REQUEST FOR PROPOSALS: Dynamic Modelling of HSV-2 and HIV Infections to Estimate the Burden of HSV-associated HIV Infections and the Predicted Impact of HSV Vaccines

APPLICATION SUBMISSION DATE: Note updated deadline: 30 March 2018

1. Introduction
This request for proposals (RFP) is made by the World Health Organization (WHO)'s Department of Reproductive Health and Research (RHR). The department seeks proposals for developing mathematical models of herpes simplex virus type 2 (HSV-2) and HIV transmission dynamics to estimate the burden of HSV-associated HIV infections and the predicted population-level impact of HSV vaccines (prophylactic and therapeutic) on HSV-2 and HIV incidence.

2. Background
HSV-2 accounted for more than 400 million infections worldwide in 2012.¹ The unmet need for a vaccine to counter the consequences of HSV-2 infection has been articulated by WHO, the National Institutes of Allergy and Infectious Diseases (NIAID), and global technical partners in a comprehensive roadmap for development of new vaccines against sexually transmitted infections (STIs).² Several factors drive the need for HSV vaccines, including: (a) HSV-2 increases HIV acquisition and transmission risk several-fold;³ (b) HSV-2 infection is lifelong and the leading cause of genital ulcer disease (GUD), a painful condition with consequences on sexual and reproductive health; (c) HSV-2 can be passed from mother to infant to cause neonatal herpes, which is rare (~1 in 10,000 live births)⁴ but lethal (60% fatality without treatment); and (d) currently available prevention measures, such as condoms and antiviral therapy, are insufficient to control HSV spread.

Two types of vaccines against HSV infection are under development: prophylactic vaccines to prevent infection and therapeutic vaccines to modify or treat existing infection. Therapeutic vaccines are currently the furthest along in development, with several candidates in Phase II trials. To articulate the investment rationale for HSV vaccines and to fully quantify the public health needs a vaccine could address, a global public health value proposition is being developed. In addition to quantifying the broader public health and financial rationale for HSV vaccines, the value proposition can identify vaccine markets, such as low and middle-income countries (LMICs), beyond those often considered by vaccine developers, to supplement vaccine developer business cases and increase the likelihood that vaccine candidates are developed for, and will reach, global populations.

To develop an HSV vaccine value proposition, the burden of HSV-related disease needs to be well characterized, and the potential impact of a vaccine predicted. Global and regional prevalence and incidence of HSV-2 infection was last estimated for 2012,¹ the global burden of neonatal herpes was recently estimated,⁴ and estimates of genital ulcer disease burden are underway. A 2017 meta-analysis of 57 studies highlighted the increased risk of HIV infection associated with HSV-2;³ however, the global and regional burden of HIV infections likely attributable to HSV-2 infection has not been estimated. Previous dynamic models of HSV-2 vaccine impact have predicted that even an imperfect vaccine could lead to population-level decreases in HSV-2 and HIV infection.⁵ However, several of these models have limited scope, are older, do not reflect vaccines currently in development nor the current public health landscape, or have other limitations. A WHO consultation on HSV vaccine modelling recommended updated vaccine impact models to address these shortcomings.⁶
3. Purpose
Proposals are sought to support development of WHO’s HSV vaccine value proposition, using transmission dynamic modelling of HSV-2 and HIV infections to estimate the global and regional burden of HSV-associated HIV infections and the predicted population-level impact of HSV vaccines on HSV-2 and HIV infections.

4. Objectives
The specific objectives are:
1. To develop transmission dynamic model(s) representing HSV-2 and HIV transmission at a population level, considering the natural history of the infections and heterogeneity related to sex, relevant risk groups, sexual activity, and/or other important factors.

2. To generate transmission model-based estimates of the population attributable fraction (PAF) of HIV due to HSV-2, and use the PAF to estimate the global and regional burden of HIV infections attributable to HSV-2.

3. To model the estimated population-level impact of an HSV-2 vaccine on incident and prevalent HSV-2 and HIV infections (prophylactic and therapeutic vaccines evaluated separately), considering different epidemiologic scenarios.

5. Submission
Proposal must be limited to a maximum of 10 pages and should include the following sections and components:
(i) **Scope**: Project description with goals and objectives.

(ii) **Approach**: Detailed proposal on the modelling approach and justification, including its strengths and limitations, and justification for the approach to incorporating heterogeneity, model parameterization, settings to be considered and data sources for model fitting, use of sensitivity analyses, and other important features. Models should assess at least two types of settings: a high HSV/high HIV prevalence LMIC setting, and a low HIV prevalence setting (high-, middle-, or low-income), although additional epidemiologic/income scenarios can be explored.

(iii) **Organization**: Proposed project organization/plan including participating institutions, researchers, and their roles and responsibilities.

(iv) **Budget**: Proposed detailed budget and justification, which should include costs per task and deliverables and the applicable Programme Support Cost (PSC), if appropriate. Total proposed costs will be considered when evaluating the application.

(v) **Timeline**: Proposed timeline including major milestones, anticipated completion dates for milestones and deliverables, and projected completion date for the project.
(vi) **Declaration:** Declaration of conflicts of interest for proposed key personnel (see enclosed Annex 1).

(vii) **Contact:** Contact information for your organization including the full name of the organization, address and, if applicable, a signed cover letter from an institutional official supporting the submission.

(viii) **Biographies:** Use additional pages as necessary to include short biographies for each core team member, including relevant expertise and experience and institutions being represented.

### 6. Deliverables

1. Manuscript for submission to a peer-reviewed journal on the PAF of HIV due to HSV-2 and estimation of HSV-associated HIV infections globally and regionally.

2. Preliminary report on the population-level impact of prophylactic and therapeutic HSV-2 vaccines on HSV-2 and HIV incidence. The report should include a description of model development and application, data generation, and main results, including any sensitivity and uncertainty analyses.

3. Manuscript(s) for submission to peer-reviewed journal(s) on the population-level impact of an HSV-2 vaccine on HSV-2 and HIV incidence and prevalence (prophylactic and therapeutic vaccines to be considered separately).

4. Data files from the global and regional estimates of HIV infections due to HSV-2 and assessments of vaccine impact.

A representative of the research team will be expected to attend WHO expert consultations, as required (maximum of two meetings). WHO will review each report/draft manuscript and submit questions and comments to the team. Teams are expected to provide a written response as to how the comments were addressed.

WHO reserves all rights to the above-mentioned deliverables including the right to (a) alter them (b) use them or (c) not use them.

### 7. Evaluation criteria

Proposals will be evaluated based on a combination of criteria including the following:

(i) **Methodological rigor of the proposed approach,** including feasibility of proposed methods and timelines, and the quality of the evidence to be generated.

(ii) **Experience** of the principal investigator and the team’s expertise in conducting and disseminating similar transmission dynamic modelling research

   – Expertise related to modelling vaccine impact, burden of disease estimation, and/or HSV-2, HIV, or a similar infection (e.g., HPV) is essential.

   – Institutional support and resources to work with LMIC partners and incorporate data from LMIC settings will be considered favourably.
(iii) **Proposed timelines** and likelihood of meeting deadlines
   - Project duration will not exceed 15 months from signature of contract, but the ability to complete the project in 12 months will be considered favourably.
   - The ability to complete Deliverables #1 and #2 in 6 months from signing the official contract will be considered favourably.

(iv) **Proposed budget** and overall value of the project

Proposals will first be evaluated for completeness and compliance with the parameters described above. Applications that pass the initial evaluation will then be reviewed by at least two independent reviewers with relevant expertise in the field for recommendations on funding.

Final authority on funding approval rests with the WHO Secretariat. All applicants will be notified of the outcome, though WHO will not be able to provide feedback on unsuccessful applications. For additional information on the WHO RFP process, see enclosed Annex 2.

8. How to apply

Proposals must be submitted by email to Dr Sami Gottlieb at gottliebs@who.int. All electronic submissions must be received by 5 pm (Geneva time) on 30 March 2018 (NOTE UPDATED DEADLINE), and should include “HSV and HIV Modelling” in the subject line. Proposals that are incomplete, or received after the due date, will not be considered.

References