifespan. Any reduction of such burden will need widespread effective interventions. Most likely, in high risk populations effective screening once or twice in the lifetime is probably the most feasible solution to prevent many of these cases to occur. Additional cases could be reduced in areas with moderate incidence by improving the efficacy of screening (see Chapter 3).

Situation in Canada

In 2012, 3,760 HPV-associated cancers were diagnosed in Canada, 64% of which were diagnosed in females and 36% in males. Among women, cancer of the cervix was the most common HPV-associated cancer, while cancer of the oropharynx was the most common among men with an estimated attributable fraction to HPV of 74%.[4,5]

Canada has one of the lowest incidence rates of cervical cancer in the world. By 2018, cervical cancer accounted for 1,434 new cases and 586 deaths.

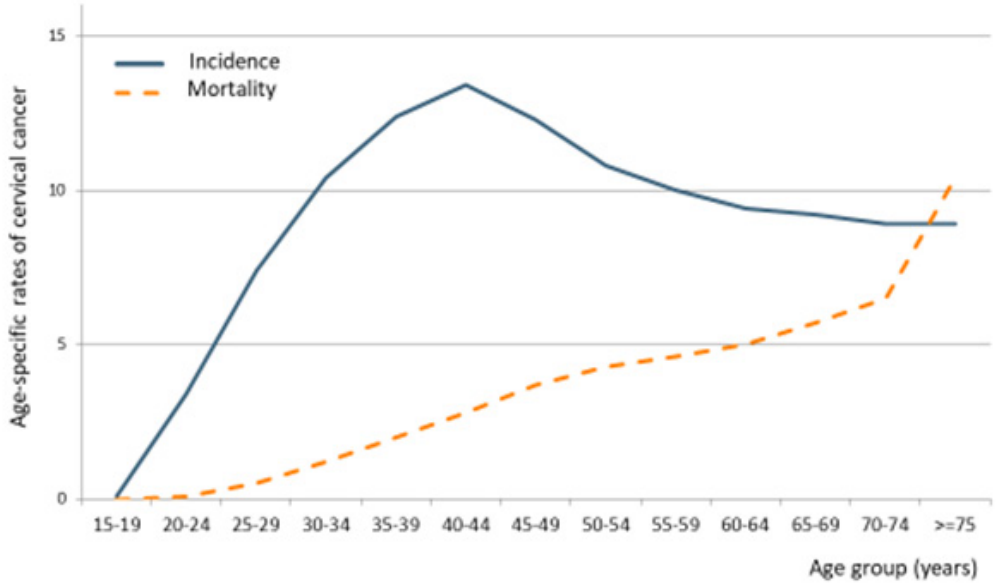
As in many countries, the burden of cervical cancer increases progressively with age (Figure 3), reaching a peak in the age group of 40-44 and slowing thereafter. More than half of the cases of cervical cancer are diagnosed in women younger than age 50. Contrary, mortality increases with increasing age.

Population based cancer registries are fundamental to estimate incidence rates in a given population and to explore differences across geographies within the country and between countries. In Canada, data from 12 registries (Table 1) show quite homogeneous age standardized incidence rates ranging between 5.5 in New Brunswick to 8.4 in Newfoundland and Labrador registry. Variations observed across registries may be due to multiple factors including data reporting but also differential access the health services or differences in risk factors.

Important efforts have been taken place in the last decades to reduce the burden of cervical cancer as reflected by the annual 2.2% decrease in incidence rates between 1995 to 2005.[5] However, data suggest that women below age 50 may not experience the same downtrend as the overall (Supplementary Figure 1, b & c). Continuous surveillance of incidence rates by age is needed to further confirm these age differences. Because cervical cancer is one of the cancers that tend to occur earlier in adult life, mortality due to the disease may have an added weight. A way to reflect the impact of premature deaths is by means of the number of years of life lost in a given population compared to the years expected to be lived. Every year in Canada, cervical cancer is responsible of over 17,000 of years of life being lost. Although the number of cervical cancer cases are relatively low, as cases tend to be diagnosed in early adulthood, the number of years of life lost are considerably high compared to other cancers with higher incidence but occurring later on in life. The accumulated number of years of life lost due to cervical cancer is comparable to that observed for brain tumors, leukemia or cancer of the uterus. The main difference is that cervical cancer is largely a preventable disease.

It is estimated that by 2030, a 10% increase of cervical cancer cases will take place in Canada due to demographic changes. Most likely, the massive HPV vaccination and

FIGURE 3. INCIDENCE AND MORTALITY FROM CERVICAL CANCER BY AGE GROUP IN CANADA, 2018.



Data accessed on 05 Oct 2018.
Rates per 100,000 women per year.
Data sources:
Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today, accessed [05 October 2018].

TABLE 1. INCIDENCE OF CERVICAL CANCER IN CANADA BY CANCER REGISTRY, 2008-12.

Cancer registry[1]	Period	N cases[a]	Crude rate[b]	ASR[b]
Alberta	2008-2012	735	8.0	6.2
British Columbia	2008-2012	883	7.9	5.7
Manitoba	2008-2012	248	7.9	6.1
New Brunswick	2008-2012	146	7.7	5.5
Newfoundland and Labrador	2008-2012	147	11.1	8.4
Northwest Territories	2008-2012	8	7.6	6
Nova Scotia	2008-2012	207	8.6	6.2
Nunavut	2008-2012	5	6.2	5.6
Ontario	2008-2012	2,822	8.4	6.3
Prince Edward Island	2008-2012	34	9.4	6.9
Saskatchewan	2008-2012	230	8.6	7.1
Yukon	2008-2012	8	9.5	6.7

Data accessed on 05 Oct 2018.
ASR: Age-standardized rate, Standardized rates have been estimated using the direct method and the World population as the reference;
Please refer to original source (available at http://ci5.iarc.fr/CI5-XI/Default.aspx)
a Accumulated number of cases during the period in the population covered by the corresponding registry.
b Rates per 100,000 women per year.
Data sources:
1 Bray F, Colombet M, Mery L, Piñeros M, Znaor A, Zanetti R and Ferlay J, editors (2017). Cancer Incidence in Five Continents, Vol. XI (electronic version). Lyon: International Agency for Research on Cancer. Available from: http://ci5.iarc.fr, accessed [05 October 2018].

* Note: no cancer registry exists for the Province of Quebec

the improved cervical cancer screening approaches in Canada (Chapters 2 & 5) will help to mitigate this expected increase.

In conclusion, it is foreseen that continuing efforts to control cervical cancer in Canada through vaccination and screening, the country can be amongst the first countries worldwide to reach the elimination criteria set up by WHO in just few years as is predicted also for Australia (See Annex). This optimistic situation must be accompanied by a vigilance for to the continuous participation in preventive screening and vaccination strategies by all age groups, social groups and geographies within the country.

RECOMMENDATIONS

1. **Sustained levels of vaccination and efficient screening in Canada are needed to eliminate cervical cancer in the years to come.**
2. **Monitoring of incidence rates of HPV related cancers in recent years are needed to control for the impact of interventions and of changes in risk factors.**
3. **Additional efforts, including but not limited to maintaining comprehensive cancer registries in each province and territory, may be required to fully understand the moderate geographical variation in cervical cancer burden observed in Canada.**

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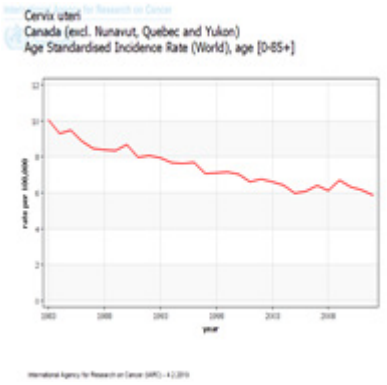
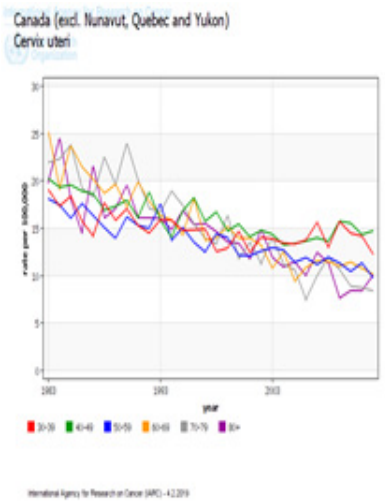
ANNEX

SUPPLEMENTARY FIGURE 1: INCIDENCE RATES OF CERVICAL CANCER 1983-2012, A) ALL AGES, B) BY AGE-GROUP AND C) BY AGE-COHORT. SOURCE: IARC CIFC.

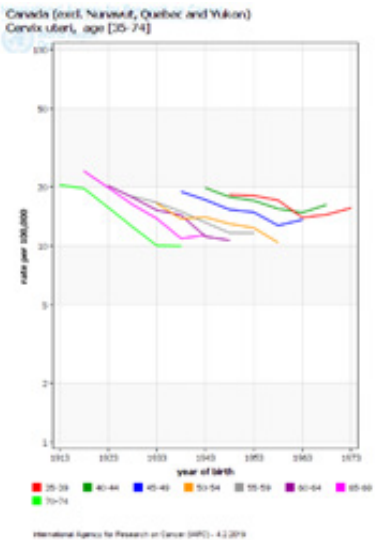
a)



b)



c)



Modeling data from Australia

Hall et al. (2019) have recently published a modelling study to estimate the age-standardized incidence of cervical cancer in Australia from 2015 to 2100. They modelled the age-specific coverage of the Australian National HPV Vaccination Program in girls, including the catch-up program, and the inclusion of boys into the vaccine program. They have also included in the model the recent introduction of HPV screening.

The paper presents two scenarios for future screening recommendations regarding the cohorts who will be and who have been offered the nonavalent vaccine: either that HPV screening every 5 years continues, or that no screening would be offered to these women.

The Figures show the impact of high coverage of both interventions and the long rank impact of adding screening. It was estimated that in Australia, the age-standardized annual incidence of cervical cancer will decrease to fewer than six new cases per 100 000 women by 2020, and to fewer than four new cases per 100 000 women by 2028. It was concluded that screening and vaccination initiatives would need to be maintained thereafter to maintain very low cervical cancer incidence and mortality rates.

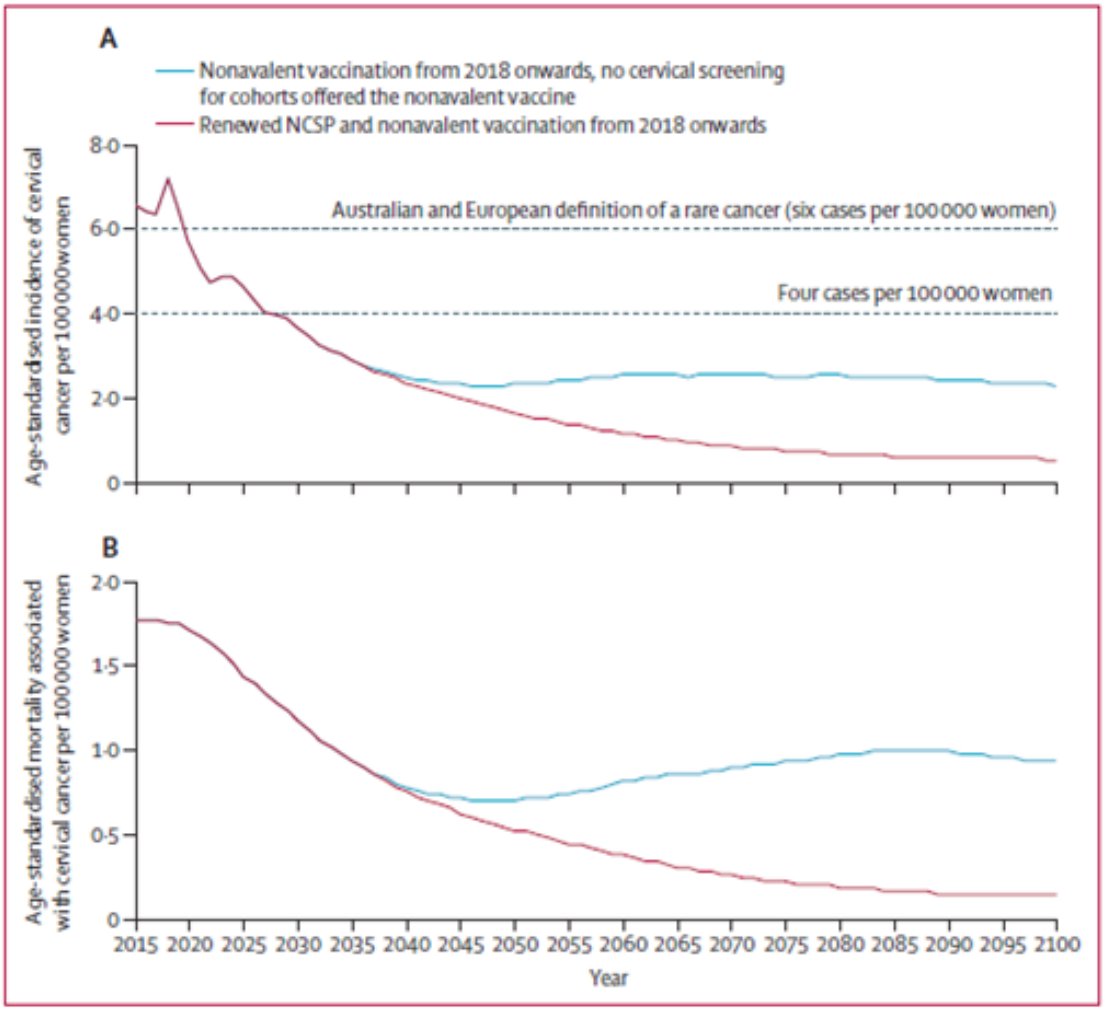


Figure 1: **The (A) age-standardised annual incidence of invasive cervical cancer and (B) associated mortality**
Data are the model predictions for rates from 2015 to 2100, accounting for the transition to primary human papillomavirus screening in 2017 (the renewed NCSP) and the switch to nonavalent vaccine in 2018.
NCSP=National Cervical Screening Programme.

Chapter 2
Human Papillomavirus Prophylactic Vaccines: Beyond the Traditional Role

- **Marina I. Salvadori**, MD, FRCPC, Division Head, Pediatric Infectious Diseases, London Health Sciences Center; Professor, University of Western Ontario

OVERVIEW

There are three vaccines against human papillomavirus (HPV) that have demonstrated excellent results in preventing HPV diseases and cancers. They have proven to be safe. In countries where the vaccine is available in publicly funded programs, barriers to uptake must be addressed in order to achieve maximum vaccination of the population. All programs should be gender neutral, and Canada should strive for once eligible, always eligible policies. The vaccine should be available in all countries in the world. At the present time there are large inequities, mostly based on economic status, gender barriers, and biases against the vaccine based on cultural values.

DATA AND DESCRIPTION

Human Papillomaviruses can affect all humans. There are more than more than 100 types, of which approximately 40 can infect the human genital tract. HPV infections are transmitted sexually by direct skin to skin contact. Rarely, the virus is transmitted to an infant exposed to the mother's birth canal. This can lead to warts in the voice box that can grow (recurrent respiratory papillomatosis) and must be repeatedly lasered off or the child will be unable to breathe. Head and neck infections also occur in adults, mostly through oral genital contact. Manifestations of HPV infection include infection with no symptoms (by far the most common), warts and cancers. Infection with a high-risk HPV (hr-HPV) type is the main cause of cervical cancer and also causes cancers of the vulva, vagina, penis, anus, mouth and throat. Low-risk HPV types are associated with the development of abnormal PAP smears and anal/genital warts.

In North America, the lifetime cumulative incidence of HPV infection with at least one serotype is estimated at more than 70%. Without vaccination, it is likely that most sexually active Canadians will have an HPV infection at some point in their lives. The highest occurrence is in young adults 20 to 24 years of age. Annually in Canada, there are over 1400 cervical cancer cases and nearly 600 deaths.

Risk factors for HPV infection include a higher lifetime number of sexual partners, previous other sexually transmitted infections, history of sexual abuse, early age of first sexual intercourse, partner's number of lifetime sexual partners, tobacco or marijuana use, immune suppression and human immunodeficiency virus (HIV) infection. HPV infection and anogenital warts and cancers are highly prominent among men who have sex with men (MSM), particularly if they are HIV-positive.

To be optimally effective in preventing long-term complications from HPV infection, the HPV vaccine must be administered before a person is exposed to the virus. Because infection can occur with the onset of any sexual touching, it is important to vaccinate before first sexual encounters. Statistics Canada data from 2005 show 29% of 15- to 17-year-olds had had first sexual intercourse: this number increased to 65% in 18- to 19-year-olds, with large regional variability.

There are three approved HPV vaccines in Canada. The vaccine approved most recently is Gardasil 9. It protects against 9 types of hr-HPV types and offers protection against 90% of female cervical cancers and 90% of genital warts. The previous Gardasil 4 will soon no longer be available. Cervarix provides two types of HPV virus protection and protects against approximately 70% of cervical cancer. If the vaccine is administered before exposure to the targeted HPV types, it offers close to 100% protection against type-specific cervical disease.

We know that vaccinating an individual protects that person, but we also know that once a population gets immunized, other people are protected, even if they are not immunized. This is called herd immunity which protects against the spread of the virus, because there are less people spreading the viruses.

As with all vaccines, the most common adverse events from HPV vaccines are pain at the site of injection,

swelling, or redness. In more than 94% of recipients, reactions are mild-to-moderate, resolve over a few days and do not prevent completion of the immunization schedule. Hundreds of millions of doses of HPV vaccine have been administered worldwide. To date, there has been no evidence to support any association between HPV vaccines and Guillain-Barré syndrome, autoimmune diseases, stroke, blood clots, multiple sclerosis or any other serious health condition. There has not been a higher than expected number of deaths following HPV vaccine.

Men who have sex with men (MSM) are known to be at higher risk for infection with HPV than are heterosexual males. Anal cancers and anogenital warts have a higher incidence among MSM. As teenagers become aware of and explore their sexual identities, same-sex encounters may not be so unusual. Men who identify as MSM may be reluctant to discuss their sexual practices with a health care provider, particularly at a young age. They may be worried about issues of confidentiality or judgment. For these reasons, the best strategy for protecting MSM against HPV-related diseases is a universal male vaccination program that does not depend on self-reporting to health care providers. Early receipt of HPV vaccine is expected to deliver maximal benefit in the MSM population.

Individuals infected with HIV are known to have a high burden of HPV-associated adverse outcomes. Anogenital warts are common and difficult to treat in this population. Anal cancers are particularly common in HIV-infected MSM. This is a very important target group for this vaccine.

Gender-neutral vaccine programs are recommended to bypass the labeling stigma associated with linking sexual behavior and HPV vaccine.

Men treated for anal cancer, and women treated for cervical cancer also have a lower recurrence risk, if they are vaccinated before or at the time of the treatment. Thus, people who have already had HPV diseases are a priority group for vaccination.

These vaccines were originally studied using a three-dose schedule. Canadian researchers, as well as others, demonstrated the immune response in adolescents up to age 15 years is the same using only two doses. This makes it easier to deliver public vaccine programs in schools and to hard to reach populations. The two doses need to be given at least 6 months apart.

One of the greatest concerns in the Canadian HPV program is the lack of uptake of the free vaccine. The rate varies considerably from province to province. This has been due to various cultural contexts, such as circulating myths that girls will be more likely to be sexually active if vaccinated (which has been scientifically disproved), worries about safety, media and social media campaigns that fear monger about the vaccine as well as differences in programs and funding across the country.

For all countries of the world, the World Health Organization (WHO) recognizes the importance of cervical cancer and other HPV-related diseases as global public health problems and reiterates the recommendation that HPV vaccines should be included in national immunization programs. Cervical cancer, which comprises 84% of all HPV-related cancers, should remain the priority for HPV immunization. Cervical cancer causes over 313,000 deaths of women globally each year. Prevention of cervical cancer is best achieved through the immunization of girls, prior to onset of sexual activity. HPV vaccines should be introduced as part of a coordinated and comprehensive strategy to prevent cervical cancer and other diseases caused by HPV. This strategy should include education about reducing behaviours that increase the risk of acquiring HPV infection, training of health workers and information to women about screening, diagnosis and treatment of precancerous lesions and cancer.

RECOMMENDATIONS

For Canada:

4. **There should be universal funding and implementation of HPV-9 vaccination programs for both sexes, in all provinces and territories. HPV-9 vaccine should be administered routinely to all children at 9 to 13 years of age. To increase the likelihood that the vaccine will be administered before the onset of any sexual activity, the vaccine should be given as early as provincial/territorial programmatic issues allow.**

5. The HPV vaccine should be administered to all unimmunized females and males 13 years of age and older, as a 'catch-up program'. It is recommended that provinces and territories implement a 'once eligible, always eligible' policy, whereby children qualifying for publicly funded vaccines would still be eligible at a later date when they did not receive all the recommended age-appropriate doses.
6. Funding and programs for high risk individuals should be implemented, especially for men who have sex with men, any person with multiple sexual partners, and anyone with a history of previous HPV disease.

For International:

7. Canada should support all countries, either through GAVI or independently to offer this vaccine. In many resource poor nations, women do not have agency over their own sexual activity and many countries do not have Pap screening programs. A vaccine program would allow prevention and can overcome some of these barriers.
8. Priority order would be women under the age of 15, and once excellent coverage in this group has been attained, men under the age of 15, all women, all men.

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Chapter 3
Validated HPV Tests for Cervical Cancer Control

- **Francois Coutlée**, MD, Chef, Service de Microbiologie médicale de la grappe du CHUM
  - Rachid Hadjeres, MD
  - Mel Krajden, MD
  - Alberto Severini, MD

DATA AND DESCRIPTION

Several randomized controlled studies have demonstrated the improved sensitivity of human papillomavirus (HPV)-based assays to detect high-grade lesions (CIN2+) and cervical cancer when compared to cytology for primary cervical cancer screening.[1,2] Furthermore, women who test HPV-negative for HPV DNA- or mRNA can safely extend their screening visit intervals to five years.[2] In Canada, two provincial agencies promote HPV testing for cervical cancer screening: Cancer care Ontario and the Institut national d'excellence en santé et en services sociaux (INESSS) of the Quebec government which mission is to promote the appropriate and efficient use of resources in health and social services.

Provincial authorities across Canada will need to involve cancer prevention and laboratory medicine specialists to implement HPV testing for primary screening of cervical cancer and outline the requisite request for proposal requirements for HPV screening. The objective of this chapter is to outline critical considerations and requirements for the writing of a call for tender for the selection of an HPV test for primary cervical cancer screening. Laboratory requirements for HPV testing will also be summarized. The use HPV testing as a test of cure of CIN2+ treatment is discussed elsewhere in this document.

Only HPV tests that have been analytically and clinically validated should be considered for cervical cancer primary screening. Over one hundred HPV nucleic acid amplification tests (NAATs) are available commercially but only a limited number of them have been validated for HPV-based primary screening in randomized controlled clinical trials,[3] two of which have been conducted in Canada, CCCaST and FOCAL.[4,5] A guideline, designated here as the Meijer protocol, written in 2009 by an international multidisciplinary team of experts, precisely defined the validation process of molecular HPV assays and the minimal assay requirements to support cervical cancer primary screening.[6] The validation criteria are based on assessing the clinic sensitivity and specificity of novel HPV nucleic acid tests to detect cervical cancer precursor lesions or cancer defined histologically and how detection correlates with clinically validated comparator tests. The value of these comparator assays, the Hybrid Capture-2 (HC-2) and GP5+/GP6+ PCR-EIA, has been formally established in randomized controlled clinical trials. The pooled sensitivity and specificity of both assays reached 96.1% (95% confidence interval, 95.9%-96.1%) and 93.3% (95% confidence interval, 92.9%-93.6%), respectively.

These molecular assays are designated as generic assays as they are based on the principle of detecting the presence of several (12 to 14) high-risk (HR) HPV genotypes all at once. The majority of unvaccinated sexually active women, will be infected with HPV during their lifetime. To be effective, HPV tests used for primary screening should reach an optimal balance between analytical and clinical sensitivity and specificity to avoid excessive investigation of HR-HPV-positive women without CIN2+ lesions.

According to the Meijer protocol, evaluation of candidate tests should be conducted in samples obtained from a subset of women undergoing organized population-based screening programs with assessed cytological/histological outcomes. An acceptable HR-HPV test should achieve a clinical sensitivity for CIN2+ of > 90% of that of a comparator test assessed by a non-inferiority test in at least 60 women >30 years old with a power of 80%. Clinical specificity of the candidate assay should be at least 98% that of a comparator test on 800 samples selected randomly. Based on analysis of 500 samples, intra- and inter-laboratory reproducibility should be >87% at the lowest limit of 95% confidence interval. The Valgent (Validation of HPV Genotyping Tests) protocol is another evaluation framework that extends the Meijer protocol to validate HPV assays with typing capability. The protocol is conducted on 1,000 consecutive samples from women

attending cervical screening programs enriched with 300 samples derived from women with various cervical lesion grades. Histological outcomes are obtained as well as a two-year follow-up to confirm the absence of CIN.

In addition to fulfilling Meijer or Valgent protocol criteria, candidate tests should be approved by health authorities and have undergone peer-reviewed publication. In Canada, committees responsible for the call for tender for HPV testing should always refer to the Health Canada internet site for Medical Devices Active License Listing (MDALL) for licensed medical devices (https://health-products.canada.ca/mdall-limh/index-eng.jsp) which lists Health Canada approved assays. As of January 2019, six assays were licensed in Canada for HPV diagnostics and have demonstrated non-inferior sensitivity and specificity for CIN2+ as well as adequate intra- and inter-laboratory reproducibility for HPV primary screening. Hybrid capture 2 (HC-2, Qiagen) is an approved semi-automated signal amplification-based assay and serves as one of the two comparator assays used for the Meijer protocol. The spectrum of HPV genotypes detected by HC-2 exceeds the 12 genotypes included in the probe cocktail (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) because of cross-hybridization with other high-risk and low-risk genotypes, resulting in a good sensitivity but lower specificity compared to NAATs. The other five approved assays are all NAAT-based: four are based on HPV DNA amplification through real-time PCR (Roche Cobas 4800 HPV, Becton Dickinson (BD) Onclarity HPV, Abbott RealTime high risk HPV, Gene Xpert HPV) and one assay is based on transcription mediated amplification of HPV mRNA (Aptima HPV, Hologic). The Gene Xpert HPV requires one hour for completion and could enable point-of-care testing. The other NAATs involve automated platforms with the high throughput capacities needed for centralized primary screening. The Roche Cobas 4800 HPV, Aptima HPV and Abbott RealTime high-risk HPV tests also identify genotypes 16 and 18 separately and report results for the other 12 HR genotypes together. Similarly, the Gene Xpert HPV assay is able to identify separately genotypes 16, 18/45 and with the other HR genotypes identified as a group. The BD Onclarity HPV assay provides separate genotyping for HPV16, 18, 45, 51, 52 and reports the remaining genotypes in three distinct groups (33/58, 56/59/66, 35/39/68). A cellular control to monitor sample quality is not included in HC-2 and Aptima HPV assays but is included as part of the other NAATs. The Aptima HPV assay does include an amplification control in each sample reaction. The Roche Linear array HPV test has been validated by the Valgent protocol and is licensed in Canada but tests for 36 HR and low risk genotypes and is largely designed to study HPV epidemiology and public health needs.

Several validated assays are available in other countries but are not licensed in Canada. Semi-automated NAATs that include a cellular control and HPV16/18 genotyping are the HPV-Risk, qPCR (E6/E7), Cervista, Anyplex vII HPV HR, CareHPV test and the GP5+/6+ LMNX assay. The latter test is a luminex/PCR-based assay with high-throughput capacity. The PapilloCheck HPV screening test is a fully automated microarray-based assay with genotyping ability and a cellular control. MALDI-TOF assays capable of genotyping all HR-HPV been developed. The Pretect HPV-proofer and CareHPV tests show a lower sensitivity than comparator tests. Health organizations can consult the list of available HPV tests from the World Health Organization presented in Chapter 12 as well as the list of licensed tests from their respective countries.[3]

HR-HPV-positive women should not be systematically referred to colposcopy as many will not have CIN2+ lesions. A triage algorithm using reliable and robust technologies is mandatory to further investigate women who are the most likely to have CIN2+. To avoid additional visits, samples collected in liquid-based cytology media can be tested for HR-HPV and undergo triage testing if needed. Since triage strategies at the first visit are not 100% sensitive, a subsequent second sample obtained 6 to 12 months later can increase the triage sensitivity to detect CIN2+ to nearly 100%. As HPV16 and 18 account for 70% of cervical cancers in Canada. HPV16/18 genotyping (with or without HPV45) identifies 50% of HR-HPV-positive women with CIN2+ and is already part of the Health Canada approved NAATs listed above. HPV16/18 genotyping results are readily available from most licensed generic HR HPV tests. Results Cytology (with or without p16 and Ki assessment) can then be applied on the same HR-HPV-positive but HPV16/18-negative sample, increasing the sensitivity to detect CIN2+ to ±80%. HR-HPV-positive women negative for HPV16/18 and with a normal cytology could be retested for HR-HPV

and cytology on a second sample collected 6-12 months later, raising the sensitivity level to nearly 100%. The role of novel triage tests (HPV viral load, HPV methylation, and cellular methylation) is not clearly defined yet. Prospective reevaluation of primary screening and the most appropriate triage strategy will be needed as HPV vaccinated women are protected from infection and become eligible for cervical cancer screening.

Several considerations related to primary HPV screening will impact the tender requirements. Only assays that comply with the Meijer protocol or Valgent protocol, or assays validated through randomized controlled trials should be eligible to submit a proposal. Candidate assays should cover 12 to 14 HR-HPV genotypes and detect at least genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59. The call for tender should not be restricted to a particular nucleic acid detection format (ex. PCR). The number of specimens requiring testing both at the start of the program and over the long term will help inform the required throughput and the platform selected to minimize overall test (reagents and labour) costs. Other considerations include laboratory information system connectivity, technical support, service and training. Of note, many of the current automated platforms can also be used to detect other infectious agent such as Chlamydia, HIV or hepatitis C. Full automation is a desirable feature if centralization of HPV screening is envisioned. The triage strategy needs to be considered as part of the tender. Samples should be collected in a cytology preservation media for HR-HPV testing enabling reflex cytology triage, if required. The shift to primary HPV screening provides opportunities to improve reach and access to underserved populations of women who are currently not engaged in cervical cancer screening. Self-collected vaginal specimens have been shown to improve cervical cancer screening uptake (see Chapter 6).

Laboratories selected for HR-HPV testing need to have adequate infrastructure and an established quality assurance program for molecular testing. Pre-analytical considerations, internal quality control as well as external quality assessment and proficiency testing are described in Chapter 4. When reflex cytology is performed on HR-HPV-positive samples, it will be important to integrate into one report to the clinician the results of the HPV test, the results of HPV genotyping, if available, and the cytology or other triage test results. Report integration is very important to identify women requiring follow up colposcopy and the urgency of follow up, and avoid confusion. For women who screen HR-HPV-DNA-negative, because of the prolonged follow up of about 5 years, there is a need to create a recall mechanism to ensure that women receive appropriate follow-up HPV screening during their life course.

Since the use of HR-HPV testing with triage of positive results is an important modification of the medical practice for the cervical cancer screening, major efforts will need to be invested on the education to the public, health care providers on how to interpret and manage women based on their HPV screening results.

RECOMMENDATIONS

For Canada:

9. **Proceed for a call for tender for the selection of a HR-HPV test for the primary screening of cervical cancer among the licensed tests in Canada that have been validated by the Meijer and/or Valgent protocols or randomized controlled trials.**
10. **Implement a triage strategy for HR-HPV-positive women with HPV16/18 genotyping followed by cytology, if required, to refer women to colposcopy**
11. **Invest in education of the public and health care providers on how to interpret and manage women based on their HR-HPV screening results.**

For International:

12. **Proceed for a call for tender for the selection of a validated HR-HPV test for cervical cancer primary screening according to the World Health organization list (refer to Chapter 12).**
13. **Implement a triage strategy for HR-HPV-positive women to refer women to colposcopy.**
14. **Invest in education of the public and health care providers on how to interpret and manage women based on their HR-HPV screening results.**

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Chapter 4
HPV Testing: Evaluation & Quality Control

- **Alberto Severini**, MD, National Microbiology Laboratory, Public Health Agency of Canada
  - François Coutlée, MD, Chef, Service de microbiologie médicale de la grappe Optilab Montréal-CHUM

OVERVIEW

In this chapter, we outline the quality evaluation and quality control programs that should support human papillomavirus (HPV) based screening in Canada. Moreover, we summarize the present status of HPV testing quality control and we outline the steps that, in our opinion, should be taken to implement HPV testing quality control in Canada.

DATA AND DESCRIPTION

Quality control and proficiency testing are an essential component of every test in every diagnostic laboratory. They ensure that the diagnostic results conform to the approved characteristic of the test method and that they are reproducible across laboratories and over time. Accreditation of tests and laboratories by regulatory agencies (e.g. national agency, professional associations or WHO) requires adherence to standard operating procedure for quality control and successful completion of periodical testing of a panel of proficiency specimens distributed by a reference laboratory.

Quality control is even more important in the case of HPV testing to ensure stability and reproducibility of the results over time, given the present heterogeneity of platforms and analytical methodologies. The results of HPV testing should consistently show optimal correlation with cervical lesion and lead to optimal clinical management.

INTERNAL QUALITY CONTROL

Internal quality control includes all the measures that a laboratory takes to ensure that its personnel and the tests that they perform remain up to the standards prescribed by the Standard Operating Procedures (SOP).

For HPV testing it is important to keep in mind that maximum sensitivity in detecting the virus is not desirable since infections with low HPV DNA amounts are not associated with cervical lesions. Therefore, all diagnostic HPV tests have a cut-off of positivity, under which the result is considered negative. Therefore, it is desirable to add to every run a negative control containing a low amount of HPV nucleic acids leading to a result consistently below the cut-off and a positive control leading to a result consistently above the cut-off1. The performance of these controls should be monitored over time to ensure that they consistently produce results in the acceptable range. This is particularly important because an accidental shift of the analytical cut-off will lead to unacceptable misdiagnosis of cervical lesions.

Most tests, but not all (see Chapter 3), also monitor the quality of each specimen by detecting the presence of human DNA, a sign that the right biological material has been successfully collected and extracted. This is a useful precaution to avoid issuing false-negative results due to an unsuitable specimen. However, when the specimens are self-collected (see Chapter 6) this control of suitability is essential, since individuals may collect their sample incorrectly or neglect to collect the sample altogether. If necessary, an additional separate test for human DNA should be performed.

EXTERNAL QUALITY ASSURANCE PROGRAMS (EQAP)

An EQAP is administered to diagnostic laboratories by an external agency, such as a national or international reference laboratory, to ensure that the results are correct and comparable across all the participating laboratories. Thus, an external proficiency program has the double aim of quality control and standardization of the results. A proficiency program usually takes the form of a number of negative and positive specimens (panel) selected to evaluate the characteristics of the test. The participating laboratories should return correct results, which fall within the average of all the participating laboratories. The laboratories should also provide proof that they can handle the testing by returning the results with an appropriately redacted report within a set turn-around-time.

HPV testing presents some peculiar issues that a proficiency program should address. The first issue is that HPV screening tests detect 14 types of high-risk of HPV (16, 18 and 12 others, see Chapter 3). A robust proficiency panel should include positive specimens that contain each of the 14 types and negative specimens that contain a cocktail of the most common low-risk types, to ensure the lack of cross-reactivity.

A second issue is that before detection of HPV the samples must be processed to prepare nucleic acids for detection, a process called extraction. This process varies greatly among the different testing platforms and instrumentation, and it is a major source of variability. Additional variability results from the use of different transport media (e.g. alcohol-based media, dry swabs or aqueous media) that can influence the performance of the test. Ideally, a proficiency program should be able to measure and address these extraction variables.

A third issue is that some tests (e.g. Hybrid Capture or Cobas 4800 HPV) detect the viral DNA, while others (e.g. APTIMA) detect viral mRNA (See Chapter 5). Previous international panels based on cloned HPV DNA would not be suitable for the latter tests.

A number of proficiency panels of different composition have been developed and distributed to testing laboratories. Since 2002, the WHO HPV Laboratory Network Global Reference Laboratory, situated in Malmo, Sweden, has periodically distributed a panel containing a number of DNAs from high and low-risk HPV types2. This panel contains cloned viral DNA and HPV-positive cell lines for HPV16 and 18, but it is more appropriate for proficiency evaluation of genotyping assays used for molecular epidemiology that for diagnostic HPV assays used for cervical cancer screening. Other limited proficiency programs using panels of various composition have been developed in various countries (summarized in references 1, 3 and 4). The results underscore the variability in performance of different HPV testing platforms in different laboratories.

Given the issues summarized above, a useful proficiency program should use a panel derived from characterized clinical specimens, similar, on a smaller scale, to the Valgent panel used for validation of new HPV tests (see Chapter 3).

Such a panel is not yet available in Canada or internationally on a global scale and it should be developed before HPV testing is used for routine screening. Development of a panel for an external quality assurance program is not technically difficult, but the delivery and administration of the program requires considerable resources and the creation of a national network of participating laboratories.

LABORATORY NETWORKS AND REFERENCE LABORATORIES

Laboratory networks are strong guardians of the quality of laboratory testing. Led by global, regional or national laboratories, networks do not just provide EQAPs, but they are also instrumental in the dissemination of knowledge and resources to low-resources jurisdictions, the development of standards and guidelines, the evaluation of new technology and the surveillance for diagnostic problems, such as poor kit performance or the emergence of undetectable variants. These activities require considerable resources.

There is a WHO HPV Laboratory Network5, which includes a number of specialized HPV laboratories across the world. However, as the routine use of HPV testing for screening becomes more widespread, the strengthening and expansion of a global network involved in EQAP and standardization is desirable.

In Canada, a reference laboratory at the National Microbiology Laboratory has been involved in HPV molecular epidemiology, but no reference laboratory in Canada has been involved in the development of a pan Canadian EQAP. An EQAP should be established while the use HPV testing for routine screening becomes widespread in Canada.

HPV SCREENING PROGRAM EVALUATION

Like the performance of Pap screening programs are evaluated periodically in term of population uptake, incidence of lesions, diagnostic accuracy and therapeutic outcomes, so the results of HPV-based screening programs

should be evaluated in every jurisdiction and, desirably, nationally.

Once HPV testing follow-up algorithms are decided and implemented (see Chapter 3), it would be possible to calculate the incidence of positive HPV results and their correlation with cytology results. This type of surveillance will be pivotal in determined the real sensitivity and specificity of the HPV screening tests.

In addition, most tests used in Canada for HPV screening will provide information on the incidence of HPV 16, HPV 18 and the other 12 high-risk types. These data can be used for surveillance of HPV vaccine effectiveness and reduction of the burden of disease.

RECOMMENDATIONS

For Canada:

15. **Through a national reference laboratory, create a formal laboratory network of HPV testing laboratories to implement a pan Canadian EQAP and standards for HPV testing.**
16. **Plan for a program for the evaluation of the performance of HPV testing as a screening tool and its clinical outputs.**

For International:

17. **Potentiate the WHO HPV Laboratory Network to include all the jurisdictions that perform HPV screening.**
18. **Develop international EQAP and standards for HPV screening.**

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Chapter 5
Integrating HPV Vaccination and Screening Registries for Efficient Surveillance of Screening Policies among Vaccinated Women

- **Salaheddin M. Mahmud**, MD, PhD, FRCPC, Professor of Community Health Sciences and Pharmacy, The Rady Faculty of Health Sciences, University of Manitoba, Winnipeg
  - Eduardo L. Franco, DrPH, PhD (Hon.), OC, FRSC, FCAHS
  - James McGill Professor and Chair, Gerald Bronfman Department of Oncology, McGill University, Montreal

OVERVIEW

Fragmented planning and delivery of cervical cancer prevention programs can hinder their ability to lessen the burden of disease, hamper safety, reduce overall client satisfaction with the services delivered, waste human and financial resources and hinder program evaluation and research.

DESCRIPTION

The discovery of the human papillomavirus (HPV) as the underlying cause of cervical cancer has led to several major advances in the effort to reduce the burden of this devastating disease. We now have three vaccines that can effectively prevent infection with the HPV types that are responsible for most cervical cancers (see Chapter 2). New HPV-based screening tests are more sensitive than conventional cervical (Pap) cytology, for the early detection of HPV-induced lesions, such as cervical dysplasia (precancerous lesions that can lead to the development of invasive cervical cancers (see Chapter 3)). HPV testing can also guide the diagnosis and management of detected precancerous lesions by cytopathologists and colposcopists (see Chapter 3).

The combination of vaccination (and other sexual health programs) to reduce HPV infection and screening programs to detect and treat precancerous lesions before they turn to cancer have become today's main prevention front against cervical cancer. In most high-income countries (including Canada), publicly-funded vaccination programs targeting adolescent and young women were implemented, typically as a component of routine school-based vaccination programs. Vaccination against HPV is expected to reduce the burden of cervical cancer substantially.[1] However, screening for cervical cancer will still be needed for the foreseeable future because older women who were not targeted by the vaccine programs will continue to develop cervical cancer. Even among targeted cohorts, some women will not be protected because of lack of vaccination, poor adherence to vaccination schedule or because they were infected by non-vaccine HPV types. Therefore, cervical screening must continue in the era of HPV vaccination, not the least on ethical grounds.[2]

But existing cervical cancer prevention programs cannot continue unaltered. As we predicted,[2] and it has now been widely proven,[3] the earliest outcome from widespread HPV vaccination is a decrease in the prevalence of precancerous lesions in screened cervical cytology specimens. This in turn will lead to substantial reduction in referrals to colposcopists for further management which should translate into initial savings for patients and the healthcare system. But in the long term, this trend can entail important consequences to Pap screening performance. Reduction in caseload is expected to be gradual and will be a function of two factors: i) the overall uptake of HPV vaccination by successive cohorts, and ii) the time it will take for vaccinated young women to reach screening age. It is well-known that as disease prevalence decreases, there will be a commensurate increase in the proportion of screened people with false-positive testing results.[2] As successive cohorts of women become vaccinated and lesion prevalence decreases to below 1% (not an unrealistic scenario), the majority of women flagged by screening will turn out to be healthy on further examination increasing the risk of anxiety and unnecessary medical referrals and interventions.[2]

Furthermore, declining disease prevalence can negatively impact the sensitivity and specificity of a screening test in both quantitative and qualitative terms. We now know that even under stringent quality assurance standards, Pap cytology's specificity does not exceed 98% whereas

its sensitivity is only slightly better than 50%.[4] As the prevalence of genuine cervical dysplasia decreases, the signal (precancerous abnormalities) to noise (e.g., benign inflammation) ratio could also decrease and less conspicuous lesions could be missed by cytotechnicians, resulting in further loss of test sensitivity. On the other hand, fear that relevant abnormalities may be missed could lead to more overcalls of benign abnormalities, and consequently, a loss in specificity.[2] To avoid malpractice lawsuits, cytotechnicians in litigation prone countries will likely become more conservative in interpreting slides, and in other settings, policy officials may recommend maintaining unnecessarily frequent screening visits to protect against false-negative diagnoses.[2]

To preserve screening efficiency in the HPV-vaccination era, several high-resource countries, including Canada, have adopted HPV-based cervical cancer screening tests to replace or supplement conventional Pap cytology testing. In particular, switching to liquid-based cytology as an alternative to traditional glass-slide cytological smears, has facilitated concurrent HPV testing and improved the efficiency of processing cervical samples in screening programs. Screening using HPV testing is more sensitive, but less specific, than liquid-based or conventional cytology in detecting precancerous lesions.[5] It is also more reproducible, not prone to the vagaries of morphologic interpretation and less likely to vary in sensitivity and specificity as a function of decreasing prevalence in infections and lesions. HPV testing is more amenable to automation, and testing can be centralized, and quality checked for large specimen throughput. If deployed for high volume testing (such as in primary screening), HPV testing can be more cost-effective than cytology. Finally, if HPV testing is combined with Pap cytology, the joint negative predictive value can be so high among vaccinated cohorts that it justifies extending screening intervals, resulting in further cost-savings.[6]

To make the most of these new technologies, screening programs will need to be redesigned from the ground up in light of the knowledge base that has accumulated over the last two decades or so on cervical cancer prevention. Planning must take into account the likely impact of HPV vaccination on the performance of the competing screening technologies and recognize that simple maintenance of existing cytology-based programs, with the added costs implied by large-scale vaccination, will place an enormous strain on public health budgets. Adopting HPV testing with Pap triage ensures that cytotechnicians would not experience the fatigue and monotony when reading smears under conditions of low prevalence of abnormalities. This approach also has the benefit of preserving a trained cytology workforce and underscores the value of cytopathology in lesion management. Future adoption of promising HPV genotyping assays and other risk markers may further improve the efficiency of cervical cancer screening.

Technological progress in HPV vaccination, screening and management has been fast-paced in the last few years requiring significant changes to both public health and clinical practice. Whereas the availability of these technologies holds the promise of eradicating cervical cancer, it also creates new and significant challenges especially in countries that had also invested heavily in the older technologies. One major challenge is the coordination of the planning, delivery and evaluation of increasingly complex prevention programs involving multiple functions, providers and levels of the healthcare system.

Like other healthcare services, cervical cancer prevention services require three essential functions: 1) program planning and design; 2) delivery of services; and 3) program evaluation and research. Program planning involves goal and target setting, budgeting and resource allocation, procurement and distribution, practice guideline development, information system management and training. Delivery of services involves case management, follow-up and recall and client education. Program evaluation and research involves data management and sharing, data analysis and feedback and knowledge translation.

In most Canadian jurisdictions, vaccination programs are typically planned, implemented and managed by regional or provincial public health authorities that also manage other routine childhood and school-based vaccination programs. By building on existing expertise and logistical and managerial infrastructure, effective HPV vaccination programs were promptly launched within few years of the approval of these vaccines. This is an example of how integrating preventive services can lead to improved

program effectiveness and client satisfaction while reducing both capital and operating outlays and logistical complexity.

In most Canadian jurisdictions, conventional cervical screening programs are also managed centrally by a regional or provincial agency. Planning, funding and evaluating cervical screening policies and programs are typically coordinated by provincial cancer care agencies. However, most of the actual delivery of Pap cytology screening services (e.g., sample collection, follow-up and management) is conducted by publicly-funded private providers (e.g., family physicians, nurse practitioners, gynecologists) whereas testing of the collected specimens is conducted by cytotechnicians and cytopathologists in private and public laboratories.

The goal of integrating preventive cancer services such as screening into provincial cancer agencies is to ensure seamless transition between screening of cancer and the diagnosis and treatment stages of cancer management. This is an important goal since gaps in the delivery of essential cancer care services can lead to poor patient outcomes and both patient and provider dissatisfaction. However, cancer care organizations tend to operate at a different level and to have a different focus (direct patient care) and culture than the public health departments with their focus on prevention and population-level interventions such as vaccination programs. Incorporation of new HPV screening tests adds another layer of complexity by involving both public and private virology laboratories which were not traditionally involved in cervical cancer screening and management. In addition, including service providers (e.g., family physicians and nurse practitioners) and their professional associations and unions as well as academic researchers is essential for the success of transition into new technologies.

The lack of coordination between these players in the planning and delivery of HPV prevention programs can hinder their ability to lessen the burden of disease, hamper safety, reduce overall client satisfaction with the services delivered, waste human and financial resources and hinder program evaluation and research. On the other hand, integration and linkage of surveillance systems for vaccination and screening enable efficient monitoring of cervical lesion prevalence consequent to changes in vaccination policy, e.g., from 3 to 2 doses, or to changes in age of vaccination, which have happened in Canadian provinces, as well as in other countries. Moreover, properly integrated vaccination and screening registries enable conducting retrospective studies aimed at determining the most appropriate screening age and interval among vaccinated women. Randomized controlled trials, the methodological gold standard of public health evidence, cannot answer such questions because of the rarity of the outcomes, which would make them prohibitively expensive and lengthy. It is only through efficient use of vaccination and screening registries that questions related to screening policy among vaccinated women can be properly and realistically addressed.

RECOMMENDATIONS

For Canada and International:

19. **Research and development of governance models, evaluation criteria and best practices for integrating cervical cancer preventive services at all levels.**
20. **Ground up redesign of how these services are managed, delivered and evaluated might be necessary.**
21. **Reduce bureaucratic and legal barriers for information sharing among the various stakeholders and incorporating "real-time" vaccine and screening information into clinical electronic health records.**
22. **Integration of HPV vaccination and cervical cancer screening registries permits efficient surveillance of adoption or changes in prevention policies and enables epidemiologic investigations of optimal screening policies among vaccinated women.**

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Chapter 6
Cervical Cancer Control in Hard to Reach Populations: Participation and Recruitment for Screening/Self-sampling

- **Ann N. Burchell**, PhD, Department of Family and Community Medicine and Centre for Urban Health Solutions, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Ontario
  - Aisha Lofters, Department of Family and Community Medicine and Centre for Urban Health Solutions, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Ontario
  - C. Sarai Racey, School of Population and Public Health, University of British Columbia, Vancouver, British Columbia
  - Laurie Smith, BC Cancer & Women's Health Research Institute, Vancouver, British Columbia

INTRODUCTION

Most cases of cervical cancer occur among women who are under-screened, either because they have never been screened or because they have not attended routine screening.[1,3] Reaching cancer prevention targets requires concerted effort to engage such populations of "hard to reach" women to participate in timely screening. In this chapter, we outline:

1. The challenges for participation in cervical cancer screening and the populations of women who are considered "hard to reach"
2. The case for self-sampling as a potential means to improve screening attendance in such populations
3. The recommendations regarding broad-scale implementation of self-sampling as a screening strategy for hard-to-reach women

BARRIERS TO SCREENING PARTICIPATION

Social determinants of health, including income, education, employment and other social and cultural factors, can influence health care attendance including cancer screening. Underscreening more commonly occurs among certain populations of women adversely affected by social determinants of health, generally for reasons related to poverty, language/culture, geography, and other social determinants. These include women who have low socioeconomic status, street-involved women, Indigenous women, immigrant women, women living in rural and remote communities, and women who identify as lesbian.[2,3] Among such women, barriers for screening may stem from embarrassment or discomfort undergoing a pelvic exam, which may be for religious or cultural reasons or past histories of abuse. Access to healthcare may also present barriers. Women may not have a family doctor. They may experience difficulties attending a clinic visit for reasons such as inconvenient clinic hours, transportation challenges, and problems taking time off work or getting childcare. Such difficulties may be particularly challenging for rural women. For some immigrant women, language issues may also pose a barrier to attending screening.

SELF-SAMPLING AS A POTENTIAL SOLUTION TO ENGAGE HARD-TO-REACH WOMEN

The transition from Pap cytology testing to HPV testing as the means of cervical cancer screening has opened the door for women to be able to collect her own vaginal sample using a swab or brush.[3] If appropriate laboratory tests are available, self-collected vaginal swabs are as good as those collected by a clinician for detection of cervical squamous intraepithelial neoplasia (CIN) grade 2 or greater. If a PCR-based test is used, self-sampling is as accurate as clinician-collected specimens1. However, the accuracy of signal amplification-based HPV tests for self-samples is inferior.[1]

An appealing feature of self-sampling is that it need not be collected at a clinic. Women can self-sample at home and mail the specimen to a laboratory for testing for high-risk types of HPV. Women whose sample is HPV positive would still need to attend a healthcare clinic, where a clinician would collect a cervical specimen for Pap cytology testing.

Thus, self-sampling eliminates the initial cervical cancer screening requirement that women visit a clinic and undergo a pelvic exam. This may remove a number of barriers for hard-to-reach women.[2,3] Mailed samples may address lack of time, not having a regular family doctor,

and difficulties attending healthcare visits. Not needing an exam may address hesitation due to embarrassment, discomfort, shame, cultural or religious reasons, and trauma for women who have past experiences of sexual abuse. In studies of its acceptability, some women may worry about self-sampling correctly. Easy-to follow illustrations and assurances regarding the test accuracy are important to alleviate such concerns.[2]

There are different ways that self-sampling can be offered to hard-to-reach women in screening programs. These are commonly distinguished as being either opt-out or opt-in strategies.[3] Opt-out strategies involve mailing a kit directly to women for screening, so that all have the immediate ability to perform screening, though some may opt out. This has the advantage of reaching the maximum number of women. If participation is low, however, it has the disadvantage of wasted kits that go unused. Opt-in strategies, on the other hand, invite women to request a kit, either online or by telephone. Opting in has the advantage of minimizing costs as kits are only sent to women who express an interest, but the requirement that women take this extra step may be a barrier to uptake.

In clinical trial settings, an offer of self-sampling to hard-to-reach women generally results in more women participating in screening, compared to sending invitation or reminder letters[1]. The gain in participation depends on the way that women are offered self-sampling. On average, participation doubles for opt-out strategies, such as when all women receive a mailed self-sampling kit and for community-wide or door-to-door campaigns1. When women receive a letter inviting them to request a self-sampling kit, on average there is only a modest improvement in participation, if any.[1]

Improvements in participation with offer of self-sampling vary widely across settings, and depend greatly on the background screening rate.[1] In Canada, two trials investigated the comparable benefits of self-sampling to standard offer of an invitation to undergo Pap testing among Indigenous women[5] and rural women.[4] The study among Indigenous women also incorporated a community campaign to promote literacy regarding cervical cancer prevention. Both observed an increase in screening participation. In rural Ontario, women who received a self-sampling kit were twice as likely to screen as women who received a mailed invitation for Pap testing (32% versus 15%, respectively).[4] Among Indigenous women living in First Nations communities in northwestern Ontario, 20% of women offered HPV self-sampling participated in screening compared to 14% of women who were offered a Pap test.[5] In both studies, women who self-sampled generally considered the procedure acceptable.

Subsequent follow-up of women who test positive for high-risk HPV types with self-sampling is essential to diagnose and treat any precancerous lesions. In clinical trials, on average 81% of such women attended follow-up care1. In roll-out of self-sampling in community settings, monitoring follow-up care will be critical. If it is low, any benefit from initial screening participation will be lost. Efforts to ensure that women attend follow-up care must be in place. Indeed, self-sampling of hard-to-reach women may be an opportunity to re-engage them in primary care. It is essential to put in place mechanisms to communicate results to women and to their family doctor (if they have one) or connect them to primary care (if they do not have a family doctor).

Implementation of self-sampling strategies for hard-to-reach women requires the availability of good quality health administrative data regarding screening histories3. Screening registry data allow for the identification of women who are long overdue for screening. History data can be used to ensure that women who are up-to-date on screening do not needlessly receive a screening invitation. Screening registries should have broad geographic coverage and means to update women's change of address so that mobile women do not fall between the cracks.

Self-sampling has been introduced, piloted, or is being considered for introduction as an option for routine screening program in a number of countries.[1,3] Lessons learned from early adopters such as the Netherlands, Australia, the United Kingdom and Denmark will be highly informative to guide program planning in Canada.

RECOMMENDATIONS

For Canada:

As provincial and territorial governments move toward implementation of HPV testing as the primary cervical

cancer screening test in Canada, the self-sampling option should be established to complement existing programs.

23. **Offer self-sampling to women who do not attend screening. There is substantial evidence that opt-out strategies using mailed kits can improve participation among hard-to-reach women. Initially, pilot implementation projects can establish logistics, costs, and participation rates that can in turn inform the ideal balance of opt-in versus opt-out approaches.**
24. **Build system capacity to support self-sampling. Data systems must be in place to correctly identify women who are due for screening and who do not respond to invitations to attend screening with their provider. Laboratories must implement validated PCR-based HPV tests for these specimens. Communication systems must be in place for women, laboratories and healthcare providers so that women whose sample is positive for high-risk HPV attend the necessary follow-up care to diagnose and treat any existing disease.**
25. **Ensure that patient and provider education is a core component of self-sampling programs. Implementation of any self-sampling strategy requires education for patients and providers, as self-sampling alone will not address poor literacy regarding HPV and cervical cancer prevention.[3] Materials included with kits should highlight the need for screening, build women's confidence in the accuracy of self-sampling, and emphasize attendance at follow-up care for women who test positive. Having materials available in multiple languages and cultural tailoring of messages may be useful, particularly for Indigenous and immigrant women.**

For International:

Non-participation in cervical cancer screening remains a challenge in many countries.[1,3] Self-sampling strategies have world-wide potential to help reach the global prevention goal that at least 90% of women participate in screening. Additional recommendations to reach that goal are as follows.

26. **Advocate for global adoption of HPV testing as the primary cervical cancer screening test. Self-sampling for screening requires that HPV testing is already in place. Globally, most countries have not yet made this essential transition.**
27. **Support the development of low-cost self-sampling kits. Reducing costs will be crucial for implementation in low resource settings. Desired improvements include those that allow for inexpensive shipping, point-of-care results, and increase the predictive value for high-grade disease via testing for biomarkers. Minimizing the number of clinical encounters needed for women to streamline those at high risk for immediate diagnosis and treatment would eliminate important barriers for screening among hard-to-reach women.**

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Chapter 7
Deciding Follow-up for Women with High-risk HPV Infection

- **Hélène M. Gagné**, MD, FRCSC, Assistant Professor, Department of Obstetrics and Gynecology, The University of Ottawa, Ottawa

OVERVIEW

The purpose of this chapter is to compare options for the triage of women with a positive HPV test in the primary screening setting. These options may differ in different resource settings. Management of HPV test positive women can include colposcopy, screen and treat protocols, and conservative follow-up. This includes planning the follow-up of HPV positive women without a cervical precancerous lesion. The population will need to be educated regarding HPV infection, and support services offered to optimize health outcomes in HPV positive women. These services can also be used for other health promotion activities such as vaccination, smoking cessation, and family planning.

DATA AND DESCRIPTION

The implementation of HPV testing as a screening modality will identify women at increased risk of cervical dysplasia or pre-cancer. This group of women once identified will require assessment and triage, to then be directed to diagnostic testing and/or treatment if appropriate.

The triage and follow-up of these women depends on the resource availability and infrastructure already existing in the community. In high resource countries such as Canada, the current infrastructure exists to assess women with abnormal cervical screening in colposcopy clinics. The colposcopy process involves examination of the cervix under low-power magnification, with the aid of acetic acid solution applied to the cervix to identify areas suspicious for dysplasia (pre-cancerous lesions). Directed biopsies are then taken of suspicious areas, for microscopic examination by a Pathologist. If there is a confirmed high-grade lesion then a treatment (usually a large loop electrosurgical excisional procedure [LEEP] procedure that excises the affected area) is offered to the patient. See and treat protocols (where diagnosis and treatment are both done in a single visit) are an acceptable option for obvious high-grade lesions in situations where the risk of the procedure is minimal (family complete) or when follow-up is uncertain (long distance travelled, less reliable patient).

The use of HPV testing instead of cervical cytology will necessitate a different algorithm to direct patients to colposcopy. The proposed algorithm is similar to that currently used in Australia and the Netherlands, and that proposed by the US Preventive Services Task Force.[1] Triaging HPV positive women with either cytology (Pap test) or HPV genotyping (identifying involved HPV types) significantly reduces the number of women referred to colposcopy by identifying the ones most at risk of high-grade disease needing treatment.

The current suggested protocols for triage are either cytology with referral to colposcopy for any abnormal result, or using HPV genotyping to tease out the patients who are at higher risk of developing high-grade lesions. If the cytology is negative then a follow-up HPV test is recommended in 12 months' time. If that test is positive then the patient is referred to colposcopy.

An alternative is using HPV genotyping to better identify high-risk disease. This HPV test also identifies HPV16/18 positive samples. These virus subtypes are more likely to cause significant disease (70% of cervical cancers). If the testing shows HPV 16/18 positivity then the recommendation is to refer directly to colposcopy. For non-16/18 HPV positive tests, then the recommendation is for reflex cytology and referral to colposcopy for any abnormal cytology. Again, should the cytology be negative it is recommended to repeat the HPV test in 12 months.

A systematic review[2] of randomized controlled trials evaluating the performance of HPV testing over two or more rounds of screening reported that in the first screening round, significantly higher numbers of high-grade lesions were detected in women who were screened with HPV testing compared with those who had cytology. In the second round, lower numbers of high-grade lesions were detected in the women who underwent HPV testing at first screening. Current evidence suggests that HPV

testing as a stand-alone screening tool, or combined with cytology, is associated with higher initial rates of referrals to colposcopy compared with cytology alone.[3] Over time these proportions will change due to HPV vaccination.

This system of HPV screening and triage depends on the ready availability of cytology and colposcopy resources. There may be an increased demand on colposcopy resources initially in areas with poor vaccination coverage. In areas with good vaccination coverage colposcopy may become more challenging as the cervical lesions become more subtle and difficult to identify. This would be due to the near elimination of HPV16, which is associated with large and easy to identify lesions. Ongoing education of colposcopy practitioners will be necessary to keep up with the changing landscape of colposcopic findings as these protocols are put in practice.

The current screening protocols and colposcopy models will likely easily adapt to HPV screening as Canada benefits from well-organized provincially administered cervical screening programs. The adoption of HPV tests for cervical screening may occur at different times across the provinces, and the chosen triage techniques may also differ. National guidelines and protocols could be beneficial considering the mobility of our patient and provider population. This would permit large scale registries and studies leading to improved patient outcomes.

Low- and medium-income countries (LMICs) face significant challenges in following women with positive HPV tests and cervical screening. Colposcopy resources and practitioners are scarce. Woman can live in remote areas and have difficulty in reaching practitioners. There is often also a lack of availability of pathology resources. Different modalities must be applied in those settings.

The World Health Organization advocates a policy of "screen and treat" to cervical screening in LMICs. This involves visual (naked eye) inspection of the cervix with acetic acid (VIA) or Lugol's iodine (VILI), followed by cervical cryotherapy treatment (freezing the cervix with a cryoprobe) if a lesion is identified. This approach still depends on patient recruitment, the availability of skilled practitioners, specific equipment and supplies, and on women being able to reach testing sites.

The comparatively high cost and resource requirements of HPV-based screening have to date prevented many LMICs from implementing HPV based screening programs. A significant development has been the introduction of new easy to use and highly accurate HPV tests that can be provided at point of care with same day results. These could enable LMICs to implement 'test and treat' approaches for cervical cancer screening. Self-collection of samples for HPV testing could also make these tests more accessible for women in remote communities or who prefer to avoid contact with health care providers.

Available technologies for treatment under "screen and treat" or "test and treat" protocols include cryotherapy, electrocoagulation, and updated technologies under development which would simplify these treatments to make them appropriate for settings without easy transportation, energy sources, and access to products. Traditional cryotherapy for example needs difficult to obtain and to transport canisters of gas. Handheld, battery powered alternatives are being developed.

This single visit approach has shown great effectiveness in reducing high-grade lesions while being much less costly and demanding of time than the multi visit approach involving colposcopy and biopsies.[4] These ablative treatments are technologically simple, easy to use, have a very low risk of adverse pregnancy outcomes, and are generally well tolerated by patients.

With recent development of low-cost HPV point of care tests and less burdensome treatments that can be initiated in a single visit, the implementation of organised screening programs in low and middle-income countries could be achievable in the short term. Financing to these countries for training of practitioners, logistical support, purchase and distribution of supplies, and patient education would accelerate the possibility of reaching testing and treatment goals in LMICs.

By changing the screening protocols to HPV testing, many women will be labelled as having a sexually transmitted infection. Depending on her environment this could have grave consequences to her safety and her family. The fear of these consequences could be a deterrent to participation in screening programs, and to treatments

that prevent cervical cancer. Education around HPV will need to be emphasized to ensure screening participation. Other factors related to HPV risk such as family planning resources and smoking cessation programs will have to be in place to support HPV positive women and improve their health outcomes. Contact with screening programs can be a privileged opportunity to introduce other public health measures to women and they families such as vaccination programs, nutritional support, and prenatal care.

The management of HPV positive women will change over time as new technologies evolve and as the landscape of HPV infection changes due to vaccination. Health practitioners and screening programs will need to adapt as new data and protocols evolve. Governments and non-governmental organizations (NGOs) will need to stay afloat with these changes to ensure that funding and policy follows to reach cervical cancer elimination goals.

RECOMMENDATIONS

For Canada:

28. **Promote a national strategy for implementation of primary HPV screening and management of positive results.**
29. **Ensure ongoing education of the population and of health practitioners to engage them in these new screening paradigms and to encourage high levels of screening participation.**
30. **Engage in funding these health innovations which benefit all Canadians.**

For International:

31. **Commit to funding international efforts to implement and study protocols that identify and treat women at high risk of cervical cancer.**
32. **Support women in countries without cervical screening programs by engaging their governments through funding and diplomatic channels.**

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Chapter 8
Treating Women with HPV-associated Cervical Lesions

- **James Bentley**, MB ChB, FRCSC, Professor and Head, Department of Obstetrics and Gynaecology, Dalhousie University, Halifax, Nova Scotia; President, Society of Gynaecologic Oncology of Canada; President, International Federation of Cervical Pathology and Colposcopy

OVERVIEW

Cervical cancer can be prevented by treating pre-invasive HPV-associated changes This chapter will discuss the management of HPV-associated cervical lesions both pre-invasive and invasive.

DATA AND DESCRIPTION - PREINVASIVE DISEASE

Conventional screening done in many countries is based on cytology and referrals to colposcopy for further evaluation are made based on findings of either persistent low-grade changes or high-grade changes. In low resource settings the primary screen is often done by VIA (visual inspection with acetic acid), women are then usually triaged using the guidelines outlined by the World Health Organisation with immediate treatment being done for positive or acetowhite findings that potentially represent pre-cancerous changes.[1] This treatment is often done by non-physician health-care providers using cryotherapy. However, there will always be a need for competent colposcopy and treatment by physicians with excisional procedures. Increasingly, HPV testing is being implemented in demonstration projects and in country-wide roll-outs. This is a sensitive test that screens women into a secondary test such as a Pap test and those that have a Pap abnormality are then referred on for colposcopy. This has the potential to improve the prevention of cervical cancer by increasing the detection of cervical cancer precursors which are then treated. It is only by the treatment of precancerous changes that cancer is prevented.

Colposcopy should be done by health care practitioners following an organized approach and as part of a quality control process, as occurs in most Canadian provinces. The ideal situation for this is a hospital-based clinic with adequate education of the patients and colposcopists who are seeing adequate numbers of patients to ensure maintenance of competence. When the patient is seen, the colposcopy should be done following an organized process and the colposcopic findings should be described using the International Federation of Cervical Pathology and Colposcopy (IFCPC) 2011 terminology. The use of this terminology, in combination with a scoring system such as the Swede score should allow for accurate reproducible diagnosis of high-grade findings on the cervix. This will allow women to be stratified into high or low risk stratifications and decisions about treatment can be made. Treatment of the abnormal cervix is usually facilitated through a large loop excision of the transformation zone (LLETZ) otherwise known as a large loop electrosurgical excisional procedure (LEEP). There is evidence that harm can occur when larger portions of the cervix are excised and this harm is manifest by preterm delivery. Recent Canadian evidence has shown that a significant proportion of pre-cancerous changes resolve spontaneously in young women. In a population-based study from Nova Scotia in women less than 25 years of age with CIN 2 regresses in over 70% of cases. CIN 2 is the middle grade of pre-cancerous changes, with CIN 1 being the lowest grade of abnormality that usually resolves without treatment and CIN 3 usually requiring treatment as it has higher rates of progression to cancer and regresses less often.

As stated, treatment in Canada is usually done with an excisional procedure in the outpatient setting. In Low resource settings cryotherapy is used, however this requires carbon dioxide (CO_2) tanks which can be problematic. Recently there has been a reintroduction of thermal coagulation. This uses electricity to heat a probe to 100oC which causes adequate depth of treatment and is comparable to cryotherapy. It had advantaged that it is portable and can be uses with a battery pack.[2]

The provision of colposcopic services should be done with a rigorous quality assurance focus. In Canada the provincial screening programs and the Pan-Canadian Cervical Screening Network (Part of the Canadian Partnership against Cancer) work together to develop standards for screening and colposcopic practice with

metrics that should be measured and reported by all jurisdictions. This should also include provisions for monitoring follow-up of abnormal screens and compliance with recommendations, to ensure that marginalized groups are not neglected. Colposcopy standards are in place in many countries but many LMIC's do need to develop integrated services with a quality focus.

The use of artificial intelligence in colposcopy is evolving, the National Cancer institute in the USA and other groups are working with new cameras and computers that analyze the image of the cervix before and after acetic acid has been applied and then more accurately recognize cervical cancer and precancer. A recent study using existing cervical images demonstrated an increased accuracy over conventional colposcopy. This may lead to an effective method of point-of-care testing.[3]

RECOMMENDATIONS

For Canada:

33. Screening and colposcopy should focus on age groups that benefit and where there has been a demonstrated reduction in cervical cancer. This means that these services should begin at age 25 at the earliest.
34. Quality colposcopy should be performed and treatment outcomes should be measured by the provinces and reported in National reports such as those published by the Screening group at CPAC.
35. Treatment should be appropriate and focus on women who truly at risk of cervical cancer.
36. Treatment modalities should be expanded to include screen and treat or screen and treat in remote areas, using thermal coagulation.

For International:

37. Screening should be done by effective methods that access as many women as possible, and are appropriate to the available resources
    a. VIA initially
    b. Primary HPV testing ideally
38. Treatment should follow WHO guidelines for VIA screening
    a. Uses a screen and treat approach for suitable cases
    b. Refer to regional colposcopy centers for: large lesions, concern re cancer, an abnormal cervix unsuitable for cryotherapy or thermal coagulation.
    c. Widespread implementation of thermal coagulation as the treatment of choice.
39. Regional, and national authorities should implement appropriate quality assurance programs.

DATA AND DESCRIPTION - CANCER

Cervical cancer management varies by stage of disease with lesions less than 4 cm (stage 1B 2 cancers and less) traditionally being offered surgical management. More advanced disease is usually treated by radiation therapy in combination with chemotherapy as a radiation sensitizer; this has been the global standard of care since 1997. Adequate radiation resources particularly brachytherapy or internal radiation are not available universally particularly in low-resource settings. This has led to the usage of neoadjuvant chemotherapy (use of chemotherapy before surgery or radiation), however at this time it is not clear if this improves the outcome over surgery for larger cancers. Ideally a decision is made to use either surgery or radiation therapy and not both, as complications are greater when both modalities are used.

The recent (2018) staging system for cervical cancer have made some changed that reflect the current surgical management.[4] A stage 1B1 cancer is greater than 5mm and less than 2 cm in maximal diameter. Conventional surgery would be a radical hysterectomy with excision of the tissue at the side of the cervix in addition to lymph node resection. There is a Canadian led international trial designed to answer the question of whether this is necessary or whether a simple hysterectomy with lymphadenectomy would be adequate. This approach has the advantage of significantly less morbidity and also requires less training for a gynecologist to become proficient, which will help with delivery of care. In assessing cases preoperatively imaging information can now be used to asses retroperitoneal lymph nodes, with positive disease being noted to be stage IIIC, appropriate imaging will correctly direct treatment towards radiation.

In surgically treated cervical cancers the route of surgery has become controversial. Minimally invasive surgery by

laparoscopy or robotically has been introduced and widely adopted. A recent randomized trial has shown that the survival outcome was better with comparable quality of life outcomes when a conventional open surgery was used.[5] This has led national societies in Canada to recommend that caution should be used and minimally invasive surgery is not the preferred route. This recommendation did note that the trial was not able to conclusively answer the safety question for tumors smaller than 2 cm.[6]

In young women with less than 2 cm lesions there is a role for a procedure called a radical trachelectomy to remove the cancer and then allow pregnancy with good results. This should be offered in high volume centers to appropriate candidates.

SOLUTIONS

- When a surgical approach is taken, focus on open surgery to improve survival.
- Follow the results of trials on surgery for < 2 cm lesions to optimize the radicality of surgery necessary.
- Need widespread global access to radiation oncology services.
- If radiation not available neoadjuvant chemotherapy may be used to make a case operable.

RECOMMENDATIONS

For Canada:

40. Colposcopic services should have an integrated quality assurance system, reporting locally, provincially and nationally

41. Treatment should be avoided in women when precancerous lesions are likely to resolve thus avoiding harm

42. Consideration should be made to a screen-and-treat or see-and-treat policy using thermal coagulation in remote areas

For International:

43. Screen and treat with thermal coagulation should be implemented in low resource settings

44. Need access to adequately trained colposcopists and LLETZ/LEEP

45. Surgery for cervical cancer should be done via laparotomy to optimize survival.

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Chapter 9
Making Surgery and Systemic Therapy Available to All

- **Laurie Elit**, MD, MSc, FRCS(C), Professor Department of Obstetrics and Gynecology, McMaster University; Division Head, Gynecologic Oncology, Juravinski Cancer Centre, Hamilton

INTRODUCTION

High risk HPV is a causative agent in almost all cases of cervical and anal (80-90%) cancers and some oropharyngeal (OPC) (25-35%), penile (40-50%), vulvar (40%), and vaginal (40%) cancers.[1] Once a cancer is diagnosed, treatment usually involves surgery, radiation, systemic therapy or a combination of these.

Across these different disease sites, surgery has a role in prevention (i.e., diagnostic excisional biopsy of the cervix for high-grade dysplastic lesions), diagnosis (i.e., wide local excision to identify depth of microscopic disease), radical excision (for curative intent in localized disease), palliation of symptoms (i.e., colostomy for bowel obstruction) and reconstruction (i.e., head and neck cases). While surgery is the usual strategy for local disease (stage 1), in anal cancer and bulky (Stage 1C) cervical cancer, primary treatment outcomes are superior with chemoradiation (CRT). Treatment of locoregional disease (stage 2-3) usually involves CRT. Those with metastatic disease (stage 4) are usually treated with chemotherapy (with or without biologics (like bevacizumab)) with a goal of palliating symptoms and prolonging short term survival.

In this chapter we will discuss Canada's role in accelerating the elimination of HPV associated cancers from the treatment perspective (surgery and systemic therapy) in the first section, within our own borders and subsequently, from the perspective of Canada's responsibility in the global epidemic of HPV related cancers.

PART 1. WITHIN CANADA'S BORDERS

Problem 1. Quality of care

In 2001, the Institute of Medicine published the "Quality Chiasm" report which identified principles of ideal care. These included 6 domains: safe (avoidance of injury), effective (service is provided based on scientific knowledge), patient centered (care that is respectful and responsive to individual patient preferences, needs and values), timely (reflects access to the health care system), efficient (avoids waste) and equitable. They showed that the performance gap between reality and ideal was wide and ongoing quality improvement was needed to close this gap.

Donabedian's[2] approach to assessing quality of care evaluated both structures and processes of care in terms of their impact on patient outcomes. Structure describes the setting in which health care is delivered (for example, accessing the hospital by measuring volumes, type of hospital and wait times). Processes of care describe the interventions actually provided to patients (like therapies). Outcomes of interest that are important to both patients and health care providers can include overall survival, 30-day mortality, and quality of life.

In Canada there are only 2 studies on impact of structures of care for outcomes of HPV related disease (Table 3 - OPC and Vulvar cancer). Our first Canadian issue revolves around access to timely comparable data not only within but between provinces. The Ontario OPC story shows how structure and process data can lead to important changes in models of care. Table 2 and 3 show examples of such variations in care. For OPC, high volume centres offered patients a survival benefit, so Ontario moved toward OPC surgical care being offered in only 9 high volume centres. To guide continuous improvement, Ontario is using guidelines, pathways and communities of practice (CoP). Thus, Canada needs to move toward more detailed data that is collected in a consistent fashion would facilitate real time health care planning decisions. This along with a quality agenda approach would lead to optimizing patient care.

Problem 2. Timely Care

Access to care is a problem when health care infrastructure cannot easily adapt to epidemiologic shifts in disease[3] or changes in technology. This is seen in Ontario with the long wait times for gynecologic surgery that in part has arisen from changes in technology (i.e., laparoscopic surgery that takes longer compared to laparotomy). It can

also be seen in the H+N domain with the rising incidence of HPV related OPC. The solution here is described in Problem 1.

Problem 3. Equitable Care

Access to care can be related to geography or circumstance (i.e., Socio-economic class [SEC]) which may influence patients' beliefs, attitudes and behaviors toward prevention and treatment of cancer. In Alberta, the rates of OPC in First Nations (FN) people are lower than the general population. The paradox is that the overall survival (OS) and Disease specific survival (DSS) in FN people are worse. In Ontario, those women in the lowest income quintiles and from rural areas have higher rates of cervical and vulvar cancer. Further research into the reasons for these observations is needed. Pilot projects are required to understand what strategies can improve access to equitable care.

PART 2. GLOBAL CANCER CONTROL

In 2015, there were 15.2 million people globally diagnosed with cancer of which 57% were in LMICs.[4] HPV related cancers account for 5.4% of cases (Table 4). Approximately 8.8 million people died and 65% came from LMICs. By 2030, the global incidence of cancer is expected to increase to 21.6 million cases and 75% of these will arise in LMIC. The reason for such astronomical rates in LMIC is reflected in their epidemiologic transition from navigating infectious diseases (like TB and malaria) and maternal mortality to dealing with lifestyle related diseases (i.e., smoking, alcohol, obesity and the like) that arise with an improved economic context. The problem however, is that LMICs lack the health system infrastructure to handle this influx of non-communicable diseases.

Where surgery is concerned, approximately 80% of people with cancer require surgery at least once in the course of their disease. In LIC less than 5% and in MIC only 22% of people have access to safe, affordable and timely cancer surgery. From a financial perspective, focusing on the patient, 25% of them face catastrophic expenditure to have their surgery. From a country's economic perspective, globally the loss of productivity is in the order of 12 trillion dollars (or 1% GNP).

The way forward is multipronged and will include aspects of political will (Table 5), financing (such as using an investment framework approach of investing in integrated health systems now to realize benefit in the future), strengthening cancer systems, research and community engagement.

Strengthening the cancer system begins with developing a national cancer control plan that is influenced by country specific disease statistics and health system related data which drive priorities. This plan must be owned by the country. This plan must be multisystem (including primary care, surgical and radiation and medical oncology, palliative care), as well as including ancillary services (i.e., pathology, diagnostic imaging). Regular evaluation to assess implementation of the plan and also quality of care helps inform priority areas for engagement moving forward.

Health care personnel development is needed. For example, of the 222 cancer surgery procedures identified in the Global Cancer Surgery Report, 54% of them require a specialist surgeon/gynecologist. Such personnel resources do not exist in many African countries and are woefully inadequate in numbers in other areas (Southeast Asia). The way forward will involve collaborations of LMICs with many partners: international government agencies, universities, cancer specific foundations, even pharmaceutical companies all working at different points in the system to define local LMIC scalable cancer control solutions.

RECOMMENDATIONS

For Canada:

Surgery and Systemic Therapy in Canada

46. **Treatment of HPV related cancers must be considered within the context of prioritizing prevention of cancer (optimize vaccine coverage, contemporary screening strategies within a vaccinated context).**
47. **Data is required to inform health systems decision making. More detailed data systems expanding on patient factors (i.e., body mass index [BMI]), aspects of the disease (i.e., grade) and treatment details are required. A national data system would allow data to be comparable and accessible more**

quickly to facilitate timely decisions. By providing more resilience to adjusting resources, health care systems would be empowered to meet changing trends in cancer incidence and innovations in care.

48. A quality agenda approach for treatment of HPV related cancers is required if improvements are to be realized (i.e., adherence to guidelines, pathways, check lists, audit and feedback, communities of practice where best practices in one region can be shared, contextualized and lead to a national improvement).

For International:

Where can Canada be engaged in the Global fight against HPV related cancers?

Franklin D Roosevelt: "The test of our progress is not whether we add more to the abundance of those who have much; it is whether we provide enough for those who have too little".

Individuals or organizations who give back (i.e., tithe) actually invest in the global community, and this financial or in-kind support actually creates opportunities for everyone's development. A mindset (or culture) of tithing is a way forward.

Governmental

49. Canada has strength in developing national and provincial cancer control plans. Governmental agencies such as the Canadian Partnership Against Cancer (CPAC) could partner with a LMIC and not only influence the development of such a plan but on-going engagement for evaluation and input on changes to improve on stressors. Canada also has a strength in hospital or systems accreditation (i.e., cytology) which can be used in partnering with a country to influence quality of care.

Practitioner(s) or Practitioner Society or University based opportunities

50. Participating in training a work force including physicians (like cancer surgeons, anaesthetists, pathologists) and ancillary staff (hospital administration, lab personnel etc.). This could include developing a competence-based curriculum and university or government-based certification processes. Participating in telemedicine models of tumor boards like the ECHO International Gynecologic Cancer Society meetings with Belarus, Kazakhstan, Kenya, Cameroon etc.

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TABLE 1. HPV RELATED CANCER INCIDENCE AND MORTALITY RATES FOR CANADA

Site	Incidence		Mortality		
	Number of new cases in 2018	Age-standardize rete per 100,000	Number of deaths in 2018	Age-standardized rate per 100,000	5 yr survival
Anal	733		140		
Cervix	1,434	7.7	586	1.7	73%
Oro-pharyngeal	4976		1483		63%
Penile	238		47		
Vaginal	194		53		
Vulvar	847		300		

Adapted from: Ferlay J, Soerjomataram I, Mery L et al. GLOBOCAN 2018: Cancer Today 2018 IARC (http://gco.iarc.fr/today) Accessed Dec 27, 2018
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TABLE 2. ASSESSMENT OF PROCESSES OF CARE ON OUTCOMES FOR SURGERY AND/OR CHEMOTHERAPY IN HPV RELATED CANCERS TREATED IN CANADA

Study	Data source	Number	Impact on Structure	Process variable
Anal Cancer chemotherapy				
Peixoto 2016	BCCA 1998-2013 Stg 1-3 Anal Cancer	300	No	RT and 5FU/Mitomycin or Capecitabine/mitomycin
Cervical cancer chemotherapy				
Kang 2015	Manitoba 1984-2008	1085	Yes	**Guideline directed treatment**
Barbera 2006	OCR 1995-2001	1039	Not assessed	**CRT** vs RT
Pearcey 2007	OCR 1998-2001	4069	Yes	**CRT** vs RT
Oropharyngeal cancer surgery				
Eksander 2018	OCR 2008-2012 H+N SCC	3898	No Surrogate endpoint: Emergency visits and unplanned hospital admissions within 90days of treatment	Type of treatment
Oropharyngeal chemotherapy				
CRT vs RT				
Hall 2018	OCR 1990-2014	2382 Supraglotic laryngeal cancer	No	CRT vs RT
Hall 2017	OCR 1998, 1999, 2003, 2004	609 OPC	No	CRT vs RT
Hall 2015	OCR 2003-2004	571 Locoregional advanced Head and neck cancer	No	CRT vs RT
Gupta 2014	OCR 1992-2008	7866 Tx with primary RT	Yes	**CRT** vs RT
Sx +CRT vs CRT				
Seikaly 2016	ACR	279 St 3-4 OPSCC	Yes	**S+CRT/RT** or CRT (+/- S)
O'Connell 2013	ACR 1998-2009	344 Advanced stage OPSCC	Yes	**S-CRT** vs CRT or S-RT
Dziegielewski 2012	ACR 1998-2008	258 T3/T4a laryngeal cancer	Yes	Sx-R/CT vs RT or CRT
Feeding tubes				
Olson 2013	BCCA 2001-2009	445	No Surrogate: SE	Prophylactic g-tubes vs none
Vulvar Cancer Surgery				
Gien 2017	OCR 1998-2007	1038	Not addressed Surrogate: Groin recurrence	Groin dissection vs none
Barbera 2016	OCR 1998-2007	1038	Not addressed Surrogate: treatment decision	Pathology review vs none

ACR – Alberta Cancer Registry. ACSS-Anal Cancer specific survival. BCCA- British Columbia Cancer Agency. CRT – chemoradiation therapy. DFS-disease free survival. OCR – Ontario Cancer Registry. OPC-Oropharyngeal cancer. OPSCC – Oral pharyngeal squamous cell cancer. RT- Radiation. 5FU – 5 Fluorouracil, SCC- Squamous cell cancer, S-RT Surgery followed by radiation, vs- versus.

Bolded process variables were superior

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TABLE 3. IMPACT OF STRUCTURAL VARIABLES ON OUTCOMES FOR HPV RELATED CANCERS IN CANADA.

Study	Data Source	Number	Structure variable assessed	Did structure impact survival	Did structure impact a surrogate variable
Oropharyngeal Cancer Surgery					
Eksander 2014	OCR 1993-2010	5720	Hospital and surgeon volume	Yes- Hospital volumes	No
Vulvar Cancer Surgery					
Gien 2015	OCR 1998-2007	1038	Yes – Surgeon type	Not assessed	Yes: Groin dissection

Eksander A, Irish J, Groome PA et al. Colume-outcome relationships for head and neck cancer surgery in a universal health care system. Laryngoscope. 2014;124(9):2081-8
Gien LT. Gyn Onc 2017;144:318-323

TABLE 4. GLOBAL INCIDENCE AND MORTALITY RATES FOR HPV RELATED CANCER RATES IN 2018

	Incidence	Percent	Mortality	Percent
Anus	48,541	0.3	19,129	0.2
Cervix	569,847	3.2	311,365	3.3
Oropharyngeal	270,309	0.9	70,134	0.6
Penile	34,475	0.2	15,138	0.2
Vagina	17,600	0.1	8,062	0.1
Vulvar	44,235	0.2	15,22	0.2
HPV related cancers	985,007	5.4	514,692	5.4
All Cancers	18,078,957		9,555,027	

Globocan 2018

TABLE 5. EXAMPLES OF A WAY FORWARD TO MEET THE GLOBAL HPV RELATED CANCER CRISIS.

	Surgery	Systemic therapy
Political will	Laws for issues related to the causes of HPV related cancers like smoking, alcohol, etc.	Country specific new drug approval vs adopting recommendations from FDA or EMA Adopt WHO Certificate of Pharmaceutical Product – registration of product in country of manufacture for quality assurance WHO essentials medicines and device listing
	Cancer control plan -Disease specific guidelines, pathways	
Financing of Health Care	Universal Health Care for cost effective packages of care	
	Tiered pricing Price according to ability to pay Pricing through central procurement	
- Limit expenditures on low benefit situations:	-omit high cost staging studies in low stage diseases (i.e., breast cancer) -omit surveillance testing	-cancer therapies for patients with advanced or metastatic disease who are unlikely to benefit -limit use of WBC stimulated growth factors in patients with limited risk for neutropenia
Strengthen cancer systems	-includes ancillary services like pathology, diagnostic imaging -includes pre and post op care (including Intensive Care Unit) -includes the basics of running water, reliable electricity	-includes laboratory, pharmacy, chemotherapy suite -waste disposal
	Development of policies and procedures Hospital accreditation	
-Health work force development	Subspecialty surgical training Anaesthesia training Biomedical engineering training Nursing training	Medical oncology training Pharmacy technician training Oncology pharmacist training
Community engagement	Patient and family social support Community education ("Cancer can be beaten" (focus on prevention and early diagnosis) versus a prevailing perspective of death (due to presentation with metastatic disease)) NGOs to mobilize funding	

EMA-European Medicine Agency. FDA – Federal Drug Agency.

Chapter 10
Making Radiotherapy Available to All

- **Magali Lecavalier-Barsoum**, MD, MSc, FRCP(C), Assistant Professor, Department of Oncology, McGill University, Division of Radiation Oncology
  - Michael Milosevic MD, Vice Chair (Research) and Professor, Department of Radiation Oncology, University of Toronto; Director of Research, Radiation Medicine Program, Princess Margaret Cancer Centre/ University Health Network, Toronto

DATA AND DESCRIPTION

Cervical cancer is a severe burden on global health, being the fourth most common cancer and fourth leading cause of cancer deaths worldwide.[8] In the United States, the introduction of cervical screening using cytology in the middle of the 20th century resulted in a significant reduction in the incidence of cervical cancer.[20] Unfortunately, many low-resource countries do not have the technical and public health infrastructures to support cervical screening. In 2008, over 85% of cervical cancer new cases and deaths occurred in developing countries.[2] In high-income countries like the United States, cervical cancer is most often diagnosed in patients who were never screened or screened over 5 years ago.[12] These patients are often living in low-resource and medically underserved regions, and have annual rates of cervical cancer much higher than the general United States' population, approaching the rates in developing countries.[21]

Nearly half of cervical cancer cases are diagnosed at locally advanced stages, for which primary surgical treatment is not an option[14]. These cases are, however, potentially curable with radiation therapy, combining both external-beam radiation and brachytherapy, a form of radiation involving placement of applicators and catheters inside or near the tumor to then allow radioactive material passing through these applicators and catheters to deliver high doses of radiation to the tumor. The biggest advance in locally advanced cervical cancer treatment in the past 20 years has been the addition of concurrent platinum-based chemotherapy to radiation, which increases 5-year overall survival to 66%, compared to 60% with radiation alone,[4] but other advances in radiation therapy have contributed to increasing tumor control and decreasing side effects of treatments. Areas of improvement for Radiation Therapy access are different in Canada and globally and will be described below.

AREAS OF IMPROVEMENT IN CANADA

As mentioned above, an important advance in treatment of cervical cancers in the last decades was the addition of platinum-based chemotherapy to radiation, but more recent advances have focused on brachytherapy delivery. Brachytherapy is a crucial component of the treatment of locally advanced cervical cancer as it is an independent treatment factor associated with improved local control and overall survival.[11] Although brachytherapy was historically planned with two-dimensional (2D) techniques, the paradigm has shifted in the last decade to three-dimensional (3D) techniques. With the advent of 3D image-guided adaptive brachytherapy, locoregional control and overall survival have improved compared to the 2D era.[18] In Canada, 3D image-guided adaptive brachytherapy was widely adopted following publication of recommendations by the American Brachytherapy Society and the Groupe Européen de Curiethérapie-European Society for Radiotherapy & Oncology.[15,17] Radiation Oncologists mostly relied on computed tomography (CT) scans initially to plan the brachytherapy delivery.

Since the adoption of 3D image-guided adaptive brachytherapy, more and more data are suggesting a benefit to using magnetic resonance imaging (MRI) for brachytherapy planning instead of CT scans as it permits more precise visualization of the internal body structures. This in turn allows better definition of the tumor and surrounding normal organs, resulting in increased precision of brachytherapy treatment, therefore maximizing the amount of radiation reaching the tumour while minimizing the amount of radiation reaching healthy tissues. There is also evidence suggesting improved dosimetric outcomes with the use of MRI-based brachytherapy planning.[13,23] MRI guidance for brachytherapy improves tumor control and is also associated with low rates of severe toxicity.[9,24]

In Canada, unfortunately, many Radiation Oncology centers do not have access to MRI guided-brachytherapy

and rely on CT scans to deliver brachytherapy. A study by Taggar et al. surveyed all Canadian centers with gynecologic brachytherapy services,[22] and 28 out of the 33 responded. They reported that 57% of the responding centers had access to MRI for at least one of the three to six brachytherapy fraction planning.

Having access to MRI for brachytherapy planning is an important first step, but ensuring continued education of radiation oncologist, physicists and radiation technologists is key to optimizing the benefits of MRI-guided brachytherapy. Planning brachytherapy with MRI-based technology can be challenging, and to deliver the best brachytherapy plan, the information provided by the MRI needs to be carefully evaluated. The skills of all involved professionals need to be continually reinforced and updated to ensure delivery of best care possible.

AREAS OF IMPROVEMENT GLOBALLY

Globally, there are significant disparities in diagnosis and treatment of cervical cancer that translate directly to differences in survival. Whereas 50–60% of women in high-income countries are alive 5 years after diagnosis of cervical cancer, the rate in several parts of Africa is in the range of 10–20%.[19] In the next 20 years, it is estimated that almost 11 million women in low-income and middle-income countries will be diagnosed with cervical cancer.[3] If nearly half of cervical cancer cases are diagnosed at locally advanced stages globally, this percentage rises to 75% approximately in low-income and middle-income countries.[3,14]

Radiotherapy is recognized as an effective treatment for cervical cancer and is used in approximately 70%, whether as a curative treatment or to control symptoms such as pain or bleeding.[16] The impact of radiotherapy on the survival of patients with cervical cancer is undeniable, as it is estimated to improve absolute 5-year survival of women with cervical cancer by 17% over and above the contribution of surgery and chemotherapy.[3]

Despite the undisputed importance of radiotherapy in treatment of cervical cancer, its access is limited, and in certain cases completely absent, in many low- and middle-income countries. For instance, there is an almost-complete absence of radiotherapy facilities in most countries in sub-Saharan Africa,[1,6,10,25] where the most common cancer is cervix cancer.[3] Unfortunately, radiotherapy resources suffer from persistent underinvestment, more so than chemotherapy and surgery resources, particularly in low-income and middle-income. This is due in part to the concern about the complexity of radiotherapy treatments. A common misconception is that deployment of radiotherapy resources in poorer nations is not feasible. This is however not supported by evidence, as several studies showed that radiotherapy can be effectively standardized and delivered irrespective of socioeconomic, political, and cultural context.[5,7]

In countries with adequate or almost-adequate treatment capacity, facilities tend to be centralized in large urban centers, creating geographical barriers to equitable access. This set-up is especially the case in large countries, such as Brazil, where health services in rural areas are lacking in parts of the country, and Australia and Canada, which have sparsely populated remote areas where the low population density does not justify investment in complex health-care facilities.

RECOMMENDATIONS

For Canada:

51. Ensure availability of MRI-guidance for brachytherapy in all centers where cervical cancer patients are treated.

52. Establish continued education workshops and teleconferences to maintain and update the skills of radiation oncologist, physicists and radiation technologists.

For International:

53. Develop sustainable financing to expand access to radiotherapy globally.

54. Train radiotherapy professionals globally.

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Chapter 11
Making Palliative Care Available to All

- **Deborah Dudgeon**, MD, FRCPC, Senior Scientific Lead, Person-Centred Perspective, Canadian Partnership Against Cancer, Toronto

OVERVIEW

HPV-related cancers cause significant morbidity and mortality internationally. Palliative Care needs to be a key component of a comprehensive approach to the management of these diseases to improve people's quality of life and decrease health care costs.

DATA AND DESCRIPTION

Worldwide human papillomavirus (HPV) infection is recognized as one of the major causes of infection-related cancer in both men and women leading to significant morbidity and mortality. In 2012, 4.5% (630,000) of all new cancer cases worldwide were attributed to HPV. HPV caused more than half of all infection-related cancer in women with cervical cancer which made it both the fourth most frequent cancer, and fourth cause of death from cancer in women. More than 80% of these deaths are in low- and middle-income countries.[1] In Canada, in 2017 there were 1550 cervical cancer cases diagnosed with 380 deaths. Between 2011 and 2015 of the new cervical cases 28.3% were staged as III or IV with 5-year survival rates 32-16% respectively. Although cervical cancer accounts for more than 80% of cancers attributable to HPV, HPV infection is also responsible for a variable fraction of cancers of the vulva, vagina, penis, anus, oropharynx, oral cavity and larynx.1 Less developed and resource-poor countries are particularly affected by HPV-related cancers with both greater morbidity and mortality.

The high burden of cervical cancer in low- and middle-income countries is partly explained by the lack of adequate health infrastructure, resources and expertise for immunization, screening, and treatment due to competing demands on the health care systems. Many women only seek treatment when symptomatic with vaginal bleeding, foul-smelling vaginal discharge, hematuria and/or abdominal pain indicating an advanced stage of the disease with a poor prognosis and increased mortality.[2] In low- or middle- income countries facilities for treatment of cervical cancer may not exist or be accessible to many women and so even those with early stage disease will not do well and the cancer will progress. It is also recognized that although comprehensive vaccination of pre-teen girls will be lifesaving the incidence of cervical cancer is not expected to drop for two decades. The World Health Organization (WHO) has therefore identified palliative care as one of the key components of a comprehensive approach to cervical cancer prevention and control.

The World Health Organization (WHO) defines palliative care as "an approach that improves quality of life of patients and their families facing problems associated with life threatening illness, through prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual." There is strong evidence that early specialist palliative care consultation improves quality of life, satisfaction with care, symptom control and anxiety and depression of patients with cancer. Data from studies also support that early palliative care decreases health care costs through decreased hospitalizations, emergency room visits and in-hospital deaths and informed avoidance of futile, aggressive interventions in people who had opportunities to discuss goals of care and treatment choices.[3]

The Bow Tie Model of 21st Century Palliative Care best captures the current concept of integrating palliative care into a patient's journey with cancer.[4] (Figure 1) The blue triangle represents disease management with appropriate chemotherapy, radiation and/or surgery. The pink triangle represents palliative care including pain and symptom management, psychosocial care and other appropriate measures. The patient's journey, represented by the arrow, will lead to 2 possible outcomes: rehabilitation and survivorship or end-of-life care and death with complementary disease management and palliative care throughout depending on patient's needs. The model depicts the early integration of both disease-oriented treatment and palliative care from diagnosis to facilitate earlier acceptance of the role of palliative care so people

FIGURE 1. BOW TIE MODEL OF 21ST CENTURY PALLIATIVE CARE[4]

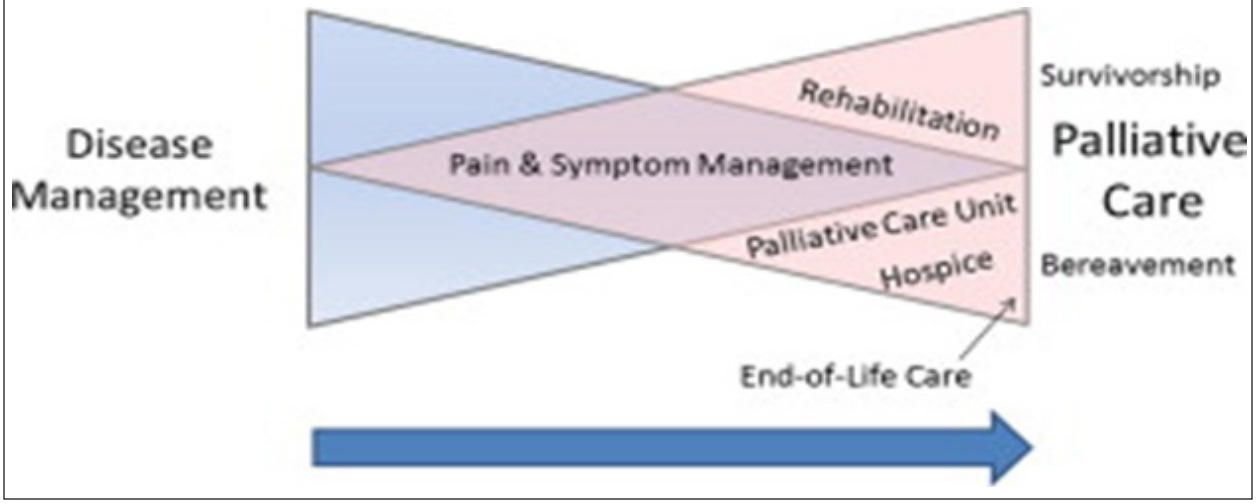
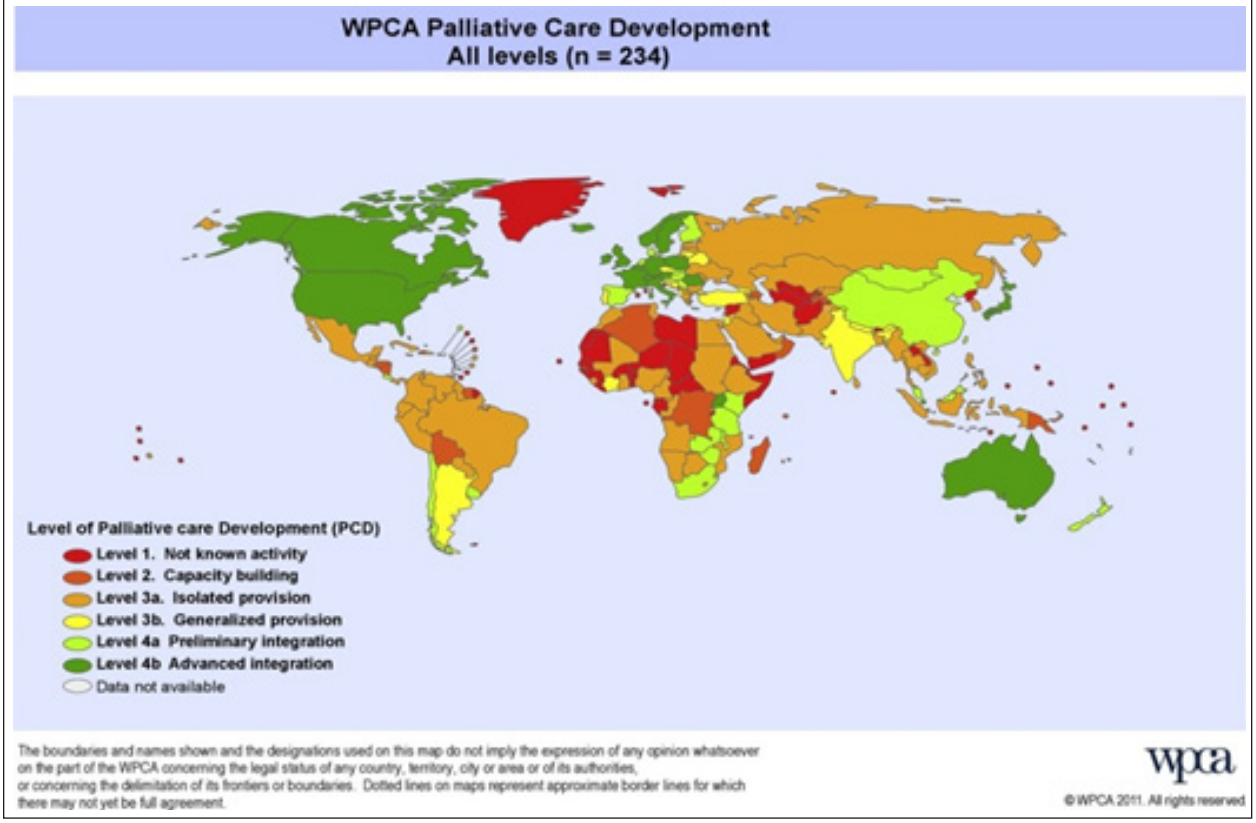


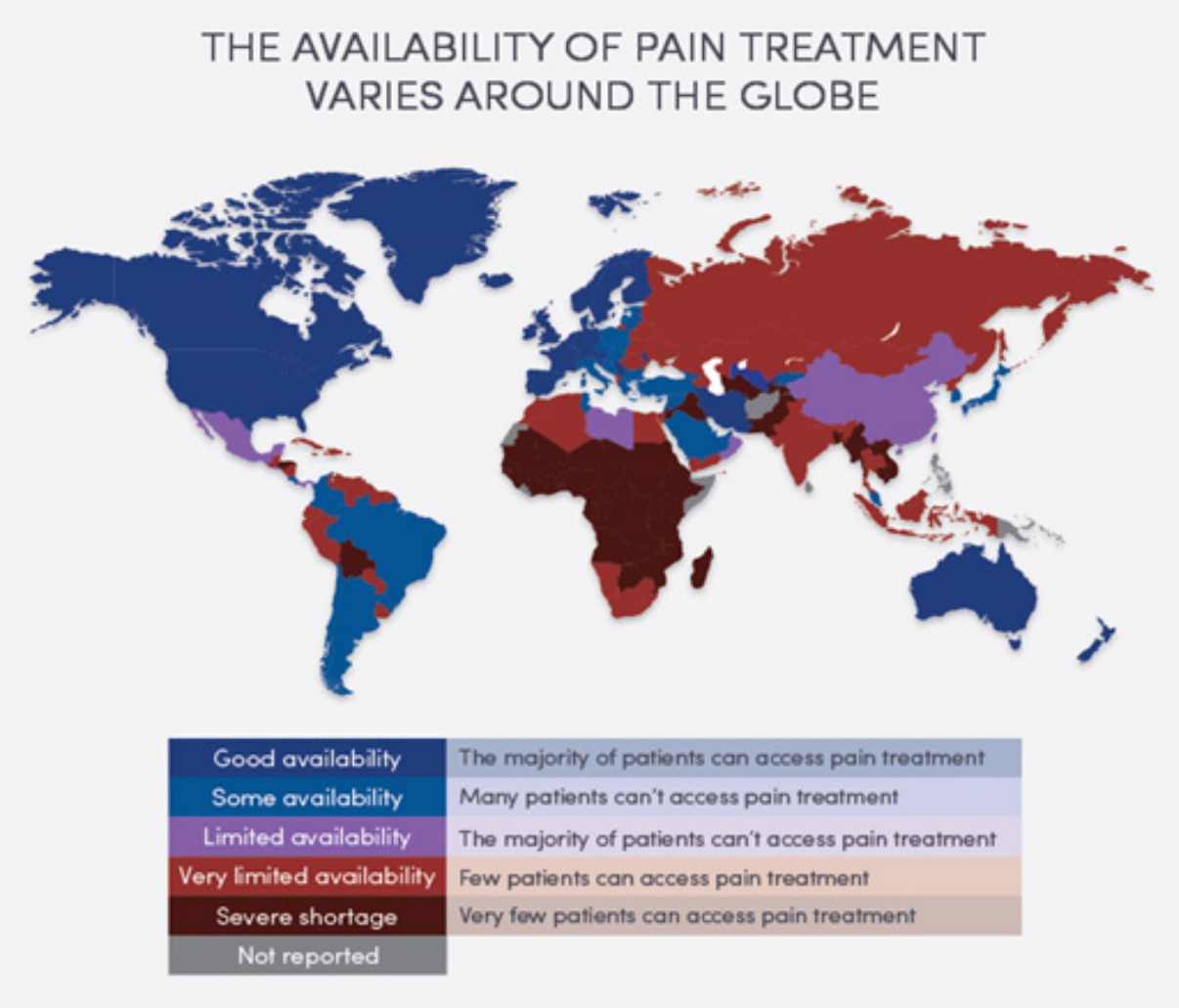
FIGURE 2 FROM MAPPING LEVELS OF PALLIATIVE CARE DEVELOPMENT: A GLOBAL UPDATE[5]



can maximize the time they could benefit from the available palliative care interventions.

Unfortunately, as outlined in a 2018 WHO Palliative Care Fact Sheet, 40 million people worldwide need palliative care with 78% of these people living in low- and middle-income countries. Thirty-four percent of the people needing palliative care have a cancer diagnosis. In a study by Lynch et al in 2011, 42% of 234 countries responding had no palliative care services; 32% had isolated services and only 20/234 (8.5%) had well integrated palliative care.[5] (Figure 2) Many of the countries identified with no or limited palliative care services are those with higher numbers of women with cervical cancer. Canada was identified in this study as having well integrated palliative care. This observation is supported by an online survey, conducted

FIGURE 3 FROM WHY MORPHINE NEEDS TO BE A GLOBAL HUMAN RIGHT. HUFF POST INDIA9



by the Canadian Partnership Against Cancer (CPAC), of the cancer centres across Canada which found that 88% had specialist palliative care clinics (range 0- 100%) with provincial averages of 0-9.2 half-day clinics per week. The proportion of palliative care consults to new patients seen at the centres ranged from 0 to 14% provincially. The referral criteria, services available and models of care (consultative vs ongoing) varied across the provinces. The centres reported that the biggest barrier to access to palliative care services was the lack of understanding of what palliative care entails among the health professionals. The 2017 Palliative and End-of-Life Care System Performance Report[6] by CPAC had a limited ability to measure and report on palliative care services across the whole care system as data were sparsely available and mostly limited to the acute care setting near end-of-life. The data suggested that most (66.4%) were only identified as "palliative" during their last hospitalization and therefore limiting their access to the full benefits of palliative care interventions.

There is also a paucity of data regarding symptom burden and functional status in women with gynecological malignancies. A population-based study of women in Ontario with gynecological cancers in the last 6 months of life showed that pain scores in the cervical cancer cohort were at twice the risk of moderate to severe pain scores as women with ovarian cancer. These women also reported moderate-severe pain scores consistently for the last 4.5 months of life.[7] These data are where palliative care is thought to be "well integrated" with readily available opioids and other modalities for treatment of pain. In 2011, Seya found that 83% of the world's population had low to non-existent access to opioid pain relief.[8] (Figure 3) As with the availability of palliative care, many of these countries

are those countries where cervical cancer is most frequently seen.

RECOMMENDATIONS

For International:

In 2014 the World Health Assembly resolution WHA67.19 called upon WHO and Member States to improve access to palliative care and make it a core component of health systems. The WHO in its Palliative Care Fact Sheet states that National Health Systems need to include palliative care in the continuum of care – linking it to prevention, early detection and treatment, including as a minimum:

55. **Policies that integrate palliative care services into the structure and financing of national health care systems at all levels of care**
56. **Policies to strengthen and expand human resources including training of existing health professionals, embedding palliative care into the core curriculum of all new health professionals, as well as education of volunteers and the public**
57. **A medication policy that ensures the availability of essential medicines, particularly opioids for relief of pain and respiratory distress**

For Canada:

In December 2018, Health Canada published and presented the Framework on Palliative Care in Canada to the Minister of Health and Parliament. The Framework provides a structure for collective action to address gaps in access and quality of palliative care across Canada to help shape planning, decision making and organizational change. The Framework set out 4 priority areas for action: Palliative Care training and education for health care providers and other caregivers; measures to support palliative care providers; research and the collection of data on palliative care and measures to facilitate equitable access to palliative care across Canada.

Within the Cancer System recommendations to improve the delivery and integration of palliative care to all cancer patients are:

The development of policies, standards and funding for the integration of specialist palliative care services within Canadian Cancer Centres and their integration with skilled community palliative care services to help maintain people at home

58. **Policies and funding to strengthen and expand basic and continuing education, intermediate training and specialist palliative care training for cancer health professionals**
59. **Standardize the collection of data related to Patient-Reported Outcomes, Patient-Reported Experience and palliative care services**

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Chapter 12
WHO List of Essential Drugs & Diagnostic Tests

- **Nitika Pant Pai**, MD, MPH, PhD, Associate Professor, Department of Medicine, Division of Clinical Epidemiology & Infectious Diseases, McGill University; Scientist, Research Institute of the McGill University Health Centre; Founder, President and CEO, Sympact X
- **Angela Karellis**, MSc, PhD, Postdoctoral Fellow, McGill University and Research Institute of the McGill University Health Centre

OVERVIEW

This chapter introduces and summarizes the recently published World Health Organization Essential Diagnostics List (EDL), highlighting the HPV-specific recommendations within the EDL and as published in the scientific literature. Furthermore, from a global health perspective, HPV diagnostic methods by nations' income levels are described. Finally, we present HPV testing innovations which are helping to pave the way in routine care to fill gaps in regard to HPV screening and access to care.

WORLD HEALTH ORGANIZATION ESSENTIAL DIAGNOSTICS LIST

Background

In May 2018, the World Health Organization (WHO) released the first edition of the Essential Diagnostics List.[1] It aimed to complement the WHO Essential Medicines List, which was initially released over forty years ago. The WHO is planning to update the EDL annually, with future issues expected to cover antimicrobial resistance, additional non-communicable diseases, emerging pathogens, emergencies and outbreaks, and neglected tropical diseases. The list is designed for use at various levels of a tiered national healthcare system. Tests included in the present EDL issue are appropriate for primary healthcare testing and for healthcare facilities with clinical laboratories.

While the EDL provides a first glimpse of internationally-recommended diagnostics, national health organizations are advised to develop region-specific diagnostics lists in order to address their particular unmet needs and priorities. Moreover, the EDL is advised to be used in line with the scope of testing services that meet the clinical needs and expectations in each country through their own particular laboratory networks.

In the first EDL edition, 113 tests are recommended overall. Of these, 58 comprise general laboratory tests to be used part of routine care and for the detection/diagnosis of various communicable and non-communicable diseases. These tests are grouped by test discipline, such as clinical chemistry, serology, hematology, microbiology and mycology, and by specific test type, for example bilirubin and complete blood count, to name a few. The remaining 55 tests were selected to target illnesses with public health importance, including human immunodeficiency virus (HIV), tuberculosis, malaria, hepatitis B and C, syphilis and human papillomavirus (HPV).

All tests included in the EDL are supported by existing WHO guidelines and manuals or are included in the WHO prequalification program for in-vitro diagnostics. The tests were chosen to account for the routine care provided in primary healthcare settings. The general idea was to provide an essential diagnostics package to be used for screening and case management. Furthermore, to additionally fulfill public health needs, WHO further advises national and regional systems to implement strategies appropriate in their specific setting to ensure appropriate access to care is provided.

Human Papillomavirus Testing

HPV causes nearly all cases of cervical cancer, with HPV types 16 and 18 accounting for approximately 70% of cases. Combined with the fact that the majority of HPV infections are asymptomatic and due to the high global burden of HPV, cervical cancer screening guidelines, such as those released by the WHO,[2] encourage regular HPV testing of women aged 30 years or above, although in Canada, Pap smears may be performed as part of cervical cancer screening as early as 25 years of age.[3]

Whilst Pap smears represented the standard of care for cervical cancer screening for many years, this practice has recently changed to add new technologies such as HPV nucleic acid tests.[2] Per the WHO cervical cancer guidelines,[3] a screen-and-treat approach encompassing

HPV testing with or without visual inspection with acetic acid (VIA) is advocated.

Many centers in low and middle-income countries (LMICs) have scarce HPV testing resources, thus limiting their ability to implement successful screening programs. Furthermore, global HPV vaccination uptake rates are low and most at-risk women are not of the vaccine age further increasing the HPV-associated burden.[4]

To fulfill global needs, the WHO guidelines present alternative approaches if HPV testing is not feasible to conduct in a particular setting, such as VIA alone or cytology followed by colposcopy. However, HPV testing is preferred over VIA alone, Pap smear followed by colposcopy, or HPV testing followed by colposcopy. In line with these suggestions and the high global HPV burden, the WHO EDL recommends HPV nucleic acid testing for cervical cancer screening1 which can detect HPV DNA.[2] Due to the HPV nucleic acid test's higher sensitivity, albeit lower specificity, when compared to Pap smears, national and international guidelines suggest to perform nucleic acid testing due to the test's improved predictive ability in the detection of potentially-serious HPV-related illness.[2]

DIAGNOSTIC STRATEGIES BY INCOME LEVEL

In light of the WHO published recommendations, cervical cancer screening programs are generally adopted by high-income countries where healthcare resources are plentiful, but healthcare is not relatively easily accessible for marginalized populations who have the highest burden of disease.

Although, the specific diagnostic strategies may yet vary between, and even within, nations.

Cytology via Pap smears, HPV testing, or a combination of both may be performed per each country's cervical cancer screening recommendations and available resources.

In Canada, federal, provincial and territorial guidelines suggest a large variety of screening technologies, age to stop screening and invitation programs, but they do not recommend a single program, thereby creating confusion among health care providers and populations on best strategies.

In the USA, women aged 21 to 29 should be tested every three years by Pap smears; for women aged 30 to 65 years, one of two approaches is to be followed: 1- co-testing, Pap smears and HPV testing, every five years, or 2- Pap smears alone conducted every three years.[4,5]

Certain jurisdictions (e.g. Australia, the Netherlands) have already implemented HPV testing. In the United Kingdom, cytology is only indicated to triage a positive result of an HPV test, the latter of which is the primary recommended test.

Despite the high incidence of, and mortality from, cervical cancer rates in LMICs, many of these settings do not have the capacity to implement any form of organized screening. Furthermore, a lack of resources and complexity of the cervical cancer screening process add confusion to the best program to recommend given burden of disease, resources and existing programs in place. Among the few countries with implemented or soon-to-be implemented programs, suggested strategies entail screening via visual inspection tests with 3-5% acetic acid. Although Pap smears represent the most widespread cervical cancer screening technique, this procedure is rarely performed in LMICs due to the high costs, resources required to perform Pap smears and difficulty in accessing high quality laboratory or point-of-care (POC) testing in time.

Screening rates remain low as a result of unsophisticated healthcare systems, a lack of awareness in the general population and a lack of resources and will to implement the best recommendations.

For the remaining countries with no screening plan in place, to ensure the successful implementation of cervical cancer programs, certain conditions need to be met. Namely, they are advised to target the appropriate population to screen, yield low expenditures while guaranteeing on-site screening and focus on quality and timely clinical management and follow-up.[4]

HPV TESTING INNOVATIONS

In recent years, the availability of HPV molecular testing has helped improve cervical cancer screening. As per the Canadian Agency for Drugs and Technologies in Health (CADTH) report both HPV testing and Pap

require a cervical sample, thus the convenience level is relatively the same. However, the rapid turnaround time of HPV molecular testing could play a role in minimizing discomfort to the patient who may worry after receiving a positive pap or a positive HPV test.

Moreover, as opposed to Pap smears which are performed by a healthcare professional (HCP), the testing of self-collected cervical or vaginal swabs have shown successes in many countries. Therefore, self-sampling for subsequent HPV detection is a good solution.[2] However, guidelines have yet to adopt these practices as part of their recommendations though test accuracy is comparable when self-collected samples and those collected by HCPs are used.

In addition, several molecular platforms are available to detect HPV, certain of which allow rapid testing providing same-day results such as XPert® HPV and careHPVTM assays, the two devices prequalified by the WHO.[1] These platforms, available in many tertiary and secondary care centers in LMICs for HIV/TB screening, could be easily optimized for HPV screening, thereby representing viable options during cervical cancer screening. This POC testing method could possibly improve time to test results and linkage to subsequent visits for confirmation/staging or care as the case may be.

Finally, self-sampling for HPV could be considered as an option to fill the unmet screening needs in LMICs, where burden of disease remains high.

GAPS IN CURRENT CARE

Despite the above-mentioned innovations and advances in cervical cancer screening, several challenges persist worldwide, highlighting the gaps in current practice. For example, HPV nucleic acid testing can only be performed in facilities with clinical laboratories, a fact confirmed in the WHO EDL,[1] therefore limiting the options for participants in primary healthcare centers without laboratories seeking HPV testing. Moreover, while LMICs generally follow the international guidelines in regard to performing VIA to screen for cervical cancer, the WHO must address the burden in countries with reduced ability to conduct HPV testing, the preferred form of screening. It would be advised to offer additional WHO-recommended HPV diagnostic testing options in order to reach the maximal number of individuals seeking testing, particularly in LMICs with limited resources and access to care.

Alternative approaches to testing in primary care, such as POC testing and use of digital innovations are also promising.

Lastly, multiplexed POC testing platforms allow us to screen for several sexually-transmitted infections simultaneously if the same sample can be utilized to screen for the multiple pathogens thereby reducing patient time, provider time, and time to test result, and expediting clinical action. However, for all POCT options, self-sampling or multiplex testing, implementation research data on impact and effectiveness will be required to complement data on test' accuracy, before they are recommended for widespread use.

RECOMMENDATIONS

For Canada:

60. For women participants: In line with current WHO and Canadian recommendations, women are advised to undergo cervical cancer screening as per local guidelines. For Canada, primary HPV testing is recommended every 5 years.

61. For researchers: In order to fill implementation gaps in regard to HPV screening, research aiming to develop and validate POC tests could be prioritized in the context of organized or opportunistic programs.

62. Self-sampling for HPV testing could be made available widely.

For International:

In order to fill the current gaps in HPV screening, we recommend the following elements be considered for inclusion in the upcoming EDL issue:

63. Additional HPV diagnostic choices to guide healthcare organizations from all nations for appropriate HPV testing, regardless of the country's income status.

For instance, Pap smears and HPV testing via self-sampling should at the minimum be discussed for inclusion, as numerous published

guidelines have recommended these practices worldwide. As the XPert® HPV and careHPVTM assays have been pre-qualified by the WHO, they warrant inclusion in the EDL as well.

64. Self-sampling must be widely recommended to improve access to timely screening. Besides accuracy, access and affordability to the new proposed testing technologies is to be assessed prior to making any recommendations.

65. An additional description regarding how to access the included diagnostic tests.

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Chapter 13
Training Issues for HPV Prevention

- **Catherine Popadiuk**, MD, FRCS(C), MBA, MSL, Medical Director Cervical Screening Initiatives, Newfoundland and Labrador; Associate Professor, Division Gynecologic Oncology, Faculty of Medicine, Memorial University

OVERVIEW

Pap test cytology screening has been the cornerstone of cervical cancer (CxCa) prevention for over 40 years. It is well understood and entrenched in the behaviors of women and health care providers (HCP) alike in developed countries. The knowledge that HPV is the causative agent of cervical (and other) cancer is relatively new and the major developments in CxCa prevention with HPV vaccination and screening through High Risk HPV (hrHPV) tests have been rapid and confusing for women and HCPs. Cervical cancer elimination through a more focused and direct approach against HPV will require a comprehensive education strategy with tools and messaging relevant to women of all ages and demographics, and HCPs at all levels of experience from trainee to seasoned professional. The education and communication strategies required in achieving the 90/70/90 targets set by the World Health Organization to achieve the elimination of CxCa to a level of 4 per 100,000 will differ among the communities served in the Developing Low-Income and Low-Middle income countries from those in the Developed world. Furthermore, the diversity of people and circumstance in the developed world, such as Canada, requires tailored education and communication strategies relevant and respectful to various communities such as the Aboriginal, Immigrant and Refugee, and Socially underprivileged.

Through its Feminist International Assistance Policy[1] and approach for gender equality to support healthy communities and society, Canada can make a critical difference in the global sphere. To do so, Canada can be a leader in the elimination of cervical cancer domestically and internationally.

DATA AND DESCRIPTION

Problem: The stigmatization of HPV as being a sexually transmitted infection underpins the challenges in getting women to participate in Cervical Cancer prevention and screening.

Global Affairs Canada is applying a feminist approach to the analysis and solutions for societal concerns. Sexuality has to be seen as a healthy expression of intimacy for relationships on an equal footing, and not a method of empowerment and violence against women. The negative connotation about HPV as a sexually transmitted infection has to be reversed and the education and dissemination of positive health messaging fits into Canada's objective to empower women and thus improve society and eradicate poverty. Sexual intimacy and potential for HPV transmission does not occur on an individual basis. It requires partner formation; equal partners in a sexual relationship. Men and women are exposed to HPV but women can acquire cervical cancer at far higher rates than men develop HPV related penile cancer. The scientific basis of such physiologic inequity is not understood. Similarly, HPV related anal cancer affects women at greater number than men, and HPV related oro-pharyngeal cancer affects men in greater proportion than women.

Situation: In many developing and some developed countries, "a mix of discriminatory laws and policies, coupled with inadequate services and harmful cultural practices, limits the sexual and reproductive health and rights of women and girls. The result is often a lack of comprehensive sexuality education." Adolescent girls are at risk for poor health when they are going through puberty and many have an inadequate understanding of their sexual and reproductive health and rights. HIV is the leading cause of death among women of reproductive age in lower and middle-income countries. Girls account for 80% of new HIV cases and women living with HIV are four to five times more likely to develop cervical cancer. Without adequate access to vaccination, screening or health care, these women have a **40% greater risk of dying from CxCa.**

An HPV awareness and educational campaign will meet the Canadian Feminist International objectives

to support positive health outcomes for women and girls in developing countries and close the gaps in sexual and reproductive health and rights for women and girls. Supporting access to HPV vaccine, care and comprehensive sexuality education and prevention and treatment of CxCa will improve the negative impact CxCa has on women in developing countries and beyond. **A critical component for any educational campaign will be to include and empower local community health workers who, for the most part, are women and trusted in their communities.**

Cervical cancer, being a disease associated with female reproductive sexual organs, has traditionally not been well understood in both the developed and developing world. Pap testing has been offered to women during reproductive health visits, such as for obstetrical care or contraception, and general awareness of what CxCa is has not been taught formally in most educational or health related settings. Being under the oversight of primary care and public health services in the developed world, or not a priority at all in developing countries, the recent onslaught of HPV related information related to HPV vaccination and testing for the causative virus of cervical cancer has arguably been overwhelming to a largely unprepared world population.

Solution: Standardized, consistent messaging starting with fundamental key points to build upon is required as a foundation for communication and education. Following Canada's feminist approach to gender equality, the empowerment and strengthening of women is paramount in this new educational campaign. There "must be a transformation of social norms and power relations." Canada is to "support the development of gender responsive curricula in schools, and work to address and transform harmful behaviors that can have negative consequences for all genders such as sexual risk taking, substance abuse and violence."

In Low-Income and Low-Middle Income Countries education must address the needs of the community.

Assisting in the building a toolkit of resources adaptable to local environments and circumstance is a fundamental first step. Change will require the identification of local champions whom are trusted in communities. Change must come from within to find success and support for the importance of HPV vaccination, screening and follow up treatment.

Toolkit would include culturally sensitive materials according to the audience. In lower income and developing countries with minimal resources, information is shared through oral and direct communication. The same message is shared in stories that resonate with story tellers and the audience. A message promoting the importance of female self-care, reproductive well-being, dignity in the female spirit and empowerment are at the core of HPV education. Pictures, oral stories Simple tools such as pictures, oral stories, and symbols overseen by local key community leaders can be complemented with more creative social network conversations, relationships, and showcasing of peers. The best way to spread new knowledge is through social connection.

The best way to spread new knowledge is through social connection. Interactive discussion is more effective than written work, best practice databases. Lead by example, shared lessons learned. Frame the lessons to resonate with the audience and the HCPs. Allow HCPs to build on framework, take ownership of education. Change is social, need dialogue and collaboration.

For the developed world and Canada, where more capacity and structured health care resources exist, education can include professionals beyond the primary community, such as nurses, physicians, allied health professionals and their trainees, and administrative leaders themselves. A number of professional organizations are moving to a more pragmatic approach to education and evaluation: Competency by Design,[2] that parallels the simple approach in the aforementioned Developing world, based on trust and relationships called Entrustable Professional Activities. Knowledge dissemination and education is done through activities such as simulation and direct interaction with various stakeholders, relevant and tailored HCP and trainee interventions and social marketing strategies.

A critical element for success to achieve the 90/90/90 objectives for 2030 is the education of women, men and parents to the import of HPV vaccination. In Canada, the

provinces and territories continue to work to increase vaccination coverage rates in provinces and territories for the school-based programs for girls and boys. Few provinces have achieved 90% vaccination rates for a full complement of vaccination. Vaccination of all eligible women and men would further support the elimination of cervical (and other HPV related) cancer over the next decade.[3]

Education is required for HPV vaccination. Research in the US, where vaccination rates are poor, show less than 63% and 50% of females and males respectively, received one dose of HPV vaccine and that parents and individuals are misinformed and feel vaccination is not needed, not recommended, not safe, not understanding of the benefits of vaccination in preventing pre-cancer and cancer, and not expecting sexual activity to begin until later. There is also a lack of understanding that the vaccine is for prevention and not treatment of active disease.[4]

With respect to HPV primary screening, the superior attributes of the test over cytology need to be collated into a standardized tool kit of information applicable to women, and health care providers and trainees including nurses, nurse practitioners, pharmacists, physicians, licensed practical nurses and anyone responsible for administered screening in the regions, provinces and territories in Canada. Very importantly, with implementation with 90% HPV screening uptake, an important expectation is the transient increase in rates of pre-cancer and cancer identifying prevalent disease.[5] "This is not a failure of the test, but success at identifying these individuals that otherwise would have presented later with possible more advanced disease. The infrastructure and supports for downstream diagnostic evaluation and treatment will have to be a part of the education strategy for policy makers, health care providers, and patients alike. Such preparations cannot be underestimated."[5]

And very importantly, tailored, culturally sensitive and relevant messaging and education will have to be prepared for communities where Cervical Cancer management: HPV vaccination, screening and follow-up treatment, are challenging and deficient, such as the Aboriginal communities, under-screened women who lack access to health care, immigrant and refugee communities and the socially disadvantaged. The Health Care providers serving these populations will require their own specialized initiatives that resonate for the special circumstances in these groups.

RECOMMENDATIONS

For Canada:

66. For Aboriginal Populations, support and implement culturally sensitive and respectful communication and education surrounding the need for HPV vaccination, screening with HPV primary testing, and appropriate cervical treatment by incorporating the local communities in educational toolkit and messaging development.
67. For the under-screened pockets in Canada: the rural, socially underprivileged, immigrant and refugee women, create respectful and culturally sensitive communication and education strategies regarding the importance of HPV vaccination for women and men, primary HPV screening, and downstream follow-up and treatment.
68. Create education and communication strategies relevant and informative for Canadian women and men, primary HCPs and high-level policy makers to support and implement widespread vaccination and primary HPV testing as the CxCa screening tool for Canada to reach 90% of the population.

For International:

69. Through support of the Feminist International Assistance Policy, offer the relevant and culturally appropriate tools to assist Low and Low-Middle income countries to create the case for investment in HPV vaccination and HPV primary screening to prevent CxCa thus empowering women in their reproductive health for the good of community development.
70. Assist low and low-middle-income countries with development of their communication and education tools for the community members and health care providers for the dissemination of information regarding the local implementation of available HPV vaccination and Primary HPV testing while supporting coordinated follow-up efforts.

71. Partner with WHO, IARC, other NGO's and organizations supporting low and low-middle-income countries in creating infrastructure and human resource planning to become self-sufficient in moving toward 90/70/90 in the most efficient manner according to local environments and circumstances.

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Chapter 14
The Importance and Necessity of Well-planned Communication

- **Laurie W. Smith**, RN(C), BN, MPH, Cancer Control Research, BC Cancer & Global Control HPV Related Diseases, Women's Health Research Institute, Vancouver
  - Ann N. Burchell MSc PhD. Dept of Family and Community Medicine and Centre for Urban Health Solutions, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto
  - Zeev Rosberger MA PhD Lady Davis Institute for Medical Research and McGill University, Montreal

PURPOSE

The purpose of this chapter is to demonstrate the importance of strategic, timely and comprehensive communication strategies in the move towards eradication of cervical cancer. Advancements in science and medicine do not stand alone, and it is only with well-planned communication approaches and thoughtful dissemination of information that advancements can improve the health of the public. Planning for effective communication with multiple target audiences should be an integral component in the implementation and scaling up of cervical cancer prevention strategies.

BACKGROUND

There exists a necessary relationship between science and communication. Communication is at the core of public health. For interventions to change behavior, effective communication is essential. Thoughtful and appropriate communication strategies have never been as important as they are today, when information, credible or otherwise, has become so readily accessible to the public through a variety of platforms. The best advancements in science with the potential to improve population health cannot be successful if not planned for and implemented through thoughtful, multilevel communication and information sharing strategies.

Despite the fact that HPV is the most common sexually transmitted infection globally, many in the general population have not heard of it or are unaware of the relationship between sexual activity and cervical cancer. Undoubtedly, a lack of awareness of HPV and its' relationship to cervical and other cancers has a significant effect on public health interventions targeted to decrease HPV related cancers. Without knowledge regarding the "cause and effect" of HPV, the public has less incentive or motivation for acceptance of measures intended to address HPV related diseases. In addition, there is an abundance of incorrect and inconsistent information about HPV and HPV related cancers in circulation, which leads to confusion, skepticism and concern by the public. This inconsistent and unclear messaging is conveyed to the public not only in the media, or the internet but sometimes from health care providers. Often health care providers are faced with providing information or answering questions related to HPV without having adequate background knowledge themselves. Health care providers are seen as trusted sources of information, and people often make health related decisions based on information received from them. When providers are not armed with appropriate and correct information regarding HPV and HPV vaccination this leads to further confusion and inconsistency. These facts underscore the need to ensure communication strategies are multipronged, targeted not only at the public but also to health care providers.

PRIMARY & SECONDARY PREVENTION

For cervical cancer eradication to be realized, there need to be significant improvements in primary and secondary prevention measures. Primary prevention improvements can be achieved through increased rates of HPV vaccination and secondary prevention, through adoption of HPV-based screening coupled with improved screening attendance. Such changes can be driven in a large part by thoughtful and sustained communication and information initiatives.

Primary Prevention

A recent meta-analysis of HPV vaccination uptake in Canada (from 2006 onwards) showed HPV vaccine uptake to be 56%, well below the target of 85% established by the Government of Canada.[1] In Canada, most jurisdictions offer publicly funded HPV vaccination through school-based or public health programs, removing the barrier of cost and accessibility of the vaccine. In British Columbia,

for example, where uptake of the HPV vaccine has not surpassed 69%, the Hepatitis B vaccine (HBV), also offered in grade 6 to males and females at the same time as the HPV vaccine, and also an infection that can be transmitted sexually, consistently has uptake rates of >80%. In 2018, uptake of the HBV was 90%, and uptake of the HPV vaccine was 67% for females and 65% for males (BCCDC immunization uptake 2018).

Despite the fact there are years of research and post-market surveillance demonstrating the safety and effectiveness of the HPV vaccine, there remains opposition and hesitancy from the public. One need only to do a simple internet search to discover endless amounts of misinformation regarding the vaccine, much of which the anti-vaccine movement is responsible for. The impact of such negative publicity and misinformation on HPV vaccine uptake rates cannot be ignored. In June 2013, the Japanese government suspended proactive recommendations for the HPV vaccination program in that country following unconfirmed reports of adverse events in the media.[2] The media reports, alongside government withdrawal of active recommendation, catalyzed fear in the public. Vaccination rates sharply declined. From 2010-2013, uptake rates in the program were 70%; however, after the government withdrew recommendation of the vaccine, rates sharply declined. Only 4% of girls born in 2000 have been vaccinated, and a dismal 1% of girls born in 2001 have been vaccinated.[2] The Japanese committee reviewing reports of these adverse events later reported there was no evidence indicating a causal association between HPV vaccination and the reported adverse events. However, as, of March 2019, Japan has not reinstated proactive recommendations for the HPV vaccine and uptake rates are dismal. Furthermore, the government has done little to communicate to the public that the allegations regarding the vaccine and adverse events were inaccurate. This is an example of a missed opportunity for government and public health programmers to initiate aggressive and comprehensive campaigns to promote the vaccine and provide the public with reassurance regarding its safety and effectiveness. This kind of initiative has the potential to significantly impact uptake of the vaccine not only in Japan, but other regions where the government and policy makers have not been proactive with dissemination of clear and factual information to the public.

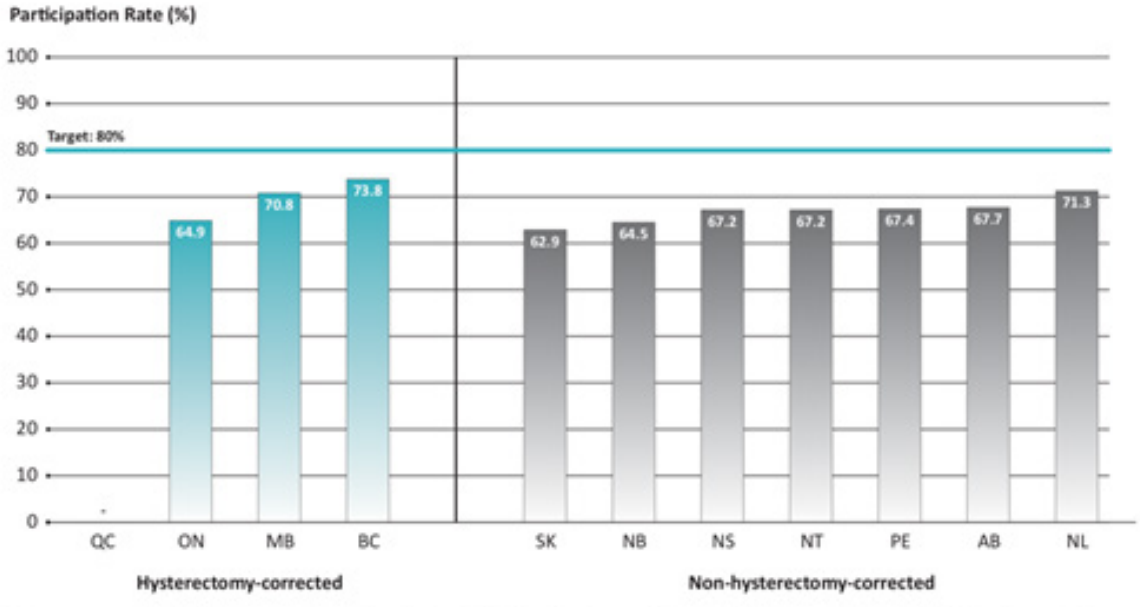
We can look to Australia for an example in successful programmatic roll-out of HPV vaccination. In 2007, Australia became the first country to launch a publicly funded, school-based national HPV immunization program with uptake rates of over 70% since program commencement. Much of the success of the Australian experience can be attributed to government and clinician endorsement with ongoing commitment, and comprehensive public education and confidence in the vaccine and the Australian vaccination program. Australia has widely disseminated information regarding the program, including information regarding successes and challenges, in an effort to educate and inform other jurisdictions.

Secondary Prevention

A recent review of cervical cancer screening in Canada3 reports that participation in screening across Canada has been decreasing. Participation is defined as the percentage of eligible women who have at least one screen in a 3-year (+6 months) period, with a target of >80% women 21 to 69 attending during this time period. From January 1, 2010 to June 30, 2013, screening participation for women 21 to 69 years uncorrected for a previous hysterectomy ranged from 63% in Saskatchewan to 71% in Newfoundland and Labrador. Hysterectomy correct participation rates were available only for British Columbia (74%), Manitoba (71%), and Ontario (65%).[3] No province is meeting the screening target rate of >80%.

Many jurisdictions are planning for implementation of primary HPV testing for cervical cancer screening. Despite the superiority of HPV-based screening over cytology, this shift in technology from cytology to HPV-based screening, there is no guarantee it will be accepted by all stakeholders and improve screening attendance without clear communication regarding the reasons for moving to HPV-based screening. With primary HPV testing, the screening interval can be extended, and the age to start HPV-based screening is higher than is currently recommended for cytology-based screening. Communicating these differences between the two approaches will be critical for adoption by health care providers and women eligible for screening.

As indicated previously, Australia has been a leader in HPV vaccination for years, being the first country to implement



Cervical Cancer screening in Canada. Monitoring and evaluation of quality indicators. Jan2011-Dec 2013. CPAC

a nationally funded HPV vaccine program.[4] In May 2017, officials planned to launch the paradigm-shifting transition from cytology to HPV-based screening. However, this change was met with widespread skepticism and an online petition was launched to oppose the changes.[4] Women reacted with alarm to the proposed change to a public health intervention they had become familiar with over decades. The petition garnered over 70,000 signatures. An analysis of petition responses found that the majority of women's concerns could have been addressed through better planned communication strategies explaining the reasons for the shift from cytology to HPV-based screening.[4] This public health response to the programming shift is one of the reasons for the delayed implementation of HPV-based screening in the program by 7 months. Had the public been better informed about HPV by the government and leaders in the screening program, knowledge of the reasons for moving towards HPV-based testing, and the differences between the two tests, some of women's concerns and anxiety may have been alleviated.

There are also lessons that can be learned from implementation efforts within Canada. In British Columbia, a large primary HPV testing screening trial found that women's concerns and questions surrounding HPV-based testing vary, and are different when they have their first HPV screen compared to when they receive HPV test results.[5] The efforts made to articulate to participating women the differences between cytology and HPV testing, the reasons behind HPV testing for cervix screening and implications for receipt of HPV positive results were helpful in alleviating women's anxiety and addressing their concerns about the significant shift from cytology to HPV-based screening.

SUMMARY

There are several considerations outlined throughout this document that provide clear recommendations to accelerate implementation strategies to eliminate cervical cancer and HPV related diseases. This chapter has focused on the role of communication in this initiative. The necessary relationship between HPV and cervical cancer has been well established. It is critical at this point to also establish the necessary relationship between science and communication. Advancements in science cannot be put into practice in isolation of well-planned communication. Many lessons can be learned by examining successes and challenges around the world regarding HPV vaccine acceptance and uptake and implementation of HPV-based screening. Since the introduction of the HPV

vaccine, negative communication, and the strength of the anti-vaccination movement have fueled skepticism and anxiety. This lack of confidence regarding the HPV vaccine, not only by the public but also by health care providers or government, has resulted in suboptimal vaccine uptake rates. In addition, there has been resistance to transitioning from cytology to HPV-based screening, where age to commence screening would be raised and the screening interval extended, when reasons behind and justification for the program shift have not been clearly articulated.

Policy leaders, health care providers and screening programs need to respond quickly and assertively to incorrect messaging and suboptimal communication surrounding HPV. Many jurisdictions have experienced declines in rates of genital warts and cervical pre-cancer since commencement of HPV vaccination. Although these findings are published in medical journals, this dissemination of information has not occurred widely to the public. These positive and impactful findings need to be communicated with as much fervor and be as accessible as false and misleading information is. By better communication of success stories and evidence regarding the safety of the vaccine, increased confidence by the public will inevitably occur. When all stakeholders, including policy makers, programmers, health care providers and the public, are involved in, and have access to timely, targeted, multi-level sources of information, much of the incorrect, unknown, and inconsistent information regarding HPV, the vaccine and HPV-based screening can be resolved.

RECOMMENDATIONS

72. Develop timely and comprehensive multilevel communication strategies and interventions that include messages tailored to various demographics, general broader population strategies. Strategies should include a variety of platforms including social marketing, social media and engage media advocacy. Messages should be developed in collaboration with and targeted to policy makers and the government

73. Strategies need to be timely but dynamic and evolving for various stages of program planning and implementation (HPV vaccine or HPV-based testing). Communication and messaging must be consistent, and clear to minimize confusion and mistrust by the public. This may require national level planning for downstream administration and sharing of tools/documents/information across Canada

74. For HPV-based screening, research should be conducted to establish where women are in their understanding of HPV and HPV testing to determine how to develop communication strategies and interventions that will be effective at all stages of planning (ex: knowledge surrounding HPV testing itself, in addition to receipt of HPV positive results)

75. Design communication strategies that meet the needs of all stakeholders (public, health care providers, programmers etc.). Strategies should be multilevel, multipronged, multiplatform

76. Greater efforts directed towards widespread communication of HPV vaccine and HPV screening success stories to the public. This will enhance acceptance by improving public trust and confidence in the safety and efficacy of the vaccine, in immunization in general, of HPV-testing for screening, and in the health system and health care providers.

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Chapter 15
Feminist Approach to Dealing with HPV

- **Teresa Norris**, Founding President, HPV Awareness, Montreal
- **Amelie McFadyen**, MA, Executive Director, HPV Awareness, Montreal
- **Marc Steben**, MD, Chair, Canadian Network on HPV Prevention, Montreal

OVERVIEW

The feminist approach is about improving upon what has been done in terms of advancements in HPV prevention, this will require being bold in our ambitions to create change and progress. It's about rethinking our collaborations and the way we do things, as well as delivering concrete results and ensuring that adequate financial commitments are put in place.[1] This approach will have its critics, but a feminist approach has the power to truly transform societies.

Through the feminist lens, it is key to identify national and international barriers to applying a successful HPV elimination strategy achieving the targets of 90% HPV vaccination rates, 90% of women being screened and 90% of women receiving adequate follow-up and treatment. It has been an oversight to not focus on equity, as it is often confused with equality, and they are different approaches. The latter is not only inadequate but leaves specific populations underserved. Shifting policies from a "supply" driven approach that prioritizes service delivery, to instead a "demand" driven approach would enable countries to reach the targets. Applying equity to the feminist approach will level the playing field by providing women the same opportunities.

CURRENT CLIMATE/BARRIERS AROUND THE WORLD

Understanding the approach and differentiation of equality versus the importance of equity within Canada's feminist approach will steer a shift in mindsets and result in better applied frameworks that will improve HPV prevention and screening nationally and globally.

Currently, the design of government policies in Canada adopts prevention, screening and treatment from the top down, this is an inadequate one shoe fits all model used in HPV vaccination school-based programs and our national recommendations for screening for females at age 21. Let's address why, albeit that it is free, we still have not reached a 90% uptake in HPV vaccination in most of Canada nor are 90% of women screened. It is not enough to offer everyone the same equal access through public healthcare because there are countless barriers within households that justify our straggling uptakes. Whereas a shift in the viewpoint to equity and fairness would guide policies differently, governments would then put in place a model where support is tailored according to the needs of different populations so that everyone may have fair access to the same opportunities.

There needs to be a shift to distribute carefully designed resources and tailored policies that take into consideration specific geographic, cultural, economic and societal barriers so everyone has the same opportunity and fair access to HPV prevention, screening and treatment.

A utopian model would be similar to Australia's situation where they are now well on their way to successfully achieving the targets of 90% HPV vaccination rates, 90% of women being screened and 90% of women receiving adequate follow-up and treatment. Indeed, if a high-coverage vaccination and screening is maintained, at an elimination threshold of four new cases per 100,000 women per year, within the next 20 years, cervical cancer could be considered as an eliminated health problem in Australia.[2]

Through the feminist lens and based on the national and international climate there are key barriers to applying the proper process to the HPV elimination strategy.

BARRIERS SPECIFIC TO DEVELOPED COUNTRIES

Due to straggling rates of cervical cancer-related deaths, HPV prevention through vaccination has been prioritized and innovative, whereas screening remains archaic. Canada has still not switched to more precise screening methods such as HPV testing and self-sampling that could be used in rural settings or even at home or in the community, reaching even more women. The feminist approach has yet to be applied to HPV prevention and

since women's rights work is sorely underfunded, policies on HPV screening and treatment is under par.

BARRIERS SPECIFIC TO LOWER- AND MIDDLE-INCOME COUNTRIES (LMIC)

There is a staggering number of females perishing due to HPV-related cancers. Meanwhile, in low- and middle-income countries (LMIC), women's rights work is not only sorely underfunded, but is far from being a priority. Gender inequality is entrenched into policy levels. Female's access to resources and HPV prevention, screening and treatment is under par. Currently, Canada's feminist approach to LMIC HPV prevention-specific aid has not been developed. Investing in women and girls has not translated into meaningful and sustainable new funding and the mechanisms remain inherently un-feminist. "The feminist approach must be applied to international assistance as to challenge systemic inequalities, unjust power systems, discriminatory laws, policies and programs at local, regional, national, and global levels."[1]

RECOMMENDATIONS FOR AN INTERSECTIONALIZED FRAMEWORK IN CANADA AND LMIC

The feminist approach needs to be properly applied to the HPV elimination strategy nationally to then be able to guide international investment and implementation.

For Canada:

Through the feminist approach, addressing the root causes of inequalities and resistance to adopt modern screening methods through HPV testing and self-sampling and cohesive HPV vaccination policies.

77. **Tackling unequal gendered power relations under the government's feminist agenda to implement decisive action and investment by applying the feminist approach strategies that will guide a cultural shift towards equity in the goal of our report to insight Canada's HPV elimination strategy.**
78. **Canada needs to lead by example by implementing the feminist approach to remove the barriers hindering the HPV elimination strategy.**

For International:

79. **Women empowerment will need to be the precondition for ending poverty and inequality to dismantle the patriarchal attempts to control women's bodies and choices. Through a feminist approach guided by Canada, systems of power and social constructions of gender need to be transformed to tackle unequal gendered power relations with decisive action and investment.**
80. **Through Canada's feminist approach, shift foreign policy to support advocacy to holding governments accountable forcing them to move from a "supply" driven approach (that is already not supplying sufficiently) which prioritizes service delivery, to a "demand" driven approach positioning women's needs and realities around access to HPV prevention, screening and treatment.**
81. **Following the feminist approach to Canada's international assistance through the adoption of an intersectional framework, the goals spelt out will be attainable. This feminist approach will allow us to identify and address complex contexts and formulate strategies to best meet the needs of all women so they can all benefit from optimal prevention, screening and treatment. In LMIC there needs to be an integration of HPV prevention in existing health programs centred on women. Funding women-centred and women-led organizations and initiatives will create this change.**

CONCLUSION TO THE FEMINIST APPROACH

The globe's goal of eliminating HPV can be achieved with the implantation of a feminist approach focusing on intersectionality, agency and process. It is critical to use the feminist principles to address the root causes of structural and systematic inequalities in the populations. By transforming systems of power, the utopic goal would be to not have any barriers at all, which can be achieved by adopting an intersectionalized framework throughout, integrating this into every level of decision-making both nationally and in LMIC.

Non-Governmental Organizations (NGOs) are experts and knowledge holders in their own right, they have the ability to transform the current status of prevention, screening and treatment. These groups have the ability to create empowerment in populations and meaningful engagement. NGOs also need to be included in every step as expert

consultants in order to position the different needs and realities in communities in both Canada and LMIC.

Canada must actively set the tone during global moments starting with leading by setting a good example for equitable prevention, screening and treatment nationally within our own country. Further, Canada must commit to guaranteeing sufficient resources to accomplish the feminist work to prioritize knowledge building, opportunities to learn from experience, and mutual learning through exchanges and Canadian collaborations. The first step is to update and revise the 1999 CIDA Gender Policy[3] to reflect the government's feminist approach, further to this we must develop and publish a feminist action plan with annual published reporting so that success and alterations can be made annually.

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Chapter 16
Engaging NGOs to Mobilize Populations for Optimal HPV Prevention

- **Teresa Norris**, Founding President, HPV Awareness, Montreal
- **Amelie McFadyen**, MA, Executive Director, HPV Awareness, Montreal
  - Marie Plante, MD, Full professor, Department of Obstetrics, Gynecology, and Reproduction, Faculty of Medicine, Université Laval; Gynecologic Oncologist, CHU de Québec
  - Therese Lethu, CEO, Global Health Objectives; Special Advisor Women's Health in Africa, Université Numérique Francophone Mondiale
  - Zeev Rosberger, MA, PhD, Lady Davis Institute for Medical Research and McGill University, Montreal

OVERVIEW

The role of non-governmental organizations (NGOs) is to work at ground level with lay populations relaying the latest evidence-based research in an intuitive way, including dissemination of the human papillomavirus (HPV) prevention and screening policies through awareness campaigns, and providing guidance and tangible support to patients in treatment and to the general public with timely, carefully thought out tailored initiatives. NGOs in this sphere report being underutilized allies of public health. It is unfortunate because NGO's typically specialize in a variety of important fields. NGOs are leaders in their own right in effective communication techniques that result in mobilizing populations, providing audible prevention awareness, and on occasion partake in passion driven lobbying efforts to improve policies that affect mass populations. WHO's 2030 objectives to end the cervical cancer epidemic is an ambitious goal that is within our grasp, with one caveat, heavy NGO involvement; they are key to spearheading population engagement globally.

KEY BARRIERS AND CURRENT CLIMATE GLOBALLY

HPV-related cancers are the modern epidemic that AIDS was in the '80s. Recent estimates show that 80% of populations will be affected by HPV.[1] Currently, the biggest barrier in HPV advocacy efforts is that the virus is highly stigmatized and is often interpreted to imply promiscuity, which an abundance of research evidence has shown to be false. There is an omnipresent lack of empowerment around HPV in stark comparison to what is being attained in the field of HIV/AIDS. This empowerment is seen in gay communities coming together to fight for HIV prevention/screening and AIDS treatment.

There is a general lack of understanding of HPV and its possible impact in people's lives. Commonly, couples in long term relationships presume that decades of being with the same partner exempts them from this concern. For global elimination efforts to be successful, rigorous improvements must be made now by the right actors, NGOs supported by policy leaders will be able to stimulate mass populations to feel compelled enough by HPV prevention and screening to then be able to successfully rally around advocacy efforts.

Many societies have unfortunately observed a lack of overt political interest, support, investment, endorsement, and leadership on the three tiers of prevention, screening and treatment of HPV-related diseases. This is apart from Australia, where non-coincidentally they are soon going to have succeeded in achieving WHO's targets due to their aggressive launch of the HPV vaccine in 2007 under Prime Minister John Howard whose wife had cervical cancer.

BARRIERS SPECIFIC TO DEVELOPED COUNTRIES

Society learned about the existence of the virus through the launch of the HPV vaccination in 2006. Initially, the HPV vaccine was made available to young girls and branded as a tool to prevent cervical cancer. Very little coherent and cohesive awareness and invested interest in education has been demonstrated to date. It was and still is a hurdle for the general public to understand this virus because there is such a lack of primary understanding. Efforts have been made by public health agencies with mass campaigns to raise awareness, and in more recent years, how HPV affects males as well. This has been a confusing message for lay populations, with many wondering why this was not conveyed from the very beginning. To date, public health driven campaigns have thought the best way to avoid confusion was to target

DEVELOPED COUNTRIES

What's working	What's not working
In the United States, some states have made the HPV vaccine mandatory for enrollment in certain grades. Furthermore, insurance plans must offer coverage for the HPV vaccine for the recommended populations, as well as pap testing and HPV testing for women.[2] In many countries, Merck has put in place assistance programs providing free HPV vaccines to uninsured low-income adults.[2] There exist multiple sources of financing, both public and private so that all children and young adults may have access to the HPV vaccine.[2] In many countries, such as Canada, free, gender-neutral vaccination is offered as part of a school-based program. Certain countries, such as the UK have a national program in place to remind women to go to their healthcare professional for HPV screening. Certain developed countries, such as Australia, have been extremely successful in HPV prevention. Australia was an early adopter of gender-neutral HPV vaccination, extending their program to boys in 2013.[3] In 2017, the Australian government introduced the HPV test as a screening method to replace the Pap test.[4] As of 2019, Australia is sending overdue reminder letters for children who have not received the HPV vaccine.[5]	In many countries, misinformation and stigma is causing unjustified fears around side effects of the vaccine and the misconception that it will permit sexual activity are causing parents to opt out and not immunize their children. In the United States, parents have to pay for immunization, and it is optional.[6] HPV vaccine coverage is less than optimal in many developed countries, including Canada and the United States.[2] Many countries do not have adequate catch-up programs in place for boys. In the UK for example, this means that approximately 2 million boys will miss out on the opportunity to receive the HPV vaccine.[7] A few factors have been identified and presented at Cancer Research UK's Early Diagnosis Conference about the barriers to women going for HPV screening such as stigmas and myths around HPV and raising fears about partner's fidelity.[8] Some countries are struggling with adversity on a political level. The most prominent case of this is ongoing in Japan. Vaccine rates plummeted going from 70% in 2013 to 1% in 2017. The main reason behind this is misinformation widely spread in social media, leading to the government's decision to not recommend the vaccine.[9] Anti-vaccine stories being seen in the media soon became the "scientific facts" and these were rarely challenged by academic organizations or even healthcare professionals.[10] The government also compounded this issue by suspending proactive recommendations for HPV vaccines despite there being no supporting evidence to support any claims made by anti-vaccine groups.[9] This decision by the government was not based on scientific evidence and caused confusion amongst public health officials, doctors and also the general population. Additionally, the Ministry of Health, Labour and Welfare prepared a "pink leaflet" that is mandatory to distribute to all parents seeking vaccination. This pamphlet warns parents that the cervical cancer vaccine is not being proactively recommended and that they should read about the risks and benefits first. It also mentions that it is a new vaccine and that there is no evidence yet to show that it prevents cervical cancer.[10]

LMIC

What's working	What's not working
Some global efforts have been put in place, for example through GAVI, the vaccine alliance, working to close the gap in HPV vaccination coverage for LMIC.[11] Strong community engagement	Vaccination programs have staggered due to cost and resources challenges.[11] HPV prevention such as vaccination campaigns have a high chance of running into some resistance in various cultures especially if local communities have not been adequately informed about the benefits and reasoning of the HPV vaccine. Low levels of literacy in many countries.[12] In many countries, little value is placed on the lives of women and if HPV is defined as a women's issue, then it will not be a priority and will not gain support.[12] In many LMIC, there is an attitude of distrust towards foreign NGOs, and pharmaceutical companies. Programs should be tailored to the culture and the populations.[12]

only one population at a time instead of using general statements like "HPV affects everybody," which has only further inflamed the issue they wished to avoid. Further havoc can be attributed to "anti-vaxxers" spreading misinformation and twisting and misusing evidence-based information, creating further distrust by promoting "big pharma conspiracies" throughout lay populations. Social media has proven to be the main vehicle for "anti-vaccine" groups to propagate fear mongering about safety and necessity for this prevention tool. Such groups have successfully caused the public further confusion and hesitancy to partake in prevention.

These major issues in communications around the topic of HPV prevention reinforce the importance of investing in NGOs to allow them to disseminate evidence-based information in a way that will instigate behaviour changes at the ground level. In order to assist NGOs in

knowledge transfer to populations, key stakeholders such as pharmaceutical companies, researchers, healthcare professionals, and caregivers must cease to work in silos.

BARRIERS SPECIFIC TO LOWER AND MIDDLE INCOME COUNTRIES (LMIC)

From a policy perspective, health-related structures and policies are not equitable in all populations. Sparse availability and accessibility to the three tiers (prevention, screening, and treatment) severely hinder HPV prevention in LMIC. Often, in some LMIC, little value is placed on the lives of women and because HPV prevention is perceived as a women's issue, it gains little support or resources. Certain LMIC also have a distrust of foreign programs and HPV prevention risk leading to resistance in some cultures, especially if local communities (and their leaders) have not been adequately informed about the benefits of the HPV vaccine. This reinforces the need to involve trusted NGOs at the local level in the process of building programs for HPV prevention from inception to ensure that they are culturally adapted to the realities of local communities.

GLOBAL OVERVIEW OF SUCCESSES AND CHALLENGES

The climate surrounding HPV-related issues within a country ultimately affect NGOs work in mobilizing populations for optimal HPV prevention. Policies, media, and culture have an effect on the general public's opinions and trust in HPV prevention methods and can either aid or hinder NGOs work.

RECOMMENDATIONS

For Canada:

82. By educating decision makers, more value would be placed on NGO lead initiatives with lay populations around HPV prevention and awareness campaigns. Canada needs to put a new focus on NGO led initiatives with sustainable financial support and endorsement.
83. There is an opportunity for stakeholders of all sectors to work in concert with the public and private sectors within the industry in line with government endorsement. There is a need for a cohesive message by all involved parties to destigmatize HPV and focus on its oncogenic risks.
84. Canada needs to ensure that all media and awareness campaigns are evidence-based, created by HPV experts, and with messaging tailored by a consortium of relevant field workers and communication experts.

For International:

85. Canada needs to invest time and resources into creating, in partnership with LMIC, comprehensive educational materials with effective language/imagery tailored to LMIC. Widespread promotion of these awareness tools is critical for NGOs to be able to raise awareness within populations.
86. Canada must lead by example by endorsing international HPV prevention initiatives. Our example will in turn encourage discernible endorsement by national and district government leaders in LMIC. A sizeable commitment to wide scale endorsement is critical to communities' acceptance of NGO work.
87. Canada's collaborations with influential groups (e.g., teachers and health care workers) will be key in LMIC to take on spokesperson roles. These ambassadors play complementary roles to NGOs in their efforts to raise awareness and create change within populations. To ensure remote areas and populations are effectively reached, prevention messages must be properly tailored.[13]

CONCLUSION

The critical next step is the professionalization of NGOs through a clear increase in political will. In order for NGOs to adequately support current HPV prevention, cervical cancer screening, and treatment programs, the times of population mobilization through financial scarcity needs to be put behind us. NGOs must have an official seat at the table with decision makers, applying their knowledge to develop, evaluate, document, and share ideas that would increase the success of programs and partnerships. The creation of a global best practices database is essential to accelerate actions, share knowledge, values and outcomes, including accountability and transparency with public health stakeholders. Joining forces with NGOs will create societal engagement and will build a strong civil society space to work towards achieving WHO's ambitious 2030 objective of eradicating cervical cancer worldwide.

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Chapter 17
Political Considerations

- **Marc Steben**, MD, Chair, Canadian Network on HPV Prevention, Montreal

OVERVIEW

"By 2030, cervical cancer is expected to kill over 474,000 women per year – over 95% of these deaths are expected to be in low- and middle-income countries."[1] No country has better cancer care or palliative care than their screening program. This means that most women of LMICs cannot prevent the disease nor the inhumane death from cervical cancer because they do not have access to HPV vaccine, screening, surgery, chemotherapy, radiotherapy and palliative care.

Women in developing countries contribute substantially more to the household economy than their male counterparts. Almost 75 percent of food production each year is a direct result of women's labour.[2] The relative contribution of cervical cancer to the total estimate of Years of Life Lost (YLL) to cancer ranges from 5% in high income countries to 22% in the more economically deprived areas of the world. In women aged 15-59 cervical cancer accounts yearly for 166,484 YLL in high-income countries, 977,633 YLL in middle-income countries and 1,240,208 YLL in low-income countries.[3]

The WHO position statement on HPV vaccines states that HPV vaccination should be included in national immunization programs, provided that:

- prevention of HPV-related diseases constitutes a public health priority
- vaccine introduction is programmatically feasible
- sustainable financing can be secured
- cost effectiveness of vaccination strategies is considered

The primary target population is likely to be girls within the age range of 9-10 through to 13.[4]

The United Nations (UN) high-level meeting on non-communicable disease (NCD) prevention and control, 19-20 September 2011, reminded us that NCDs – like cancers – account for over 63% of deaths in the world today and kill 9 million people under 60 years of age per year. Their socio-economic impact is staggering. The UN meeting recognized the loss of productivity that is threatening the economies of Member States and having a direct impact on the achievement of the internationally-agreed development goals, including the Millennium Development Goals.

The political declaration of the high-level meeting of the General assembly on the prevention and control of NCDs called for:

- Possible linkages between non-communicable diseases and some communicable diseases, such as HIV/AIDS, and call for their integration
- Recognize the importance of strengthening local, provincial, national and regional capacities to address and effectively combat non-communicable diseases
- Promote increased access to cost-effective vaccinations to prevent infections associated with cancers, as part of national immunization schedules;
- Promote increased access to cost-effective cancer screening programs, as determined by national situations;
- Promote the inclusion of non-communicable disease prevention and control within sexual and reproductive health and maternal and child health programs, especially at the primary health-care level, as well as other programs, as appropriate

Since the high-level meeting on NCDs, the UN has transited for Millennium Development Goals 2000-2015 to Sustainable Development Goals (SDGs) 2015-2030 where reduction of STIs will contribute to SDG goals:

- Goal 3 for health
- Goal 5 for gender equality, and empowerment of women and young girls
- Goal 10 to reduce inequality and stigma within and between countries
- Goal 17 to create global partnerships for research and sustainable development

Going forward in preventing cervical cancer will require the integration of vaccination and screening strategies:

- Strategies that integrate HPV screening or cervical cancer screening and HPV vaccination are complex and should be carefully deployed.

- It is essential that governments and resources are not pulled apart into two separate programs (vaccination and screening) but proper attribution of resources is of utmost importance.
- In young women, cervical cancer screening should not be provided too early and vaccine should be prioritized early in adolescence.

The challenge of eliminating cervical cancer seems to be quite a high goal but it is as achievable as other previously challenging goals. In previous decades it was decided that Millennium Goal 5 (about reducing pregnancy-related complications including maternal mortality) would be a challenging goal and yet great results were obtained. In 1990, 358,000 women died annually. Since then we have seen a decrease of 34% in mortality from 1990-2008 as a result of US$12 billion being invested yearly toward the goal of improving maternal health from pregnancy-related complications. But in the meantime, 270,000 women die annually, representing an increase of 45% mortality rate during the 2000-2008 period. It is now prioritized but investments are only trickling in.

To eliminate cervical cancer, we need to reduce to zero, or near zero, the incidence of disease in a defined geographic area5. HPV and cervical cancer satisfy most of necessary pre-conditions for elimination:

1. No animal reservoir for the virus is known or suspected
2. Sensitive and specific tools are available for diagnosis and surveillance (and treatment)
3. Transmission from one individual to another can be interrupted
4. Non-lethal infection or vaccination confers life-long immunity
5. The burden of disease is important to international public health
6. Political commitment to elimination efforts exist

Pre-conditions 1 to 5 have been well-discussed prior in the text. What about the political will now? The objectives of the 2030 goal will be feasible for Canadians and the world only if politicians commit to the objectives now since it takes time for vaccine to fully bring value to prevention of cervical cancer. The same goes for cervical cancer to reach all those that need to be screened and are not being screened now. Those not screened and not vaccinated will be harder to reach than those already screened and will most likely take more time. The Canadian government needs to step in for the elimination of cervical cancer and make it a National priority.

RECOMMENDATIONS

88. Canada should clearly adhere to, and commit to, the WHO goal of cervical cancer elimination for 2030.

89. Canada, as a world leader in women's health issues, should assume its leadership role in identifying funding for the full deployment of Canadian expertise and efforts, particularly in LMIC, to achieve the 2030 WHO cervical cancer objectives.

90. Canada should organize an international meeting to identify adequate global funding toward these efforts.

91. Canada, as a champion of women's health issues and feminist approaches to development, should lead an international effort to sustain the development of community-based approaches and call an international concertation meeting to help deployment of a coalition of community advocates.

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Chapter 18
Commentary on the Role of Professional Societies in the Elimination of Cervical Cancer

- **Jennifer Blake**, MD, MSc, FRCSC, Adjunct Professor of Obstetrics and Gynecology, University of Toronto and University of Ottawa; CEO, SOGC

The elimination of cervical cancer, or indeed HPV-related cancers, is attainable - it was called for by the WHO in May 2018,[1] and the path is outlined in the chapters of this volume - but is by no means assured. The stated goal is to see the incidence of cervical cancer drop to a level in the population where it becomes uncommon or even rare. However, the outcome that we need to avoid is one in which the incidence level remains highly prevalent in pockets of the population – pockets that will keep the virus in circulation. This would be a problem from an infectious disease control prospective, but more importantly, populations that, if current disease patterns prevail, will have higher morbidity and mortality from the disease than mainstream Canadians. The definition of elimination – to eliminate as a public health problem – must apply to all segments of the population; to aim for any less would lead to an unacceptable healthy inequity. Professional societies speak for our members, health care providers, who know both the science and the human impact better than any other. Our motivation comes from that knowledge, and our goal to ensure that future generations will not experience this, or other HPV related diseases.

Framing the question is likely to be the first order of business. There remains confusion in the general population about what HPV is, and in the minds of many, confusion with HIV. As decisions to vaccinate are often emotional decisions, negative connotations, or alarming associations, can lead to hesitation. In the face of confusion, the natural human instinct is to take no action, and wait. We need to help reduce confusion by being clear in our goal. Currently we are not. The lack of clarity is reasonable; this is opportunity for debate and decisions. In order to deliver clear goals and waypoints, we need to make choices. Are we talking about cervical cancer elimination, or HPV elimination? Or elimination of those preventable cancers that are caused by a virus? What do we mean by elimination? It is a plain English term with well understood meaning. To qualify it as "elimination as a public health concern" sounds disingenuous- above all we must be clear, consistent, and honest. Perhaps we should talk about steps on the road to elimination, and give ourselves opportunities to celebrate multiple victories.

HPV is the second most common cancer among women from ages 20-64,[2] but is a disease that has a disproportionate impact in poorer countries. It is also the second most common among women in Canada aged 20-44.[3] In low resource countries, lacking vaccination or screening programs, and without access to cancer treatment, cervical cancer is the leading cause of cancer deaths among women. The International agency for Research in Cancer projects that the number of cervical cancer cases is projected to rise, with changing demography, over the next several decades.[4] As an African colleague observed, "we are saving the lives of our children, we are saving the lives of our mothers, only to have them die from cervical cancer. Canada has had the benefit of long-established cancer treatment programs, a long-established screening program, and has school-based gender-neutral vaccination programs, for which professional societies have been strong advocates. But Canada is not leading in the race to elimination, and has significant disparities in cancer incidence and outcome within the population.[5] Nevertheless, Canada does have the three necessary elements to achieve genuine elimination: vaccination, screening, and early and effective treatment - if we can garner the professional consensus around this goal, with public and political support. Professional societies are key players in achieving that consensus, through five activities:

1. **Guidelines:** While health care delivery in Canada is at the level of the provinces and territories, the guidance that is provided, ideally, is national. It is confusing to both health care professionals and to the public if practices differ between provinces – and leaves women with a sense of inequality. Effective clinical guidelines can and are implemented by local health authorities – they should outline the agreed consensus amongst health care professionals, leaving health jurisdictions the latitude to implement.

2. **Professional Development:** Professional societies play a key role in the sharing of advances in science and in educating members on best clinical practice. Adult learners want to understand what they need to do, and to have the tools to be able to succeed at their essential role whether it is counseling, screening, monitoring or treating.
3. **Public Education:** Outbreaks of measles have shown that, in an infectious disease model of elimination, pockets of resistance to vaccination have the ability to permit resurgences of diseases, and sporadic public health crises. Without public support, we are unlikely to achieve elimination. Public education has moved from pamphlets and public lectures to the internet. Online, scientific credibility is necessary but not sufficient. The WHO SAGE[6] working group pointed out that the vaccine hesitant are not homogenous, and that there is a need to segment and target messages. Respecting that the majority of the hesitant are those who are genuinely confused, and fearful of making a wrong choice, targeted messaging can give those groups the tools and information that they need to make sound decisions. Myths abound, including that we are vaccinating with live virus. The web is a crowded place, credible and informative websites are important,[4] but not sufficient – it is important to include videos, to be present in social media and to interact with an audience in a meaningful way. These are skills that societies are learning, to keep up with the media expectations of the public.[7]
4. **Storytelling:** Public messaging must be relatable. Health professionals are able to share the human stories that help make the statistics real, but more than that, we can give our patients the chance to tell their stories. Women's voices need to be heard online and from the podium. The same patients whose stories motivate us to want to eliminate these preventable cancers have the most profound impact on the public.
5. **Advocacy:** One of the most misunderstood CanMEDS roles is advocacy, but the elimination of cervical cancer can only be achieved if we do our jobs as advocates well. Advocating for women who may feel reluctant because of stigma to speak out, advocating for resources at the provincial program, advocating the policies that will enable progress to be made, and providing the spaces in which the voices of our patients are heard, are key. We are not lobbyists, and should not be; we simply need to speak out and be heard, clearly and consistently.[8] We have many tools at our disposal, our clinical and scientific meetings, our journal social media channels, and the news media. In Canada, the first call for elimination was made by a professional society, the SOGC, at the press conference announcing Canada's HPV Prevention Week, October 1, 2017, but no voice was more clearly heard then, or in any public forum, than the voice of a woman telling her story. For women to speak up they must overcome stigma and shame. Our presence at their side, or in the background, is an important support.

There are three critical success factors that should be built in to our work:

1. **Clinical Expertise:** Our credibility comes from our expert knowledge of the field; we are both evidence-based and deeply knowledgeable about these diseases and their impact.
2. **Consensus Building:** There are many health care providers who play an integral role in cervical cancer prevention: pediatricians, family physicians, nurses, nurse practitioners, community health workers, pharmacists, gynecologists, colposcopists, infectious disease specialists, pathologists, cytologists, and gynecologic oncologists – all of whom play a role. It is important that we meet amongst ourselves and sort out the essential issues on which all are agreed, and have frank and respectful discussions of the contentious areas. Politicians and policy makers are unlikely to move if they sense that we have not reached consensus amongst ourselves.
3. **Independence:** Our credibility is lost if we are perceived to be acting out of self-interest, or as a mouthpiece for others. Professional societies operate under ethical guidelines that require transparency and full disclosure of potential conflicts of interest, which protect our credibility.

FUTURE CHALLENGES

As the incidence of cervical cancer gradually declines the challenge will grow. Vaccination rates are below target in most provinces, and vaccine skeptics are finding support amongst some health care providers, as well as online. Participation in screening is waning9; moving cancer screening to an episodic from an annual activity has disrupted a deeply ingrained behavior, and there is more change to come. HPV molecular testing has higher sensitivity, but lower specificity; it has the potential to generate anxiety, unless introduced with clear messages and counselling resources for both patients and providers. New technology, such as self-sampling, will play an increasing role, disrupting the HCPs role in screening. Follow-up of abnormal results is an ongoing challenge, an even greater one may be the need to keep hands off and simply monitor a positive HPV screen with cytologic change in a young low-risk patient – essential if we are to do no harm. Perhaps the greatest challenge will be the pressure to reallocate resources away from the HPV related cancers, to other areas of public health concern.

There will be many other issues and questions that arise. Using the resources of our professional bodies we should be able to anticipate and provide clear guidance to ensure that we do achieve an ultimate goal of the elimination of cervical cancer.

RECOMMENDATIONS

For Canada, and high resource countries:

92. **Set an inspiring, achievable goal: There is considerable urgency to galvanize public and political sentiment to pursue the elimination of cervical cancer, with meaningful thresholds that can be achieved in a foreseeable future. Thus, for example, an initial target of the elimination for the vaccine inception cohort will be more effective than a population-wide ultimate goal. Forgoing agreement on these critical messages needs the active leadership and anticipation of professional societies.**

93. **Advocate for all: For the goal of elimination to be achieved, we cannot allow the virus to take refuge and become a burden on the most vulnerable.**

94. **Mobilize expertise: From providing a forum for breaking research, to communicating change in established practice, to empowering women with the knowledge they need to make decisions in their best interest, professional societies have a key role in strengthening vaccination, screening and in early detection and treatment.**

For Canada and low resource countries:

95. **Advocate for vaccination programs. Vaccination will be the most effective strategy for low-resource countries. In a world of competing interests, the unanimous support of professional societies for this public health priority will be hard to ignore. Those that have yet to make an official statement can take advantage of the opportunities to endorse the global initiative lead by WHO.**

96. **Build Capacity for screening and treatment. For low resource countries acquiring the needed skills for population-based screening programs, and to treat women with cancer, whether with surgery or radiation, is an ongoing challenge. North-South partnerships such as that launched by the Caribbean Society of Gynecologic Cancer, or the International Gynecologic Cancer Society10 can build capacity and supportive networks of scholarship and care.**

CONCLUSION

Setting a goal of elimination is the first step along a route with many challenges. Professional societies, whether based in Canada and the high-resource world or in low- and mid-income countries, have a crucial role to play as advocates for our patients, providing context and leadership and in much needed clinical expertise.

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SOME WEB RESOURCES FROM CANADIAN AND INTERNATIONAL PROFESSIONAL ASSOCIATIONS:

GOC
https://g-o-c.org/resources/clinicians/contemporary-clinical-questions-in-hpv-related-diseases-and-vaccination/

FIGO
https://www.figo.org/news/statement-accelerating-cervical-cancer-elimination-0016139

IGCS
https://igcs.org/who-initiative-to-eliminate-cervical-cancer/

IPVS
https://ipvsoc.org/hpv-day/

SOGC
https://www.sexandu.ca/stis/hpv/
https://youtu.be/r8R7y0rMybY
https://www.digitaldoctors.ca/

Chapter 19
The Potential of Artificial Intelligence and Digital Health

- **Roger Simard**, B. Pharm, Montreal, Quebec

OVERVIEW

The purpose of this chapter is to understand the role that artificial intelligence and digital health can play in the eradication of HPV-associated diseases

DEFINITIONS AND TERMINOLOGY

Artificial intelligence (AI): the theory and development of computer systems able to perform tasks that normally require human intelligence, such as visual perception, speech recognition, decision-making, and translation between languages.[1]

Digital health: healthcare services provided electronically via the Internet.[1]

There has been considerable hype surrounding artificial intelligence in medicine and a good deal of skepticism about both AI and digital health in general. But the combination of labeled big data, ubiquitous and powerful computing power associated with cloud storage has already proven game changing in several areas of medicine. This is particularly true in situations where large amounts of data need to be collected, images have to be interpreted with speed and precision, and cheaper methods to diagnose and treat patients have to be created.

To use AI, one has to "train" a computer by feeding it millions of images and then eliminating the unnecessary pieces so it becomes as close as possible as the human eye in detecting patterns. The computer can then be shown, for example, images of a healthy cervix, a cervix with some cellular changes and a cervix with pre-cancer. Researchers from the NIH completed such a project using nearly 60,000 images from a screening program in Costa Rica and obtained remarkable accuracy in screening for cervical cancer.[2] Except for a few images where colours were fading, the computer was able to identify the 241 known pre-cancers and 38 known cancers. The same researchers are now equipping smartphones with a special device so they can screen at a very low cost large underserved populations for cancer lesions.

Another area where AI could play a particularly useful role is in pathology. Pathologists are among the physicians who have been the slowest at adopting digitization of scans as compared to radiologists.[3] This could lead to inconsistency among pathologist's interpretations. Deep learning of digitized pathology slides offers the potential to improve the accuracy and speed of interpretation.[4]

The rapid adoption of smartphones around the globe and the rapid advancement of the technology built into these devices (camera, microphone and accelerometer) make the smartphones extremely valuable in collecting high-quality data. Recently, Apple presented the results of a 400,000-patient clinical trial at the American College of Cardiology, something no one would have believed could happen five years ago. Similarly, studies in sleep patterns and Parkinson's disease have shown how easy it would be to use these technologies to create registries of HPV vaccinated vs non-vaccinated individuals at a fraction of today's program costs.

Coupled with this technology, the deployment of medical applications from the app stores has ushered a new era where the patients feel empowered and comfortable sharing data with their healthcare professionals or participate in registries.

There are a number of smartphone-enabled AI applications approved by regulatory bodies for the screening of atrial fibrillation, diabetic retinopathy and skin cancer. And several will come in the near future. Almost every aspect of HPV eradication efforts can be looked at to see if such applications could be useful.

The ability to combine and analyze different sets of data that on the surface would not be linked and was not possible before the advent of AI, Big Data and Cloud storage could yield important findings and accelerate certain developments. One can think about the combination of Google research requests with provincial or national data that would make possible the prediction of drug interactions and side effects, disease prevalence or even diagnosis of HPV.

Canada is uniquely positioned in the field of AI as illustrated by the Canadian government awarding significant grants to three leading academic institutions, the Montreal Institute for Learning Algorithms (MILA), the Alberta Machine Intelligence Institute (AMII) in Edmonton, and the Vector Institute for Artificial Intelligence, based in Toronto.

Also, two of the three recipients of the 2018 Turing Award, Yoshua Bengio (University of Montreal and Director of MILA) and Geoffrey Hinton (The Vector Institute, and University Professor Emeritus at the University of Toronto) are from Canada.

The Turing Award is a prestigious annual prize given by the Association for Computing Machinery to an individual or individuals selected for contributions "of lasting and major technical importance to the computer field." Both Dr Bengio and Hinton are known worldwide for their work on artificial intelligence.

On Dec. 4, 2018, the "Montreal declaration for responsible development of artificial intelligence" was officially launched, confirming the role that Canada intends to play in the field of artificial intelligence.

Furthermore, it is estimated that there are about 350 companies whose activities revolve around artificial intelligence making Canada a significant hub in the field. Coupled with the desire of the Canadian and provincial governments and the academic institutions to invest significantly in the area, the country is very well positioned to launch significant initiatives in all aspects of HPV-related disease control and elimination where AI could be useful.

RECOMMENDATIONS

For Canada:

97. Create a registry of all the organizations (private and public) involved in the use of AI in Health.

98. Develop a list of areas in HPV where AI and digital health could be transformative:

- Diagnosis
- Screening
- Self-sampling in screening for cervical cancer
- Communications and awareness campaigns

For International:

99. Identify existing projects that could be catalyzed by AI and digital health and link up with the Canadian AI resources (academic, public or private organizations)

100. Create an inventory of the projects that were successful in Canada but who could not be replicated for economic reasons and determine whether the use of technologies related to AI or digital health could make these programs possible in low- and middle-income countries (LMIC).

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Chapter 20
Financing the Acceleration of HPV Prevention toward the 2030 Objectives

- **Catherine Popadiuk**, MD, FRCS(C), MBA, MSL, Medical Director Cervical Screening Initiatives, Newfoundland and Labrador; Associate Professor, Division Gynecologic Oncology, Faculty of Medicine, Memorial University

OVERVIEW

Problem

The World Health Organization has set the ambitious target of Cervical Cancer (CxCa) elimination by 2030. The Global target to have 90% of eligible men and women vaccinated against human papillomavirus (HPV), 90% of women being screened with HPV testing, and 90% of women receiving timely follow-up and treatment of cervical lesions is expected to bring cervical cancer incidence down to 4 per 100,000 women. Although many developed countries have already reached close to this target with incidence of approximately 7 to 10 per 100,000, other low-income countries such as the sub-Saharan still have incidence rates of 50 per 100,000. The gap is significant and thus the strategies and funding requirements to achieve CxCa elimination will differ among the developing and developed worlds. Low-income and low-middle income countries will have differing priorities and resources available to them over the next decade in achieving the goal than the developed world.

Furthermore, in the developed world, there are populations that have CxCa incidence rates akin to those in the developing world. In Canada, although considered among the leaders in Cervical Cancer screening and management, there are pockets of populations not achieving the present CxCa incidence rate of 7 per 100,000. Some Aboriginal communities, women in more rural locations, and populations of women such as the immigrant and refugee groups, and the socially disadvantaged, have to be considered in costing and financing evaluations. Canada thus must address the more average "affluent" population and the underserved groups, and any financial acceleration to meet the 90/90/90 2030 objectives must address both groups.

At the international level, the low-income and low-middle income countries have their own unique local challenges to achieving the CxCa global target of 4 per 100,000 women. Greater emphasis will be on infrastructure creation, operational and human resource implementation, and prioritization among HPV vaccination, HPV screening and downstream follow-up and treatment. Does a country concentrate upon one component of vaccination, screening and treatment or address all three elements in parallel in select groups?

Situation

The benefit of HPV vaccination for the primary prevention of cervical cancer cannot be overstated. Numerous randomized controlled trials and surveillance observational analysis continue to show the persistent prevention of HPV infection, abnormal screening tests and cervical pre-cancer. Similarly, screening with Primary HPV testing has been shown to have superior sensitivity over cytology in the detection of precancerous lesions. The lessened specificity has been accommodated through well-developed screening protocols and strategies, and as the proportion of women vaccinated against HPV mature and progress through the screening system, Primary HPV testing is the rational complementary test.

Unfortunately, the widespread adoption of HPV vaccination and Primary HPV testing has not been uniformly embraced around the world and throughout Canada. Given resource limitations, human and financial, developing countries do not offer organized universal screening programs and HPV vaccination is similarly limited.

In the developed world, the inertia after over 40 years of cytology screening, and its associated infrastructure, is challenging to mobilize and change. National professional bodies recognize the challenge and are struggling to bring all the key stakeholders together to move towards primary HPV testing. Furthermore, despite the investment in HPV vaccination, the rollout and uptake among various provinces and territories has been limited although improving.[1]

Solution

A number of modeling analyses support the cost effectiveness and utility of using both HPV vaccination and HPV Primary screening for the more rapid elimination of cervical cancer in the developed world, and developing low and low-middle income countries.

In the developed world where organized cytology screening has been successful in decreasing CxCa incidence to 7 per 100 000, HPV vaccination has already resulted in positive effects on the burden of HPV in the population even at vaccination rates less than 50%. Herd immunity has had beneficial effects in the population as evidenced by data in Australia, the United States and Canada.

In 20 eligible studies from 9 high income countries, with 140 million person years follow up, even in countries with less than 50% vaccination rates, HPV 16 and 18 infections decreased by 68% in girls 13 to 19 years between pre and post vaccination periods.[2] Furthermore, vaccination of women until age 25 years beyond sexual debut was found to be cost effective.[3]

In another analysis of 19 eligible models from 10 high income countries, strong herd effects are expected from vaccinating girls only, even if coverage is as low as 20%. Elimination of HPV16 and 18 is possible if there is 80% coverage in girls and boys and if high vaccine efficacy is maintained over time.[4] At 40% girls vaccine coverage only, the relative risk (RR) prevalence of HPV 16 among women and men was 0.53 and 0.36 after 70 years. With 80% girls' coverage, RR prevalence of HPV 16 among women and men was 0.93 and 0.83. Vaccinating boys in addition to girls increased the RR prevalence of HPV 16 among women and men by 0.18 and 0.25 for 40% coverage, and 0.07 and 0.16 for 80% coverage.

And when evaluating the impact of Primary HPV testing in a vaccinated population, HPV screening is predicted to reduce the lifetime risk of CxCa diagnosis by 18% and death 20% in unvaccinated women. The quadrivalent vaccine will provide further reduction in diagnosis of 54% and death 53%. The nonavalent vaccine is expected to contribute a further reduction of 11% for incidence and mortality compared to cytology in unvaccinated.[5]

Furthermore, high income countries have reported large reductions in HPV prevalence following "catch-up" vaccination of multiple age cohorts in the year of HPV vaccine introduction. Mathematical modeling applying a similar principle to 73 low- and lower-middle-income countries shows that multiple age cohort vaccination could increase the number of cervical cancer deaths prevented by vaccine introductions in 2015 to 2030 by 30% to 40% or an additional 1.23 to 1.79 million over the lifetime of vaccinated cohorts.[6] Results suggest that multiple age-cohort vaccination of 9- to 14-year-old girls could accelerate HPV vaccine impact and be cost-effective.

Finally, an analysis and estimate of the capital investment and recurrent costs of national cervical cancer screening with visual inspection acetic acid and precancer treatment programs with cryotherapy in 23 high-incidence countries in Sub-Saharan Africa was done to provide estimates of the investment required to address the burden of cervical cancer in this region. The 23 countries in Sub-Saharan Africa account for 64% of the annual cervical cancer deaths in this region.

It would take less than US $10 per woman screened to significantly decrease the cervical cancer deaths that will occur in Sub-Saharan Africa over the next 10 years. Nonetheless, even an investment of $10 US per woman is significant in this region.

Complex computer modeling of costs for lower income and lower middle-income countries have estimated the contributions of 2 dose HPV vaccination in younger ten-year-old girls and direct medical costs for screening and downstream treatment costs of detected precancerous lesions for women 30 to 49 years. There was an assumption that vaccination and screening would be rolled out over five years until full capacity and importantly VIA would transition to Primary HPV testing during that five-year interval. Health outcomes included incidence, mortality and Disability adjusted Life years averted due to vaccination, screening and treatment over the lifetime of 165 million women being screened from 2015 to 2024.[7]

The model estimated the total costs over this ten-year period to be 3.06 billion US dollars. The cost per girl for vaccination is $14.13. The cost per woman reached for screening is $8.36 being higher in lower to middle income

Table 1. Cost, outcomes, and cost effectiveness in low-income and lower-middle-income countries.

	Program cost (millions)	Number reached (millions)	Deaths averted (1000s)	DALYs averted (millions)	CCTx cost averted (millions)	Net cost (millions)	Program cost per girl/woman reached*	Program cost per death averted*	Net cost per DALY averted
Vaccine									
LI	$629	61	1,256	5.0	$23	$605	$12.25	$598	$122
LMI	$1,272	99	1,099	4.7	$183	$1,089	$15.29	$1,379	$222
Total	**$1,901**	**160**	**2,355**	**9.7**	**$207**	**$1,694**	**$14.13**	**$962**	**$170**
Screening									
LI	$369	74	395	3.9	$83	$286	$5.71	$1,063	$66
LMI	$792	91	836	8.1	$363	$429	$10.52	$1,139	$71
Total	**$1,161**	**165**	**1,231**	**12.0**	**$446**	**$715**	**$8.36**	**$1,115**	**$70**
Combined									
LI	$997	135	1,651	8.9	$107	$891	$8.68	$709	$100
LMI	$2,064	190	1,935	12.8	$546	$1,518	$13.01	$1,276	$119
Total	**$3,062**	**325**	**3,586**	**21.7**	**$653**	**$2,409**	**$11.21**	**$1,015**	**$111**

Low income (LI) = GNI pc < $1045, Lower-middle income (LMI) = GNI pc $1046 - $2585, CCTx = treatment of invasive cervical cancer, DALY = disability-adjusted life year

* The Program Cost per Girl/Woman Reached and Program Cost per Death Averted figures were derived from undiscounted program costs (not shown) to be consistent with the undiscounted denominator.

countries where more HPV testing would be offered over VIA. **Approximately 11% of program costs are offset by averted cancer treatment costs in low income settings and 26% in LMI settings.**

Vaccination will prevent 2.36 million cervical cancer deaths in 160 million young girls over the lifetime of the 160 million girls vaccinated; and 1.23 million cervical cancer deaths will be averted in 164 million women due to screening and treatment.

The NET cost per DALY averted is $170 for vaccination and $70 for screening. 300 million per year over ten years is a small price to pay in the Global scheme to empower and assure gender equity of women to a virtually entirely preventable disease condition.

In another model, Policy1-Cervix, the authors aimed to quantify the potential cumulative effect of scaled up global vaccination and screening coverage on CxCa incidence over 50 years from 2020 to 2069, to identify the earliest years when CxCa rates could drop below 6 cases per 100,000 and 4 cases per 100,000.[8]

With no change in practice of vaccination and screening, there would be 44.4 million CxCa cases globally between 2020-69, 2/3rd of which are in LMIC. Vaccination scale up to 80-100% coverage by 2020 globally could avert 6.7 to 7.7 million cases by 2069, with over half the cases averted after 2060. Implementation of HPV based screening twice per lifetime in LMIC at 35 and 45 years with 70% coverage will avert 12.5-13.4 million cases in the next 50 years. Combined high coverage vaccination and screening from 2020 onwards would result in average annual incidence declining to less than 6 per 100,000 cases by 2045-49 for very high human development index (HDI) countries, 2065-69 for medium HDI countries, and 2085-89 for low HDI countries. 4 cases CxCa per 100,000 women under high coverage screening and vaccination circumstances would be achieved by 2055-2059 for very high HDI countries, 2070-79 for medium HDI countries, and 2090-2100 or beyond for low HDI countries.

Benefit in the short term, ten to twenty years, requires focus on screening for older women who will not benefit in the same manner from HPV vaccination as younger women who will achieve the benefits of HPV vaccination in three to four decades.

And finally, the Canadian Partnership Against Cancer Oncosim HPV-Cervix model[9] was used to evaluate Canada, considered a very high HDI country with cytology

screening coverage of 70 to 80%, and HPV vaccination rates in public school-based programs from 50 to 95%. To achieve Cervical Cancer elimination of 4 per 100,000 cases by 2050, a concerted and intense effort would be required including perfect 100% coverage of HPV vaccination with catch up of men and women until the age of 45 years, and 100% screening with HPV and cytology co-testing.

RECOMMENDATIONS

For Canada:

101. Promote the rapid transition and implementation to Primary HPV testing for Cervical Cancer screening

102. Continue to advance the importance of HPV vaccination as a concerted effort for all young boys and girls eligible through the school-based program, catch up, and men and women eligible as adults.

103. Create culturally appropriate strategies to reach the under-screened and unvaccinated eligible populations such as some Aboriginal communities, immigrant and refugee groups, socially disadvantaged groups or individuals sceptical regarding the import of HPV elimination and each individual's role to play in achieving this goal.

For International:

104. Through Canada's Feminist International Assistance Policy, offer support for local initiatives in low-income and low-middle-income countries to build upon and gain momentum in their HPV vaccination and screening efforts.

105. With other like-minded organizations such as Gavi, WHO, IARC and other NGO's and charitable organizations, assist in human resource and operational requirements needed to promote HPV vaccination and HPV testing together according to local requirements of low-income and low-middle income countries.

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Conclusion
Canada's Role in Accelerating Global Elimination of Cervical Cancer

We have seen through the lens of Canadian experts that Canada has the scientific expertise and the tools to reach the WHO 2030 objective of decreasing cervical cancer incidence to fewer than 4 per 100,000 women per year, which is arguably an easy target for Canada because annual cervical cancer incidence rates in most Canadian provinces are already below 7 per 100,000. In fact, given the resources on hand and the Canadian expertise and experience with HPV vaccination and screening, Canadian provinces can aim for a more ambitious target of less than 2 per 100,000.

We now need the full support from the Government of Canada (lead by Global Affairs Canada and the Health Portfolio) so that cervical cancer can be eliminated in Canada and around the world. We need to accelerate deployment of proven innovative strategies such as self-sampling for HPV testing. We need to be more vocal about the safety and efficacy of HPV vaccination in national campaigns. We need to rapidly deploy innovative strategies for those people most at risk because they are not being reached due to various reasons including geographical and socio-economic isolation, and chronic distrust due to stigmatization from the healthcare system. We know that Indigenous populations, people experiencing extreme poverty and/or homelessness/street-involved individuals, people who use injection drugs, refugees and immigrants - to name only a few groups of people with increased risk of exposure - are not being reached by most of the preventive efforts being recommended in Canada and around the world.

In this monograph, Canadian experts contributed a list of recommended strategies to address these needs for Canada and the international community. Canada has the science, expertise and tools to prevent and control this terrible disease. The experts are ready to help. The pressing requirement that will allow us all to move forward is to receive the full and expedited support of the Government of Canada and its departments and agencies. This support must be made a priority to allow Canada to accelerate disease control and to help reach the WHO goal of eliminating cervical cancer.

Canadian HPV experts agree that Canada needs to actively support the Call for Action from WHO to eliminate cervical cancer by 2030. There is an opportunity and a need for Canada to assume a leadership position to help eliminate cervical cancer in Canada and around the globe. It is clear that national and international efforts need to adhere to the feminist approach to development. Canadian experts have made specific recommendations at the end of each chapter that point to directions of development for both Canada and on an international basis. We list below the overarching domestic and international objectives:

INTERNATIONAL OBJECTIVES

One of the challenges in the planning of cervical cancer elimination is to secure funding both at home and internationally. Similar to the Global Fund to Fight AIDS, Tuberculosis and Malaria, there should be adequate funding from the start. To reach the goal of eliminating cervical cancer, Canada should undertake two activities:

1. call a national consultation meeting to solidify support for the elimination strategy; and
2. organize an international funding meeting to secure proper funding for the drive to eliminate cervical cancer.

Another challenge is the lack of a coalition of community advocates that would be very helpful in the drive to eliminate cervical cancer. Canada should support the creation of, and provide financial support for, an international community assembly to increase the competencies of non-governmental organizations similar to ICASO (International Council of AIDS Service Organizations) based in Toronto.

Canada is a world leader in the field of digital health and artificial intelligence. A specific fund for the development of numerical health in the field of cervical cancer prevention should be established.

DOMESTIC OBJECTIVES

Canada has its own pockets of inequity with regard to cervical cancer prevention. There are groups not reached by HPV immunization or cervical screening. In order to reach the objective of eliminating cervical cancer, we will need to develop innovative approaches with community leaders to bring the reality of cervical cancer elimination to those communities that experience higher rates of cervical cancer. Canada needs a comprehensive implementation plan to reach these communities.

Canada also needs an infrastructure plan to make HPV testing available and accessible in all parts of the country. A committee should plan the deployment of a Canadian-specific infrastructure for HPV testing to accelerate the transition from cytology to HPV molecular testing. The Canadian Partnership Against Cancer could take the leadership in mediating this transition.

We have two powerful tools in this drive to cervical cancer elimination by 2030: HPV prophylactic vaccines and cervical cancer screening. But to take greatest advantage of these tools, Canada must assume international leadership now. If Canada delays, we will not reach the international elimination objective, with the possible exception of a few rich countries that are already approaching the cervical cancer elimination goal. Consistent with its international profile advancing important charitable causes, Canada must take a leadership role towards the elimination of cervical cancer. Having been one of the world's pioneers adopting cervical cancer screening in the 1950's and HPV vaccination in 2007, Canada has the requisite experience and know-how to advise other countries in reaching this important target.