Status of vaccine research and development of vaccines for herpes simplex virus

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ABSTRACT

Herpes simplex virus type-1 (HSV-1) and -2 (HSV-2) are highly prevalent global pathogens which commonly cause recurrent oral and genital ulcers. Less common but more serious complications include meningitis, encephalitis, neonatal infection, and keratitis. HSV-2 infection is a significant driver of the HIV epidemic, increasing the risk of HIV acquisition 3 fold. As current control strategies for genital HSV-2 infection, including antiviral therapy and condom use, are only partially effective, vaccines will be required to reduce infection. Both preventive and therapeutic vaccines for HSV-2 are being pursued and are in various stages of development. We will provide an overview of efforts to develop HSV-2 vaccines, including a discussion of the clinical need for an HSV vaccine, and status of research and development with an emphasis on recent insights from trials of vaccine candidates in clinical testing. In addition, we will touch upon aspects of HSV vaccine development relevant to low and middle income countries.

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1. About the disease and pathogen

Herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) are responsible for recurrent, painful oral and genital ulcers, and cause meningitis, encephalitis, neonatal infection, and keratitis. HSV infection affects all age groups around the globe. These large DNA viruses are members of the human herpesvirus family, which also includes the pathogens varicella-zoster virus (VZV), Epstein-Barr virus, cytomegalovirus, human herpesvirus-6, -7 and -8. HSV-1 and HSV-2 are closely related, sharing >80% identity on the amino acid level and both types are capable of infecting the oral or genital skin or mucosa and cause recurrent ulcerations [1]. The virus infects epithelial cells at skin or mucosal surfaces, and then infects nerve endings, traveling via retrograde transport to the nerve axon, where it establishes persistent infection in the trigeminal or lumbosacral ganglia. The virus returns to epithelial surfaces via the axon to cause oral or genital ulcers or frequent asymptomatic viral shedding. The ability of the virus to be acquired and transmitted in the absence of symptoms allows it to spread efficiently throughout the population. As most infections are subclinical, disease incidence and prevalence data underestimate the impact of HSV infection.

Although the clinical manifestations of infection are similar between HSV-1 and HSV-2, the age groups affected and severity of infection are influenced by the infecting virus type, the portal of entry, host immune status and whether the infection is initial or recurrent. HSV-1 has been more traditionally associated with oral-facial infections, although it is now a leading cause of first episode genital herpes and neonatal herpes in high-income countries (HIC) [2,3], which is likely related to declining HSV-1 acquisition during childhood in these settings [4]. In LMIC, HSV-1 is rapidly acquired during childhood, with more than 90% people infected by adolescence [5]. HSV-1 causes oral ulcers of varying severity, from herpes labialis to gingivostomatitis and pharyngitis. It is the leading cause of sporadic infectious encephalitis (HSV encephalitis) and infectious blindness (HSV keratitis) in HIC; the burden of these complications of HSV-1 infection in LMIC is unknown but is likely to be high.

Herpes simplex virus type 2 (HSV-2) is a sexually transmitted infection that is the leading cause of genital ulcer disease (GUD) worldwide [6,7]; HSV-2 also causes neonatal herpes and
increases the risk of acquiring HIV infection. An estimated 417 million persons aged 15–49 years old are infected with HSV-2, with an incidence of 19 million infections per year [8]. HSV-2 is rapidly acquired among men and women initiating sexual activity in settings with high HSV-2 seroprevalence. For instance, in sub-Saharan Africa, the incidence among women is up to 23 per 100 person years and among men is up to 12 per 100 person years [9]. Neonatal herpes incidence in HIC is ∼10 cases/100,000 live births [10]; the incidence in LMIC is unknown. Although rare, neonatal herpes is associated with high morbidity and mortality and no prevention strategies have been identified. HSV-2 fuels the HIV epidemic by increasing the risk of HIV acquisition 3-fold [11], likely through HSV-2 associated genital tract inflammation [12,13]. In addition, genital ulcer disease increases the risk of HIV transmission [14]. In settings with high HSV-2 prevalence, an estimated 25–50% of HIV infections are attributable to HSV-2 [15,16].

Global estimates for the economic burden of HSV infection are not available. In the United States, HSV-2 infection is estimated to have a total lifetime cost of $540 million US dollars (adjusted to 2010 dollars), behind only HIV and HPV in costs among 8 major STIs [17]. These cost estimates exclude neonatal herpes, which had a total hospitalization charge of $35 million in 2006 in the United States [10]. These costs also exclude sequelae of HSV-1 infection and the contribution of HSV-2 infection to HIV susceptibility. The updated Global Burden of Disease Study (GBD) estimates that genital HSV resulted in 311,600 years lived with disability (YLD) in 2013 (95% uncertainty interval 98,300–748,500) due to genital ulcer disease alone [18]. GBD 2013 likely underestimates the impact of genital HSV, as these YLD estimates do not include disability due to neonatal herpes nor the contribution of genital HSV to HIV susceptibility, which are the most devastating consequences of infection.

The diagnosis of HSV infection may be made by demonstrating the virus in oral and genital lesions, using polymerase chain reaction assays, viral culture or antigen detection. In addition, commercially available “type-specific” serologic assays based on the glycoprotein surface proteins can differentiate between HSV-1 and HSV-2 infection. Serologic assays for HSV-2 are limited by low positive predictive value in low prevalence settings and false positive results in some populations [19].

Although HSV clinical recurrences are commonly self-limited, some complications can be life-threatening, particularly in those with immature or compromised immune systems. Treatment strategies for genital herpes are limited to the antiviral agents, acyclovir, valacyclovir, or famciclovir [20]. HSV genital ulcer disease can be treated by the antiviral agent acyclovir, which is now included in WHO guidelines for syndromic management of GUD [21]. While episodic therapy for genital ulcers shortens the duration of the ulcer by approximately 1 day, daily suppressive therapy prevents most recurrences. Although daily suppressive therapy for HSV-2 infected persons decreases the risk of transmission by ∼50% in discordant heterosexual partnerships in the US [22], such therapy was not effective for prevention of HSV-2 transmission from HIV-1/HSV-2 co-infected adults to HIV-1/HSV-2 seronegative partners in discordant heterosexual African couples [23]. In addition, suppressive antiviral therapy for HSV does not reduce the risk of HIV-1 acquisition or HIV-1 transmission [24,25]. Condoms have partial efficacy in preventing acquisition of genital herpes [26].

2. Overview of current efforts

2.1. Biological feasibility for vaccine development

There are no vaccines currently available for HSV infection, but the pipeline is rich with candidates in various phases of development. Vaccines are currently being developed both to prevent HSV-2 infection (preventive) and to treat HSV-2 infection (therapeutic). While most HSV vaccine research has prioritized HSV-2 rather than HSV-1, HSV-2 vaccines may also have benefits in preventing or treating HSV-1 infection given the homology between these viruses.

There are several lines of evidence that an HSV vaccine is feasible:

1. There is a safe and efficacious vaccine for varicella zoster virus (VZV), a closely related alpha-herpesvirus. Both a live-attenuated vaccine for preventive (prevention of varicella “chicken pox”) and therapeutic (prevention of herpes zoster or “shingles”) indications have been developed [27]. In addition, a subunit vaccine with a novel adjuvant was shown to prevent herpes zoster with 97% efficacy in a recent Phase III clinical trial [28].

2. Whether protective genital mucosal immunity could be induced by an intramuscular (IM) vaccination has been a concerning unknown for the HSV vaccine field. The development of the human papillomavirus (HPV) vaccine provides ample proof of concept that an IM vaccine can be highly efficacious against a mucosal genital viral pathogens [29].

3. The Herpevac trial, which tested a truncated glycoprotein D (gD2t) vaccine in >8000 HSV-1/HSV-2 seronegative women showed 58% vaccine efficacy for prevention of genital HSV-1 disease and 32% efficacy for prevention of HSV-1 infection [30]. The vaccine did not prevent HSV-2 disease or infection. Titers of antibodies to gD2t were identified as a correlate of HSV-1 protection, based on increasing vaccine efficacy with increasing titers of gD2t [31]. Further studies showed that sera of vaccinees neutralized HSV-1 3-fold better than HSV-2, suggesting that vaccine-induced antibodies to gD2 were sufficient to prevent HSV-1 but not HSV-2 infection. These are the first data suggesting that antibody titers are a correlate of anti-HSV-1 immunity and provide a benchmark for inducing protective immunity.

4. Successful vaccination based eradication campaigns have been implemented for alphaherpesviruses which infect animals, such as bovine herpesvirus-1 and swine herpesvirus-1 (pseudorabies virus) [32,33].

The recent availability of full-length viral sequences from around the world for both HSV-1 and HSV-2, will allow selection of vaccine targets that could potentially provide protection against both pathogens and targets that are not geographically restricted [34–36]. This combined with increasing knowledge regarding the role of neutralizing antibodies and T-cell responses in preventing infection or modulating recurrent disease could help improve the design of future candidate vaccines.

2.2. General approaches to vaccine development for this disease for low and middle income country markets

Two approaches are being pursued for HSV-2 vaccine development: preventive vaccines and therapeutic vaccines. Preventive vaccines would provide protective immunity against genital HSV-2 infection prior to exposure, with a possible secondary effect of prevention of HIV infection in high risk populations. The target population would be adolescent men and women prior to the initiation of sexual activity. Prior studies of preventive HSV vaccines have focused on HSV-2 discordant couples or HSV-1/HSV-2 seronegative women in HIC; these studies have been limited by low numbers of study endpoints (acquisition of genital herpes disease), resulting in large sample sizes and prolonged Phase III trials. Preventive vaccines have not been tested in LMIC. However, given the disproportionate burden of both HSV-2 and HIV infection in LMIC, an HSV-2 vaccine must be effective in these populations to
have a global impact. HSV vaccines that will be tested in LMIC must be designed to have efficacy in both HSV-1 seropositive and HSV-1 seronegative persons, and geographic strain diversity must be accounted for in vaccine design. In addition, testing of preventive vaccines in LMIC where HSV-2 is rapidly acquired among young adults will allow for more efficient trials. If a candidate vaccine were found to protect against HSV-1 as well as HSV-2 in adolescents in HIC, shifting the timing of vaccination to infancy/childhood with possible booster in adolescence could also be considered. Such a vaccine may also prevent HSV-1 related eye and neurologic disease. These issues do not have clear consensus in the field.

Therapeutic vaccines are being tested in HSV-2 seropositive persons to reduce genital lesions and genital shedding, which may provide both personal and public health benefits. The target population for these vaccines is persons who already have recurrent genital HSV-2 infection. Phase I/II studies of 2 candidate therapeutic vaccines have demonstrated antiviral effects, with decreased rate of shedding and lesions and decreased quantity of virus shed [37]. Mathematical models suggest that there is a genital viral load threshold associated with sexual transmission [38]. Therapeutic vaccines are being tested in HIC at this time, and there is no consensus regarding prioritization of testing these vaccines in LMIC. An essential issue that will need to be addressed is the effect of therapeutic vaccines on genital inflammation. A therapeutic HSV-2 vaccine could reduce genital inflammation if viral shedding is contained; alternatively, therapeutic vaccines could result in increased genital inflammation as additional T-cells traffic to the genital tract, theoretically further increasing the risk of acquiring HIV.

3. Technical and regulatory assessment

Preclinical development of HSV vaccines utilizes well-established animal models to screen and test promising candidate vaccines. However, HSV is a uniquely human pathogen, and the host-virus interactions differ in people, likely accounting for limited predicted value for efficacy observed in animal models. The mouse model is convenient due to the availability of many tools to dissect the immune response, but has limitations, including lack of genital reactivation and high mortality in initial infection [39]. The guinea pig model appears to mimic human HSV-2 infection better than the mouse model as spontaneous reactivation in the genital track occurs [40]. However, promising vaccines in the guinea pig model have not translated to efficacy in humans. There is often a long delay in testing vaccine candidates with efficacy in animal models in clinical trials.

For therapeutic vaccines in early stages of clinical development, HSV genital shedding has recently been used as a surrogate endpoint rather than the more traditional endpoint of recurrence frequency. Genital shedding has the potential to more precisely define the most effective vaccine dose rather than recurrences, which may not be recognized by participants [41]. In addition, the use of a cross-over design in which the effect of the intervention can be directly measured allows for efficient trial design with a limited follow-up period and a relatively small number of participants.

4. Status of vaccine R&D activities

Multiple vaccine candidates with diverse platforms have been studied in the preclinical phase and several are being tested in clinical trials, with early development supported mainly by academic institutions, government, and biotech companies. Several pharmaceutical companies have also been involved with testing HSV vaccines.

The most widely used product for HSV vaccines in human clinical trials has been glycoprotein subunit vaccines. Glycoprotein D is expressed on the viral surface and responsible for most neutralizing antibody activity and, therefore, is a rationale target [42]. The largest clinical trial of an HSV subunit vaccine, Herpevac, enrolled HSV-1/HSV-2 seronegative women and used glycoprotein D-2 (gD2) with alum/MPL adjuvant [30]. Although the Herpevac trial did not show efficacy against HSV-2 disease, the finding that the vaccine prevented genital HSV-1 disease (vaccine efficacy = 58%, 95% CI 12–80%) is a significant advance for the HSV field [30]. In addition, identification that the gD2 antibody concentrations correlated with protection against HSV-1 infection, provides proof of concept that protective mucosal immunity can be stimulated.

### Table 1

<table>
<thead>
<tr>
<th>Candidate name/identifier</th>
<th>Pharmaceutical developer</th>
<th>Platform/antigens</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEN-003</td>
<td>Genocea</td>
<td>Subunit vaccine: gD2/ICP4 with Matrix M2 adjuvant</td>
<td>(T)</td>
<td>(T)</td>
<td></td>
<td></td>
<td>[37,51,52]</td>
</tr>
<tr>
<td>HerpV</td>
<td>Agenus</td>
<td>32 35-mer peptides, complexes with HSP, QS-21 adjuvant</td>
<td>(T)</td>
<td>(T)</td>
<td></td>
<td></td>
<td>[53]</td>
</tr>
<tr>
<td>Codon optimized polynucleotide vaccine VCL-HB01/HM01 HSV529</td>
<td>Admedus</td>
<td>DNA vaccine: gD2 codon optimized/ubiquitin-tagged</td>
<td>(T)</td>
<td></td>
<td></td>
<td></td>
<td>[54]</td>
</tr>
<tr>
<td>gD2/gC2/gE2 HSV-2 0∆NLS</td>
<td>Vical</td>
<td>DNA vaccine: gD2Δ+ UL46/Vaxfectin</td>
<td>X (P&amp;T)</td>
<td></td>
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<td>[55]</td>
</tr>
<tr>
<td>gD2/gC2/gE2</td>
<td>Sanofi</td>
<td>Replication-defective HSV-2 with deletions of UL5 and UL29</td>
<td>X (P&amp;T)</td>
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<td></td>
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<td>[56]</td>
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<td>gD2</td>
<td>Live, attenuated replication-competent HSV-2 with deletion of ICP0</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>[49]</td>
<td></td>
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<tr>
<td>HSV-1/HSV-2 0∆NLS</td>
<td>Live, attenuated replication-competent HSV-1 mutated for UL43, UL49.5, UL55, UL56, LAT</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>[57]</td>
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<tr>
<td>ΔgD2</td>
<td>Live, attenuated HSV-2 deleted in gD2</td>
<td>X</td>
<td></td>
<td></td>
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<td>[58]</td>
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<tr>
<td>AD472</td>
<td>HSV-2 mutated for g34.5, UL43.5, UL55-56, US10, US11, US12</td>
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<td></td>
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<tr>
<td>Cj2-gD2</td>
<td>Non-replicating gD2 dominant neg HSV-2</td>
<td>X</td>
<td></td>
<td></td>
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<td>[49]</td>
<td></td>
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<tr>
<td>Prime-pull strategy</td>
<td>“Prime” with live attenuated HSV-2 followed by “pull” with topical intravaginal CXCL9/CXCL10 chemokine</td>
<td>X</td>
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<tr>
<td>Inactivated HSV-2 in MPL/alum</td>
<td>Formalin inactivated HSV-2</td>
<td>X</td>
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<tr>
<td>HSV-1 glycoprotein B lentiviral vector</td>
<td>Lentiviral vector expressing gB1</td>
<td>X</td>
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<td></td>
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<td>[62]</td>
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</tr>
<tr>
<td>gB1s−NISV</td>
<td>Intravaginal non-ionic surfactant vesicles containing recombinant HSV-1 gB</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>[63]</td>
<td></td>
</tr>
</tbody>
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gD, glycoprotein D; ICP, infected cell protein; HSP, Heat shock protein; UL, unique long; gC, glycoprotein C; gE, glycoprotein E; US, unique short; TK, thymidine kinase; MPL, monophosphoryl lipid A; gB, glycoprotein B; T, therapeutic; P, preventive.
through vaccination [31], although it is not clear whether this is a mechanistic correlate [43]. Second generation preventive vaccines may need to stimulate higher titers of neutralizing antibody or induce other immune responses for more complete protection against HSV-1 or HSV-2.

There are several live-attenuated or replication-defective virus vaccine candidates in the preclinical phase (Table 1). A replication-defective HSV-2 vaccine (HSV529) has entered Phase I trials for both preventive and therapeutic indications. A live-attenuated virus deleted in gD2 prevented skin, neural and vaginal disease in the mouse model, and also is the first construct to eliminate establishment of latency in the dorsal root ganglia [44]. Concerns about recombination with wild type virus and retained pathogenic potential (especially with respect to central nervous system invasion) have limited the investigations into live-attenuated candidate products [45].

Within the past 2 years, 4 additional candidates have entered into Phase I/II trials as therapeutic vaccines. These vaccine candidates have novel adjuvants which stimulate T cell immunity. Preliminary results were reported for GEN-003, a gD2/ICP4 protein subunit vaccine with Matrix M adjuvant, with ~50% decline in genital HSV shedding rate after the therapeutic vaccine series [37]. This candidate vaccine is currently in a Phase II dose-ranging safety and efficacy trial. Preliminary results from a Phase II study of HerPv, a peptide vaccine with 32 peptides linked to heat shock protein (HSP) and QS-21 adjuvant, showed a 15% decrease in viral shedding, which persisted up to 6 months after the initial vaccine series [46]. A DNA vaccine with gB/UL46, adjuvanted with AdvaxtectRx™ has also entered Phase I/II trials for a therapeutic indication, with initial results expected in mid-2015.

The realization that genital HSV infection induces tissue resident memory T cells in human genital mucosa has been a recent advance in the field [47]. Animal studies have demonstrated the importance of stimulating tissue resident memory T-cells for prevention of HSV infection in the mouse model using a “prime and pull” approach, in which a topical chemokine applied to the genital mucosa after subcutaneous vaccination drew HSV specific CD8+ T cells and was associated with decreased clinical disease upon challenge with HSV-2 [48]. While this approach has not entered clinical trials, it is an innovative and highlights the importance of tissue resident T cells in the genital tract.

Novel delivery methods of glycoproteins, including lentiviral vectors expressing glycoprotein B and intranasal delivery, are being explored. Glycoprotein candidates with novel platforms are still being investigated. For instance, a gD/gC/gE subunit glycoprotein candidate is promising in mice [49].

5. Likelihood for financing

As HSV-2 infection greatly enhances the risk of HIV acquisition and transmission, it is possible that prevention of HSV-2 infection with a vaccine would have a substantial impact on reducing incident HIV infections, as predicted by modeling studies [50]. In this case, the vaccine may be supported in part by the Global Fund to Fight AIDS, Tuberculosis and Malaria in addition to GAVI. New global estimates for neonatal herpes, which are currently being completed, and better primary data on neonatal herpes incidence in LMIC will additionally help inform the likelihood of GAVI prioritization based on under 5 lives saved in GAVI eligible countries. Although neonatal HSV is relatively rare in HIC, there are few data regarding incidence in LMIC. This condition has a 60% fatality rate without treatment and can result in lifelong neurological deficits, even with successful treatment. Although concerns have been raised in some settings about providing an STI vaccine to pre-adolescents, GAVI support for HPV vaccine offers a clear precedent for GAVI prioritization of an adolescent vaccine against a sexually transmitted infection.

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