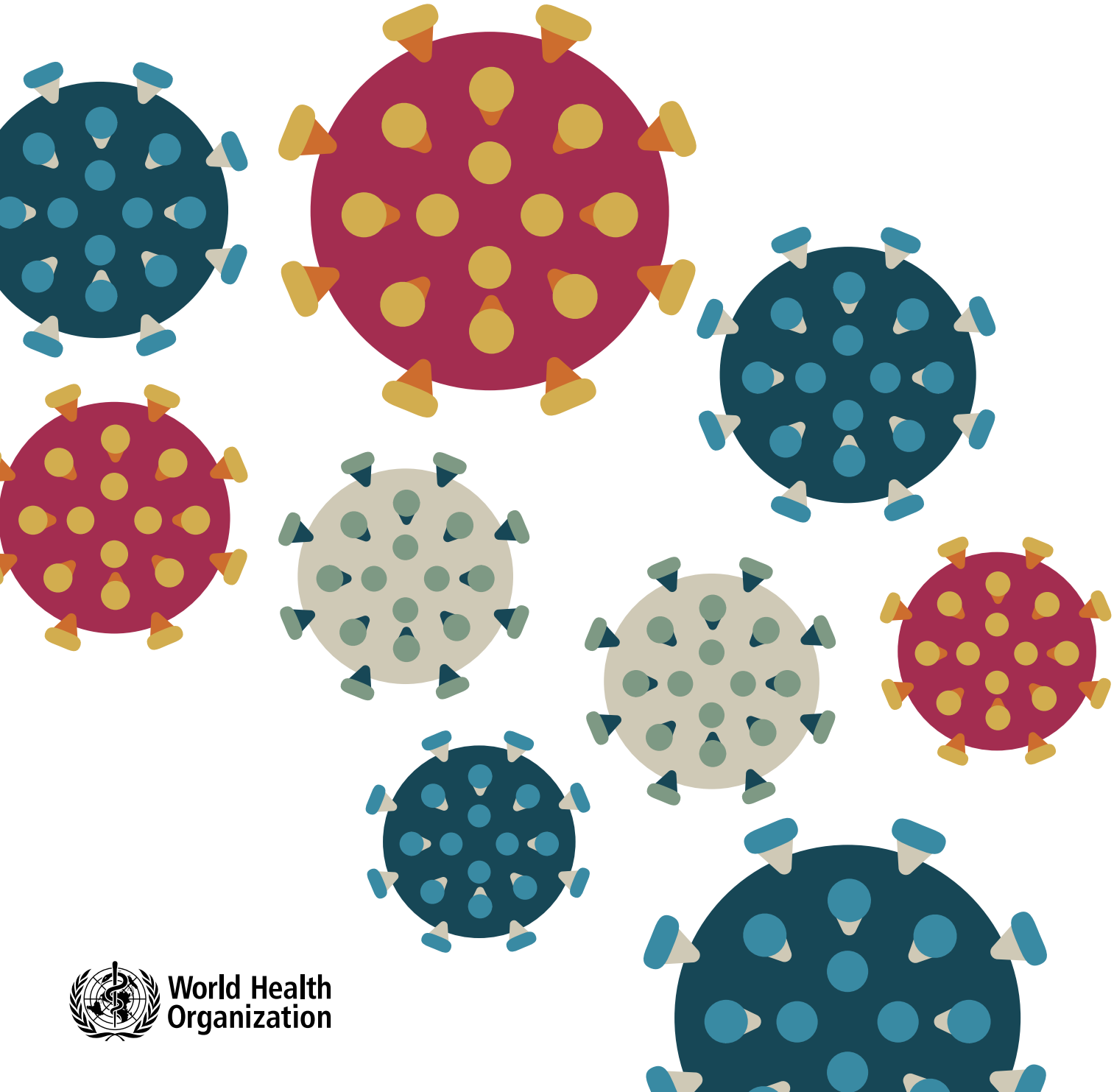
WHO preferred product characteristics for herpes simplex virus vaccines



World Health Organization

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ISBN 978-92-4-151558-0

Suggested citation. WHO preferred product characteristics for herpes simplex virus vaccines. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

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Design and layout by Lushomo.

Printed in Switzerland.

Contents

Acknowledgements

The Department of Reproductive Health and Research and the Department of Immunizations, Vaccines and Biologicals at the World Health Organization (WHO) would like to thank the many individuals who contributed to the development of this document. The consultation process for developing herpes simplex virus (HSV) vaccine preferred product characteristics (PPCs) and preparation of this publication were coordinated by Sami Gottlieb, Department of Reproductive Health and Research, and Birgitte Giersing, Department of Immunizations, Vaccines and Biologicals.

We thank the members of the HSV Vaccine PPC writing and working groups for their assistance with drafting and revising this document: Jeff Cohen, National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, United States of America (USA); Carolyn Deal, NIAID, Bethesda, MD, USA; Sinead Delany-Moretlwe, University of Witwatersrand, Johannesburg, South Africa; Birgitte Giersing, WHO, Geneva, Switzerland; Sami Gottlieb, WHO, Geneva, Switzerland; Julian Hickling, WHO consultant, Cambridge, UK; Christine Johnston, University of Washington, Seattle, WA, USA; Rebecca Jones, WHO consultant, Cambridge, UK; David Kaslow, PATH, Seattle, WA, USA; David Koelle, University of Washington, Seattle, WA, USA; Nelly Mugo, Kenya Medical Research Institute (KEMRI), Nairobi, Kenya; Francis Ndowa, Skin and GU Medicine Clinic, Harare, Zimbabwe; Julia Schillinger, US Centers for Disease Control and Prevention (CDC) and New York City Department of Health and Mental Hygiene, New York, NY, USA; Deborah Watson-Jones, London School of Hygiene and Tropical Medicine, London, United Kingdom (UK) and National Institute for Medical Research, Dar es Salaam, United Republic of Tanzania.

We gratefully acknowledge the contributions of the expert participants at the initial consultation on HSV vaccine PPCs in March 2017: Ian Askew, WHO, Geneva, Switzerland; Marie-Claude Boily, Imperial College, London, UK; Martha Brady, PATH, Washington, DC, USA; Nathalie Broutet, WHO, Geneva, Switzerland; Z. Mike Chirenje, University of Zimbabwe, Harare, Zimbabwe; Carolyn Deal (Co-Chair), NIAID, Bethesda, MD, USA; Sinead Delany-Moretlwe, University of Witwatersrand, Johannesburg, South Africa; Birgitte Giersing, WHO, Geneva, Switzerland; Sami Gottlieb, WHO, Geneva, Switzerland; Raymond Hutubessy, WHO, Geneva, Switzerland; Christine Johnston, University of Washington, Seattle, WA, USA; David Kaslow (Co-Chair), PATH, Seattle, WA, USA; David Koelle, University of Washington, Seattle, WA, USA; Peter Leone, University of North Carolina, Chapel Hill, NC, USA; Odile Leroy, European Vaccine Initiative, Universitäts Klinikum, Heidelberg, Germany; Katharine Looker, University of Bristol, Bristol, UK; Nicola Low, University of Bern, Bern, Switzerland; Purnima Madhivanan, Florida International University, Miami, FL, USA; Nelly Mugo, KEMRI, Nairobi, Kenya; Nicolas Nagot, University of Montpellier, Montpellier, France; Julia Schillinger, US CDC and New York City Department of Health and Mental Hygiene, New York, NY, USA; James Southern, Medicines Control Council, Pretoria, South Africa; João Paulo Toledo, Ministry of Health, Brasília, Brazil; Anna Wald, University of Washington, Seattle, WA, USA; Pingyu Zhou, Shanghai Skin Disease and STD Hospital, Shanghai, People's Republic of China.

We are grateful to the members of the WHO Product Development for Vaccines Advisory Committee for their review of the document: Klaus Cichutek, Paul Ehrlich Institut, Langen, Germany; Sinead Delany-Moretlwe, University of Witwatersrand, Johannesburg, South Africa; Bernard Fritzell, BFL Conseils, Jau-Dignac-et-Loirac, France; Barney Graham, NIAID, Bethesda, MD, USA; Gagandeep Kang, Translational Health Science and Technology Institute, Faridabad, India; Ruth Karron, Johns Hopkins School of Public Health, Baltimore, MD, USA; Jerome Kim, International Vaccine Institute, Seoul, Republic of Korea; David Kaslow, PATH, Seattle, WA, USA; Claudio Lanata, US Naval Medical Research Unit No 6, Lima, Peru; Shabir Mahdi, University of Witwatersrand, Johannesburg, South Africa; Mark Papania, US CDC, Atlanta, GA, USA; Yiming Shao, Chinese Center for Disease Control and Prevention, Beijing, People's Republic of China; Peter Smith, London School of Hygiene and Tropical Medicine, London, UK; Marian Wentworth, Management Sciences for Health, Medford, MA, USA.

Finally, we thank the members of the public and HSV community who commented on the document through the online public consultation process.

Funding

This work was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (Grant U01 AI108543) and by the UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP).

Abbreviations

GUD ..... genital ulcer disease (genital ulcers, blisters, or other painful lesions)

HIC ..... high-income country

HIV ..... human immunodeficiency virus

HPV ..... human papillomavirus

HSV-1 ..... herpes simplex virus type 1

HSV-2 ..... herpes simplex virus type 2

Ig ..... immunoglobulin

LMIC ..... low- or middle-income country

PBMC ..... peripheral blood mononuclear cell

PPCs ..... preferred product characteristics

SAGE ..... WHO Strategic Advisory Group of Experts on Immunization

SRH ..... sexual and reproductive health

STI ..... sexually transmitted infection

WHO ..... World Health Organization

Executive summary

The development of one or more herpes simplex virus (HSV) vaccines is an important goal for sexual and reproductive health (SRH) worldwide. Sexually transmitted genital HSV infections are estimated to affect more than 500 million people worldwide. Most of these infections are caused by HSV type 2 (HSV-2) but can also be caused by HSV type 1 (HSV-1). Genital infection with either type is lifelong and can lead to genital ulcer disease (GUD) and neonatal herpes. GUD caused by HSV-2 can recur frequently, and HSV-2 infection is also linked to increased risk of acquiring and transmitting HIV infection.

Although several candidate HSV vaccines have been tested in humans, currently there are no licensed vaccines against either HSV type. In addition to potential direct effects on HSV-associated morbidity and mortality, HSV vaccines might also have indirect effects on HIV acquisition and transmission, especially in settings with a substantial burden of HIV infection.

World Health Organization (WHO) preferred product characteristics (PPCs) provide guidance on the Organization's preferences for new vaccines in priority disease areas, specifically from the perspective of low- and middle-income countries (LMICs). Articulation of product attributes that meet LMIC needs, in addition to those that address high-income country (HIC) concerns, can help advance the development of vaccines that are suitable for global use. As a first step to define HSV vaccine PPCs, WHO convened a global stakeholder consultation in March 2017, which proposed two overarching global public health goals, of equal priority, for HSV vaccines:

- to reduce the burden of HSV-associated disease, including mortality and morbidity due to neonatal herpes and other impacts on SRH;
- to reduce the acquisition of HSV-2-associated HIV infection, particularly in settings or populations with high HIV prevalence.

This document describes two sets of PPCs for HSV vaccines:

- **PPCs for prophylactic HSV vaccines** to be used primarily before exposure to HSV-2 to prevent infection. Prevention of HSV-2 infection would prevent associated GUD and HSV transmission, including to neonates as neonatal herpes, as well as HSV-2-associated HIV acquisition.
- **PPCs for therapeutic HSV vaccines** that reduce symptomatic HSV-2 GUD in individuals who are already infected with HSV-2. For broader public-health impact, disease will need to be modified in a way that reduces HSV transmission and/or HSV-2-associated HIV acquisition.

Prophylactic vaccines are preferred for LMIC use, but therapeutic vaccines are more advanced in development and might also have public health benefits if they can be delivered effectively within existing health systems. HSV-2 is a higher priority vaccine target than HSV-1, based on its larger burden of SRH outcomes in LMICs; however, vaccines that also prevent HSV-1 infection or disease would have added benefits.

1. Background and purpose of WHO preferred product characteristics

The mission of WHO's Initiative for Vaccine Research is to accelerate the development and optimal use of safe and effective vaccines and related technologies that could have global public health impact. Priority areas include: the promotion and acceleration of vaccine candidates in early development, up to and including phase 2 clinical trials, towards licensure; and research to generate evidence to inform policy recommendations and vaccine introduction for candidate vaccines at advanced stages of development. Identifying and articulating vaccine preferences that meet the needs of LMICs, early in product development, is fundamental to achieving this mission.

Vaccine PPCs, published by the Initiative, describe preferred parameters pertaining to vaccine indications and target populations, as well as considerations for safety and efficacy evaluation, research and development and immunization strategies *(1)*. WHO identifies priority disease areas for PPC development, primarily based on the unmet public health need for vaccines, the stage of vaccine product development, and technical feasibility.

WHO PPCs are intended to encourage innovation and promote development of vaccines for use in settings most relevant to the global unmet public health need. The greatest disease burden is often in LMICs; however, vaccine developers typically target their products for initial launch in HIC markets. For this reason, first-generation vaccines are often not suitable for use in LMIC contexts and their introduction, and impact, is significantly delayed. WHO PPCs aim to emphasize LMIC perspectives, to inform vaccine developers and other key stakeholders and encourage development of a vaccine for global use, i.e. incorporating both LMIC and HIC attributes. PPCs are pathogen-specific and do not include minimally acceptable characteristics. They are intended to provide early guidance on vaccine development strategies and to inform development of product-specific target product profiles. PPCs are updated in the event of product or technology innovations, or any other change in the identified need or research and development landscape.

> WHO PPCs emphasize low- and middle-income country (LMIC) perspectives to inform development of vaccines for global use.

The primary target audience for WHO PPCs is any entity intending to develop a vaccine for LMIC use and eventually seek WHO policy recommendation and prequalification for their products *(2)*. However, it is important to note that 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 vaccine development *(3, 4)*.

2. HSV vaccines – a strategic priority for WHO

The Decade of Vaccines and the Global Vaccine Action Plan *(5)* call for new research to expand the benefits of vaccination to all people. Concurrently, several global efforts are focussing on the critical role of new innovations to improve SRH; good SRH can be defined as '*a state of complete physical, mental and social well-being in all matters relating to the reproductive system. It implies that people are able to have a satisfying and safe sex life…*' *(6)*. The WHO 2016 Global Health Sector Strategy on Sexually Transmitted Infections (STIs), which is based on the principles of universal health coverage, notes that vaccine development for STIs is a key innovation for future control of these infections *(7)*. In addition, WHO, the US National Institutes of Allergy and Infectious Diseases and global technical partners have outlined a comprehensive roadmap for development of effective new vaccines against STIs *(8, 9)*

The STI vaccine roadmap highlights the importance of developing a vaccine against HSV to address substantial unmet public health need. A large number of HSV infections exist worldwide, in both HIC and LMIC settings, and over half a billion people are estimated to have genital HSV infection *(10, 11)*.

These infections are lifelong, incurable, often stigmatizing, and no existing interventions can effectively prevent them at the population-level *(12)*. Genital HSV infections adversely affect SRH, by leading to a range of outcomes, including recurrent, painful GUD. More rarely, they cause neonatal herpes, which can be fatal or disabling *(13)*. HSV-2 has also been shown to increase the risk of HIV acquisition and transmission, which is especially important in populations with a high prevalence of HIV. Beyond genital infection, HSV causes oral and, less commonly, ocular and central nervous system infection and disease.

> The WHO 2016 Global STI Strategy highlights HSV vaccine development as a key innovation for future STI control.

In 2016, WHO's Product Development for Vaccines Advisory Committee further highlighted the need for HSV vaccines for global use *(14)*.

2.1. WHO strategic public health goals for HSV vaccines

HSV vaccines could have a range of potential benefits, including prevention of symptomatic, recurrent GUD; prevention of neonatal HSV; reduction of HSV transmission to sexual partners; reduction of psychosocial harm and stigma surrounding acquisition of genital herpes and transmission to neonates and sexual partners; reduction of HIV acquisition and transmission risk; and prevention of symptomatic oral disease and other non-genital outcomes of HSV infection.

Considering these potential benefits in the context of the needs and perspectives of LMICs, the following two

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overarching strategic public health goals, of equal priority, have been defined for HSV vaccines for global use *(12)*:

- to reduce the burden of HSV-associated disease, including mortality and morbidity due to neonatal herpes and other impacts on SRH;
- to reduce the acquisition of HSV-2-associated HIV infection, particularly for settings or populations with high HIV prevalence.

These strategic public health goals incorporate the understanding that HSV infection can have a broad range of adverse consequences that, when considered collectively, could amplify the impact of HSV vaccines on overall health and well-being beyond the effect on any single disease outcome. For example, HSV vaccination could reduce the burden of SRH outcomes such as GUD and neonatal herpes, and could also be an additional tool for HIV prevention. Although HSV vaccines could potentially benefit any individual at risk of HIV infection, broader population impact would likely be greatest in settings with a substantial burden of HIV infection, or for subpopulations at increased HIV risk even in lower-prevalence settings. Despite the focus of PPCs on vaccine attributes for LMIC contexts, these public health goals remain important targets for HICs as well.

3. Background to HSV infection and disease

Two closely related HSV types cause disease in humans. HSV-1 is mainly transmitted by oral contact and secretions to cause oral-facial herpes but can also be transmitted to the genital tract to cause genital herpes. HSV-2 is almost exclusively sexually transmitted, causing genital infection. Globally, HSV-2 is the leading cause of GUD.

Understanding the biology of HSV and the immune response to infection are important when considering the issues, opportunities and challenges in HSV vaccine development.

3.1. Primary HSV infection

During primary genital infection, with either HSV-1 or HSV-2, people can experience multiple genital ulcers, blisters, or other painful lesions (hereafter referred to as GUD), which can last for up to three weeks if untreated, and can be associated with systemic symptoms *(15)*. This primary infection is, however, often asymptomatic or unrecognized (subclinical).

3.2. Virus latency, reactivation, and transmission

One of the key characteristics of all human herpesviruses, including HSV, is that following infection, they establish persistent or latent infections, with periodic reactivation.

After sexual acquisition of HSV-2, the virus replicates in epithelial cells of the genital tract and then travels up neurons to lumbosacral ganglia to establish latency. Infection is lifelong. Subsequent reactivation of virus in the ganglia results in replication and shedding of infectious virus at genital surfaces. Reactivation can occur throughout a person's life; the frequency is highest in the first year after infection and typically declines slowly thereafter. HSV-2 shedding can be detected from the genital mucosa on 10% of days, even decades after infection *(16)*. Up to 84% of shedding episodes are unrecognized, and most HSV-2 transmission occurs while the source partner is asymptomatic, or when genital lesions are unnoticed *(17, 18)*. HSV transmission rates, particularly from asymptomatic shedding, might vary between populations, especially when rates of genital co-infection such as bacterial vaginosis, or sexual practices differ. The quantity and frequency of HSV-2 shedding are higher in people co-infected with HIV *(19)*. Prior HSV-1 infection does not reduce the risk of subsequent acquisition of HSV-2 infection but has been shown to reduce the likelihood of GUD symptoms upon HSV-2 infection *(20)*.

3.3. Common impacts of HSV infection

Beyond the pain and discomfort of both genital and systemic HSV symptoms, genital HSV infection can have important effects on sexual relationships and quality of life *(21)*. Genital herpes is often stigmatizing, and the social consequences of the infection can have profound effects on sexual health and well-being, especially for adolescents and young adults *(22)*. Most data on herpes-related quality of life are from HICs; however, a recent study in a rural area of Kenya *(23)* found that HSV-2 infection was associated with decreased sexual quality of life for women. Because HSV-2 GUD often recurs over many years, frequent HSV-related health care visits may place an economic burden on both individuals and the health-care system *(24, 25)*. Again, more data exist on these aspects from HICs, while the economic burden of HSV is less well understood in LMICs.

3.4. Mother-to-child transmission of HSV

Neonatal herpes is a rare outcome of HSV infection but is the most severe direct clinical consequence, having an estimated case fatality rate of 60% without treatment. Even with treatment, neonatal herpes can lead to long-term neurological disabilities *(26)*.

The incidence of neonatal herpes is estimated at around 10 per 100 000 live births globally *(27)*. It usually results from exposure to HSV-1 or HSV-2 in the genital tract during delivery, although it can result from *in utero* or postnatal infection.

3.5. Interactions between HSV and HIV

Epidemiological studies have identified a strong and consistent synergistic relationship between HIV and HSV-2 infections *(28, 29)*. The risk of HIV acquisition is approximately tripled in the presence of prevalent HSV-2 infection, and five times higher for those with incident HSV-2 infection *(30)*. The increased risk could be mediated by at least two possible mechanisms *(31)*: first, HSV-2 infection and reactivation stimulate infiltration into the genital mucosa of immune cells expressing receptors for HIV (CD4+ T cells and DC-SIGN+ dendritic cells) *(32, 33)*. Second, HSV-associated breaks in the skin and genital mucosa, including microscopic ulcerations, provide a more effective portal of entry for HIV *(34)*.

Co-infections with HSV-2 and HIV are common, and recurrent HSV GUD is clinically more severe with higher HSV shedding among people living with HIV/AIDS. In addition, the presence of GUD has been estimated to increase the risk of HIV transmission approximately fourfold *(35)*. Higher HIV titres are found in genital secretions during HSV-2 reactivation episodes. In addition, HSV-2 infection increases HIV load in the plasma, perhaps due to HSV-2 proteins upregulating HIV replication *(28, 36, 37, 38)*.

3.6. Outcomes of HSV-1 infection

Infection with HSV-1 in childhood can result in symptomatic oral-facial herpes and, in some cases, severe gingivostomatitis. HSV-1 can also result in less common outcomes such as HSV keratitis, which is an important infectious cause of vision loss globally, and HSV encephalitis, which is the leading cause of sporadic viral encephalitis in HICs *(39, 40)*. HSV-2 can also cause oral, ocular, and central nervous system disease, albeit rarely.

When HSV-1 is transmitted to the genitals, symptomatic primary infection is clinically indistinguishable from HSV-2 infection; however, the natural history of HSV-1 infection is milder, with fewer recurrences over time than for HSV-2. Whether HSV-1 genital infection increases the risk of acquiring HIV is unknown.

4. Burden of HSV-associated disease

In recent years, there has been a greater understanding of the burden of HSV disease, especially from modelling studies; however, there are still significant gaps in primary data from many LMICs.

4.1. HSV-2 infections

In 2012, an estimated 417 million people worldwide aged 15–49 years were infected with HSV-2, which is equivalent to a global prevalence of 11.3% *(10)*. Of these, 267 million (64%) were women, who have a greater biological susceptibility to HSV-2 infection. Africa contributed most to the global total due to its large population and high prevalence of HSV-2 infection (32%). Some subpopulations have very rapid acquisition of HSV-2 infection after initiating sexual activity; for example, young women in sub-Saharan Africa at high risk of acquiring HIV infection *(41, 42)*. In a recent meta-analysis incorporating data from 37 000 sub-Saharan African women, HSV prevalence was 40–50% among 15–24 year-olds and 70–80% among 25–49 year-olds *(43)*. South-East Asia and the Western Pacific had lower prevalence (both 8%) but, because of their large populations, had high numbers of infected people (estimates of 74.6 million and 81.2 million, respectively) *(10)*.

4.2. HSV-1 infections

In 2012, the global prevalence of HSV-1 was 67% in people aged up to 49 years (equivalent to 3.7 billion people), with most HSV-1 being acquired in childhood as an oral infection *(11)*.

Acquisition of HSV-1 in childhood has been declining in HICs such as in the USA *(44)*, thus increasing numbers of adolescents are susceptible to HSV-1 on initiation of sexual activity. Consequently, genital HSV-1 infection is now an important cause of genital herpes in the Americas, Europe and the Western Pacific and, in some HIC settings, is the main cause of first-episode HSV GUD *(11)*. Overall, an estimated 140 million people have genital HSV-1 infection globally, although the prevalence of genital HSV-1 infection is still thought to be relatively low in Africa and South-East Asia *(11)*. It is not known, however, whether the proportion of individuals acquiring HSV-1 orally before adolescence is also starting to decrease in these regions.

4.3. Genital ulcer disease

Estimates of the global burden of HSV GUD are in progress. Assuming that approximately 20% of HSV-2-infected people have recognized, recurrent symptoms, an estimated 80 million people could have ongoing symptomatic HSV-2-associated GUD worldwide *(10)*. HSV-2 infections are often also associated with mild symptoms that might not be recognized as GUD but can still prompt frequent health-care seeking. While genital HSV-1 infections are the main cause of first-episode HSV GUD in several HICs, they are less likely to recur than HSV-2 infections. Even assuming no recurrences, because approximately 25% of new HSV-1 infections result in symptomatic first-episode GUD *(45)*, an additional 35 million people might have had at least one episode of HSV-1-associated GUD in their lifetime.

4.4. Neonatal herpes

Globally, an estimated 14 000 cases of neonatal herpes, due to either HSV-1 or HSV-2, occurred annually between 2010 and 2015 *(27)*; however, these estimates have a high degree of uncertainty and rely heavily on data from studies in the USA, with only one large prospective study providing data on transmission risk *(46)*. The number of cases has, therefore, probably been underestimated in low-resource settings, where factors that likely increase mother-to-child transmission, such as lack of caesarean section capacity and higher HIV prevalence, are more common than in HICs *(47)*. The lack of primary data on transmission risks and case rates in LMICs is an important gap in epidemiological knowledge.

4.5. HSV-2 associated HIV burden

It is challenging to estimate precisely how HSV-2-associated increased HIV acquisition risk translates into the number of HIV infections that could be averted if HSV-2 infections were prevented; however, according to existing modelling studies, HSV-2 infection might account for 30–50% of new HIV infections in some populations that have high HIV prevalence *(48, 49)*.

4.6. Additional HSV-1-associated disease

The overall burden of HSV-1-associated oral, ocular, and central nervous system disease has not been estimated. Oral HSV-1 infection is very common globally, so even if only 25% of those infected have recurrent oral-facial herpes *(45)*, this would translate into hundreds of millions of people with a history of symptomatic HSV-1 infection. HSV keratitis has been estimated to affect more than a million people every year *(40)*.

5. Existing HSV diagnosis, management, and prevention measures

Several approaches to HSV diagnosis, management, and prevention exist. While these measures can provide some benefits to individual patients, they do not translate into effective population-level prevention and control of HSV infection. In addition, access to these interventions is highly variable, especially in LMICs.

5.1. Diagnosis of HSV

Genital HSV infection is often diagnosed clinically, especially when characteristic grouped vesicles or ulcers are present *(50)*. Genital herpes can, however, have varied presentations, including fissures, erythema, and other atypical genital lesions, which are referred to collectively in this document as GUD. Thus, clinical diagnosis lacks sensitivity and specificity *(51, 52)*.

Laboratory confirmation, by culture or viral DNA detection, can be used to evaluate genital signs of HSV infection and rule out other causes of genital ulcers. Viral culture with herpesvirus typing has been used historically, but more sensitive methods based on polymerase chain reaction have been developed to detect and/or quantify HSV DNA in clinical samples. Both culture and polymerase chain reaction have been used to detect subclinical shedding of virus in research studies.

Most HSV infections are unrecognized, although they can be determined by the presence of HSV type-specific immunoglobulin (Ig) G antibodies in the blood, which can usually be detected within 12 weeks after a primary infection and persist indefinitely. The utility of commercially available serologic assays for HSV-2 has been limited by reduced accuracy in some settings *(53)*. Serological tests based on IgM are not recommended. Western blot assays are considered the gold standard for type-specific antibody measurement but are only available in specialized laboratories, and are labour-intensive and expensive. In LMICs, laboratory testing for HSV is often unavailable and most diagnoses are made clinically.

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5.2. Herpes antivirals for treatment of infection

Antiviral medications such as acyclovir, famciclovir, and valacyclovir are available to treat the symptoms of genital HSV infections but are not curative. Global management guidelines recommend strongly the use of oral anti-herpesvirus therapy for the treatment of the first, symptomatic episode of GUD. Antiviral treatment for recurrences of HSV can also be used episodically at the time of recurrences, but this strategy has a weaker recommendation because it shortens recurrences only by approximately one day. Daily use of antivirals, termed 'suppressive therapy', is effective in reducing the frequency of subsequent symptomatic recurrences, but requires (often twice-) daily dosing *(54)*. Antiviral therapy is not universally accessible for people with HSV symptoms *(55)*.

5.3. Prevention of HSV infection

Primary prevention strategies for genital HSV-2 infection include condom use, daily suppressive antiviral therapy by symptomatic partners, and medical male circumcision. At best, the efficacy of these interventions ranges from only 30–50% for individuals *(56, 57, 58)*. In addition, widespread serologic testing and suppressive antiviral therapy are costly and unlikely to be feasible for most LMICs. Some tenofovir-containing products, such as microbicides and oral pre-exposure prophylaxis, have decreased HSV-2 acquisition in some HIV prevention trials *(59, 60)*; however, these medications are not currently recommended for prevention of HSV-2.

Neonatal herpes prevention efforts, primarily in HICs, have included selective use of caesarean section for HSV lesions at delivery, and suppressive antiviral therapy for GUD in late pregnancy. However, available prevention options are imperfect, often expensive, and typically depend on good existing medical infrastructure *(27)*. Because neonatal herpes is rare, it has been challenging to determine the appropriate targeting of prevention efforts, and at what cost.

5.4. Prevention of HSV-associated HIV infection

HSV antiviral medications can decrease genital ulceration and shedding. In clinical trials, however, daily suppressive therapy with oral acyclovir did not reduce the risk of HIV acquisition or transmission among HSV-2-infected people *(61, 62, 63)*. In follow-up studies, standard treatment with acyclovir did not suppress the HSV-2-stimulated enrichment of HIV target cells in the genital mucosa, which can persist long after ulcer healing *(32)*.

5.5. Surveillance for HSV infections and disease

Surveillance systems for HSV infections are not typically available and serial, nationally representative HSV serosurveys, such as the US National Health and Nutrition Examination Survey, are resource-intensive and uncommon. In LMICs, studies of HSV seroprevalence tend to be opportunistic, although population-based HSV-2 assessments have been successful, particularly in combination with HIV serosurveys *(64)*.

A limited number of countries or areas conduct surveillance of varying completeness for GUD, typically without etiologic confirmation, including in LMICs. Additionally, some HICs, or regions within HICs, conduct surveillance for neonatal herpes *(65)*.

6. HSV vaccine approaches to meet the public health need

Existing tools for prevention or treatment of HSV are unlikely to have an impact on the incidence and prevalence of HSV-2 infection at the population level. HSV vaccines might, therefore, be the only affordable and accessible option to achieve this goal, especially in LMICs but also in HICs.

Two types of HSV vaccines are under development:

- prophylactic HSV vaccines given before exposure to prevent acquisition of infection or disease, for example before first sexual contact for prevention of HSV-2 infection, or in infancy to prevent infection by HSV-1 and HSV-2;
- therapeutic HSV vaccines targeted to individuals known to have HSV infection, to (a) reduce disease severity and (b) reduce reactivation of infection, including shedding of HSV that can be transmitted to others.

Both types of vaccine might play a role in reducing sequelae of HSV infection such as neonatal herpes

and the HSV-2-associated risk of HIV acquisition and transmission. For a variety of reasons, outlined in Table 1, prophylactic HSV-2 vaccines would be the most useful and appropriate for use in LMICs. In addition, for global public health benefit, particularly for global SRH, HSV-2 is a higher priority target for vaccine development than HSV-1; however, HSV vaccines with additional impact on HSV-1 infection and disease are desirable, especially in HICs where HSV-1 is increasingly implicated in genital infections.

> HSV vaccines might be the only option for controlling HSV infection at the population level.

Currently, the primary focus of the vaccine industry is the development of therapeutic vaccines to reduce GUD in HICs *(12)*. Some of the therapeutic HSV-2 vaccine candidates might also have potential as prophylactic vaccines due to their antigenic composition, but this would need to be demonstrated in clinical studies.

Table 1. Advantages and disadvantages of prophylactic and therapeutic HSV-2 vaccines for LMICs

	Advantages	Disadvantages
Prophylactic vaccines	Prophylactic vaccines that prevent HSV infection would reduce the burden of disease and likely decrease the HSV-2-associated risk of HIV acquisition and transmission. The burden of HSV-2 and of HSV and HIV co-infection is greatest in LMICs, particularly in sub-Saharan Africa; prophylactic HSV vaccines might have the greatest public health benefit in these settings but would also be valuable in HICs. Established immunization platforms could be used to deliver prophylactic HSV vaccines in LMICs, such as school-based systems for human papillomavirus (HPV) vaccine, and the Expanded Programme on Immunization (EPI) for delivering vaccines to infants.	Prophylactic HSV-2 vaccines administered in early adolescence would need to be effective in people who are HSV-1-seropositive. This is because HSV-1 is acquired in childhood and seroprevalence is high by the onset of adolescence in many LMICs. The average age at which individuals are newly infected with HSV-1 is increasing in some HICs. For protection against both HSV types, the vaccine would need to be administered very early in life. Prophylactic vaccine development is likely to require larger clinical trials than for therapeutic vaccines.
Therapeutic vaccines	Therapeutic vaccines might be available for implementation sooner than prophylactic vaccines due to interest by vaccine developers (and investors) related to the large potential market in HICs and, potentially, faster and less costly clinical development. Therapeutic vaccines might have public health impact in LMICs, especially if they decrease disease activity in a way that reduces HSV transmission to partners, or risk of HSV-2-associated HIV acquisition or transmission. Therapeutic HSV vaccines could be a good alternative to antiviral therapy for symptomatic HSV infection, particularly if they have more favourable cost, dosing, and delivery options.	Only a relatively small proportion of people with HSV-2 infection have symptoms and seek care for it. People who have HSV-2 infection are at an increased risk for HIV acquisition, regardless of symptoms. Without a reduction in HSV-2 transmission or in the risk of HIV acquisition along with a reduction in GUD symptoms, therapeutic vaccines might not have broad population-level impact in LMICs. It might be difficult to measure these outcomes pre-licensure. It is not clear how a therapeutic vaccine would be delivered within existing immunization platforms, particularly in LMICs. How a therapeutic vaccine might affect the concentration of cells expressing receptors for HIV in the genital tract is unknown. An increase in these cells could, theoretically, increase the risk of HIV acquisition.

7. HSV-2 vaccine pipeline

The pipeline of HSV-2 vaccine candidates is relatively diverse at the discovery and early preclinical stages but there are fewer candidates in clinical development. All the ongoing clinical trials are being conducted in HICs *(12)*.

7.1. HSV-2 vaccine pipeline: preclinical stages

Potential HSV vaccine candidates are based on a variety of platforms. These include whole-virus (killed, live-attenuated or genetically disabled); monovalent or multivalent protein subunits with adjuvants; DNA, messenger RNA (mRNA) or live-virus vectors; and peptides and nanoparticles *(12, 66)*.

7.2. HSV vaccine pipeline: clinical stages

The HSV vaccine clinical pipeline was evaluated at the 2017 global stakeholder consultation *(12)*. Previous candidate prophylactic HSV vaccines had progressed to phase 3 trials but were not subsequently pursued due to low efficacy. None of the HSV vaccine candidates known to be in clinical trials are being evaluated primarily as prophylactic vaccines. Several therapeutic HSV vaccine candidates have recently been, or are currently in, phase 1 and 2 clinical trials *(12, 67)*.

8. HSV vaccine product development

There is general consensus that the development of prophylactic and/or therapeutic HSV vaccines should be scientifically feasible.

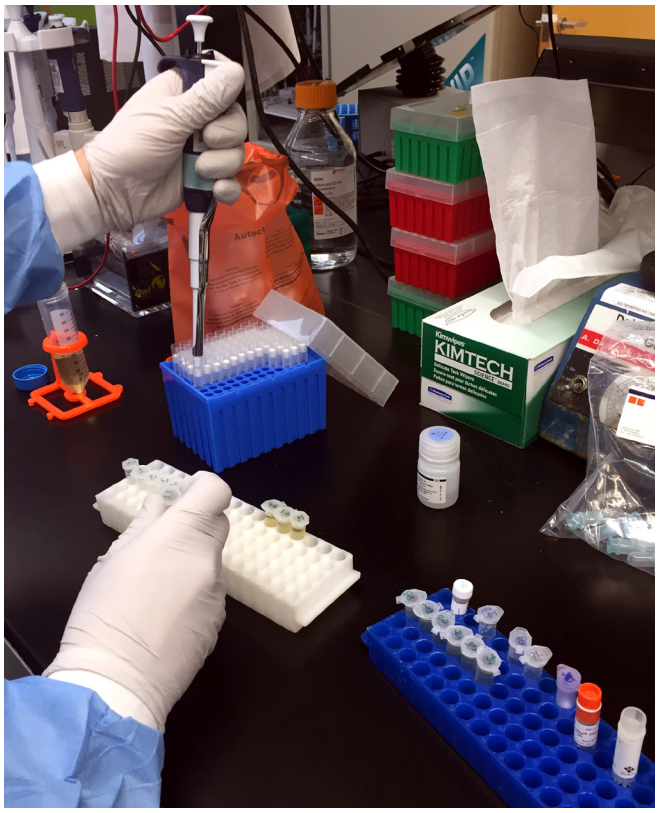
8.1. Preclinical development of HSV vaccines

In brief, there is good knowledge of the virology and pathology of HSV, but the precise mechanism of immunity required for protection and, specifically, the antigen(s) required for an effective prophylactic or therapeutic HSV-2 vaccine have not been defined *(68, 69)*. In general terms, an effective prophylactic vaccine is likely to act, at least in part, by inducing neutralizing antibodies against one of the envelope glycoproteins of HSV. An effective therapeutic vaccine is likely to act via cell-mediated immunity, possibly by stimulating resident memory T cells in the genital tract *(70)*.

8.1.1. Animal models

Animal models that are truly representative of human disease do not exist for HSV-2 *(66, 71)*.

For prophylactic HSV vaccine development, protection against intravaginal challenge in mice is often used, and protection against the establishment of latency can also be tested *(72)*. Guinea pigs have been used as a model for testing both prophylactic and therapeutic HSV vaccines, because they experience a short period of recurrent genital disease after intravaginal HSV challenge *(66)*. Neither model, however, has so far proved to be useful for predicting vaccine efficacy in humans. Better animal models are needed to screen candidates effectively and de-risk vaccine development.



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8.1.2. Assay harmonization

Assays to measure neutralizing antibodies and T-cell responses to HSV antigens have been developed. Most studies, particularly for therapeutic HSV vaccines will evaluate cell-mediated immunity in peripheral blood mononuclear cells (PBMCs). PBMC responses might not, however, reflect important immunologic changes in the genital mucosa.

Standardized reagents (such as virus strains, immunogens, adjuvants, and sera with known HSV-neutralizing activity) and standardized assays (such as assays for HSV-neutralizing antibody) are needed to monitor immune responses and to compare vaccine studies *(71)*.

8.2. Clinical development of prophylactic HSV vaccines

This section introduces the clinical evaluation considerations that inform the PPCs for prophylactic vaccines described in section 9.1.

8.2.1. Clinical trial design

Phase 1 and 2 trials for prophylactic HSV-2 vaccine development focus on safety and immunogenicity, and identifying biomarkers for possible immunological correlates of protection. No immunological correlates have been identified for HSV-2 vaccines *(71)*, although protection against HSV-1 induced by an HSV-2 vaccine candidate was shown to be correlated with neutralizing antibodies *(68)*.

Phase 3 randomized, controlled trials for prophylactic HSV-2 vaccines would enroll study participants who had not previously been infected with HSV-2 and follow them for acquisition of HSV infection and/or other HSV-disease outcomes. To date, evaluations of prophylactic HSV-2 vaccines have required large trials. For example, the Herpevac Trial in North America followed over 8000 women for 20 months, which reflected the low incidence of HSV-2 infection (1.1 per 100 person-years) in the study population *(73)*. HSV-2 prevalence is decreasing in at least some regions of some HICs *(74)*. In areas with higher HSV-2 incidence rates, such as sub-Saharan Africa where rates among women can reach over 20 per 100 person-years, clinical trials could be conducted with fewer participants or for a shorter duration *(41)*. Clinical studies of HSV-2 vaccine candidates would need to include and evaluate vaccine efficacy in HSV-1-seropositive participants because of the very high HSV-1 seroprevalence by adolescence in most LMIC settings. For ethical reasons, once licensed, HSV vaccines should be made available in the countries in which they were tested clinically.

Controlled human infection models with HSV challenge would not be considered safe or ethical. Couples who are discordant for HSV-2 infection have participated in efficacy studies for prophylactic HSV-2 vaccine candidates. Long-term discordant couples might not, however, be sufficiently representative of the intended target population *(73)*.

8.2.2. Vaccination outcome and clinical endpoint considerations

At the 2017 global stakeholder consultation, possible outcomes of prophylactic HSV vaccination, and considerations related to their measurement and inclusion as vaccine indications, were discussed and summarized *(12)*. The possible outcomes include prevention or reduction of HSV infection, GUD, shedding and/or transmission; neonatal herpes; HIV acquisition and transmission risk; and improvement in overall SRH.

In previous prophylactic HSV-2 vaccine trials in HICs, development of symptomatic HSV GUD has been the primary clinical endpoint. Secondary endpoints have included HSV-1 and HSV-2 seroconversion to evaluate prevention of infection *(73, 75)*. From a technical standpoint, it might be easier to achieve a reduction in HSV-2 disease rather than complete protection against infection *(76)*.

In LMICs, prevention of HSV-2 infection could be an important primary goal, not least because HSV-2 infection, regardless of symptoms, is linked to increased risk of HIV acquisition. For prevention of HSV-2 infection to be the main goal, prophylactic HSV-2 vaccines would not necessarily need to induce a 'sterilizing' immune response in all recipients. They could aim to reduce the probability of HSV-2 infection for most people and, ideally, modify the consequences of breakthrough HSV-2 infection in the remainder.

8.2.3. Safety and efficacy considerations

Vaccines used in HSV-uninfected people will be expected to be well tolerated and acceptable to recipients, and to have a safety profile at least as favourable as those for current WHO-recommended vaccines.

No clear efficacy cut-off has been defined for achieving a minimal public health benefit for prophylactic HSV vaccines. Acceptable thresholds for efficacy can be informed by updated vaccine impact models, and by market research with key stakeholders. New dynamic models of the potential impact of prophylactic HSV vaccines on population-level outcomes, considering the current epidemiologic and public health environment, are being developed. Previous modelling studies had limitations, but suggest that even an imperfect HSV-2 vaccine (for preventing HSV-2 infection) could reduce HSV-2 incidence and HIV incidence at the population level, especially if HSV-2 reactivation is decreased during breakthrough infection *(77, 78)*.

8.3. Clinical development of therapeutic HSV vaccines

This section introduces the clinical evaluation considerations that inform the PPCs for therapeutic HSV vaccine candidates described in section 9.2.

8.3.1. Clinical trial design

For therapeutic HSV-2 vaccines, adequately powered clinical trials can be conducted with fewer participants, and more quickly, than for prophylactic HSV-2 vaccine trials. This is because all the participants will have already acquired HSV-2 infection and outcomes can be based on HSV-2 GUD or HSV-2 virologic activity followed over a defined period of time.

Recent phase 1 and 2 studies, focusing on therapeutic HSV vaccine safety and immunogenicity, have used a one-way, crossover study design in which participants can serve as their own controls, comparing before and after vaccination. These HSV-2 vaccine trials have typically enrolled up to a few hundred subjects and have followed subjects for up to 12 months *(69)*. In later-stage studies, a longer follow-up would be desirable to monitor the longevity of any protection.

8.3.2. Vaccination outcome and clinical endpoint considerations

As for prophylactic vaccines, the 2017 global stakeholder consultation examined possible outcomes of therapeutic HSV vaccination and considerations related to their measurement and inclusion as vaccine indications *(12)*. Possible outcomes include reduction in GUD, HSV shedding and transmission, neonatal herpes, HIV acquisition and transmission risk, and improvement in overall SRH.

In recent therapeutic HSV-2 vaccine trials, reduction in GUD and shedding have been evaluated with the following endpoints: (i) HSV-2 GUD frequency and duration *(79)*; (ii) time to first HSV-2 GUD recurrence *(80)*; and (iii) rates of genital HSV-2 shedding *(69)*.

Criteria for HSV GUD outcome assessment can be standardized in trials; however, atypical presentations are common, and lesions can be hard for study volunteers or staff to visualize and document, especially between follow-up visits. Genital symptoms can also be non-specific to HSV and require virologic confirmation. Even in the placebo group, there might not be documented recurrences during the follow-up period.

For HSV-shedding outcomes, clinical studies have asked volunteers to perform multiple and frequent swabs. This monitoring is more intensive for participants than recording lesions and can be costly for vaccine developers but has been successfully carried out. Using the frequency of HSV shedding has the advantages of being relatively consistent over time for each individual and correlating with lesion rates, recurrence history, or time to recurrence but with more statistical power *(81)*. A consistent, quantifiable marker of genital herpes infection activity, pre- and post-intervention, facilitates a more efficient crossover study design, as discussed above.

Precise HSV-2 shedding levels required for HSV transmission, or correlating with risk of HIV acquisition, are unknown. For this reason, it is currently difficult to extrapolate directly reductions in HSV-2 shedding to these outcomes.

Policy decisions on introduction of therapeutic HSV vaccines in LMICs will likely involve consideration of data related to vaccine impact on HSV-2 transmission or HIV acquisition or transmission endpoints. Clinical trials of daily suppressive therapy by HSV-2-infected partners in discordant couples to prevent HSV transmission have been successfully performed in HICs. Large randomized controlled trials of daily acyclovir suppressive therapy to prevent HSV-2-associated HIV acquisition and transmission have also been successfully performed in LMICs *(61, 62, 63)*. Clinical trials of therapeutic HSV vaccines using similar designs would be feasible. Collecting supporting evidence and planning and designing studies to assess vaccine impact on these outcomes, including study timing (i.e. pre- or post-licensure), should be carefully considered in advance.

8.3.3. Safety and efficacy considerations

Therapeutic HSV vaccines will be expected to be well tolerated and acceptable to recipients, and have a safety profile at least as favourable as those for current WHO-recommended antiviral regimens for suppressive therapy of recurrent HSV GUD.

In addition, supplementary data might be needed to determine whether a therapeutic HSV vaccine increases or decreases the presence of activated CD4+ T cells in the genital tract, which are targets for HIV infection *(82)*. If the mechanism of action of the vaccine involves generating these cells, it could, theoretically, enhance the risk of sexual HIV acquisition (section 3.5). It might be difficult, however, to establish how the presence of these cells will translate into overall risk of HIV acquisition for vaccine recipients. Before implementing therapeutic HSV vaccines in populations with high HIV prevalence or people at high risk of HIV acquisition, the risks will need careful consideration and further evaluation *(31, 82)*.

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No clear efficacy threshold has been defined for achieving a minimal public-health benefit with therapeutic HSV vaccines. Acceptable thresholds for efficacy can be informed by updated vaccine impact models, and by market research with key stakeholders. It is likely, however, that therapeutic HSV vaccines will be expected to be at least as effective as existing oral suppressive HSV antiviral therapy. Therapeutic HSV-2 vaccines with lower efficacy than antivirals might still have similar, or greater, programmatic effectiveness, due to issues of delivery, dosing, and compliance.

New dynamic models of the potential impact of therapeutic HSV vaccines on population-level outcomes, considering the current epidemiologic and public health milieu, are being developed. Previous modelling data are limited, but assuming that reductions in HSV shedding could translate into reductions in HSV (or HIV) transmission, therapeutic vaccines could have benefits in populations beyond the individual benefits to vaccine recipients *(77)*.

9. Preferred product characteristics for HSV vaccines

The overarching strategic public health goals for HSV vaccines, which emphasize LMIC considerations, form the basis for HSV vaccine PPCs (section 2.1). Prophylactic HSV vaccines would be more useful for LMICs because of HSV-related public health needs as well as practical considerations related to vaccine implementation. However, both prophylactic and therapeutic HSV vaccines could play a role in achieving public health goals in LMIC and HIC settings. For these reasons, and the fact that the two vaccine approaches are different, separate PPCs have been developed for each.

9.1. PPCs for prophylactic HSV vaccines

PPCs for prophylactic HSV vaccines are described in Table 2. Additional characteristics that are common to both prophylactic and therapeutic vaccines are listed in section 9.3.

Table 2. Preferred product characteristics for prophylactic HSV vaccines

Parameter	Preferred characteristic	Notes
HSV type	HSV-2 is the primary target, but additional protection against HSV-1 would be beneficial.	HSV-2 is a higher priority target than HSV-1, based on its more serious natural history in terms of recurrent GUD symptoms and its well-established association with increased risk of HIV acquisition. Most GUD and other outcomes of genital infection result from HSV-2 infection in LMICs; however, in HICs, a substantial and increasing proportion of GUD and neonatal herpes is caused by HSV-1. Vaccines that also prevent HSV-1 infection or disease, including oral infection, would have added benefits and would be desirable, but protection against HSV-2 is a higher public health priority in LMICs. Further research is needed to characterize the potential impact on vaccine efficacy of the sequence variation observed between some geographically distinct HSV-2 isolates.
Indication	Prevention of HSV-2 infection.	Prevention of HSV-2 infection should reduce HSV-2 GUD and neonatal herpes, HSV-2-associated risk of HIV acquisition and transmission, and other impacts on SRH caused by HSV-2. HSV-2 infection, regardless of symptoms, is linked to increased risk of HIV acquisition; thus, prevention of HSV-2 infection is desirable, especially in populations with high HIV incidence. Vaccines preventing HSV-2 infection might be more difficult to achieve technically than those preventing symptomatic HSV-2 disease alone. Prevention of HSV-2-related GUD, without requiring prevention of HSV-2 infection, might be of sufficient value for LMICs if breakthrough infection is modified in a way that also reduces risk of HSV transmission and/or HSV-2-associated HIV acquisition. Vaccine effects on risk of HSV transmission and HIV acquisition would likely be difficult to demonstrate pre-licensure; therefore, consideration should be given to collecting supporting evidence for a positive impact on these outcomes and to designing post-licensure studies to evaluate them. If a prophylactic HSV vaccine did not prevent HSV-2 infection but reduced HSV-2 symptoms, it is unclear how decreased awareness of infection in a greater proportion of infected people might influence HSV-2 transmission.

Parameter	Preferred characteristic	Notes
Target population	For routine immunization, girls and boys in early adolescence (for example, as for the HPV vaccine) *(83)*. If a prophylactic vaccine also protects against HSV-1, or is only effective in the absence of HSV-1, then an infant population could be considered.	The aim would be to vaccinate, ideally, before the first sexual exposure to HSV-2, while providing maximal protection during the period of highest HSV-2 incidence, which is generally in late adolescence and young adulthood. WHO defines adolescence as ages 10–19 years. Specific target ages for vaccination can be refined based on efficacy data, immunogenicity bridging studies, and programmatic considerations. Aligning the target age group for HSV vaccination with the target age group for HPV vaccination would allow use of a similar delivery infrastructure. Given the high prevalence of HSV-1 infection by adolescence in LMICs, HSV-2 vaccines that are efficacious only in HSV-1-seronegative individuals would likely have only limited utility in the preferred target population in LMICs.
Schedule	Ideally, a single dose for primary immunization, but two or three doses could be acceptable for strong and long-lasting immunity.	Depending on the vaccine platform and formulation, two to three doses might be needed for primary immunization. Research should determine the requirements for alternative primary dosing or booster doses. This might be post-licensure, as for HPV vaccines. If more than one dose is needed, aligning the dosing schedule with existing delivery platforms (for example, the delivery schedule for HPV vaccination) is preferable.
Safety	A safety and reactogenicity profile at least as favourable as current WHO-recommended routine vaccines.	A favourable safety profile may need to be demonstrated in adults before progressing to vaccination of young adolescents, as was done for HPV vaccine.
Efficacy and duration	Minimum acceptable thresholds for efficacy can be informed by updated vaccine impact models, and by market research with key stakeholders. The duration of protection will need to exceed the period of highest sexual transmission risk.	Exposure to, and risk of acquiring, HSV infection can last for many years, or be lifelong, although the greatest risk is in the first decade or two after initiation of sexual activity. Previous modelling studies suggest that even imperfect HSV-2 vaccines for preventing infection could reduce HSV-2 incidence at the population level. Post-licensure studies can play an important role to fill data gaps about efficacy of HSV vaccines for rare endpoints, such as neonatal herpes and, possibly, the impact on risk of HIV acquisition and transmission.

9.2. PPCs for therapeutic HSV vaccines

PPCs for therapeutic vaccines are listed in Table 3. Additional characteristics that are common to both prophylactic and therapeutic vaccines are listed in section 9.3.

Table 3. Preferred product characteristics for therapeutic HSV vaccines

Parameter	Preferred characteristic	Notes
HSV type	HSV-2 is the primary target.	In LMICs, most genital HSV outcomes result from HSV-2 infection. HSV-2 infection has more frequent recurrent GUD symptoms compared with HSV-1 and is also associated with increased risk of HIV acquisition. In HICs, a substantial proportion of first-episode GUD is caused by HSV-1; however, it recurs infrequently. A therapeutic HSV-2 vaccine that also reduces HSV-1-related disease, particularly oral disease, might have added global benefits but is a lower public health priority than HSV-2 for SRH outcomes. Further research is needed to characterize the potential impact on vaccine efficacy of the sequence variation observed between some geographically distinct HSV isolates.
Indication	For initial licensure: reduction in symptomatic HSV GUD. For introduction in LMICs: reduction in symptomatic HSV GUD and also reduction in a) HSV transmission, and/or b) HSV-associated risk of HIV acquisition or transmission.	Therapeutic HSV vaccines that reduce HSV symptoms, and are preferable to existing HSV antiviral drugs considering efficacy, cost, dosing, and delivery, could be a useful intervention for individuals in LMIC settings. In LMICs, reduction in GUD alone might not have sufficient population-level value. Achieving broader public health impact would likely require modification of HSV disease in a way that also reduces HSV transmission and/or HSV-associated risk of HIV acquisition or transmission. Vaccine effects on risks of HSV transmission and HIV acquisition might be difficult to demonstrate pre-licensure; therefore, consideration should be given in advance to collecting supporting evidence for a positive impact on these outcomes and to designing studies to evaluate them.
Target population	People with symptomatic HSV GUD.	Individuals would need to have sought care or been identified within an existing health care setting, such as primary care or family planning clinics. In LMICs, no established immunization platform exists for this target population. Confirmatory HSV (or HSV-2) testing might be required in some settings, depending on the benefit/risk profile and cost and feasibility considerations. Testing may not be feasible in all settings and might not be needed, especially in areas with high HSV prevalence. Criteria for clinical diagnosis of symptomatic GUD, the need for HSV-diagnostic testing, and eligibility for therapeutic vaccination will need to be well defined. If therapeutic HSV vaccines are ultimately shown to reduce HSV-2 transmission or risk of HIV acquisition or transmission, consideration could be given to expanding the target population to asymptomatic HSV-2-infected people identified by serologic screening. Performance of current commercial type-specific HSV serologic tests is suboptimal. In LMICs, HSV-2 serologic testing is not widely available. The target population could include people living with HIV, who are frequently co-infected with HSV-2, have more severe HSV GUD, and can have higher plasma and genital HIV load during HSV reactivations. If therapeutic vaccines are also efficacious against HSV-1, people who have recurrent symptomatic oral disease could also be considered for vaccination.

Parameter	Preferred characteristic	Notes
Schedule	Ideally, a single dose for primary immunization, but two or three doses could be acceptable for strong and long-lasting disease modification. Annual booster doses might be acceptable for lasting disease modification.	Depending on the vaccine platform and formulation, multiple doses might be needed for initial immunization or to maintain longer-term disease modification. In most LMICs, no established immunization platform exists for initial vaccine delivery or for regular long-term booster doses for the preferred target population.
Safety	A safety profile that is at least as favourable as current WHO-recommended therapies for HSV infection.	If data suggest a vaccine might increase the presence of target cells for HIV in the genital tract, evaluation and careful consideration of additional evidence will likely be needed before introducing the vaccine in settings with a substantial burden of HIV or for people at high risk of HIV acquisition.
Efficacy and duration	Efficacy and duration that result in a favourable comparison with current WHO-recommended suppressive antiviral therapy, factoring in programmatic considerations.	Minimally acceptable thresholds for vaccine efficacy can be further informed by vaccine impact modelling studies and market research with key stakeholders. Therapeutic HSV vaccines that have lower efficacy than antivirals in clinical trials might still have similar, or greater, programmatic effectiveness, due to issues of delivery, dosing, and compliance. Knowledge of the vaccine's efficacy in reducing HSV-2 transmission, combined with evidence about vaccine coverage in populations, will help determine how broad the public health benefit could be. The duration of vaccine efficacy, and the need for repeat dosing, will need to match the expectations of reduction in HSV symptoms or transmission in the population in question.

9.3. Parameters common to both HSV vaccine strategies

Several parameters included in the WHO PPCs for HSV vaccines are common to both prophylactic and therapeutic HSV vaccines (Table 4).

Table 4. Parameters common to both prophylactic and therapeutic HSV vaccines

Parameter	Preferred characteristic	Notes
Adjuvant requirement	Preference for the absence of an adjuvant unless required for immunogenicity.	The majority of prophylactic HSV-2 vaccine candidates tested in clinical trials have included an adjuvant. Adjuvant formulations with previously demonstrated safety profiles in the target population are likely to be well tolerated.
Immunogenicity	Establishment of a correlate or surrogate of protection, based on a validated assay measuring immune effector levels and functionality.	A correlate of protection has yet to be identified for HSV-2. The longevity of the immune response should be characterized, and the relationship to the duration of protection should be investigated. Collaborative efforts towards reagent and assay harmonization would be expected to accelerate development.
Non-interference	Demonstration of favourable safety and immunologic non-interference upon co-administration with other vaccines recommended for use.	For HSV prophylactic vaccines in early adolescence, this will include the use of HPV vaccines (mainly in females) and, in some settings, the use of meningitis vaccines. HSV therapeutic vaccines will need to be compatible with other adult vaccines, including travel vaccines.
Route of administration	Oral, or more likely, injectable (intramuscular, intradermal, or subcutaneous, using standard volumes for injection) or needle-free delivery *(2, 84)*.	Local mucosal immunity might play an important role in protection against HSV GUD. Mucosal delivery, via the pharynx or nasopharynx, could be considered. Needle-free delivery would be preferred.
Registration, prequalification and programmatic suitability	The vaccine should be prequalified according to the process outlined *(85)*.	WHO-defined criteria for programmatic suitability of vaccines should be met *(2, 84)*.
Value proposition	The vaccine should be cost–effective and price should not be a barrier to access, including in LMICs. Dosage, regimen and cost of goods should be amenable to affordable supply.	In addition to any direct effects on HSV- or HIV-associated disease, the broader social and economic benefits of vaccination are likely to be relevant, including overall effects on SRH, and the potential impact on standard medical practice. The vaccine's impact on health systems and other aspects of implementation science should be evaluated pre- or post-approval.

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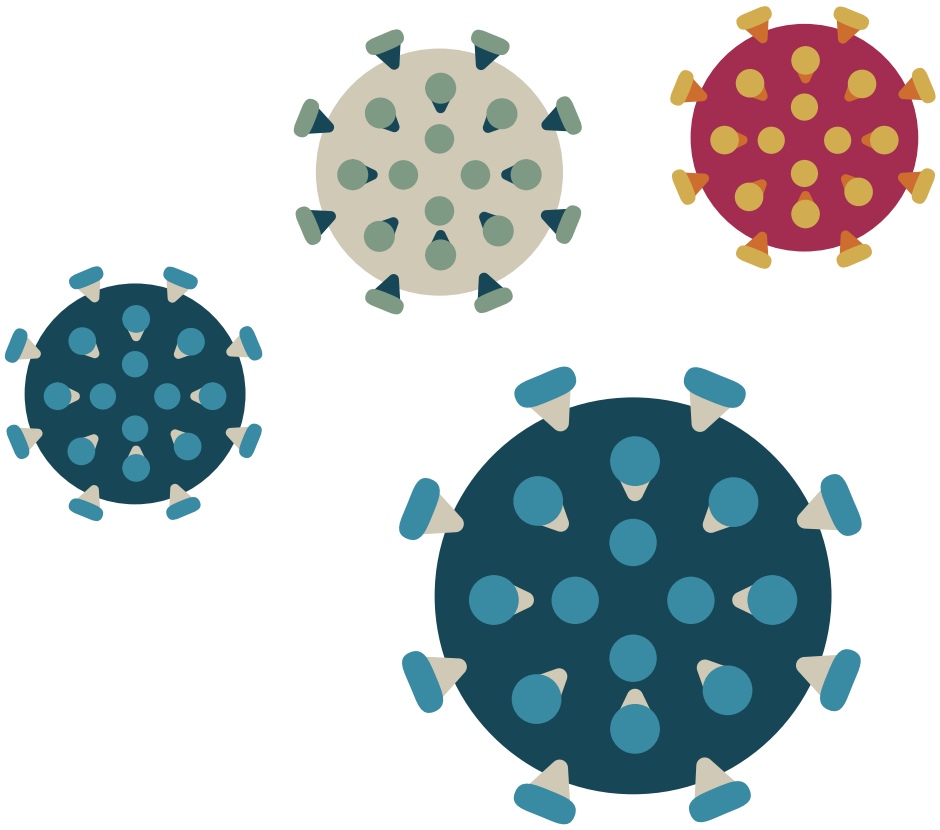

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ISBN 978-92-4-151558-0