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Human Papillomavirus and Considerations for Prevention Post-COVID-19

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Introduction

Although it is a preventable and potentially curable disease, cervical cancer is still a common cause of cancer mortality worldwide. Human papillomavirus (HPV) infection is the leading cause of more than 90% of cervical cancer cases. It is also the cause of other anogenital cancers such as vulvar (70%), vaginal (70%) and penile (60%) and oropharyngeal cancer (60%). Both cervical cancer screening and advanced treatment have contributed to a steady decline in cervical cancer incidence in Canada. The introduction of HPV vaccines has also been instrumental in reducing transmission of the HPV strains that cause cervical and other cancers.

The COVID-19 pandemic has had unintended consequences on global and Canadian health systems and the health of Canadian populations. Due to concerns over COVID-19, some patients were hesitant to seek medical attention and the resources and services needed to diagnose cancer became limited.

The social disruption caused by the pandemic has also delayed and disrupted routine immunization programs including immunization against the human papillomavirus (HPV). This document reviews the evidence on HPV immunization effectiveness in Canada and investigates what HPV vaccines are, why they are important for population health in Canada, and how the COVID-19 pandemic is affecting the future epidemiology of HPV in Canada.

Human Papillomavirus

The human papillomavirus (HPV) is a non-enveloped virus with a double-stranded DNA genome of approximately 8,000 base pairs that belong to the Papillomaviridae family. Papillomaviridae members primarily infect mucosal and keratinized epithelia. The HPV viral particles (virions) have a conserved icosahedral morphology, measuring 50-55 nm in diameter and weighing 5x 106 Da. HPV-specific genes include 35 that are specific to the cervical and anal epithelium [1-3].

Cancer is an irreversible process that begins when normal cells are exposed to physical, chemical, or biological agents that cause genetic damage (mutation) and genomic instability. Viral infections contribute to 15-20% of all human cancers, and several viruses play significant roles in the multistage development of malignant cancers. The most common is HPV [1].

Pathogenesis

HPV infections are transmitted sexually through direct epithelial (skin or mucosa) to epithelial contact, vertically to an infant exposed to the virus in the maternal genital tract, and orally through mucosal contact in head and neck infections. HPV cannot be spread through casual contact like hugging, shaking hands, sneezing, or coughing. HPV is not spread through the air, food, or water [4-9]. Papillomaviruses exhibit strict species and tissue tropism, infecting only stratified epithelia in humans

and only rarely transmitting between species. HPV infection occurs via tissue lesions that the virus uses to gain access to basal keratinocytes. Cell transformation sites are the most vulnerable to tumorigenesis (the squamocolumnar junction). This category includes both the cervix and the anus. The process of viral replication begins shortly after the virus enters a host cell [1, 9-11].

Significant progress has been made in understanding the molecular biology of HPV and the HPV genotyping in recent decades. The HPV viral DNA genome is integrated into the host's genome. Many early (E1, E2, E4, and E5) and late (L1 and L2) genes are frequently deleted as a result of this process. During integration, E2 promotes carcinogenesis by increasing the expression of E6 and E7. [10].

Nearly 200 HPV types have been identified, over 40 of which infect the genital area. Types are designated based on the nucleotide sequence of specific regions of the genome. All HPVs have an 8 kb circular genome enclosed in a capsid shell composed of the major and minor capsid proteins L1 and L2 (late genes), respectively. HPV types have been grouped into low-risk and high-risk categories. Fourteen HPV genotypes (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered pathogenic or "high-risk" for causing the development of cervical cancer. HPV types 6 and 11 are considered low risk, and cause benign condylomas, whereas HPV 16 and 18 genotypes, which are frequently found in association with cervical cancer, are considered the most oncogenic types. These two types have been identified as the two most prevalent HPV types and are responsible for approximately 62.6% and 15.7% of invasive cervical cancers, respectively. HPV 16 and 18 account for approximately 68% of squamous cell cancers and 83% of adenocarcinomas. Other HPVs, which are also considered carcinogenic, are less frequent in cervical carcinomas [1, 6, 11-16].

Epidemiology

HPV infection is the leading cause of more than 90% of cervical cancer cases and of other anogenital cancers such as vulvar (70%), vaginal (70%) and penile (60%) and oropharyngeal cancer (60%). The HPV infection is the causative agent for anogenital warts (Condylomata acuminate) and Recurrent Respiratory Papillomatosis (RRP). Cervical cancer is the most common among them [1, 2, 17-19].

Cervical precancer, if unattended, can progress to invasive carcinoma. The time between HPV infection and cancer development may vary from 10 to 30 years. Transient HPV infection is not sufficient for the development of cervical malignancy, and oncogenesis may require persistent infection as well as the presence of cofactors. Seventy percent of new HPV infections clear within 1 year, and approximately 90% clear within 2 years. The risk factors for HPV infections include, previous sexually transmitted infections, history of sexual abuse, early age of first sexual intercourse, the number of lifetime sex partners, tobacco or marijuana use, immune suppression, and HIV infection [20, 21].

HPV is considered the second most significant human carcinogen after tobacco, accounting for 5% of all cancers, 10% of cancers in women, and 15% of all cancers in developing countries. According to the 2020 World HPV Information Center report, approximately 604,000 women were diagnosed with cervical cancer, and 342,000 died from the disease annually. That is nearly 8% of all female cancer

deaths [1, 20, 22, 23]. HPV infection is highly prevalent and affects approximately 80% of the sexually active population; almost half of the infections occur in the 15- to 24-year-old age group [1, 24].

If not immunized, it is estimated that 75% of sexually active Canadians will have an asymptomatic HPV infection at some point in their lives. If not tested, most of them will never know they've been infected because HPV often does not cause any symptoms, however not having symptoms does not mean cancers will not develop [25].

There is significant geographic variation. High incidence rates and high mortality rates of cervical cancer occur mainly (90% for both) in low- and middle-income countries [17, 26].

Despite the prevalence of invasive cervical cancer and its association with HPV being the subject of numerous studies, few studies have looked at the trends of all HPV-associated cancers in both sexes. Men who have sex with men (MSM) are more likely to develop HPV-related cancers. Compared with cervical cancer, anal cancer is a rare disease in the general population, affecting a much smaller proportion of people. However, anal cancer can be caused by HPV 16 in as many as 70% of cases [27].

In 2017, a study in the United States discovered that the overall incidence of HPV-associated cancer in men was 11.0 per 100,000. Oropharyngeal cancer was responsible for 80.1% of these cancers, with an incidence rate of 8.89 per 100,000 people. White men had the highest incidence of HPV-associated cancers, at 12.50 per 100 000, compared with Asian/Pacific Islander men, who had the lowest incidence (2.92 per 100 000). [17, 28]. Sexually active heterosexual men infected with HPV are also a source of infection for others. [6, 9, 16, 19, 26, 29-32]

GLOBOCAN is a database presented via the Global Cancer Observatory and hosted by the International Agency for Research on Cancer (IARC). Data extracted from GLOBOCAN 2020 indicated that there are decreasing trends in cervical cancer. The declining trends may be the result of effective precautionary procedures combined with a series of sociocultural factors, including access to health care, changes in marriage age and family planning behavior, and enhancements in education [33].

About 1,400 new cervical cancer cases are diagnosed annually in Canada. Cervical cancer ranks as the 14th leading cause of female cancer in Canada. According to Human Papillomavirus and Related Diseases Report, Canada 2021, annual estimated number of cervical cancers for 2020 was 1,422, with 637 related deaths [34, 35]

Table 1. Cervical Cancer in Canada (estimates for 2020)

Women at risk for cervical cancer (Female population aged >=15 yrs.)	15.9 million
Annual number of cervical cancer cases	1422
Annual number of cervical cancer deaths	637

Source: Human Papillomavirus and Related Diseases Summary Report, Canada, October,2021

Both cervical cancer screening and advanced treatment have contributed to a steady decline in cervical cancer incidence in Canada. The age-standardized mortality rate (ASMR) for cervical cancer was estimated to be 2.0 per 100,000 persons in 2019 [36]. The Canadian Cancer Statistics Advisory Committee stated an estimated 1,450 Canadian women will be diagnosed with cervical cancer in 2022 and an estimated 380 will die from it [37].

Table 2. Burden of cervical cancer and other HPV-related cancers (estimates for 2020)

	Crude incidence rates per 100,000 population	
	Male	Female
Cervical cancer	-	7.48
Anal cancer	1.22	2.79
Vulva cancer	-	4.91
Vaginal cancer	-	0.95
Penile cancer	1.21	-
Oropharyngeal cancer	5.42	1.22
Oral cavity cancer	11.1	4.77
Laryngeal cancer	4.46	0.79

Source: Human Papillomavirus and Related Diseases Summary Report, Canada, October, 2021

In Canada, about two-thirds of HPV-related cancers happen in areas other than the cervix. HPV infection is related to:

- 80% to 90% of anal cancers
- 40% of vaginal and vulvar cancers
- 40% to 50% of penile cancers
- 25% to 35% of mouth and throat cancers

Most of these cancers are related to high-risk HPV types 16 and 18 [38]

HPV Prevention

Although it is a preventable and potentially curable disease, cervical cancer is still a common cause of female cancer mortality worldwide. There is no treatment for HPV infections. Only HPV-associated lesions, including genital warts, RRP, precancers, and cancers are treated. Understanding HPV and the cause of cervical cancer has led to major advances in the primary and secondary prevention of cervical cancer. Comprehensive cervical cancer control includes primary prevention (vaccination against HPV), secondary prevention (screening and treatment of pre-cancerous lesions), tertiary prevention (diagnosis and treatment of invasive cervical cancer) and palliative care [19, 39, 40].

One of the United Nations Sustainable Development Goals (SDGs), Goal 3.4, is the reduction of one-third in premature mortality from non-communicable diseases by 2030 [39]. On November 17, 2020, at the World Health Assembly, WHO launched "The Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem." The goal is that by 2050, 40% of new cervical cancer cases

and 5 million related deaths could be prevented with successful implementation of vaccination, screening, and treatment of the disease. The strategy is to achieve some targets by 2030. They are to complete HPV vaccination of 90% of girls by the age of 15 years, screening of 70% of women by the age of 35 years and then by 45 years, and treatment of 90% of women diagnosed with cervical disease, including both women with cervical pre-cancer and women with invasive malignancy [18, 29, 39-41].

Pap smear

Early detection of any cancer will improve the outcome. In the case of cervical cancer, as long as it is detected in the preinvasive stage, which allows for preventive measures and possible cures, outcomes are favourable. A comprehensive screening program will help to identify the cancer lesions at an early stage, allowing patients to get prompt, appropriate treatment. Routine screening is an effective method for detecting precancerous lesions.

The Pap smear is a screening method that has enabled the effective prevention of cervical cancer; it is a procedure where cells from the cervix are collected and studied under a microscope to detect pre-cancer and cancer cells [42-44]. The introduction of this cytology (Papanicolaou test or liquid-based cytology) screening yearly (every 3 years now in Canada) globally has significantly reduced cervical cancer incidence and mortality due to early interventions, including among women who have no symptoms and appear to be perfectly healthy. In the past 50 years cervical screening has helped to improve detection of cervical cancer and decrease mortality, particularly in high-income countries [35, 40, 45].

As noted, several human papillomavirus (HPV) genotypes are probably carcinogenic and are the cause of all invasive cervical cancers. HPV cannot be cultured directly from patient specimens, so tests detect HPV genetic information. HPV tests have proven more sensitive (89.9% vs72.9%), reproducible and allow for safer extended screening intervals than conventional cytology or visual inspection with acetic acid, though HPV testing is more expensive than cytology in primary screening. Most of the commercially available assays detect DNA. Because HPV is cell-associated, cellular samples are required. While the HPV mRNA test only detects HPV types 16, 18, 31, 33, and 45, the HPV DNA test will be able to identify HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. [46]. WHO now encourages countries to use HPV tests for cervical screening, including HPV DNA and HPV mRNA tests [39, 40, 45]. While HPV-DNA testing detects high-risk strains of HPV, which cause all cervical cancers, HPV mRNA detects HPV infections leading to cellular transformation. After a negative HPV test, women may be advised to wait up to 10 years before getting another screening. [21, 45, 47-49].

Although not included in a woman's routine checkup or Pap test, the Public Health Agency of Canada reports that HPV DNA testing is accessible in Canada although availability varies by region. Where HPV DNA testing is not covered by provincial or territorial insured services, HPV self-swab tests may be made available both inside and outside of medical facilities [46, 50]

The Canadian Task Force on Preventive Health Care was established by the Public Health Agency of Canada (PHAC) to develop clinical practice guidelines that support primary care providers in delivering preventive health care. According to their recommendation, routinely screening sexually active people under the age of 25 should not be done. However, screening begins at the age of 21 in some provinces and at the age of 25 in others. Only Alberta, British Columbia, Ontario, and Prince Edward Island have implemented these newer recommendations nine years later [46, 51].

In 2020, coverage for cervical cancer screening in Canada was 72.8% for women aged 18 to 69. The frequency of pap smears varies by region; in Manitoba, Ontario, Quebec, and Nova Scotia, it is every three years (ages 21–65 or 69). In Prince Edward Island (ages 21-65), every two years; in other areas, every 2-3 years after three consecutively negative annual tests (ages 21–70) [34, 36].

Despite the existence of publicly funded cervical cancer screening programs across Canada, inequities in access to screening services persist. HPV testing is largely reserved for higher-risk patients; some provinces are working toward using HPV testing for primary screening. To improve cervical cancer screening rate one of the strategies is to introduce HPV self-testing which can be performed on vaginal samples collected by the woman herself. This means a visit to health care provider is not necessary. Self-swabbing HPV tests have been incorporated into some national screening programs in Australia and some European countries and has been found to increase screening coverage. Including self-swabbing HPV tests in cervical screening programs has increased the screening's coverage. Most studies have demonstrated that HPV-SS is the most practical and cost-effective method for promoting cervical cancer screening and preventing cervical cancer. [45, 46, 52-54]. Canada has approved HPV self-testing kits which may be available both inside and outside of medical facilities. A Manitoba study supports a growing body of research that suggests HPV self-tests should take the place of Pap tests in the screening for cervical cancer. It proves that offering at-risk women HPV self-sampling kits as a screening option is feasible [52, 55, 56].

Urine HPV detection is also promising, due to its non-invasiveness and favorable acceptability profile. Although devices to collect the urine and preservation mediums have been identified, there is currently no HPV assay that is specifically modified and marked for first-void urine. Therefore, additional research is necessary [57, 58].

Scientific evidence showed male circumcision reduces female-to-male HIV transmission. Similarly, male circumcision and condom use has been shown to have a significant protective effect against HPV transmission [34, 59-63].

Vaccination

Vaccination against HPV has proven to be the best global strategy to control the spread of the virus and its consequences. The vaccine triggers the host antibody response which in turn neutralize the virus entry into the cells. The non-infectious subunit vaccines are composed primarily of virus-like particles (VLPs), which are completely non-infectious and non-oncogenic. The L1 major capsid protein of HPV is

the antigen used for HPV vaccination. The HPV vaccine protects against infection with some types of HPV that cause cancer and some types of HPV that cause genital warts [18, 64].

Significant progress has been made in understanding the molecular biology of HPV and the HPV genotyping in recent decades. The HPV viral DNA genome will be integrated into the host's genome. Many early (E1, E2, E4, and E5) and late (L1 and L2) genes are frequently deleted as a result of this process. During integration, E2 promotes carcinogenesis by increasing the expression of E6 and E7. [10].

There are three HPV vaccines authorized for use in Canada: the bivalent vaccine "Cervarix®" (HPV2) contains the VLPs of HPV16 and 18, the two types that cause 70% of cervical cancer worldwide and even greater proportions of HPV-associated vulvar, vaginal, penile, anal, and oropharyngeal cancers. The quadrivalent vaccine "Gardasil®" (HPV4) contains VLPs of types 6, 11, 16, and 18. Adding VPL 6 and 11, as HPV 6 and 11 cause approximately 90% of external genital warts in both men and women, vaccine Gardasil® 9 (HPV9), a nine-valent human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, and 58], protects against anogenital cancers and genital warts [6, 50, 64-69]. These vaccines can almost completely protect against HPV-16 and HPV-18 infections. The goal of HPV vaccination is to reduce the number of cervical cancer cases 71–84%. Cervical cancer screening should continue in all vaccinated women due to the risk of exposure to other oncogenic HPV types [16].

In high-income countries, programs are in place that enable girls to be vaccinated against HPV and women to get screened regularly and treated adequately. HPV vaccines work best when given prior to HPV exposure. Females who are not sexually active can be expected to benefit fully from vaccination. Yet, a small percentage of sexually active females may have been infected with all four of the HPV types. The Advisory Committee on Immunization Practices (ACIP) USA and National Advisory Committee on Immunization (NACI) Canada 2017 recommend routine vaccination of females aged 11–12 years, with two to three doses of the quadrivalent HPV vaccine. The vaccination series can be started as early as 9 years of age. Additionally, unvaccinated people can receive catch-up vaccinations until the age of 26. The most reported adverse events following HPV vaccination are injection site pain, swelling or redness, like any other vaccine. HPV vaccines are highly immunogenic and have been shown to protect against cervical intraepithelial neoplasia grade 2 or higher [11, 16, 70, 71]. Because HPV is sexually transmitted, a potential herd effect might be further decreased with increasing number of sexual partners and increasing age. HPV vaccination has been recommended for adolescents in the U.S. since 2006 for females and 2011 for males, and in Canada for females since 2007 and for males since 2010 [14, 39, 71-76].

According to the *Canadian Immunization Guide 2017, Human Papillomavirus Vaccine*, the HPV4 and HPV9 vaccines are nearly 100% effective against HPV types 16 and 18-related cervical disease. Protection against external genital lesions caused by HPV types 6, 11, 16, or 18, including genital warts, is 95% to 99% in women aged 16 to 26; protection against high-grade disease caused by HPV types 31, 33, 45, 52, and 58 is over 96% in women aged 16 to 26. In men aged 16 to 26, the efficacy of the HPV4 vaccine against vaccine-type-related external genital lesions ranges from 84% to 100%, and the efficacy

against persistent vaccine-type-related infection ranges from 70% to 96%. The HPV4 vaccination reduced the overall number of abnormal PAP smears [77]

HPV vaccines are administered in provinces and territories across Canada through publicly funded school-based programs. The quadrivalent vaccine is given to girls in grades 4 through 10 in two or three doses. While British Columbia and Quebec provide only two doses, other provinces provide three [6, 14, 68, 78]. Since 2016, boys can get vaccinated for free in the school setting [79, 80]. The Canadian Immunization Committee (CIC) recommends HPV vaccination coverage targets of 80% and 90% of eligible students within two and five years of program introduction, respectively. But under HPV vaccination programs, coverage has been below the public health goals in several provinces and territories. According to the Childhood National Immunization Coverage Survey (cNICS) 2015, 2017, and 2019, 75%, 84%, and 87% of 14-year-old girls in Canada received at least one dose of the HPV vaccine, respectively [68, 74, 75, 81].

The Childhood National Immunization Coverage Survey (cNICS) 2017, indicated coverage for the HPV vaccine is lower than for the hepatitis B virus vaccine, even though both viruses have a similar risk profile, are sexually transmitted, and can cause cancer. A population-based study in BC found 65.1 % of females received the HPV vaccine while 88.4 % of females received the Hepatitis B vaccine (both viruses have similar risk profile, are sexually transmitted, and can lead to cancer) [82, 83]. This raises questions about whether parents have concerns about HPV vaccines for girls.

A review of the effects of the quadrivalent human papillomavirus vaccine based on ten years of clinical experience in Canada, found that qHPV-vaccinated people had a lower prevalence of HPV types 6, 11, 16, and 18 than unvaccinated people (1.5% vs. 11.0%, respectively). In vaccinated cohorts, the risk of AGW incidence decreased by up to 45%, and the incidence of cervical intraepithelial neoplasia type 2 + was reduced by up to 86% [69, 84].

According to the Canadian Immunization Guide and advised by National Advisory Committee on Immunization (50, 64, 77):

- HPV2, HPV4 or HPV9 vaccine is recommended for prevention of cervical cancer and precursors in girls and women 9 to less than 27 years of age, including those who have had previous Pap test abnormalities, cervical cancer or genital warts.
- HPV4 or HPV9 vaccine is recommended for the prevention of vulvar, vaginal, anal cancers and their precursors, and genital warts in girls and women, 9 to less than 27 years of age.
- HPV2, HPV4 or HPV9 vaccine may be administered to women 27 years of age and older at ongoing risk of exposure.
- HPV4 or HPV9 vaccine is recommended for prevention of anogenital cancer and genital warts in boys and men, 9 to less than 27 years of age.
- HPV4 or HPV9 vaccine may be administered to men 27 years of age and older at ongoing risk of exposure.
- HPV2 vaccine is not authorized for use in boys and men.

Following the implementation of the HPV vaccination program in the Canadian province of Manitoba, rates of anogenital warts (AGW) began a steady decline from 2008 to 2017. AGW incidence decreased

by 72% (54-83%) for 16-18-year-old girls and 51% (14-72%) for 16-18-year-old boys after the female-only program was implemented [50, 76].

HPV Therapeutic Vaccine

The current HPV preventative vaccines cannot eliminate an infection that has already started. Therefore, the large number of individuals already infected with HPV do not benefit. In addition, the preventative vaccination is used to protect against high-risk HPV types 16 and 18.

Therapeutic vaccines create cell-mediated immunity, whereas prophylactic vaccinations induce antibodies against a viral capsid protein, which can destroy the virus and so prevent cell infection. Therefore, therapeutic vaccines not only manage HPV-related lesions but also establish a systemic immunological memory to help prevent disease recurrence. Therapeutic HPV vaccines are made of a recombinant, attenuated form of the vaccinia virus's HPV, which represents tumor-specific antigens oncoproteins E6 and E7 [10, 88].

Development of therapeutic vaccines that might control an existing infection and worldwide clinical trials for therapeutic HPV vaccinations are currently underway [41, 85-87].

The Impact of the COVID-19 Pandemic and HPV prevention

As with many other programs are affected by the COVID-19 pandemic, the number of cervical cancer screening tests and the number of cytological abnormalities identified have also been affected. A studies indicated the overall odds of a woman receiving a given preventive service in 2020 was 20% to 30% lower than 2019 [89, 90].

HPV vaccination has been one of the most disrupted programs due to COVID-19, which resulted in school closures and interruptions to routine immunization services. HPV vaccination had fallen lower on the list of priorities. Studies estimated a substantial reduction in HPV vaccine coverage nearly 25% in 2020 compared to 2019 [93-97]. There was a decline in the doses of HPV vaccines administered in the U.S. during the first quarter of 2020 compared to the same period in the two preceding years [75, 91-94].

As a result of COVID-19, missed HPV vaccinations will bring about a rise in genital warts, cervical cancer, and other HPV-related diseases and cancers. The vaccination is required to ensure that those who are currently eligible, as well as those who may have missed doses in the previous two years, are vaccinated. According to recent studies, interest in HPV vaccines has increased along with positive attitudes in the COVID-19 era. The WHO recommended that nations prioritize immunization and

regularly assess whether extensive catch-up vaccination campaigns are necessary. Decision-makers require country-specific, evidence-based information regarding vaccine deficits because the scope and trends of vaccine deficits can vary by country in order to plan precise and effective catch-up initiatives [91, 92, 98]. Because of the COVID vaccine's preventive effects, perceptions of the importance and safety of vaccination are likely to have a positive overall effect on the acceptance of a newly developed vaccine [93].

Summary and Conclusion

HPV is a highly infectious virus transmitted through oral, anal, or genital sexual contact, as well as through nonpenetrative sex involving skin-to-skin contact. HPV is a well-established cause of cervical cancer, anogenital cancers (anus, vulva, vagina and penis) and head and neck cancers [17, 19].

Cervical screening has decreased the number of cases and deaths caused by precancerous lesions. The lifetime incidence of cervical cancer was 1.5% in 1972 and 0.7% in 2013. The primary reason for this is that routine cervical cancer screening programs are still in use. The Canadian Task Force on Preventive Health Care recommends routine cervical cancer screening every three years for women aged 30-69 [51]. The availability of self-swabbing HPV tests is expected to increase the use of cervical cancer screening and, as a result, cervical cancer prevention [46, 54, 95].

In Canada, all provinces and territories have implemented school-based HPV immunization programs more than a decade now though uptake varies (from 47% in the North West Territories to 93% in Newfoundland) in each province and territories [73, 84].

The vaccine can prevent over 90% of cancers caused by HPV, but vaccine uptake remains suboptimal. In 2019 only 87% of 14-year-old girls in Canada received at least one dose of the HPV vaccine. Vaccination coverage targets 90% of eligible students within five years [81]. Despite a significantly low level of reported instances of severe adverse reactions and nearly 99 % efficacy, uptake of the vaccines remains low. The most prevalent concerns for low vaccination coverage are insufficient and inadequate information about HPV vaccination; potential side effects of the vaccine; issues surrounding the trust of health authorities, and new vaccines; and perceived low vaccine effectiveness. Issues related to the sexual health aspects of the vaccine have been reported in many qualitative studies that affect vaccine uptake. Continued efforts are needed to ensure that health care professionals understand the importance of vaccinating adolescents before they become sexually active [51, 99].

It was found HPV vaccine among Canadian adolescent girls, the overall 27.7% of girls aged 12–14 y in 2013 had not received any doses of the HPV vaccine and 14.4% of parents reported having refused the HPV vaccine for their daughter. Higher vaccine refusal rates are observed among parents with higher education [80].

Even in the face of overwhelming scientific evidence to the contrary, parental beliefs about vaccines being dangerous or HPV vaccination encouraging unprotected sexual activity persist. This is still a

barrier to broad coverage. The social stigma and discomfort associated with STDs and sexual health may deter doctors and parents from having productive conversations about the HPV vaccine. Raising awareness about HPV and its link to cancers other than cervical cancer may be advantageous. Efforts should also be made to increase medical professionals' awareness of the problem [69, 100].

The public's attitude toward vaccine confidence is influenced by vaccine effectiveness and safety, as well as trust in the national health care system. Each student should be provided with an informational pamphlet along with a consent form. As a result, by providing accurate information on the efficacy and safety of the HPV vaccine, it will be possible to increase vaccination rates. Most jurisdictions have expanded their public HPV vaccination programs to include high-risk populations such as men who have sex with men, transsexuals, and HIV-infected people. [101, 102].

Opportunities to link vaccine delivery to other health interventions targeting adolescents should also be explored. In the USA, ACIP recommends routine HPV vaccination for 11- or 12-year–old girls and boys during their routine vaccine appointment [75, 78]. School nurses play an important role in improving HPV vaccine coverage[99, 103, 104].

WHO's priority is to eliminate cervical cancer globally, but vaccine supply and logistics limit widespread implementation of the current two- or three-dose HPV vaccine schedule. In April 2022, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) evaluated the evidence and recommended a one-dose schedule for girls and young women who are 9–20 years old. SAGE also recommended incorporating the HPV vaccine into immunization programs [68, 105-107].

To be successful, HPV vaccination programs will need to raise public awareness about HPV, cervical cancer, and the benefits of HPV vaccination in general. Adolescent vaccination coverage could be increased by implementing a multifaceted intervention package for vaccination service providers, such as education, repeated contact, individualized feedback, and incentives, or by using class-based vaccine delivery approaches rather than age-based vaccine delivery approaches. HPV vaccination programs may benefit cervical cancer prevention strategies, ultimately lowering the burden of cancer and other HPV-related illnesses [69, 102, 103].

The HPV vaccine will not eliminate the need for cervical cancer screening because not all HPV types that cause cervical cancer are included in the vaccine [16]. Policymakers should make sure that the vaccination is firmly in place for young adolescent girls who can benefit the most from it and concentrate on screening-based approaches for cervical cancer prevention among older women [18].

References

1. Araldi, R.P., et al., The human papillomavirus (HPV)-related cancer biology: An overview. Biomed Pharmacother, 2018. 106: p. 1537-1556.
2. Humans, I.W.G.o.t.E.o.C.R.t., Human papillomaviruses. IARC Monogr Eval Carcinog Risks Hum, 2007. 90: p. 1-636.
3. Obeid, D.A., et al., Human papillomavirus epidemiology in populations with normal or abnormal cervical cytology or cervical cancer in the Middle East and North Africa: A systematic review and meta-analysis. J Infect Public Health, 2020. 13(9): p. 1304-1313.
4. Kero, K. and J. Rautava, HPV Infections in Heterosexual Couples: Mechanisms and Covariates of Virus Transmission. Acta Cytol, 2019. 63(2): p. 143-147.
5. Trottier, H., et al., Human papillomavirus (HPV) perinatal transmission and risk of HPV persistence among children: Design, methods and preliminary results of the HERITAGE study. Papillomavirus Res, 2016. 2: p. 145-152.
6. Canadian Immunization Committee. Recommendations for human papillomavirus immunization programs. 2014, Public Health Agency of Canada.
7. WHO, Human papillomavirus (HPV) and cervical cancer. 2019, World Health Organization.
8. Rombaldi, R.L., et al., Perinatal transmission of human papilomavirus DNA. Virol J, 2009. 6: p. 83.
9. Schneider, A., Pathogenesis of genital HPV infection. Genitourin Med, 1993. 69(3): p. 165-73.
10. Yang, A., et al., Perspectives for therapeutic HPV vaccine development. J Biomed Sci, 2016. 23(1): p. 75.
11. Serrano, B., et al., Human papillomavirus genotype attribution for HPVs 6, 11, 16, 18, 31, 33, 45, 52 and 58 in female anogenital lesions. Eur J Cancer, 2015. 51(13): p. 1732-41.
12. McLachlin, C.M., Pathology of human papillomavirus in the female genital tract. Curr Opin Obstet Gynecol, 1995. 7(1): p. 24-9.
13. Alhamany, Z., et al., Prevalence of human papillomavirus genotype among Moroccan women during a local screening program. Journal of Infection in Developing Countries, 2010. 4(11): p. 732-739.
14. Rogers, C. and R.J. Smith, Examining Provincial HPV Vaccination Schemes in Canada: Should We Standardise the Grade of Vaccination or the Number of Doses? Int Sch Res Notices, 2015. 2015: p. 170236.
15. Andersson, S., et al., The relative distribution of oncogenic types of human papillomavirus in benign, pre-malignant and malignant cervical biopsies. A study with human papillomavirus deoxyribonucleic acid sequence analysis. Cancer Detect Prev, 2005. 29(1): p. 37-41.
16. Dunne, E.F., et al., Recommendations on the Use of Quadrivalent Human Papillomavirus Vaccine in Males-Advisory Committee on Immunization Practices (ACIP), 2011 (Reprinted from MMWR, vol 60, pg 1705, 2011). Jama-Journal of the American Medical Association, 2012. 307(6): p. 557-559.
17. Forman, D., et al., Global burden of human papillomavirus and related diseases. Vaccine, 2012. 30 Suppl 5: p. F12-23.
18. Giannone, G., et al., HPV vaccination and HPV-related malignancies: impact, strategies and optimizations toward global immunization coverage. Cancer Treat Rev, 2022. 111: p. 102467.
19. Trottier, H. and E.L. Franco, The epidemiology of genital human papillomavirus infection. Vaccine, 2006. 24: p. 4-15.
20. Schmeler, K.M. and S.H. Batman, Human papillomavirus-independent cervical cancer: what are the implications? Int J Gynecol Cancer, 2022. 32(1): p. 8.

21. Zhu, Y., et al., Performance of p16/Ki67 immunostaining, HPV E6/E7 mRNA testing, and HPV DNA assay to detect high-grade cervical dysplasia in women with ASCUS. BMC Cancer, 2019. 19(1): p. 271.
22. Sung, H., et al., Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin, 2021. 71(3): p. 209-249.
23. Mann-Barnes, T., et al., Factors that Predict HPV Vaccination Behavior Among Young Men-Who-Have-Sex-with-Men in the Greater Philadelphia Region. J Racial Ethn Health Disparities, 2022.
24. Chandler, E., et al., Epidemiology of Any and Vaccine-Type Anogenital Human Papillomavirus Among 13-26-Year-Old Young Men After HPV Vaccine Introduction. J Adolesc Health, 2018. 63(1): p. 43-49.
25. Gates, A., et al., Screening for the prevention and early detection of cervical cancer: protocol for systematic reviews to inform Canadian recommendations. Syst Rev, 2021. 10(1): p. 2.
26. Pimple, S. and G. Mishra, Cancer cervix: Epidemiology and disease burden. Cytojournal, 2022. 19: p. 21.
27. Palefsky, J.M., Human papillomavirus-related disease in men: not just a women's issue. J Adolesc Health, 2010. 46(4 Suppl): p. S12-9.
28. Liao, C.I., et al., Trends in Human Papillomavirus-Associated Cancers, Demographic Characteristics, and Vaccinations in the US, 2001-2017. Jama Network Open, 2022. 5(3).
29. Miasko, A., et al., [The role of human papilloma viruses (HPV) in the pathogenesis of lung neoplasms]. Pneumonol Alergol Pol, 2000. 68(7-8): p. 379-87.
30. Luhn, P., et al., The role of co-factors in the progression from human papillomavirus infection to cervical cancer. Gynecol Oncol, 2013. 128(2): p. 265-70.
31. Daling, J.R., et al., The relationship of human papillomavirus-related cervical tumors to cigarette smoking, oral contraceptive use, and prior herpes simplex virus type 2 infection. Cancer Epidemiol Biomarkers Prev, 1996. 5(7): p. 541-8.
32. Gatechompol, S., et al., Incidence, Persistence, and Factors Associated With HPV Infection Among Male Adolescents With and Without Perinatally Acquired HIV Infection. Jaids-Journal of Acquired Immune Deficiency Syndromes, 2020. 85(5): p. 553-560.
33. Deo, S.V.S., J. Sharma, and S. Kumar, GLOBOCAN 2020 Report on Global Cancer Burden: Challenges and Opportunities for Surgical Oncologists. Annals of Surgical Oncology, 2022. 29(11): p. 6497-6500.
34. Bruni L, A.G., Serrano B, Mena M, Collado JJ, Gómez D, Muñoz J, Bosch FX, de Sanjosé S., Human Papillomavirus and Related Diseases summary Report, Canada October,2021, ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre): WHO.
35. Bruni, L., et al., Cervical cancer screening programmes and age-specific coverage estimates for 202 countries and territories worldwide: a review and synthetic analysis. Lancet Glob Health, 2022. 10(8): p. e1115-e1127.
36. Caird, H., et al., The Path to Eliminating Cervical Cancer in Canada: Past, Present and Future Directions. Curr Oncol, 2022. 29(2): p. 1117-1122.
37. Committee, C.C.S.A., Cervical cancer statistics. 2022: Canadian Cancer Society.
38. Human Papillomavirus. 2022, Canadian Cancer Society.
39. Canfell, K., et al., Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet, 2020. 395(10224): p. 591-603.
40. Das, M., WHO launches strategy to accelerate elimination of cervical cancer. Lancet Oncology, 2021. 22(1): p. 20-21.

41. Prudden, H.J., et al., Understanding the public health value and defining preferred product characteristics for therapeutic human papillomavirus (HPV) vaccines: World Health Organization consultations, October 2021-March 2022. Vaccine, 2022. 40(41): p. 5843-5855.
42. Bigoni, J., et al., Cervical cancer screening in sub-Saharan Africa: A randomized trial of VIA versus cytology for triage of HPV-positive women. International Journal of Cancer, 2015. 137(1): p. 127-134.
43. Shree, P., N. Mittal, and V. Verma, Comparison of Visual Inspection using Acetic Acid and Liquid Based Cytology for Cervical Cancer Screening in Rural Area: A Cross-Sectional Study. Journal of Clinical and Diagnostic Research, 2021. 15(3).
44. Nandini, N.M., et al., Manual Liquid Based Cytology in Primary Screening for Cervical Cancer - a Cost Effective Preposition for Scarce Resource Settings. Asian Pacific Journal of Cancer Prevention, 2012. 13(8): p. 3645-3651.
45. Serrano, B., et al., Worldwide use of HPV self-sampling for cervical cancer screening. Prev Med, 2022. 154: p. 106900.
46. Doleeb, Z., et al., The pandemic and cervical cancer screening: Is it finally time to adopt HPV self-swabbing tests in Canada? Can Fam Physician, 2022. 68(2): p. 90-92.
47. Slama, J., et al., Importance of addition of HPV DNA testing to the cytology based cervical cancer screening and triage of findings with p16/Ki67 immunocytochemistry staining in 35 and 45 years old women LIBUSE trial data analysis. Ceska Gynekol, 2020. 85(6): p. 368-374.
48. Ronco, G. and P. Giorgi Rossi, Role of HPV DNA testing in modern gynaecological practice. Best Pract Res Clin Obstet Gynaecol, 2018. 47: p. 107-118.
49. Gilham, C., et al., HPV testing compared with routine cytology in cervical screening: long-term follow-up of ARTISTIC RCT. Health Technol Assess, 2019. 23(28): p. 1-44.
50. PHAC, Human papillomavirus (HPV). 2017, Public Health Agency of Canada.
51. Dickinson, J., et al., Recommendations on screening for cervical cancer. Canadian Medical Association Journal, 2013. 185(1): p. 35-45.
52. Fedyanova, Y., Canada isn't making the most of DIY tests for HPV. CMAJ, 2018. 190(10): p. E304.
53. Star, J., et al., The First Year of the COVID-19 Pandemic: Changes in Preventive Services in Community Health Centers. Am J Prev Med, 2022.
54. Malone, C., et al., Cost-effectiveness studies of HPV self-sampling: A systematic review. Prev Med, 2020. 132: p. 105953.
55. Scan, C.H., Self-Sampling Devices for HPV Testing. Canadian Journal of Health Technologies 2021. 1(12).
56. Jalili, F., et al., Assessing the impact of mailing self-sampling kits for human papillomavirus testing to unscreened non-responder women in Manitoba. Curr Oncol, 2019. 26(3): p. 167-172.
57. Daponte, A., et al., Urine HPV in the Context of Genital and Cervical Cancer Screening-An Update of Current Literature. Cancers (Basel), 2021. 13(7).
58. Van Keer, S., et al., Clinical and analytical evaluation of the RealTime High Risk HPV assay in Colli-Pee collected first-void urine using the VALHUDES protocol. Gynecologic Oncology, 2021. 162(3): p. 575-583.
59. Smith, J.S., et al., Male Circumcision Reduces Penile HPV Incidence and Persistence: A Randomized Controlled Trial in Kenya. Cancer Epidemiology Biomarkers & Prevention, 2021. 30(6): p. 1139-1148.
60. Tobian, A.A., et al., Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. N Engl J Med, 2009. 360(13): p. 1298-309.
61. Shapiro, S.B., et al., Male Circumcision and Genital Human Papillomavirus (HPV) Infection in Males and Their Female Sexual Partners: Findings From the HPV Infection and Transmission

Among Couples Through Heterosexual Activity (HITCH) Cohort Study. J Infect Dis, 2022. 226(7): p. 1184-1194.
62. Liu, C.M., et al., Male circumcision significantly reduces prevalence and load of genital anaerobic bacteria. mBio, 2013. 4(2): p. e00076.
63. Malagon, T., et al., Sex- and Type-specific Genital Human Papillomavirus Transmission Rates Between Heterosexual Partners: A Bayesian Reanalysis of the HITCH Cohort. Epidemiology, 2021. 32(3): p. 368-377.
64. NACI, Updated Recommendations on Human Papillomavirus (HPV) Vaccines: 9-valent HPV vaccine 2-dose immunization schedule and the use of HPV vaccines in immunocompromised populations. 2017, National Advisory Committee on Immunization: PHAC.
65. Gillison, M.L., A.K. Chaturvedi, and D.R. Lowy, HPV Prophylactic Vaccines and the Potential Prevention of Noncervical Cancers in Both Men and Women. Cancer, 2008. 113(10): p. 3036-3046.
66. Sankaranarayanan, R., et al., Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study. Lancet Oncol, 2016. 17(1): p. 67-77.
67. Schiller, J.T., X. Castellsague, and S.M. Garland, A review of clinical trials of human papillomavirus prophylactic vaccines. Vaccine, 2012. 30 Suppl 5: p. F123-38.
68. Gilca, V., et al., Early use of the HPV 2-dose vaccination schedule: Leveraging evidence to support policy for accelerated impact. Vaccine, 2018. 36(32 Pt A): p. 4800-4805.
69. Rubin, R., Why the "No-Brainer" HPV Vaccine Is Being Ignored. Jama-Journal of the American Medical Association, 2015. 313(15): p. 1502-1504.
70. Gomes, J.M., et al., Human Papillomavirus (HPV) and the quadrivalent HPV Vaccine among Brazilian adolescents and parents: Factors associated with and divergences in knowledge and acceptance. PLoS One, 2020. 15(11): p. e0241674.
71. Goessl, C.L., et al., Human papillomavirus vaccine beliefs and practice characteristics in rural and urban adolescent care providers. BMC Public Health, 2022. 22(1): p. 1322.
72. Dube, E., et al., Challenges and opportunities of school-based HPV vaccination in Canada. Hum Vaccin Immunother, 2019. 15(7-8): p. 1650-1655.
73. Gilbert, N.L., et al., Estimates and determinants of HPV non-vaccination and vaccine refusal in girls 12 to 14 y of age in Canada: Results from the Childhood National Immunization Coverage Survey, 2013. Human Vaccines & Immunotherapeutics, 2016. 12(6): p. 1484-1490.
74. Damgacioglu, H., et al., Long-term impact of HPV vaccination and COVID-19 pandemic on oropharyngeal cancer incidence and burden among men in the USA: A modeling study. Lancet Reg Health Am, 2022. 8: p. 100143.
75. Osaghae, I., O.G. Chido-Amajuoyi, and S. Shete, Healthcare Provider Recommendations and Observed Changes in HPV Vaccination Acceptance during the COVID-19 Pandemic. Vaccines (Basel), 2022. 10(9).
76. Righolt, C.H., et al., Incidence of anogenital warts after the introduction of the quadrivalent HPV vaccine program in Manitoba, Canada. PLoS One, 2022. 17(4): p. e0267646.
77. PHAC, Canadian Immunization Guide -Human papillomavirus vaccine. 2021, Public Health Agency of Canada.
78. Oshman, L.D. and A.M. Davis, Human Papillomavirus Vaccination for Adults Updated Recommendations of the Advisory Committee on Immunization Practices (ACIP). Jama-Journal of the American Medical Association, 2020. 323(5): p. 468-469.
79. Grewal, R., et al., Human papillomavirus (HPV) vaccination across a cascade of knowledge, willingness, and uptake among gay, bisexual, and other men who have sex with men in

Canada's three largest cities. Human Vaccines & Immunotherapeutics, 2021. 17(12): p. 5413-5425.
80. Gilbert, N.L., et al., Estimates and determinants of HPV non-vaccination and vaccine refusal in girls 12 to 14 y of age in Canada: Results from the Childhood National Immunization Coverage Survey, 2013 (vol 12, pg 1484, 2016). Human Vaccines & Immunotherapeutics, 2017. 13(6): p. 1485-1485.
81. PHAC, Vaccination Coverage Goals and Vaccine Preventable Disease Reduction Targets by 2025. 2022.
82. Kessels, S.J., et al., Factors associated with HPV vaccine uptake in teenage girls: a systematic review. Vaccine, 2012. 30(24): p. 3546-56.
83. PHAC, Vaccine Coverage in Canadian Children: Highlights From the 2013 Childhood National Immunization Coverage. January 2020: Public Health Agency of Canada.
84. Steben, M., et al., A Review of the Impact and Effectiveness of the Quadrivalent Human Papillomavirus Vaccine: 10 Years of Clinical Experience in Canada. Journal of Obstetrics and Gynaecology Canada, 2018. 40(12): p. 1635-1645.
85. Chabeda, A., et al., Therapeutic vaccines for high-risk HPV-associated diseases. Papillomavirus Res, 2018. 5: p. 46-58.
86. Ramos da Silva, J., et al., A therapeutic DNA vaccine and gemcitabine act synergistically to eradicate HPV-associated tumors in a preclinical model. Oncoimmunology, 2021. 10(1): p. 1949896.
87. Burki, T.K., Therapeutic HPV vaccine for cervical intraepithelial neoplasia. Lancet Oncol, 2019. 20(5): p. e250.
88. Deligeoroglou, E., et al., HPV infection: immunological aspects and their utility in future therapy. Infect Dis Obstet Gynecol, 2013. 2013: p. 540850.
89. Becker, N.V., et al., Utilization of Women's Preventive Health Services During the COVID-19 Pandemic. Jama Health Forum, 2021. 2(7).
90. Liu, H., et al., Impact of COVID-19 Outbreak on the Gynecological Outpatients HPV Infection Rate in Wuhan, China: A Retrospective Observational Study. Front Med (Lausanne), 2022. 9: p. 799736.
91. Murthy, B.P., et al., Impact of the COVID-19 Pandemic on Administration of Selected Routine Childhood and Adolescent Vaccinations-10 US Jurisdictions, March-September 2020. Mmwr-Morbidity and Mortality Weekly Report, 2021. 70(23): p. 840-845.
92. Turner, K., et al., Impact of the COVID-19 pandemic on human papillomavirus (HPV) vaccination among a national sample of United States adults ages 18-45: A cross-sectional study. Prev Med Rep, 2023. 31: p. 102067.
93. Ryan, G., et al., Challenges to Adolescent HPV Vaccination and Implementation of Evidence-Based Interventions to Promote Vaccine Uptake During the COVID-19 Pandemic: "HPV Is Probably Not at the Top of Our List". Prev Chronic Dis, 2022. 19: p. E15.
94. Saxena, K., et al., Impact of the COVID-19 pandemic on adolescent vaccinations: projected time to reverse deficits in routine adolescent vaccination in the United States. Current Medical Research and Opinion, 2021. 37(12): p. 2077-2087.
95. Rodriguez, N.M., et al., Leveraging COVID-era innovation for cervical cancer screening: Clinician awareness and attitudes toward self-sampling and rapid testing for HPV detection. PLoS One, 2023. 18(3): p. e0282853.
96. Chao, C.R., et al., Trends in HPV vaccine administration and HPV vaccine coverage in children by race/ethnicity and socioeconomic status during the COVID-19 pandemic in an integrated health care system in California. Vaccine, 2022. 40(46): p. 6575-6580.

97. Chao, C.R., et al., Trends in HPV vaccine administration and HPV vaccine coverage in children by race/ethnicity and socioeconomic status during the COVID-19 pandemic in an integrated health care system in California. Vaccine, 2022. 40(46): p. 6575-6580.
98. Daniels, V., et al., Impact of reduced human papillomavirus vaccination coverage rates due to COVID-19 in the United States: A model based analysis. Vaccine, 2021. 39(20): p. 2731-2735.
99. White, L.S., et al., HPV Vaccination Rates of 7(th) Grade Students After a Strong Recommending Statement from the School Nurse. J Sch Nurs, 2022: p. 10598405221118824.
100. Beavis, A.L., et al., Exploring HPV vaccine hesitant parents' perspectives on decision-making and motivators for vaccination. Vaccine X, 2022. 12: p. 100231.
101. Foley, S., J. Nkonga, and M. Fisher-Borne, Engaging health plans to prioritize HPV vaccination and initiate at age 9. Human Vaccines & Immunotherapeutics, 2023.
102. Reiter, P.L., et al., Advancing Human Papillomavirus Vaccine Delivery: 12 Priority Research Gaps. Acad Pediatr, 2018. 18(2S): p. S14-S16.
103. Scott, K. and M.L. Batty, HPV Vaccine Uptake Among Canadian Youth and The Role of the Nurse Practitioner. J Community Health, 2016. 41(1): p. 197-205.
104. Rhodes, D., et al., Public Health and School Nurses' Perceptions of Barriers to HPV Vaccination in Missouri. Journal of Community Health Nursing, 2017. 34(4): p. 180-189.
105. Kreimer, A.R., et al., Evaluation of Durability of a Single Dose of the Bivalent HPV Vaccine: The CVT Trial. Jnci-Journal of the National Cancer Institute, 2020. 112(10).
106. Kreimer, A.R., et al., Public health opportunities resulting from sufficient HPV vaccine supply and a single-dose vaccination schedule. J Natl Cancer Inst, 2022.
107. Barnabas, R.V., et al., Single-dose HPV vaccination efficacy among adolescent girls and young women in Kenya (the KEN SHE Study): study protocol for a randomized controlled trial. Trials, 2021. 22(1).