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Vaccine value profile for herpes simplex virus

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ABSTRACT

Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are chronic, highly prevalent viral infections that cause significant morbidity around the world. HSV-2 is sexually transmitted and is the leading cause of genital ulcer disease (GUD). It also increases the risk of HIV acquisition, fueling the HIV epidemic. HSV-1 is typically acquired in childhood through nonsexual contact and contributes to oral and ocular disease, but it can also be sexually transmitted to cause GUD. Both HSV-1 and HSV-2 cause neonatal herpes and neurologic disease. Given the ubiquitous nature of HSV-1 and HSV-2 infections and the limited existing prevention and control measures, vaccination would be the most efficient strategy to reduce the global burden of morbidity related to HSV infection. Vaccine strategies include prophylactic vaccination, which would prevent infection among susceptible persons and would likely be given to adolescents, and therapeutic vaccinations, which would be given to people with symptomatic genital HSV-2 infection. This document discusses the vaccine value profile of both types of vaccines.

This 'Vaccine Value Profile' (VVP) for HSV is intended to provide a high-level, holistic assessment of the information and data that are currently available to inform the potential public health, economic and societal value of pipeline vaccines and vaccine-like products. This VVP was developed by subject matter experts from academia, non-profit organizations, government agencies and multi-lateral organizations. All contributors have extensive expertise on various elements of the HSV VVP and collectively aimed to identify current research and knowledge gaps. The VVP was developed using only existing and publicly available information.

1. The global public health need for a vaccine

Herpes simplex virus (HSV) is common and widespread globally, with infections that are lifelong and characterized by periodic reactivations. HSV type 1, most commonly presenting as oral-facial ulcers ("cold sores"), is primarily transmitted through oral-to-oral contact starting in childhood. HSV type 2 is almost exclusively sexually transmitted and can lead to recurrent painful genital lesions known as genital ulcer disease (GUD).[1] HSV-1 can also be transmitted to the genital tract through oral-genital contact. A substantial proportion of genital HSV infections are clinically unrecognized, though infections can still be transmitted when asymptomatic, contributing to a high prevalence

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globally, with disproportionately high prevalence in women.[2] Sexually transmitted genital HSV infections were estimated to affect more than 500 million people worldwide in 2016.[2] HSV type 2 also increases the risk of HIV acquisition and transmission, thus contributing to HIV incidence and prevalence.[3,4] The World Health Organization's (WHO's) Global Health Sector Strategy on Sexually Transmitted Infections (STIs) and the joint WHO-National Institute for Allergy and Infectious Diseases (NIAID) Global STI Vaccine Roadmap have emphasized the need for HSV vaccine development, given the large burden of infection and disease outcomes, the lack of curative therapy, and the fact that existing interventions, which include daily suppressive or episodic antivirals, are unlikely to provide broad population impact.[5,6] WHO preferred product characteristics (PPCs) for HSV vaccines highlight that both prophylactic and therapeutic vaccines could play an important role in addressing genital HSV and its impact on sexual and reproductive health.[7] Prophylactic vaccines would be used prior to exposure to prevent infection and, in turn, genital ulcer disease (GUD) and further transmission, including that of HSV-associated HIV infection. Therapeutic vaccines would be targeted toward those already infected with HSV-2 to reduce symptomatic GUD and decrease both symptomatic and asymptomatic genital HSV-2 shedding, which may also reduce the risk of transmission of both HSV and HSV-associated HIV.[7] Vaccines targeted against HSV-2 infection would have even broader public health benefits if they also had activity against HSV-1. Details of HSV epidemiology and natural history that have implications for vaccine development are shown in Table 1.

Table 1
Summary of epidemiology and potential indirect public health impact.

Feature	Summary and evidence
Epidemiology	
Reservoir	HSV is transmitted from person-to-person • HSV-1 is mostly transmitted orally, although sexual transmission also occurs[1] • HSV-2 is transmitted almost entirely through sexual contact[1] HSV establishes a lifelong infection in its host, periodically reactivating with or without symptoms. It is during these reactivation periods that virus is shed from skin or mucosal surfaces and transmission occurs.[8] Both HSV-1 and HSV-2 are highly prevalent in the general population. • Globally, an estimated 492 (95 % CI 430–611) million people aged 15–49 years had genital HSV-2 infection and 192 (95 % CI 123–294) million had genital HSV-1 in 2016. • Over 3,584 million (3322–3712 million) people aged < 50 years were estimated to be infected with oral HSV-1. • Since infection is lifelong, the prevalence of both HSV-1 and HSV-2 increases with age.[2].
Populations at higher risk of infection	As noted above, HSV infection is highly prevalent in the general population, and genital HSV infection correlates with sexual risk behaviours. Prevalence is higher in those with higher numbers of sexual partners, in men who have sex with men (MSM), in female sex workers (FSWs), and in people living with HIV (PLHIV).[9–11] Infants may also be infected vertically during vaginal delivery or by caregivers (oral HSV-1) postnatally, with severe sequelae.
Mortality	Several of the direct disease consequences of HSV infection are potentially fatal, such as neonatal herpes, HSV encephalitis, or disseminated infection, but these are relatively rare. For example, there are an estimated 14,000 cases of neonatal herpes globally annually (10.3 cases per 100,000 livebirths), of which around two-thirds are attributable to HSV-2 and one-third to HSV-1.[12] Without treatment, about 60 % of neonatal herpes cases are fatal, and even with treatment, fatality rates and lasting neurological impairment remain substantial.[13] HSV encephalitis at other ages has similarly poor recovery rates, with case-fatality rates of 5–20 % even with treatment.[14,15]
Morbidity	Although many HSV infections are asymptomatic, a number of adverse health consequences are associated with HSV, of which the following are of most public health concern: Predominantly related to genital infection: • Genital ulcer disease (GUD; more commonly due to HSV-2 than HSV-1) • Neonatal herpes (more commonly due to HSV-2 than HSV-1, globally) • Severe disease, e.g., disseminated infection, meningitis, hepatitis, pneumonitis (predominantly HSV-2) • Psychosocial consequences (both HSV types) Predominantly related to oral infection: • Oral-facial ulcer disease, e.g., "cold sores", stomatitis (HSV-1) • HSV ocular infection, e.g., keratitis (predominantly HSV-1) • HSV encephalitis (predominantly HSV-1) • Other severe disease, e.g., disseminated infection (predominantly HSV-1) <u>Genital ulcer disease</u> HSV is the most common cause of GUD globally, with an estimated 187 million people (5.0 %) aged 15–49 years having at least one episode of HSV-related GUD globally in 2016.[16] The majority of HSV GUD is caused by HSV-2, particularly because genital HSV-2 infections are much more likely to recur frequently than genital HSV-1 infections.[16] A large proportion of GUD is not diagnosed and treated but frequently causes pain in affected individuals. GUD recurrence rates are likely to be higher where HIV is prevalent and use of antiretrovirals (and antivirals) is low.

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Table 1 (*continued*)

Feature	Summary and evidence
	Neonatal herpes Rates of neonatal herpes have been estimated to be approximately 10 per 100,000 livebirths globally.[12] However, rates of neonatal herpes may be underestimated as most data are from the USA, which has high caesarean section rates. About 30 % of neonatal herpes cases develop central nervous system disease, ~25 % disseminated disease, and ~ 45 % skin, eye, and mucosa disease.[17] Those with CNS and disseminated disease are more likely to suffer long-term disability. Oral-facial disease Most children with oral HSV-1 infection are asymptomatic, but symptoms can include painful blisters or ulcers in or around the mouth (cold sores), which can recur at varying frequencies. Symptoms can be more severe when infection is acquired during adolescence or adulthood, or when there are pre-existing oral infections. Other rare complications of HSV-1 infection include Bell's palsy, sudden hearing loss and vestibular neuritis. Ocular infection An estimated 1.7 (95 % CI 1.0–3.0) million people were estimated to have HSV keratitis in 2016, with about 9 % of epithelial keratitis cases thought to lead to mild or greater vision impairment.[18] HSV uveitis and retinitis may together contribute a further 100,000 cases, but data are limited.[18] Both can lead to detachment of the retina and significant associated sight loss in the affected eye. Central nervous system disease HSV is the most common cause of viral encephalitis in high- income countries (HICs), with an incidence of about 2–4 cases per million people, peaking in the young and the elderly. Most (90 %) is due to HSV-1, with HSV-2 encephalitis usually only seen in immuno-compromised individuals and neonates. About 5–20 % of HSV encephalitis cases are fatal with treatment.[14,15] HSV-2 meningitis has a similar incidence to HSV encephalitis and is sometimes recurrent (known as Mollaret's meningitis). Overall HSV accounts for 0.5–3 per cent of all suspected viral meningitis cases. HSV meningitis is rarely fatal, though, as with all of the rarer clinical manifestations of HSV, studies outside of HICs are lacking. Recent epidemiologic, in vitro, and animal model data provide further evidence for an association between HSV-1 infection and increased risk of Alzheimer's Disease. While additional studies are required to understand the mechanisms by which HSV-1 infection contributes to neurodegenerative disorders, such an association may greatly increase the value of prevention of HSV-1 infection.[19] Other severe disease consequences Particularly among immunocompromised people, HSV infection can lead to other severe disease outcomes, including disseminated infection, hepatitis, and pneumonitis. In addition, acyclovir-resistant herpes may be seen in these groups, which leads to significant morbidity due to extensive lesions, and for which alternative antiviral treatments are limited by toxicity and the need for intravenous therapy.[20] HSV can also cause HSV myelitis and radiculitis, although these conditions are rare.[21,22] Psychosocial There are also psychosocial effects of HSV infection affecting mental health and quality of life such as depression, anxiety around transmission, feelings of shame and stigma, and effects on personal relationships.[23,24]
Geographical and seasonal distribution	The number of people living with HSV-2 infection is highest in the WHO Africa region (102.9 million females and 59.3 million males living with HSV-2), followed by the Western Pacific, South-East Asia and Americas regions.[2] Correspondingly, the prevalence of GUD is also highest in the WHO Africa region. The number of people living with oral HSV-1 infection is highest in the WHO South-East Asia region, followed by the Western Pacific; while the prevalence is highest in the WHO Africa region.[2] The number living with genital HSV-1 infection is highest in the WHO Americas region, followed by the European region.[16] Genital HSV-1 infection rates have risen in those regions where oral HSV-1 infection rates during childhood have declined, because more individuals are susceptible to acquiring HSV-1 upon sexual debut.[25] Genital HSV-1 prevalence is thought to be low in the WHO Africa and South-East Asia regions, because prevalence of oral infection is high in childhood, but the same increasing trend in genital infection may be starting in these regions too.[26] HSV infection does not follow a seasonal pattern.
Gender distribution	Prevalence of HSV-2 is higher in women than men, because of a greater biological susceptibility to HSV-2 infection in women. In 2016, an estimated 314 million women aged 15–49 years had HSV-2 infection compared to 178 million men. Correspondingly, rates of GUD are also higher in women than in men.[2] Both HSV-1 (genital) and HSV-2 can be passed vertically to the neonate during birth or by caregivers (oral HSV-1) postnatally. Although transmission risk is highest when new maternal infection is acquired close to term (likely because antibodies have yet to develop and cross the placenta),[27] the large number of prevalent infections among women contributes most to neonatal incidence.[12]
Age distribution	The seroprevalence of HSV-1 and HSV-2 increases with age. • In the 2016 global estimate of HSV infection, most HSV-1 was acquired in childhood, with HSV-1 seroprevalence increasing from 27.4 % among 0–4-year-olds to 67.1 % among 10–14 year-olds and 70.7 % among 45–49 year-olds. • HSV-2 is acquired after sexual debut, with HSV-2 seroprevalence increasing from 4.8 % of 15–19 year-olds to 20.8 % of 45–49 year-olds.[2]

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Table 1 (*continued*)

Feature	Summary and evidence
Differences by socio-economic status (equity/ wealth quintile)	Although HSV infections are widespread in both low-and middle-income countries (LMICs) and high-income countries (HICs), there are some differences by socio-economic status. Lower socio-economic status has been associated with higher rates of oral HSV-1 infection earlier in childhood.[28] Conversely, genital HSV-1 infection incidence is higher in HICs where more people are still susceptible to HSV-1 upon sexual debut. HSV-2 infection prevalence is the highest in sub-Saharan African countries with the highest HIV rates, which may reflect the synergy between HSV-2 and HIV infections.[2]
Natural immunity	Most oral infection is acquired during childhood, while genital HSV infections start with onset of sexual activity. Infection is lifelong, because of the ability of the virus to establish latency in the ganglia and reactivate.[8] 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.[29,30] HSV-2 dual strain infection is rare but can occur, suggesting that natural immunity may not be sufficient to prevent reinfection in all cases. The finding that HIV infection is a risk factor for dual strain infection suggests that an intact immune response is important for protection against re-infection. [31]
Pathogenic types, strains, and serotypes	The two HSV types, HSV-1 and HSV-2 each contain ~ 74 open reading frames and share a high degree of homology overall. However, the surface glycoproteins, which are key vaccine candidates, vary between 11.8 and 64.6 % between the two viral types at the DNA level. [32] Distant, stable recombination events have occurred between HSV-1 and HSV-2, with HSV-1 DNA found in circulating HSV-2 genes UL29, UL30, and UL39. [33] A clinically isolated HSV-2 strain from South Africa, SD-90, is more difficult to prevent compared to laboratory strains in animal models using candidate vaccines, suggesting that it may be important to ensure that vaccines are effective against clinical strains for diverse regions. [34] It has been proposed that SD-90 serve as the reference sequence for HSV-2. [35]
Potential indirect impact	
Anti-microbial resistance (AMR) threat	Resistance of HSV-1 and HSV-2 to acyclovir has been observed, especially in people with immunocompromising conditions. While resistance is rare, the complexity and toxicity of current alternatives contribute to health care costs and morbidity. If resistance to generic anti-viral drugs becomes more prevalent, cost of newer treatments will affect access to treatment for those in need.
Epidemic and outbreak potential	Infections are common, lifelong, and often asymptomatic, so it is not considered an epidemic or outbreak-prone infection.
Transmission route/potential	HSV-1 is primarily transmitted orally, although sexual transmission through oral-to-genital contact also occurs. HSV-2 is transmitted almost entirely through sexual contact.
Acquired/herd immunity	Modelling studies suggest that single sex-based vaccination strategies can have a positive impact on population-wide HSV incidence through herd immunity.[36,37]
Co-associated mortality	There is evidence from longitudinal studies that the risk of HIV acquisition is approximately 2–3 times higher in those with HSV-2 infection, after controlling for other potential confounders. The risk seems to be greater when the HSV-2 infection is newly-acquired. [38] The population attributable fraction (PAF) of incident HIV attributable to HSV-2 among those aged 15–49 years, assuming an interaction for HSV-2 infection on HIV acquisition, is estimated to be around 30–37 %. The PAF is estimated to be highest for the WHO Africa region because of the high prevalence of HSV-2 infection.[3,4] There is also some evidence that in those co-infected with HSV-2 and HIV, HIV increases HSV-2 transmissibility, and HSV-2 (and particularly GUD) increases HIV transmissibility.[39–42]
Economic burden	
Health facility costs/out of pocket costs/ productivity costs	The total global economic burden of genital HSV infection was estimated to cost $35.3 billion in 2016 (genital HSV-2 infection: $31.2 billion and genital HSV-1 infection $4.0 billion). Direct medical costs ($22.0 billion) were responsible for the majority (62.3 %) of the total costs associated with HSV infection, while direct non-medical costs ($1.0 billion) and indirect costs ($12.3 billion) contributed about 2.8 % and 34.9 %, respectively.[43] A recent model of economic burden just among 90 LMICs predicted that genital herpes contributed approximately US$2.2 billion in episodic and suppressive treatment costs and US$8.7 billion in outpatient clinical costs in these countries in 2019.[44]

1.1. Current methods of surveillance, diagnosis, prevention, and treatment

HSV diagnosis can be confirmed via viral DNA detection or culture of genital ulcer lesions. Lesion culture may be inexpensive relative to PCR, though sensitivity is also significantly lower than that of PCR. A variety of serological tests are commercially available, but many of these have low specificity for HSV-2 and sensitivity for HSV-1.[45] The higher accuracy tests are expensive and labour-intensive. As such, reliable screening is often unavailable, and diagnoses are made clinically. Surveillance for HSV infection or disease is very limited geographically and in terms of the scope of data collected.[7,46].

No new treatment options have been approved in most countries in the last several decades, with antivirals (typically acyclovir, valacyclovir or famciclovir) used as episodic treatment or suppressive therapy for genital or oral infection.[47] Episodic treatment is used for 2–10 days when symptoms are present, depending on the drug and the type of episode with the benefit of reducing the duration of the episode and its symptoms.[47] Antivirals have the most impact on first episodes of genital herpes. For subsequent recurrences, episodic therapy only reduces episode duration minimally. Suppressive therapy, taken daily, reduces the number of recurrences, thus improving quality of life, and reduces genital viral shedding, which can decrease the risk of transmission.[48–51] However, reduction of transmission risk is incomplete (~50 % risk reduction), and suppressive therapy requires once or twice daily dosing, making it not universally accessible. Amenamevir, a novel antiviral agent that inhibits the activity of the helicase-primase complex and interrupts viral replication, was recently approved for treatment of recurrent genital herpes in Japan, after a Phase 3 trial showed that a single dose of patient-initiated therapy decreased the time to healing of HSV-2 genital ulcers compared to placebo.[52] Condom use and male circumcision are also primary prevention measures, although no preventive intervention exceeds 50 % efficacy and none have had a substantial impact at the population level.[53–55] Neonatal herpes prevention strategies include elective caesarean section if there are visible HSV lesions, and suppressive antiviral therapy late in pregnancy.[27,56] These interventions may not be available nor utilized in many low- and middle-income countries (LMICs) due to cost and health infrastructure. In addition, most settings have no surveillance or reporting for neonatal herpes, limiting our understanding of the true burden of this complication, particularly in LMICs.[12] Acyclovir suppressive antiviral therapy has been shown not to reduce the incidence of HSV-associated HIV infection.[57,58].

1.2. Summary of knowledge and research gaps in epidemiology, potential indirect public health impact and economic burden

- Although robust global and regional estimates of genital HSV infection exist, particularly for HSV-2, estimates of disease burden, e.g., related to neonatal herpes and GUD, are largely based on extrapolation using natural history data from high-income countries (HICs), with relatively few countries represented.
- Quality of life data is nearly absent outside of HICs, reflecting a lack of understanding of the perceived burden at the individual and societal levels in other settings.
- More precise estimates of genital HSV-1 infection and better quantification of non-genital disease outcomes related to HSV-1 more generally could broaden understanding of the value of a vaccine that has effects on both HSV-1 and HSV-2 infection. HSV vaccines could have an important impact on oral, ocular and neurologic manifestations of HSV infection, but the full benefits have not been estimated to date. In particular, the incidence of ocular disease has recently been estimated.[18]
- Health economic models rely on disease burden estimates and therefore also suffer from their limitations. In addition, healthcare

Table 2a
Overview of potential target populations and associated delivery strategies for HSV **prophylactic** vaccines.

Potential target populations	Key considerations and delivery strategies
Girls and boys in early adolescence	• This target population would be the primary focus for HSV-2 vaccines. • WHO defines adolescence as age 10–19 years. The goal is to immunize prior to first sexual exposure, thus the focus on early adolescence. Efficacy and immunogenicity data will determine optimal age for effectiveness in adolescent populations. • Programmatically, utilizing existing adolescent vaccine delivery infrastructure would be the most feasible and efficient platform, e.g., HPV vaccination platform. o In many settings, school-based delivery platforms have been the most efficient strategy in this age range. o Co-administration data on immunological interference should be collected. • If efficacy against HSV-2 is limited to HSV-1 seronegative individuals, utility would be limited in LMICs with a high prevalence of HSV-1 infection by early adolescence.
Infants	• This target population should be considered if the vaccine also protects against HSV-1 or is only efficacious in absence of HSV-1 infection. • Safety, efficacy, duration of protection and schedule would determine whether and how this would fit within the EPI schedule.

Table 2b
Overview of potential target populations and associated delivery strategies for HSV **therapeutic** vaccines.

Potential target populations	**Key considerations and delivery strategies**
People diagnosed with symptomatic HSV genital ulcer disease	• May be done in primary care, sexual health, or family planning clinics where adult immunization services are available. No established immunization platform currently exists for this target population. o This assumes individuals have access to and seek care. o Would require availability of confirmatory HSV-2 testing and/or well-defined guidelines for vaccine eligibility. o Reasonable assumptions about the volume of patients eligible would be needed to reduce stock outs.
People with HSV-2 infection	• If vaccine demonstrates ability to also reduce HSV-2 transmission or HIV acquisition or transmission in those infected with HSV, may consider expanding target population to all HSV-2-infected adults, even if asymptomatic. o As above, this would require accurate serological screening and clear guidelines for defining risk groups for screening and vaccination.
People with recurring symptomatic oral HSV-1 disease	• May be used in this population if vaccine also effective against HSV-1. o This assumes that those with symptoms seek treatment and that diagnostic and eligibility guidelines are clear and well-defined.

resource utilization related to HSV infection in different settings has not been well characterized.

- Estimates of the proportion of new HIV infections attributable to HSV vary depending on geographic setting and model parameters, and the magnitude of the effect may reflect some degree of confounding rather than a true causal link. If impact on HIV acquisition is determined to be a necessary effect of HSV vaccination in LMICs, the potential benefits of an HSV vaccine on reducing HIV infection must be better understood.
- HSV vaccine impact models have shown varying results depending on epidemiological settings and model assumptions. [37,59] A more precise delineation of the range of potential impacts is needed to engage with stakeholders regarding the full public health value of a vaccine.
- All of the above would be needed to determine the relative value of prophylactic vs. therapeutic vaccines and to engage with global, national and local stakeholders to assess the perceived value of HSV vaccination overall.

2. Potential target populations and delivery strategies

The WHO PPC document outlines preferences and key considerations related to target populations for HSV vaccines.[7] Target populations and associated delivery strategies will differ for prophylactic and therapeutic HSV vaccines, as outlined in Tables 2a and 2b.

3. HSV and its consideration as a public health priority by global, regional, or country stakeholders

The large global burden of infection and disease and the lack of any effective population-level control measures for genital HSV infection have led global and national stakeholders to call for development of HSV vaccines (Table 3).

WHO has emphasized the importance of developing new innovations for sexual and reproductive health, including vaccine development for STI control.[60–62] WHO joined with the U.S. National Institutes of Allergy and Infectious Diseases (NIAID) and technical partners and experts in STIs from around the world to jointly create a global roadmap to advance development of effective new vaccines against various STIs.[5,63] HSV vaccine development was highlighted in this roadmap as a global priority and feasible goal for sexual and reproductive health. WHO convened global experts to develop PPCs for HSV vaccines.[7] Global support for HSV vaccines has also emerged in alignment with the Immunization Agenda 2030, which calls for increased research and development towards new vaccines for health and well-being across the life course.[64].

Most of the research support and strategic focus on HSV vaccine development at the national level has been among HICs. For example, recently the U.S. Centers for Disease Control and Prevention (CDC) and NIAID partnered to hold a large virtual workshop on genital herpes, at which HSV vaccine development was a key component.[65] However, the lack of effective prevention and control interventions has made genital HSV less prominent in national strategies. Nascent civil society efforts have begun to highlight the need for new HSV prevention and treatment innovations. Global stakeholder engagement priorities include expanding data collection and communication specific to LMICs to enable more awareness of the public health burden and need for a vaccine.

4. Existing guidance on preferences/preferred product attributes for vaccines against HSV

WHO developed PPCs for HSV vaccines in 2019 through a global consultative process. Tables 4a and 4b, for prophylactic and therapeutic vaccines, respectively, are reproduced from the WHO PPCs with permission.[7] Table 4c summarizes information applicable to both

Table 3
Overview of non-commercial stakeholders engaged, their interest and potential demand.

Stakeholders engaged	Summary of position/interest	Potential demand and uptake	References
Global level	Through the Global STI Vaccine Roadmap, STI strategies, and the HSV Vaccine PPCs, WHO has emphasized the need to accelerate development of HSV vaccines to address a large and often underrecognized burden on sexual and reproductive health, particularly in LMICs.[5,63]	Examples: The WHO Global Health Sector Strategies on HIV, Viral Hepatitis and STIs outline the need to accelerate access to innovations by developing new preventive interventions, including vaccines. HSV vaccines are particularly needed given the paucity of alternative public health measures. The WHO PPCs for HSV vaccines provides guidance on WHO's preferences for emerging HSV vaccines to optimize global impact. The PPCs incorporate the perspectives of LMICs, to support HSV vaccine development for global use (both HICs and LMICs).	Global roadmap to advance development of STI vaccines[61] WHO Global Health Sector Strategies on HIV, Virus Hepatitis and STIs, 2022–2030 [62] WHO Global Health Sector Strategy on Sexually Transmitted Infections, 2016–2021[61] WHO HSV vaccine PPCs[7]
National	U.S. NIAID has highlighted with WHO the importance of HSV vaccines through the joint Global STI Vaccine Roadmap, and recently partnered with the U.S. CDC to hold a large virtual workshop on genital herpes, at which HSV vaccine development was a key component. The U.S. National Institutes of Health has developed an HSV Research Strategic Plan.[66]	Examples: NIAID has sponsored large clinical trials of HSV vaccines. The recent national NIAID-CDC workshop on HSV focused on several promising pathways to HSV vaccine development.	NIAID/CDC Workshop Agenda [65] NIH Strategic Plan for Herpes Simplex Virus Research, 2023–2028[66]
Civil society	Civil society efforts related to genital herpes have been limited in the past, but advocacy groups have begun to highlight the need for new HSV prevention and treatment innovations, including HSV vaccines.	Examples: Herpes Cure Advocacy is an international advocacy organization whose priority is to advance the development of treatments, cures and preventative strategies for HSV-1 and HSV-2. AVAC, global advocates for HIV/AIDS prevention, has been successful at championing biomedical HIV prevention options, and has recently added STI vaccines as a focus.	https://herpescureadvocacy.com/ https://stiwatch.org/hsv/ https://www.avac.org/prevention-option/sti-vaccines

Table 4a
Summary of existing guidance on preferences for product attributes of vaccines intended for use in LMICs: 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, ocular, and neurologic 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 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.
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 the effectiveness of HSV vaccines for rare endpoints, such as neonatal herpes and, possibly, the impact on risk of HIV acquisition and transmission.

Table 4b
Summary of existing guidance on preferences for product attributes of vaccines intended for use in LMICs: 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 equivalent or superior 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 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 and ocular disease could also be considered for vaccination.
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.

Table 4c
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.
Immuno-genicity	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 as specified in programmatic suitability for prequalification) 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.

types of vaccines. WHO PPCs are not specific to a particular product, rather they describe preferred attributes for vaccines for global use, with a particular focus on LMICs. They are intended to provide early guidance to inform subsequent product-specific target product profiles (TPPs), which have not yet been developed for HSV vaccines on a global level. Table 5 reviews the factors that suggest that vaccine development is feasible for LMIC market use.

5. Vaccine development

5.1. Probability of technical and regulatory success (PTRS)

Extensive research in both animal models (mouse, guinea pig, cotton rat and rhesus macaques) and human studies have led to an improved but incomplete understanding of the immune responses that need to be stimulated by a vaccine.[67–69] These include HSV antigen-specific neutralizing antibody responses, which are thought to be particularly important for a prophylactic vaccine. Adaptive cellular immune responses have been shown to be important for clearance of virus in people with HSV infection, and stimulation of these responses will likely be essential for therapeutic vaccines.[70] In addition, stimulation of mucosal immune responses at the site of infection will be important for both prophylactic and therapeutic vaccines.[71] The tools to measure HSV-specific humoral and cell-mediated immune responses in blood are well developed. HSV provides a unique vaccine challenge because correlates of immunity may be tissue-based rather than seen solely in the blood compartment.[72,73] The importance of generating mucosal immune responses is demonstrated by the "prime and pull" strategy which has been used in animal models.[74] Vaccination with adjuvanted glycoproteins followed by genital application of imiquimod, an immune response modifier, was shown to have a greater effect on reducing recurrent genital herpes compared to vaccination alone.[75] Tools to measure cellular and antibody responses in tissue are also available and may be useful in early phase clinical trials.

Recent studies using whole-genome sequencing of HSV have shown that HSV antigenic targets are highly conserved and there are "type-common" antigens that would protect against HSV-1 and HSV-2.[32] Therefore, there is potential to create an HSV vaccine that could be effective against both HSV-1 and HSV-2.

Clinical endpoints have been debated for HSV vaccines. Endpoints for prophylactic vaccines have included disease (occurrence of clinically apparent genital herpes) and infection (conversion from HSV seronegative to seropositive). Ideally, a prophylactic vaccine would prevent infection, which would eliminate the risk of transmission to others. However, infection is a high bar, and prevention of herpes-related disease may be more attainable. As genital herpes causes chronic inflammation that is thought to increase the risk of HIV infection and potentially other genital tract infections such as bacterial vaginosis,[76] measures of inflammation and/or risk of HIV may be secondary outcomes in clinical trials. Measurement of clinical endpoints of genital herpes disease or HSV infection is feasible in LMICs.

For therapeutic vaccines, genital tract HSV shedding is a well-accepted biomarker endpoint, with novel trial designs utilizing within person comparison of shedding rates pre and post interventions.[77] Genital herpes shedding is highly associated with clinical lesions and is a more sensitive measure of HSV reactivation than lesions, and is an excellent biomarker for clinical trials, particularly in early phases of development. In such studies, recurrence of genital herpes lesions is a secondary endpoint, and both shedding and lesions are feasible to ascertain in a variety of clinical settings. Genital tract shedding studies have been successfully conducted in LMICs.[78,79] In addition, genital tract shedding may be a biomarker of risk of viral transmission.[80] Similar to prophylactic vaccines, secondary outcomes may include genital tract inflammation or co-infections. These secondary endpoints

Table 5
Overview of parameters that inform scientific feasibility of developing an effective vaccine for LMIC public market use.

Parameter	Issues and evidence
Diagnosis/case ascertainment	In many LMIC settings, diagnosis is made clinically, without use of diagnostic tests. Disease manifestations of HSV can be diagnosed by detection of virus through HSV PCR or HSV viral culture. PCR in particular may be less available in LMIC. Whether symptomatic or asymptomatic, HSV-1 and HSV-2 infection can be determined by serology, which can be used in LMICs but is not widely available. Many commercially available serological tests have low specificity for HSV-2 and low sensitivity for HSV-1. Higher accuracy serological tests are available for trials but expensive and labour-intensive.
Biomarkers/correlates of risk and/or protection	HSV genital tract shedding, regardless of symptoms, is accepted as a biomarker of HSV reactivation. The assays to measure HSV shedding in clinical trials are well established.[77] In prior vaccine studies, increased antibody titres to glycoprotein D2 have been associated with protection against HSV-1 infection.[83] A correlate of protection for HSV-2 infection has not yet been identified. Antibody assays to gD2, an antigen used in several vaccine platforms, are available.
Sero-epidemiological data	Large sero-epidemiological studies of HSV-1 and −2 have been done in various settings and have been used to estimate HSV prevalence in the population and monitor trends over time (e.g., US NHANES study).[28,89] Global and regional estimates are based on HSV seroprevalence studies.[2]
Clinical endpoints	Prophylactic studies: Genital herpes disease has been used as a primary clinical endpoint in past studies.[82] HSV infection may also be considered as a primary endpoint (e.g., seroconversion). Therapeutic studies: Genital shedding has been used as the primary endpoint in early phase studies.[85] Genital HSV recurrence would be the likely outcome in Phase III studies.
Controlled human infection model (CHIM)	No CHIM exists. However, there are well established studies of the natural history of oral and genital HSV infection. Mice and guinea pigs serve as the pre-clinical model for vaccine development.
Opportunity for innovative clinical trial designs	For pivotal prophylactic HSV vaccine studies, the sample size and duration will depend upon the population studied, with smaller, more rapid trials in settings where HSV acquisition is more common.[7] Therapeutic HSV-2 vaccine studies have used within-person comparisons of genital HSV shedding pre/post intervention as an outcome in early phase I/II trials. Measures of HIV acquisition and genital tract inflammation, and genital tract co-infections may be secondary outcomes in both prophylactic and therapeutic vaccine studies.
Regulatory approach(es), including potential accelerated approval strategies	HSV vaccines are expected to have a global market and will likely be first introduced in HICs with a dual market strategy. Therefore, licensure will probably be through FDA and EMA with subsequent WHO prequalification (PQ). Post-licensure effectiveness studies, e.g., to evaluate the effects of HSV vaccines on HIV, could be conducted after initial licensure.
Potential for combination with other vaccines	Combination with other vaccines would be possible depending upon the target population, but would need to be studied. Harmonizing vaccine schedules with existing vaccines should be considered when designing HSV vaccines.
Feasibility of meeting presentation and stability requirements	Stability conditions for shipping, storage and deployment in LMIC setting should be considered in vaccine design. There are no apparent barriers to meeting feasibility requirements based on vaccines in preclinical and clinical development (see Table 6).
Vaccine platform	May be a protein-subunit with adjuvant, an mRNA vaccine, a DNA vaccine, or a full-length live attenuated vaccine.
Large scale Manufacturer capacity / interest	There are no apparent barriers to large-scale manufacturing based on the types of vaccine candidates and vaccine platforms in preclinical and clinical development.

would also be feasible in LMICs.

In some LMIC settings, there are high rates of HSV-2 acquisition during adolescence and young adulthood.[81] Conducting trials in these populations where there is a strong infrastructure in place for STI/HIV clinical trials would provide the most efficient clinical trial design for Phase III efficacy studies and would also potentially study the vaccine in communities that have the most to benefit from effective HSV vaccines.

The ultimate goal for this vaccine would be for use in adolescents (to prevent genital herpes) and children (to prevent HSV-1 infection). Given the association of HSV-2 acquisition and infection with HIV acquisition, countries with high rates of HIV acquisition during adolescence and young adulthood may be candidates for early registration for a prophylactic vaccine. Vaccines to prevent genital herpes could be incorporated into existing campaigns for adolescent vaccines, and they could be bundled with other vaccines such as HPV. Therapeutic vaccines could be pursued as well in LMICs with ongoing HIV epidemics. There is not necessarily a candidate setting for childhood HSV vaccinations.

Until recently, vaccine strategies for prophylactic and therapeutic vaccination have included subunit vaccines targeting HSV surface glycoproteins which generate strong neutralizing antibody responses, live-attenuated or replication-incompetent whole virus vaccines, and DNA-based vaccines. While these prior strategies have not produced a licensed vaccine, they have provided important information about correlates of protection and proof of concept which will inform future HSV vaccine studies. In addition, it is possible that different immune responses will be required for persons who are HSV-naïve versus HSV-infected, and therefore different vaccine platforms may be needed for prophylactic and therapeutic vaccines.

5.2. *Lessons from prophylactic vaccination studies*

Subunit vaccines containing HSV-2 surface glycoprotein gD2 with or without gB2 plus adjuvant have advanced to Phase III clinical trials. The most recent Phase III trial, the Herpevac Trial for Women, was published

Table 6
Overview of vaccine candidates in clinical trials.

Candidates currently in active phase clinical trials						
Candidate	**Antigen platform**	**Developer/ manufacturer**	**Phase of development**	**Route of administration, no. of doses, schedule**	**Vaccine approach**	**Registration ID**
BNT163	mRNA vaccine containing gD2, gE2, gC2	BioNTech	Phase 1	IM (schedule TBD)	Prophylactic	NCT05432583
GSK3943104A	Recombinant Protein-Adjuvanted	GlaxoSmithKline	Phase 1/2	IM, Day 1 and Day 29	Therapeutic	NCT05298254/EUCTR2021-003586–35-BE
mrRNA-1608	mRNA	Moderna	Phase 1/2	IM, Day 1 and Day 57	Therapeutic	NCT06033261

Candidates that have completed clinical trials in the past 5 years (since 2017)						
Candidate	**Antigen platform**	**Developer/ manufacturer**	**Phase of development**	**Route of administration, no. of doses, schedule**	**Vaccine approach**	**Registration ID**
HSV529	Replication-defective live virus	NIH/Sanofi	Phase 1	IM, Day 0, 30 180	Therapeutic and prophylactic	NCT01915212
VCL-HB01	Plasmid DNA vaccine encoding two HSV-2 proteins, formulated with Vaxfectin	Vical	Phase 2	IM, Three, 4 weekly doses	Therapeutic	NCT02837575
GEN-003	Protein vaccine with 2 HSV-2 antigens and Matrix M−2 adjuvant	Genocea	Phase 2	IM, Three, 3-weekly doses	Therapeutic	NCT01667341
COR-1	DNA, with 2 codon-modified and optimized plasmids encoding full length gD2 and truncated gD2	Admedus	Phase 2	ID, Three, 4-weekly doses followed by 6 month booster	Therapeutic	ACTRN12615000094572

IM: intramuscular, ID: intradermal.

in 2012 and enrolled over 8,000 HSV-1 and HSV-2 seronegative sexually active women in North America and tested a gD2 subunit vaccine adjuvanted with alum and 3-O-deacylated monophosphoryl lipid A against a blinded placebo control (Hepatitis A), with the primary outcome of genital herpes disease.[82] The gD2 vaccine did not prevent genital HSV-2 disease or infection, but some level of efficacy for prevention of genital HSV-1 disease and infection was demonstrated: VE (disease) = 58 %, 95 % CI = 12–80 %, VE (infection) = 35 %, 95 % CI = 13–52 %. The titers of elicited gD2 antibody were associated with protection against HSV-1 infection, providing the first evidence of a correlate of protection.[83] Stimulating higher levels of antibody to gD2 or, alternatively, stimulating antibodies to other surface glycoproteins is hypothesized to prevent genital HSV-1 and HSV-2 infection.

HSV529 is a replication-defective HSV-2 vaccine with deletions in UL5 and UL29. This virus can infect but not replicate in cells and was studied in a small placebo-controlled Phase I trial in 3 groups: persons seronegative for HSV-1 and HSV-2 (n = 20), persons seropositive for HSV-2, regardless of HSV-1 serostatus (n = 20), and persons seropositive for HSV-1 and seronegative for HSV-2 (n = 20) [84]. The vaccine was safe and well tolerated overall, with most participants noting mild injection site pain/tenderness and some systemic reactions. Neutralizing antibody was induced to whole virus and was sustained for 1 year among HSV-1/HSV-2 seronegative persons only, and gD2 antibody increased among all 3 groups post vaccination. However, the vaccine induced CD4+ and CD8+ T cell responses in a minority of persons among HSV seronegative participants. Among HSV-seropositive persons, polyfunctional HSV-2 specific CD4+ T cells were induced, but CD8+ T cells were not. These results provide a proof of concept that immune responses can be stimulated to replication-defective virus. Future designs may combine replication-defective HSV-2 with additional modalities, such as adjuvant or a prime-boost strategy, to optimize immune responses.

5.3. Lessons from therapeutic vaccination studies

Protein subunit and DNA vaccines have been tested as therapeutic vaccines for HSV-2 seropositive persons with symptomatic genital herpes disease. In a Phase I/II dose-finding clinical trial using a protein subunit vaccine containing truncated gD2/ICP-4.2 with Matrix M adjuvant, the risk of HSV shedding was reduced by 53 % immediately post vaccination and by 42 % 6 months post vaccination, with significant declines in the lesion rate as well. [85] In a follow up Phase II/III study in a similar population, the optimal dose (GEN-003, 60ug each antigen/75ug adjuvant) was associated with a 55 % reduction in shedding immediately post vaccination, which was sustained through 12 months post vaccination [86]. In addition, the lesion rate decreased by 47 % at 12 months post vaccination. The optimized vaccine dosages induced antigen specific IgG and CD4+ T cell responses which remained above baseline values for 12 months. [87] While this candidate is not currently being pursued further, it provides proof of concept that natural immunity can be boosted by vaccines to alter the natural history of genital HSV infection among people with chronic HSV-2 infection.

A recent Phase I/IIa study has also been published using a DNA vaccine candidate, COR-1, which has two plasmids containing codon-modified full length gD2 and a truncated gD2 fused to a ubiquitin sequence, designed to stimulate the CD8+ T cell response. HSV-2 seropositive persons with a history of symptomatic genital herpes were enrolled in a randomized, placebo-controlled study to evaluate safety and humoral and cellular immune responses in response to the vaccine. [88] In this study, the vaccine appeared safe and there were trends suggesting that vaccine-specific immune responses were induced, but the sample size was too small to determine if COR-1 stimulates immune responses.

Taken together, these prior vaccine studies exploring both prophylactic and therapeutic HSV vaccine candidates have revealed that vaccines can stimulate immune responses to HSV but that additional studies to understand the local and systemic immune responses and how to

Table 7
Overview of modelling studies that measure health impact on disease burden and transmission – prophylactic vaccines.

Policy question	Assessment method/ measure	Additional information specific to models	Assumptions	Outcomes/interpretation
Prophylactic HSV-2 vaccine impact on HSV-2 infection and disease[37]	Systematic review of transmission dynamic models of prophylactic or therapeutic HSV-2 vaccination at the population level, summarizing model results on HSV-2 outcomes, model structure, assumptions and heterogeneity. [37] Health outcomes measured were HSV-2 incidence rate or cumulative, HSV-2 prevalence, number of cases, and 1 model included impact on HIV-1 incidence rate. Time horizon was generally over 10–30 years. No models included health economic outcomes or neonatal transmission. The review focused on HSV-2 incidence as few studies had outcomes and scenarios that could be directly compared.	7 published models of prophylactic vaccines reviewed, 6 compartmental deterministic and 1 individual-based model. Sensitivity analyses were limited, mainly to varying vaccine efficacy, duration of vaccine protection, coverage.	Settings were sub-Saharan Africa (N = 2), North America (N = 3) or unspecified (N = 2) and baseline HSV-2 prevalence modelled ranged from 15 to 60 %. Target populations modelled were HSV-2 negative, both sexes, female-only, before or after sexual debut. Various vaccine efficacies were explored, typically > 30 %, with duration of protection varying from 5 years to lifelong, across studies. Proportion adequately protected following vaccination (take) assumed to be < 100 % in only 1 model. Degree of protection against HSV-2 infection, and other vaccine 'breakthrough' effects such as reduction in shedding, disease and/ or infectivity were explored in 5 studies. No model considered HSV-2 or HIV treatment. Only one assumed a fraction of the population had been infected with HSV-1, for which HSV-2 vaccine would not be effective. Most were calibrated to one HSV-2 prevalence time point. Vaccination strategies included routine vaccination before sexual activity debut or of sexually active population, with and without catch-up, and mass vaccination. Uptake was varied between 5 % and 100 % annually.	Reduction in HSV-2 incidence across studies ranged from 5 % after 30 years to 72 % after 10 years depending on scenario modelled (e.g., varying efficacies, uptake). Studies that explored a wider range of scenarios contributed most to this uncertainty range. Impact on HSV-2 incidence was larger when measuring incidence rate rather than cumulative incidence. Few studies had outcomes and scenarios that could be directly compared. Incremental impact of breakthrough effects was more important when reduction in susceptibility was low (e.g., <30 %) & increased over time as more breakthrough infections accumulated. Catch-up vaccination greatly accelerated impact of vaccine, especially in the shorter term (10–20 years). A vaccine that does not also work among those with HSV-1 will be less useful at the population level due to high prevalence of HSV-1 infection. Duration of vaccine protection was very important across studies, especially to maintain impact in the long term.
Prophylactic HSV-2 vaccine impact on HSV-2 infection and disease[97]	Transmission dynamic model of vaccination impact.	Compartmental deterministic model, both sexes, stratified by age, sexual activity. Calibration: Fitted to sex- and age-stratified HSV-2 prevalence data over time, 1 best fit identified. Sensitivity analysis on vaccine efficacy, duration of protection, coverage. Uncertainty ranges provided by varying parameter by +/-40 % of point estimate value.	Setting was US with HSV-2 incidence: ~4/1000 person-years. Assumed vaccine reduced susceptibility to infection by 50 % (with no breakthrough effects) and protection lasts 20 years for all scenarios, apart from infant vaccination. Various vaccination strategies of HSV-2 negative individuals modelled: routine vaccination of adult (15–49 yo) males or females only, males and females aged 10–14 yrs, and infants (assuming 30 years duration of protection). Vaccination scale-up at constant rate to achieve 80 % coverage in 2030 (after 10 years).	Prophylactic vaccine of intermediate efficacy can reduce HSV-2 incidence by > 50 % and would require 50 vaccinations to avert one new HSV-2 infection. Routine vaccination of a large fraction of male and female adults was more impactful in the short-term than other strategies and was deemed essential to achieve a sizable impact rapidly. Prioritizing vaccination to younger age groups, highly sexually active, and women rather than men increased efficiency further, as it required less vaccination to avert one new HSV-2 infection. In contrast, adolescent or infant vaccination could be impactful but required a long time before generating sizeable impact.
Prophylactic HSV-2 vaccine impact on HSV-2 infection and disease and HIV infection[98]	Transmission dynamic model of prophylactic and therapeutic vaccination impact on HIV and HSV-2 in South Africa.	Compartmental deterministic model of 15–49 year-olds, both sexes, stratified by HSV-2 and HIV status (including HIV-HSV-2 interactions) and sexual activity (six risk sub-populations including MSM and FSWs). HSV-2 infected individuals	Setting was South Africa with HSV-2 prevalence ~ 50 % and HIV infection 19 %. HIV-HSV-2 interactions modelled were (i) HSV-2 infection increases HIV acquisition risk, (ii) HSV-2	A prophylactic vaccine offering lifetime protection with 80 % efficacy and uptake could reduce HSV-2 and HIV incidence by > 80 % and 65 % after 40 years, respectively. This impact decreases with reduced efficacy, uptake and

(continued on next page)

Table 7 (*continued*)

Policy question	Assessment method/ measure	Additional information specific to models	Assumptions	Outcomes/interpretation
		grouped into three disease levels. Calibration: Fitted using Bayesian framework to HIV prevalence (by risk group), HSV-2 prevalence (by gender and HIV status), and ART coverage. Model validated using HSV-2 and HIV data not used in model calibration. 5,000 model fits were used to give the median and 95 % credibility intervals (95 %CrI; 2.5th to 97.5th percentile range) for all model projections.	infection increases HIV transmission risk, and (iii) HIV infection increases HSV-2 transmission risk. For (i) and (ii), the increased risk of HIV acquisition/transmission with HSV-2 infection was further elevated during GUD periods. For (iii), the effect of HIV co-infection on increasing the days with HSV-2 shedding and the effect of ART on reducing this was incorporated. Annual cohort prophylactic vaccination of 9-year-olds implemented as a percentage of individuals entering the model at age 15 years being protected. Various scenarios for vaccine efficacy and uptake modelled. Sensitivity analyses: Take-type (vs degree-type) vaccine efficacy, shorter duration of protection, additional therapeutic benefits for prophylactic vaccine in breakthrough infections and catch-up prophylactic vaccination.	duration of protection. Impact of vaccination on time with GUD also modelled. Results show that prophylactic and therapeutic vaccines offer two complementary approaches for reducing HSV-2 and that in high HIV prevalence populations both vaccines could be important additional tools for controlling HIV.

stimulate them to develop effective vaccines are needed. Nonetheless, the field has increasing knowledge demonstrating the feasibility of development of HSV vaccines.

5.4. Overview of the vaccine candidates in the clinical pipeline

HSV vaccine development is a rapidly evolving field, with several novel candidates and platforms in early phase clinical trials and others have near-term targets for Phase I clinical trials (reviewed in [90]). The vaccines that are currently recruiting in clinical trials or that have completed studies in the last 5 years are shown in Table 6. There are a variety of platforms including mRNA, protein subunit, DNA, and replication-defective live virus candidates that have already been testing in clinical trials. Candidates may be tested as therapeutic vaccines, prophylactic vaccines or both. In the preclinical realm, novel designs include a single-cycle replication gD2 deletion HSV-2 strain [91], a live-attenuated HSV-2 with deletions in ICP0,[92] a live-attenuated HSV-1 with mutations in UL37 which is non-neuroinvasive,[93] and a subunit gD2/gB2 with nanoemulsion adjuvant that is being studied with intranasal administration.[94] In addition, in the animal HSV-1 ocular model, HSV-1 0ΔNLS has also been shown to produce robust antibody responses and protect against ocular infection upon challenge [95].

6. Health, social, and economic impacts of a vaccine on burden of disease and transmission

Several models have examined the public health impact of prophylactic and therapeutic vaccines on HSV, with few also exploring potential impact on HIV acquisition and transmission. In 2015, WHO convened a meeting of experts to consult on HSV-2 impact modelling in order to summarize what had been done and what gaps remained. In preparation for that meeting, a review of relevant models was conducted and subsequently published.[37] This review summarized and compared eight vaccine impact models, six for a hypothetical prophylactic vaccine, one therapeutic, and one modelling impact of both prophylactic and therapeutic vaccines. Subsequent to this, three additional models have been published, one for therapeutic [96] and two others for prophylactic and therapeutic vaccines.[97,98] An overview of these 11 models is provided in Tables 7 and 8. Direct model comparisons were challenging as assumptions and outcomes reported differed. A disproportionate number of published models focused on prophylactic HSV vaccines, when much of the current development focus is on therapeutic vaccines Table 9.

To date, no study has specifically estimated the social and economic impact of HSV vaccines, thus limiting the full understanding of the potential benefits that HSV vaccines can afford. Economic burden estimates can be used to understand potential costs averted with predicted decreases in incidence or prevalence with modelled vaccine implementation. Cost-effectiveness estimates are still needed to fully investigate the social and economic impact of HSV vaccines.

6.1. Summary of knowledge and research gaps in modelling studies that measure anticipated socio-economic impact of the vaccine

There are many gaps in our understanding of the impact of HSV on quality of life.[99] Several studies have attempted to measure the effect of genital herpes on health-related quality of life, using tools or scales for health utility measures to determine quality-adjusted life years (QALYs). However, most of these were done more than a decade ago, focused on HICs and could not be converted to disability/utility weights; this literature needs to be updated with more contemporary measures and in diverse settings.[99] The lack of HSV-specific measures highlights the need for more and better data to understand the impact on quality of life across populations which could then be used to explore the socioeconomic impact of vaccination.

Also, we have witnessed the effects of vaccine equity during the COVID-19 pandemic, and a similar scenario may occur if we do not consider the socio-economic impact of HSV vaccine when it is developed. This can result in lasting and profound impact in LMIC which currently bear the largest burden of HSV.

Table 8
Overview of modelling studies that measure health impact on disease burden and transmission – therapeutic vaccines.

Policy question	Assessment method/ measure	Additional information specific to models	Assumptions	Outcomes/interpretation
Therapeutic HSV-2 vaccine impact on HSV-2 disease burden[37]	Systematic review of transmission dynamic models of prophylactic or therapeutic HSV-2 vaccination at the population level, summarizing model results on HSV-2 outcomes, model structure, assumptions and heterogeneity. [37] Health outcome measured was HSV-2 infection. No models included health economic outcomes or neonatal transmission.	2 models were on therapeutic vaccines, both simple compartmental deterministic models. Both only represented 1 sex and none were age structured. Sensitivity analyses were limited, mainly to varying vaccine efficacy, duration of protection, coverage.	Settings were unspecified (N = 1) and US (N = 1), baseline HSV-2 prevalence modelled ranged from 11 % to 60 %. Vaccine efficacy was varied but generally > 30 % with duration of vaccine protection ranging from 5 years to lifelong. No model considered HSV-2 or HIV treatment, or HSV-1 infection. Models assumed proportion adequately protected *(*i.e. *take, < 100 % in only 1 model)*, reduction (degree) in frequency or duration of disease progression, severity and/or reduction in infectivity, symptomatic or asymptomatic shedding. Target populations were HSV-2 positive adults among both sexes (all or asymptomatic latent infection). Vaccination strategies were routine or mass vaccination of sexually active individuals.	Impact ranged from 24 to 80 % reduction in cumulative HSV-2 incidence over 10 years, across models, and scenarios.[37] Impact was larger and manifested more rapidly than with a prophylactic vaccine because the target population was all HSV-2 positive adults, which may not be realistic.
Therapeutic HSV-2 vaccine impact on HSV-2 infection and disease[97]	Transmission dynamic model of vaccination impact.[97] Outcomes measured were HSV-2 incidence and prevalence rates within 30 years of vaccine introduction.	Compartmental deterministic model, 2-sex, stratified by age, sexual activity. Calibration: Fitted to sex and age stratified HSV-2 prevalence over time, 1 best fit identified. Sensitivity analysis to vaccine efficacy, duration, coverage. Uncertainty" ranges provided by varying parameter by +/-40 % of point estimate value.	Setting was US with HSV-2 incidence ~ 4/1000 person-year. Vaccine was assumed to reduce HSV-2 shedding frequency/re-activation (and therefore infectivity) by 50 % and to last 10 years. Vaccination strategy: routine vaccination of male, female or both, symptomatic HSV-2 positive (25 % of those who acquire HSV-2). Scale-up at a constant rate to achieve 80 % coverage within 10 years.	Routine male & female vaccination resulted in a 13 % overall reduction in HSV-2 incidence rate after 30 years. Number needed to vaccinate to avert one HSV-2 infection was 15 over 10 years and 8 over 30 years. Vaccine can have substantial population-level impact even if only used in symptomatic individuals. Vaccination was more efficient if younger age groups were prioritized. Model did not assess impact on disease, but authors suggested minimum efficacy needed for licensing could be lower than for a prophylactic vaccines, given the direct and immediate benefits on quality of life.
Therapeutic HSV-2 vaccine impact on HSV-2 infection and disease[96]	Transmission dynamic model of vaccination impact.[96] Outcomes measured were number of prevalent HSV-2 infections and number of individuals shedding over 30 years.	Compartmental model + analytical solution and stochastic simulation. Simple 1-sex model without age or other heterogeneity. Parameter assumptions not comprehensively justified. Calibration: Minimal, one parameter set reproducing overall HSV-2. Prevalence, no uncertainty analysis. No sensitivity analysis apart from a few vaccination scenarios.	Assumes 12 % HSV-2 prevalence (similar to US) in a hypothetical population, 100 % vaccine efficacy against recurrence of symptoms and shedding/infectivity with 2-year duration of protection. Vaccination strategy was routine vaccination of symptomatic HSV-2 positive (at rates of 0.001, 0.01, 0.1 per day), with or without booster (0 %, 20 %, 50 %, 100 % individuals when they lose their vaccine protection), and with or without also routinely vaccinating asymptomatic.	Reduced number of HSV-2 prevalent infections by 6 %, 25 % and 42 % after 30 years when 0.001, 0.01, 0.1 vaccinated per day. Adding booster had a negligible impact, especially when rates of primary routine vaccination were high. The impact of adding asymptomatic vaccination was marginal unless the primary rate of vaccination of symptomatic was very low.
Therapeutic HSV-2 vaccine impact on HSV-2 infection	Transmission dynamic model of prophylactic and therapeutic	Compartmental deterministic model of 15–49 year-olds, both sexes, stratified by HSV-2 and HIV status	Setting was South Africa with HSV-2 prevalence ~ 50 % and HIV infection 19 %.	A therapeutic vaccine offering lifetime protection with 40 % coverage among symptomatic

(*continued on next page*)

Table 8 (*continued*)

Policy question	Assessment method/ measure	Additional information specific to models	Assumptions	Outcomes/interpretation
and disease and HIV infection[98]	vaccination impact on HIV and HSV-2 in South Africa.	(including HIV-HSV-2 interactions) and sexual activity (six risk sub-populations including MSM and FSWs). HSV-2 infected individuals grouped into three disease levels. Calibration: Fitted using Bayesian framework to HIV prevalence (by risk group), HSV-2 prevalence (by gender and HIV status)., and ART coverage. Model validated using HSV-2 and HIV data not used in model calibration. 5,000 model fits were used to give the median and 95 % credibility intervals (95 %CrI; 2.5th to 97.5th percentile range) for all model projections.	HIV-HSV-2 interactions modelled were (i) HSV-2 infection increases HIV acquisition risk, (ii) HSV-2 infection increases HIV transmission risk, and (iii) HIV infection increases HSV-2 transmission risk. For (i) and (ii), an increased risk of HIV acquisition/transmission with HSV-2 infection was further elevated during GUD periods. For (iii), the effect of HIV co-infection on increasing the days with HSV-2 shedding and the effect of ART on reducing this was incorporated. Therapeutic vaccination implemented as percentage of symptomatic HSV-2-infected individuals vaccinated at a constant rate with rate proportional to time with GUD. Various scenarios for vaccine efficacy and coverage modelled. Sensitivity analyses: Take-type (vs degree-type) vaccine efficacy, shorter duration of protection and use of boosters, mode of therapeutic vaccine effect, and additional therapeutic vaccination of HIV-HSV-2-co-infected individuals.	individuals could reduce HSV-2 and HIV incidence by almost 30 % and $>$ 25 % after 40 years, respectively. This impact decreases with reduced efficacy, coverage and duration of protection. Although the impact of therapeutic vaccination is generally less than that of prophylactic vaccination, it is nevertheless still substantial, while the impact per vaccination is greater for therapeutic vacccination. Impact of vaccination on time with GUD also modelled. Results show that prophylactic and therapeutic vaccines offer two complementary approaches for reducing HSV-2 and that in high HIV prevalence populations both vaccines could be important additional tools for controlling HIV.

6.2. Summary of knowledge and research gaps in modelling health impact on disease burden and transmission

The model review by Spicknall, et al.[37] identified many gaps, including the following:

- Most models were relatively simple and did not incorporate heterogeneities of specific populations and settings and represented a limited range of settings.
- Outcomes were primarily limited to HSV-infections (incident or prevalent), with few results on GUD, HIV-1 or neonatal herpes.
- No model studied the contribution of HSV-1 to morbidity, including the psychosocial burden.
- Uncertainty and sensitivity analyses remain limited.
- Most studies did not consider HSV-2/HIV treatment.
- Model results are difficult to compare across models since the vaccination scenarios modelled are very different from one another and information on coverage and outcomes was not reported consistently across studies.
- No studies investigated the combined use of a therapeutic and prophylactic vaccine if both became available.
- No studies considered potential risks associated with vaccination.

Possible directions for improvement to fill gaps:

- Cost-effectiveness analyses of HSV vaccines.
- Models assessing the impact of therapeutic vaccines are still limited; needs study of realistic and aspirational assumptions on vaccine efficacies (only 2 new studies published since the last review).
- Better head-to-head comparison of prophylactic and therapeutic vaccine, with comparable and more realistic scale-up scenarios over time.
- Model that considers heterogeneity in population and can reproduce different vaccination strategies (i.e., sex and age structure, symptomatic and asymptomatic infections).
- Define public health target/goals at population-level to help determine PPC needed to achieve these (e.g., reaching % reduction in x years).
- Define minimum set of standard vaccination scenarios (coverage over time, target population) to include in all modelling analyses to facilitate model comparison.
- Assessment in more diverse settings and analysis that includes wider range of outcomes.
- Sensitivity analysis to understand influence of model assumptions (especially on HSV-2 natural history) on intervention impact to facilitate model comparison.
- Explore the dynamics and interactions between HSV-1, HSV-2 and HIV, the relationship between HSV shedding, viral load and infectivity, and the simplest way to model the natural history of HSV whilst retaining the key features important to vaccination impact will be critical in informing development of these more complex models.
- Estimate potential impact of HSV-1 vaccination on herpes-related oral, ocular and neurologic disease.
- Models could also explore the multi-dimensional parameter space defined by epidemiological context (e.g., sexual behaviours, HSV-2 and HIV prevalence), vaccine characteristics (e.g., biological vaccine effects, duration of protection), and vaccination strategy (e.g., target population, coverage) in greater detail.

Table 9
Overview of expectations of evidence that are likely to be required to support a global / regional / national policy recommendation, or financing.

Parameter for policy/ financing consideration	Assumptions	Guidance/reports available
Problem	Stakeholders consider the problem a sufficient public health priority. Many LMICs do not adhere to their own treatment guidelines, nor procure the medicines necessary, largely due to lack of adequate financing. Stigma and cultural beliefs contribute to the limited resources devoted to STIs, and patients must often pay out of pocket for treatment which is prohibitively expensive for many.	[100]
Health impact	We can specifically define the primary public health goal(s), i.e., reduction in burden of HSV-associated disease (GUD, neonatal herpes, etc.), new infections, and/or reduction in acquisition of HSV-2-associated HIV infection in high HIV-prevalence populations. If HIV impact is a primary public health goal, HSV vaccines could potentially have a notable impact on HIV, and modelling studies can measure anticipated reductions in HIV as a result of HSV vaccination.	Models of HSV-2 vaccination have been heterogeneous in basic assumptions and composition. In evaluating prophylactic and/or therapeutic vaccination strategies, models showed wide ranging effects reducing the HSV-2 incidence rate by as little as 5 % after 30 years or up to 88 % after 10 years depending on various assumptions including efficacy, uptake, speed or roll out, target population. The range of impact on new HIV infections was similarly wide (see Section 6). [37,59,101–103]
Value for money	Modelling studies can measure anticipated cost-effectiveness of vaccination, based on reasonably accurate disease burden and vaccine impact modelling.	The global economic burden of HSV has now been estimated, but cost-effectiveness analyses of HSV vaccines are still needed. [43,44] Country-specific models estimating costs (aggregate annual and lifetime) are needed for settings outside of the US and should incorporate neonatal herpes, HSV-2 associated HIV infections, cost of diagnosis and treatment of HSV infection, other HSV-related conditions (psychosocial morbidity). Based on assessments for HPV vaccines, assessment of broader economic consequences of HSV-2 vaccination could be helpful from the government perspective – using a fiscal analytic approach increasing quality and quantity of human capital and increasing the tax base in the country.[104] Value assessments can also be informed by country-specific assessments of whether the improvement in health outcomes offered by HSV-2 vaccination exceeds the improvement in health that would have been possible if resources had been diverted to other healthcare activities instead, i.e., net health benefit.[105]
Equity and social protection impact	Modelling studies that measure anticipated health impact of HSV vaccination can be stratified by relevant subpopulations to predict equity impacts.	Examples of model-based predictions of the impact of vaccination on disparities in health are available for other vaccines.[106]
Economic impact	Modelling studies can measure anticipated reductions in productivity costs as a result of vaccination.	Examples from HPV vaccination.[104–106]
Overall quality of this evidence for the critical outcomes	Licensing, pre-qualification and economic/cost-effectiveness data are considered robust.	No reports available, unknown for HSV vaccines.
Gavi comparative advantage	Potential for Gavi support to catalyse additional investment or for vaccines for HICs to be affordable to LMICs.	No reports available, unknown for HSV vaccines.
Feasibility	Vaccination schedule in target populations and healthcare worker behaviour change are feasible.	No reports available, unknown for HSV vaccines.
Acceptability	Acceptable to stakeholders – funders, ministries of health, immunization managers, target populations.	No reports available, unknown for HSV vaccines.
Vaccine cost	Total procurement cost to Gavi and countries is acceptable.	No reports available, unknown for HSV vaccines.
Operational cost	Incremental in-country operational costs per vaccinated person.	No reports available, unknown for HSV vaccines.

Table 10
Access and implementation feasibility assessment for HSV prophylactic and therapeutic vaccines.

	Intervention	
	Prophylactic HSV vaccines	**Therapeutic HSV vaccines**
Possibility of implementation within existing delivery systems	High to very high Vaccines targeted to young adolescents before their sexual debut could be implemented with existing adolescent vaccination programs, including school-based programs, e.g., with HPV vaccines. Targeting this population without needing boosters before the period of highest risk will require a sufficient duration of protection.	Low to moderate No vaccine delivery systems currently exist for target populations for therapeutic HSV vaccines, which are symptomatic HSV patients presenting to care. However, a variety of sexual health service platforms, e.g., PrEP clinics for HIV prevention, could be leveraged for vaccination programs. Experience with COVID-19 vaccine implementation might also improve reaching these groups. Care-seeking behavior for HSV GUD may be low, particularly in LMICs, although an effective therapeutic vaccine might increase demand for HSV GUD care.
Commercial attractiveness	High Large target populations distributed across HIC and LMIC markets. Target populations in LMICs tend to be larger (e.g., some countries have very high general population prevalence). Gavi support will likely depend on cost-effectiveness in different settings.	High Both HIC and LMIC targets exist. Although target populations are smaller than for prophylactic vaccines, care seeking and expenditures on HSV antiviral medications in HICs has been substantial. Thus, HIC markets may drive development.
Clarity of licensure and policy decision pathway	Moderate to high The licensure pathway is relatively clear, although an infection indication is preferred over a disease indication for various reasons, e.g., the role of asymptomatic infections in HSV transmission and in increasing risk of HIV infection. Regulators often prefer disease indications, although not uniformly. Policy decisions may vary greatly in HICs vs LMICs and among countries in both settings, based cost-effectiveness and other factors.	Moderate The licensure pathway will likely depend upon demonstration of decreased symptomatic GUD recurrences, although decreased viral shedding may have significant impact on potential for transmission to sexual partners and genital tract inflammation.
Expected financing mechanism	Moderate Interest from global funders, including Gavi, is unclear and will likely depend on data related to predicted impact and cost-effectiveness. There is limited country-level data on HSV epidemiology and disease burden to inform decision-making by national procurement agencies once the vaccines are available.	Low to moderate Additional funding to identify patients with genital herpes and to provide vaccination outside of currently available vaccine schedules will be required, the financing mechanism is not yet defined.
Ease of uptake	Low to Moderate For adolescents, a well-defined target population exists, as for HPV vaccines. However, in many settings, vaccine hesitancy has been an issue for HPV vaccines, which are widely seen as cancer-prevention vaccines; HSV vaccines will be more clearly associated with a sexually transmitted infection, which may affect acceptability, particularly to parents of adolescents.	High The likelihood of acceptability is higher for symptomatic patients. Care-seeking for HSV GUD has been low in many settings; however an effective therapeutic vaccine might increase demand for HSV GUD care.

7. Social and/or economic impact of a vaccine

This section has been covered in section 6, above.

8. Policy considerations and financing

WHO policy recommendations are made through the Strategic Advisory Group of Experts on Immunization (SAGE). These policy recommendations, along with WHO pre-qualification of the product, will be considered in decisions for financing by Gavi, the Vaccine Alliance. Any HSV vaccine that becomes available is expected to be evaluated by Gavi through its Vaccine Investment Strategy (VIS), which is conducted on a 5-year cycle. The VIS process is centred around a robust and transparent mechanism for evaluation of vaccine products based on a number of criteria, which include elements such as health and economic impact, contribution to equity and social protection, feasibility and implementation costs.

However, an HSV vaccine is likely to be desirable to many MICs and other non-Gavi countries that will still face challenges to affordability if the product and its manufacturers are focused on the HIC markets. Many countries are likely to look to a WHO policy recommendation in their decision-making. However, decisions to introduce are more likely to be based on public demand and health economic modelling, in particular cost savings to the health system and even individual productivity and quality of life. Therefore, it will be important to better understand the vaccine's target population and how it can be accessed to achieve maximum individual and population-level impact.

9. Access and implementation Feasibility

Considerations for access and implementation of potential future HSV vaccines are summarized in Table 10.

10. Conclusion

HSV-1 and HSV-2 are highly prevalent infections with multiple clinically relevant presentations affecting human health. HSV-1 and HSV-2 cause chronic, incurable infections which vary in disease presentation in individuals and throughout the lifespan. While most people will have subclinical infection, others will have intermittent symptoms and be at risk of transmission to sexual partners and neonates (in the case of genital HSV infection), or will have HSV-1 related oral, ocular, or neurologic infection. As such, vaccine development for HSV has focused on two strategies in parallel: 1) prophylactic vaccination, with the goal of preventing infection among susceptible persons and 2) therapeutic vaccination, with the goal of decreasing symptoms in persons who are already infected, and potentially also to decrease risk of onward transmission. Development of both prophylactic and therapeutic HSV vaccines has the potential to greatly improve human health, particularly in populations most affected by HSV infections such as women and sexual minorities, and can reduce disparities in infection between LMICs and HICs.

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Appendix A. Supplementary data

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References

[1] Gnann JW, Whitley RJ. Genital herpes. N Engl J Med 2016;375(7):666–74.
[2] James C, et al. Herpes simplex virus: global infection prevalence and incidence estimates, 2016. Bull World Health Organ 2020;98(5):315–29.
[3] Looker KJ, et al. Global and regional estimates of the contribution of herpes simplex virus type 2 infection to HIV incidence: a population attributable fraction analysis using published epidemiological data. Lancet Infect Dis 2020;20(2):240–9.
[4] Silhol R, et al. What is the burden of heterosexually acquired HIV due to HSV-2? global and regional model-based estimates of the proportion and number of HIV infections attributable to HSV-2 infection. J Acquir Immune Defic Syndr 2021;88(1):19–30.
[5] Gottlieb SL, et al. The global roadmap for advancing development of vaccines against sexually transmitted infections: Update and next steps. Vaccine 2016;34(26):2939–47.
[6] World Health Organization. *Global health sector strategies 2022-2030*. 2023 [cited 2023 05 March]; Available from: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/strategies/global-health-sector-strategies.
[7] World Health Organization, *WHO preferred product characteristics for herpes simplex virus vaccines*. 2019, World Health Organization: Geneva. Available from: https://www.who.int/publications/i/item/9789241515580.
[8] Gupta R, Warren T, Wald A. Genital herpes. Lancet 2007;370(9605):2127–37.
[9] AlMukdad S, et al. Epidemiology of herpes simplex virus type 2 in Asia: A systematic review, meta-analysis, and meta-regression. Lancet Reg Health West Pac 2021;12:100176.
[10] Harfouche M, et al. Epidemiology of herpes simplex virus type 2 in sub-Saharan Africa: Systematic review, meta-analyses, and meta-regressions. EClinicalMedicine 2021;35:100876.
[11] Harfouche M, Maalmi H, Abu-Raddad LJ. Epidemiology of herpes simplex virus type 2 in Latin America and the Caribbean: systematic review, meta-analyses and metaregressions. Sex Transm Infect 2021;97(7):490–500.
[12] Looker KJ, et al. First estimates of the global and regional incidence of neonatal herpes infection. Lancet Glob Health 2017;5(3):e300–9.
[13] Melvin AJ, et al. Neonatal herpes simplex virus infection: Epidemiology and outcomes in the modern era. J Pediatric Infect Dis Soc 2022;11(3):94–101.
[14] Mailles A, et al. Changing profile of encephalitis: Results of a 4-year study in France. Infect Dis Now 2022;52(1):1–6.
[15] Mailles A, et al. Long-term outcome of patients presenting with acute infectious encephalitis of various causes in France. Clin Infect Dis 2012;54(10):1455–64.
[16] Looker KJ, et al. The global and regional burden of genital ulcer disease due to herpes simplex virus: a natural history modelling study. BMJ Glob Health 2020;5(3):e001875.
[17] Samies NL, James SH, Kimberlin DW. Neonatal Herpes Simplex Virus Disease: Updates and Continued Challenges. Clin Perinatol 2021;48(2):263–74.
[18] McCormick I, et al. Incidence of herpes simplex virus keratitis and other ocular disease: Global review and estimates. Ophthalmic Epidemiol 2022;29(4):353–62.
[19] Itzhaki RF. Overwhelming evidence for a major role for herpes simplex virus type 1 (HSV1) in alzheimer's disease (AD); Underwhelming evidence against. Vaccines (Basel) 2021;9(6).
[20] Kotton BD, Kotton CN. Resistant herpes simplex virus infections - who, when, and what's new? Curr Opin Infect Dis 2022;35(6):530–5.
[21] Eberhardt O, et al. HSV-2 sacral radiculitis (Elsberg syndrome). Neurology 2004;63(4):758–9.
[22] Nardone R, et al. Herpes simplex virus type 2 Myelitis: Case report and review of the literature. Front Neurol 2017;8:199.
[23] Patel R, et al. Patients' perspectives on the burden of recurrent genital herpes. Int J STD AIDS 2001;12(10):640–5.
[24] Bennett C, et al. Impact of primary and recurrent genital herpes on the quality of life of young people and adults: a mixed methods systematic review. JBI Evid Synth 2022;20(6):1406–73.
[25] Ayoub HH, Chemaitelly H, Abu-Raddad LJ. Characterizing the transitioning epidemiology of herpes simplex virus type 1 in the USA: model-based predictions. BMC Med 2019;17(1):57.
[26] Brijwal M, et al. Herpes simplex virus type 1 genital ulcer disease at a tertiary care hospital in north india. Clin Infect Dis 2019;68(10):1783–4.
[27] Brown ZA, et al. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. JAMA 2003;289(2):203–9.
[28] Xu F, et al. Seroprevalence of herpes simplex virus type 1 in children in the United States. J Pediatr 2007;151(4):374–7.
[29] Looker KJ, Garnett GP. A systematic review of the epidemiology and interaction of herpes simplex virus types 1 and 2. Sex Transm Infect 2005;81(2):103–7.
[30] Langenberg AG, et al. A prospective study of new infections with herpes simplex virus type 1 and type 2. Chiron HSV Vaccine Study Group. N Engl J Med 1999;341(19):1432–8.
[31] Johnston C, et al. Dual-strain genital herpes simplex virus type 2 (HSV-2) infection in the US, Peru, and 8 countries in sub-Saharan Africa: A nested cross-sectional viral genotyping study. PLoS Med 2017;14(12):e1002475.
[32] Lamers SL, et al. Global Diversity within and between Human Herpesvirus 1 and 2 Glycoproteins. J Virol 2015;89(16):8206–18.
[33] Koelle DM, et al. Worldwide circulation of HSV-2 × HSV-1 recombinant strains. Sci Rep 2017;7:44084.
[34] Dudek TE, et al. Evidence for differences in immunologic and pathogenesis properties of herpes simplex virus 2 strains from the United States and South Africa. J Infect Dis 2011;203(10):1434–41.
[35] Colgrove R, et al. Genomic sequences of a low passage herpes simplex virus 2 clinical isolate and its plaque-purified derivative strain. Virology 2014;450–451:140–5.
[36] Garnett GP. Role of herd immunity in determining the effect of vaccines against sexually transmitted disease. J Infect Dis 2005;191(Suppl 1):S97–.
[37] Spicknall IH, et al. Review of mathematical models of HSV-2 vaccination: Implications for vaccine development. Vaccine 2019;37(50):7396–407.
[38] Looker KJ, et al. Effect of HSV-2 infection on subsequent HIV acquisition: an updated systematic review and meta-analysis. Lancet Infect Dis 2017;17(12):1303–16.

[39] Gray RH, et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai. *Uganda* Lancet 2001;357(9263):1149–53.
[40] Todd J, et al. Effect of genital herpes on cervicovaginal HIV shedding in women co-infected with HIV AND HSV-2 in Tanzania. PLoS One 2013;8(3):e59037.
[41] Augenbraun M, et al. Increased genital shedding of herpes simplex virus type 2 in HIV-seropositive women. Ann Intern Med 1995;123(11):845–7.
[42] Schacker T, et al. Frequent recovery of HIV-1 from genital herpes simplex virus lesions in HIV-1-infected men. JAMA 1998;280(1):61–6.
[43] Chaiyakunapruk, N., et al., Estimated global and regional economic burden of genital herpes simplex virus infection among 15-49 year-olds in 2016. BMC Glob Public Health 2024; in press.
[44] Silva S, et al. Estimated economic burden of genital herpes and HIV attributable to herpes simplex virus type 2 infections in 90 low- and middle-income countries: A modeling study. PLoS Med 2022;19(12):e1003938.
[45] Agyemang E, et al. Performance of commercial enzyme-linked immunoassays for diagnosis of herpes simplex virus-1 and herpes simplex virus-2 infection in a clinical setting. Sex Transm Dis 2017;44(12):763–7.
[46] Johnston C, Gottlieb SL, Wald A. Status of vaccine research and development of vaccines for herpes simplex virus. Vaccine 2016;34(26):2948–52.
[47] Workowski KA, et al. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep 2021;70(4):1–187.
[48] Reitano M, et al. Valaciclovir for the suppression of recurrent genital herpes simplex virus infection: a large-scale dose range-finding study. International Valaciclovir HSV Study Group. J Infect Dis 1998;178(3):603–10.
[49] Romanowski B, Marina RB, Roberts JN. Patients' preference of valacyclovir once-daily suppressive therapy versus twice-daily episodic therapy for recurrent genital herpes: a randomized study. Sex Transm Dis 2003;30(3):226–31.
[50] Fife KH, Almekinder J, Ofner S. A comparison of one year of episodic or suppressive treatment of recurrent genital herpes with valacyclovir. Sex Transm Dis 2007;34(5):297–301.
[51] Corey L, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med 2004;350(1):11–20.
[52] Kawashima M, et al. *Single-Dose, Patient-Initiated Amenamevir Therapy for Recurrent Genital Herpes: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study*. Open Forum Infect Dis 2022;9(10):p. ofac494.
[53] Martin ET, et al. A pooled analysis of the effect of condoms in preventing HSV-2 acquisition. Arch Intern Med 2009;169(13):1233–40.
[54] Stanaway JD, et al. Case-crossover analysis of condom use and herpes simplex virus type 2 acquisition. Sex Transm Dis 2012;39(5):388–93.
[55] Tobian AA, et al. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. N Engl J Med 2009;360(13):1298–309.
[56] Sheffield JS, et al. Valacyclovir prophylaxis to prevent recurrent herpes at delivery: a randomized clinical trial. Obstet Gynecol 2006;108(1):141–7.
[57] Celum C, et al. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. Lancet 2008;371(9630):2109–19.
[58] Celum C, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. N Engl J Med 2010;362(5):427–39.
[59] Gottlieb SL, et al. Modelling efforts needed to advance herpes simplex virus (HSV) vaccine development: Key findings from the World Health Organization Consultation on HSV Vaccine Impact Modelling. Vaccine 2019;37(50):7336–45.
[60] Child Health and Development, et al., *The Global Strategy for Women's, Children's, and Adolescents' Health (2016-2030)*, World Health Organization, Editor. 2018.
[61] World Health Organization, *Global health sector strategy on Sexually Transmitted Infections, 2016-2021: towards ending STIs*, World Health Organization, Editor. 2016. Available from: https://www.who.int/publications/i/item/WHO-RHR-16.09.
[62] World Health Organization, *Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030.* Geneva. Available from: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/strategies/global-health-sector-strategies.
[63] Broutet N, et al. Vaccines against sexually transmitted infections: the way forward. Vaccine 2014;32(14):1630–7.
[64] World Health Organization, *Immunization Agenda 2030: a global strategy to leave no one behind*. Available from: https://www.immunizationagenda2030.org/.
[65] NIAID. *Join NIAID staff workshop on genital herpes*. [cited 2023 March 16]; Available from: https://www.niaid.nih.gov/grants-contracts/join-niaid-staff-workshop-genital-herpes.
[66] National Institutes of Health. Strategic plan for herpes simplex virus research (2023-2028), NIH 2023. Available from: https://www.niaid.nih.gov/sites/default/files/nih-herpes-simplex-strategic-plan-2023.pdf.
[67] Yim KC, et al. The cotton rat provides a novel model to study genital herpes infection and to evaluate preventive strategies. J Virol 2005;79(23):14632–9.
[68] Lo M, et al. Acute infection and subsequent subclinical reactivation of herpes simplex virus 2 after vaginal inoculation of rhesus macaques. J Virol 2019;93(2).
[69] Hook LM, Friedman HM, Awasthi S. Guinea pig and mouse models for genital herpes infection. Curr Protoc 2021;1(12):e332.
[70] Koelle DM, et al. Clearance of HSV-2 from recurrent genital lesions correlates with infiltration of HSV-specific cytotoxic T lymphocytes. J Clin Invest 1998;101(7):1500–8.
[71] Truong NR, et al. Mechanisms of Immune Control of Mucosal HSV Infection: A Guide to Rational Vaccine Design. Front Immunol 2019;10:373.
[72] Ford ES, et al. B cells, antibody-secreting cells, and virus-specific antibodies respond to herpes simplex virus 2 reactivation in skin. J Clin Invest 2021;131(9).
[73] Zhu J, et al. Immune surveillance by CD8 αα + skin-resident T cells in human herpes virus infection. Nature 2013;497(7450):494–7.
[74] Shin H, Iwasaki A. A vaccine strategy that protects against genital herpes by establishing local memory T cells. Nature 2012;491(7424):463–7.
[75] Bernstein DI, et al. Successful application of prime and pull strategy for a therapeutic HSV vaccine. NPJ Vaccines 2019;4:33.
[76] Shannon B, et al. Distinct Effects of the Cervicovaginal Microbiota and Herpes Simplex Type 2 Infection on Female Genital Tract Immunology. J Infect Dis 2017;215(9):1366–75.
[77] Agyemang E, et al. Herpes Simplex Virus Shedding Rate: Surrogate Outcome for Genital Herpes Recurrence Frequency and Lesion Rates, and Phase 2 Clinical Trials End Point for Evaluating Efficacy of Antivirals. J Infect Dis 2018;218(11):1691–9.
[78] Phipps W, et al. Genital Herpes Simplex Virus Type 2 Shedding Among Adults With and Without HIV Infection in Uganda. J Infect Dis 2016;213(3):439–47.
[79] Manguro GO, et al. Genital HSV Shedding among Kenyan Women Initiating Antiretroviral Therapy. PLoS One 2016;11(9):e0163541.
[80] Schiffer JT, et al. Herpes simplex virus-2 transmission probability estimates based on quantity of viral shedding. J R Soc Interface 2014;11(95).
[81] Madebe R, et al. Herpes Simplex virus type 2 seroprevalence and risk factors among adolescents and youth with HIV-1 in Northern. *Tanzania* J Infect Dev Ctries 2020;14(4):398–403.
[82] Belshe RB, et al. Efficacy results of a trial of a herpes simplex vaccine. N Engl J Med 2012;366(1):34–43.
[83] Belshe RB, et al. Correlate of Immune Protection Against HSV-1 Genital Disease in Vaccinated Women. J Infect Dis 2014;209(6):828–36.
[84] Dropulic LK, et al. A Randomized, Double-Blinded, Placebo-Controlled, Phase 1 Study of a Replication-Defective Herpes Simplex Virus (HSV) Type 2 Vaccine, HSV529, in Adults With or Without HSV Infection. J Infect Dis 2019;220(6):990–1000.
[85] Bernstein DI, et al. therapeutic vaccine for genital herpes simplex Virus-2 Infection: Findings from a randomized trial. J Infect Dis 2017;215(6):856–64.
[86] Van Wagoner N, et al. Effects of different doses of GEN-003, a therapeutic vaccine for genital herpes simplex Virus-2, on Viral shedding and lesions: results of a randomized placebo-controlled trial. J Infect Dis 2018;218(12):1890–9.
[87] Bernstein DI, et al. Therapeutic HSV-2 vaccine decreases recurrent virus shedding and recurrent genital herpes disease. Vaccine 2019;37(26):3443–50.
[88] Chandra J, et al. Immune responses to a HSV-2 polynucleotide immunotherapy COR-1 in HSV-2 positive subjects: A randomized double blinded phase I/IIa trial. PLoS One 2019;14(12):e0226320.
[89] McQuillan G, et al. Prevalence of herpes simplex virus Type 1 and Type 2 in Persons Aged 14–49: United States, 2015–2016. NCHS Data Brief 2018;304:1–8.
[90] Stanfield BA, et al. Rational design of live-attenuated vaccines against herpes simplex viruses. Viruses 2021;13(8).
[91] Burn C, et al. A Herpes Simplex Virus (HSV)-2 Single-Cycle Candidate Vaccine Deleted in Glycoprotein D Protects Male Mice From Lethal Skin Challenge With Clinical Isolates of HSV-1 and HSV-2. J Infect Dis 2018;217(5):754–8.
[92] Halford WP, et al. A Live-Attenuated HSV-2 ICP0- Virus Elicits 10 to 100 Times Greater Protection against Genital Herpes than a Glycoprotein D Subunit Vaccine. PLoS One 2011;6(3):e17748.
[93] Bernstein DI, et al. The R2 non-neuroinvasive HSV-1 vaccine affords protection from genital HSV-2 infections in a guinea pig model. npj Vaccines 2020;5(1):104.
[94] Bernstein DI, et al. Intranasal nanoemulsion-adjuvanted HSV-2 subunit vaccine is effective as a prophylactic and therapeutic vaccine using the guinea pig model of genital herpes. Vaccine 2019;37(43):6470–7.
[95] Royer DJ, et al. Vaccine-induced antibodies target sequestered viral antigens to prevent ocular HSV-1 pathogenesis, preserve vision, and preempt productive neuronal infection. Mucosal Immunol 2019;12(3):827–39.
[96] Venturino E, Shoukat A, Moghadas SM. Dynamics of HSV-2 infection with a therapeutic vaccine. Heliyon 2020;6(7):e04368.
[97] Ayoub HH, Chemaitelly H, Abu-Raddad LJ. Epidemiological Impact of Novel Preventive and Therapeutic HSV-2 Vaccination in the United States: Mathematical Modeling Analyses. Vaccines (Basel) 2020;8(3).
[98] Stone J, et al. The population impact of herpes simplex virus type 2 (HSV-2) vaccination on the incidence of HSV-2, HIV and genital ulcer disease in South Africa: a mathematical modelling study. EBioMedicine 2023;90:104530.
[99] Devine A, et al. Health-related quality of life in individuals with genital herpes: a systematic review. Health Qual Life Outcomes 2022;20(1):25.
[100] Corbell C, et al. Genital ulcer disease treatment policies and access to acyclovir in eight sub-Saharan African countries. Sex Transm Dis 2010;37(8):488–93.
[101] Alsallaq RA, et al. Population level impact of an imperfect prophylactic vaccine for herpes simplex virus-2. Sex Transm Dis 2010;37(5):290–7. https://doi.org/10.1097/OLQ.0b013e3181d3d023.
[102] Freeman EE, et al. Population-level effect of potential HSV2 prophylactic vaccines on HIV incidence in sub-Saharan Africa. Vaccine 2009;27(6):940–6.
[103] Gottlieb SL, et al. Meeting report: Initial World Health Organization consultation on herpes simplex virus (HSV) vaccine preferred product characteristics, March 2017. Vaccine 2019;37(50):7408–18.
[104] Setiawan D, et al. Assessment of the broader economic consequences of HPV prevention from a government-perspective: A fiscal analytic approach. PLoS One 2016;11(8):e0160707.
[105] Ochalek J, et al. Assessing the value of human papillomavirus vaccination in Gavi-eligible low-income and middle-income countries. BMJ Glob Health 2020;5(10).
[106] Burger EA, et al. Racial and ethnic disparities in human papillomavirus-associated cancer burden with first-generation and second-generation human papillomavirus vaccines. Cancer 2016;122(13):2057–66.