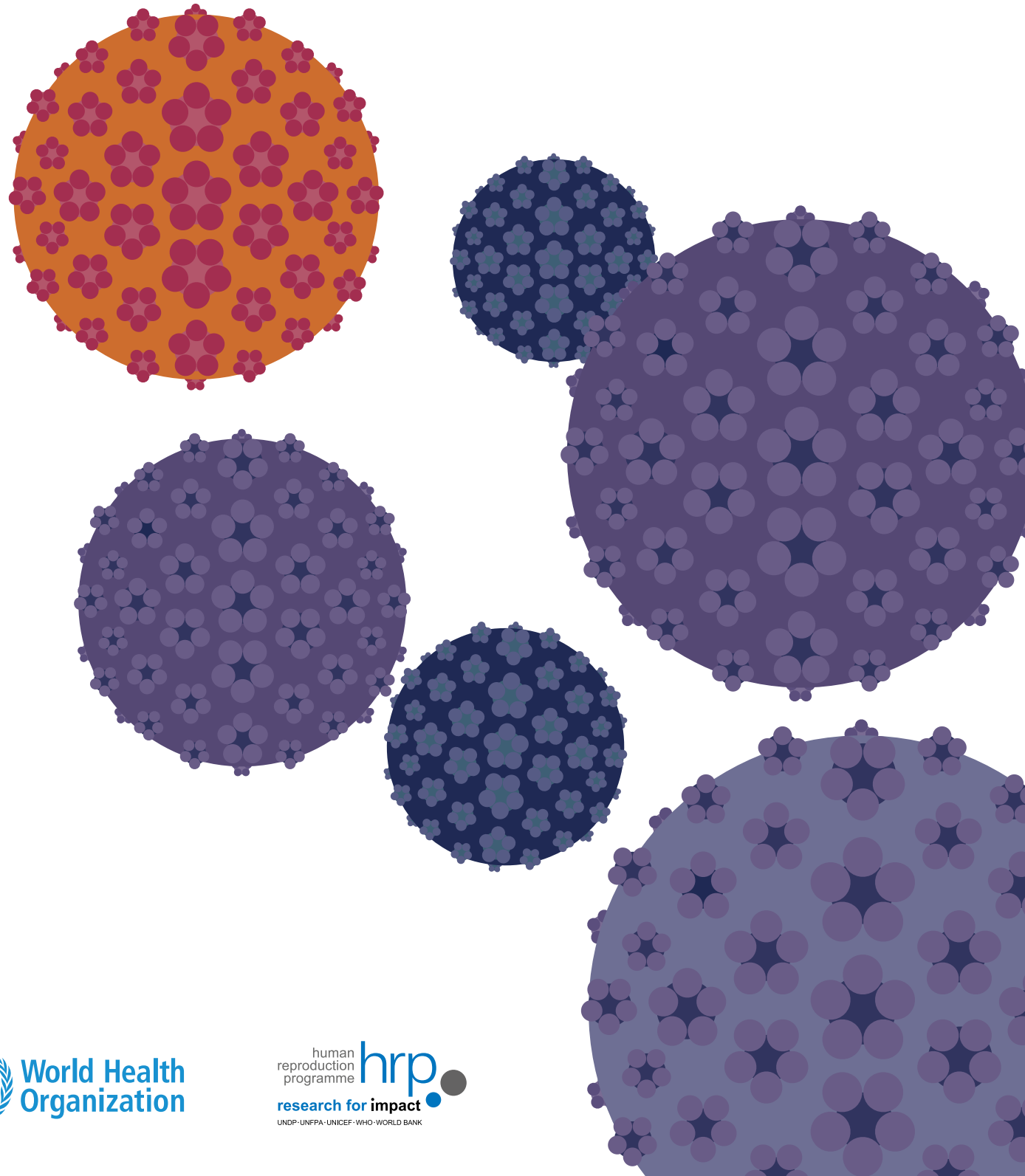
WHO preferred product characteristics for therapeutic HPV vaccines



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Declarations of interest

All external attendees at the WHO therapeutic HPV vaccine consultations completed WHO Declaration of Interests statements, and their participation in the consultations and their commenting on PPC document drafts were in accordance with WHO's guidelines for Declaration of Interests for WHO experts.

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[1] For the WHO Product Development for Vaccines Advisory Committee, see: https://www.who.int/groups/product-development-for-vaccines-advisory-committee (accessed 31 December 2023).

Abbreviations

ART . . . . . Antiretroviral therapy
CIN: . . . . . Cervical intraepithelial neoplasia
CIN2/3: . . . . . Cervical intraepithelial neoplasia grade 2 and grade 3
CKC: . . . . . Cold knife conization
DART: . . . . . Development and reproductive toxicology
HDI: . . . . . Human development index
HICs: . . . . . High-income countries
HIV: . . . . . Human immunodeficiency virus
HPV: . . . . . Human papillomavirus
LEEP: . . . . . Loop electrosurgical excision procedure
LLETZ: . . . . . Large loop excision of the transformation zone
LMICs: . . . . . Low- and middle-income countries
MSM: . . . . . Men who have sex with men
NAAT: . . . . . Nucleic acid amplification test
PDVAC: . . . . . WHO's Product Development for Vaccines Advisory Committee
PPCs: . . . . . Preferred product characteristics
SAGE: . . . . . WHO's Strategic Advisory Group of Experts on Immunization
STI: . . . . . Sexually transmitted infection
VIA: . . . . . Visual inspection with acetic acid
WHO: . . . . . World Health Organization
WLHIV: . . . . . Women living with HIV

Executive summary

The development of therapeutic vaccines for human papillomavirus (HPV) may provide an important addition to current methods for preventing and treating HPV-related cancers. Cervical cancer, caused almost exclusively by sexual transmission of oncogenic types of HPV, is an important public health problem globally *(1)*. In 2022, an estimated 662 000 women[2] were diagnosed with cervical cancer, and approximately 349 000 women died from the disease *(2)*. Over 90% of cervical cancer-associated deaths occurred in women in low- and middle-income countries (LMICs), largely due to inequitable access to effective cervical cancer prevention and management measures.

The World Health Organization (WHO) has published the *Global strategy to accelerate the elimination of cervical cancer as a public health problem (3).* On the path to elimination, the strategy could result in more than 62 million lives saved by 2120 *(4,5)* if three key targets are achieved by 2030, namely: vaccination of 90% of girls with prophylactic HPV vaccines; screening of 70% of women for cervical cancer with a high-performance test twice in their lifetime; and provision of treatment to 90% of women with cervical precancers and invasive cancers.

Implementation of the global strategy currently lags far behind the 2030 targets. The cost and complexity of cervical cancer screening and treatment programmes, which may require several visits for women testing positive for oncogenic HPV infection, as well as persistent inequities in access to cervical cancer prevention programmes are major hurdles to reaching the strategy's goals, particularly in LMICs *(6)*.

Therapeutic HPV vaccines are currently in early clinical development and might offer an additional tool to address gaps in cervical cancer programmes. Unlike existing prophylactic HPV vaccines, which prevent new infections, therapeutic vaccines would be designed to clear or treat existing HPV infections, HPV-associated precancers or invasive cervical cancer. This document focuses on potential therapeutic vaccines for HPV infection and/or cervical precancers, which could be part of efforts to prevent cervical cancer.

WHO documents on preferred product characteristics (PPCs) provide guidance to vaccine developers, policy-makers, and programme implementers on preferences for new vaccines in priority disease areas, including from the perspectives of LMICs. Articulation of product attributes that meet the needs of LMICs, while also addressing concerns of high-income countries (HICs), can advance the development of vaccines that are suitable for global use.

As a first step to defining therapeutic PPCs for HPV vaccine, WHO convened a group of experts to assess the public health needs that might be addressed by therapeutic HPV vaccines with the aim of saving additional lives on the path towards cervical cancer elimination – especially during the next 3–4 decades as prophylactic vaccination is scaled up. The expert group identified two overarching contexts, namely:

- in settings where it has been difficult to scale up cervical cancer screening and treatment, there is a need to reach women who are unlikely to have received prophylactic HPV vaccines to reduce the overall proportion that will develop or already have cervical precancers; and

- in settings where screening and treatment occur, it would be valuable to have an alternative, simpler treatment to reduce loss to follow-up and increase the overall proportion of women who are effectively treated following a positive test.

Therapeutic HPV vaccines would ideally have high efficacy in both: 1) clearing high-risk HPV infection to prevent development of cervical precancers; and 2) treating (causing regression of) high-grade precancers that have already developed. However, depending on their mechanisms of action, the vaccines may have differential activity against these outcomes. Thus, this document describes PPCs for two types of therapeutic HPV vaccines:

- **Therapeutic HPV vaccines that primarily clear oncogenic HPV infection**: First-generation vaccines would be expected at a minimum to clear infection and/or prevent high-grade cervical precancer due to HPV types 16 and 18,

[2] All people have the right to sexual and reproductive health care. This document recognizes that most of the available evidence on cervical cancer is based on study populations of cisgender women, and that cisgender women, transgender men, non-binary, gender-fluid and intersex individuals born with a female reproductive system require cervical cancer prevention services. However, to be concise and facilitate readability, the term "women" is used to refer to all gender-diverse people at risk of cervical cancer. Cervical cancer prevention services must consider the needs of – and provide equitable care to – all people independently of their gender identity or its expression.

but activity against additional HPV types and in treating existing precancers would broaden impact and be desirable. These vaccines could be used in adult women (e.g. ages 25–49 years) through population-based vaccine delivery without a preceding diagnostic test or, where feasible, possibly through targeted delivery after a positive HPV test.

- **Therapeutic HPV vaccines that primarily cause regression of high-grade cervical precancers** (at a minimum those associated with HPV types 16 and 18): These vaccines could be used as an alternative or adjunct to existing cervical treatments among women who have, or who might have, cervical precancer according to positive screening tests. However, depending on their attributes and the setting, these vaccines could be used more broadly, with or without testing.

Both types of vaccine could potentially play a role in addressing each of the identified gaps in cervical cancer prevention programmes. The choice of target population, including the optimal age range and the delivery strategy in a given setting (e.g. broad population-based vaccination or targeted vaccination based on HPV testing), will not only depend on intrinsic vaccine characteristics – such as efficacy in clearing infection rather than causing regression of high-grade precancers – but also on factors related to the environment into which these vaccines are introduced. These factors could include the extent to which prophylactic HPV vaccination and cervical cancer screening and treatment programmes have been scaled up; the prevalence of oncogenic HPV infection and/or cervical precancers at different ages, which may vary according to the proportion of women living with HIV (WLHIV); cost-effectiveness; and additional programmatic and health system factors.

Women at a gynecology clinic in Nepal.
Credit: © WHO / Tom Pietrasik

1. The purpose of WHO preferred product characteristics

The World Health Organization (WHO) has a mandate to accelerate the development and optimal use of safe and effective vaccines that could have global public health impact. Priority areas include facilitating the advancement of desirable vaccine candidates towards licensure and generating evidence to inform future policy recommendations and vaccine introduction. Identifying and articulating vaccine preferences that meet global health needs early in product development are fundamental to this mission.

WHO documents on the preferred product characteristics (PPCs) of vaccines describe such parameters as vaccine indications and target populations, considerations for safety and efficacy evaluation, and delivery strategies *(7)*. WHO PPCs are intended to encourage product innovation and facilitate vaccine development, particularly for use in low- and middle-income countries (LMICs). These countries often have the largest unmet public health need. Because vaccine manufacturers often develop vaccines for initial use in high-income countries (HICs), first-generation vaccines may not be suitable for use in LMICs and broader introduction and impact of the vaccines can be substantially delayed. WHO PPCs emphasize the perspectives of LMICs in addition to those of HICs in order to encourage the development of vaccines for global use.

PPCs are pathogen-specific rather than product-specific and are intended to provide guidance early in product development. As such, the PPC guidance is intended to be broad in order to encourage innovation and stimulate further dialogue regarding the desired product attributes that will optimally address the public health need and facilitate real-world use. PPCs can inform subsequent target product profiles as product development progresses. PPCs can also be updated with more specific guidance when further clinical trial data become available, or in the event of changes in the identified need or in the research and development landscape.

The primary target audience for WHO PPCs is any entity intending to develop a vaccine for use in LMICs and planning to seek WHO policy recommendations and prequalification for its products *(8)*. The PPCs also aim to reach policy-makers and programme implementers in order to highlight data needs and other considerations for future use. However, while PPCs define aspirational goals for vaccine attributes, they do not supersede the evidence-based assessment by WHO's Strategic Advisory Group of Experts on Immunization (SAGE) or other existing WHO guidance on vaccines *(9,10)*.

From October 2021 to April 2023, WHO convened a series of global multidisciplinary consultations of scientists, clinicians, epidemiologists, vaccinologists and public health programme and policy experts from LMICs and HICs, with the goal of developing PPCs for therapeutic human papillomavirus (HPV) vaccines. Discussions at these meetings and iterative feedback from the experts on drafts of the therapeutic HPV vaccine PPCs played an important role in the development of this document. The PPC document was posted for public comment in September 2023 and endorsed by the WHO Product Development for Vaccines Advisory Committee (PDVAC) in December 2023.

2. Therapeutic HPV vaccines – the global public health need

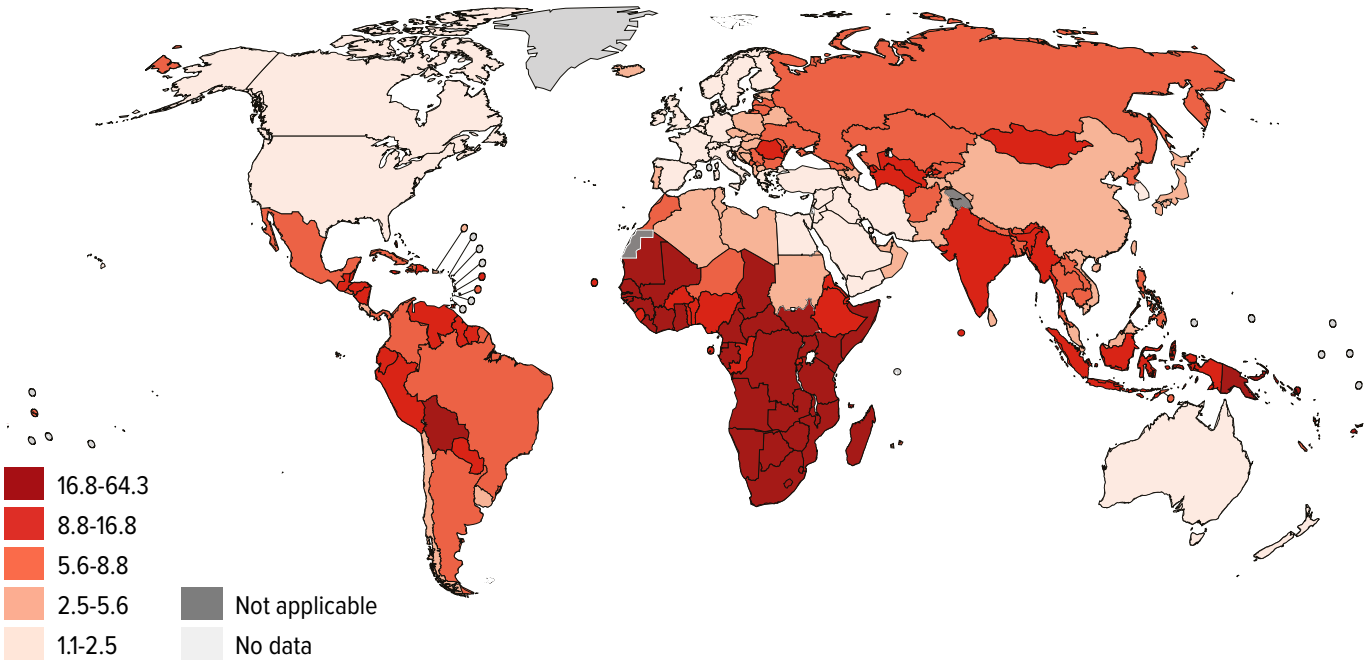
Addressing cervical cancer is a global health priority. Despite being a preventable disease, cervical cancer remains one of the most common causes of cancer-related death in women worldwide. One woman dies of cervical cancer every 90 seconds *(2)*. Furthermore, few diseases reflect global inequities as much as cervical cancer does, with over 90% of cervical cancer deaths occurring in LMICs *(2)* (Figure 1).

At the World Health Assembly in 2020 WHO's 194 Member States approved the *Global strategy to accelerate the elimination of cervical cancer as a public health problem (3)*. The strategy set a goal of reducing cervical cancer cases below a global threshold of four cases per 100 000 women-years. Because cervical cancer is almost exclusively caused by cervical infection with oncogenic types of HPV, key components of the strategy include efforts to prevent, detect and treat precancerous cells infected with HPV.

Cervical cancer can be eliminated as a public health problem within the next century, with the potential to save 62 million lives in the process, if three key targets are successfully reached by 2030 and sustained *(4,5)*. The targets are:

- 90% of girls are fully vaccinated with a prophylactic HPV vaccine by 15 years of age;
- 70% of women are screened using a high-performance test (e.g. HPV DNA testing) by the age of 35 years, and again by 45 years; and
- 90% of women identified with cervical disease receive treatment (90% of women with precancer treated, and 90% of women with invasive cancer managed).

Figure 1. Estimated age-standardized cervical cancer mortality rates in 2022 (all ages)



Source: Globocan/International Agency for Research on Cancer, 2022 *(2)*.

Although prophylactic vaccination against HPV and screening and treatment for HPV-related precancerous lesions are cost-effective methods to prevent cervical cancer, significant challenges exist in scaling up these interventions. Many countries, particularly LMICs, are far from reaching the strategy's targets for implementing the interventions. Thus, while efforts are redoubled to improve scale-up of existing interventions, the strategy also calls for exploration of new innovations – including advances in developing new medicines, vaccines, diagnostics and treatment modalities – to reach global goals *(3)*.

One such potential innovation is the development of therapeutic HPV vaccines designed to clear or treat existing HPV infections or HPV-associated cervical disease, unlike prophylactic vaccines that prevent infection. During the global multidisciplinary consultations convened by WHO, experts from LMICs and HICs discussed the need for, and the goals and potential value of, therapeutic HPV vaccines and the key considerations for developing therapeutic HPV vaccine PPCs *(11)*. The consultations focused on potential therapeutic vaccines for HPV infection and/or cervical precancers. Vaccines to treat invasive cervical cancer are beyond the scope of this document.

The experts agreed that the strategic public health goal of therapeutic HPV vaccines should be to save additional lives as progress is made towards cervical cancer elimination, particularly in the next 30–40 years – i.e. the interim period before the full impact of prophylactic HPV vaccine scale-up is likely to be seen. Development of therapeutic vaccines would also aim to address gaps in scale-up of cervical cancer screening and treatment programmes since many LMICs currently have almost no national programmes in place. The full rationale for the public health goals and key background considerations for therapeutic HPV vaccine PPCs can be found in the meeting report of the initial WHO consultations *(11)*.

3. Background: HPV and cervical cancer

3.1 HPV infection and routes of transmission

Human papillomaviruses are DNA viruses belonging to the family Papillomaviridae. HPV exclusively replicates in squamous epithelium and is mainly associated with cutaneous and mucosal infections. While there are over 200 types, anogenital HPVs are broadly classified into low-risk and high-risk types. The low-risk HPVs (e.g. types 6 and 11) are predominantly responsible for cutaneous and anogenital warts, and the high-risk types (e.g. types 16 and 18) are responsible for cervical cancer, other anogenital cancers (including anal, vaginal, vulvar and penile cancers) and oropharyngeal cancers *(12)*. Multiple HPV genotype infections are common, particularly in women living with HIV (WLHIV) *(13)*.

High-risk HPV types infect basal epithelial cells of the anogenital mucosa via micro-abrasions in the epithelial lining. Consequently, the predominant route of transmission is through penetrative sex, although transmission has also been associated with other types of sexual activity *(14)*. The probability of HPV transmission per sex act has been estimated to be around 40% (range 5–100%) *(15)*. In a large meta-analysis, among male partners of women testing HPV-positive, 36% had concurrent type-specific infection, while among female partners of HPV-positive men, 55% had concurrent infection *(16)*. The risk of oropharyngeal cancer is increased in women with cervical infection and in their partners, providing evidence of genital-oral transmission *(17)*.

3.2 High-risk HPV types associated with cervical and other cancers

High-risk HPV types, but not low-risk types, encode genes whose protein products can transform normal healthy cells and cause cancer (i.e. they are oncogenic) *(18)*. Virtually all cervical cancers are caused by infection with a high-risk HPV, of which there are at least 12 *(19)*. Two high-risk types, HPV types 16 and 18, are associated with 70% of all cervical cancers (20). An additional five high-risk types – HPV types 31, 33, 45, 52 and 58 – are estimated to be responsible for a further 20% of cervical cancers *(21)*. Several additional HPV types – i.e. types 35, 39, 51, 56 and 59 – are also listed as carcinogenic to humans *(19)*. In addition to cervical cancer, oncogenic high-risk HPVs, particularly HPV type 16, are associated with other anogenital cancers and a proportion of oropharyngeal cancers. Overall, HPV causes around 5% of all cancers globally *(22)*.

3.3 Natural history of HPV infection

3.3.1 General population

Most HPV infections are asymptomatic and resolve spontaneously. Approximately 40–70% of incident HPV infections in women clear on their own in one year, depending on the population studied *(23)*. Clearance rates as high as 70–100% have been observed in young women 2–5 years post-infection *(24)*. Infections with the same HPV type tend to clear at the same rate, regardless of age *(25)*. However, high-risk HPV infections are more likely than low-risk HPV infections to lead to persistent infections that progress to precancer *(26)*. Among women with persistent infection, progression to cervical intraepithelial neoplasia (CIN) grade 2 or grade 3 (CIN2/3) – high-grade cervical precancer – is estimated to occur in 8–28%, depending on the HPV type. This progression may take months or years. Without intervention, an additional 3–5% of these lesions will progress to invasive cervical cancer *(24)*. In women with normal immune systems, cervical cancer generally takes 15–20 years to develop from the time of HPV infection.

3.3.2 Women living with HIV

For women with weakened immune systems, such as untreated WLHIV, cervical cancer may develop faster (i.e. in 5–10 years) *(27)*. HIV infection is associated with a six-fold increase in the risk of cervical cancer, in part due to HIV's modifying effect on HPV pathogenesis *(22)*. In addition to an increased risk of HPV acquisition among WLHIV, the time to clearing infection is longer *(28)* and the chances of recurrent infection are higher compared to HIV-uninfected women *(29)*. The risk of HPV acquisition and progression inversely correlates with CD4 T cell count, although this association can be mitigated in people who are virally suppressed on antiretroviral therapy (ART) *(27)*.

3.4 Epidemiology of HPV infection

Data from high-income settings show that some 50–79% of women acquire a genital HPV infection over their lifetime, with 40% of women infected within the first two years of sexual debut *(30)*. Consequently, adolescent girls and women under 25 years of age have the highest incidence rates of HPV infection *(31)*. A summary report from 2023 showed that the estimated global prevalence of HPV type 16 or 18 at any point in time was 3.9% among women with normal cervical cytology, 25.8% in women with low-grade cervical lesions (i.e. CIN1), 51.9% in women with high-grade cervical lesions (i.e. CIN2/CIN3) and 69.4% in women with cervical cancer *(32)*.

The global prevalence of genital HPV infection in men is similar to that seen in women *(33)*, with increased risk of infection and progression to disease such as anal cancer in men who have sex with men (MSM) and men living with HIV *(34)*. For men, HPV infection rates are high across all age groups *(35)*.

Cervical cancer screening in Malaysia.
Credit: © WHO / Ahmad Yusni

3.5 Epidemiology of cervical cancer

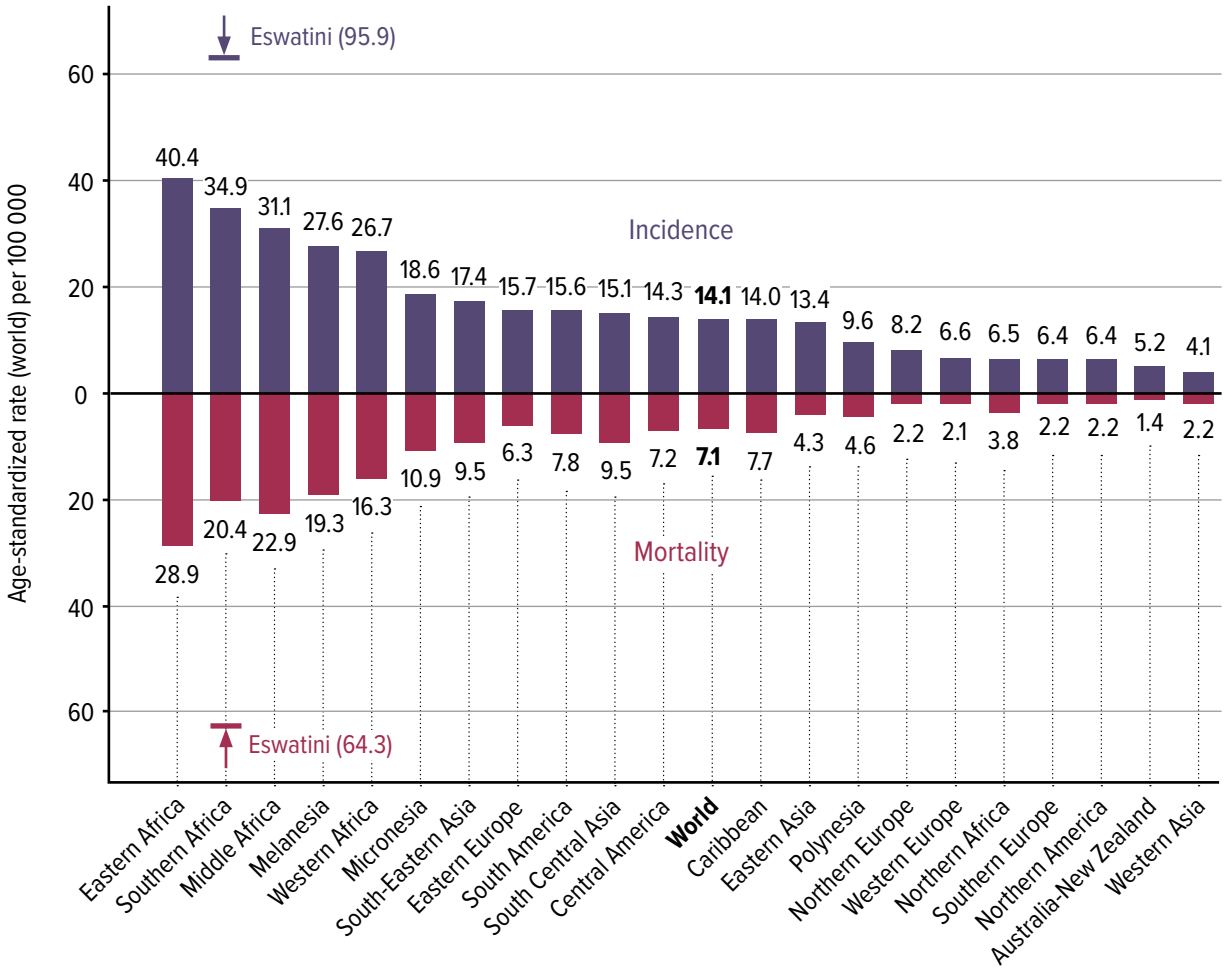
In 2022 globally, there were an estimated 662 000 new cases of cervical cancer (age-standardized incidence rate 14.1 per 100 000 women) and 349 000 cervical cancer deaths (age-standardized mortality rate 7.1 per 100 000 women) (Figure 1) *(2)*. However, these figures reflect marked disparities in the global distribution of cases and deaths (Figure 2) *(2,36)*. In many HIC settings, cervical cancer incidence is below 7 cases per 100 000, while incidence rates are above 24 per 100 000 in many countries in sub-Saharan Africa, where mortality rates may also be over 20 times higher compared to those in HICs (Figure 1) *(2,36)*. In some countries – many of which are in sub-Saharan Africa – cervical cancer is the most commonly diagnosed female cancer and the leading cause of women's cancer deaths *(37)*.

While higher rates of cervical cancer in sub-Saharan Africa may be partly explained by lower rates of cervical cancer screening and treatment, a higher prevalence of HIV is also a major contributory factor *(27)*. In southern Africa in 2018, an estimated 64% of women with cervical cancer were living with HIV, as were 27% of women in Eastern Africa *(38)*. Over 77% of new HIV infections among adolescent girls and young women globally in 2022 occurred in sub-Saharan Africa *(39)*.

3.6 Other HPV-related cancers

In addition to causing cervical cancer, HPV is also associated with anal, penile, vaginal, vulvar and oropharyngeal cancers. In 2020, the total number of non-cervical HPV-associated anogenital cancers was estimated to be 150 100 in men and women. Of these, 30.1% were vulvar cancer, 24.0% were penile cancer, 33.9% were anal cancers and 12.0% were vaginal cancers *(32)*. A further 98 400 estimated HPV-related cancers were oropharyngeal *(32)*.

Figure 2. Age-standardized incidence and mortality rates of cervical cancer, by region



Source: Globocan/International Agency for Research on Cancer, 2022 *(2,36)*.

4. Existing interventions for cervical cancer management and control

Programmes to prevent cervical cancer morbidity and mortality currently have three essential pillars: primary prevention, which includes administration of prophylactic HPV vaccines; secondary prevention, which involves screening of women to identify those who may have HPV-related precancers and treatment to prevent progression to cervical cancer; and tertiary prevention, which involves treatment of invasive cervical cancer and access to palliative care. These three pillars form the basis for the targets of WHO's *Global strategy to accelerate the elimination of cervical cancer as a public health problem (3)*.

4.1 Primary prevention

Clinical trials have shown prophylactic that HPV vaccines are safe and highly efficacious in preventing persistent infection with vaccine-type HPV and related precancers *(40,41)*. The first HPV vaccines were licensed in 2006. Currently-available prophylactic vaccines include quadrivalent vaccines protecting against HPV types 6, 11, 16 and 18, bivalent vaccines protecting against HPV types 16 and 18, and 9-valent vaccines protecting against HPV types 6, 11, 16, 18 ,31, 33, 45, 52 and 58 *(42)*. Although there is evidence that some of the available vaccines provide limited cross-protection against acquisition of other, non-vaccine HPV types *(43)*, the vaccines do not have a therapeutic effect on pre-existing HPV infection or cervical lesions.

WHO recommends the use of prophylactic HPV vaccines in early adolescence, with the primary target being 9–14-year-old girls before the typical initiation of sexual activity, and the primary focus being the prevention of cervical cancer *(42)*. Vaccination of girls only, when coverage is high, provides herd protection to boys as well as providing direct protection against cervical cancer, and is typically more cost-effective than vaccinating both sexes *(42)*. However, vaccination of both boys and girls is carried out in some settings. Further, in 2022, based on evidence that single-dose HPV vaccination offers significant protection against persistent HPV infection, WHO issued advice that countries may now choose a one- or two-dose schedule for 9–14-year-old girls and for women aged 15–20 years *(42,44,45)*. This has opened opportunities for extending multi-age cohort vaccination to older females, as well as expanding vaccination to males after the primary target group of 9–14-year-old girls has been vaccinated. School-based programmes are the main vaccine delivery strategy in LMICs, resulting in higher coverage than facility-based programmes *(46)*.

Countries that have achieved high coverage of adolescent girls with prophylactic HPV vaccination have observed dramatic declines in HPV prevalence, incidence of cervical precancers and invasive cervical cancers *(47,48,49)*.

4.2 Secondary prevention

To prevent cervical cancer, women can be screened using several tests to identify those who have, or are at risk of, cervical precancer. The three main approaches are molecular tests, cytologic tests and visual inspection *(50)*. Molecular methods include nucleic acid amplification tests (NAATs) for HPV DNA or mRNA. These are the most sensitive and cost-effective diagnostic tests, although the current cost of the test kits and the infrastructure required for processing and testing are a barrier in many settings. Cytological tests (e.g. Papanicolaou tests, liquid-based cellular assessments) require trained cytologists in addition to higher-cost laboratory infrastructure *(51)*. A lower-cost alternative is visual inspection with acetic acid (VIA), which involves clinician visualization of the cervix after applying diluted acetic acid solution. Despite the lower cost and infrastructure, the sensitivity and specificity of this method are strongly dependent on the experience of the clinician and, even with a highly skilled practitioner, the sensitivity and specificity remain poor compared with molecular screening *(52)*.

WHO recommends HPV DNA detection as the primary screening test, starting at age 30 years for women in the general population and repeated every 5–10 years *(50)*. Either provider-collected or self-collected samples can be used. HPV mRNA testing on provider-collected samples is an alternative option for the general population when screening can be repeated every 5 years *(53)*. For WLHIV, HPV DNA detection is the recommended primary screening test, starting at age 25 years and repeated every 3–5 years *(50)*. For both groups after the age of 50 years, WHO recommends stopping testing following two consecutive negative screening results.

Health worker at a clinic in Malawi.
Credit: © WHO / Fanjan Combrink

For women with a positive HPV test, WHO recommends either a "screen and treat" or "screen, triage and treat" approach for the general population and a "screen, triage and treat" approach for WLHIV. In the "screen and treat" approach, the decision to treat is based on a positive primary screening test only, preferably an HPV DNA test. Before treatment, all women who have screened positive should undergo a visual examination of the cervix to exclude cervical cancer and to determine eligibility for ablative treatment. In the "screen, triage and treat" approach, the decision to treat is based on a positive primary screening test followed by a positive second test ("triage"). WHO suggests using partial genotyping, colposcopy, VIA or cytology to triage women after a positive primary screening test *(50)*.

If treatment is indicated and the lesion is appropriate (small and entirely visible on the ectocervix), it can be treated with ablation that destroys abnormal tissue by freezing (cryotherapy) or application of heat (thermal ablation). If the lesion is not appropriate for ablation, it can be surgically excised by removing the entire abnormal transformation zone, using large loop excision of the transformation zone (LLETZ)[3] or cold knife conization (CKC). Women with suspected cancers must be referred for further evaluation and management *(50)*.

4.3 Tertiary prevention

Cervical cancer case management is based on staging of the disease. Early-stage cervical cancer has long-term survival and cure rates of around 80% where timely diagnosis and high-quality treatments are available *(54)*. WHO recommends surgery and/or radiotherapy, with or without chemotherapy, for early stages of cervical cancer *(50)*. WHO also recommends integrating palliative care into the treatment plan throughout the course of the disease. Effective early-stage treatment is paramount, as standard radio- and chemotherapies of late-stage cervical cancers tend to have low cure and survival rates *(55)*.

[3] In some countries, this terminology was changed to LEEP (loop electrosurgical excision procedure), and the two terms are often used interchangeably.

5. Public health need for therapeutic HPV vaccines in the context of existing interventions

Current and predicted future gaps in scaling up existing interventions provide a potential role for therapeutic HPV vaccines, with the overarching aim of reducing cervical cancer deaths globally over the next 3–4 decades.

5.1 Implementation and scale-up of prophylactic HPV vaccine programmes

As of January 2024, a total of 141 countries had introduced HPV prophylactic vaccines into their national immunization programmes *(56)*. Global coverage for the first dose of HPV in girls reached 21% in 2022 *(57)*. However, many of the countries with the highest cervical cancer rates have not yet introduced prophylactic HPV vaccines *(2,56)*.

Among the 47 countries in the WHO African Region, which is the WHO region with the highest rates of cervical cancer, 28 countries had introduced prophylactic HPV vaccine into their national immunisation programmes as of January 2024, with coverage ranging from 6% to 99% for the first vaccine dose *(56)*. Challenges associated with meeting vaccination targets have included insufficient global supply of vaccines, costs of the programme, low acceptance of the vaccine, and the need for additional resources to engage stakeholders. Challenges in areas such as cold-chain management and integration into existing vaccination programmes have also been reported.

Nonetheless, it has been demonstrated that it is feasible to achieve high coverage of prophylactic HPV vaccines, even in resource-poor settings *(58)*. Furthermore, countries can now choose a one-dose schedule for prophylactic HPV vaccination of adolescent girls *(42,44,45)*, which will simplify immunization implementation, increase supply and reduce production bottlenecks and overall costs.

5.2 Implementation and scale-up of cervical cancer screening and treatment

Access to cervical cancer screening is very limited in many LMICs (Figure 3). Around a third of countries have managed to screen over 70% of women with any method at least once in their lifetimes; 126 countries have screening coverage below this level *(6)*. On average, only around 10% of women in LMICs have ever received cervical cancer screening *(6)*.

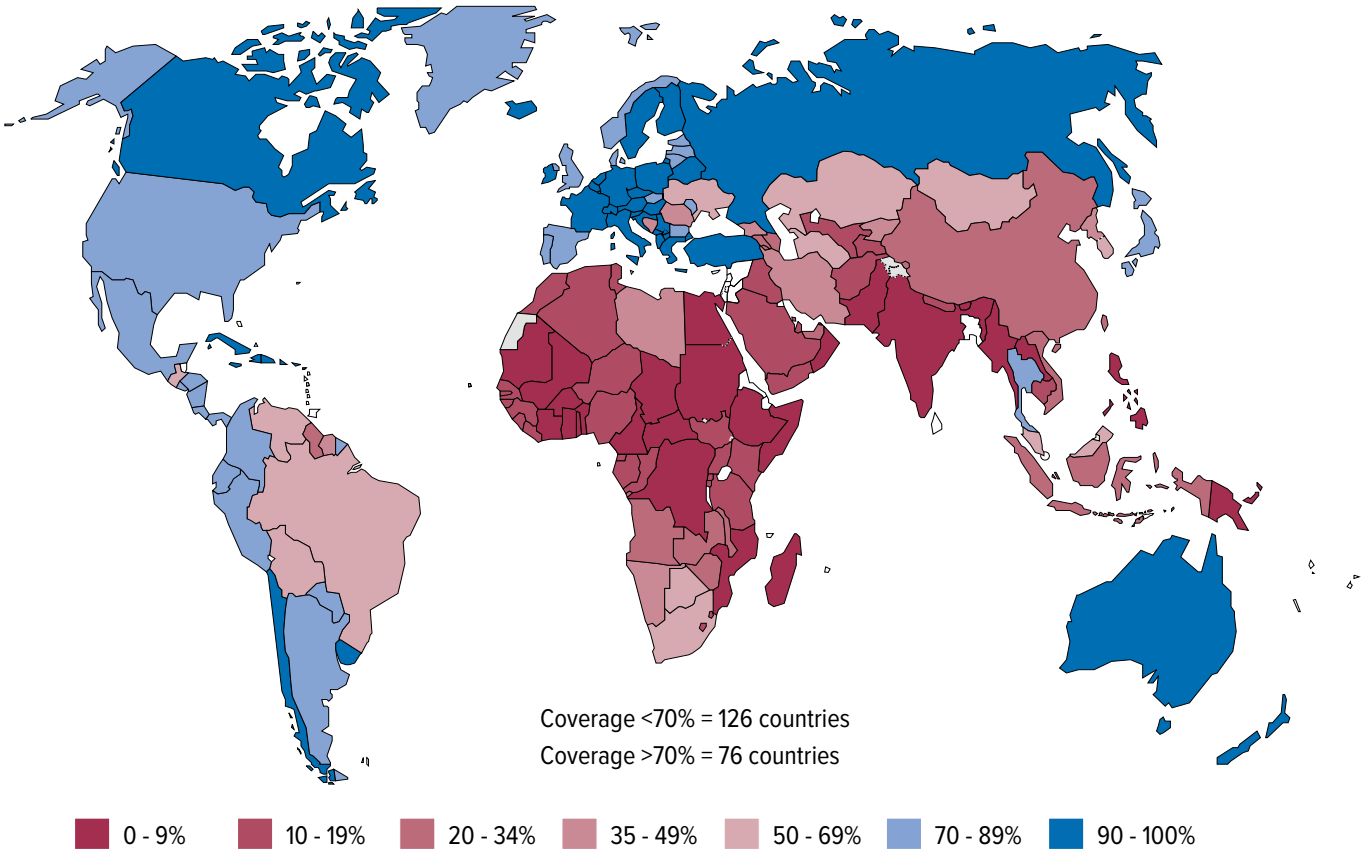
Of those countries with cervical screening recommendations, only 35% (48 out of 139) recommend primary HPV-based screening. Visual inspection with acetic acid is the most recommended test in LMICs *(6)*. Given the poor sensitivity and specificity of VIA compared to other screening methods, high-grade precancers and early stages of cervical cancer may be missed, and high false-positive rates may lead to unnecessary treatment. Thus, reported levels of coverage are still likely to fall short of impact goals for this pillar of the global strategy to eliminate cervical cancer.

The complexity and cost of screening and treatment programmes, which may require several visits, have been the primary barriers in many LMICs. Many settings report challenges in switching to primary HPV DNA testing – including inadequate laboratory facilities and staffing, high costs of the diagnostic assay, and weak communication systems to contact and refer women who test positive. Even when screening does occur, the biggest gap within the cascade of care is often from screening to treatment, with substantial loss to follow-up after a positive screening test or limited capacity of the system to deliver quality treatment.

A lack of trained clinicians and difficulties with quality control in referral centres have also been challenging. Treating larger lesions or lesions that occur predominantly inside the endocervical canal has been more difficult in LMICs *(59)*. Building capacities to perform LLETZ to treat such lesions in LMIC settings can be challenging. Peri-operative and pregnancy complications following LLETZ and other excision methods such as potential scarring and stenosis of the cervix, or risk of sexually transmitted infection (STI) acquisition during the healing period, are also concerns *(60)*.

In countries with high HIV prevalence, major barriers to cervical cancer prevention include high recurrence rates of dysplasia following treatment in WLHIV *(61)*. Recent studies have highlighted the higher failure rates of current ablative therapies for cervical precancers among WLHIV. Rates of histologically confirmed disease post-treatment were 23% in a South African setting *(62)* and 34% in a setting in Kenya *(63)*, compared with a global failure rate of 14% among general populations of women in LMICs *(64)*.

Figure 3. Ever in lifetime screening coverage among women aged 30–49 years, by country (2019)



Source: Adapted from Bruni et al., Lancet Global Health, 2022 *(6)*.

5.3 Implementation and scale-up of cervical cancer management

Cancer diagnostic and treatment services show wide disparities. Coverage levels of cervical cancer management services in the public sector are generally above 90% in HICs. However, coverage of such services is generally under 30% in low-income countries and ranges from around 40% to 70% for access to cancer centres, surgery, radiotherapy, chemotherapy and pathology services in lower-middle-income countries *(3)*. Cost, complexity and lack of health system infrastructure and human resources remain barriers to effective widespread implementation.

5.4 Identified public health needs for therapeutic HPV vaccines

Large gaps exist in scale-up of current cervical cancer prevention interventions. Prophylactic HPV vaccines are expected to prevent tens of millions of deaths as the world moves towards cervical cancer elimination *(5)*. However, given the long natural history of HPV infection leading to cervical cancer, the full benefits of prophylactic HPV vaccination programmes will not be observed for several decades. Modelling has reinforced how crucial cervical cancer screening is for the many age cohorts of women who were not vaccinated in adolescence; to identify and treat those who may already have cervical precancers or invasive cancers will save millions of additional lives *(4,5)*. Although coverage both for prophylactic vaccination and for screening and treatment is currently low globally, the group of experts convened by WHO felt that there is much more promise in rapidly scaling up adolescent prophylactic HPV vaccination in the coming years. The group noted, however, that scaling up screening and treatment programmes is likely to be much more challenging and may lag further behind global targets.

These challenges present an opportunity in the near term for new innovations to contribute to cervical cancer prevention while existing interventions are scaled up. The WHO-convened group of experts identified two overarching contexts with public health needs for potential therapeutic HPV vaccines, namely:

- in settings where it has been difficult to scale up quality cervical cancer screening and treatment, and particularly areas where prophylactic HPV vaccine programmes have been delayed, there is a need to reach women who probably have not received prophylactic vaccination in order to reduce the overall proportion that will develop or already have cervical precancers (and thus invasive cancers); and

- in settings where screening and treatment are being implemented, it would be valuable to have an alternative, simpler and more accessible treatment following a positive test to decrease loss to follow-up and to increase the overall proportion of women with high-risk HPV infections and/or precancers who are effectively treated.

Health worker conducting community outreach in Pakistan.
Credit: © WHO / HRP / Saiyna Bashir

6. Therapeutic HPV vaccine development

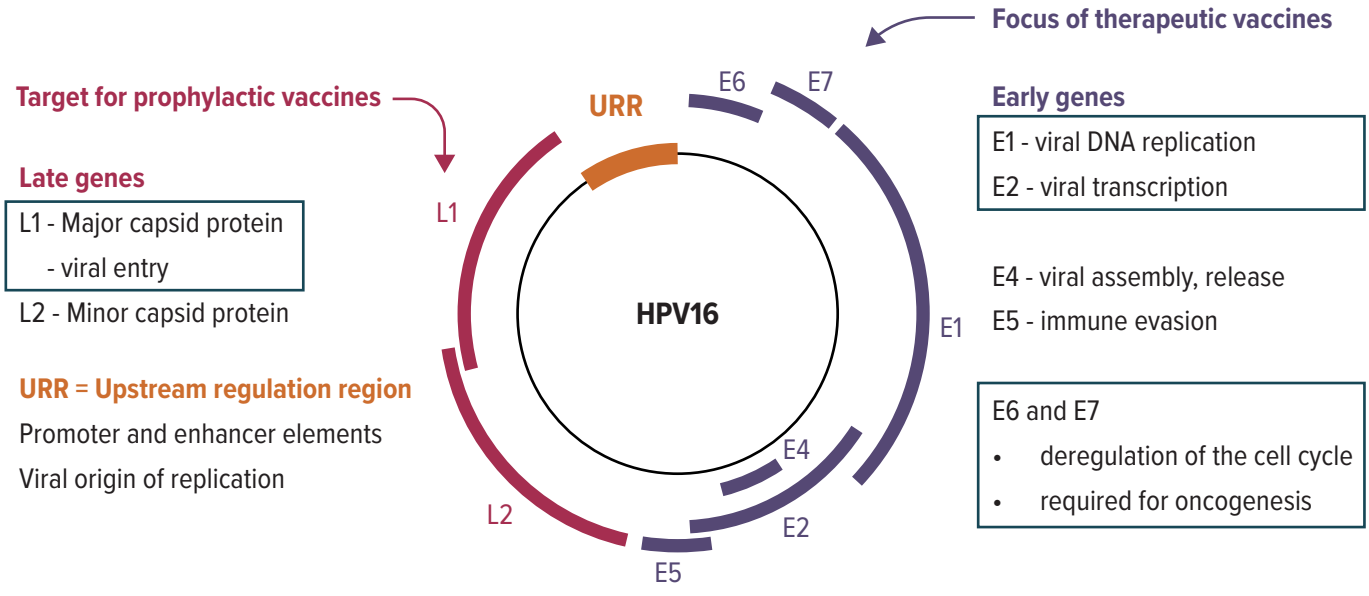
The experts explored the potential feasibility, pipeline and clinical development considerations for future therapeutic HPV vaccines that could meet identified public health needs. The focus was on vaccines that primarily clear high-risk HPV infection and/or cause regression of high-grade cervical precancers. Therapeutic vaccines for the treatment of invasive cervical cancer were beyond the scope of the consultations.

6.1 Feasibility of therapeutic HPV vaccine development

Therapeutic HPV vaccines are intended to act in the setting of ongoing, active infection. Thus, they differ from prophylactic vaccines which prevent infection. All HPV types encode "early" proteins (E-proteins: E1, E2, E4–E7) and "late" virion structural proteins (L-proteins: L1, L2) (Figure 4). To cause infection, HPV virions bind to basal cells in the epithelium using the viral capsid protein L1. All current highly efficacious prophylactic HPV vaccines target L1. In infected cells, E1 and E2 proteins are responsible for viral replication and transcription, and E6 and E7 proteins drive cell proliferation. As E6 and E7 play a significant role in cellular transformation, these viral proteins have been the main targets of most therapeutic vaccine candidates to date, designed to treat later stages of HPV-driven disease such as precancer and invasive cervical cancer *(65)*. However, for therapeutic vaccines that are intended to target early stages of pathogenesis such as persistent infection, the inclusion of proteins such as E1 and E2, which are more highly expressed at these early stages, may be critical for successful termination of HPV infection and the prevention of precancer *(66,67)*.

Therapeutic HPV vaccine development is challenging for several reasons. HPV has a relatively slow life cycle that is non-cytolytic, actively evades the innate and adaptive immune response, and does not induce a high level of inflammation that would alert the host to infection *(68)*. Antibodies are insufficient to clear persistent HPV infection or to reduce precancerous lesions *(69)*. Therefore, while current prophylactic HPV vaccines rely on antibody-mediated protection, post-exposure therapeutic vaccines are likely to require the induction of cell-mediated immunity with effective T cell responses against early viral proteins across genetically diverse populations.

Figure 4. HPV genome organization and focus of therapeutic vaccines



Source: Adapted with permission from Stanley M, Clin Microbiol Rev, 2012 *(68)*.

In addition, advanced cervical lesions have often undergone immune selection and display a highly immunosuppressive local environment that presents scientific and immunological challenges to achieving an efficacious vaccine *(70)*. Consequently, it may be easier to develop efficacious therapeutic HPV vaccines that target HPV infection or low-grade precancerous lesions than vaccines that target high-grade precancers or invasive cervical cancer. This is because the vaccines focused on earlier stages will act upon cells that are more conducive to clearance by robust immune responses. It is unknown to what extent the therapeutic immune responses will persist and thus provide ongoing activity against new vaccine-type infections or recurrences of either infection or dysplasia; however, the experts felt that some degree of this "immune memory" is likely.

The experts felt that, for a vaccine targeting either persistent high-risk HPV infection or more advanced cervical disease, an effective single-dose vaccine is unlikely. Mucosal delivery, such as oral or intravaginal, for either initial or booster dosing might improve the immune response and could also allow self-administration *(71)*. Intravaginal administration may have the added benefit of recruiting T cells into the relevant tissue site.

6.2 Therapeutic HPV vaccine pipeline and development approaches

No licensed therapeutic HPV vaccines currently exist. However, the clinical pipeline is active, and a wide variety of approaches have been used to develop therapeutic HPV vaccine candidates, including peptide, protein, DNA, RNA, and bacterial- and viral-vectored vaccine platforms *(72)*.

To date, therapeutic HPV vaccine development has primarily focused on candidates targeting the regression of CIN2/3 lesions and invasive cervical cancer, although a few candidates focusing on clearance of high-risk HPV infection are now in phase 1 and 2 studies.[4]
A systematic review of completed phase 2 and 3 clinical trials of therapeutic HPV vaccine candidates targeting CIN2/3 lesions identified 12 published studies by 2022 – six studies with vector-based vaccines, three with peptide- and protein-based vaccines, and three with nucleic acid-based vaccines *(73)*. In addition, at least six therapeutic vaccine products were registered as being in active phase 1 or 2 studies as of June 2023.[5]

Several of the completed studies have demonstrated regression of high-grade (CIN2/3) to low-grade (CIN1) or no precancer following therapeutic HPV vaccination, with modest but significant differences when compared with natural regression *(72,73)*. In a meta-analysis of the controlled studies, the proportion achieving regression after vaccination was about 50% higher than that observed in the placebo group *(73)*. These findings provide proof of concept that a therapeutic vaccine can generate immune responses that can cause regression of high-grade precancer, although efficacy will need to be improved. In addition, existing early phase studies have demonstrated that clearance of infection – operationally defined as loss of HPV detection using a sensitive NAAT – often occurs at the same time as regression of precancers *(73)*.

All candidates to date have been multiple-dose products (most commonly three doses), administered at set intervals over several months. The most common route of administration in clinical studies has been parenteral (subcutaneous and intramuscular) delivery. Other delivery methods have included oral delivery and direct injection at the site of the cervix.

6.3. Clinical development considerations

6.3.1 Vaccine candidates designed primarily to clear HPV infection

Therapeutic HPV vaccine products in the pipeline that are primarily focused on clearing infection have not yet progressed to late-stage clinical development, and no specific regulatory pathways have been defined. Primary clinical endpoints for trials of therapeutic HPV vaccine candidates focusing on infection might include clearance of vaccine type-specific HPV infection, prevention of high-grade cervical precancer, or a composite of both outcomes (e.g. clearance of infection without progression to precancer).

Clearance of infection can be defined as a negative follow-up test (using a highly sensitive and specific test, such as type-specific HPV DNA NAAT) at a predetermined

[4] See: www.clinicaltrials.gov: NCT04607850; NCT03913117; NCT04490512, accessed 27 June 2023.

[5] See: www.clinicaltrials.gov: NCT04607850; NCT03913117; NCT04490512; NCT00788164; NCT04131413; NCT03911076, accessed 27 June 2023.

Women at a COVID-19 vaccination campaign in Mali.
Credit: © WHO / Fatoumata Diabaté

point in time (e.g. at 12 or 24 months) in someone who had a positive test at baseline *(73)*. Evaluating prevention of, or progression to, high-grade cervical precancer will require histological evaluation. The precise time frame for evaluating clearance or progression and whether infection clearance will require two negative tests will need to be determined in discussions with regulators. Although complete resolution of oncogenic infection following therapeutic vaccination would be expected to prevent progression to high-grade cervical precancers, which in turn would be expected to prevent progression to cervical cancer, regulatory guidance will be needed to confirm whether durable clearance of infection without progression to high-grade precancer, as measured in trials, is an acceptable surrogate for prevention of cervical cancer, as has been established with prevention of infection for prophylactic HPV vaccines *(74)*.

Secondary endpoints should be collected where possible, including clearance of non-vaccine HPV types, incidence of reinfections or recurrences, and clearance of vaccine-type infections at non-cervical sites (e.g. oropharynx, anus). Evaluation of therapeutic HPV vaccines in combination with or compared with prophylactic HPV vaccination will also be important, as this can inform potential synergies between the vaccine types (e.g. in reducing the risk of recurrent or new infection).

For evaluating therapeutic HPV vaccines with an infection clearance endpoint, adequately powered clinical trials can be conducted with fewer participants, and more quickly, than prophylactic HPV vaccine trials. This is because all participants will have already acquired high-risk HPV infection, and outcomes can be based on the continued presence or absence of HPV infection on serial testing over a defined period. Because a large proportion of infections will clear naturally, a control group will be essential to quantify efficacy. Although studies pursuing these indications need not be prohibitively large, they can be complex to conduct and require thoughtful planning. No therapy is currently recommended for HPV infection when high-grade precancer has been ruled out, so a placebo comparator is acceptable. Inclusion of only those persons with persistent HPV infection at baseline, defined by the presence of type-specific HPV DNA on repeated clinical biological samples over a specified period, would decrease the number who would clear infection naturally but would lengthen the screening portion of the study.

Even with vaccine candidates primarily designed to clear infection, separate evaluation of the efficacy of these vaccines in causing regression of high-grade cervical precancers would be useful in understanding whether their use can be broadened to increase potential public health value. Although vaccines could be valuable even with short

duration of therapeutic efficacy (i.e. clearing infection at or near the time of administration), it will be important to evaluate for ongoing therapeutic immune responses and longer-term activity against new vaccine-type infections or recurrences and the duration of these effects.

6.3.2 Vaccine candidates designed primarily to cause regression of CIN2/3 lesions

Clinical trials of therapeutic HPV vaccine candidates focusing on regression of high-grade cervical precancers will need to be carefully designed to ensure that they are ethically and methodologically sound. Important considerations for clinical trial design specialists and regulators include the timeline of the follow-up period, whether the comparator group would be placebo or an alternative treatment, and appropriate primary and secondary outcomes. Of critical importance is the need to ensure that women with high-grade cervical precancers are not left untreated. WHO guidelines state that it is good practice to initiate treatment as soon as possible within 6 months following a positive screening test to reduce the risk of loss to follow-up. Trials comparing with an alternative treatment would need large study sizes because of the high efficacy of current alternative treatments that would act as comparators.

A woman holds her immunization card in Viet Nam.
Credit: ©WHO / Loan Tran

In previous clinical studies of therapeutic HPV vaccines, women with histologically confirmed CIN2 and/or CIN3 associated with HPV types 16 and 18 have received therapeutic HPV vaccines with or without a placebo control arm and have typically been followed for histopathological regression of cervical lesions to CIN1 or no dysplasia *(73)*. Clearance of viral infection should also be evaluated. However, discussion with regulators can determine whether associated viral clearance is an essential component of the primary outcome and how it should be assessed, and whether endpoints will require biopsy or could be based on an alternative, such as HPV testing in the setting of negative colposcopy results.

Several trials to date have measured clearance of HPV infection as part of the primary outcome along with regression of high-grade precancers, and several have evaluated viral clearance as a secondary endpoint *(73)*. Experts speculate that vaccines capable of regressing CIN2/3 lesions are also likely to have some efficacy against clearing high-risk HPV infection which is the precursor to precancer. Additional secondary endpoints may include evaluation of cross-protection against cervical precancers associated with other oncogenic HPV types, clearance of non-vaccine type HPV infection or low-grade cervical lesions, prevention of recurrent cervical lesions and reinfections, and clearance of HPV infection at multiple anatomical sites.

While first-generation vaccines may be developed as stand-alone treatment, future vaccines with primary indications of regression of cervical precancers may also be considered as an adjunct to existing ablative or surgical treatments *(72,75)*. in order to enhance overall treatment outcomes and/or reduce disease recurrence rates. This may be particularly relevant for WLHIV, who have higher recurrence rates and for whom existing treatments have lower efficacy *(62,63)*. Studies involving WLHIV may require closer monitoring and longer follow-up periods.

6.3.3 Considerations for both vaccine approaches

Some outcomes (e.g. prevention of precancers for vaccines with a primary indication of clearance of infection, or extension of benefits to other anatomical sites, cross-protection, or impact on reinfections and recurrences) could be evaluated post-licensure. If a multi-dose regimen is evaluated, efficacy and effectiveness data should be gathered whenever possible from those who receive only one dose in order to inform potential possibilities for improving dosing regimens. Additionally,

co-administration with prophylactic HPV vaccines and side-effect profiles in women who have previously received prophylactic vaccines should be assessed. Research would also be needed on whether therapeutic vaccination programmes influence the prevalence of non-targeted HPV types or affect future assessment and diagnosis of cervical precancers or invasive cancer.

Consideration should be given to the inclusion in clinical trials of those populations of end-users who would accrue the greatest potential benefit from the vaccine – specifically people from LMICs. Clinical trials should include adequate planning for implementation priority for trial populations in instances where the vaccine is later approved and licensed. In addition, the inclusion of pregnant women is desirable if determined to be safe and ethical.

7. Potential public health value of therapeutic HPV vaccines

7.1 Potential approaches for therapeutic HPV vaccines to meet public health needs

Therapeutic HPV vaccines that primarily clear high-risk HPV infection and those that primarily cause regression of high-grade cervical precancers could both play a role in addressing unmet needs in cervical cancer prevention programmes. Possible use cases include a population-based approach in which all women in a prespecified age group receive vaccine and targeted vaccination based on HPV testing. Vaccines that primarily clear infection would be favoured for use on a population basis in relatively younger age groups, perhaps at or before the recommended starting age for screening which is age 30 years in the general population and age 25 years among WLHIV. Vaccines designed primarily to treat existing precancers may be favoured for use following testing in relatively older ages within cervical cancer screening and treatment efforts. However, these approaches are not mutually exclusive, and efficacious therapeutic HPV vaccines with either of these attributes – or preferably some degree of both – might be useful additions to cervical cancer prevention efforts in both contexts, depending on additional vaccine characteristics and how they might be used within the existing health infrastructure at different points in time.

7.2 Public health value considerations for therapeutic HPV vaccines

Multiple factors will need to be considered simultaneously in order to understand the potential value of therapeutic HPV vaccines and their optimal characteristics within the context of broader cervical cancer prevention programmes. A full value of vaccine assessment for therapeutic HPV vaccines should be done to provide a detailed understanding of the potential added benefits of these products *(76)*. Initial mathematical models suggest that, under the right circumstances, therapeutic HPV vaccines could make important contributions to cervical cancer prevention efforts *(77,78,79)*. A preliminary impact model across 78 LMICs reinforced the view that the greatest benefits are seen by reaching the 90-70-90 targets of the global strategy to eliminate cervical cancer. However, when existing interventions have not been scaled up, therapeutic HPV vaccines could be an important addition. For instance, in this scenario a vaccine with 90% efficacy in clearing HPV infection and 50% efficacy against cervical precancers, with twice-lifetime delivery to women aged 30 and 40 years at 90% coverage, and multi-age cohort catch-up in the first year, could avert approximately 2 million cervical cancer deaths by 2070 and 10.5 million deaths by the end of the century in sub-Saharan Africa alone *(77)*. Another model in nine high-burden LMICs *(78)* showed that, even with 90% background prophylactic vaccine coverage, a therapeutic HPV vaccine that clears 90% of HPV infections and regresses 50% of high-grade precancers, reaching 70% of 35–45-year-old women starting in 2030, could avert 500 000–1.2 million cervical cancer deaths and 20–40 million disability-adjusted life years over 30 years.

However, these models have shown that the potential value of these vaccines can vary greatly according to several overarching factors, as discussed below.

7.2.1 Timeline for development and use

The value of therapeutic HPV vaccines will be higher when the timeline to develop and implement them is shorter. For

Women at a health campaign in Guatemala.
Credit: © Pan American Health Organization PAHO

example, one model found that a 10-year delay in introduction of a therapeutic vaccine from 2030 to 2040 resulted in a 45% decrease in the number of deaths averted by 2070 *(77)*. The greatest window of opportunity for therapeutic HPV vaccines is in the decades during which there is ongoing scale-up of prophylactic vaccination programmes, ageing of cohorts vaccinated with prophylactic HPV vaccines in adolescence, and efforts to broaden access to cervical cancer screening and treatment programmes in different settings. Thus, implementing less-than-perfect vaccines sooner might be more important than waiting longer for vaccines with all desired characteristics. Vaccines targeted toward cervical precancer regression could continue to play an important role even after screening and treatment programmes have reached target scale-up if they could serve as favourable alternatives or adjuncts to existing treatments.

7.2.2 Background epidemiology and intervention scale-up

The added benefits of therapeutic HPV vaccines fall substantially as background scale-up of interventions approaches the 90-70-90 targets of the global strategy to eliminate cervical cancer *(77,78)*. The potential added value of therapeutic HPV vaccines will be greatest in the setting of lower coverage of existing interventions, and thus therapeutic vaccines could be scaled up in parallel with efforts to scale up other interventions – particularly prophylactic vaccines – to capture adult women who have already been infected. In addition, therapeutic HPV vaccines can have greater value in the setting of higher background rates of vaccine-type oncogenic HPV infection, cervical precancers and invasive cancers. These factors also affect the number of women it would be necessary to vaccinate in order to prevent a cervical cancer case or death and thus vaccine cost-effectiveness.

7.2.3 Vaccine characteristics

A key factor in determining potential value will be specific vaccine attributes. The available models have identified three attributes that are particularly influential. First, the models have demonstrated that, for vaccines primarily focused on clearing infection, additional efficacy in causing regression of high-grade cervical precancer is important in increasing impact. Even modest additional

efficacy (i.e. 50%) in regressing precancers was predicted to more than double the number of cases and deaths averted by 2070 compared with high efficacy (i.e. 70–90%) in clearing infection alone *(77,78)*. Second, the presence of immune memory (i.e. preventing reinfection or recurrence with the same HPV types) was a major contributor to overall impact *(77,78)*. Third, efficacy or cross-protection against oncogenic HPV types beyond types 16 and 18 was also predicted to broaden value *(77,78)*, as was activity against other HPV-related cancers. This is particularly important for vaccines that would be used as an alternative to treatment within screening and treatment programmes, given that ablative or surgical therapies act on cervical cells regardless of HPV type. Proven efficacy among WLHIV will also increase impact in settings with high HIV prevalence.

Factors that will ease delivery and increase coverage – such as fewer doses, a simple route of administration, few side-effects, a schedule that aligns with the existing care infrastructure, and simplified cold chain and storage requirements – are particularly important for LMICs.

7.2.4 Health system and programmatic factors

Health system and programmatic factors will necessarily intersect with vaccine characteristics to determine the most appropriate delivery approach for therapeutic HPV vaccines and the ability to achieve high coverage, which has an impact on potential added value. This will include access to health care for people at risk, the capacity to provide vaccination and/or other cervical cancer interventions at points of care, the availability of HPV diagnostics, and social and community factors affecting awareness, communication and acceptability of therapeutic HPV vaccines.

Modelling has shown that, for population-based vaccine delivery, the greatest benefits in terms of averting cervical cancer cases and deaths result from targeting multiple age cohorts (e.g. age 30–49 years) upon vaccine introduction and ongoing routine vaccination (e.g. age 30 or 35 years, depending on the vaccine's effectiveness against viral clearance and high-grade lesion regression, respectively) *(77,78)*. Therefore, even if the time window of use is narrow for therapeutic vaccines, a large number of women might still be reached. One model showed that providing therapeutic HPV vaccines only after a positive diagnostic test can reduce the number needed to vaccinate to avert a cervical cancer case or death but can also slightly reduce the overall impact *(77)*. The modellers noted that this trade-off largely relates to the assumed diagnostic sensitivity of clinically available screening tests, which have intentionally high thresholds for HPV detection that could potentially be adjusted for a future therapeutic vaccine application *(77)*.

For vaccines primarily being used as alternative treatment for cervical precancers within screening programmes, the relative impact depends not only on the efficacy of the vaccine in relation to the efficacies of existing cervical precancer treatments (e.g. cryotherapy or thermal ablation) but also on the ease with which each can be delivered within the health system to avoid loss to follow-up, which significantly influences treatment outcomes.

Future modelling analyses for a full vaccine value assessment should include further exploration of impact in the setting of different vaccine characteristics and delivery considerations, with and without co-administration of prophylactic HPV vaccines, with realistic background intervention scale-up in different settings, additional analyses for WLHIV, detailed cost-effectiveness analyses and other social and economic impacts. Incremental cost-effectiveness should assess the value of population-based vaccine delivery without a preceding diagnostic test over time, as increasingly greater proportions of women will have received prior prophylactic vaccination. In addition to modelling, evaluation of end-user preferences and predicted acceptability of therapeutic vaccines will also be important in understanding potential value.

8. Considerations for vaccine implementation

How therapeutic HPV vaccines should be implemented to meet public health goals optimally will be determined by several key factors within each setting, including the preferred target populations, the vaccine characteristics and the capacity of the health systems to deliver new and existing interventions over time.

8.1 Target populations

Factors that should be considered when defining the most appropriate target populations include determination of the population that would receive the greatest direct benefit from vaccination, the benefit-risk profile of the vaccine, the epidemiology and natural history of the infection, the ability to reach the population through programmes, the cost and cost-effectiveness, and equity.

Because cervical cancer has by far the largest disease burden, cisgender women, transgender men, and other gender-diverse people at risk of cervical cancer will receive the largest direct benefit from therapeutic HPV vaccines and are the primary focus of vaccination. Provision of therapeutic HPV vaccines to cisgender men and transgender women may contribute to reductions in population-wide HPV transmission and can also bring individual benefits related to other HPV-related cancers, such as anal cancers among MSM and transgender women, particularly to those living with HIV and oropharyngeal cancers. Thus, additional vaccine efficacy related to other HPV-related cancers could help to broaden the value of the vaccines and increase equity in prevention services for people disproportionately affected by HPV-related disease.

The age of women to be targeted is an important consideration; target age may vary according to the vaccine indication, use case and setting. For example, for broad population-based delivery without testing, targeting younger ages of adult women (i.e. starting at or before the typical ages of cervical cancer screening – age 30 years in general populations and age 25 years among WLHIV) would occur before many women have precancer lesions but would also clear many infections that would be likely to clear naturally. Vaccinating at earlier ages would also run the greatest risk of new infections being acquired after vaccination (assuming therapeutic HPV vaccines act only against current infections and not future infections), given the age-associated incidence of infection. Targeting older ages (e.g. among those recommended for screening – age 30–49 years in general populations) would capture more persistent HPV infections but may also occur in the setting of more precancer lesions or invasive cancers that have already developed. Across these age targets, in the absence of preceding testing, therapeutic HPV vaccines would be given to a large proportion of women without vaccine-type infection.

Although the primary focus would be on women in their twenties, thirties or forties, the availability of these vaccines may have benefits for special populations outside of this group, such as children or adults following sexual assault or abuse, or people on chronic immunosuppressive treatments. Considerations for choice of target population will also include the existing infrastructure to reach a particular group in order to achieve good uptake of therapeutic HPV vaccines, and background coverage with prophylactic vaccination and cervical cancer screening and treatment.

8.2 Vaccine characteristics

Decisions about when, how and whom to vaccinate will depend on the vaccine's characteristics. HPV therapeutic vaccines would ideally have high efficacy in clearing high-risk HPV, preventing progression to precancer and regressing precancerous lesions. They would also ideally have an excellent safety and side-effect profile and could feasibly be delivered to target groups within health systems in both LMICs and HIC settings. Vaccines to be used on a population basis are likely to require a more favourable safety profile than those to be given after a positive test since most population-based vaccinees will not have infection or disease.

Vaccine efficacy in clearing high-risk HPV infection and/or regressing precancerous lesions, cross-protection against non-vaccine HPV types, and immune memory against reinfection or recurrence will help to determine the population impact and cost-effectiveness according to the target group(s) or delivery strategy. Ideally, vaccines will show comparable efficacy in treating WLHIV and immunocompromised individuals, and they will be safe

and effective in pregnant women. Vaccine characteristics such as the number and timing of doses, route of administration and cold chain requirements will all affect programmatic feasibility.

8.3 Programmatic and delivery considerations

The choice of delivery strategy for therapeutic HPV vaccines would depend on vaccine indications and target populations against the backdrop of existing cervical cancer prevention efforts and overall health infrastructure. One delivery option, if benefit-risk and cost-effectiveness assessments are favourable, is broad population-based delivery to adult women without preceding testing, which may be the most appropriate strategy for addressing the public health need in settings with very limited screening and treatment access or testing capacity. In settings with ongoing screening and treatment programmes or the capacity to conduct HPV testing, targeted vaccination following a positive test could provide an important approach which may become more feasible over time.

A population-based delivery strategy would not require cervical cancer screening infrastructure but would require an adult vaccination platform. Historically there has not been an immunization platform for women of reproductive age, other than for maternal immunization which has been varyingly implemented and typically achieves lower coverage than childhood vaccines. However, the COVID-19 pandemic has provided adult vaccination strategies that may be a new opportunity for delivery of other vaccines. Whether they will be as successful outside of a pandemic is unclear, but the infrastructure and staff training required for delivering vaccines has been established in many settings. Campaigns may also provide an effective means to deliver such a programme. In addition, the acceptability, feasibility, and ethical and regulatory implications of mass therapeutic vaccination in the absence of screening will need to be considered.

Inclusion of therapeutic HPV vaccines within existing screening and treatment programmes, or where some testing infrastructure exists, could increase the efficiency of vaccinating those with high-risk infection or precancer. A vaccine that is less invasive or otherwise easier to deliver than current treatments could reduce the high rates of loss to follow-up observed after screening in many settings. In this respect, the development of improved rapid point-of-care HPV diagnostics, and use with self-collected specimens, could significantly improve programmatic outcomes *(80,81)*. Such tests would allow therapeutic vaccination immediately after a positive test in a single visit, even if a woman is referred for further evaluation and management. A “test and vaccinate” approach that is simpler to deliver than existing programmes could also help to broaden coverage and improve equity. Such an approach could be taken in primary care, family planning clinics, HIV prevention and care services, postpartum or infant immunization visits, or in community-based outreach efforts.

Acceptability of therapeutic HPV vaccines to potential vaccine recipients will be a critical component of any delivery strategy. Many countries achieve excellent coverage rates for vaccines, with high vaccine acceptability; however, countries are now increasingly influenced by vaccine hesitancy. Although the demonstration of both safety and efficacy is crucial to counter vaccine hesitancy, communication strategies will also be important, in addition to raising awareness more generally regarding cervical cancer and prevention. Prophylactic HPV vaccines have historically been promoted as vaccines that prevent cervical cancer rather than preventing an STI because STI vaccines may be perceived as stigmatizing *(82)*.

A cervical cancer survivor in Guinea.
Credit: © WHO / Blink Media - Ricci Shryock.

In addition to distinguishing therapeutic HPV vaccines from prophylactic vaccines, consideration should be given as to whether they are discussed as "vaccines" or as "treatment" – particularly because not all people who receive therapeutic vaccines will have infection or disease. Communication and marketing strategies should be planned in advance, with careful consideration and input from potential end-user communities.

A variety of other programmatic factors will be important in ensuring that therapeutic HPV vaccines can be delivered in LMICs as well as in HIC settings. Scale-up and implementation will need to take account not only of health system differences but also of cultural and social differences between countries. The requirements of vaccine procurement, cold chain and transportation, links with other health system services, and data systems also need to be considered. A critical factor in global access to and uptake of vaccines is related to their cost-effectiveness and overall costs. The number needed to vaccinate to prevent a single case of cervical cancer will be higher in a population-based strategy without testing than in a targeted strategy; however, cost-effectiveness will be determined by the costs of diagnostic testing relative to vaccination *(77)*. A full value of vaccine assessment should evaluate the trade-offs involved in investing in development and implementation of therapeutic HPV vaccines versus increased investment in scaling up current programmes, or their expansion (e.g. delivering prophylactic HPV vaccines at older ages). It should also evaluate concurrent use of prophylactic and therapeutic HPV vaccines through population-based delivery. This strategy could potentially provide benefits to adult women with and without infection, but the relative benefits would depend on the risks of having existing HPV infection versus acquiring a new, future infection at different ages.

9. Preferred product characteristics for HPV therapeutic vaccines

The identified areas of unmet public health need for therapeutic HPV vaccines (Section 5) and potential therapeutic HPV vaccine development approaches (Section 6) form the basis for therapeutic vaccine PPCs. Ideally, therapeutic vaccines would have activity in both clearing infection and regressing precancers, for multiple oncogenic HPV types and with prolonged activity against reinfection or recurrence. However, depending on their mechanisms of action, individual vaccines may have differential activity against these outcomes. First-generation vaccines with just some of these attributes could still play a role in achieving public health goals in LMICs and HIC, particularly in early stages of cervical cancer elimination efforts. They can also provide insight into the development of future-generation vaccines that could be more broadly applicable, even as background cervical cancer prevention interventions are scaled up.

Vaccines that primarily clear oncogenic HPV infection and those that primarily cause the regression of high-grade cervical precancers may require different considerations in terms of how and for whom they are used, and their optimal characteristics. Consequently, to be illustrative of these considerations, separate PPCs have been developed for each.

The prospect of therapeutic vaccines must not delay or diminish the urgency around introduction and scale-up of prophylactic HPV vaccination and cervical cancer screening and treatment. This PPC guidance should not supersede existing WHO guidelines relating to cervical cancer prevention *(3,42,50)*. Efforts to develop therapeutic HPV vaccines should be undertaken in parallel with efforts to scale up these existing prevention interventions which are paramount. In all settings, to the extent that is possible, women should follow WHO guidelines for cervical cancer screening and treatment starting at age 30 years in the general population and age 25 years for WLHIV *(50)*.

9.1 PPCs for therapeutic HPV vaccines used to clear infection

PPCs for therapeutic HPV vaccines that **primarily clear oncogenic HPV infection** are described in Table 1. Additional attributes that are preferred for therapeutic HPV vaccines regardless of vaccine type are listed in Section 9.3.

Table 1. Preferred product characteristics for therapeutic HPV vaccines used to clear oncogenic HPV infections

Parameter	Preferred characteristic	Notes
Indication	For first-generation vaccines: Clearance of oncogenic HPV infection, at a minimum types 16 and 18, and/or prevention of high-grade cervical precancers associated with these HPV types. Increased global public health value would result from additional vaccine activity in: • regression of cervical precancers AND/OR • clearance of additional oncogenic HPV-type infections AND/OR • prolonged effects against reinfection or recurrences.	The goal of clearing oncogenic infection would be prevention of progression to high-grade cervical precancers, which in turn would be expected to prevent progression to cervical cancer. Regulatory guidance will be needed to confirm whether durable clearance of infection as measured in clinical trials of therapeutic vaccines (e.g. HPV no longer detected using a sensitive NAAT) is an acceptable surrogate for prevention of cervical cancer, as has been established for prevention of infection by prophylactic HPV vaccines. Discussions with regulators can also establish the appropriate time frame for measuring clearance and whether prevention of high-grade precancers should be evaluated instead of, or in addition to, clearance of infection in clinical trials. HPV types 16 and 18 account for 70% of cervical precancers that progress to invasive cervical cancer. Therefore, minimally viable first-generation vaccines to prevent cervical cancer should include types 16 and 18. Efficacy in causing regression of high-grade cervical precancers, cross-protection against additional oncogenic HPV types, and/or prolonged responses against repeat vaccine-type HPV infection ("immune memory") would expand the public health benefits of therapeutic HPV vaccines and could affect recommendations for broader use. Consideration should be given to collecting supporting evidence on these outcomes during pre-licensure studies and designing post-licensure studies to evaluate them. Inclusion of additional HPV types in the vaccine may also add benefit. The next priority for inclusion should be HPV types 45, 35, 31, 33, 52 and 58. However, inclusion of additional types may result in trade-offs such as cost and complexity of manufacturing, potential effects on immunogenicity, and higher vaccine prices. The primary indication relates to cervical infection; however, additional efficacy against HPV infections at other sites (e.g. anal, vaginal, oropharyngeal) would be valuable.

Parameter	Preferred characteristic	Notes
Target population	Adult women[6] (e.g. ages 25–49 years) Particularly in settings where a high proportion of women have not already received prophylactic HPV vaccines in adolescence or have not been screened and therefore are more likely to have existing HPV infection.	The optimal target populations of adult women who should receive therapeutic vaccines, including the precise age range, may vary by setting, by delivery strategy and over time, and may depend on: • scale-up, ages of delivery, and time since introduction of prophylactic vaccines; • scale-up of cervical cancer screening and treatment; • prevalence of oncogenic HPV and/or precancer at different ages; • proportion of women living with HIV [WLHIV] in the setting, who may require vaccination at earlier ages; • benefit–risk assessments and cost-effectiveness analyses; • vaccine attributes such as additional efficacy in regressing precancer, and duration of action of the vaccine. Epidemiological data and modelling will determine age thresholds that optimize benefits of therapeutic HPV vaccination for different settings and populations, and for vaccines with different attributes. Modelling can also explore the relative value of using prophylactic HPV vaccines in addition to, or instead of, therapeutic vaccines at different ages. In general, vaccinating younger women will result in vaccination of more women who would clear their HPV infections naturally or who may acquire new infections later. Vaccinating older ages will result in capturing more women with persistent infections, but also more women who already have cervical precancers or invasive cancers. Women should be encouraged to receive cervical cancer screening and treatment where available through existing programmes, and receipt of therapeutic vaccine should not alter this guidance. WLHIV with oncogenic HPV infection have more frequent and rapid progression to cervical precancer and invasive cancer, and current precancer treatments are less effective among WLHIV. Efficacy of therapeutic vaccines should be evaluated in this subpopulation who might require earlier and more frequent dosing. Vaccines that are effective in the general population but not in WLHIV (e.g. because of immune dysfunction) would still be valuable, but efforts should be undertaken to develop vaccines that could be used by WLHIV. Cisgender women and all gender-diverse people with a female reproductive tract are the primary focus of therapeutic HPV vaccines, given the large disease burden related to cervical cancer. Nonetheless, cisgender men and transgender women could receive individual benefits from therapeutic vaccines related to other HPV-related cancers, such as anal cancers among men who have sex with men (MSM) and transgender women (particularly those living with HIV) and oropharyngeal cancers. Pregnant and breastfeeding women should be considered for inclusion in the target population as soon as possible, following collection of vaccine safety and efficacy/effectiveness data related to pregnancy and lactation as soon as ethically appropriate.

[6] To facilitate readability, the term "women" is used throughout this document to refer to all gender-diverse people at risk of cervical cancer, including cisgender women, transgender men, and non-binary, gender-fluid and intersex individuals born with a female reproductive system.

Parameter	Preferred characteristic	Notes
Vaccine delivery strategy	Population-based delivery, with no requirement for a preceding screening test OR Targeted vaccination based on positive test results.	Therapeutic HPV vaccines should be used in conjunction with efforts to scale up existing interventions. The most appropriate vaccine delivery strategy will be determined by existing health systems and vaccine delivery platforms, programmatic and testing infrastructure, benefit–risk assessments, cost-effectiveness and other population-specific considerations, which may also change over time. In settings where a large proportion of adult women have not already received prophylactic HPV vaccines in adolescence and screening coverage or testing capacity is low, and benefit–risk and cost-effectiveness assessments are favourable, population-based delivery without a preceding test is likely to be the optimal approach. Use of prophylactic HPV vaccines together with therapeutic vaccines could potentially provide benefits for women both with and without type-specific infection, particularly in settings where there remains a substantial risk of new infections at target ages. The impact and cost-effectiveness of this strategy should be evaluated. Options for population-level delivery include mass vaccination campaigns and delivery within points of contact within the health-care setting. HPV vaccination could be incorporated into a variety of health delivery settings, including primary care, family planning, antenatal and postpartum care, HIV services and other sexual and reproductive health services, and for delivery to mothers during their children's immunization visits. Experience with delivery of COVID-19 vaccines to the target population and other programmes including prophylactic HPV vaccines may be informative. HPV testing could be used to guide therapeutic HPV vaccination on a population level through a "test and vaccinate" strategy, particularly as screening and testing infrastructure is scaled up and costs and feasibility of the tests improve. If testing is used to target vaccination, use of self-collected samples and point-of-care testing would be highly desirable. Therapeutic HPV vaccines focused on infection could also be used within well-established screening programmes (e.g. after a positive HPV test and a negative follow-up triage test or no evidence of precancer on further evaluation). Communication, community outreach and marketing strategies regarding therapeutic HPV vaccines should be considered in advance. Distinguishing therapeutic from prophylactic vaccines will be important, as will language around "vaccines" versus "treatment" – particularly in settings where women without known infection will be vaccinated. Messaging may have a significant impact on vaccine acceptability and hesitancy.

Parameter	Preferred characteristic	Notes
Schedule	A single dose for primary immunization would be ideal. A two-dose primary schedule, and possible booster dosing, would be considered acceptable, particularly for first-generation vaccines.	Single-dose vaccination would greatly facilitate population-based vaccine delivery. However, it is likely to be difficult, from a biological standpoint, to develop a single-dose therapeutic vaccine with a sufficient immune response. Depending on the vaccine platform and formulation, multiple doses might be needed and, where possible, should be aligned with existing points of contact with the health-care system. WLHIV, in particular, may require multiple doses to enhance efficacy. The ability to provide a take-home subsequent dose for self-administration may also facilitate population-based delivery of vaccination. Acceptability of a multiple dose schedule is likely to be greater in a setting with targeted vaccination based on positive test results. Research should determine the requirements, including the timing of doses and intervals between them, for primary dosing and/or booster doses. Refinements could be made post-licensure, as for other vaccines (e.g. prophylactic HPV vaccines, COVID-19 vaccines).
Route of administration	Parenteral or oral delivery.	Parenteral routes of administration include injection (intramuscular or subcutaneous) and intradermal (needle-free transdermal or microarray patch). Needle-free methods are preferred for ease of administration, including self-administration. Local mucosal immunity likely plays an important role in the mechanism of action of therapeutic HPV vaccines. In addition to oral delivery, other potential mucosal routes of administration include nasal, vaginal and rectal delivery. Self-administered intravaginal products are increasingly used in many contexts. However, the acceptability and feasibility of this route are likely to be lower than for parenteral or oral administration and would need to be explored within a population-based delivery strategy. Research should determine the route of administration to balance vaccine efficacy and delivery considerations optimally. Feasibility, acceptability and other end-user preferences of formulation for vaccine administration need to be further evaluated for consideration within a broad population-based delivery strategy.
Safety	A safety profile that is comparable to current WHO-recommended adult vaccines.	Consideration should be given in advance to understanding the safety of therapeutic HPV vaccines during pregnancy and lactation, including early DART studies and measures taken for ethical and safe inclusion of pregnant and breastfeeding women in clinical trials. Evidence should be generated on safety and longitudinal outcomes when women receive therapeutic HPV vaccines in the setting of an undiagnosed cervical precancer or invasive cervical cancer. Natural HPV cervical infection induces an influx of activated target T cells for HIV. Evidence should be evaluated and considered carefully to determine whether a therapeutic vaccine might transiently increase similar populations of HIV target cells in the genital tract.

Parameter	Preferred characteristic	Notes
Efficacy	For vaccines only clearing HPV types 16 and 18, high efficacy will likely be needed (e.g. 70–90%).	Initial modelling results suggest that a relatively high efficacy in clearing HPV 16 and 18 infections will be needed to drive broad population impact and cost-effectiveness, particularly as scale-up of existing cervical cancer interventions expands.
	Lower efficacies against HPV types 16 and 18 infection could be acceptable in the setting of other favourable vaccine attributes, such as some efficacy in causing regression of precancers, cross-protection against other HPV types, or ongoing immune responses that could clear reinfections.	However, impact and cost-effectiveness would be increased in the setting of cross-protection against other HPV types, some efficacy in regressing precancers, and ongoing immune responses that could clear reinfections. These influential attributes will need to be evaluated. Minimally acceptable thresholds for vaccine efficacy can be further informed by a full value of vaccine assessment, additional information about likely vaccine characteristics from ongoing research, and input from key stakeholders. The impact of therapeutic HPV vaccines will also be higher when the timeline to develop and implement them is shorter. Thus, trade-offs between efficacy and time to development should be evaluated in future value assessments. Consideration should also be given to evaluating the impact of co-administration of prophylactic HPV vaccine with therapeutic HPV vaccine. Separate studies conducted in WLHIV should determine efficacy and the potential need for additional doses in this subpopulation.
Concomitant use	Demonstration of favourable safety and immunological non-interference upon co-administration with other vaccines recommended for use.	Evidence should be collected on the ability to co-administer therapeutic HPV vaccines with other vaccines given in similar target populations, including prophylactic HPV vaccines, and with currently recommended treatments for HPV-related precancers. Lack of clinically important interference in immunogenicity for HPV therapeutic vaccines and for co-administered vaccines, as well as safety of co-administration, should be documented in pre- or post-licensure studies.

9.2 PPCs for therapeutic HPV vaccines used to treat cervical precancers

PPCs for therapeutic HPV vaccines that **primarily treat (cause regression of) high-grade cervical** precancers are described in Table 2. Additional attributes that are preferred for therapeutic HPV vaccines regardless of vaccine type are listed in Section 9.3.

Table 2. Preferred product characteristics for therapeutic HPV vaccines used to treat cervical precancers

Parameter	Preferred characteristic	Notes
Indication	Regression of high-grade cervical precancers (i.e. CIN2/3), at a minimum those associated with HPV types 16 and 18. Regression of high-grade cervical precancers due to other oncogenic HPV types or clearance of additional HPV infections or low-grade cervical lesions would have added benefit.	Therapeutic HPV vaccines that cause regression of cervical precancers and are preferable to existing cervical precancer treatments with respect to efficacy, safety, cost, delivery and/or acceptability to women could be useful interventions in a variety of settings globally. Therapeutic HPV vaccines might also provide benefit as an adjunct to existing treatments in improving efficacy or reducing recurrences (e.g. among WLHIV). Reduction of precancer is an established proxy for prevention of invasive cervical cancer, which is the goal of therapeutic HPV vaccines. Clinical endpoints – including the time frame for assessing precancer regression and whether associated viral clearance is an essential component of the primary outcome and how to assess it – will need to be refined in discussion with regulators. HPV types 16 and 18 account for 70% of cervical precancers that progress to invasive cervical cancer. Therefore, minimally viable first-generation vaccines should include HPV 16 and 18. Cross-protection against cervical precancers associated with additional oncogenic HPV types or clearance of associated HPV infection or low-grade cervical lesions would have added benefit. Inclusion of additional types in the vaccine may also add benefit. The next priority for inclusion should be HPV types 45, 35, 31, 33, 52 and 58. However, the inclusion of additional HPV types may result in trade-offs such as cost and complexity of manufacturing, potential effects on immunogenicity, and higher vaccine prices. The primary indication is related to cervical precancers; however, additional efficacy against other HPV-related precancers (e.g. vaginal, anal, head and neck) would be valuable.

Parameter	Preferred characteristic	Notes
Target population	Women with a positive cervical cancer screening test (e.g. HPV DNA testing) who would require treatment according to current screening guidelines.	WHO recommends screening for cervical cancer with a high-performance test (e.g. HPV DNA testing) in the general population of women at age 30 years, with repeat screening every 5–10 years up to age 49 years. WHO recommends screening of WLHIV with a high-performance test starting at the age of 25 years and repeated every 3–5 years through to 49 years. The target population includes WLHIV who have more frequent and rapid progression to cervical precancers and invasive cancer following oncogenic HPV infection. The efficacy and safety profile of the vaccine may require additional evaluation in this population. The extent to which the therapeutic vaccine clears infection, in addition to effects on precancer, can determine the role of vaccination even when precancer has been ruled out (e.g. vaccinating in a "screen-triage-and-treat" scenario with a positive primary test and negative triage test). Screening with a high-performance test before vaccination is desirable. However, in settings or populations with high rates of cervical precancers, and with constrained accessibility to screening, vaccination without testing could be considered, assuming a favourable benefit–risk assessment. Consideration should be given in advance to understanding the safety of therapeutic HPV vaccines during pregnancy, including early DART studies and measures taken for ethical and safe inclusion of pregnant women in initial clinical trials whenever possible.

Parameter	Preferred characteristic	Notes
Vaccine delivery strategy	Alignment with existing cervical cancer screening and treatment programmes. HPV testing and vaccination may occur outside of structured screening programmes.	The most appropriate vaccine delivery strategy in different settings will be determined by related health systems and programmatic factors, as well as the extent to which cervical cancer screening programmes are well established. Depending on their final attributes and how they compare with or add to existing treatments, on balance and with respect to efficacy, safety, cost, ease of delivery and/or acceptability to women, therapeutic HPV vaccines may replace or supplement current WHO-recommended treatments within programmes. Ideally, vaccination would occur at the time of receiving positive HPV testing results – preferably the same day as testing. Use of self-collected samples and point-of-care testing to target vaccination would be highly desirable. HPV testing followed by immediate therapeutic HPV vaccination for those testing positive – a "test and vaccinate" approach – can be done in a variety of settings, including primary care, family planning, postpartum care, and other sexual and reproductive health services, as well as for mothers during their children's immunization visits. For WLHIV, delivery of therapeutic HPV vaccine could be facilitated through HIV treatment and care services where cervical cancer screening should be considered an essential part of care. Whenever possible, women with positive HPV tests should receive a cervical evaluation to rule out invasive cancer. Immediate receipt of a vaccine can occur as a woman is referred for cervical evaluation. If vaccine characteristics allow, a population-based vaccination delivery strategy, without preceding testing, may be considered in certain settings with high prevalence of cervical precancers and/or a lack of feasible screening services. In addition to meeting other criteria, such as programmatic feasibility and cost-effectiveness, a more rigorous safety profile may be needed when vaccinating those without a preceding positive HPV test, as more women without disease will also be vaccinated. Mass vaccination campaigns or routine delivery could be considered. Depending on the performance of the product, women should be encouraged to receive cervical cancer screening according to existing guidance when services become available. Communication, community outreach and marketing strategies regarding therapeutic HPV vaccines should be considered in advance, particularly in relation to current communication for prophylactic vaccines. Messaging may affect acceptability.

Parameter	Preferred characteristic	Notes
Schedule	Ideally, up to two doses for primary immunization. Additional booster doses may also be acceptable for lasting disease modification.	It is likely to be difficult, from a biological standpoint, to develop a single-dose therapeutic vaccine with a sufficient immune response. Depending on the vaccine platform and formulation, 2–3 doses might be needed for initial immunization or to maintain longer-term disease modification. Research should determine the requirements for primary dosing and booster doses. Refinement could be done post-licensure, as for other vaccines (e.g. prophylactic HPV vaccines, COVID-19 vaccines). If more than one dose is required, aligning the dosing schedule with existing delivery platforms or points of contact with the health-care system, where possible, would be preferable. Clinical trials among WLHIV will be important to understand if additional doses are required to achieve optimal efficacy, including comparisons with existing treatments.
Route of administration	Parenteral or mucosal (e.g. oral, vaginal) delivery.	Parenteral routes of administration include injection (intramuscular or subcutaneous) injections and intradermal (needle-free transdermal or microarray patch). Needle-free methods are preferred for ease of administration, including self-administration. Mucosal routes of administration include oral, nasal, rectal and vaginal delivery. Mucosal formulations also enable self-administration, and self-administered intravaginal products are increasingly used in many contexts. Local mucosal immunity is likely to play an important role in the mechanism of action of therapeutic HPV vaccines. Research should determine the route of administration in order to optimize vaccine efficacy and delivery considerations. Mucosal delivery other than oral administration, such as intra-vaginal delivery, has traditionally been considered difficult to deploy; however, this is likely to be less of a constraint within cervical cancer prevention programmes. Potential intravaginal products would require criteria for standardization (e.g. related to menses, intercourse, use of other products). Feasibility, acceptability and other end-user preferences of formulation for vaccine administration need to be further evaluated.

Parameter	Preferred characteristic	Notes
Safety	A safety profile that compares favourably with current WHO-recommended treatments for cervical precancers and has a favourable benefit–risk assessment.	A favourable comparison with existing treatments for cervical precancers might take into consideration additional factors such as relative efficacy, acceptability, ease of delivery and overall benefit–risk assessment. Evidence should be generated on safety and longitudinal outcomes of therapeutic HPV vaccines, particularly when women might be vaccinated in the setting of an undiagnosed invasive cervical cancer. Consideration should be given to collecting supporting evidence on these outcomes during pre-licensure studies and designing post-licensure studies to evaluate them. Consideration should also be given in advance to understanding the safety of therapeutic HPV vaccines during pregnancy and lactation, including early DART studies and measures taken for ethical and safe inclusion of pregnant and breastfeeding women in clinical trials whenever possible. Natural HPV cervical infection induces an influx of activated target T cells for HIV. Evidence should be evaluated and carefully considered to determine whether a therapeutic vaccine might transiently increase similar populations of HIV target cells in the genital tract, and whether this differs from other treatments (e.g. ablation).
Efficacy	Efficacy that results in a favourable comparison with current WHO-recommended treatments for cervical precancers, factoring in programmatic considerations.	Therapeutic HPV vaccines that have lower efficacy than existing treatments in clinical trials might still have similar, or greater, programmatic effectiveness if they result in improved delivery and uptake. Minimally acceptable thresholds for vaccine efficacy can be further informed by vaccine impact modelling studies, input from key stakeholders, and further information about likely vaccine characteristics from ongoing research. Therapeutic HPV vaccines may result in ongoing immune responses that could clear reinfections or prevent recurrences over time. The extent to which this occurs and the duration of immune memory after therapeutic vaccination will need to be evaluated. Consideration should also be given to evaluating the impact of co-administration of prophylactic HPV vaccine with therapeutic HPV vaccine in terms of long-term response.

9.3 Parameters common to both types of therapeutic HPV vaccines

Several parameters included in the WHO PPCs for therapeutic HPV vaccines are applicable to both types of vaccine (Table 3).

Table 3. Parameters common to both types of therapeutic HPV vaccines

Parameter	Preferred characteristic	Notes
Product stability and storage	Stability under refrigerated conditions (2–8°C, the standard cold chain) for 24 months would be acceptable, but stability at room temperature (20°C) would be ideal.	Vaccine stability characteristics that facilitate storage and deployment in LMIC settings are preferred. Typically, vaccines or any component presented for WHO prequalification should not require storage at less than -20°C *(8,83)*. However, deviations from these characteristics have occurred (e.g. for Ebola and COVID-19 vaccines), after assessing whether issues can be mitigated (e.g. appropriate management of ultracold chain). Higher-temperature storage immediately prior to administration should use 40°C as the target threshold temperature whenever possible *(83)*.
Concomitant use	Demonstration of favourable safety and immunological non-interference upon co-administration with other vaccines or with precancer treatments recommended for use.	Evidence should be collected on the ability to co-administer therapeutic HPV vaccines with other vaccines given in similar target populations, including prophylactic HPV vaccines, and with currently recommended treatments for HPV-related precancers. Lack of clinically important interference in immunogenicity for HPV therapeutic vaccines and for co-administered vaccines, as well as safety of co-administration, should be documented in pre- or post-licensure studies.
Value assessment and affordability	The vaccine should be cost-effective and should have a favourable value assessment relative to existing cervical cancer prevention interventions. Dosage, regimen and cost of goods amenable to affordable supply; price should not be a barrier to access in LMICs.	A full value of vaccine assessment for therapeutic HPV vaccines should be conducted, both for vaccines that primarily clear HPV infections and for those that primarily treat cervical precancers, and associated delivery strategies, in the context of realistic scale-up of competing interventions *(76)*. Future development and availability of HPV point-of-care tests, with increased uptake (e.g. using self-sampling), may increase the value of therapeutic HPV vaccines by enabling a rapid "test and vaccinate" approach. Alternatively, such tests may make existing screening and treatment programmes more feasible and cost-effective. The greatest value should be placed on saving additional lives on the path to cervical cancer elimination in the next 30–40 years – i.e. the interim period before the impact of prophylactic HPV vaccine scale-up is likely to be seen. Thus, the value assessment will depend on how soon therapeutic HPV vaccines can be developed and implemented. The impact and cost-effectiveness of co-administration of therapeutic and prophylactic HPV vaccines should also be assessed.
Prequalification and programmatic suitability	The vaccine should be prequalified according to the WHO process outlined *(84)*.	WHO-defined criteria for programmatic suitability of vaccines should be met *(8,83)*.

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