WHO preferred product characteristics for therapeutic HPV vaccines

NOTE: This draft document is being posted for the purpose of inviting public comments and suggestions on the content contained herein, before the document will be considered by WHO's Product Development for Vaccines Advisory Committee (PDVAC) for endorsement. Written comments proposing modifications to this text must be received by 6 October 2023 and entered in the Comment Form (available separately) and should be addressed to Dr Holly Prudden at pruddenh@who.int with the subject line “Comment: WHO PPCs for therapeutic HPV vaccines”.
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Abbreviations

ART: anti-retroviral 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
NAATs: nucleic acid amplification tests
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

Development of therapeutic vaccines for human papillomavirus (HPV) may provide an important addition to the current methods to prevent and treat cervical cancer. Cervical cancer, caused almost exclusively by sexual transmission of oncogenic types of HPV, is an important public health problem globally (1). In 2020, an estimated 604,000 women¹ were diagnosed with cervical cancer, and approximately 342,000 women died from the disease (2). Nearly 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 a 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) if three key targets are achieved by 2030: 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 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, and persistent inequities in access to cervical cancer prevention programmes are major hurdles to reaching the Strategy goals, particularly in LMICs (5).

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 cervical cancer prevention efforts.

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

As a first step in defining therapeutic HPV vaccine PPCs, a WHO-convened group of experts assessed the public health needs that might be addressed by therapeutic HPV vaccines,

¹ All individuals have the right to sexual and reproductive health care. In this document, we recognize that most of the available evidence on cervical cancer is based on study populations of cisgender women, and we also recognize 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, we use the term “women” to refer to all gender-diverse people at risk for cervical cancer. Cervical cancer prevention services must consider the needs of – and provide equitable care to – all individuals independently of gender identity or its expression.
considering the goal of saving additional lives on the path to cervical cancer elimination, especially within the next 3 to 4 decades as prophylactic vaccination is scaled up. They identified two overarching contexts:

- In settings where it has been difficult to scale up cervical cancer screening and treatment, there is a need to reach women who have likely not received prophylactic HPV vaccines to reduce the overall proportion that will develop or already have cervical precancers, and

- In settings where screening and treatment is occurring, there is a need for an alternative, simpler treatment to reduce loss-to-follow-up and increase the overall proportion of women that are effectively treated following a positive test.

Ideally, therapeutic HPV vaccines would have high efficacy in both clearing high-risk HPV infection to prevent development of cervical precancers and in 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: For initial licensure, these vaccines would be expected at a minimum to clear infection and/or prevent high-grade cervical precancer due to HPV types 16 and 18, 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. They could also be used to clear infection 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 would be used mainly 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 as opposed to targeted vaccination based on HPV testing, will not only depend on vaccine characteristics such as efficacy in clearing infection versus causing regression of high-grade precancers, but also on factors such as: the extent to which prophylactic HPV vaccination and cervical cancer screening and treatment programmes have been scaled up; the prevalence of cervical precancers at different ages, which may vary according to the proportion of women living with HIV (WLHIV); cost-effectiveness; and programmatic and health systems factors.
1. 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 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, is fundamental to this mission.

WHO vaccine preferred product characteristics (PPCs) documents describe such parameters as vaccine indications and target populations, considerations for safety and efficacy evaluation, and delivery strategies (6). WHO PPCs are intended to encourage product innovation and facilitate vaccine development, particularly for use in low- and middle-income countries (LMICs), which 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 vaccine introduction and impact can be substantially delayed. WHO PPCs emphasize LMIC perspectives, in addition to those for HICs, to encourage 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, 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 LMIC use and planning to seek WHO policy recommendations and prequalification for their products (7). The PPCs also aim to reach policy makers and programme implementers 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 (8)(9).

2. HPV therapeutic vaccines – 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 two minutes (10). Furthermore, few diseases reflect global inequities as much as cervical cancer, with 90% of cervical cancer deaths occurring in LMICs (10).
In 2020, the World Health Assembly, comprised of 194 WHO Member States, approved a Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem (3). The WHO Strategy set a goal of reducing cervical cancer cases below a global threshold of 4 cases per 100,000 women-years. Because cervical cancer is almost exclusively caused by cervical infection with oncogenic types of human papillomavirus (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 2030 targets are successfully reached by 2030 and sustained (4)(11):

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

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 Strategy targets for implementation of these 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 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 October 2021 to November 2022, WHO convened a series of global multidisciplinary consultations comprised of basic scientists, clinicians, epidemiologists, vaccinologists and public health programme and policy experts from LMICs and HICs, to discuss the need, goals, and potential value of therapeutic HPV vaccines and key considerations for developing therapeutic HPV vaccine PPCs (12). 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.

Experts agreed that the strategic public health goal of therapeutic HPV vaccines should be aimed at saving additional lives on the path to cervical cancer elimination, particularly in the next 30-40 years, the interim period before the impact of prophylactic HPV vaccine scale-up is likely to be seen. Development of therapeutic vaccines would also aim to address gaps in scaling-up cervical cancer screening and treatment programmes, as many LMICs currently have virtually 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 from the WHO consultations (12).
3. Background on HPV and cervical cancer

3.1 HPV infection and routes of transmission

Human papillomviruses 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 (13). Multiple HPV genotype infections are common, particularly in women living with HIV (WLHIV)(14).

High-risk HPV types infect basal epithelial cells of the anogenital mucosa via micro-abrasions in the epithelial lining. Thus, the predominant route of transmission is through penetrative sex, although transmission has also been associated with other types of sexual activity (15).

The probability of HPV transmission per sex act has been estimated to be around 40% (range 5-100%) (16). 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 (17). The risk of oropharyngeal cancer is increased in women with cervical infection and in their partners, providing evidence of genital-oral transmission (18).

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., are oncogenic) (19). Virtually all cervical cancers are caused by infection with a high-risk HPV, of which there are at least twelve (20). Two high-risk types, HPV types 16 and 18, are associated with 70% of all cervical cancers (21). An additional five high-risk types, HPV types 31, 33, 45, 52 and 58, are estimated to be responsible for another 20% of cervical cancers (22). 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 (10).

3.3 Natural history of HPV infection

3.3.1 General population

Most HPV infections are asymptomatic and resolve spontaneously. Approximately 40% to 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 to persist than low-risk HPV infections (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 may take months to years. Without intervention in these women, an additional 3–5% 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 those with weakened immune systems, such as untreated women living with HIV infection (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 (24). In addition to an increased risk of HPV acquisition among WLHIV, the time to clear infection is longer (28) and the chances of recurrent infection are higher compared to HIV-uninfected women (29). Risk of HPV acquisition and progression inversely correlates with CD4 T cell count, although this association can be mitigated in those virally suppressed on anti-retroviral therapy (ART) (27).

3.4 Epidemiology of HPV infection

Data from high-income settings show that between 50% to 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). Thus, adolescent girls and women under age 25 years 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 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).

3.5 Epidemiology of cervical cancer

In 2020 globally, there were an estimated 604,000 new cases of cervical cancer (age-standardized incidence rate 13.3 per 100,000 women) and 342,000 cervical cancer deaths (age-standardized mortality rate 7.3 per 100,000 women) (Figure 1) (32). However, these figures reflect marked disparities in the global distribution of cases and deaths (Figure 2) (2). In many HIC settings, cervical cancer incidence is below 7 cases per 100,000, while incidence rates are above 29 per 100,000 in many countries in sub-Saharan Africa, where mortality rates may also be over 20 times higher compared to HICs (Figure 1) (2). In some countries, the majority of which are in Sub-Saharan Africa and Southeast Asia, cervical cancer is the most commonly diagnosed female cancer and leading cause of women’s cancer deaths (36).

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
contributing factor (27). In southern Africa, an estimated 64% of women with cervical cancer are living with HIV, as are 27% of women in Eastern Africa; HIV prevalence in these settings ranges from 2% to 27% in the general population (37)(38).

### 3.7 Other HPV-related cancers

In addition to causing cervical cancer, HPV is also associated with anal, penile, vaginal, vulvar, and oropharyngeal cancer. In 2020, the total number of non-cervical HPV-associated anogenital cancers was estimated to be 150,087 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 are oropharyngeal (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 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 the WHO Global Cervical Cancer Elimination Strategy (3).

#### 4.1 Primary prevention

Clinical trials have shown prophylactic HPV vaccines to be safe and highly efficacious in preventing persistent infection with vaccine-type HPV and related precancers (39)(40). 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 nine-valent vaccines protecting against HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 (41). Although there is evidence of some limited cross-protection against acquisition of other, non-vaccine HPV types (42), the vaccines do not have a therapeutic effect on pre-existing HPV infection or cervical lesions.

WHO recommends use of prophylactic HPV vaccines in early adolescence, with the primary target being girls 9-14 years old, before the typical initiation of sexual activity, and the primary focus being prevention of cervical cancer (43)(44). Vaccination of girls only, when coverage is high, provides herd immunity to boys as well as providing direct protection against cervical cancer, and is typically more cost-effective than vaccinating both sexes (41). However, vaccination of both boys and girls is carried out in some settings. School-based programmes are the main vaccine delivery strategy among LMICs, resulting in higher coverage than facility-based programmes (45).
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 (46)(47)(48).

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. 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. Cytologic tests (e.g., Papanicolaou tests, liquid-based cellular assessments) require trained cytologists in addition to higher-cost laboratory infrastructure. 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 relative to molecular screening.

WHO recommends HPV DNA or mRNA NAAT testing on provider-collected cervical samples as the primary screening test, starting at age 30 years for women in the general population and repeated every 5–10 years (49). Women can also provide self-collected vaginal swabs for HPV DNA testing. For WLHIV, HPV DNA or mRNA NAATs are also the recommended primary screening test to start at age 25 years, and repeated every 3–5 years (49). For both groups, after the age of 50 years, WHO recommends stopping testing following two consecutive negative screening results.

For women with a positive HPV test, WHO recommends either a “screen and treat” or “screen, triage and treat” approach. In the “screen and treat” approach, the decision to treat is based on a positive primary screening test only, preferably an HPV DNA or mRNA test. Before treatment, all women who have screened positive should undergo a visual examination of the cervix to exclude cervical cancer and 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”) with or without histologically confirmed diagnosis. The WHO recommended primary test is HPV DNA or mRNA detection followed by partial genotyping, VIA or cytology as a triage test (49).

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)2 or cold knife conization (CKC).

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2 In some countries, this terminology was changed to LEEP (loop electrosurgical excision procedure), and the two terms are often used interchangeably.
Women with suspected cancers must be referred for further evaluation and management (49).

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 (50). WHO recommends surgery and/or radiotherapy, with or without chemotherapy, for early stages of cervical cancer (49). WHO also recommends integrating palliative care into the treatment plan throughout the disease course. Effective early-stage treatment is paramount, as standard of care radio- and chemotherapies of late-stage cervical cancers tend to have low cure and survival rates (51).

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 global cervical cancer deaths over the next three to four decades.

5.1 Implementation and scale-up of prophylactic HPV vaccine programmes

As of July 2023, a total of 131 countries had introduced HPV prophylactic vaccines into their national immunization programmes (52). However, only an estimated 13% of young girls are fully vaccinated globally (10), and HPV vaccines have not reached those settings most in need: 60% of cervical cancer cases occur in countries that have not yet introduced prophylactic HPV vaccines (37).

Among the 47 countries in the WHO African region, which has the highest rates of cervical cancer in the world, only 23 countries have introduced HPV prophylactic vaccine into their national immunisation programmes as of April 2022, with coverage ranging from 0–77%. Challenges associated with meeting vaccination targets have included insufficient global supply of vaccines, costs of the programme, low acceptance of the vaccine, and additional resources required 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 (53). Furthermore, a Strategic Advisory Group of Experts on Immunization (SAGE) meeting held in April 2022 advised that countries may now choose a one- or two-dose schedule for 9–14-year-old girls, the primary target cohorts, and for women aged 15–20-years-old (44) that will simplify immunization implementation, increase supply, and reduce production bottlenecks and overall costs (54).
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). Only around a third of countries have managed to screen over 70% of women at least once in their lifetimes, with only 126 countries having screening coverage below this level (5). On average, only around 10% of women in LMICs have ever received cervical cancer screening (5).

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 (5). 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 likely still fall short of impact goals for this pillar of the cervical cancer elimination strategy.

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. 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 a concern (55).

In countries with high HIV prevalence, major barriers to cervical cancer prevention include high recurrence rates of dysplasia following treatment in WLHIV (56). There are also difficulties in treating larger lesions or lesions that occur predominantly inside the endocervical canal. These lesions tend to have higher failure rates and are more common in unscreened populations in LMICs (57). Building capacities to perform LLETZ to treat such large lesions in LMIC settings can be quite challenging.

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 on the road to cervical cancer elimination (58). 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 not vaccinated in adolescence, to identify and treat those who may already have cervical precancers or invasive cancers, and thus to save millions of additional lives (59). Although coverage for both prophylactic vaccination and screening and treatment is currently low globally, experts felt that there was much more promise to rapidly scale up adolescent prophylactic HPV vaccination in the coming years. However, scaling up screening and treatment programmes was felt to be much more challenging and predicted to lag further behind global targets.

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

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

- In settings where screening and treatment is being implemented, there is a need for an alternative, simpler, and more accessible treatment following a positive test to decrease loss-to-follow-up and increase the overall proportion of women with high-risk HPV infections and/or precancers who are effectively treated.

6. Therapeutic HPV vaccine development

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 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 have different mechanisms than 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 (60). However, for therapeutic vaccines intended to target early stages of pathogenesis such as persistent infection, 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 prevention of precancer (61)(62).

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 (63). Antibodies are insufficient to clear persistent HPV infection or reduce precancerous lesions (64). Thus, while current prophylactic HPV vaccines rely on antibody-mediated protection, post-exposure therapeutic vaccines will likely require induction of cell-mediated immunity with effective T cell responses against early viral proteins across genetically diverse populations.

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 (65). Thus, 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, because the vaccines focused on earlier stages will be acting upon cells that are more conducive to clearance by robust immune responses.

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 (66). 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 (67).

To date, therapeutic HPV vaccine development has primarily focused on candidates targeting 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. A systematic review of completed phase 2 and 3 clinical trials of therapeutic HPV vaccine candidates targeting CIN2/CIN3 lesions identified 12 published studies through

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2022: 6 studies with vector-based vaccines, 3 with peptide and protein-based vaccines, and 3 with nucleic acid-based vaccines (68). In addition, at least 6 therapeutic vaccine products were registered as being in active Phase 1 or 2 studies as of June 2023.4

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 (67)(68). 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 (68). 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, also occurs at the same time as regression of precancers (68).

All candidates to date have been multiple-dose products (most commonly 3 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

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.

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 pre-determined point in time (e.g., at 12 months) in someone who had a positive test at baseline. Evaluating prevention of high-grade cervical precancer will require serial histological evaluation and calculation of rates of progression from low-grade (e.g., CIN1) or no precancer to high-grade (e.g., CIN2/3) precancer. The appropriate clinical endpoints, including the precise time frame for evaluating clearance or progression, and whether infection clearance will require two negative tests (e.g., at 12 and 15 months), 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 and/or prevention of high-grade precancers, as measured in trials, is an acceptable surrogate for

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4 www.clinicaltrials.gov: NCT04607850; NCT03913117; NCT04490512; NCT00788164; NCT04131413; NCT03911076, accessed 27 June 2023.
prevention of cervical cancer, as has been established with prevention of infection for prophylactic HPV vaccines (69). Conversely, a vaccine might prevent progression to high-grade cervical precancer without entirely clearing infection.

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 may also occur compared with or in combination with prophylactic HPV vaccination.

For evaluating therapeutic HPV vaccines with an infection clearance endpoint, adequately powered clinical trials can be conducted with fewer participants, and more quickly, than for 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 important in understanding efficacy. No therapy is currently recommended for HPV infection when high-grade precancer has been ruled out, so a placebo comparator is acceptable. Including only those with persistent HPV infection at baseline, defined by the presence of type-specific HPV DNA on repeated clinical biological samples over a period (typically 6 months), 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 against high-grade cervical precancers would be useful in understanding whether their use can be broadened to increase potential public health value.

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 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 women with high-grade cervical precancers are not left untreated. WHO guidelines recommend treatment is initiated no later than 6 months following a positive screening. 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.

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 typically followed for histopathological regression of cervical lesions to CIN1 or no dysplasia (68). 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 to assess it, 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 (68). Experts speculate that vaccines capable of regressing CIN2/3 lesions are also likely to have 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 initial licensure may be as a standalone treatment, future vaccines with primary indications of regression of cervical precancers may also be considered as an adjunct to existing ablative treatments, or in combination with newer immune checkpoint inhibitors or genetically engineered T-cell therapy (70)(71), to enhance overall treatment outcomes and/or reduce disease recurrence rates. This may be particularly interesting for WLHIV, who have lower efficacy and higher recurrence rates with existing treatment.

6.3.3 Considerations for both vaccine approaches

Some outcomes could be evaluated post-licensure, e.g., progression to precancer in vaccines with a primary indication of clearance of infection, or extension of benefits to other anatomic sites, cross-protection, co-administration with prophylactic HPV vaccines, or different dosing regimens. If a multi-dose regimen is evaluated, efficacy data should be gathered whenever possible from those who only receive one-dose to inform potential possibilities for improving dosing regimens, e.g., if women don’t return for a second dose, they should still be followed for outcomes. Research will also be needed on whether therapeutic vaccination affects future assessment and diagnosis of cervical precancers or invasive cancer.

Consideration should be given for including in clinical trials populations of end-users that would accrue the greatest potential benefit from the vaccine, in particular individuals 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, inclusion of pregnant women in an ethical fashion whenever possible is desirable.

7. Potential public health value of therapeutic HPV vaccines

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

Aligning the potential mechanisms of action of future therapeutic HPV vaccines with the public health needs, the use of vaccines that primarily clear infection would be more favoured for clearing infection and preventing precancers 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. Those designed primarily to treat existing precancers may be more appropriate following testing in
relatively older ages as part of cervical cancer screening and treatment efforts. However, these approaches are not mutually exclusive, and efficacious therapeutic HPV vaccines with either of these actions – or preferably some degree of both – might be useful additions to cervical cancer prevention efforts in both contexts, depending on their attributes and how they are used within existing health infrastructure.

7.2 Public health value considerations for therapeutic HPV vaccines

Multiple factors will need to be simultaneously considered to understand the potential value of therapeutic HPV vaccines, and their optimal characteristics, within the context of broader cervical cancer prevention programmes. Overarching factors include:

- Timeline for development: The value of therapeutic HPV vaccines will be higher when the timeline to develop and implement them is shorter, relative to ongoing scale-up of prophylactic vaccination programmes, aging of cohorts vaccinated with prophylactic HPV vaccines in adolescence, and efforts to broaden access to cervical cancer screening and treatment programmes in different settings.

- Background epidemiology and intervention scale-up: The potential added value of therapeutic HPV vaccines will be greater in the setting of lower coverage of existing interventions and higher background rates of vaccine-type oncogenic HPV infection, cervical precancers, and invasive cancers. These factors also affect the number of women needed to be vaccinated to prevent a cervical cancer case or death and thus vaccine cost-effectiveness.

- Vaccine characteristics: A key factor in determining potential value will be specific vaccine attributes, particularly the overall and relative efficacy in clearing or controlling high-risk HPV infection to prevent precancerous lesions versus causing regression of existing lesions. Efficacy or cross-protection against oncogenic HPV types beyond types 16 and 18 will broaden value (72), as will the presence of immune memory to clear future reinfections or prevent lesion recurrences. Factors that will ease delivery and increase coverage are important, particularly for LMICs, such as decreased number of doses, a simple route of administration, few side effects, a schedule that aligns with existing care infrastructure, and simplified cold chain and storage requirements.

- Health system and programmatic factors: These considerations 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 impacts potential added value. This includes healthcare access for those at risk and 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.
7.3 Modelling of therapeutic HPV vaccine impact

A well-validated model in 78 LMICs was developed as part of the Cervical Cancer Elimination Consortium and was instrumental in showing the potential lives that can be saved if the targets in the Global Strategy to Eliminate Cervical Cancer are achieved (4). It also highlighted the importance of scaling up screening and treatment in the next several decades, before the benefits of prophylactic vaccine scale-up are fully observed.

Preliminary modelling of therapeutic HPV vaccine impact using this platform demonstrated that population-based vaccination with a therapeutic HPV vaccine with high efficacy in clearing HPV infection and high coverage can have a substantial impact in reducing cervical cancer cases and mortality, particularly when there has been no scale-up of existing interventions (73). These findings are reinforced by models of the impact of therapeutic HPV interventions in Uganda (74) and in India (75), which showed that an HPV therapeutic vaccine might avert up to 25-35% of cervical cancers over 30 years, depending upon the product characteristics and level of intervention scale-up. Added benefits of therapeutic HPV vaccines drop as background scale-up of interventions approaches the Global Cervical Cancer Elimination Strategy 90-70-90 targets (3). The available models have demonstrated that efficacy in causing regression of high-grade cervical precancer in addition to efficacy in clearing infection, as well as the presence of immune memory (i.e., preventing reinfection or recurrence with the same HPV type), were very influential in increasing impact. Even modest additional efficacy (i.e., 50%) in regressing precancers was predicted to approximately double the number of cases and deaths averted, compared with high efficacy in clearing infection (i.e., 70-90%) alone (75)(73).

The LMIC 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; however, the overall impact was slightly reduced because of a drop off in the assumed proportion of women receiving the test and the current test sensitivity for infection. Planned cost-effectiveness analyses will better elucidate these trade-offs. For vaccines primarily being used as an alternative treatment for cervical precancers within screening programmes, the relative impact depends on the efficacy of the vaccine relative to the efficacies of existing cervical precancer treatments (e.g., cryotherapy or thermal ablation) and the degree to which each can be delivered in the fewest number of visits to avoid loss to follow up, which significantly impacts treatment outcomes.

Future analyses will include further exploration of impact in the setting of different vaccine characteristics and delivery considerations, realistic background intervention scale-up, additional analyses for WLHIV and cost-effectiveness analyses. In addition to modeling, 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 optimally meet public health goals 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.

### 8.1 Target populations

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

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

The age of women to be targeted is an important consideration, and target age may vary according to the vaccine indication and use case. 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 likely have cleared naturally. Vaccinating at earlier ages would also run the greatest risk of new infections being acquired after vaccination (assuming therapeutic HPV vaccines only act 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, availability of these vaccines may have benefits for special populations outside of this group, such as children or adults post-sexual assault or abuse, or people on chronic immunosuppressive treatments. Choice of target population will also need to take into consideration existing infrastructure to reach a particular group to achieve good uptake of therapeutic HPV vaccines, and its 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. Ideally HPV therapeutic vaccines would have high efficacy in clearing high-risk HPV, preventing progression to precancer, and regressing precancerous lesions, with an
excellent safety profile, and which could be feasibly delivered to target groups within health systems in both LMIC and HIC settings. 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 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 number and timing of doses, route of administration, and cold chain requirements will all affect programmatic feasibility.

8.3 Programmatic and delivery considerations

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 is broad population-based delivery to adult women, without preceding testing, which may be the most appropriate strategy to address 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 treatment approach.

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. 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. For a population-based strategy without testing, the number needed to vaccinate to prevent a single case of cervical cancer will be high, making cost-effectiveness a potential issue.

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, development of improved rapid point-of-care HPV diagnostics, and use with self-collected specimens, could significantly improve programmatic outcomes (76)(77). 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 broaden coverage and improve equity. Such an approach could be done 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 affected by vaccine hesitancy. Although 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 around cervical cancer and prevention. Prophylactic HPV vaccines have historically been promoted as vaccines to prevent cervical cancer rather than prevention of an STI, as STI vaccines may be perceived as stigmatizing (78). 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 as not all those receiving 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 therapeutic HPV vaccines can be delivered in LMIC as well as HIC settings. Scale-up and implementation will not only need to account for health system differences, but also cultural and social differences among countries. Requirements of vaccine procurement, cold chain and transportation, linkages with other health system services, and data systems also need to be considered. A critical factor in global access and uptake of vaccines is related to their cost-effectiveness and overall costs. A full value of vaccines 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).

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 against both infection and precancers. However, vaccines that are primarily designed to clear oncogenic HPV infection and those primarily designed to cause regression of high-grade cervical precancers may have different considerations in terms of how and for whom they are used, and their optimal characteristics. Both could play a role in achieving public health goals in LMIC and HIC settings. Thus, separate PPCs have been developed for each, as described in Tables 9.1 and 9.2 below. Preferred characteristics that are common to both vaccine approaches are described in Table 9.3.

This PPC guidance should not supersede existing WHO guidelines related to cervical cancer prevention, nor efforts to scale up existing prevention interventions (3). In all settings, to the extent 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(49)(41).
Table 9.1 Preferred product characteristics for therapeutic HPV vaccines used to clear oncogenic HPV infections.

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<td><strong>Indication</strong></td>
<td>For initial licensure: Clearances of HPV type 16 and 18 infection and/or prevention of high-grade cervical precancers associated with these HPV types.</td>
<td>The goal of clearing oncogenic infection would be preventing 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 (e.g., loss of HPV detection using a sensitive NAAT) is an acceptable surrogate for prevention of cervical cancer for therapeutic vaccines, as has been established with prevention of infection for prophylactic HPV vaccines. Discussions with regulators can also establish 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 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 in other sites (e.g., anal, vaginal, oropharyngeal) would be valuable.</td>
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<td><strong>Target population</strong></td>
<td>Adult women (e.g., ages 25 to 49 years) in settings where a high proportion have not already received prophylactic HPV vaccine.</td>
<td>The precise age range of adult women who should receive therapeutic vaccines may vary by setting, the delivery strategy, and over time, and may depend on: - Scale up and ages of delivery of prophylactic vaccines - Scale up of cervical cancer screening and treatment - Prevalence of existing precancer at different ages - Proportion of women living with HIV (WLHIV) in the setting; WLHIV may require vaccination at earlier ages - Cost-effectiveness analyses</td>
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5 To facilitate readability, the term “women” is used throughout this document to refer to all gender-diverse people at risk for cervical cancer, including cisgender women, transgender men, non-binary, gender-fluid and intersex individuals born with a female reproductive system.
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<td>Vaccine delivery strategy</td>
<td>In settings where a high proportion have not already received prophylactic HPV vaccine nor screening: Population-based delivery, with no requirement for a preceding screening test. In settings with HPV testing capacity: Targeted vaccination based on positive test results may be used.</td>
<td>The most appropriate population-level vaccine delivery strategy will be determined by existing health systems and vaccine delivery platforms, including mass vaccination campaigns and delivery within points of contact within the health care setting. Experience with delivery of COVID-19 vaccines to the target population and other programmes including prophylactic HPV vaccines may be informative. 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. In some settings, HPV testing may be used to guide therapeutic HPV vaccination on a population level through a “test and vaccinate” strategy. The choice of widespread vaccination without testing or</td>
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Targeted vaccination based on testing will depend on programmatic and testing infrastructure, cost-effectiveness, and other population-specific considerations. 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 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 an important impact on vaccine acceptability.

**Schedule**

A two-dose primary schedule, and possible booster dosing, would be considered acceptable; a single dose for primary immunization would be ideal.

It will likely 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 should be aligned with existing points of contact with the health care system where possible. WLHIV, in particular, may require multiple doses to enhance efficacy.

Single-dose vaccination and/or the ability to provide a take-home subsequent dose for self-administration will likely be important for population-based delivery of vaccination.

Research should determine the requirements, including the timing and intervals between doses, 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. Although self-administered intravaginal products are increasingly used in many contexts, acceptability and feasibility would need to be explored within the context of a population-based delivery strategy.

Research should determine route of administration to optimize vaccine efficacy and delivery considerations. Feasibility and acceptability, and other end-user preferences of formulation for...
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<tr>
<td>Safety</td>
<td>A safety profile that is comparable to current WHO-recommended adult vaccines.</td>
<td>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 carefully considered to determine whether a therapeutic vaccine might transiently increase similar populations of HIV target cells in the genital tract.</td>
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<tr>
<td>Efficacy</td>
<td>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.</td>
<td>Initial modelling results suggest that a relatively high efficacy in clearing HPV 16 and 18 infection will be needed for broad population impact in the setting of existing cervical cancer interventions. However, impact 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. The extent of cross-protection, regression of precancers, and duration of immune memory after therapeutic vaccination will need to be evaluated, as each of these parameters will influence the public health value and cost-effectiveness of therapeutic HPV vaccines. 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 will need to be assessed to determine efficacy and the potential need for additional doses.</td>
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<tr>
<td>Concomitant use</td>
<td>Demonstration of favourable safety and immunologic non-interference upon co-administration with other vaccines recommended for use.</td>
<td>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.</td>
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### Table 9.2 Preferred product characteristics for therapeutic HPV vaccines used to treat cervical precancers

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<td><strong>Indication</strong></td>
<td>Regression of high-grade cervical precancers (i.e., CIN2/3) associated with HPV types 16 and 18.</td>
<td>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 a useful intervention 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 ultimate goal of therapeutic HPV vaccines. Clinical endpoints will need to be refined in discussion with regulators, including the timeframe for assessing precancer regression and whether associated viral clearance is an essential component of the primary outcome and how to assess it. 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 (e.g., 31, 33, 35, 45, 52, 58) 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.</td>
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<td><strong>Target population</strong></td>
<td>Women with a positive cervical cancer screening test (e.g., HPV DNA testing) who would require treatment according to current screening guidelines.</td>
<td>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 through age 49 years. WHO recommends screening of WLHIV with a high-performance test starting at age 25 years and repeated every 3-5 years through 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 might require additional evaluation in this population.</td>
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<td>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).</td>
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<td>Although screening with a high-performance test before vaccination is desirable, in settings or populations with high prevalence of cervical precancers, and with constrained accessibility for screening, vaccination without testing could be considered. 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.</td>
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<td>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.</td>
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<tr>
<td>Vaccine delivery strategy</td>
<td>Alignment with existing cervical cancer screening and treatment programmes. HPV testing and vaccination may occur outside of structured screening programmes.</td>
<td>The most appropriate vaccine delivery strategy in different settings will be determined by related health systems and programmatic factors, and the extent to which cervical cancer screening programmes are well established. Depending on their final attributes and how they compare to or add to existing treatments, on balance, 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, which is 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, other sexual and reproductive health services, and 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. Mass vaccination campaigns or routine delivery could be considered. Depending on the</td>
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<td>Schedule</td>
<td>Ideally, up to two doses for primary immunization. Additional booster doses might also be acceptable for lasting disease modification.</td>
<td>It will likely 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, two to three 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.</td>
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<tr>
<td>Route of administration</td>
<td>Parenteral or mucosal (e.g., oral, vaginal) delivery.</td>
<td>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 likely plays an important role in the mechanism of action of therapeutic HPV vaccines. Research should determine route of administration to optimize vaccine efficacy and delivery considerations. Mucosal delivery other than oral administration, such as intra-vaginal delivery, have traditionally been considered difficult to deploy; however, this is likely 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.</td>
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<tr>
<td>Safety</td>
<td>A safety profile that compares favourably with current WHO-</td>
<td>A favourable comparison with existing treatments for cervical precancers might take into consideration additional factors such as</td>
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<tr>
<td><strong>Efficacy</strong></td>
<td>Efficacy that results in a favourable comparison with current WHO-recommended treatments for cervical precancers, factoring in programmatic considerations.</td>
<td>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.</td>
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<td>recommended treatments for cervical precancers and has a favourable benefit/risk assessment.</td>
<td>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).</td>
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Natal 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).
### Table 9.3 Parameters common to both types of therapeutic HPV vaccines.

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<td>Product stability and storage</td>
<td>Stability under refrigerated conditions (2–8°C) for 24 months would be acceptable, but stability at room temperature (20°C) would be ideal.</td>
<td>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 (7)(79). 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).</td>
</tr>
<tr>
<td>Concomitant use</td>
<td>Demonstration of favourable safety and immunologic non-interference upon co-administration with other vaccines or with precancer treatments recommended for use.</td>
<td>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.</td>
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<tr>
<td>Value assessment and affordability</td>
<td>The vaccine should be cost effective and 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.</td>
<td>A full value of vaccines assessment should be conducted for therapeutic HPV vaccines, both for vaccines that primarily clear HPV infections and those that primarily treat cervical precancers, and associated delivery strategies, in the context of realistic scale-up of competing interventions. 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, 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 could be developed and implemented. The impact and cost effectiveness of co-administration of therapeutic and prophylactic HPV vaccines should also be assessed.</td>
</tr>
<tr>
<td>Prequalification and programmatic suitability</td>
<td>The vaccine should be pre-qualified according to the WHO process outlined (80).</td>
<td>WHO-defined criteria for programmatic suitability of vaccines should be met (7)(79).</td>
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</table>
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vaccines—recommendations


82.

83.

84.

85.
Figure 1: Estimated age-standardized cervical cancer incidence rates and mortality rates in 2020 (all ages). From GLOBOCAN 2020, IARC (32).

Figure 3: Distribution of lifetime screening coverage among women aged 30–49 years, by country (2019). Adapted from Bruni et al, Lancet Global Health, 2022 (5).
Figure 4: HPV genome organization and focus of therapeutic vaccines