Vaccines against sexually transmitted infections: The way forward ☆

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1. Introduction

The World Health Organization (WHO), recognizing the profound impact of sexually transmitted infections (STIs) on global sexual and reproductive health and the need for new prevention strategies, organized a technical consultation on STI vaccines in April 2013. International experts in STI basic science, epidemiology, clinical care, program implementation and policy from multiple world regions and countries gathered in Geneva, Switzerland to review current progress toward the development of new STI vaccines and discuss strategies for ensuring their future availability.

The objectives of the consultation were:

○ To review and evaluate the need, development status, and future prospects for new, effective vaccines against STIs, as well as policy and programmatic implications for their introduction;
○ To identify the critical gaps in knowledge and current barriers to the development of effective vaccines against the selected STIs;
○ To propose potential solutions and lay the framework for a global roadmap for the development and introduction of these STI vaccines;
○ To engage researchers, donors and the private sector to continue research and development of STI vaccines for global use.

Adhering to the goals of the 2012 Global Vaccine Action Plan [1], which calls for research to develop new vaccines to extend the life-saving benefits of vaccination to all people, meeting participants focused on development of new, effective vaccines against the following five STIs: herpes simplex virus (HSV), *Chlamydia trachomatis* (chlamydia), *Neisseria gonorrhoeae* (gonorrhea), *Trichomonas vaginalis* (trichomoniasis) and *Treponema pallidum* (syphilis) infections, and the diseases they cause. As effective vaccines against hepatitis

B virus (HBV) and human papillomavirus (HPV) already exist, these vaccines were discussed only insofar as lessons learned from their development and implementation could shed light on new STI vaccine development. HIV vaccines were excluded as they are already part of a specific WHO intiative [2]. Nonetheless, meeting participants emphasized the important association between all five STIs under consideration and the acquisition and transmission of HIV infection.

For each of the five STIs, meeting participants discussed the current knowledge base and vaccine development status, critical gaps in knowledge, and important next steps for accelerating vaccine development and availability. These discussions and a roadmap outlining the key priorities for global STI vaccine development and introduction are described below.

2. Gaps in knowledge and future needs for vaccine development

Meeting participants evaluated the need for each STI vaccine, reviewed currently available epidemiologic, basic science, translational and clinical research data, and summarized past experience with STI vaccine development. They also discussed key considerations for future vaccine clinical development and evaluation. In each of these areas, participants pinpointed important gaps in knowledge and crucial needs for the future.

2.1. HSV

Meeting participants agreed on the urgent need for an HSV vaccine, based on the large global burden of infection [3], the fact that HSV type 2 (HSV-2) fuels the HIV epidemic by increasing the risk of HIV acquisition and transmission [4], and the limited population impact of current HSV prevention measures [5]. Numerous seroprevalence studies provide a solid understanding of the substantial prevalence of HSV-2 infection globally, and the natural history of HSV infection has been well delineated. However, data are more limited with respect to genital herpes caused by HSV-1, which cannot be distinguished serologically from oral infection. Several lines of basic and translational research have shown that both antibodies and innate immunity are important in preventing HSV infection, while T-cells are important in controlling infection [5].

Several candidate prophylactic HSV-2 vaccines have been evaluated in clinical trials involving more than 20,000 human volunteers and have been described by Johnston et al. in this issue [5]. Despite some promising early findings [6], in a large follow-up trial a recombinant glycoprotein subunit vaccine failed to prevent HSV-2 infection or disease [7]. These vaccines have been evaluated almost exclusively in high-income countries. The current HSV vaccine pipeline includes a variety of novel prophylactic vaccine platforms beyond glycoprotein targets that have shown efficacy in animal models, including replication-competent and replication-incompetent HSV-2 vaccines, as well as some therapeutic vaccines that are in early clinical development [5].

More immunological data are needed to understand differences in vaccine responses observed in previous vaccine trials – between HSV-discordant couples and the general population, between sexes, and according to HSV-1 serostatus – and also to understand the disparate clinical and virological manifestations of HSV-2 infection. Ideally, a series of immunological studies would be done using specimens from people with well-defined HSV-2 severity and partnership status, including women from high- and low-income countries, involving assessment of mucosal T-cell and antibody responses, antibody avidity, and strategies to induce mucosal responses. Mucosal and systemic immune responses should be compared to look for systemic correlates of mucosal immunity. These studies may provide insight as to which antigens should be included in a potential vaccine and how antibody and T-cell immunity could be stimulated.

Based on the experience from previous trials, vaccine development is feasible, although providing complete immunity against infection may be challenging, compared with reducing viral shedding or clinical disease. A vaccine is needed against genital HSV infection caused by either HSV-2 or HSV-1, which ideally would be effective for people already seropositive for HSV-1 infection, acquired in childhood in most of the world. Clinical trial sites and supporting laboratories in low-income countries should be identified and developed to conduct phase 1 trials, and public–private partnerships should be encouraged. Prophylactic vaccines must be tested in populations where the prevalence and incidence of HSV-2 are the highest and where the vaccines are most desperately needed. To accomplish this, ongoing assessment of robustness and performance of diagnostic assays and standardization across high- and low-income sites will be needed. Any future clinical trials should consider randomization and analysis by sex and HSV-1 serostatus. Finally, mathematical modeling will be important to predict the population impact of varying levels of vaccine efficacy, incorporating potential differences by sex and HSV-1 serostatus.

2.2. Chlamydia

Meeting participants agreed that pursuit of a chlamydia vaccine is important, because of the substantial prevalence of chlamydial infection throughout the world [8], the link with adverse outcomes such as tubal-factor infertility, and the difficulty and expense of chlamydia control using current opportunistic screening strategies [9]. Chlamydia is a global problem, but the prevalence of chlamydia has been much better described in high-income than low-income countries. In addition, although numerous studies have established the associations between chlamydia and pelvic inflammatory disease (PID), ectopic pregnancy, tubal-factor infertility, and other sequelae, the global disease burden related to chlamydia has been difficult to estimate precisely. Gaps in knowledge of the natural history of chlamydial infection include the progression rate, timing, and factors associated with ascension from lower genital tract infection to upper tract disease.

The mechanisms for chlamydia-induced protective immunity versus immunopathology have not been fully defined, but several

animal models, the human "model" provided by ocular infection, and translational studies have elucidated several key factors, which are summarized by Hafner et al. in this issue [10]. It is clear that T-cell driven interferon-gamma responses are critical for clearing infection, and antibody responses, while not protective alone, are also important. Early clinical trials of killed or live whole organism vaccines against ocular *C. trachomatis* infection (trachoma) showed that it was possible to induce short-term immunity to infection and to reduce the incidence of scarring sequelae; however, use of these crude whole organism vaccines resulted in increased severity of inflammation upon subsequent challenge in some animal models [11].

Further research is needed to continue the search for target antigens providing the greatest amount of vaccine protection and to confirm that a new vaccine does not lead to more severe disease on subsequent exposure to infection. Reverse vaccinology [12] and other methods have resulted in a large selection of potential target antigens, including the major outer membrane protein (MOMP) and polymorphic membrane proteins (Pmps) [10]. The concept of targeting several proteins, at different stages of the chlamydial developmental cycle, is being explored. The recent ability to genetically manipulate *Chlamydia* may allow deletion or inactivation of key genes to understand their role in pathology [13]. For example, plasmid-free vaccine strains have shown protection against ocular infection in non-human primates, without immunopathology [14]. Research must be translated to humans, and immunologic and host factors associated with transmission and acquisition should be explored using clearly defined clinical cohorts.

The ultimate profile of a chlamydia vaccine remains to be determined. For example, a chlamydia vaccine that induces more rapid clearance of infection could have a notable impact on transmission, even if complete immunity against infection may be difficult to achieve [15]. A vaccine with limited protection against infection could also still protect against upper genital tract disease. Of note, upper genital tract infections and disease are currently difficult to diagnose. Efforts to develop better diagnostic tests, including potential immunological biomarkers or radiological imaging strategies, are essential not only for vaccine trials but also for elucidating chlamydial natural history and clinical care.

2.3. Gonorrhea

Meeting participants recognized the increasing urgency of developing a vaccine against gonorrhea, because of rising gonococcal antimicrobial resistance globally [16]. The epidemiology of gonorrhea is fairly well understood in high-income countries, where gonorrhea infection is mostly limited to higher-risk core groups; however, better epidemiologic data are needed in lower-income countries. More precise data on gonorrhea strains, contributions to complications such as PID and infertility, antimicrobial resistance, and co-infections will allow modeling to understand the global health and economic impact of gonorrhea, and how antimicrobial resistance will affect its spread.

As reviewed by Jerse et al. in this issue, basic and translational research has shown that *N. gonorrhoeae* has adapted to evade the host immune response through antigenic variation and immunosuppression, e.g., the induction of regulatory T-cells [17]. The high genetic variation of *N. gonorrhoeae* frustrated early vaccine efforts. Two vaccine approaches, killed whole cells and purified pilin, were tested in clinical trials over 30 years ago and were unsuccessful. Interest in gonorrhea vaccines has been limited ever since, despite major new technological advances such as use of proteomics and genome mining, which enabled development of vaccines against group B *Neisseria meningitidis* [18]. These technologies have uncovered several conserved peptides that may be potential antigens for

vaccine development, including AniA, TbpAB, MtrE, and a peptide mimic of the 2C7 oligosaccharide epitope [17,19].

Critical gaps in basic and translational research include correlates of immunity, antigenic variability across strains, and correct antigen configuration. Animal and in vitro research on basic pathology and host responses should generate hypotheses to be tested in humans to determine immune defense mechanisms in the male and female genital tracts. The effects of the microbial environment and the reproductive cycle on gonococcal immunobiology should also be explored.

The feasibility of a prophylactic vaccine still needs to be determined. Consideration should be given to early evaluation of rational vaccine candidates in Phase I clinical trials to assess safety and nature of the immune responses generated. Trial endpoints are needed that would balance ethical, scientific, and regulatory considerations. As with chlamydia, diagnosing PID is a barrier to assessing disease as an endpoint in vaccine trials. Efforts to streamline the human gonorrhea challenge model currently used in one academic setting and to address regulatory issues affecting the model's efficiency will be important future pursuits [20].

2.4. Trichomoniasis

Meeting participants discussed the potential for developing a vaccine against *T. vaginalis* infection, the most common of all the curable STIs, with 276 million new cases estimated globally in 2008 [8]. Infection has been linked with adverse pregnancy outcomes and increased HIV transmission [21], and associations with other potential outcomes, such as prostate cancer and vaginal symptoms in older women, are being explored [22,23]. However, improved understanding of the epidemiology and natural history of trichomoniasis is a critical first step toward vaccine development. Trichomoniasis prevalence, incidence, and natural history, including risks of sequelae such as pre-term labor, low birth weight, and HIV acquisition and transmission, need to be better defined. In addition, the global economic impact of trichomoniasis should be carefully modeled.

Smith and Garber discuss the current status of *T. vaginalis* vaccine development in this issue [21]. Two strains of *T. vaginalis* have been identified; both of these interact with the genital microbiome in several ways. However, the host-pathogen interaction in the genital tract is not well delineated, and no correlates of immunity are known. Newer genomic and proteomic approaches have identified *T. vaginalis* proteins that could be potential candidate vaccine antigens [21]. However, further work is needed on the factors associated with pathogenicity, immune responses during trichomoniasis, and the role of *T. vaginalis* in immunomodulation of the lower genital tract, including interactions with the vaginal microbiome and other infections.

2.5. Syphilis

Meeting participants explored some promising findings related to syphilis vaccine development. Although a wide range of data show that syphilis rates have been decreasing globally, syphilis is still a generalized problem in many low-income countries and a resurgent problem in high-risk groups such as men who have sex with men (MSM) in many higher-income countries [24,25]. Syphilis causes adverse pregnancy outcomes, including fetal deaths and stillbirths, as well as enhanced HIV transmission [9,26], and the global disability-adjusted life-years (DALYs) lost from syphilis are the highest of all curable STIs [27]. Screening and treatment programs in antenatal care clinics can effectively prevent the adverse outcomes of syphilis in pregnancy, but they are inadequately implemented in many settings [28]. To develop an investment case for syphilis vaccine development, modeling is needed to understand the comparative benefits and economic rationale of a vaccine versus a screening program, or both, for syphilis control or potential eradication [29]. In addition, the role of syphilis vaccine as part of a vaccine against multiple STIs should be explored.

As discussed by Cameron in this issue, barriers to development of a syphilis vaccine include an insufficient number of basic researchers, technical difficulties associated with experimentation on *T. pallidum*, and a lack of industry interest in the field [30]. Nonetheless, a useful rabbit model for syphilis infection has enabled excellent insights into the correlates of disease protection and has yielded some promising vaccine candidates [30]. Two candidate vaccines are currently being evaluated in the rabbit model, although only a limited number of rabbits have been assessed thus far [30]. There have been no human clinical trials. Thus, in addition to needing vaccine studies in a larger numbers of rabbits over a longer time period, it will also be important to facilitate exchange of information and samples between basic research laboratories and clinical settings, to translate important findings from animal models to humans. Access to human samples from clearly defined clinical cohorts will allow study of human immunologic markers and how markers vary according to previous infection.

3. The way forward: a roadmap to accelerate STI vaccine development

Based on the identified knowledge gaps and needs described above, participants of the 2013 STI Vaccine Technical Consultation discussed key priorities for future STI vaccine development, evaluation, and introduction. These discussions formed the basis for a roadmap outlining the most important next steps for advancing new STI vaccines. Although the vaccine science is in different stages for the five STIs, the roadmap summarizes critical overarching action points related to the epidemiologic and scientific groundwork for STI vaccine development, preferred product characteristics and clinical development, advanced planning for vaccine introduction, and vaccine funding and investment strategies. Many of these priorities can be pursued in parallel to expedite development of STI vaccines.

3.1. Obtain better epidemiologic data

Meeting participants agreed that existing epidemiologic data show that STIs are a global threat to sexual and reproductive health. Nonetheless, better data on STI prevalence, incidence, and STI interactions, particularly in low- and middle-income countries, would help build a better investment case for STI vaccines and guide future vaccine evaluation and implementation efforts.

- *Update and improve global STI prevalence and incidence estimates*
  - Update global curable STI estimates from 2008 and global HSV-2 infection estimates from 2003 and improve STI estimation methodology
  - Partner with research sites to obtain existing but non-published STI prevalence and incidence data collected as part of clinical studies, especially in low-income settings, e.g., from HIV prevention trials, microbicide trials, and HPV vaccine studies
  - Consider strategically determined, selective additional prevalence studies in low- and middle-income areas where most data are currently imputed
  - Promote development and validation of cheap, accurate diagnostic tests for STIs that are feasible in low-income settings, e.g., rapid point-of-care tests

- *Strengthen existing and nascent STI surveillance systems*
  - Increase the quantity and quality of relevant STI data reported through established global and regional surveillance systems, e.g., antenatal syphilis test results reported through the Global AIDS Response Progress Reporting (GARPR) system [31]
  - Explore possibilities for new sentinel surveillance sites for STIs in low-income settings
  - Implement surveillance strategies for monitoring resistant gonorrhea outlined in the "Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae*" [16]
- *Use basic epidemiology findings to inform vaccine evaluation and implementation*
  - Choose and develop clinical trial sites, especially in expanding to low- and middle-income settings. This is currently an important need for HSV-2 vaccine trials.
  - Refine the design of STI vaccine trials, e.g., outcomes, populations, stratification, etc.
  - Define target populations and indications for future vaccine use.
- *Review and summarize the epidemiologic overlap among the STIs*, in terms of both infection and disease sequelae, to guide consideration of combination vaccines, an important future goal.

3.2. Improve understanding of STI natural history and burden of sequelae

One of the most urgent needs for making an investment case for vaccines against STIs is more precise data on the burden of infection-related disease sequelae, especially in low- and middle-income settings.

- *Conduct a review and explore potential data sources on the incidence of PID, tubal factor infertility, ectopic pregnancy, and other complications of chlamydia and gonorrhea in low-income settings*
  - Support current efforts to assess the attributable fraction of tubal factor infertility due to chlamydia and explore expansion to other settings
  - Review recent studies of the proportion of infertility that is tubal factor in low-income countries and consider updating the landmark study on this from the 1980s [32]
  - Review studies of the microbiology of PID in low-income countries
- *Review and explore potential data sources on the incidence of pre-term labor and other adverse pregnancy outcomes related to chlamydia, gonorrhea, and trichomoniasis in low-income settings*
- *Critically review and summarize the literature on the link between the curable STIs and HIV.* All five STIs under discussion have been associated with HIV acquisition and transmission. However, while the link between HSV-2 and HIV has been well studied, better refinement of the magnitude of association between other STIs and HIV would help refine prevention benefits.
- *Discuss innovative, ethical study designs to assess the natural history of STIs*
  - Design studies to clarify rates of progression from infection to disease and, for chlamydia and gonorrhea, to elucidate the timing and predictors of ascension to the upper genital tract
  - Estimate the contribution of subclinical upper tract infection to long-term sequelae globally
  - Explore use of specimens from existing prospective cohort studies, for example from microbicide trials, as a way to shed light on STI natural history
- *Improve, validate, and standardize definitions of STI-related sequelae*
  - Identify diagnostic criteria for PID that correlate with upper genital tract infection
  - Review literature and prioritize new studies to determine valid biomarkers or radiological techniques (e.g., magnetic resonance imaging or transvaginal ultrasound) for determining upper genital tract inflammation and damage
- *Update STI-related disability-adjusted life-year (DALY) estimates done in the 2010 Global Burden of Disease Study* [27]
  - Refine tools to measure DALYs for STI-associated outcomes
  - Provide input from STI experts to the Global Burden of Disease Study process
  - Encourage inclusion of DALY estimates for HSV-2 in Global Burden of Disease Study updates

3.3. Model the theoretical impact of STI vaccines

Meeting participants agreed that it will be extremely important to model data on STI epidemiology, natural history, and burden of disease, along with data on the human and financial costs of these outcomes, to determine the theoretical impact of each potential STI vaccine.

- *Design models of the potential effectiveness and cost effectiveness of a future STI vaccine in the context of the observed epidemiology and disease burden*
  - Strengthen data on burden of infection and disease, as above, to input into models
  - Determine innovative methods of estimating STI-related costs in low- and middle-income countries
  - Agree upon important model assumptions for each STI
- *Model the potential effectiveness of future STI vaccines against different assumptions and scenarios, for example:*
  - Vaccines that provide complete immunity against infection versus those reducing viral shedding or enhancing bacterial clearance or preventing clinical disease
  - Vaccines with varying levels of efficacy
  - Vaccination of different target populations
  - Vaccination versus other currently available interventions (e.g., screening programs)
  - Vaccination under changing epidemiologic scenarios (e.g., increasing gonorrhea antimicrobial resistance)
- *Conduct modeling to guide critical characteristics of each STI vaccine, for example:*
  - The degree of reduction in viral shedding or bacterial load required to reduce transmission in the population
  - The potential role for prophylactic versus therapeutic vaccines

3.4. Advance basic science research for STI vaccines

Although the key priorities for basic science research vary according to each organism, several research needs were identified that had implications for all of the STIs.

- *Define appropriate animal models and other experimental systems*
  - Outline parameters for appropriate animal models for each STI
  - Describe advantages and limitations of available models
  - Develop models allowing high-throughput screening of vaccine candidates
- *Employ technological advances to screen for a wide variety of potential target antigens*
  - Capitalize on powerful new techniques such as genomics and proteomics
  - Explore use of reverse vaccinology to rapidly identify potential antigens for STI vaccines
  - Optimize antigen selection and determine rational combinations of target antigens for evaluation
- *Develop appropriate adjuvants and delivery systems for STI vaccines*

3.5. Conduct basic and translational studies in human clinical settings as soon as possible

- *Conduct studies to explore immunological, host, and pathogen factors associated with acquisition and control of infection among well-defined cohorts of people*
  - Utilize clinical cohorts defined by clinical or disease severity, e.g., those with frequent versus infrequent HSV-2 shedding
  - Evaluate cohorts of concordant and discordant sexual partners, e.g., those who are exposed and uninfected versus those who are exposed and infected
  - Explore collaborations with existing clinical cohorts, especially those that enroll couples or do contact tracing to find sexual partners for STIs, and possibilities for using stored clinical specimens
  - Explore the relationship between host and pathogen genomes and disease severity
  - Seek new collaborations for specimen collection and testing as new studies are developed
- *Expand knowledge base on mucosal immunity in the genital tract*
  - Evaluate gender differences in the immune response to infection
  - Compare systemic and mucosal immune responses and compartmentalization of mucosal immune responses
  - Assess the role of the microbiome, the impact of sex hormones, and their interactions
  - Develop robust mucosal assays
- *Determine correlates of protection*
  - Compare systemic and mucosal immunologic responses among well-defined cohorts
  - Develop innovative prospective human studies to look for correlates of repeat infection for curable STIs

3.6. Define preferred product characteristics (PPCs) for 1st generation vaccine

WHO is establishing a consensus-building process aimed at defining "preferred product characteristics" (PPCs) for vaccines addressing critical, unmet public health needs in low-income countries. PPCs are intended to help guide development of target product profiles by vaccine developers and link upstream vaccine research and development with downstream public health and programmatic considerations.

- *Define and reach consensus on the desired characteristics of STI vaccines that would meet priority public health and programmatic goals, especially for low-income countries, e.g., considering*:
  - Prophylactic versus therapeutic vaccines
  - Prevention of morbidity versus prevention of infection
  - Choice of target population
  - Transmission-interruption goals
  - Measures intended to increase acceptability.
- *Conduct consultations with multiple stakeholders*, including WHO officials involved in vaccine approval processes and immunization and disease control staff from low-income countries, to provide PPC guidance

3.7. Expedite clinical development and evaluation

Among the STIs discussed during the consultation, only HSV-2 vaccines have made it into clinical trials in recent years. There was a sense that the field is currently stalled in animal studies that do not always facilitate the transition of candidate vaccines into human clinical trials.

- *Encourage more rapid initiation of early clinical trials*
  - Utilize a more iterative relationship between animal studies and early human studies, once animal studies have provided necessary assurances of safety and some indications of efficacy
  - While clinical trials advance, continue pre-clinical studies to accumulate additional knowledge and inform downstream phases of human clinical trials
  - For chlamydia vaccines, explore possibilities for evaluating safety and immunogenicity in trachoma endemic populations
- *Choose and agree upon efficacy endpoints for test-of-concept or pivotal clinical trials*
  - Discuss and reach consensus on the necessity and feasibility of measuring clinical disease versus infection acquisition as the desired primary efficacy endpoint
  - Determine additional laboratory endpoints and harmonize assays across trials, e.g., HSV viral shedding to measure acquired disease and model impact of vaccination on HSV transmission
  - Improve measurement of clinical disease endpoints, e.g., valid biomarkers or radiological techniques to diagnose PID
  - Develop correlates of protection that could in the future be used as surrogate readouts to replace clinical efficacy endpoints, differentiating vaccine-induced and natural responses
  - Determine strategies for monitoring vaccine effectiveness in post-licensure studies
- *Agree on clinical trial design and strengthen clinical trial sites, especially in low-income settings*
- *Involve regulatory agencies early*
  - Reach consensus on vaccine development pathways allowing licensure
  - Come to consensus on the information regulators will need to make decisions
  - Strengthen the capacities of regulatory agencies from low- and middle-income countries

3.8. Plan for vaccine introduction in advance

- *Consider communication issues* related to vaccine delivery early
  - Use lessons learned from HPV vaccine introduction to guide communication about future STI vaccines, and how issues may differ since HPV vaccine was introduced as a cancer vaccine
  - Develop clear messages related to outcomes and prevention benefits, especially when the STI leads to multiple outcomes or when STI-related outcomes have multiple causes
  - Educate health care provider groups about adolescent and sexual health in addition to specific information about new STI vaccines
  - Advocate for normalizing conversations about sexual health and destigmatizing STI
- *Support development of adolescent health care platforms* in both high- and low-income settings, to facilitate delivery of the STI vaccines that will be targeted to adolescents
- *Delineate systems for outcome monitoring well in advance*

3.9. Encourage investment in STI vaccine development

Development of effective, affordable STI vaccines will require collaboration and communication among large companies, smaller biotechnology enterprises, and research and policy partners from academia and the public sector. Although it is clear that industry is engaged particularly with herpes and chlamydia vaccine development, it is much less so with other STIs, which are at an earlier stage of development. Meeting participants agreed that development of partnerships between the public and private sectors is essential for making STI vaccines a reality.

- *Explore innovative collaborations* among academia, industry, and public health institutions to share knowledge and resources and advance STI vaccine science
  - Encourage exchange of ideas among institutions in low-, middle- and high-income countries
  - Forge strategic public-private partnerships to maximize efficient use of resources and collaboration toward vaccine development
- *"De-risk" STI vaccine development for industry*
  - Generate improved data on STI burden of infection and disease, natural history, and associated costs to clarify the public health need and make a better investment case for STI vaccines
  - Conduct modeling to characterize the potential public health impact of STI vaccines
  - Work with public health agencies and regulators to determine preferred product characteristics, efficacy endpoints, and other factors to increase industry confidence in future vaccine approval
  - Conduct studies on acceptability of STI vaccines to predict future demand
- *Encourage more investment in STI vaccines*
  - Use innovative partnerships to maximize advocacy efforts
  - Explore the role of important donors and strategize how to incentivize STI vaccine research

4. Conclusions

With more than a million people acquiring a new STI every day [3,8], innovative new measures are needed to prevent STIs and their often devastating reproductive health consequences. Increasing calls to action to promote global sexual and reproductive health, including STI prevention [33,34], have dovetailed with global efforts to extend the life-saving benefits of vaccination to all people, through the Decade of Vaccines (2011–2020) [35,36] and the Global Vaccine Action Plan [1]. Making progress toward new STI vaccines will be crucial in advancing these two global health efforts.

Meeting participants at the 2013 STI Vaccine Technical Consultation outlined a roadmap for accelerating development and introduction of new STI vaccines. This roadmap establishes clear priorities and points of action for catalyzing progress toward these important public health needs, and the articles published in this special issue of *Vaccine* provide further details for critical action steps for each individual STI vaccine [5,10,17,21,30]. Epidemiologists, basic scientists, clinical researchers, policy-makers, and other stakeholders in civil society, governments, public health organizations, academia, and industry will all have a role to play in carrying out these important next steps: laying the epidemiologic and scientific groundwork for STI vaccine development, promoting future clinical development and evaluation, and advocating for renewed interest and investment in STI vaccines.

Innovative, strategic public-private and other product development partnerships should be sought for STI vaccines, as has been done successfully for development of vaccines against other neglected diseases, such as *N. meningitidis* serogroup A [37,38]. Alliances across multiple disciplines will be critical for pushing STI vaccines forward. Participants at the 2013 STI Vaccine Technical Consultation stressed the importance of identifying STI vaccine development as a fundamental measure for STI control and working in a coordinated fashion to accomplish the next steps in the roadmap. While many gaps and barriers remain, there are considerable opportunities to advance STI vaccine development and address the profound impact of STIs on global sexual and reproductive health.

Declarations of interest

N.B., U.F., C.D., S.L.G. and H.R. report no conflict of interest.
Of the 34 experts who participated in this work, 14 declared an interest related to the development of new technology to control infectious diseases. Although not all of these interests are specifically related to STI vaccines, they are nonetheless all disclosed and summarized below.
R. BRUNHAM: His employer, the University of British Columbia, has filed a patent application on chlamydia proteins discovered during government funded research, and received research grants in the amount of US$250,000 for chlamydia vaccine development work from Prevent, a non-profit vaccine development enterprise funded by the government of Canada.

C. CAMERON: Her employer, the University of Victoria, is in the initial stages of filing a patent covering a recombinant *T. pallidum* protein that shows promise as a syphilis vaccine candidate, and received grants (in the total amount of US$1,500,000) from the US government and Canadian government to support Dr Cameron's work to develop a syphilis vaccine.

J. CARLTON: is performing ongoing consultancies for BioHelix Inc. and Atlas Genetic Inc. related to the development of a diagnostic test for *T. vaginalis*, bioinformatics work, genome mining and provision of *T. vaginalis* strains and isolates for testing. Over the last four years, the total income received for these consultancies is approximately US$30,000.

G. GARNETT: prior to 2011 received funding from GSK for his work in HPV epidemiology, with no payment in the last 4 years.

P. GRAVITT: Her employer (JHSPH) has received: (1) one grant from Merck & Co. (in the amount of US$100,472 between 2012 and 2013) for HPV-related epidemiological work; (2) a grant from Roche Molecular Systems (in the amount of US$500,000 between 2005 and 2010). PG has received a grant from Qiagen as a member of the Women's Health Advisory Board (<US$10,000 per annum between 2008 and 2012).

A. HOFSTETTER: Her employer has received a grant from Merck & Co. (in the amount of US$130,000) for an investigator-initiated retrospective cohort study examining HPV vaccination and cervical cytology abnormalities among adolescent and young adult females in a low income underserved community.

A. JERSE: is employed by the US Uniformed Services University. The Henry M. Jackson Foundation and the US Uniformed Services University have filed a patent application for potential gonorrhea vaccine antigens being developed by Dr Jerse.

Ch. JOHNSTON: Her employer, the University of Washington, has received funding and salary support in the amount of US$6,750 from the company AiCuris GmbH for Dr Johnston to be a principal investigator of a trial on a new compound to treat HSV-2. Dr Johnston is also a co-investigator on studies of HSV vaccines funded by Agenus Inc and Genocea Biosciences.

N. LOW: Her employer, the University of Bern, received a consultancy fee in the amount of US$5,000 from GSK for her work as chair of a scientific advisory board on chlamydia vaccines in 2010.

S. ROSENTHAL: She has performed consultancy work for Merck & Co. in the field of behavioral medicine in Pediatrics and Psychiatry (for which she has received approximately US$1,000). In addition, her employer, the Trustees of Columbia University in the City of New York, has received a grant in the amount of US$130,000 from Merck & Co. for the work of Dr Karen Soren's research unit in the field of human papilloma virus vaccination and cervical cytology for which Dr Rosenthal has served as unpaid consultant.

M. RUSSELL: His employer, the University at Buffalo, has filed a nonprovisional patent application for genital tract infection therapies developed by Dr Russell (in which he holds a 45% interest. The University at Buffalo has furthermore received grants (in the total amount of US$475,000) for his STI-related research work from the US Government and the John Oishei Foundation.

L. STANBERRY: He has performed consultancies in the field of vaccines for different companies and received the following: GSK (US$10,400), Sanofi Pasteur (US$2,500), Agenus (US$2,500) and Medimmune (US$2,500)

P. TIMMS: His employer, the Queensland University of Technology, has received research grants (in the total amount of US$710,000) from the Australian and Queensland Governments for his work on the development of a chlamydia vaccine.

D. VANROMPAY: Her employer, the University of Ghent, Belgium, has received funding support (in the amount of 40,000 €) from Nobilon for her work on Chlamydia vaccine research.

The roadmap was peer reviewed by the following experts prior to publication:

1- Michael J. Brennan, Ph.D. Senior Advisor,
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None of these reviewers declared an interest in the subject matter. Reviewers agreed that contributors to this manuscript are experts in particular STI diseases and have been called together by the WHO to provide a thoughtful strategy for "the way forward" for development of safe and effective STI vaccines. This is a fine example of what WHO does best, that is, convening a group of experts to provide a blueprint for solving global health problems. There is no indication in the recommendations that any particular STI has been selected for emphasis or that any "expert" in this group has unduly influenced the recommendations. It is also clear from the summary that the implementation of the recommendations for STI vaccines will only occur if there is a successful partnership between researchers, clinicians, manufacturers, government officials and community advocates.

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