I. About the Disease and Pathogen

Basic information on pathogen, including transmission, estimated global disease burden for those at risk, for morbidity and for mortality, including uncertainties/data gaps, geographical distribution, economic burden if available, age groups affected and target groups for vaccination. Existing preventive, diagnostic and treatment measures and their limitations.

The Herpes simplex viruses are responsible for a broad-spectrum of diseases affecting all age groups across the developed and developing world. The viruses are members of the herpesvirus family, which also includes the human pathogens Varicella-Zoster virus, Epstein-Barr virus, Cytomegalovirus, Human herpes virus -6 and -8. Herpes simplex virus type -1 (HSV-1) and -2 (HSV-2) are serotypically differentiated based on genetically different surface glycoproteins, but both types are capable of infecting the oral or genital mucosa and causing lifelong, incurable infections (1). The virus infects epithelial cells at skin or mucosal surfaces, and then infects nerve endings, travels up the nerve axon, and establishes persistent infection in the trigeminal (HSV-1) or lumbosacral (HSV-1 or HSV-2) ganglia, where it is protected from the host immune response. The virus returns down the axon to cause oral or genital ulcers or asymptomatic viral shedding. Asymptomatic viral shedding occurs frequently, and during these periods the virus is transmissible. The ability of the virus to be acquired and transmitted in the absence of symptoms allows it to spread efficiently and silently throughout the population. As most infections are subclinical, disease incidence data are thought to underestimate the magnitude of HSV infection.

Although the clinical manifestations of primary infection may be similar between HSV-1 and HSV-2, the nature of the disease, age groups affected and severity 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), which is likely related to declining HSV-1 acquisition during childhood in these settings. Typically universally acquired early in childhood in lower middle-income countries (LMIC), it causes oral ulcers of varying severity from herpes labialis to gingivostomatitis and pharyngitis. It is the leading cause of sporadic encephalitis (HSV encephalitis) and infectious blindness (HSV keratitis) in HIC; the burden of these complications of HSV-1 infection in LMIC is unknown but likely to be high. Almost universal exposure to HSV-1 appears to be supported by the high rates of global seroprevalance. More than half of the world’s populations is seropositive for HSV-1, with over 90% people infected by adolescence in LMIC (2)).

Herpes simplex virus type 2 (HSV-2) is a sexually transmitted infection that is the leading cause of genital ulcer disease (GUD) worldwide; HSV-2 also causes neonatal herpes and increases the risk of HIV infection. An estimated 535 million persons are infected with HSV-2 with an incidence of 24 million infections per year (3). HSV-2 is rapidly acquired among adolescent 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 (4). Neonatal herpes incidence in HIC is ~10 cases/100,000 live births; 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 through HSV-2 associated genital tract inflammation. In addition, genital ulcer disease increases the risk of HIV transmission. In settings with high HSV-2 prevalence, 25-50% of HIV infections are attributable to HSV-2.

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),
There are several lines of evidence that an HSV vaccine is feasible from a biologic standpoint:

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.

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

3. The Herpevac trial, which tested a truncated glycoprotein D2 (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 (7). The vaccine did not prevent HSV-2 disease or infection. Titers of gD2t were identified as a correlate of protection, based on increasing vaccine efficacy with increasing titers of gD2t (8). Further studies showed that sera of vaccinees neutralized HSV-1 3-fold better than HSV-2, suggesting that induced titers of 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.
HSV-1 and HSV-2 are large DNA viruses that are highly conserved at the amino acid level. The viral genomes encode for over 80 proteins including numerous surface glycoproteins (targets of humoral immunity). 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. This, combined with increasing knowledge regarding the role of neutralizing antibodies and T-cell responses in preventing infection versus preventing recurrent disease could help improve the design of future candidate vaccines.

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

*What are the scientific approaches and indications and target/age/geographic groups being pursued? What public health needs will these vaccines meet if successfully developed? Where there are several different possible indications/target groups, how much consensus is there as to prioritization between these for vaccine development in LMIC.*

Two approaches are being pursued for HSV-2 vaccine development: preventive vaccines and therapeutic vaccines. Preventive vaccines would ideally 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 long trials. Preventive vaccines have not been tested in LMIC. However, the field is moving toward realization that an HSV-2 vaccine must be effective in LMIC and may be tested in these countries. HSV vaccines that will be effective in LMIC must be designed to be effective in both HSV-1 seropositive and HSV-1 seronegative persons, and geographic strain diversity must be accounted for in vaccine design. In addition, testing in LMIC where HSV-2 is rapidly acquired during adolescence will allow for more efficient trials. If a candidate vaccine was found to protect against HSV-1 as well as HSV-2 in adolescents, shifting the timing of vaccination to infant/childhood could also be considered. Such a vaccine may also prevent HSV-1 related eye and neurologic disease. Many of these and other related considerations 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 benefit. The target population is persons who have already acquired genital HSV-2 infection. Initial studies of 2 candidate vaccines have shown positive results. These vaccines are being tested in HIC at this time, and there is no consensus to prioritizing therapeutic vaccines in LMIC. A potential issue that will need to be addressed is whether the therapeutic vaccines result in increased genital inflammation as additional T-cells traffic to the genital tract, which may further increase the risk of acquiring HIV.

**III. Technical and Regulatory Assessment**

*Highlight perceived positive/negative aspects in clinical/regulatory pathways e.g. well established product development and regulatory pathway to licensure, accepted immune correlates and/or functional assays, accepted surrogate efficacy endpoints, existence of well accepted animal or challenge models, agreed trial designs and endpoints. Possibilities to develop case for correlates/surrogates should be included.*

Preclinical development of HSV vaccines utilizes well-established animal models to test and screen promising candidate vaccines. The mouse model presents a well-developed model of genital infection and is convenient but does not recapitulate human infection as genital reactivation does not occur, and mortality is high in initial infection. The guinea pig model is a well-established model of genital HSV-2
infection that mimics infection in humans and that is used to test candidate vaccines. However, promising vaccines in the guinea pig model have not translated to efficacy in humans. There is often a long delay in testing promising preclinical candidates in clinical trials.

The clinical pathways to licensure and implementation for an adolescent vaccine have been well established through the HPV vaccine. Identified challenges include effective marketing of a vaccine to prevent an STI, which the HPV vaccine was able to circumvent to a certain degree through marketing the vaccine as cancer prevention.

There are no accepted immune correlates of protection, although the recent finding of an immune correlate for protection of genital HSV-1 infection is promising (8). In infected persons, genital shedding is becoming more accepted as a biomarker for efficacy of therapeutic vaccines.

For preventive vaccines, there is no consensus on designs or endpoints, but in the wake of the Herpevac trial, there is growing interest in use of HSV-2 infection (seroconversion) as an endpoint rather than HSV-2 disease (clinically recognized genital ulcer syndrome). In addition, we have learned that large phase III vaccine trials must be performed in populations with substantial HSV-2 incidence.

IV. Status of vaccine R&D activities

Summarize status of vaccine design, preclinical and clinical trial activity, including platforms, vectors, and adjuvants. Note academic, government, biotech and industry entities engaged. Summarize antigenic targets (if subunit approaches). Section on major advances in last 3-5 years, including key opportunities highlighted by recent science developments in the area.

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, including Sanofi Pasteur and GlaxoSmithKline.

The most widely used approach in human clinical trials has been glycoprotein subunit vaccines. Glycoproteins are expressed on the viral surface and induce neutralizing antibodies and therefore are a rational target. The largest clinical trials to date include the Herpevac trial, which used glycoprotein D-2 (gD2) with alum/MPL adjuvant (7) and the Chiron HSV Vaccine using glycoprotein gB2/gD2 with MF59 adjuvant (9). Although the Herpevac trial did not show efficacy against HSV-2 disease, the findings that HSV-1 infection could be prevented and that there is an immune correlate of protection is a significant advance for the HSV field and provides proof of concept that mucosal immunity can be stimulated through vaccination and that genital infection can be prevented; second generation preventive vaccines may need to stimulate higher titers of neutralizing antibody.

Glycoprotein candidates with novel platforms are still being explored. For instance, a gD/gC/gE subunit glycoprotein candidate is promising in mice (10). Novel delivery methods of glycoprotein including lentiviral vectors expressing glycoprotein B and intranasal delivery are being explored. There are several live-attenuated or replication-incompetent virus vaccine candidates in the preclinical phase. A replication-incompetent HSV-2 vaccine (HSV529) has entered Phase I trials for both preventive and therapeutic indications.

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 gD/ICP4 protein subunit vaccine with Matrix M adjuvant, with ~50% decline in genital HSV shedding rate after the therapeutic vaccine series. Preliminary results from a Phase II study of HerpV, a 32 peptide vaccine linked to HSP and QS-21 adjuvant, showed a 15% decrease
in shedding after the initial vaccine series. A DNA vaccine with gD/UL46/UL47, adjuvanted with Vaxfectin® has also entering Phase I trials for a therapeutic indication.

The realization that genital HSV infection induces tissue resident memory T cells has been a major recent advance in the field. 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 (11). 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.

Table 1: Development Status of Current Vaccine Candidates (POC = Proof of concept trial)

<table>
<thead>
<tr>
<th>Candidate Name/Identifier</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>POC</th>
<th>Phase III</th>
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<tr>
<td>GEN-003 (gD2/ICP4/MM adjuvant)</td>
<td>X</td>
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<td>HerpV (32 35-mer peptides, HSP adjuvant)</td>
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<td>Coridon (gD2 codon optimized/ubiquitin-tagged)</td>
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<td>VCL-HB01 (gD2/UL46/UL47/Vaxfectin)</td>
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<td>HSV529 (HSV-2 mutated for UL5/UL29)</td>
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<td>Herpevac (gD2/MPL/alum)</td>
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<td>gD/gC/gE (Trivalent glycoprotein)</td>
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<td>0ΔNLSICP0 live attenuated</td>
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<td>HF10 (HSV-1 mutated for UL43, UL49.5, UL55, UL56, LAT)</td>
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<td>AD472 (HSV-2 mutated for g34.5, UL43.5, UL55-56, US10, US11, US12)</td>
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<td>CJ-2-gD2 HSV-2 gD dominant neg</td>
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<td>HSV-2 mutated for TK, prime/pull</td>
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<td>Inactivated HSV-2 in MPL/alum</td>
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<td>HSV-1 glycoprotein B lentiviral vector</td>
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<tr>
<td>Recombinant HSV-1 gB intranasal</td>
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References