This publication aims to provide conceptual and methodological guidance on measuring the impact of the HPV vaccine in Latin American and Caribbean countries and territories. It provides a broad overview of the designs used and available for assessing the impact of HPV vaccination, and prioritizes outcomes by relevance to vaccination programs and proposing study designs for each outcome under consideration. The feasibility of each approach will depend on the objectives of the HPV vaccination program and the assessment in the country or territory, as well as the resources, data, and time available.

Evaluating the impact of the human papillomavirus vaccine in Latin America and the Caribbean
Evaluating the impact of the human papillomavirus vaccine in Latin America and the Caribbean
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The development of this publication was coordinated by Lucia Helena de Oliveira of the Comprehensive Immunization Special Program and Silvana Luciani of the Noncommunicable Diseases, Violence and Injury Prevention Unit, Pan American Health Organization (PAHO).

The key contributors for this publication have been Maria Brotons, Laia Bruni, and Claudia Robles (Institut Català d’Oncologia, IDIBELL, CIBERESP, L’Hospitalet de Llobregat, Spain). Other contributors: Maria Tereza da Costa Oliveira, Nathalie El Omeiri (PAHO, Washington D.C., USA), Cara Bess Janusz (independent consultant to PAHO, Michigan, USA), Julia Brotherton (VCS Population Health, Melbourne School of Population and Global Health, Victoria, Australia), Lauri Markowitz and Elissa Meites (U.S. Centers for Disease Control and Prevention, Atlanta, USA), Iacopo Baussano and Maribel Almonte (International Agency for Research on Cancer, Lyon, France), Raul Murillo (Centro Javeriano de Oncología, Bogotá, Colombia), and Paul Bloem (World Health Organization, Geneva, Switzerland).

Special thanks to the group of experts from Latin American countries that participated in the meeting organized by PAHO to discuss the draft of the document in April 2019 for their contributions and improvements: Eliana Wendland (Brazil), Ana Goretti Kalume (Brazil), Jeannette Dabanch (Chile), and Cecilia Gonzalez (Chile).

Disclaimer

This guidance document was written in 2019. Subsequently, in 2021, the document was reviewed by an international group of experts (listed as contributors) and some updates were made. In December 2022, prior to publication, the information on HPV vaccines (Section 2.2) was updated.
## Abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AIS</td>
<td>adenocarcinoma in situ</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CIN</td>
<td>cervical intraepithelial neoplasia</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>HPV</td>
<td>human papillomavirus</td>
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<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
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<tr>
<td>PAHO</td>
<td>Pan American Health Organization</td>
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<tr>
<td>PBCR</td>
<td>population-based cancer registry</td>
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<tr>
<td>STI</td>
<td>sexually transmitted infection</td>
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<tr>
<td>TAG</td>
<td>Technical Advisory Group (on vaccine-preventable diseases)</td>
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<tr>
<td>VIA</td>
<td>visual inspection with acetic acid</td>
</tr>
<tr>
<td>VILI</td>
<td>visual inspection with Lugol's iodine</td>
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<td>WHO</td>
<td>World Health Organization</td>
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¡YO ME VACUNE! contra el VPH
1. Introduction

Cancer is the second leading cause of death among adults in the Region of the Americas. In women, cervical cancer is the leading cause of cancer death in six countries and the second leading cause of death in 14 others. Each year, 72,719 new cervical cancer cases are diagnosed, and 36,797 women in the Region will die due to this disease; a significant proportion (52%) of deaths occur during a woman’s economic productive years before the age of 60.

Since the adoption of the Regional Strategy and Plan of Action for Cervical Cancer Prevention and Control in 2008 (1), countries in the Region have strengthened their cervical cancer programs by introducing human papillomavirus (HPV) vaccination, adopting new approaches to screening, and improving the quality of cancer treatment, palliative care, and cancer registration. Recognizing the importance of cervical cancer and other HPV-related diseases as a public health problem, both the World Health Organization (WHO) and the Pan American Health Organization (PAHO) through the WHO Strategic Advisory Group of Experts on Immunization (SAGE), and the PAHO Technical Advisory Group (TAG) on vaccine-preventable diseases, recommend that HPV vaccination be included in routine national immunization programs.

As of December 2022, 47 countries and territories in the Americas (92%) have incorporated HPV vaccines into their national immunization programs, an adoption rate higher than any other region of the world. All these 47 countries and territories in Latin America and the Caribbean routinely include HPV vaccine in their immunization programs, prioritizing vaccination of adolescent girl cohorts aged 9–14, following PAHO’s TAG recommendations.

In 2018, PAHO Member States approved a plan to accelerate progress toward eliminating cervical cancer as a public health problem in the Region of the Americas by reducing incidence and mortality rates by one-third, by 2030. To attain progress toward this goal, countries must achieve high vaccination and screening coverage to maximize the benefits of these prevention measures. It is also important to monitor and evaluate the performance of HPV vaccination programs and their impact on HPV-related morbidity and mortality. The introduction of HPV vaccines in the Americas has been successful, but HPV vaccination has posed social and cultural challenges, compared to other new vaccines, related to the target populations, outreach strategies, and other specific aspects of the infection and disease.

There is global evidence demonstrating the efficacy, effectiveness, and impact of various HPV vaccines. Countries of the Region have used available evidence to inform their decisions to introduce HPV vaccination into their national programs. In the post-introduction phase, substantiating the value of HPV vaccination with local evidence could help sustain countries’ investments, especially in Latin American and Caribbean countries, where vaccination is provided without cost to the public. In addition, this evidence can serve to promote the benefits of HPV vaccination, enhance recommendations by health professionals and acceptability to adolescent target groups and their parents, and increase vaccination coverage.

Compared to other vaccines, assessing the impact of HPV vaccination presents unique challenges due to the long period from infection to cancer development, the multiple biological outcomes by which impact can be measured such as HPV infection, precancerous lesions, and cancer, and the difficulty in identifying comprehensive, accurate, and quality information sources for these outcomes. Also, the coexistence of other cervical cancer prevention measures in countries, such as screening for cervical cancer and management of cervical precancerous lesions, adds complexity to the assessment of HPV vaccine impact, as they also can contribute to decreases in incidence and mortality from this cancer.
In response to the request from countries in Latin America and the Caribbean during the regional meeting on lessons learned in the introduction of the HPV vaccine, which took place in Guatemala in 2017, PAHO has collaborated with multidisciplinary experts to develop this guidance document on HPV impact assessment. The objective of this document is to provide conceptual and methodological guidance on measuring the impact of the HPV vaccine in Latin American and Caribbean countries. The document aims to offer a broad overview of the designs used for assessing the impact of HPV vaccination, prioritizing outcomes by relevance to vaccination programs and proposing study designs for each outcome under consideration. The feasibility of each approach will depend on the objectives of the HPV vaccination program and the assessment in the country, as well as the resources, data, and time available.

The primary audience for this document includes managers and professionals of national immunization programs, epidemiologists from ministries of health or institutions involved in vaccination impact studies, professionals from HPV reference laboratories, and epidemiologists working on cervical cancer prevention. In addition, this document could be useful for epidemiologists working on other HPV-related diseases, researchers in academic universities or other institutions, pathologists who interpret cervical screening Pap tests (cytology), nongovernmental organizations, public health leaders and officials, and medical professionals.

This document aims to be a useful resource both for the conceptualization of new studies and for the interpretation or use of findings from previously conducted impact studies for decisionmaking. It is important to emphasize that measuring the impact of HPV vaccination strategies is fundamental to documenting progress toward the goal of eliminating cervical cancer. However, impact measurement is a long-term investment and in the short term all countries should systematically be evaluating HPV vaccination coverage to inform programmatic decisions to improve reach and effectiveness of existing strategies.
2. Background

2.1 Human papillomavirus (HPV)

HPV infection of the anogenital tract is the most common sexually transmitted infection (STI) worldwide and while usually asymptomatic and transient can also cause a wide range of lesions, from anogenital warts to cancer. Persistent infection with an oncogenic HPV is the sole causative agent of cervical cancer, and an attributable cause for a proportion of some other anogenital, head and neck area cancers (2, 3).

HPV genotypes that infect the female genital tract are classified according to the risk of developing cervical cancer into oncogenic or non-oncogenic. The oncogenic or probable oncogenic HPV genotypes, also called high-risk, are HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 (4). The two genotypes HPV16 and HPV18 are responsible for 70% of cervical cancer cases globally, and if HPV31, 33, 45, 52, and 58 genotypes are also considered, these seven genotypes are responsible for 90% of cervical cancer cases (5, 6). Additionally, prevalent, low-risk genotypes include HPV6 and HPV11, which cause 90% of anogenital warts (7).

Sexual contact is the primary means of transmission of an HPV infection. It is a very common infection, and first infection usually occurs soon after sexual debut. It is estimated that over 80% of women and men who have had at least one sex partner will be infected with HPV in their lifetime (8). Higher rates of infection are associated with young age at sexual debut, high number of sexual partners, and high-risk sexual behaviors. However, the vast majority of HPV infections are transient, and 90% become undetectable after two years (9).

Only a small portion of high-risk and persistent HPV infections will develop into precancerous lesions or cancer. High-risk HPV infections that persist are associated with the development of precancerous lesions: high-grade cervical intraepithelial neoplasia (CIN, grade 2 or 3) and adenocarcinoma in situ (AIS). If not identified and treated properly, these precancerous lesions may progress to cancer, usually over decades (10). Factors that may contribute to the progression of infections to lesions are tobacco use, oral contraceptive use, number of pregnancies, human immunodeficiency virus (HIV) (associated with the HIV-induced immunosuppression), or coinfection with other STIs, but the most important determinant in progression is the type of HPV (HPV16 or HPV18 are the most carcinogenic types) (9).

The natural history of cervical cancer involves gradual progression through four main stages over an average of 10–20 years: infection of the cervical epithelium by an oncogenic HPV type, persistence of infection, progression to precancerous cervical lesion, and invasive cancer.

In 2020, it is estimated that 57,748 new cases of cervical cancer were diagnosed in Latin America and the Caribbean, and that 30,454 women died due to this cancer. Age-standardized incidence rates ranged from 6.9 new cases of cervical cancer per 100,000 population in Martinique to 36.6 per 100,000 in the Plurinational State of Bolivia, while mortality rates ranged from 2.8 deaths per 100,000 population in Puerto Rico to 19.0 deaths per 100,000 in Paraguay (12).

In addition to cervical cancer, oncogenic HPV infection is an attributable cause in a fraction of other cancers. In women, HPV is implicated in 24.9% of vulvar cancers, 78.0% of vaginal cancers, and in men in 51.0% of penile cancers. In all sexes, HPV caused 88.0% of anal tumors and 30.8% of oropharynx tumors. In 2018, in Latin America and the Caribbean, there were an estimated 67,000 new cancer cases attributable to HPV (13). Men and women living with HIV and other forms or immunosuppression, and men who have sex with men are populations with a particularly high risk of HPV-related diseases (11).
Cervical cancer is largely preventable through a combination of two preventive strategies that are described in Sections 2.2 and 2.4: HPV vaccination (primary prevention) and cervical cancer screening (secondary prevention).

### 2.2 HPV vaccines

There are currently six prophylactic HPV vaccines on the market: three bivalent vaccines (Cervarix, Cecolin, and Walrinvax), which provide protection against genotypes 16 and 18, two quadrivalent vaccines (Gardasil and Cervavax), which in addition to protecting against genotypes 16 and 18 also protect against two non-oncogenic genotypes (genotypes 6 and 11), and a nonavalent vaccine (Gardasil9), which protects against all four genotypes above and additionally protects against genotypes 31, 33, 45, 52, and 58. Four of these vaccines have been prequalified by WHO: Cervarix, Cecolin, Gardasil, and Gardasil9. The six vaccines are administered according to a schedule of two or three doses depending on the target age for administration: two doses (0, 6 months) are recommended for children aged 9 through 14 years; whereas three doses (0, 1–2, 6 months) are recommended for young adults aged 15 years and older, and for all those immunocompromised or HIV-positive. Since December 2022, WHO recommends, as an off-label option, a 2-dose schedule for all age groups for which HPV vaccines are licensed and an alternative single-dose schedule in girls and boys aged 9 through 20 years (14).

All six vaccines are indicated for the prevention of cervical precancerous lesions and cancers. As per their product labels, Cervarix (bivalent vaccine), Gardasil (quadrivalent vaccine) and Gardasil9 (nonavalent vaccine) are indicated also the prevention of precancerous lesions of the vulva, vagina, and anus, and for the prevention of anal cancers. In June 2020 the United States Food and Drug Administration (FDA) approved an expanded indication for Gardasil9 for the prevention of oropharyngeal and some other head and neck cancers. Gardasil and Gardasil9 are also indicated for the prevention of anogenital warts. The efficacy of vaccines in preventing precancerous cervical lesions (CIN2/3 and AIS) associated with the genotypes targeted by the vaccine is close to 100% in women who are known to be naïve to these genotypes. Below is a summary of the efficacy of the HPV vaccines prequalified by WHO.

The quadrivalent vaccine Gardasil clinical trials demonstrated a vaccine efficacy of 98.2% (95% CI [93.3, 99.8]) against CIN2+ related to the genotypes targeted by the vaccine (for HPV6, 11, 16, and 18) in women naïve to these genotypes prior to vaccination, and an efficacy of 51.5% (95% CI [40.6, 60.6]) in women who had prevalent infection at the time of vaccination (intention-to-treat analysis) (15). Efficacy against high-grade (grade 2+) vulvar and vaginal intraepithelial neoplasia related to the genotypes targeted by the vaccine was 100% (95% CI [82.6, 100]) in susceptible women and 79.0% (95% CI [56.4, 91.0]) in the intention-to-treat analysis (15). Clinical trials of this vaccine also demonstrated nearly 100% efficacy against anogenital warts related to HPV genotypes 6 and 11 in susceptible women, and 83% efficacy against all anogenital warts (regardless of genotype) (16). In men, efficacy of this vaccine against external genital lesions related to HPV6, 11, 16, and 18 in the per-protocol analysis was 90.4% (95% CI [69.2, 98.1]) and efficacy in the intention-to-treat population was 65.5% (95% CI [45.8, 78.6]) (17); regarding anal intraepithelial neoplasia associated with vaccine-targeted genotypes, the vaccine efficacy in the per-protocol analysis was 77.5% (95% CI [39.6, 93.3]) and in the intention-to-treat population was 50.3% (95% CI [25.7, 67.2]) (18).

Clinical trials of the bivalent vaccine Cervarix also demonstrated high efficacy against cervical lesions related to HPV genotypes 16 and 18 in women who were naive to these genotypes (19, 20). In one clinical trial, the efficacy of this vaccine against CIN2+ independent of HPV genotype in susceptible women was 64.9% (95% CI [52.7, 74.2]), while the efficacy against CIN3+ independent of HPV in susceptible women was 93.2% (95% CI [78.9, 98.7]) (20). For the other and new bivalent vaccine Cecolin, in the per-protocol cohort the efficacy against high-grade genital lesions and persistent infection were
100.0% (95% CI [55.6, 100.0]) and 97.8% (95% CI [87.1, 99.9]), respectively. Robust antibody responses for both types were induced and persisted for at least 42 months (21).

Finally, the nonavalent vaccine demonstrated 97.4% efficacy (95% CI [85.0, 99.9]) against high-grade cervical, vulvar, and vaginal lesions related to HPV genotypes 31, 33, 45, 52, and 58 in susceptible women, and further demonstrated an immune response against HPV6, 11, 16, and 18 non-inferior to that of the quadrivalent vaccine (22).

HPV vaccines have an excellent safety profile. Safety data are available for more than 16 years of follow-up since the first vaccine was marketed, during which more than 500 million doses have been distributed worldwide (14). The WHO Global Advisory Committee on Vaccine Safety (GACVS) has regularly reviewed the available evidence on safety since the marketing of HPV vaccines, totaling eight complete reviews. In the most recent review, conducted in December 2019, the committee stated that the safety profile of HPV vaccines continues to be extremely favorable and no adverse events of concern have been observed since licensure of HPV vaccines (23).

Hereafter, when we use the term quadrivalent vaccine we will refer to Gardasil and when we use the term bivalent vaccine, we will refer to Cervarix.

2.3 HPV vaccination programs

2.3.1 Introduction of HPV vaccines in the Americas

As of December 2022, 47 countries and territories in the Americas had introduced the HPV vaccine into their national immunization programs. Most countries and territories use quadrivalent HPV vaccine and seven use the nonavalent vaccine.
2.3.2 Evaluation of vaccination programs

Monitoring the performance of immunization programs is critical to assess their progress toward established goals. This is even more relevant when there is a goal of eliminating a public health problem as is the case for cervical cancer (24). Monitoring HPV vaccination poses greater challenges compared to traditional vaccination schedules because various countries in the Region have used different vaccine administration and delivery alternatives.

The vaccine has been included in national vaccination schedules in different countries and territories in the following ways:

- Immunization in schools and/or health services
- Two- or three-dose schedules (since December 2022 with the alternative of one dose)
- First and subsequent doses in different calendar years
- Different target populations: one or more cohorts of girls selected by age at vaccination, or by school grade, or vaccination of girls only or both boys and girls, or certain special populations such as immunocompromised people.

Data on the target populations to be vaccinated are not always available and/or updated.

Estimating and monitoring vaccination coverage is useful for demonstrating the program’s achievements, identifying problems, analyzing the causes of these problems, and ultimately defining and applying efficient measures to achieve high vaccination coverage. Typically, Latin American and Caribbean countries have estimated vaccination coverage using administrative data, actually a few countries are using nominal registers. In addition, countries may use field investigations such as rapid coverage monitoring or larger surveys, but these methods are used less frequently than routine assessment of administrative reporting.

The PAHO TAG on Vaccine-preventable Diseases, at its 24th meeting in July 2017 in Panama, recommended that countries and territories in the Region improve their documentation of HPV vaccination coverage at the subnational and national levels and generate the information needed to define targeted strategies and achieve optimal coverage of the full vaccination series in target groups. A workshop organized by PAHO, in October 2017, on lessons learned from the introduction of the HPV vaccine in the Region concluded that countries had difficulty reaching their defined target populations (25). However, school-based vaccination was deemed the most feasible strategy for reaching these populations. The need to standardize coverage estimates was also emphasized, which led PAHO to develop guidance material on calculating vaccination coverage (26).

In its 10th meeting on 31 May 2023, the PAHO TAG on Vaccine-preventable Diseases issued the recommendation that countries should ensure that all girls between the ages of 9 and 14 years receive at least one dose of the HPV vaccine and immunocompromised individuals or HIV-positive persons (regardless of age or antiretroviral therapy status) should receive at least two doses of HPV vaccine (at a 6-month interval) and, where possible, three doses.

2.3.3 Summary of the evidence on population impact of HPV vaccination programs

There is substantial evidence documented in research literature regarding the effectiveness of HPV vaccines and their population-level impact on reducing HPV infection, precancerous cervical lesions, and genital warts, with more than 100 articles published until 2019 citing results from studies in 18 countries (27) (See Figure 2).

A meta-analysis of 65 studies on the population impact of HPV vaccination programs from 14 countries that compared the frequency of HPV-associated outcomes in the general population between the pre-vaccine and post-vaccine periods was published in 2019 (28). All these studies were conducted in the context of programs that administered a three-dose vaccine schedule. After 5–8 years following the start of the vaccination program, the prevalence of HPV16 and 18 decreased in girls and women aged 13–29 years,
with the largest decrease (83%) observed in women aged 13–19 years. In addition, these studies showed evidence of cross-protection against HPV31, 33, and 45, with a 54% decline in the prevalence of infection by these genotypes in women aged 13–19. After 5–8 years of vaccination, diagnosed cases of anogenital warts decreased in women aged 15–29 years, and in unvaccinated men aged 15–24 years, demonstrating herd effects of vaccination. The largest decline in diagnoses of anogenital warts, 67%, was observed in women aged 15–19. Finally, after 5–9 years of vaccination, precancerous cervical lesions (CIN2+) declined by 51% in women aged 15–19, and 31% in women aged 20–24. These ecological analyses of cervical precancerous lesions included only women participating in screening programs, to limit the effect of potential changes in screening recommendations and participation rates between the pre- and post-vaccine introduction eras. In a subgroup analysis, studies from countries that vaccinated several cohorts of girls against HPV and achieved coverage above 50% showed a greater and faster decline in anogenital wart diagnoses in women and men aged 14–29, and a greater decline in CIN2+ in women aged 15–24, compared to countries with less than 50% coverage or that vaccinated a single cohort (28).

A milestone study undertaken in Sweden documented in 2020 for the first time that HPV vaccination substantially reduces the risk of cervical cancer (29). This nationwide study included nearly 1.7 million women aged 10–30 years that were followed-up through Swedish registries from 2006 to 2017 and assessed the association between HPV vaccination and the risk of cervical cancer, controlling for age at follow-up, calendar year, county of residence, and parental characteristics. During the study period, 19 of the vaccinated women were diagnosed with cervical cancer, compared with 538 of the unvaccinated women. After adjusting for all covariates, the risk of cervical cancer among women who had initiated vaccination before the age of 17 years was 88% lower than among those unvaccinated (incidence rate ratio 0.12; 95% CI [0.00, 0.34]), and the risk among women vaccinated at age 17–30 years was 53% lower with incidence rate ratio 0.47 (95% CI [0.27, 0.75]) (29).

Tables 1 and 2 summarize the findings of studies on the impact of HPV vaccination programs in Australia and the United States of America, respectively.

**FIGURE 2.** Countries (in red) that published impact or effectiveness results associated with HPV vaccination programs, February 2019

Australia implemented an HPV vaccination program in 2007, offering free quadrivalent HPV vaccine to girls and women aged 12–26 years, and achieving high HPV vaccination coverage. In 2013 the program was expanded to boys aged 12–13 years (with catch-up to 14–15 years old). Since January 2018, the nonavalent vaccine is being used.

Below is a summary of the principal findings from studies published on the impact and effectiveness of Australia’s vaccination program published until 2018.

### Impact on HPV infection prevalence

Decrease in the prevalence of the genotypes targeted by the quadrivalent vaccine (HPV6/11/16/18) in young women since the introduction of the program:

- In vaccinated women aged 18–24 years who participated in cervical screening in the post-vaccine period 2010–2012, the prevalence of HPV6/11/16/18 was lower (at 2.3%) compared to women aged 18–24 years who were screened before the start of the HPV vaccination program in 2005–2007 (when prevalence was 28.7%).
- In women aged 25–35 who attended sentinel family planning clinics in Victoria and New South Wales, the prevalence of HPV6/11/16/18 also declined from 22.7% in the pre-vaccine era to only 1.5% eight years after the introduction of the vaccine.

Decrease in the prevalence of genotypes targeted by the quadrivalent vaccine in young unvaccinated men (herd protection):

- The prevalence in men aged 12–25 with chlamydia infection in 2015 declined relative to the prevalence in men aged 12–25 with chlamydia infection in 2004. Prevalence among unvaccinated men post-vaccine introduction was 7% vs. 18% prevalence among unvaccinated men pre-vaccination.

### Precancerous cervical lesions

Decreased incidence rates of high-grade cervical lesions in the post-vaccine period in the cohorts eligible for the vaccination program. The largest reduction (more than 50%) was observed between 2007 and 2014 for women younger than 20 years. Women aged 20–24 also showed a decrease of around 30% between 2011 and 2014. The vaccine was shown to be 14% effective in preventing high-grade cytological lesions and 47% effective in preventing high-grade lesions confirmed by histology in women up to the age of 26.

### Anogenital warts

Dramatic decrease in the incidence of anogenital warts in women eligible for the program. The largest reduction was seen in women younger than 21 years, where the proportion of diagnosed anogenital warts fell from 18.4% in 2004 to 1.1% in 2014.

- Evidence of the impact of vaccination on Indigenous women.
- Substantial herd effect in unvaccinated heterosexual men.

### Juvenile-onset recurrent respiratory papillomatosis

Decrease in incidence of juvenile-onset recurrent respiratory papillomatosis from 0.16 per 100 000 in 2012 to 0.02 per 100 000 in 2016.

---

**TABLE 1.** The experience of Australia: 10-year impact of the quadrivalent HPV vaccination program (30)
HPV vaccine has been recommended in the United States since 2006 for females aged 11–12 years, with catch-up vaccination through age 26 years. In late 2011, the recommendation was expanded to boys aged 11–12 years (with catch-up vaccination for most males through age 21 years, and immunocompromised persons or men who have sex with men through age 26 years). The vaccine mostly administered was the quadrivalent vaccine through 2015. In 2015 there was a gradual transition to the nonavalent vaccine, which is the only vaccine available in the United States since the end of 2016. The HPV vaccination coverage achieved in females aged 13–17 years has increased over time, with an estimated full-dose coverage of 57% in 2019. In 2019, catch-up recommendations expanded to all persons through age 26 years, with shared clinical decisionmaking recommended for some adults age 27 through 45 years (31).

Impact on HPV infection prevalence

- Decrease in the prevalence of the vaccine-targeted genotypes (HPV6/11/16/18) in young women screened for cervical cancer since the introduction of the vaccine (32):
  - After 9–10 years of vaccine introduction, the prevalence of vaccine-targeted genotypes decreased by 78% in the 20–24 years and 38% in the 25–29 years age groups.
  - Prevalence of vaccine-targeted genotypes decreased in both vaccinated and in unvaccinated women, demonstrating herd protection.

Precancerous cervical lesions

Incidence rates of high-grade cervical lesions (CIN2+) decreased in the post-vaccine period (2008–2015) among women aged 18–24 years in five states. The largest reduction (56%) was observed among screened women aged 18–20 years in the period 2014–2015 compared to 2008–2009. Among screened women aged 21–24 years, incidence rates were lower for the latter two time periods (2012–2013 and 2014–2015) (33).

Anogenital warts

Prevalence of anogenital warts decreased from 2008 to 2014 among women aged 15–19 years (annual decrease 14.1%), and decreased from 2009 to 2014 among women aged 20–24 (annual decrease 12.9%) and among women aged 25–29 (annual decrease 6.0%) (34). Prevalence of anogenital warts decreased during 2009 to 2014 among men aged 20–24 years (annual decrease 6.5%), with the decrease likely attributable to herd effects (34).

Juvenile-onset recurrent respiratory papillomatosis

Decrease in incidence of juvenile-onset recurrent respiratory papillomatosis from 2.0–2.9 cases per 100 000 births in 2004–2005 to 0.5–0.7 cases per 100 000 births in 2012–2013 (35).

### TABLE 2. Impact of the HPV vaccination program in the United States of America

<table>
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<tr>
<th>Impact on HPV infection prevalence</th>
<th>Description</th>
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<tr>
<td>Decrease in the prevalence of the vaccine-targeted genotypes (HPV6/11/16/18) in young women screened for cervical cancer since the introduction of the vaccine (32):</td>
<td></td>
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<tbody>
<tr>
<td>Prevalence of anogenital warts decreased from 2008 to 2014 among women aged 15–19 years (annual decrease 14.1%), and decreased from 2009 to 2014 among women aged 20–24 (annual decrease 12.9%) and among women aged 25–29 (annual decrease 6.0%) (34). Prevalence of anogenital warts decreased during 2009 to 2014 among men aged 20–24 years (annual decrease 6.5%), with the decrease likely attributable to herd effects (34).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Juvenile-onset recurrent respiratory papillomatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in incidence of juvenile-onset recurrent respiratory papillomatosis from 2.0–2.9 cases per 100 000 births in 2004–2005 to 0.5–0.7 cases per 100 000 births in 2012–2013 (35).</td>
</tr>
</tbody>
</table>

BACKGROUND 9
2.3.4 Assessing the impact and the effectiveness of HPV vaccination in Latin America and the Caribbean: the experience of Argentina and Brazil

Tables 3 and 4 summarize experiences with HPV vaccination in Argentina and Brazil.

**TABLE 3.** Strong reduction in prevalence of HPV16/18 and closely related HPV types in sexually active adolescent women following the introduction of HPV vaccination in Argentina (36)

In 2011 Argentina launched a comprehensive government-funded national HPV prevention program as part of its cervical cancer control efforts, offering the bivalent HPV vaccine to 11-year-old girls with a three-dose schedule delivered at intervals of 0-1-6 months. The initial program achieved high coverage with the first dose. In 2014, the program opted to replace the use of bivalent vaccine for the quadrivalent vaccine and extend HPV vaccination recommendations to males and females aged 11–26 years and living with HIV or who had undergone organ transplant. After January 2015, the program recommended the number of doses in the schedule be reduced from 3 to 2, based on the available evidence, for girls aged 11 years, and later in 2017 the same recommendation was extended to boys aged 11 years.

Following is a summary of the principal findings from a pre-vaccine/post-vaccine HPV prevalence study assessing the impact of Argentina’s vaccination program (36).

<table>
<thead>
<tr>
<th>Impact on HPV infection prevalence</th>
<th>Decrease in the prevalence of the genotypes targeted by the quadrivalent vaccine (HPV6/11/16/18) in young women since the introduction of the program:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• In vaccinated women aged 15–17 who participated in screening in the post-vaccine era (February 2017–November 2018), the prevalence of HPV16, 18, 6, 31, 33, and 45 (all high-risk types targeted by the vaccines used or associated with the vaccine-types) decreased significantly compared to the prevalence in women aged 15–17 years who participated in cervical screening prior to the introduction of the HPV vaccine (April 2014–October 2015). Specifically, the prevalence of HPV16 declined from 11.1% to 0.8% and the prevalence of HPV18 declined from 6.0% to 0.4%, in this age group.</td>
<td></td>
</tr>
<tr>
<td>• The overall HPV prevalence declined significantly between unvaccinated women recruited in 2014–2015 and vaccinated women recruited in 2017–2018, from 56.3% to 49.8%.</td>
<td></td>
</tr>
</tbody>
</table>
Cervical cancer screening aims to detect precancerous lesions, which, if not treated, may progress to cervical cancer. Several tests can be used in cervical cancer screening, including cervical cytology (Pap smear), visual inspection with acetic acid (VIA), visual inspection with Lugol's iodine (VILI), HPV testing, and combination approaches.

Cervical cytology is a highly specific screening tool that facilitates early diagnosis of precancerous cervical lesions, which has reduced the disease incidence and mortality due to cervical cancer by up to 80% in Western Europe, North America, Japan, Australia, and New Zealand over the past 50 years (38). However, cytology is a subjective test that involves demanding technical training, quality control, and due to its low sensitivity (51%–53%), despite being highly specific (96%–98%), it must be repeated frequently. Shortcomings in the quality of cytology programs and in the subsequent follow-up and treatment of abnormal results, poor program management, and low coverage have led to reduced success of screening programs in many resource-constrained countries (39).

There are alternative methods of detecting lesions such as VIA or VILI, which provide immediate results, and alternative programmatic approaches such as “screening and treatment in one or two visits,” in which treatment with cryotherapy or cold coagulation is provided to women who are screened positive but have no histopathological confirmation (40). These tests can have equal or greater sensitivity than cytology (41, 42) but are also highly subjective and reliant on training and, although their specificity is lower, because they allow immediate treatment they can potentially be effective methods for reducing cervical cancer (43).

Brazil implemented a public HPV vaccination program in 2014, offering the quadrivalent vaccine to girls aged 11–13 years for primary prevention of cervical cancer. This indication was expanded in 2015 to girls aged 9–13 years, and in 2017 to girls aged 9–14 years, boys aged 11–14 years, HIV-positive population aged 9–26 years, oncologic patients, and people who had undergone solid organs or bone marrow transplantation.

Following is a summary of the findings of a cross-sectional, nationwide survey conducted during 2016–2017 in Brazil, where the effectiveness of the quadrivalent HPV vaccine on HPV infection in young women (16–25 years) was evaluated (37).

<table>
<thead>
<tr>
<th>Effectiveness on HPV infection</th>
<th>Within 4–5 years of the introduction of the HPV vaccination program in Brazil, the prevalence of the genotypes targeted by the quadrivalent vaccine (HPV6/11/16/18) was reduced in vaccinated women:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• The use of the vaccine decreased the vaccine-types by 56.8%, from 15.6% in unvaccinated women to 6.8% in vaccinated women.</td>
</tr>
<tr>
<td></td>
<td>• Vaccinated women had lower HPV16 prevalence (2.3% vs. 8.9% in unvaccinated) and lower HPV6 prevalence (2.1% vs. 5.8% in unvaccinated).</td>
</tr>
</tbody>
</table>

| TABLE 4. Effectiveness of a universal vaccination program with an HPV quadrivalent vaccine in young Brazilian women (37) |
The use of HPV testing for cervical cancer screening, already approved as a primary screening tool, has expanded in the past 10 years because of its higher sensitivity in detecting disease and greater ability to identify women at lower risk of subsequent disease after a negative result (negative predictive value) than conventional cervical cytology (or indeed VIA or VILI) (44, 45). HPV detection from age 30 as a primary test provides 60%–70% greater protection against invasive cancer compared to cytology (46). HPV testing is a high-performance, objective, and highly reproducible test. For low-resource settings, solutions and platforms are being developed that require little technical skill (one of the main problems in resource-constrained settings: the shortage of trained personnel [47]) and point-of-care HPV tests for possible treatment on site (47).

In light of recent advances in cervical cancer screening, where possible, WHO recommends initially an HPV test followed by cryotherapy or triage with VIA and then cryotherapy as a high-impact strategy in resource-limited settings (48).
3. Methods for assessing the impact of vaccination programs

3.1 Defining the effects of vaccines

The efficacy of a vaccine is defined as the direct effect of a vaccine measured in randomized clinical trials: it is the proportional reduction in the incidence of disease among the vaccinated attributable to the vaccine administered under ideal conditions. In clinical trials, the vaccine is randomly assigned, and it is assumed that the vaccinated and unvaccinated trial participants have similar opportunity for exposure to the pathogen and similar susceptibility to the disease.

In contrast, vaccine effectiveness is defined as the direct effect of a vaccine on the vaccinated group measured at the population level (under field conditions, e.g., in a vaccination program), and takes into account programmatic factors such as injection techniques, cold chain issues, different intervals of administration, or special characteristics of the population (such as comorbidity profiles that may make individuals more or less susceptible to the vaccine-preventable disease). Effectiveness or direct effect is measured by comparing the frequency of disease/infection between vaccinated and unvaccinated persons in the same population subject to a vaccination program (Figure 3). Effectiveness is estimated through observational studies (without vaccine randomization). Individual HPV vaccination data are needed to assess effectiveness.

**FIGURE 3.** Effects of vaccination programs based on comparison populations for their evaluation

Source: Adapted from Halloran ME, Longini IM, Struchiner CJ. Design and analysis of vaccine studies. New York: Springer; 2010 (49)
The overall impact or effect is defined as the reduction of the incidence of disease/infection in the entire population, including vaccinated and unvaccinated, and is measured by comparing the occurrence of disease pre-and post-vaccine introduction. These types of effects are generally estimated using ecological designs (i.e., observational studies in which the unit of observation is the population). The impact of the vaccine considers both the total effect of vaccination in those vaccinated as well as the indirect effects observed among the unvaccinated persons resulting from herd protection.

The direct effect is measured by comparing vaccinated and unvaccinated persons belonging to the same population and exposed to the same vaccination program to cancel the program-specific effect.

The indirect effect (or herd protection) is the effect of population vaccination on individuals who have not been vaccinated but benefit by the reduced transmission of the infectious agent and decreased risk of infection. It is measured by comparing disease occurrence in unvaccinated persons post-vaccine introduction with disease occurrence in the pre-vaccine period.

The total effect among vaccinated individuals is the combined effect of individuals being vaccinated and belonging to a population with a vaccination program (sum of the direct effect and the indirect effect among vaccinated). It is measured by comparing the frequency of disease occurrence in vaccinees with the disease occurrence in the population before the start of the vaccination program (historical rates).

In this practical guide, we focus on the design and interpretation of studies to assess the impact of vaccination programs. Hereafter, we use the term vaccine impact when referring to the overall effect and the term vaccine effectiveness when referring to the direct effect of HPV vaccination.

3.2 Design of studies to evaluate population impact

Conducting observational studies to assess the effectiveness and impact of the HPV vaccine in countries with an existing HPV vaccination program can provide public health policymakers with evidence about the effect of the vaccination program on HPV-related disease burden. In this section we will present recommended designs of studies to evaluate the population impact of HPV vaccination. For design of effectiveness studies, see Annex 1.

Vaccine impact studies compare the disease frequency in population which has a vaccination program with the disease frequency in populations without a similar program (the reference population). A comparison can be made:

- In the same period, between two comparable populations with a vaccination program and without a vaccination program (control group). In an HPV vaccine impact assessment, this option (with a control group) will generally not be feasible, as the vaccine is usually introduced nationally, and populations not covered by the program are older and therefore at different risk of developing HPV-related outcomes.
- At different time periods, before and after the introduction of the vaccine, in populations with the same characteristics (sex and age group). This will be the most used option to assess the impact of the HPV vaccination.

The study designs that can be used to assess the impact of the HPV vaccine include:

- Pre-vaccine/post-vaccine study: compares frequencies of HPV-related outcomes by sex and age group in the same population before and after HPV vaccine introduction (Figure 4).
- Population-based or sentinel epidemiological surveillance: time trend analysis of HPV-related outcomes or estimation of the percentage reduction in the post-vaccine period relative to the pre-vaccine period.
When these outcomes are measured in the entire population (for both vaccinated and unvaccinated), the overall effect of the vaccine is measured, whereas if they are measured in the unvaccinated population before and after the introduction of the vaccine, the indirect effect (or herd protection) of the vaccination is measured (Figure 3).

As per the definition used in this guidance document, vaccine impact studies—studies that measure the overall effect—analyze the effect of the vaccine on the entire population and therefore do not account for the individual history of HPV vaccination. In these studies, the frequency of the outcome is assessed in different populations. As a result, there could be changes in risk.

**FIGURE 4.** Example of a before/after study: HPV prevalence before (2005–2007) and after (2010–2012) the introduction of the quadrivalent HPV vaccine in Australia

![Graph showing HPV prevalence before and after vaccine introduction](image)

Australia's HPV vaccination program was launched in April 2007, offering free quadrivalent vaccine to girls and women aged 12–26. This repeat cross-sectional study recruited women aged 18–24 years who were screened for cervical cancer in the same metropolitan areas and then compared the prevalence of cervical HPV among samples collected in the two years prior to vaccine introduction with the prevalence three to five years after introduction (i.e., in women with a vaccination). The prevalence of the HPV genotypes targeted by the vaccine was significantly lower in the post-vaccine period than in the pre-vaccine period (29% pre-vaccine vs. 7% post-vaccine), while no decline was observed for nonvaccine genotypes.

factors or other characteristics of the study population, or changes in case detection procedures that could lead to an underestimation or overestimation of the effect of the vaccine. For example, if surveillance systems for a certain outcome are strengthened after the introduction of the vaccine and these systems capture more cases, then the effect of vaccination could be underestimated; on the other hand, an overestimation of vaccine effectiveness could occur due to a deterioration in the quality of epidemiological surveillance or population loss. It is important to consider the confounding factors that could explain the potential differences between the two populations and that are independent of vaccination and to take them into account in the analysis and interpretation of the results. (See Section 3.4 Study design considerations for evaluating the impact of the HPV vaccine.)

3.3 Considerations for evaluating the impact of HPV vaccination programs

Assessing the impact of HPV vaccination on the various outcomes associated with HPV infection is a complex task that presents several unique challenges (52, 53). Specifically, the challenges that require attention when designing and conducting impact studies include:

1. The long period from infection to cancer progression. Unlike other vaccine-preventable diseases, HPV-vaccination programs require years or decades to be able to assess the impact of vaccination.

2. The multiple biological endpoints against which the impact of the vaccine can be assessed: the endpoints can be HPV infection, anogenital warts, precancerous lesions, and cancer. These outcomes differ in the time between infection and outcome detection, the setting in which they are diagnosed, and the procedures by which they are detected.

This implies that it is necessary to coordinate between professional disciplines, programs, or institutions across different settings that may not be aware of HPV immunization (e.g., reproductive health, STI, adolescent health, cancer prevention, cancer registries, virus laboratories, pathology laboratories).

A feasibility plan will therefore be required to identify which program or institution has responsibility for the different outcomes to be evaluated in order to create the collaborative networks required for such an undertaking.

3. The coexistence of a cervical cancer screening program. Screening programs also aim to decrease cervical cancer incidence and mortality. Therefore, the reduction of cervical cancer will be the result of the combined implementation of both cancer screening and HPV vaccination programs. In addition, the ability to detect and diagnose precancerous lesions will be determined by the performance and quality of the screening program.

4. The availability of surveillance systems or registries for HPV-related outcomes so that data can be obtained with consistent methodology over time. If these are not available, it will be necessary to set up surveillance systems or conduct specific epidemiological studies to assess the impact of the HPV vaccine.

3.4 Study design considerations for evaluating the impact of the HPV vaccine

Regardless of the outcome selected, the following aspects should be considered in order to measure the impact of HPV vaccination: 1. Determining the need for an impact study; 2. HPV vaccination coverage; 3. Sources of information/data; 4. Time-dependent confounding factors; 5. Sample size; 6. Staff; 7. Time required to carry out a study; and 8. Costs.
1. Determining the need for an impact study

Before beginning a study, it is advisable to gather the available scientific evidence by conducting a literature review and evaluating available data from other groups and/or countries. At this stage, discussions with other key stakeholders would take place to ascertain whether the results of the study will be useful. Once the decision to evaluate a particular outcome is taken, it is recommended to review similar published evaluations to consider how their methodology is applicable or not and reach out to authors or colleagues who have undertaken similar studies.

2. HPV vaccination coverage

The magnitude of impact for an HPV vaccination program will depend on the vaccination coverage achieved and maintained over time. Ensuring that accurate data on HPV vaccination coverage by age are available is a prerequisite for any impact assessment (i.e., ensuring that an information system is in place to monitor HPV vaccination coverage).

3. Sources of information/data

Regardless of the type of data used for the analysis, its quality (reliability, consistency) should be confirmed. Data should be collected systematically following the same methodology over time. It should be determined whether data are representative of the general population.

There are generally two types of data to be analyzed:

A. Existing data

This refers to data that are collected for other reasons but could be used to assess the impact of the vaccination program (e.g., data from registries or computerized administrative databases). If individual records and aggregated data are used, the quality of the aggregated data source should be assessed (e.g., fidelity of transcription and methods of aggregation to ensure accuracy).

Types of data used will be determined by:

- Availability (What data are collected). It will be necessary to identify what type of information is collected, where, and when. Depending on the selected outcome, it may be necessary to include data from various sources.
- Access (How to obtain the data). Depending on the source of data, partnership agreements or collaborative networks will be required. Ethical aspects should also be assessed (obtaining informed consent or the approval of an ethics committee, for example).
- Format (How the data are collected). Some examples might be paper-based, or electronic medical records, or data collected in free format versus coded.
- Data quality. Pre-validation (or quality audits) of data is important because the quality of results depend on the data and the quality is critical for interpreting the results.

If problems are identified in any of these aspects, it should be assessed whether they can be solved by implementing changes.
B. New data
If, after examining any existing data sources, it is concluded that the information available is insufficient to measure vaccine impact, planning for appropriate data collection will be required. This may require designing a revised protocol for specimen collection and/or a questionnaire for data collection and defining how, when, and from whom the data will be collected.

4. Time-dependent confounding factors
There are a number of factors external to HPV vaccination that will directly influence outcomes and should therefore be taken into account:

a. Cervical cancer screening programs also aim to decrease the incidence and mortality of cervical cancer. Therefore, the combined impact of both vaccination and screening will be measured. In addition, changes in the coverage of the screening program and changes in the type and frequency of diagnostics tests and associated follow-up will also affect the incidence of precancerous lesions. Therefore, in the interpretation of vaccine impact, consideration will need to be given to whether a screening program exists and what changes in the screening program may have occurred over time.

b. Changes in sexual behavior, which could result in changes in the risk of HPV infection with respect to the risk of the reference population. Whenever possible, information on sexual behavior variables will be collected from both pre- and post-vaccine comparison groups (see Section 4.6 Covariates of interest). If the outcome to be evaluated is anogenital warts, it is also recommended that the incidence of another STI with similar incidence by age group is measured, as an approximation for detecting changes in sexual behavior (i.e., comparison with a control disease).

c. Changes in methods of measuring the outcome (e.g., technical or scientific resources such as HPV assay type or diagnostic criteria). Where such changes (e.g., new test type implemented) have unavoidably occurred, they should be documented. Supporting data should identify how the outcome measurement compares to the previous method (in terms of relative sensitivity and specificity). The change in method must be explicitly considered in interpretation.

5. Sample size
It is important to determine the sample size needed to ensure that an adequate number of observations will be available to allow for sufficient statistical power to measure the impact.

For example, in order to estimate the sample size in a before–after study, it is important to define:
- the expected frequency of the outcome (e.g., prevalence of infection) in a given population during the pre-vaccine period (reference population)
- the expected reduction in the post-vaccine period (according to vaccine efficacy and coverage achieved).

The sample size will determine the level of resources needed for conducting the study as well as the time required to carry it out. For studies that measure multiple outcomes, it will be necessary to calculate the sample size for each outcome of interest and for each of the subgroups in which the effect of the vaccine is to be evaluated (e.g., age groups). An example of sample size calculation for prevalence of HPV infection is presented in Section 4.4.3 Study population.
6. Staff

In order to design and carry out a study to assess the impact of the HPV vaccine, the involvement of the following staff will be required:

- Epidemiologist, or similar profile, for proper study design, protocol development, and data collection design, with knowledge of HPV epidemiology, natural history, and prevention.
- Coordinator with knowledge of the health system and, if possible, with contacts at different levels to establish possible collaborations or networks.
- Statistician, or similar profile, to estimate the necessary sample size, formulate the analysis plan considering the different possible methodologies, and analyze the data.
- Staff for data collection, database entry, and data cleaning.
- Administrative staff.

(This is in addition to the staff required specifically to measure the impact of a given outcome detailed in the specific paragraphs of Section 4. Outcomes for measuring the impact of HPV vaccines).

7. Time required to carry out a study

Depending on the outcome (see Table 5), it may be necessary to wait until the vaccinated cohorts reach the age that the outcome begins to occur. However, it may take several years until the incidence is sufficient to assess the impact (see Section 4.1 Outcomes of HPV vaccines). In addition, in the case of opting for a pre–post evaluation, consideration should be given to the need for carrying out the pre-vaccination measurements in a comparison group before the vaccinated cohorts reach the chosen study age. Finally, another factor to consider is the time required for planning and designing the study, conducting the necessary training, and field work.

8. Costs

Before carrying out any impact study, the costs and budgetary impact should be assessed, considering whether it is only an initial investment or whether it will have to be maintained over time. Where coverage is suboptimal, increasing vaccination coverage is a higher priority than conducting impact studies.
4. Outcomes for measuring the impact of HPV vaccines

4.1 Outcomes of HPV vaccines

Measuring the impact of outcomes associated with HPV infection is not an essential requirement for implementing an HPV vaccination program due to its complexity and the challenges it poses. Before undertaking any impact study, countries should have accurate data on coverage by age (54).

Where HPV vaccination coverage is suboptimal, priority should be given to increasing HPV vaccination coverage in the target population before impact studies are conducted (55). The positive impact of HPV vaccination programs worldwide is consistent, and there is no indication that any differences should be observed specifically in Latin America and the Caribbean.

The impact of HPV vaccination can be measured by assessing different outcomes caused by HPV infection. When the impact can be measured depends on:

- Age the HPV vaccine is administered
- Average age of sexual debut
- Time that normally elapses between HPV infection and the outcome of interest.

Table 5 presents the different outcomes for impact assessment, indicating the approximate time interval between initiating a vaccination program and measuring impact if vaccination is carried out in preadolescence/early adolescence and there is no catch-up vaccination program for older age groups, and the different indicators for which impact can be assessed.

### TABLE 5. Biological outcomes to assess the impact of HPV vaccination

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time span for measuring impact</th>
<th>Approximate time range after initiation of preadolescent/early adolescent vaccination program</th>
<th>Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV infection (vaccine type-specific)</td>
<td>short term</td>
<td>5 years or more</td>
<td>Prevalence of vaccine type-specific HPV infection</td>
</tr>
<tr>
<td>Anogenital warts*</td>
<td>short term</td>
<td>5 years or more</td>
<td>Incidence of anogenital warts</td>
</tr>
</tbody>
</table>
| Precancerous cervical lesions        | medium term                    | 10 years or more (could be sooner, depending on the age of recommended initiation for cervical screening) | 1) Incidence of precancerous cervical lesions  
2) Proportion of precancerous cervical lesions attributable to high-risk genotypes targeted by HPV vaccines |
| Cervical cancer                      | long term                      | 20 years or more                                                                             | 1) Incidence of cervical cancer  
2) Cervical cancer mortality  
3) Proportion of cervical cancer cases attributable to high-risk genotypes targeted by HPV vaccines |

Note: *In countries administering the quadrivalent or the nonavalent vaccine.
4.2 Cervical cancer

4.2.1 General considerations
The primary objective of any impact assessment of HPV vaccination programs is to demonstrate a reduction in cervical cancer incidence and mortality (56), so this will be the primary outcome targeted for evaluation. However, given the natural history of the disease and the fact that girls are vaccinated before the onset of sexual activity, it will take several decades from the implementation of the vaccination program until full impact on the incidence of cervical cancer can be assessed. Before then, other HPV-related outcomes can be assessed (Table 5).

| Expected outcomes in the incidence of cervical cancer | The incidence of cervical cancer will change as a result of the combination of the two preventive strategies against cervical cancer: HPV vaccination; and cervical cancer screening and treatment of precancerous lesions. These preventive strategies are two of the three key steps of the WHO Global Strategy to Accelerate the Elimination of Cervical Cancer. This strategy proposes the following 90–70–90 targets that need be met by 2030 for countries to be on the path toward the elimination of cervical cancer as a public health problem (24):
• 90% of girls fully vaccinated with HPV vaccine by age 15 years
• 70% of women are screened with a high-performance test by 35 and again by 45 years of age
• 90% of women identified with cervical precancerous lesions and cervical cancer treated.

An overall reduction in the incidence of cervical cancer and a reduction in the number of cervical cancer cases attributable to the HPV genotypes targeted is expected when the vaccinated cohorts reach the age that cervical cancer begins to occur most frequently (for example, 30 years of age). It is important to note that before the vaccinated cohorts reach this age, any observed changes in these endpoints probably have other causes. For example, if years after the introduction of the vaccine there is an increase in the incidence of cervical cancer, but the vaccinated cohorts have not yet reached age 30 years, this increase could be due to sexual behavior or changes in detection patterns associated with the screening program, which are independent of HPV vaccination. |

| Important aspects to consider | In order to evaluate the impact on any indicator, the items discussed in Section 3.4 Study design considerations for evaluating the impact of the HPV vaccine should be considered. |

**INDICATORS**

Studying the impact of HPV vaccination on cervical cancer outcomes will be based on the following indicators:

1) Incidence of cervical cancer.
2) Cervical cancer mortality.
3) Proportion of cervical cancer cases attributable to high-risk genotypes targeted by HPV vaccines.

Each of these indicators will require the availability of resources such as, for example, population-based cancer registries or national mortality data, in order to carry out an adequate evaluation.

**TIME REQUIRED**

In order to assess the impact of vaccination on cervical cancer, more than one decade will be needed before some members of the vaccinated cohorts become sexually active (i.e., become susceptible to HPV infection) and enough time has passed for cancer to develop.
4.2.2 Description of indicators

1) Incidence of cervical cancer

| Indicator definition | Number of new cervical cancer cases arising in women over a period of time (typically one year), expressed as an age-adjusted rate per 100 000 women. The observed incidence of cervical cancer will reflect the combined effect of HPV vaccination and cervical screening/treatment of precancerous lesions. The incidence of other HPV-related cancers can be monitored, although the percentage of these cancers that are attributed to HPV varies depending on the location (see Section 2.1 Human papillomavirus [HPV]): cancers of the vagina, vulva, anus, penis (in countries that also vaccinate men), and head and neck cancers (mainly oropharynx). However, it should be noted that these cancers have a typically older age of onset and a very low incidence compared to the burden of cervical cancer in Latin America and the Caribbean. |
| Resources required | Monitoring the incidence of cervical cancer or any other HPV-related cancer will require a population-based cancer registry (PBCR) that meets quality standards. PBCRs systematically collect and classify information on all new cancer cases that occur in a defined geographic area from multiple information sources such as hospitals, diagnostic laboratories, and death certificates. Those PBCRs included in the latest edition of Cancer Incidence in Five Continents (CIS) are accredited by the International Agency for Research on Cancer (IARC), which evaluates the comparability, validity, and completeness of data provided by registries prior to inclusion to ensure that they meet the standard of quality. Annex 2 lists the locations for PBCRs for Latin America and the Caribbean included in the latest edition of Cancer Incidence in Five Continents (Vol. XI). The PCBRs provide reliable data on trends in cervical cancer incidence. Non-population-based cancer registries (such as hospital registries) are not an adequate source of information for monitoring cervical cancer incidence, as they may be subject to reporting bias. All countries should consider establishing or improving PBCRs in order to measure the impact of HPV vaccination program and screening, to support national cervical cancer elimination programs, while monitor progress toward the elimination of cervical cancer. Countries with an existing PBCR should consider recording the HPV vaccination background variable and HPV type detection for all HPV-related cancers or establish linkages between population-based cancer and vaccination, screening, and pathology registries. |

2) Cervical cancer mortality

| Indicator definition | Number of deaths due to cervical cancer occurring in women over a period of time (typically one year), expressed as an age-adjusted rate per 100 000 women. Observed cervical cancer mortality will reflect the combined effect of HPV vaccination (over time), cervical screening, access to and quality of treatment. Similarly, mortality from other HPV-related cancers can be monitored. |
| Resources required | To monitor cervical cancer mortality, a country will need to have robust vital statistics. Most countries in the Americas have nationally representative death registry systems and the information collected from these systems is reported to the WHO mortality database. However, as can be seen in Table 6, data quality varies, with some countries having low coverage and others having unsatisfactory information on cause of death. Therefore, in the latter countries cervical cancer mortality rates can not be reliably monitored. |
### TABLE 6. Quality and coverage of mortality data in Latin American and Caribbean countries and territories

<table>
<thead>
<tr>
<th>Country</th>
<th>Percentage of ill-defined codes*</th>
<th>Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>&lt;35%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Bahamas</td>
<td>&lt;15%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Barbados</td>
<td>&lt;20%</td>
<td>&gt;60%</td>
</tr>
<tr>
<td>Belize</td>
<td>&lt;15%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Bolivia (Plurinational State of)</td>
<td>≥40%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Brazil</td>
<td>&lt;20%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Chile</td>
<td>&lt;15%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Colombia</td>
<td>&lt;10%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>&lt;10%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Cuba</td>
<td>&lt;10%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>&lt;20%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Ecuador</td>
<td>&lt;25%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>El Salvador</td>
<td>&lt;40%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>France, Guadeloupe</td>
<td>&lt;25%</td>
<td>100%</td>
</tr>
<tr>
<td>France, Martinique</td>
<td>&lt;25%</td>
<td>100%</td>
</tr>
<tr>
<td>French Guiana</td>
<td>&lt;25%</td>
<td>100%</td>
</tr>
<tr>
<td>Guatemala</td>
<td>&lt;25%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Guyana</td>
<td>&lt;15%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Haiti</td>
<td>≥40%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Honduras</td>
<td>&lt;10%</td>
<td>10%–50%</td>
</tr>
<tr>
<td>Jamaica</td>
<td>&lt;15%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Mexico</td>
<td>&lt;10%</td>
<td>100%</td>
</tr>
<tr>
<td>Nicaragua</td>
<td>&lt;15%</td>
<td>&gt;60%</td>
</tr>
<tr>
<td>Panama</td>
<td>&lt;20%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Paraguay</td>
<td>&lt;25%</td>
<td>&gt;60%</td>
</tr>
<tr>
<td>Peru</td>
<td>&lt;25%</td>
<td>&gt;60%</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td>&lt;15%</td>
<td>100%</td>
</tr>
<tr>
<td>Saint Lucia</td>
<td>&lt;20%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Suriname</td>
<td>&lt;20%</td>
<td>&gt;60%</td>
</tr>
<tr>
<td>Trinidad and Tobago</td>
<td>&lt;10%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Uruguay</td>
<td>&lt;25%</td>
<td>100%</td>
</tr>
<tr>
<td>Venezuela (Bolivarian Republic of)</td>
<td>&lt;15%</td>
<td>&gt;80%</td>
</tr>
</tbody>
</table>

Note: *Based on the percentage of deaths certified to a list of ill-defined codes or garbage codes that is, as defined in the World Health Statistics 2017, a cause which is not a valid underlying cause of death or is ill-defined (61).

4.3 Precancerous high-grade cervical lesions

4.3.1 General considerations

Precancerous high-grade cervical lesions (CIN2, CIN2/3, CIN3, and AIS, hereinafter defined as CIN2+) are lesions that are detected by cervical screening. These lesions are precursors to cervical cancer and develop over a shorter period of time than cancer. Therefore, demonstrating the impact of the HPV vaccine on these lesions is a reliable approximation of the future impact on cervical cancer. However, the incidence of these precancerous lesions is directly affected by changes in screening recommendations, screening practices (detection methods), or program participation. Therefore, changes in any of these over time could lead to errors in interpretation of findings.

| Indicator definition | Proportion of cervical cancer attributable to high-risk genotypes targeted by HPV vaccines (HPV16/18 or HPV16/18/31/33/45/52/58), stratified by age. Attribution may be defined as detection of a vaccine-type (for example, HPV16 or HPV18) in a cancer case, independent of co-detection of other types. The proportion of cervical cancer attributable to vaccine-types in the pre- and post-vaccine period can be estimated, or a time trend analysis can be performed to detect a decrease in the proportion of cervical cancers attributable to vaccine-types. |
| Resources required | The following will be required:  
• Clinics that perform colposcopy and biopsy  
• Pathology laboratory that meets quality standards  
• Laboratory that can perform HPV DNA detection and genotyping on tissue specimens (see requirements in Section 4.4.4 Resources needed to perform HPV determination/genotyping). |
| Study population | The most feasible strategy is to select the population accessing treatment and/or care at colposcopy clinics or sentinel pathology laboratories. To reduce bias in the overestimation of the prevalence of a certain HPV genotype if cases are selected on the basis of histological types, cases diagnosed consecutively can be selected. |

| Expected outcomes | At the population level, we expect to see a decrease in the incidence rates of CIN2+, and a reduction in the number of CIN2+ attributable to the HPV genotypes targeted by the vaccines. |
| Important aspects to consider | In order to evaluate the impact on any indicator, the items discussed in Section 3.4 Study design considerations for evaluating the impact of the HPV vaccine should be taken into account.  
INDICATORS  
The study of the impact on high-grade precancerous cervical lesions will be based on the following indicators:  
1) Incidence of CIN2+.  
2) Proportion of CIN2+ attributable to high-risk genotypes targeted by HPV vaccines.  
Alternatively, other indicators such as cytological alterations (high-grade squamous intraepithelial lesion, HSIL) or colposcopy referrals may be considered. However the limitations to interpreting trends of these events must be considered. For example, colposcopy referrals may change over time due to variations in screening guidelines. |
**4.3.2 Description of indicators**

1) **Incidence of CIN2+ lesions**

| Indicator definition | Number of new CIN2+ lesions diagnosed in women over a period of time, stratified by age and expressed as a rate per 100,000 women. The time trends in the incidence of CIN2+ will be analyzed. It is recommended to express the incidence of CIN2+ lesions as a rate per women who have had a Pap smear in the same year (i.e., women who have been screened), as this will adjust for changes in participation in the screening program (this denominator has been chosen in several studies assessing the impact on CIN2+ lesions, for example [33, 62]). All screening programs, whether organized or opportunistic, should keep records of number of women screened per month and their ages, making this estimation feasible. |
| Resources required | 1) A population-based or opportunistic cervical cancer screening program with established frequency of diagnostic testing and follow-up protocols that are maintained over time. Monitoring the incidence of precancerous lesions outside an established population-based screening program can lead to misinterpretation, as the incidence is directly influenced by the screening program. Therefore, countries that plan to make changes to the screening program should consider another indicator or make plans to account for these changes.  
2) A centralized registry of histopathology screening results or mandatory reporting of CIN2+ cases. Countries with centralized reporting of screening results should consider recording the HPV vaccination variables for cases, or establishing mechanisms for linkages between screening and vaccination records for potential effectiveness studies. |

2) **Proportion of CIN2+ attributable to high-risk genotypes targeted by HPV vaccines**

| Indicator definition | Proportion of CIN2+ attributable to high-risk genotypes targeted by HPV vaccines, stratified by age. Attribution may be defined, for example, as detection of a vaccine-type (for example, HPV16 or HPV18) in a lesion, independent of co-detection of other types. The proportion of CIN2+ attributable to vaccine-types in the pre- and post-vaccine period can be estimated, or a time trend analysis can be performed to determine changes in this proportion over time. |
| Resources required | • Clinics that perform colposcopy and biopsy  
• Pathology laboratory that meets quality standards  
• Laboratory that can perform HPV DNA detection and genotyping on tissue specimens (see requirements in Section 4.4.4 Resources needed to perform HPV determination/genotyping). |
| Study population | The most feasible strategy is to select the population accessing treatment and care at colposcopy clinics or sentinel pathology laboratories. To reduce bias in the overestimation of a particular HPV genotype if cases are selected on the basis of histological types, cases diagnosed consecutively can be selected. |
4.4 HPV infection

4.4.1 General considerations

Determining the prevalence of vaccine type-specific cervical infections in sexually active women is the earliest biological outcome that can be used to assess the impact of the HPV vaccination program. Periodic assessment of HPV infection will help document changes in the prevalence of infection by the HPV types targeted by the HPV vaccines over time.

<table>
<thead>
<tr>
<th>Expected outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A progressive decrease in the prevalence of vaccine type-specific infection is expected as the proportion of vaccinated women in the adult population studied increases. It is important to emphasize that a decrease in infection by the genotypes targeted by the vaccines can be observed without a change in the overall prevalence of HPV infection (which includes HPV types not targeted by vaccine). This does not necessarily mean that there has been any replacement of genotypes. Many HPV coinfections occur (infection with multiple types concurrently).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important aspects to consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>To evaluate the impact on any outcome, the items discussed in Section 3.4 Study design considerations for evaluating the impact of the HPV vaccine should be considered. Studying the impact on the prevalence of HPV infection will, in some situations, require significant resources to be allocated and sustained over several years. Consistent procedures should be followed during the assessment period for recruitment, sampling, sample processing, HPV detection and genotyping, and data collection. A pilot evaluation is recommended to establish whether the proposed methodology is feasible and acceptable to the participants, so that it can be replicated in future impact studies. The pilot evaluation could also be used to determine the baseline prevalence for estimating the required sample size in a given population. NECESSARY RESOURCES AND THEIR AVAILABILITY The detection of HPV infection depends on molecular diagnostic techniques that identify the presence of HPV DNA or RNA and also allow a partial or individual genotyping result to be obtained, thus identifying the viral genotypes that are present in a positive sample. HPV DNA detection can be performed on cervical or noncervical samples (e.g., on vaginal, oral, or urine samples). However, each of these specimens have different requirements. This section focuses on assessing the prevalence of cervical/vaginal HPV infection. Ability to assess vaccine impact on the prevalence of HPV infection will depend on the infrastructure available for sample collection, processing, and analysis, which determine costs and feasibility. Countries that have a cervical cancer screening program with HPV testing as the primary screening or triage test will generally have the necessary infrastructure in place, while those that use conventional cytology or VIA in their screening programs, or those that do not have a screening program, will need to establish the necessary protocols for proper sample processing and analysis. An assessment of costs will also be required (see Section 4.4.4 Resources needed to perform HPV determination/genotyping). TIME REQUIRED After implementation of the HPV vaccination program, 5–10 years will need to pass before assessing the impact on the prevalence of HPV infection, depending on the age of vaccination.</td>
</tr>
</tbody>
</table>
4.4.2 Description of indicator

The main indicator for assessment will be the prevalence of HPV16/18 infection in sexually active women.

In populations vaccinated with the quadrivalent or nonavalent vaccine, the prevalence of infection with other genotypes targeted by the vaccine (HPV6/11 or HPV31/33/45/52/58) may be considered as a secondary objective of the analysis. The prevalence of high-risk HPV infection, or the prevalence of other genotype-specific infection, may also be further assessed. Where the prevalence of genotype-specific infection is assessed, the prevalence of nonvaccine genotypes may be used as a measure of HPV exposure, although the cross-protective effect of vaccines against some genotypes should be considered.

The prevalence of infection stratified by age is estimated as the number of women with a positive HPV infection detected among all women with a valid test result. The objective is to compare the prevalence of age-stratified HPV infection in the female population before and after vaccine introduction. Depending on the study design, the difference between the prevalence of infection in the pre-vaccine and post-vaccine period, or the time trends in prevalence, can then be estimated.

4.4.3 Study population

Selection of the study population

The study population can be selected using different strategies. The strategy should be based on the epidemiological design of the study and, also, on the resources available. The economic feasibility and practicality should be assessed, and it should be ensured that the necessary resources are available for both infrastructure and human resource needs (see Section 4.4.4 Resources needed to perform HPV determination/genotyping).

As an initial guidance, three possible strategies can be considered:

1) Sampling of the general population

Unlike the other strategies that are explored below (sampling from women who participate in cervical cancer or Chlamydia trachomatis screening programs), the use of a general population sample requires investigators to identify the type of sample specimen for collection (cervical, vaginal, vaginal self-collection, or urine) at an early stage of the study design, as this will influence the recruitment strategy. Table 7 lists examples of recruitment sources for the three possible strategies with their advantages and disadvantages.

To sample from the general population, a population-based study design is recommended, with either a representative sample of the general population or utilizing opportunistic recruitment through healthcare clinics. With opportunistic recruitment, the population may not be representative of the population in which vaccine impact is to be assessed. Studies using opportunistic recruitment should ensure that the reference population is comparable between the pre- and post-vaccine periods (in terms of age group, geographical origin, etc.) and where appropriate adjust for the fact that HPV vaccination coverage in the sample analyzed may differ from national coverage. Therefore, it is necessary to ensure in both studies that the variables of interest described in Section 4.6 Covariates of interest (socioeconomic level, sexual behavior, history of HPV vaccination, etc.) are collected.

Using this general population-based approach, vaccine impact can be assessed beginning 5–10 years after the start of the vaccination program, depending on the age of vaccination and the age of the study population.

2) Sampling from women who participate in a cervical cancer screening program

The use of this strategy to measure vaccine impact is highly feasible if the following conditions are met:
• Existence of an organized or opportunistic screening program in which the protocols through which women are invited to participate in the screening program remain stable over time. If possible, a population representative of the reference population in which the vaccine impact is to be assessed should be chosen.
• HPV detection/genotyping test exists as a primary screening test or as a triage (in women over 30 years).
• Use of the same HPV test over time.
• Age at start of the screening program is 20–25 years.

This will allow the use of the existing cervical screening guidance and platform in a country for the collection, handling, processing, and analysis of samples, which results in considerable cost savings when considering the alternative of designing a specific study.

Countries with an organized screening program performing liquid-based cytology will be able to use surplus sample for HPV testing, while programs that perform conventional cytology or VIA could use the existing screening program to recruit women for additional specific samples collected in liquid medium for HPV detection/genotyping, and therefore need to ensure that the necessary resources are available. Table 7 presents the advantages, disadvantages, and feasibility of conducting recruitment through the different cervical cancer screening programs, including examples of studies that have evaluated vaccine impact through a screening program.

The time requirements for assessing vaccine impact on HPV prevalence following the introduction of the HPV vaccine using this strategy will depend on the age of initiation of screening, with 10–15 years needed from program implementation to assessment if the age of screening initiation is 25 years. However, in those countries where screening begins at age 25 or later, a specific strategy to target younger women is possible, provided that the representativeness of the women recruited for early screening is ensured with respect to the population where impact is to be assessed and this strategy can be replicated and sustained over time.

3) Sampling from women participating in chlamydia trachomatis screening program
This strategy reduces the cost of the study, since surplus of samples tested for chlamydia trachomatis will be analyzed. However, the necessary resources for HPV testing should be ensured (see Section 4.4.4 Resources needed to perform HPV determination/genotyping).

If this strategy is followed, the timing for assessment of vaccination impact following the introduction of HPV vaccine will depend on the recommended age for screening of Chlamydia trachomatis, but generally this strategy will allow vaccine impact to be assessed starting 5–10 years following HPV vaccine introduction.

Selecting the target age in the study population
The prevalence of HPV infection should be measured in sexually active women. In order to study the impact of HPV vaccines in the short term, it is recommended that the prevalence of HPV infection be estimated shortly after the average age of initiation of sexual activity. Generally, it is recommended to include young adult women, for example under the age of 25 years, although the following factors should be considered when deciding the age of the population to be included in the study:
• Age at which the vaccine is administered in the program (including catch-up, if any) (see Annex 3).
• Average age of sexual debut.
• Age of first vaccinated cohorts by the time a vaccine impact study is planned (see Annex 3).

Furthermore, focusing the study on women who are of legal age to give informed consent would facilitate participation as the consent of legal guardians is not required.
### TABLE 7. Possible sources of recruitment for studies of vaccine impact on HPV prevalence

<table>
<thead>
<tr>
<th>Recruitment sources</th>
<th>Comments</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Feasibility</th>
<th>Examples of recruitment sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexually active women in the general population</td>
<td>In countries where this type of repeat study already exists, the incorporation of HPV determination by self-sampling can be considered</td>
<td>Population based</td>
<td>If there are no such studies, it is not feasible because the design entails a high cost</td>
<td>-</td>
<td>(63–65)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Representativeness</td>
<td>If cervical sampling is required, protocols will need to be established</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nationally representative population study</td>
<td>Population based</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population mail-based survey</td>
<td>Sampling in this type of study is usually by self-sampling</td>
<td>Population based</td>
<td>Response rate is usually low</td>
<td>+</td>
<td>(66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Possible selection bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Requires efficient mail service</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High cost</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Feasibility is lower in countries with large territorial size, high population, and great diversity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family planning, sexual health, or prenatal clinics</td>
<td>Consider including several clinics from different geographical locations to increase representativeness of the population</td>
<td>Opportunistic recruitment</td>
<td>Representativeness: socioeconomic level (will depend on the country’s health care referral systems)</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women that attend these clinics are sexually active.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gynecological visits make it easier to take a cervical sample</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexually transmitted infection clinics</td>
<td>Consider including several clinics in different geographical locations to increase the representativeness of the population</td>
<td>Opportunistic recruitment</td>
<td>Representativeness: higher risk sexual behavior, HPV prevalence will be overestimated</td>
<td>++</td>
<td>(67, 68)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women that attend these clinics are sexually active</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gynecological visits make it easier to take a cervical sample</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recruitment sources</td>
<td>Comments</td>
<td>Advantages</td>
<td>Disadvantages</td>
<td>Feasibility</td>
<td>Examples of recruitment sources</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>---------------------------------------------------</td>
<td>-------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Primary care centers or health posts serving young women</td>
<td>Consider including several clinics in different geographical locations to increase the representativeness of the population</td>
<td>Opportunistic recruitment</td>
<td>Representativeness</td>
<td>++</td>
<td>(69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Represents transformation</td>
<td>Allows cervical sampling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital of any level</td>
<td>Consider including several hospitals in different geographical locations to increase the representativeness of the population</td>
<td>Opportunistic recruitment</td>
<td>Representativeness will be limited to women attending the services where recruitment took place</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Represents transformation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary schools/ universities</td>
<td>It will depend on the ages of schooling</td>
<td>Easy access to women &lt;25 years</td>
<td>Representativeness: higher socioeconomic level.</td>
<td>++</td>
<td>(70, 71)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feasible if the sample is taken by self-collection in urine.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feasible if the sample is taken by self-collection in urine.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>In the case of requiring a cervical sample, it will be necessary to establish the procedures for the sample collection.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women participating in the cervical cancer screening program</td>
<td></td>
<td></td>
<td></td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Programs that have HPV testing as a primary screening/triage</td>
<td>Age of onset of screening 20–25 years. If screening starts at age 25–30 years, consider inviting also specifically women aged &lt;25 years</td>
<td>Screening program is a potential source for recruitment</td>
<td>Specific sampling will be required if it is not liquid cytology</td>
<td>++++</td>
<td>(72)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infrastructure is available to perform HPV analysis</td>
<td>The population being screened may not be representative</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Some of the variables of interest may not be collected (sexual behavior, HPV vaccination).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Programs that perform liquid-based cytology</td>
<td>Age of onset of screening 20–25 years. If screening starts at age 25–30 years, consider inviting also specifically women aged &lt;25 years</td>
<td>Screening program is a potential source for recruitment</td>
<td>The population being screened may not be representative.</td>
<td>+++</td>
<td>(32, 50, 73–75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample collected in the appropriate medium, the remainder of the diagnostic sample is used</td>
<td>Some of the variables of interest may not be collected (sexual behavior, HPV vaccination).</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Need to ensure that the infrastructure is in place to conduct HPV testing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Choice of the comparison group

In order to compare changes in the prevalence of HPV infection in the post-vaccine period with respect to the pre-vaccine period, a comparison group of women not included in the HPV vaccination program should be identified. This comparison group is denominated historical control. These women should be in the same age group as the cohort or group being studied for impact associated with HPV vaccination.

If previous HPV prevalence studies exist in the country, these prevalence estimates can be used as a reference. This can be used provided that age-stratified data on HPV16/18 infection prevalence are available, if the population included is representative of the population in which the impact is to be assessed, and if the subsequent study methodology including the vaccinated cohorts is comparable. Many countries, however, do not have data on the prevalence of HPV infection in young women before the start of the HPV vaccination program.

In countries where HPV vaccine has been administered for several years, a prevalence study which includes unvaccinated cohorts should be conducted as soon as possible. Specifically, the study should be conducted before the vaccinated cohorts reach the age when impact is to be assessed. Annex 3 shows the description of HPV vaccination programs in Latin America and the Caribbean including the year of introduction, the targeted age in the first years of the national program, the year of birth of the first female vaccinated cohort, and the age of the first vaccinated birth cohort in three specific time points (2020, 2025, and 2030). For example, Barbados started the HPV vaccination program in 2014 targeting 11-year-old girls (see Annex 3 for additional details). Supposing that there is no previous HPV prevalence study in Barbados, if the country wants to carry out an impact evaluation study starting in 2020, then the age group 18–24 years could be selected because the first vaccinated cohort would have been 17 years in 2020. Therefore, the baseline could be performed in 2020 including unvaccinated women aged 18–24 years, and the post-vaccine study, including vaccinated women aged 18–24 years, could be performed in 2027 (i.e., once the vaccinated cohorts reach the age of 24 years).
In the case of Colombia, where the HPV vaccination program started in 2012, women aged 9–17 years were targeted. If the country wants to carry out an impact study in 2020 and supposing that there is no baseline prevalence study, then the age group 25–29 years could be selected, because the first vaccinated cohort turned 24 years of age in 2020. The post-vaccine study could be performed in 2025 at the earliest (i.e., when the first vaccinated cohort turns 29 years).

The women included in both studies (pre-vaccine/post-vaccine) should ideally be from the same geographical areas. The methodology used in both studies should be comparable in terms of recruitment, population included, sampling, detection/genotyping test used, sample processing, and data collection.

**Sample size required**

As a guideline, an example of sample size calculation for estimating the impact of an HPV vaccination program on the prevalence of HPV infection is presented in Table 8. For a discussion of sample size estimation see Section 3.4 Study design considerations for evaluating the impact of the HPV vaccine. Depending on the coverage of HPV vaccination and the expected prevalence of infection by HPV types targeted by the vaccine in the reference population (e.g., HPV16/18), the sample size required for a desired power of 80%, at a significance level of 5%, and a vaccine efficacy of 90% is shown in Table 8.

<table>
<thead>
<tr>
<th>Prevalence of HPV16/18 Infection in the Reference Population (%)</th>
<th>90%</th>
<th>80%</th>
<th>70%</th>
<th>60%</th>
<th>50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5%</td>
<td>4 350</td>
<td>5 900</td>
<td>8 200</td>
<td>11 800</td>
<td>18 000</td>
</tr>
<tr>
<td>1%</td>
<td>2 150</td>
<td>3 000</td>
<td>4 100</td>
<td>5 900</td>
<td>8 950</td>
</tr>
<tr>
<td>2%</td>
<td>1 100</td>
<td>1 500</td>
<td>2 100</td>
<td>3 050</td>
<td>4 650</td>
</tr>
<tr>
<td>5%</td>
<td>450</td>
<td>600</td>
<td>850</td>
<td>1 200</td>
<td>1 800</td>
</tr>
<tr>
<td>10%</td>
<td>200</td>
<td>300</td>
<td>400</td>
<td>550</td>
<td>850</td>
</tr>
<tr>
<td>20%</td>
<td>100</td>
<td>130</td>
<td>180</td>
<td>250</td>
<td>400</td>
</tr>
<tr>
<td>30%</td>
<td>60</td>
<td>80</td>
<td>110</td>
<td>160</td>
<td>250</td>
</tr>
</tbody>
</table>

*Note: The numbers indicate the total study population. Therefore, half of the sample size will be in the interest group (post-vaccine) and half in the comparison group (pre-vaccine). The calculation is estimated at 80% power, 5% significance level, and 90% vaccine efficacy.*

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**4.4.4 Resources needed to perform HPV determination/genotyping**

This section describes the minimum infrastructure and human resource requirements that a country must have in order to perform HPV identification/genotyping. For additional information, see the guidelines for *Integrating HPV Testing in Cervical Cancer Screening Programs* (80) and the *Human Papillomavirus Laboratory Manual* (81). If the necessary infrastructure is not available, consideration should be given to sending samples to a foreign reference laboratory.

**Obtaining the samples**

The personnel in charge of obtaining the biological specimen samples should be properly trained and qualified in the technique of sample collection, using collection devices and tubes that allow the sample to be deposited in a suitable transport medium, the use of which has been previously validated for the detection of HPV. The use of sterile collection devices and tubes with individual presentation containers is recommended to avoid possible contamination and to ensure correct labeling of the samples.

---

**TABLE 8. Required sample size for estimating the impact of an HPV vaccination program on the prevalence of HPV16/18 infection in different scenarios of prevalence of HPV and coverage**
If a woman is taking the sample herself (vaginal self-collection) or if the sample is collected in urine, health workers should be trained to explain to the woman step by step how to obtain the sample. The collection of this type of sample can be done in the home and does not require special infrastructure for sample collection.

If it is necessary to send the biological samples from the collection center to the detection laboratory, a protocol must be established to ensure safe transport under appropriate temperature conditions according to the collection medium used.

**Infrastructure and personnel**

The laboratory used for HPV determination/genotyping should have the necessary infrastructure for registering, processing, and storing the samples under optimal conditions, ensuring the preservation and stability of the samples. Facilities where the HPV test is performed must have ventilation, controlled temperatures, and be free of possible sources of contamination. It is important to respect the maximum temperatures and times described for each means of transport before the samples are processed.

The samples received must be processed following standardized working protocols defined according to the chosen HPV detection/genotyping technique, which minimize any possibility of contamination and ensure reproducibility, quality control, and traceability of results. Staff should be trained in the handling of biological samples and the molecular techniques used for HPV detection/genotyping. Ideally, the laboratory should have an external and internal quality control to ensure the quality of the results.

**HPV detection/genotyping techniques**

The majority of HPV detection techniques are based on identifying the presence of viral DNA from 13–14 HPV genotypes defined as high-risk genotypes, resulting in a positive or negative value for each of the samples tested. Some of these techniques also allow a partial or individual genotyping result to be obtained, thus identifying the viral genotypes that are present in a positive sample. Some techniques incorporating partial genotyping allow the separate identification of HPV16 and HPV18 genotypes, while others with extended genotyping facilitate the identification of a range of additional high-risk genotypes. When assessing the impact of HPV vaccination, it is necessary to use a technique that allows genotyping of at least HPV16/18 types.

Validated techniques for cervical cancer screening, or techniques that have demonstrated analytical sensitivity, specificity, and reproducibility compared to a gold-standard, can be used in HPV detection/genotyping.

The choice of HPV detection/genotyping method should take into account which types of HPV are the target for detection, as well as supply and operation costs (also considering initial investment costs such as purchase of equipment or training of personnel who process the sample). The possibility of using HPV testing in the form of a self-collection test and scaling work capacity according to the volume of samples to be tested should also be considered. For self-collection, PCR-based tests should be used in preference to signal amplification assays as there is a significant loss of sensitivity with signal amplification tests (82).

Concerning ethical aspects, the decision to return results to the patient should be assessed. This will depend on the methodology of the study, the age of the population studied, and the clinical protocol in the country. In women younger than 30 years, the prevalence of HPV infection is very high with most infections being transient, so returning a positive HPV infection result to women in cases where this result will not change clinical management and consequently no follow-up will be performed could be counterproductive because of the distress this result could produce. It is therefore recommended to follow the current clinical management protocol and, in cases where the result does not change the course of clinical management, to assess whether or not to return the information to the patient.
### 4.4.5 Considerations for monitoring HPV infection in men

If there is interest in measuring the prevalence of HPV infection or HPV-related disease in men from the general population, either to assess the impact of the HPV vaccination program in countries that include preadolescent/early adolescent boys as a target population for the program or to assess possible herd effects associated with a girls-only vaccination program, the following considerations should be taken into account (83):

- Recruitment sources may be the same as for women in the general population sampling and screening strategies for *Chlamydia trachomatis*.
- HPV tests are not commonly used for screening men in clinical settings. However, HPV tests may be conducted on specimens from men for research purposes.
- The prevalence of infection may differ by anatomical location, and skin sampling of the external genitalia or anus is required. Obtaining a valid sample requires that the technique is adequate, which could be facilitated by self-collection of specimens, which has been shown to be an acceptable option in men.
- Obtaining a urine sample in men is not sensitive for HPV testing purposes.
- Whichever sampling methods are used, they should be standardized.

### 4.5 Anogenital warts

#### 4.5.1 General considerations

Anogenital warts or condylomata acuminata are the short-term clinical outcome available for assessing the impact of HPV vaccination in those countries administering the quadrivalent or nonavalent HPV vaccine (bivalent HPV vaccine is not expected to prevent anogenital warts).

| Expected outcomes | A decrease in the incidence of anogenital warts in the post-vaccine period is expected in countries that administer the quadrivalent or nonavalent vaccine. Anogenital warts are mostly caused by HPV6/11 infection, which are low-risk (non-oncogenic) types, so the extent of the impact of the vaccine observed on anogenital warts would not necessarily directly correspond to the extent of the impact on cervical cancer. |
| Important aspects to consider | To evaluate the impact on any outcome, the items discussed in Section 3.4 Study design considerations for evaluating the impact of the HPV vaccine, should be taken into account. |
| **RESOURCES REQUIRED** | Monitoring anogenital warts does not require specific tests or any particular infrastructure, unlike monitoring other indicators such as the prevalence of HPV infection or precancerous cervical lesions. In most countries, anogenital warts are not considered a notifiable disease, therefore no national registry exists. National public health systems will need to find a valid source of information to monitor this outcome. Surveillance for anogenital warts will make it possible to assess the impact of HPV vaccination in both women and men. |
| **TIME REQUIRED** | Anogenital warts usually appear within a few months after HPV infection (7, 84), and the peak incidence in women is usually seen before age 24 (85). Therefore, the impact of the HPV vaccine on this outcome can be assessed soon after the vaccinated cohorts start having sex, within 5–10 years after the implementation of the vaccination program. |
4.5.2 Description of indicator
The indicator used will be the incidence of anogenital warts per 100 000 population in a given period of time, stratified by age group, in women and in men. In men, if possible, the indicator could be further stratified by the sex or gender of the sexual partner (men who have sex with men, or men who have sex exclusively with women). The objective will be to compare the incidence of anogenital warts stratified by age in the adult population before and after the introduction of the vaccine. Depending on the study design, the impact can be estimated by evaluating the difference between the incidence in the pre-vaccine and post-vaccine period or assessing changes in the incidence rates over time.

In cases where it is not possible to estimate the incidence because the reference population (denominator) is unknown, the number of patients attended at the selected centers can be used as an approximation. See examples in (86–88).

4.5.3 Case definition
Any clinical diagnosis of anogenital warts (i.e., anal warts and/or genital warts) will be defined as a case of anogenital warts.

If clinical diagnosis of anogenital warts is not available, some approximation to clinical diagnosis may be considered if feasible. However, the limitations of using an approximation in a time trend study should always be considered, as trends may be affected by other factors independent of vaccination. Some approaches to approximating clinical diagnosis in existing published studies that have evaluated the impact of the quadrivalent vaccine and the limitations of each approach are described below:

- Prescription, application, or use of anogenital wart treatments (89): genital wart treatments may vary over time, due to changes in clinical practice guidelines or because of the varying availability/access to other treatment options (such as cryotherapy).

- Reimbursement of anogenital wart treatments by insurance (34, 90): in addition to variations in genital wart treatments, reimbursements may also vary for other reasons.

- Hospital admissions for anogenital warts (91, 92) and/or outpatient visits for anogenital warts (51, 91–93): the number of hospital admissions could vary over time due to changes in treatment patterns or in the healthcare system that affect access to hospital care (for example, more treatments in primary care would reduce hospital admissions for surgery, but this reduction in admissions would be independent of vaccination).

Investigators should clearly define a new case of anogenital warts, to differentiate it from the recurrent/prevalent cases. Articles that have evaluated the impact of the quadrivalent vaccine on anogenital warts have mainly considered the following definitions as a new case:

- A patient’s first diagnosis of anogenital warts (86–88), or
- A patient’s first diagnosis of anogenital warts or, in patients with more than one diagnosis, the first diagnosis which in the previous 12 months is not preceded by another diagnosis (34, 94, 95).

4.5.4 Study population
Monitoring the population-based incidence of anogenital warts is often not a feasible option when there is no established universal surveillance system in a country, since patients with anogenital warts often consult in a variety of settings such as primary care centers, community care centers, emergency rooms, hospitals, or STI clinics. However, monitoring the incidence of anogenital warts in selected locations, such as a sentinel network of STI clinics, can provide valid information about the impact of HPV vaccination, provided that this network is stable and the reference population remains unchanged over the study period. Some countries in Latin America and the Caribbean have an STI surveillance system and the same system could be used for monitoring anogenital warts, provided that the necessary information is computerized.
Table 9 describes the sources of information used in studies that have evaluated the impact of HPV vaccination on the incidence of anogenital warts, noting their advantages and disadvantages. All these studies have evaluated the impact on anogenital warts from databases (administrative health, hospital, or insurance databases, among others).

**Table 9. Sources of information used in studies of short-term vaccine impact on anogenital warts**

<table>
<thead>
<tr>
<th>Source of information</th>
<th>Comments</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Examples of sources of information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sentinel clinics (STI diagnosis and treatment clinics/sexual health centers)</td>
<td>The participating clinics should be the same throughout the study period</td>
<td>Large volume of diagnosed cases Monitoring of other STIs</td>
<td>Representativeness: higher risk sexual behavior, overestimation of anogenital warts</td>
<td>National sentinel surveillance data (86) Single sentinel center (87)</td>
</tr>
<tr>
<td>Primary/community care doctor activity database</td>
<td></td>
<td>General population</td>
<td>The number of diagnosed cases could be low</td>
<td>(96, 97)</td>
</tr>
<tr>
<td>Administrative health databases</td>
<td>Validity will depend on whether it is population-based and on the coverage</td>
<td>Representativeness</td>
<td></td>
<td>(98, 99)</td>
</tr>
<tr>
<td>Health insurance/health services billing database</td>
<td>Validity will depend on whether it is population-based and on the coverage</td>
<td></td>
<td>There could be changes in the reference population during the study period</td>
<td>(34, 90, 100, 101)</td>
</tr>
<tr>
<td>Hospital database (admissions, procedures, outpatient visits)</td>
<td></td>
<td>Feasibility</td>
<td>Influenced by changes in treatment patterns/assistance circuit</td>
<td>(51, 91, 92, 102)</td>
</tr>
<tr>
<td>National health records (e.g., Chile)</td>
<td>Very few countries have such records</td>
<td>Representativeness</td>
<td></td>
<td>(95, 103)</td>
</tr>
<tr>
<td>Treatment database</td>
<td></td>
<td></td>
<td>Influenced by changes in treatment patterns Genital wart treatments may not be specific.</td>
<td>(89)</td>
</tr>
</tbody>
</table>
Use of a control STI

In time trend studies, the incidence of anogenital warts is measured in different populations, so the differences observed between these populations may be due to differences in sexual behavior. Therefore, when analyzing time trends in anogenital warts, consideration should be given, as much as is feasible, to also analyzing trends in the incidence of other STIs, to detect changes in sexual behavior patterns over time that may have affected anogenital wart trends. Some of the STIs that can be used as controls are *Chlamydia trachomatis* infection or first episode of genital herpes (see examples of studies that have used a control STI in [51, 88, 96, 104]).

The choice of control STIs will depend on the specific epidemiology of the region, as the STI(s) selected for control should have a similar epidemiology to anogenital warts, with sufficient frequency in a young population, and should also have shared risk factors with HPV infection. The existence and changes in STI screening programs should also be assessed, as STI rates could change based on changes in the screening program (e.g., *Chlamydia trachomatis*) and could vary independent of sexual behavior.

### 4.6 Covariates of interest

In studies assessing the impact of HPV vaccination, the distribution of risk factors in a population could vary over time, and this would influence the apparent effect of vaccination (for example, if an impact of the vaccine is observed but during the study period the risk of disease acquisition or development increased, this would suggest that the impact of the vaccine is greater than that observed). The availability of assessing covariates will depend largely on the source of information from which the study is conducted.

The covariates considered important to assess for possible use in analysis include:

- Sexual behavior (age of first sexual encounter, condom use, number of sexual partners in the last 12 months and/or throughout life); if these variables are not available, use other proxy variables
- Use of hormonal contraceptives
- Smoking
- Socioeconomic factors (e.g., type of health insurance, residential area, income, poverty rate, access to health services)
- Previous *Chlamydia trachomatis* infection or other STIs
- HIV infection
- Screening history
- Age at diagnosis
- Region.

In pre–post studies where the population studied may not be representative of the general population for which the impact is to be assessed, it is recommended that HPV vaccination coverage be estimated, so that it can be compared to coverage at the national level. In order to calculate the coverage, the following will need to be collected:

- History of HPV vaccination: vaccinated yes/no
- Number of doses administered
- Type of vaccine
- Age at vaccination.

Confirmation of vaccination status at the individual level may be done through individual vaccination records, immunization records, school vaccination database, seroprevalence studies, or self-reported history.
5. Algorithm for selecting outcomes to evaluate impact

Once the country has decided on a need for country-specific HPV vaccine impact estimates (see Section 3.4 Study design considerations for evaluating the impact of the HPV vaccine), the first thing to evaluate is whether the HPV vaccine coverage in the country is high. If HPV vaccination coverage is suboptimal, the priority should be to increase coverage rather than carrying out any impact studies. In addition, as impact measurement is a long-term investment, the availability of necessary resources should be guaranteed before starting an impact study.

Figure 5 aims to aid program managers, researchers, and policymakers in their prioritization of outcomes, indicators, and related study characteristics for measuring the impact of HPV vaccination. It lists the main aspects to consider in the decision on which indicator will be evaluated and proposes a decision algorithm for prioritizing indicators, taking into account their importance in relation to cervical cancer.
Assuming HPV vaccine coverage is optimal and resources are available, the main aspects to consider in the decision on which indicator will be evaluated are:

- Purpose of the assessment
- Infrastructure available in the country
- Availability of baseline data
- Years since the program introduction and years of aging in the vaccinated cohorts
- Sources of information available in the country
- Budgetary implications of the different options, considering start-up costs and recurrent investments
- Ability to maintain indicator monitoring over time
- Strategies that could be applied for recruitment
- Calendar and timeline for expected results

The following decision algorithm aims to aid program managers, researchers, and policymakers in their decisions regarding the prioritization of outcomes, indicators, and related study characteristics for measuring the impact of HPV vaccination. It should be noted that the following is a proposal for prioritizing indicators for study taking into account their importance in relation to cervical cancer, which is the objective of the vaccination program. An alternative could be prioritizing indicators considering the timeliness of information regarding the impact of HPV vaccination; in this case, short-term outcomes (i.e., HPV infection, anogenital warts) should be considered in the first step.

*In countries administering the quadrivalent or the nonavalent vaccine.
CIN2+: Cervical intrapithelial lesion grade 2 or superior
6. Suggestions for an HPV vaccine impact evaluation report

In any report or article made for the communication and/or dissemination of vaccine impact study results, it will be necessary to provide certain information at a minimum for a proper understanding and interpretation of the results obtained. The following checklist has been created following the guidelines of Consolidated Standards of Reporting Trials (CONSORT), Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and REporting of studies Conducted using Observational Routinely-collected health Data (RECORD). These guidelines are accessible at http://www.equator-network.org.

INTRODUCTION

a) Current status/burden of cervical cancer disease in the country or region with incidence and mortality data.

b) Existing cervical cancer prevention strategies in the country or region:

Data from the cervical cancer screening program:
• Start date of the program.
• Characteristics of the screening program:
  • type of screening (population, opportunistic),
  • primary test (HPV, cytology, or VIA),
  • target population (age range),
  • time interval between tests.
• Differences in screening strategies will be detailed according to the region, if applicable.
• Coverage by age group.
• Changes in program features, indicating the year of change.

Data about the HPV vaccination program:
• Start date of the program.
• Target population: age and sex of routine vaccination and vaccine administration strategy. If the vaccine is administered in schools, indicate the school grade and the age targeted.

• If catch-up vaccination has been carried out, indicate the years in which it was carried out and the target population.
• Type of HPV vaccine administered: bivalent, quadrivalent, or nonavalent. In case of changes in the vaccine administered, the periods when each vaccine was used should be detailed.
• Full vaccine schedule coverage (two or three doses) according to age and year of administration.
• Changes in the program (target population, age, strategy, type of vaccine) and date.

c) Objective of the evaluation.

METHODOLOGY

a) Study design:
• Type of study that has been carried out (trends, pre-post).
• Years of fieldwork (data collection, sampling).

b) Sources and selection of the study population:

• Eligibility criteria: (age), sex, and exclusion criteria for participants.
• Sampling of the study population: (convenience or population).
• Scope of the evaluation: (sites/types of centers where the sampling has been carried out).
• Health records: it may be useful to provide a flow chart.
• Ethical considerations: consent procedures, ethical review and approval of study protocol, and incentives provided for study participation (if any).

c) Outcome selected:
• Reason for the selection of this outcome.
• Definition of the outcome.
• Procedure for measurement (e.g., details of detection techniques used for the detection of HPV16/18 infections or use of preestablished registers or surveillance networks).

d) Variables and data:
• Indicate the main data collected, with special emphasis on data that can serve as a control for other external factors or to minimize bias, such as data collection on other STIs.

e) Statistical analysis:
• Statistical methods for comparison between groups and estimation of impact measurement.
• Additional analysis methods, such as subgroups or sensitivity analysis.
• Estimated sample size or power achieved depending on the final sample used.

RESULTS
a) Data on participation (consider using a flowchart):
• Number of subjects invited to participate.
• Number of subjects that participated (if known, provide reasons for nonparticipation).
• Number of subjects finally included in the analysis after exclusions.

b) Description of the study population, separated by vaccinated population and reference population, indicating the number of missing observations:
• Demographic, clinical and/or social characteristics.
• Vaccination status and doses administered, if known.
• Other variables of interest (adjustment/confounding variables).

c) Outcomes, measures of occurrence, and measures of impact, if possible, by age or by birth cohort:
• Provide the number of outcomes and frequency measurements for each group.

• Provide the measure of crude (unadjusted) impact.
• If an adjusted impact measurement is provided, the accuracy of that measurement (95% confidence interval) and the adjustment factors included in the model should be indicated.

a) Others:
• In the case of categorization of continuous variables, such as age, the limits of these categories should be indicated.
• Include data from subgroup analysis (e.g., by age) or sensitivity (e.g., exclusion of a first vaccinated cohort with low coverage).

DISCUSSION
a) Summarize the main results or findings of the evaluation.

b) Analyze the results into context:
• Compare with previous studies, if possible, in regions or countries with similar characteristics.
• Consider the time between vaccination and measurement of the outcome when interpreting the results.

c) Include the limitations of the study, taking into account possible biases or sources of inaccuracy, and detail how they may affect the results.

d) Assess the representativeness of the results.

e) For the conclusion, make a cautious general interpretation of the results, taking into account the objectives and items detailed in the discussion.

FUNDING
Include the sources of funding for the evaluation as well as other material support (e.g., material donations) and their role in the evaluation.
Impact assessment of HPV vaccination can be a challenge for countries because of the time between vaccination and when the main outcome can be assessed (cervical cancer), the scarcity of registration systems for other outcomes, the coexistence with another preventive strategy against cervical cancer (screening), and the need to create collaborative networks with other involved programs to be able to assess the impact on different outcomes (cancer prevention programs, cancer registries, reproductive health, STIs, or adolescent health, among others). In addition, this is a complex task that may involve a multidisciplinary team of HPV epidemiologists, statisticians, and technicians for the proper design and development of impact studies, as well as ensuring that the necessary resources are available to carry out the studies.

This document is a methodological and conceptual guide for countries that wish to carry out impact studies, proposing possible studies and prioritizing the outcomes to be evaluated according to their relevance to the vaccination program. The feasibility of carrying out impact studies on one or several outcomes will be determined by the existing resources in the country. Countries should ensure that they have a good record of HPV vaccination coverage before considering an impact assessment and should make it a priority to achieve optimal levels of vaccination coverage before the impact evaluation.
References


REFERENCES


REFERENCES


Further reading


Annex 1.
**Design of vaccine effectiveness studies**

Vaccine effectiveness studies are observational studies that compare the frequency of a given outcome in vaccinated and unvaccinated individuals.

In order to carry out a vaccine effectiveness study, the **vaccination status of each individual must be known**. When only the vaccination status of cases is known the screening method can be used.\(^1\)

The various information sources about vaccination status each have limitations. Therefore, information on vaccination status can be obtained from various sources or a combination of sources. A discussion of the constraints of various information sources is presented here:

1. **Interviews and self-reported histories**: subject to recall bias and information may not be accurate. In addition, it may not provide accurate data on the dates of vaccination, number of doses received, or the intervals between doses.
2. **Vaccination certificates or personal vaccine cards**: can be lost or incomplete.
3. **Health databases, medical charts, or electronic health records that include information on HPV vaccination**: may be incomplete if the vaccination strategy is school-based.
4. **Vaccination registries**: this would be the ideal source of data, especially if it would allow linking with other databases. However, few countries have centralized vaccination registries. Registry data can vary in timeliness and completeness.
5. **Health insurance databases, including reimbursement databases**: may be incomplete as only include insured individuals.

The **study designs** that can be used to evaluate the effectiveness of the vaccine are:

- **Cohort study**: compares rates of HPV-related outcomes by sex and age group in vaccinated and unvaccinated individuals.
- **Case–control study**: compares the odds of vaccination in cases (individuals with an HPV-related outcome) and in controls (noninfected individuals), by sex and age group. Given the latency time for precancerous cervical lesions and cervical cancer, if the study is based on interviews rather than records, recall bias will be present. In these studies, the population frame for the selection of controls will be critical, as it should reflect the vaccine coverage of the source population that presents cases.

Depending on the selection of the controls, studies are classified as:

- **Traditional case–control study**: random selection of the population that is not sick at the end of the recruitment period.
- **Case–cohort study**: random selection of the total population at risk of the disease at the beginning of the study.
- **Nested case–control study**: randomized selection of people who are still at risk of disease at the times when cases occur during follow-up.

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Annex 2.
List of population-based cancer registries included in Vol. XI of Cancer Incidence in Five Continents

<table>
<thead>
<tr>
<th>Country/territory</th>
<th>Population-based cancer registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>Chaco</td>
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<td></td>
<td>Entre Rios</td>
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<td></td>
<td>Cordoba</td>
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<td></td>
<td>Mendoza</td>
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<td></td>
<td>Tierra del Fuego</td>
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<td>Brazil</td>
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<td>Poços de Caldas</td>
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<td>Bio Bio</td>
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<td>Concepcion</td>
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<td>Colombia</td>
<td>Cali</td>
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<td>Bucaramanga</td>
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<td>Costa Rica</td>
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<td>French Guiana</td>
<td>French Guiana</td>
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<td>Jamaica</td>
<td>Kingston and St. Andrew</td>
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<td>Martinique</td>
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<td>Peru</td>
<td>Lima</td>
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<td>Puerto Rico</td>
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<td>Uruguay</td>
<td>Uruguay</td>
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</tbody>
</table>

Annex 3.
Description of HPV vaccination programs in Latin America and the Caribbean

<table>
<thead>
<tr>
<th>Country</th>
<th>Year of nationwide introduction</th>
<th>Target age for first years of the national program</th>
<th>Year of birth of first female vaccinated cohort</th>
<th>Age of first vaccinated birth cohort in 2020</th>
<th>in 2025</th>
<th>in 2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigua and Barbuda</td>
<td>2018</td>
<td>9–13</td>
<td>2005</td>
<td>15</td>
<td>20</td>
<td>25</td>
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<tr>
<td>Argentina</td>
<td>2011</td>
<td>11</td>
<td>2000</td>
<td>20</td>
<td>25</td>
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<td>Bahamas</td>
<td>2015</td>
<td>9–12</td>
<td>2003</td>
<td>17</td>
<td>22</td>
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<td>Belize</td>
<td>2016</td>
<td>10</td>
<td>2006</td>
<td>14</td>
<td>19</td>
<td>24</td>
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<td>Bolivia (Plurinational State of)</td>
<td>2017</td>
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<td>Canadaa</td>
<td>2007</td>
<td>varies by region</td>
<td>1992</td>
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<td>38</td>
</tr>
<tr>
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<td>Year of birth of first female vaccinated cohort</td>
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<td>Age of first vaccinated birth cohort in 2025</td>
<td>Age of first vaccinated birth cohort in 2030</td>
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Notes:

a. Year of introduction in Canada varied by region.


c. Year of national introduction (Mexico implemented HPV vaccination in 125 municipalities in 2008 and expanded its HPV vaccination program to include 182 municipalities in 2009).

d. In the United States of America, HPV vaccination was recommended until age 26 years.

This publication aims to provide conceptual and methodological guidance on measuring the impact of the HPV vaccine in Latin American and Caribbean countries and territories. It provides a broad overview of the designs used and available for assessing the impact of HPV vaccination, and prioritizes outcomes by relevance to vaccination programs and proposing study designs for each outcome under consideration. The feasibility of each approach will depend on the objectives of the HPV vaccination program and the assessment in the country or territory, as well as the resources, data, and time available.