Meeting report: Initial World Health Organization consultation on herpes simplex virus (HSV) vaccine preferred product characteristics, March 2017

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Abstract

The development of vaccines against herpes simplex virus (HSV) is an important global goal for sexual and reproductive health. A key priority to advance development of HSV vaccines is the definition of preferred product characteristics (PPCs), which provide strategic guidance on World Health Organization (WHO) preferences for new vaccines, specifically from a low- and middle-income country (LMIC) perspective. To start the PPC process for HSV vaccines, the WHO convened a global stakeholder consultation in March 2017, to define the priority public health needs that should be addressed by HSV vaccines and discuss the key considerations for HSV vaccine PPCs, particularly for LMICs. Meeting participants outlined an initial set of overarching public health goals for HSV vaccines in LMICs, which are: to reduce the acquisition of HIV associated with HSV-2 infection in high HIV-prevalence populations and to reduce the burden of HSV-associated disease, including mortality and morbidity due to neonatal herpes and impacts on sexual and reproductive health. Participants also considered the role of prophylactic versus therapeutic vaccines, the HSV types that should be targeted, important target populations, and infection and disease endpoints. This article summarizes the main discussions from the consultation.

Keywords: Herpes simplex virus; sexually transmitted infections; vaccines; HSV vaccines; preferred product characteristics

1 Introduction

Coinciding with the Decade of Vaccines and the Global Vaccine Action Plan, which calls for new research to expand the benefits of vaccination to all people, several global efforts have focused on the critical role of new innovations to improve sexual and reproductive health [1, 2]. In the 2016 Global Health Sector Strategy for Sexually Transmitted Infections (STIs), vaccine development was noted as a key innovation for future STI control [2]. The World Health Organization (WHO), the US National Institutes of Allergy and Infectious Diseases and global technical partners have outlined a comprehensive roadmap for development of effective new vaccines against STIs [3, 4]. The roadmap highlights the importance of focusing on herpes simplex virus (HSV) vaccine development because: (a) over half a billion people are estimated to have genital HSV infection globally [5, 6]; (b) HSV-2 is the leading cause of genital ulcer disease (GUD) worldwide; (c) HSV-2 fuels the HIV epidemic by increasing the risk of HIV acquisition and transmission [7]; (d) current HSV prevention measures have limited population impact [7]; and (e) product development of new candidate vaccines is more advanced for HSV than for other STIs, with the exception of human papillomavirus (HPV), for which approved vaccines already exist. In 2016, the need for HSV vaccines for global use was further highlighted by WHO's Product Development for Vaccines Advisory Committee [8].

Two priority activities have been identified by WHO to facilitate and accelerate the development of HSV vaccines for global use. The first is defining preferred product characteristics (PPCs), which provide strategic guidance on WHO's preferences for new vaccines, specifically from a low- and middle-income country (LMIC) perspective [9]. PPCs

67 are pathogen-, rather than product-specific, and summarize the preferences for parameters
68 such as indications, target groups, immunization strategies, safety and efficacy, to address
69 priority global public health and programmatic needs. The second activity is developing a
70 value proposition (or investment case) for HSV vaccines that incorporate these PPCs, from a
71 global public health perspective.

72 As a first step in defining PPCs for HSV vaccines, WHO convened a stakeholder consultation
73 in March 2017 with HSV experts from academia, industry, and clinical medicine, as well as
74 public health epidemiologists, regulators, and policymakers. The aims of this meeting were
75 to: review data on HSV infection and disease, define the priority public health needs that
76 should be addressed by an HSV vaccine, outline key considerations for establishing HSV
77 vaccine PPCs, and assess how the current HSV vaccine pipeline aligns with public health
78 need, especially for LMICs. This article summarizes the main discussions from the
79 consultation.

80 2 HSV infection and disease

81 Two closely related HSV types cause human infection and disease. HSV-2 is almost
82 exclusively sexually transmitted and causes genital infection. It is the leading cause of GUD
83 globally. HSV-1 is mainly transmitted by oral contact to cause oral-labial herpes, but can also
84 be transmitted to the genital tract to cause genital herpes. During primary genital infection
85 with either HSV-1 or HSV-2, patients can experience multiple genital ulcers, which can last
86 for up to three weeks without antiviral therapy, alongside systemic symptoms such as fever,
87 myalgia and headaches [7]. Primary infection can also be asymptomatic or unrecognized
88 (subclinical) but still renders the individual infectious to partners. After replication in

epithelial cells of the genital tract, HSV travels up neurons to lumbo-sacral ganglia where it establishes latency. The immune response typically clears the mucosal infection, but not the latent virus in the ganglia. Over many years, viral reactivation is frequent, particularly for HSV-2, resulting in repeated replication and shedding of infectious virus at the genital-mucosal surface, with or without associated symptomatic recurrences of GUD. It had been thought that these reactivation episodes were rare, sporadic events; however, studies employing frequent genital swabbing [10] and modelling [11] suggest that HSV-2 infection is not a quiescent latent infection, but involves near-constant, low-grade release of virus from sensory neurons into the genital mucosa, where replication is controlled by local immune responses [11].

Up to 84% of shedding episodes are thought to be asymptomatic [12]. It has been estimated that transmission of HSV-2 is unlikely if the viral load during a shedding episode is less than 10^4 copies of HSV-2 DNA; however, much higher levels of HSV-2 shedding (10^6 copies of HSV DNA) can be present even when lesions are very difficult to detect [13]. This is consistent with epidemiological observations that most HSV-2 transmission is due to asymptomatic shedding [14–16]. While estimates are based mainly on data from the USA, there has been a rigorous study of genital HSV-2 shedding conducted in Uganda that showed similar rates and quantities of total and subclinical shedding of virus [17]. However, whether transmission rates, particularly from asymptomatic shedding, are actually similar in LMICs and high-income countries (HICs) is not known. It is possible that transmission thresholds vary according to the presence of other genital infections, such as bacterial vaginosis, in

susceptible partners. In this regard, it has been shown that the quantity and frequency of HSV-2 shedding are increased in HIV co-infected people [18].

2.1 Epidemiology of HSV infection

In 2012, an estimated 417 million people aged 15 to 49 years (range 274 to 678 million) worldwide were HSV-2-infected, equivalent to global prevalence of 11.3% [5]. Of these, 267 million (64%) were women, who have greater biological susceptibility to HSV-2 infection. Africa contributed most to the global total due to its large population and high HSV-2 infection prevalence (32%). South East Asia and the Western Pacific had lower prevalence (both 8%) but have large populations and, therefore, had high numbers of infected people (estimates of 74.6 million and 81.2 million, respectively). The global burden of HSV GUD has not been clearly elucidated, but assuming 10 to 20% of HSV-2 infected people have symptoms, and most recurrent GUD is related to HSV-2, an estimated 40 to 80 million people could have recurrent GUD worldwide [5].

By contrast, in 2012, the global prevalence of HSV-1 was 67% in 0 to 49 year olds (equivalent to 3.7 billion people), with most HSV-1 being acquired in childhood as an oral infection [6]. Acquisition of HSV-1 in childhood is however declining in several HICs such as the USA [19], so that increasing numbers of adolescents are susceptible to HSV-1 on initiation of sexual activity. Consequently, genital HSV-1 infection is now the leading cause of first episode genital herpes in some populations in HICs and is an important cause of genital herpes in the Americas, Europe and Western Pacific [6]. Overall, an estimated 140 million people have genital HSV-1 infection globally [6]. While the prevalence of genital HSV-1 infection is still thought to be relatively low in Africa and South East Asia [6], it is unknown whether the

proportion of individuals acquiring HSV-1 orally prior to adolescence may be starting to decrease in these regions as has been observed elsewhere [19], so that a growing number of people may first encounter HSV-1 via sexual contact. This is a gap in our understanding of HSV epidemiology globally.

2.2 Neonatal herpes

Neonatal herpes is the most severe direct clinical consequence of HSV infection. It usually results from exposure to either HSV-1 or HSV-2 in the genital tract during delivery, although *in utero* and postnatal infections can occur. It is associated with high mortality, having an estimated case fatality rate of 60% without treatment. Morbidity is also high, often in the form of long-term neurological disabilities regardless of treatment [20]. Globally, an estimated 14,000 cases of neonatal herpes occurred annually during 2010 to 2015 (range 3,703 to 34,415 cases), equivalent to 10.3 cases per 100,000 births [20]. These estimates, however, rely heavily on data from studies in the USA, with only one study providing data on transmission risk [21]. The global estimates might under-estimate the number of cases in low resource settings, where Caesarean section rates can be lower and HIV prevalence higher than in HICs. There is a pressing need for primary data on the incidence of neonatal herpes in LMICs, especially in sub-Saharan Africa.

2.3 HSV-2 interactions with HIV

Epidemiologic studies have identified a complex and synergistic relationship between HIV and HSV-2 infections [22], raising the possibility that an effective HSV vaccine could have an important impact on the acquisition and transmission of HIV.

153 A recent meta-analysis found that the risk of HIV acquisition is approximately tripled in the
154 presence of prevalent HSV-2 infection, and five times higher for those with incident HSV-2
155 infection [23]. There are at least two possible mechanisms for this increased risk [24]: (a)
156 breaks in the mucosa due to HSV-related ulcers that provide a more effective portal of entry
157 for HIV [25]; and (b) HSV-2 infection and reactivation resulting in an infiltration into the
158 genital mucosa of cells expressing receptors for HIV. Infiltration of $CD4^+$ T cells expressing
159 CCR5 or CXCR4 and DC-$SIGN^+$ dendritic cells create a pool of target cells susceptible to HIV
160 infection [26] (Figure 1). Increased densities of $CD4^+$ T cells have also been detected in
161 foreskin samples from HSV-2 infected, HIV-uninfected men [27].

162 In an effort to reduce the excess risk of HIV among HSV-2-infected people, two clinical trials
163 evaluated the impact of daily suppressive therapy with oral acyclovir, an antiviral drug that
164 can reduce the frequency and duration of HSV symptoms, on HIV acquisition [28, 29].
165 Suppressive acyclovir therapy did not reduce the risk of HIV acquisition in these trials, even
166 when GUD was reduced [29]. Investigators have since observed that acyclovir treatment, at
167 current doses, is insufficient to suppress the enrichment of T cells and dendritic cells in the
168 genital mucosa stimulated by HSV-2 infection, which often persist long after ulcer healing
169 [26]. These findings support the importance of HSV-induced mucosal infiltration of HIV
170 target cells as a mechanism for enhanced HIV risk.

171 HSV-2 infection is also implicated in an increased risk of HIV transmission. The presence of
172 HSV-2-associated GUD has been estimated to increase the risk of HIV transmission
173 approximately four-fold [30]. Higher HIV titres are found in genital secretions during HSV-2-
174 reactivation episodes, and HSV-2 proteins might upregulate HIV replication, increasing HIV

viral load in plasma [22]. Several studies have shown that acyclovir and valacyclovir can decrease the frequency and quantity of genital HIV shedding and the plasma load of HIV [31], and a large double-blinded randomized clinical trial [31], found that acyclovir reduced the HIV plasma load, and the amount of HIV RNA in male and female genital fluids. A clinical trial in HIV-discordant couples, however, found that suppressive acyclovir had no effect on HIV transmission to the HIV negative partner, although GUD in the HIV-infected partner was reduced by 73% [32].

2.4 Other adverse outcomes

Genital HSV infection can have important effects on sexual relationships and quality of life [33]. Genital herpes is often stigmatizing and the social consequences of the infection can have profound effects on sexual health and well-being, especially for adolescents and young adults.

Although most vaccine-development efforts to date have focused on HSV-2 infection, a future HSV vaccine might be effective against both HSV-1 and HSV-2. Orolabial herpes affects hundreds of millions of people, and can cause severe gingivostomatitis in childhood. HSV-1 can also result in less common outcomes such as HSV keratitis, an important cause of infectious corneal blindness globally, and HSV encephalitis, the leading cause of sporadic viral encephalitis.

2.5 Country perspectives

Much of the data on epidemiology and burden of HSV disease have been collected from HICs, especially the USA. A broader global perspective is required to inform the WHO PPCs;

196 therefore, at the global stakeholder meeting, brief reports were presented on the nature
197 and perception of HSV infection (including informal surveys and unpublished data) from
198 Brazil, Burkina Faso, China, India, Kenya, South Africa and Zimbabwe.

199 Awareness and perceptions of HSV infection and disease and its impact on health varied
200 between countries. Common themes in these LMICs included a relatively low awareness of
201 the burden of HSV-2-related disease outcomes, even when several in-country studies had
202 collected data on HSV-2 seroprevalence. In countries in sub-Saharan Africa, concerns about
203 the increased risk of HIV infection associated with HSV-2 and the increased severity of HSV
204 GUD among HIV-infected people were paramount. However, these concerns might change
205 somewhat with increased roll-out of anti-retroviral therapy and newly available HIV
206 prevention measures such as pre-exposure prophylaxis. Representatives from other
207 settings, such as India, suggested that other maternal and sexual health outcomes such as
208 neonatal herpes might be more important to policy makers. Country representatives were
209 uncertain whether current data were sufficient to convince policy makers and purchasers in
210 LMICs of the public health need for an HSV vaccine.

211 There has been little national policy-related activity regarding non-HIV STIs in many LMICs,
212 although several have introduced HPV vaccines. HPV vaccines are, however, often promoted
213 as anti-cancer rather than anti-STI vaccines, which can increase acceptability in adolescents
214 and parents. Some discussion focused on the importance of an HSV vaccine to improve
215 sexual and reproductive health generally. Many countries, including LMICs in Africa, are
216 experiencing a youth bulge [34]; consequently, the need for, and potential impact of,

interventions targeting young people and those during their reproductive years in these countries could increase interest in HSV vaccines.

3 Priority public health needs for HSV vaccines

After reviewing the natural history and epidemiology of HSV infection and disease, meeting participants discussed the priority public health needs for HSV vaccines, particularly in LMICs. These discussions focused on the strategic goals of HSV vaccines, which can then guide more specific discussions on characteristics such as target populations, indications, clinical endpoints, safety and efficacy requirements, and vaccination strategies to meet these goals.

During the meeting, the group proposed the following primary public health goals for HSV vaccines in LMICs:

- to reduce the acquisition of HSV-2-associated HIV infection in high HIV-prevalence populations, and
- to reduce the burden of HSV-associated disease, including mortality and morbidity due to neonatal herpes, and impacts on sexual and reproductive health.

The group emphasized that the two goals listed above are in no particular order. The potential impact of HSV-2 vaccines on HIV infection could yield the most important reductions in morbidity and mortality and could strengthen the value proposition for investment in HSV vaccine development. However, because there are other existing and emerging tools for HIV prevention, such as broad delivery of anti-retroviral therapy and use of interventions such as pre-exposure prophylaxis, the role of HSV vaccines could become

less important to HIV prevention in the longer term. Furthermore, this goal only applies to areas of the world, such as sub-Saharan Africa, that have high prevalence of both HSV and HIV. Nonetheless, the meeting participants considered effective HSV vaccines to be an important strategy for HIV prevention, in addition to a range of other potential benefits.

In discussing the goal of reducing HSV-associated disease, meeting participants recognized that neonatal herpes is the most devastating direct consequence of genital HSV infection but thought to be rare, although the true incidence of this condition is not fully understood. The value proposition for HSV vaccines will need to balance these considerations, and the collection of primary data on neonatal herpes in LMICs will inform future discussions on the global public health need.

The burden of HSV-associated disease also includes overall effects on sexual and reproductive health, and several participants advocated for explicitly stating the benefits a vaccine would offer for sexual and reproductive health. It was emphasized that HSV infection has a range of potential adverse outcomes that, in sum, could drive the comprehensive impact of the vaccine beyond each individual disease outcome. The full range of effects on sexual and reproductive health – especially for young people – needs to be examined within the value proposition for HSV vaccines.

Meeting participants agreed that, in considering the greatest public health need, the priority should be on development of vaccines against HSV-2, because of its demonstrated role in propagating the HIV epidemic, and as the primary source of recurrent GUD and neonatal herpes in LMICs. However, an HSV vaccine that protects against both HSV-1 and HSV-2 could have farther-reaching benefits than one that only protects against HSV-2 and would be

particularly important in HIC settings, where genital HSV-1 is an increasing cause of first-episode genital herpes and an important cause of neonatal herpes [20]. More HSV-1 seroprevalence data from LMICs could help determine whether similar trends in HSV-1-related genital herpes and other outcomes will become important.

4 Development of vaccines against HSV

There are two broad approaches to developing vaccines against HSV: prophylactic (preventive) vaccines, to prevent new infections, and therapeutic vaccines, to treat or modify existing infections. There are currently no licensed vaccines against HSV-1 or HSV-2, but encouragement is provided by the development of therapeutic vaccines and a prophylactic vaccine against varicella-zoster virus, another human α-herpesvirus, closely related to HSV [35].

4.1 Prophylactic vaccines

Prophylactic vaccines would be given before exposure to HSV, e.g., before first sexual contact (for prevention of HSV-2), or in infancy (for prevention of HSV-1). It is generally assumed that an effective prophylactic vaccine would act, at least in part, by inducing neutralizing antibodies against one or more of the 11 envelope proteins of HSVs. These include glycoprotein D (gD), which has been included in all candidate prophylactic HSV-2 vaccines tested clinically to date, and/or glycoprotein B (gB), which was a component in earlier HSV-2 vaccines [36, 37].

A few prophylactic vaccine candidates have been tested in clinical studies (Figure 2), the most advanced being a gD2-based vaccine with alum and monophosphoryl lipid A adjuvant

(GlaxoSmithKline, GSK). In a phase III trial, this vaccine showed 73% efficacy against GUD but only in a subset of participants: women who were seronegative for both HSV-1 and -2 when they entered the trial [38]. A second phase III trial (Herpevac), conducted only among women seronegative for HSV-1 and HSV-2, failed to show any protection against HSV-2 but did demonstrate 58% (95% CI, 12-80%) efficacy against HSV-1 GUD [39]. Efficacy against HSV-1 GUD appeared to correlate with anti-gD2 antibody titres [40]. The anti-HSV-1 activity may have been due to strong cross-reactivity between gD of HSV-1 and HSV-2, and greater susceptibility to neutralization for HSV-1 than HSV-2 [41].

4.2 Therapeutic vaccines

Therapeutic vaccines against HSV-2 would be given to individuals with a known history of HSV-2 disease, with the aims of reducing disease severity and shedding of HSV-2 (both asymptomatic and during GUD recurrences), thereby reducing transmission of HSV-2.

Several different therapeutic vaccines have been, and are currently being, tested in phase I/II studies (Figure 2). An effective therapeutic vaccine is likely to act via cell-mediated immunity, possibly by stimulating resident memory T cells in the genital tract [42]. There is evidence that long-term resident CD8$\alpha\alpha^+$ T cells at the dermis-epidermis junction in the skin of the genital tract might play a role in immune surveillance and containment of reactivation episodes [42]. If it is to control HSV release from sensory neurons and replication in mucosal epithelial cells, a therapeutic vaccine would need to induce a faster, more-effective immune response than that stimulated by reactivation episodes.

4.3 The HSV vaccine pipeline

There are currently at least four HSV vaccines in clinical development, with at least one additional candidate likely to enter phase I studies in 2018, and all of the vaccines currently undergoing clinical testing are being evaluated as HSV-2 therapeutic vaccines. In addition, there are at least 20 candidates either in discovery or being researched by academic groups (Figure 2). Some of the candidates might also have potential as prophylactic vaccines because they include gD2 which has been a component of all prophylactic vaccines tested to date, although it should be noted that gD2 has not been shown to be an essential component for an HSV-2 prophylactic vaccine, nor does the inclusion of gD2 mean the vaccine will be effective. The key features of the HSV-2 vaccines currently in clinical trials are summarised in Table 1. None of these vaccines are being evaluated in LMIC populations.

HSV vaccines based on many other formats and platforms are being evaluated pre-clinically, including whole-virus (killed, live-attenuated or genetically disabled), monovalent or multivalent subunits with adjuvants, DNA, mRNA, live-virus vectors, peptides and nanoparticle-based [35].

4.4 Issues in the development of HSV vaccines

Representative animal models do not currently exist for HSV infection or disease [35, 59], especially for the recurrent phase. For prophylactic vaccines, protection against intravaginal challenge in mice is often used; protection against the establishment of latency can also be tested in this model [56]. For both prophylactic and therapeutic vaccines, guinea pigs have been used because they experience a short period of recurrent genital disease after intravaginal HSV challenge [35]. Neither model has, however, been predictive of clinical

performance. Better animal models, possibly in non-human primates, could be used to screen candidates and de-risk vaccine development, particularly if the model exhibits recurrences following sexual transmission of the virus and/or long-term HSV shedding.

There are no known immunological correlates of protection for prophylactic or therapeutic HSV-2 vaccines [59]. Furthermore, prophylactic vaccines require very large trials; for example, the Herpevac trial in the USA enrolled 8,323 females who were seronegative for both HSV-1 and HSV-2 [39]. In addition, HSV-2 prevalence is decreasing in some areas of the USA, e.g., by as much as 50% in Seattle [60], so efficacy trials of prophylactic vaccines may have to be even larger in these settings. In areas with high HSV-2 incidence rates, such as sub-Saharan Africa, trials could be conducted with fewer participants [61], provided the vaccine would be made available to these areas once developed. Importantly, for prophylactic vaccines based on whole-virus platforms, a new diagnostic test may be required to distinguish infected individuals from vaccinated individuals.

In the past, GUD and/or infection (as measured by HSV-2 seroconversion) have been used as endpoints in phase III trials of prophylactic vaccines [38, 39]. From a technical standpoint, there is general consensus that it will be easier to achieve reduction in disease activity than to achieve complete immunity to infection [62]. Data from mouse models suggest that even if complete protection against infection is not achieved, vaccination can moderate the severity of primary infection and reduce the amount of virus establishing latency [56]. Murine models can be used to differentiate between vaccines that protect against disease and those that are functionally sterilizing, i.e. prevent infection [56, 58], but with the limitation that it is unclear if performance in mice is predictive of efficacy in humans.

For therapeutic vaccines, the frequency of HSV-2 shedding has been used as a primary endpoint in early phase trials, along with reduction in lesion rate and duration of recurrence (Table 1; [47, 51]). As an endpoint, frequency of shedding has the advantages of being relatively consistent over time within an individual and correlating with, but having more statistical power than, both lesion rate and recurrence history. This allows for a one-way crossover study design in which participants can serve as their own controls. Thus, adequately powered therapeutic vaccine trials can be done with fewer participants, and more quickly than prophylactic vaccine trials, which can potentially de-risk these studies for industry. Phase I and II trials of therapeutic vaccines have typically enrolled up to a few hundred subjects.

5 Key considerations for HSV vaccine preferences for LMICs

Given the priority public health needs discussed above, and the realities of HSV vaccine development and the vaccine pipeline, meeting participants discussed how to translate the strategic goals for HSV vaccines for LMICs into key considerations for HSV vaccine preferences. These discussions were intended to be the starting point for ongoing development of HSV vaccine PPCs.

5.1 Vaccine approaches

There was consensus that both prophylactic and therapeutic vaccines could play roles in achieving the public health goals for HSV vaccines, and that the two vaccine approaches are sufficiently different that separate PPCs (or sections) should be developed for each.

Prophylactic vaccines would be the most appropriate for use in LMICs for the goal of preventing HSV-2-associated HIV acquisition, because any HSV-2 infection, regardless of symptoms of GUD, increases HIV risk. Nonetheless, both prophylactic and therapeutic HSV vaccines might reduce risk of HIV acquisition if they decreased or modified symptomatic and asymptomatic HSV infection in a way that reduces micro-ulcerations and HSV-induced inflammatory target cells for HIV. Prophylactic vaccines could use existing vaccine-delivery infrastructure, for example targeting adolescents receiving HPV vaccines, whereas therapeutic vaccines would need to be delivered to individual HSV-infected patients within the health-care system.

Several therapeutic HSV-2 vaccine candidates are in phase II trials in HICs, so a product might be available for implementation in LMICs sooner than for prophylactic vaccines. Therapeutic vaccines could be more attractive to vaccine developers (and investors) due to there being a sufficient market in HICs, and faster clinical development than for prophylactic vaccines. Therapeutic vaccines would, ideally, be at least as efficacious against GUD (and HSV transmission) as acyclovir. The effect of a therapeutic HSV vaccine on the increased risk of HIV acquisition among HSV-2-infected people remains unknown and could vary according to its immunologic mechanism and whether it may increase or decrease the presence of activated $CD4^+$ T cells in the genital tract, which are targets for HIV infection [24].

5.2. Target populations

An HSV-2 prophylactic vaccine would most likely be offered to adolescents before first sexual exposure and immunity would need to last for at least the highest incidence period in young adulthood. Because many LMIC populations have high HSV-1 seroprevalence by

adolescence, HSV-2 prophylactic vaccines would need to be effective regardless of HSV-1 serostatus. If protection against both HSV types is required and/or achievable, then prophylactic HSV vaccines could be administered during infancy, for this strategy, it is possible that booster doses would be required later in life.

Therapeutic vaccines would most likely be offered to people with symptomatic GUD. To identify these people, they would need to seek care and be identified within an existing health care setting, such as primary care or family planning clinics. Implementation would be complex, as virologic assays for diagnosis of genital lesions may not be available and widely available serologic assays for HSV-2 infection are limited by poor specificity at the manufacturer recommended cut-offs [63]. Additional studies will be required to determine whether people with asymptomatic HSV infection, assuming they could be identified through serological screening, might also gain benefits from HSV vaccination. This might depend on whether the objectives are to reduce symptomatic HSV disease, reduce HIV acquisition, and/or prevent HSV or HIV transmission to sexual partners. Therapeutic vaccination of asymptomatic individuals would require the development of a diagnostic test (most likely blood-based) that is appropriate for use in LMICs.

5.2 Potential HSV-vaccine outcomes and endpoints

One key issue is whether an HSV vaccine needs to prevent infection or disease. Prophylactic vaccines preventing HSV infection would be ideal because (a) even asymptomatic infection is associated with increased HIV acquisition [7, 26], and (b) many neonatal herpes cases are related to incident, rather than pre-existing, maternal infection [20, 21]. However, HSV vaccines that modify, but do not prevent infection might also have an impact on important

outcomes. Modelling studies presented at the meeting suggest that even imperfect HSV-2 vaccines (for preventing infection) could reduce HSV-2 incidence at the population level, especially when HSV-2 reactivation was reduced during breakthrough infection [64, 65]. Meeting participants emphasized that prophylactic vaccines do not need to induce an all-or-nothing "sterilizing" immune response, but rather an important objective is reducing the probability of infection for most people, and modifying the infection in the remainder so they have reduced reactivation-related disease. It remains unclear whether reducing the clinical intensity of primary genital HSV-2 infection through vaccination will lead to less frequent or severe symptoms or HSV-2 shedding after acquisition. Table 2 outlines some possible outcomes of HSV vaccination and considerations related to endpoints, which will be further reviewed during the PPC process.

5.3 Gaps in knowledge

There are still gaps in knowledge that, if addressed, would greatly facilitate HSV vaccine development (Table 3). For several of the topics listed, there are data from HICs but the equivalent information is missing, or not recent, for LMICs.

6 Conclusions

Defining PPCs for HSV vaccines is a key priority for advancing development of HSV vaccine candidates that will have global benefits and will be suitable for use in LMICs. The March 2017 WHO HSV vaccine global stakeholder consultation laid the groundwork for developing these PPCs, by defining priority public health needs that should be addressed by HSV vaccines and discussing key considerations for establishing HSV vaccine preferences for

LMICs. Meeting participants concluded that the global public health goals for HSV vaccines, in no particular order, should be reducing acquisition of HSV-associated HIV in high-prevalence populations and reducing the burden of HSV-associated disease, including mortality and morbidity due to neonatal herpes and impacts on sexual and reproductive health. The meeting attendees considered these goals to have similar priority, and sexual and reproductive health was highlighted as a framework around which multiple potential benefits of an HSV vaccine (e.g., preventing GUD and psychosocial sequelae) could be brought together. The group noted that the PPCs will need to be defined in parallel with generation of a public health value proposition for HSV vaccines, to attempt to quantify and weigh different aspects of the public health need with the potential costs and benefits of HSV vaccines in addressing that need.

In addition to HSV prophylactic vaccines, which would be ideal for LMIC use, the therapeutic HSV-2 vaccines that are the current focus of development efforts for HICs could also play an important role in addressing global public health need. Meeting participants agreed that PPCs should be defined for each. A working group, established by WHO, will now prepare draft PPCs, which will then be circulated for open comment from a larger group of stakeholders, before being finalized and communicated by WHO. The discussions from this consultation meeting, addressing considerations such as which HSV types should be targeted, vaccine indications, important target populations, infection and disease endpoints, critical efficacy and safety considerations, and pertinent vaccination strategies, will serve as the basis for defining and finalizing comprehensive PPCs for HSV vaccines.

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721 **Table 1**

722 *Summary of leading HSV vaccines in clinical and preclinical development, March 2017*

Vaccine; developer	Composition	Type	Status	Data
COR-1; Admedus	**DNA**: a mixture of two plasmids coding for full length gD2, and truncated gD2 with a ubiquitin tag; codon optimized.	Therapeutic	Phase II	**Preclinical:** [43]. **Phase I.** T-cell responses in 19 of 20 subjects; no increase in antibody response [44].
HerpV; Agenus	**Subunit plus adjuvant:** Thirty-two 35-mer peptides, complexed with human heat shock protein 70, plus QS-21 adjuvant.	Therapeutic	Not known	**Preclinical**: [45]. **Phase I**: Boosting of $CD4^+$ and $CD8^+$ T cells [46]. **Phase II:** 15% reduction in shedding [47].
GEN-003; Genocea	**Subunit plus adjuvant:** truncated gD2 plus 39.2 kD fragment of ICP4 (infected cell protein 4) plus Matrix M2 adjuvant.	Therapeutic	Phase II	**Preclinical**: [48, 49]. **Phase I/IIa**: Boosting of T cells (γ-interferon producing) and antibodies [50]. Reduction in HSV-2 shedding (31 to 52%) and lesion rates immediately after dosing [51].
HSV529; Sanofi Pasteur	**Live, genetically disabled:** replication-defective HSV-2, with deletions of UL5 and UL29 genes.	Therapeutic	Phase I	**Preclinical**: [52–54]. **Phase I:** NCT01915212 and NCT02571166; data not available.
VCL-HB01; Vical	**DNA plus adjuvant**. DNA coding for HSV-2 UL46 (tegument protein VP11/12) and gD2, plus Vaxfectin® adjuvant.	Therapeutic	Phase II	**Preclinical:** [55–57]. **Phase I/II:** 49% reduction in lesion rate at 3 months and 57% reduction in lesion rate at 9 months in bivalent vaccine group; induction of γ-

Vaccine; developer	Composition	Type	Status	Data
				interferon-producing T cells [47]
G103; **Immune Design Corp**	**Subunit plus adjuvant:** trivalent gD, UL19 (truncated VP5, capsid) and UL25 (DNA packaging protein, structural); adjuvanted with proprietary glucopyranosyl lipid A in a stable emulsion (GLA-SE).	Therapeutic	Preclinical; phase I scheduled for 2018.	**Preclinical:** [58].

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725 **Table 2**

726 *Possible outcomes and clinical endpoint considerations for HSV vaccines*

Possible outcome of vaccination	Advantages, notes	Disadvantages, notes
Prevention or reduction in HSV infection	To the extent that HSV infections can be prevented, all HSV-related sequelae (such as GUD, neonatal herpes, increased HIV risk) will be prevented. Thus, this will have the largest impact for individuals. To have an impact on HIV risk, prevention of infection might be needed, because HSV-2 increases HIV risk regardless of symptoms. Seroconversion can be used as an endpoint, especially if current assays are improved.	Prevention of infection will be more difficult to achieve than prevention of disease. Vaccine developers are likely to prefer a less difficult endpoint: for example, in the first phase III trial of a gD2 prophylactic vaccine, there was 73% efficacy against disease, but only 38% efficacy against infection in women who were seronegative for both HSV-1- and HSV-2 [38].
Prevention or reduction in GUD	A vaccine could prevent the most important symptoms of genital herpes even if infection is not completely prevented. Could be a potential outcome of both prophylactic and therapeutic vaccination. There is likely to be a strong market for preventing or reducing GUD in HICs, which could help advance vaccine development for LMICs.	It is not yet known if the societal cost of GUD alone is sufficient to justify HSV vaccine development and purchase for LMICs. The burden of HSV-related GUD and its effect on quality of life is unknown in many LMICs.

Possible outcome of vaccination	Advantages, notes	Disadvantages, notes
Reduction in HSV shedding	A vaccine could reduce HSV shedding and risk of transmission even if infection is not completely prevented. This could be a potential outcome of both prophylactic and therapeutic vaccination. Reduction in HSV shedding is relatively easy to measure and is likely to be a marker for disease activity and potential transmission to partners or neonates.	The transmission threshold of HSV in humans is not known, and it is not clear how this data could be obtained. Assays could be developed that detect low levels of infection, sufficient to induce seroconversion but low enough that transmission doesn't occur, or rarely (Table 3).
Reduction in HSV transmission	A vaccine could reduce HSV transmission even if infection is not completely prevented. Modeling suggests that even an imperfect HSV vaccine could reduce HSV incidence in a population [64]. Reduction in HSV transmission risk to a sexual partner may be a desirable characteristic for patients (for example for therapeutic vaccines in HICs)	Direct measurement of HSV transmission following vaccination would be difficult, though not impossible, for example via discordant couple studies. The transmission threshold of HSV in humans is not known, and it is not clear how these data could be obtained.
Reduction in HIV acquisition or transmission risk	Reduction in HSV-related HIV infection could have a significant public health benefit, and would strengthen the public health investment case for HSV vaccines in LMICs.	It might be difficult to measure impacts on HIV acquisition and transmission in clinical trials (though not impossible) and, therefore, be difficult to include as a primary indication for

Possible outcome of vaccination	Advantages, notes	Disadvantages, notes
	Modelling suggests that even an imperfect HSV vaccine could reduce HIV incidence in a population [64].	vaccination. Interest in effects on HIV compared with those on other outcomes will vary between countries, depending on HIV prevalence. Consideration will need to be given to the marginal benefit HSV vaccination could have on HIV given improved access to anti-retroviral therapy and new HIV prevention measures. Acyclovir has been shown to reduce GUD but without having an effect on HIV acquisition. A therapeutic vaccine would need to perform better than antivirals. The effect of therapeutic vaccines on modifying HIV risk requires evaluation.
Prevention or reduction in neonatal herpes	Neonatal herpes is the most severe direct outcome of HSV infection and its prevention could strengthen the public health value proposition for HSV vaccine development.	Neonatal herpes is rare and so it will be difficult to measure as an outcome in clinical trials. The health and societal costs of neonatal herpes needs to be better quantified globally, balancing severe morbidity and mortality with its rare occurrence.
Improved sexual and	Improved sexual and reproductive health is	Quality of sexual and reproductive health is

Possible outcome of vaccination	Advantages, notes	Disadvantages, notes
reproductive health	considered by some to be an important rationale for HSV vaccines, incorporating the totality of benefits of the vaccine. Data should be collected on the impact of HSV vaccines on exploratory endpoints such as relationships and quality of life.	difficult to quantify. Existing quality of life scales for genital HSV need to be used to determine health utilities for HSV infection.

727

728 **Table 3**

729 *Gaps in knowledge*

	Gap	Notes
Clinical	What is the level of HSV shedding (infectious dose) below which transmission of HSV-1 and HSV-2 does not occur?	Knowing this threshold would allow for smaller clinical trials with virus shedding as a primary endpoint. It will, however, be very difficult to design human studies to define the infectious dose. This could also be important for genital HSV-1 infections, where there are fewer symptomatic reactivations.
	What are the asymptomatic transmission rates of HSV-1 and HSV-2 in LMICs? Can we assume they are the same as in HICs, and that they are responsible for most transmissions?	It is possible that the transmission threshold(s) are different in LMICs compared with HICs due to differences in presence of other reproductive tract infections.
	What is the burden of HSV-related GUD in LMICs? Is GUD regarded as a public health problem? What are the consequences of HSV-2 on the quality of life, including parameters such as mental health, productivity, and relationships?	More epidemiological data need to be collected, using standardized protocols, to quantify the impact of HSV-associated disease in LMICs, and to develop a public health value proposition for HSV vaccines to present to stakeholders.
	What is the burden of neonatal herpes in LMICs?	There are very limited data from LMICs. Current estimates depend on data from studies in the USA

	Gap	Notes
		only [20].
	How might a therapeutic vaccine affect the risk of HIV acquisition if it stimulates increased numbers of $CD4^+$ T cells and dendritic cells in the genital mucosa? Can the potential risk be quantified in advance of clinical studies?	It might be difficult to design studies to predict this risk, but this is an important question. The rate of HIV acquisition could be measured in large clinical trials in high-risk populations.
	What are the best settings and populations for trials of prophylactic vaccines?	Discordant couples might not be representative of the general population, and some HICs now have a low incidence of HSV-2 in some populations who usually volunteer for vaccine studies. Are there settings relevant to LMICs with sufficiently high HSV-2 incidence that could be used?
Virology and immunology	What are the correlates of protection from infection, disease and shedding, for prophylactic and therapeutic vaccines?	Correlates of protection, especially for cell-mediated immunity, are largely unknown for both HSV-1 and HSV-2. Data from clinical studies of varicella zoster virus therapeutic vaccines might provide information on potential cell-mediated immunity correlates that might be measurable in clinical studies with HSV therapeutic vaccines. In some HSV-1 studies, CD8+ T cell responses to specific regions of HSV and exhaustion markers on T cells in blood have been proposed as correlates of severity [66] .

	Gap	Notes
		In most HSV clinical trials, peripheral blood is sampled for cell-mediated immunity, but the most relevant cells might be resident in the mucosal tissue and, therefore, less available for measurement.
	An improved understanding of the neutralizing antibody responses to HSV-1 and -2 is needed, including epitope mapping and analysis of structure-function relationships.	Higher-throughput assays for neutralizing antibodies, and with better specificity, will be required; some of which are being developed [67].
	For use in future trials of prophylactic vaccines, is it possible to develop assays that measure prevention or reduction of future transmission of HSV? These could be used as an alternative to seroconversion and achievement of, so-called, sterilizing immunity.	Serological studies (such as antibody avidity) or measurements of cell-mediated immunity (such as T-cell maturation) might predict risk of HSV transmission and could be used as surrogate endpoints. Measuring the amount of virus shed over a three-month period might be another option.
	A better understanding of the sequence variation between different isolates of HSV from different geographic regions is needed [68] and is being developed [69]. The impact of genomic diversity on diagnostics, non-vaccine therapeutics and HSV-vaccine design and use also needs to be studied [7].	This should determine whether HSV vaccine development should focus on proteins that are more conserved between isolates and/or whether different vaccines are needed for different regions.

	Gap	Notes
Regulatory	Which endpoint(s) will national regulatory authorities view as acceptable for licensing HSV prophylactic and therapeutic vaccines? Can effects on HIV be incorporated into the license (and label) for HSV vaccines?	For first-generation HSV vaccines, clinical endpoints such as prevention of infection or GUD (for prophylactic vaccines) and reduction in GUD (therapeutic vaccines) may be most likely to be adopted by regulators If prevention of HIV is to be included as an HSV vaccine indication, HIV endpoints measureable in clinical trials are likely to be required.

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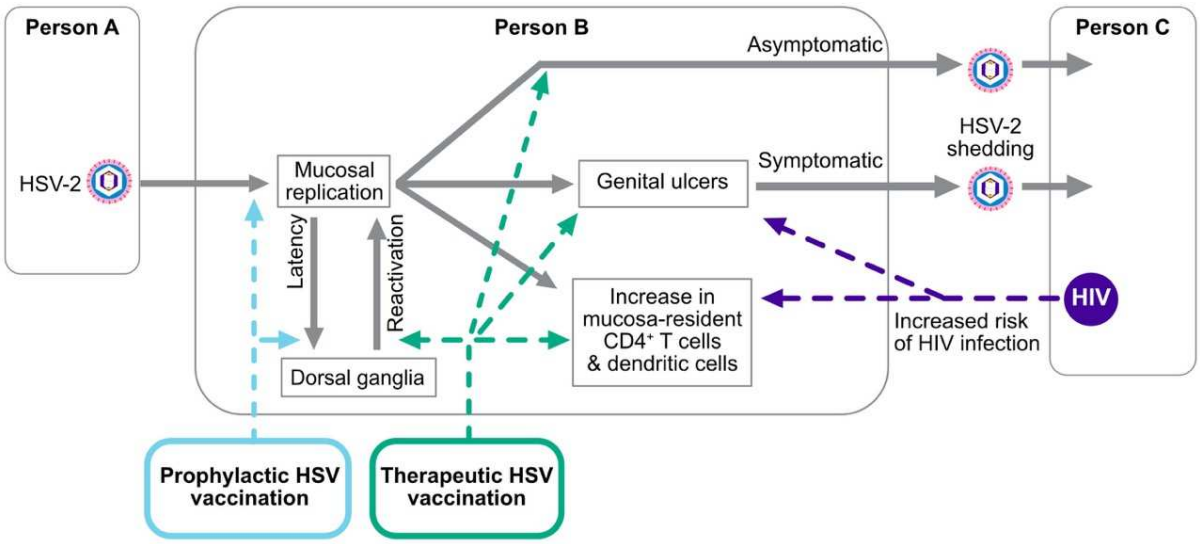

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732 **Figure 1. Summary of the possible impacts of HSV-2 infection and HSV vaccines on HIV acquisition**

733 Upon HSV infection of Person B (HSV-2 susceptible partner) from Person A (HSV-2 source partner), initial
734 mucosal replication results in establishment of latency in the dorsal ganglia, with subsequent reactivation
735 episodes. Mucosal replication during initial infection or reactivation can result in HSV-associated genital ulcer
736 disease (in Person B) and HSV transmission, through either asymptomatic or symptomatic HSV-2 shedding (to
737 Person C). The presence of genital ulcers during primary infection or a reactivation episode, and infiltration of
738 ($CD4^+$) immune cells responding to either asymptomatic or symptomatic mucosal infection, increase Person B's
739 risk of HIV acquisition (from Person C). Prophylactic HSV vaccination of Person B could prevent HSV infection
740 from Person A or reduce subsequent reactivation on breakthrough infection. Thereby, prophylactic HSV
741 vaccination could reduce genital ulcer disease, HSV shedding, and infiltration of mucosal ($CD4^+$) immune cells,
742 which could decrease risk of HIV acquisition. Therapeutic vaccination of Person B after HSV infection could
743 reduce reactivation of HSV, or could reduce genital ulcers and HSV shedding, and alter immune cells in the
744 mucosa directly. Depending on the vaccine's mechanism, it may increase or decrease activated CD4+ T cells in
745 the genital tract, which could have varying effects on the risk of HIV acquisition.

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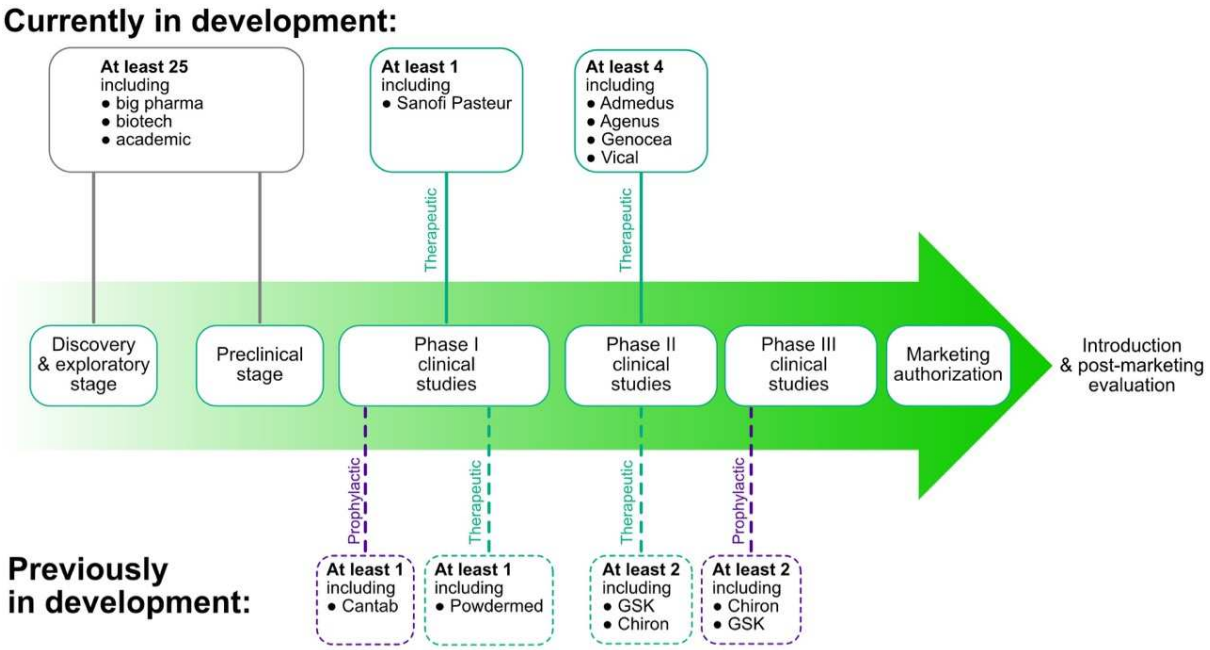

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749 **Figure 2. Summary of the HSV vaccine pipeline**