Sexually Transmitted Infection Vaccines: Opportunities for Development, Research, and Implementation

Symposium Report
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Key Messages

- Increasing STI rates globally are contributing to an increased burden on healthcare systems, and over one million individuals are infected everyday with an STI.
- Antimicrobial resistance in gonorrhea strains pose a significant risk to the treatment and control of this infection.
- Scientists should continue to gather and publish the data on the burden of STIs to inform policy, funding, and strategic initiatives.
- Continued engagement with all stakeholders globally will allow for a unified, well-informed approach to STI vaccination programs once vaccines are available.
## Abbreviations Used

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AMR</td>
<td>Antimicrobial resistance</td>
</tr>
<tr>
<td>BCCDC</td>
<td>BC Centre for Disease Control</td>
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<tr>
<td>CIHR</td>
<td>Canadian Institutes of Health Research</td>
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<tr>
<td>GSK</td>
<td>GlaxoSmithKline Inc.</td>
</tr>
<tr>
<td>HIC</td>
<td>High income country</td>
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<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>HPV</td>
<td>Human papillomavirus</td>
</tr>
<tr>
<td>HSV</td>
<td>Herpes simplex virus</td>
</tr>
<tr>
<td>LMIC</td>
<td>Low-middle income country</td>
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<tr>
<td>MOMPs</td>
<td>Major outer membrane proteins</td>
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<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases</td>
</tr>
<tr>
<td>PID</td>
<td>Pelvic inflammatory disease</td>
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<tr>
<td>PPC</td>
<td>Preferred product characteristics</td>
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<tr>
<td>STI</td>
<td>Sexually transmitted infection</td>
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<tr>
<td>STRIVEBC</td>
<td>Sexually transmitted infections vaccine consortium</td>
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<tr>
<td>T_{RM}</td>
<td>Tissue response memory (cells)</td>
</tr>
<tr>
<td>UBC</td>
<td>University of British Columbia</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Introduction

Sexually Transmitted Infection Vaccines: Opportunities for Research, Development, and Implementation was a pre-conference symposium held at the STI & HIV 2019 World Congress July 2019 in Vancouver, Canada, on the traditional territory of the Musqueam, Squamish, Tsleil-Waututh, Stó:lō, and Stz’uminus nations. This event was organized by STRIVEBC (Sexually Transmitted Infection Vaccine Consortium) – a group of leading public health researchers, scientists and clinicians embedded in sexually transmitted infection (STI) practice, research, and policy in the province of British Columbia, Canada. Current membership includes researchers from the University of British Columbia, University of Victoria, the Vaccine Evaluation Center at the BC Children’s Hospital Research Institute, and the BC Centre for Disease Control. The group aims to create and catalyze priorities related to STI vaccine funding, research, and development, while anticipating these conversations will reach and engage global audiences and engage a broader network of people.

The catalyst for this symposium was the World Health Organization (WHO) STI Vaccine Roadmap (1), which outlines steps to advocate and prepare for STI vaccines. This need for this symposium was further reaffirmed by the urgent need to address increasing rates of STIs globally, coupled with the threat of antimicrobial resistant (AMR) strains of Neisseria gonorrhoeae. Its relevance was also confirmed by the alarming rise of STIs over the past decade consistently across nations and continents (2, 3). STIs include bacterial infections, such as chlamydia, gonorrhea, and syphilis (caused by Chlamydia trachomatis, N. gonorrhoeae, and Treponema pallidum, respectively); viral infections from the human papillomavirus (HPV), herpes simplex virus (HSV), and human immunodeficiency virus (HIV); and protozoan infections like trichomoniasis caused by the Trichomonas vaginalis parasite. Untreated or undetected STIs can lead to pelvic inflammatory disease (PID), infertility, and can have devastating neonatal outcomes, including death (3, 4).

The goals of this unique session were to create and enhance connections with key stakeholders in the global research community; to catalyze the ground-breaking work that is currently being
planned and performed; and to gain insights regarding priorities and to discuss funding. Specifically, this symposium’s presentations and discussions focused on chlamydia, gonorrhea, syphilis, and HSV infections. The four-hour session featured 14 notable presenters and panelists from a variety of institutions in Canada, the United States, and abroad from both public and private sectors. There were 86 registered attendees (including trainees) from around the globe in a variety of roles related to STI service provision and research.

**Setting the Stage**

To start the afternoon, STRIVEBC member Dr. Troy Grennan of the BC Centre for Disease Control (BCCDC) and the University of British Columbia (UBC) welcomed the day’s distinguished guests and attendees. Dr. Grennan highlighted the importance of this topic, as STIs are increasing globally at an estimated rate of one million new infections per day – an issue not contained to any particular region (2).

Dr. Carolyn Deal of the National Institute for Allergy and Infectious Diseases ([NIAID] United States of America [USA]) contextualized the presentations to come with an overview of the current landscape of STI vaccines, including a background into the vaccine development process and the work that has been conducted to date. She highlighted that increasing rates of STIs are a global problem, and provided specific updates on STI infection rates in the USA (5). Even though infection rates are high around the world, a disparity exists between infection rates and access to treatment options in high-income countries (HICs) and low-middle income countries (LMICs). Dr. Deal took the audience through the vaccine development process, where the steps necessary to move from basic science through to implementation of a vaccination program can take ten to 15 years, and upwards of one billion dollars (6). Dr. Deal emphasized that preventing STIs does more than just prevent the infections on an individual level; on a broader scale, prevention decreases burdens related to health care costs, morbidity, infertility, health of youth overall, and improved health of neonates on a population level.
Following, Dr. Sami Gottlieb of the WHO provided a breakdown of the nine areas in the WHO STI Vaccine Roadmap (1), highlighting the need for more data to quantify the burden of disease STIs pose for all settings to inform continued research, and to help bridge the translation and implementation gaps in vaccine development (7, 8). Dr. Gottlieb also introduced key considerations for WHO preferred product characteristics (PPCs) that will inform and focus the STI vaccine development process. These PPCs were created to provide early guidance to scientists so that the vaccines that progress to the implementation stage and clinical trials are suitable for LMICs from the beginning. This will help bridge the implementation gap for vaccines from high income settings to low incomes settings. As an example, PPCs for an HSV vaccine were published earlier this year (9). Discussions surrounding PPCs for a gonococcal vaccine have also occurred but these PPCs have not yet been released.

Dr. Simon Dobson of Sidra Medicine, Qatar presented some key insights about ‘Lessons Learned from the HPV vaccine’, the most recently introduced STI vaccine. He highlighted statistics that showed a lack of trust in science and government, and that income status of a country is not necessarily a key predictor of vaccine acceptance (10). He implored the group to share their stories – to have meaningful conversations and anecdotes when discussing vaccination – particularly for those who are in a care-providing role. Exploring why some people may or may not be more inclined to vaccinate, Dr. Dobson presented results from a parental attitudes study that explored factors of parental intent to vaccinate their child (girls) with the HPV vaccine in the 2008-2009 school year (11). From these data, a parent’s main reason to provide the HPV vaccine to their daughter was to prevent HPV infection and cervical cancer, and that the main barrier was concern about the safety of the vaccine (11). As these results are from a decade ago, re-evaluating parental perceptions in the present day could generate new results. Dr. Dobson noted that, as confirmed by several years of post-market studies, evaluations of millions of doses of HPV vaccines administered have confirmed they are safe and effective at reducing the risk of acquiring HPV, and therefore, preventing cervical cancer (12). He also highlighted the need for appropriate risk communication, and the threats of sensationalized media.
Vaccine Development Updates

Syphilis

Dr. Caroline Cameron from the University of Victoria presented ground-breaking work occurring at three laboratories as they strive to develop a vaccine for syphilis, targeting the *T. pallidum* bacterium. Dr. Cameron’s lab has been focusing on the adhesion binding process initiated by *T. pallidum* on the endothelial cells in the host (the infected person). These Tp0751 adhesions separate endothelial cells, which allow the bacteria to move through the layers of these cells and into the bloodstream following a mucosal infection (13). When immunized with a component that prevents this process, the bacteria is unable to separate the endothelial cells, and therefore, cannot move in to the bloodstream, preventing systemic infections (14).

Next, Dr. Cameron discussed work being completed at the University of Washington led by Dr. Sheila Lukeheart and Dr. Lorenzo Giancani. This group is focusing on repeat protein families in the *T. pallidum* genome that code for exposed protein loops on the cell’s surface. Targeting these conserved proteins for a syphilis vaccine means that a potential candidate could be useful in protecting against different strains of *T. pallidum* (15-17). A vaccine cocktail approach combining the techniques of this lab and Dr. Cameron’s lab is currently being tested.

Finally, Dr. Cameron presented work from the University of Connecticut by Dr. Kelly Hawley and colleagues. This group is looking at the outer membrane beta-barrel proteins of *T. pallidum*, and the binding process of antibodies to these proteins as an option to enhance the immune response that is already mounted by a host (18, 19). Looking forward, the goal for this field is to develop a syphilis vaccine within the next five years with the NIAID U19 Collaborative Opportunity.
**Gonorrhea**

Dr. Rino Rappuoli from GlaxoSmithKline Vaccines Inc. (GSK) presented updates related to *N. gonorrhoeae* vaccine development, and more specifically, how the meningoococcal B vaccine (Bexsero, GSK) could be providing protection against gonorrheal infections in vaccinated populations. For example, in New Zealand and one Quebec county, groups that received the meningitis B vaccine saw a decreased incidence of gonorrhea infections (20-22). This is believed to be because the meningococcal B and *N. gonorrhoeae* bacterium are phylogenetically related, and therefore, some of the proteins and regions are conserved between these two organisms. This means that vaccination for meningococcal B may also be providing protective benefits against some infections of *N. gonorrhoeae* because the vaccine is targeting the related areas (23, 24).

Dr. Rappuoli also discussed the benefits that reverse vaccinology can have to identify appropriate vaccine candidates and take them through the vaccine development time line (25). This process incorporates machine learning and information-based design to determine a vaccine candidate from the pathogen’s genome, and working backwards to identify a targetable area for a scientist to focus on (25).

**Chlamydia**

For the third pathogen specific update, Dr. Kevin Hybiske from the University of Washington provided an overview of chlamydia vaccine development. He highlighted that great progress has been made in this field, and that the outlook for further development of a *C. trachomatis* vaccine looked promising (26). He added that a phase 1 clinical trial of a chlamydia vaccine candidate was recently completed at the Statens Serum Institut in Denmark and Imperial College London, and that phase 2 trials could be starting this year. The results for this phase 1 trial were recently published (27).

Related to the composition of the vaccine, the current body of research indicates that whole cell vaccine candidates (28-31) or those targeting major outer membrane proteins (MOMPs) of the
bacterium will be the likely components of a successful vaccine. The immune response elicited will need to boost the responses of two types of white blood cells - CD4 and tissue resident memory (T_{RM}) cells. Additionally, Dr. Hybiske emphasized that there were still questions that needed answering related to further vaccine development, such as key target populations for vaccination, who would be used in human challenge trials, and what adjuvants would be used in the vaccine.

**Herpes Simplex Virus**

Dr. Anna Wald, also from the University of Washington, closed this section with developments in the search for an HSV vaccine. As an important note, when considering the course of infections and pathogenicity, Dr. Wald illustrated that HSV-1 infections are contributing to a large proportion of genital herpes cases, despite the amount of attention on HSV-2 (32).

Compared to the aforementioned bacterial infections, HSV infections are chronic, and cannot be cured once acquired. However, HSV can be clinically managed. When someone has HSV, viral shedding can lead to transmission of the virus between partners. Viral shedding can occur regardless of the presence of symptomatic lesions, and serves as a good clinical marker for how well a potential vaccine candidate could be performing (33). For HSV, there is an added element in considering a therapeutic and / or a prophylactic vaccine. A recipient of a prophylactic vaccine would be protected from acquiring a new infection from a partner, whereas, the recipient of a therapeutic vaccine would ideally reduce or eliminate their risk of transmitting the virus to someone else, reduce viral shedding, and reduce the recurrence of infections. This has been demonstrated in a GEN-003 clinical trial from Genocea Sciences (34, 35); however, at this time, continued studies have been suspended due to a lack of investment.
Priority Setting for Future Science and Research

This panel, chaired by Dr. Scott LaMontagne of PATH, started off by provocatively posing the question: “Which STI vaccine should be prioritized?” and through the discussion that followed, a vaccine to prevent gonorrhea infections emerged as the priority due to the AMR of the pathogen and the consequences this has on limiting treatment options. Dr. Carolyn Deal emphasized that you could look at this issue through different lenses – a concept echoed by Dr. Peter Dull of the Bill & Melinda Gates Foundation. One is a public health lens, which is dynamic and changing based on emerging events, such as the AMR of *N. gonorrhoea*. The other could be a feasibility lens, based on where the vaccine science is currently, and amount of public interest. Dr. Dull added that being able to proceed in vaccine development can include the ability (or lack thereof) to identify and secure an appropriate adjuvant for a vaccine, because they are proprietary intellectual property of the companies that have developed them.

It was then propositioned if, as a field, research should be focused on continued advancement in STI vaccines which already have a large body of work, or if the focus should be on “catching up” vaccines for STIs that are not as far along in the development process. Dr. Carolyn Deal and Dr. Charu Kaushic of the Canadian Institutes for Health Research (CIHR) reflected on the differences in funding types for basic scientific enquiry as related to vaccine development, and strategic funding. Dr. Deal noted that it is just as important to discover what kind of science does not work for vaccine development, as it is to identify the options that are viable moving forward. Dr. Kaushic, speaking from a CIHR perspective, indicated that approximately 75% of the funding between these two streams would go to open, basic science, and 25% to strategic investment projects. Dr. Deal described that the per dollar value in early discovery science research is also much higher than it is in a clinical trial, which is another reason why funding for more preliminary work is attractive. It is also easier to take risks earlier along the vaccine development pathway, rather than getting too deep to discover a candidate does not work well or work well in humans.
To navigate some of these areas when seeking funding opportunities, Dr. Cameron highlighted the value of PPCs, mentioning that having these guidelines while research of a vaccine candidate is still ongoing is helpful in steering a successful project. She recalled that they have transformed the way she does her research in order to improve the chances that an end product will be beneficial in the target populations and in multiple settings.

**Implementation Challenges in Public Health**

In this second panel, also moderated by Dr. LaMontagne, the discussion continued to focus on factors that could affect the implementation of STI vaccine programs once the vaccines have passed through the necessary clinical and regulatory steps.

An important area to consider in this conversation included: *Why should people want to receive an STI vaccine?* As Dr. Manish Sadarangani (Vaccine Evaluation Center) discussed, there is no way around the fact that these vaccines are for STIs and their sequelae. This contrasts with the HPV vaccine, where cervical cancer prevention messages were a critical component in the communication about this vaccine. However, he asserted that there are many other angles that these discussions could take to exemplify the overall burden of STIs not only in individuals, but within populations as a whole. These considerations could include the health economic benefits, preventing infertility, and preventing poor neonatal outcomes.

Speaking from a global health lens, Dr. Sami Gottlieb and Dr. Peter Dull highlighted some issues LMICs face, as well as strategies to adopt now to help bridge this implementation gap. Dr. Gottlieb impressed that sharing data about the burden of these infections – whether epidemiological, cost, or healthcare related – will benefit the field as a whole, as it works to quantify these infections globally. Having this information available can be used to convince investors and pharmaceutical companies to continue pushing forward with STI vaccine science and development.
Dr. Gottlieb also impressed that one size does not fit all - countries have varied needs and will react differently to the addition of another vaccine into their national program. Therefore, it is critical to have conversations early, and assess what a given country would like a vaccine to achieve so that those desires can be built into a developing product, rather than retroactively forcing a program to fit into the established system.

Transitioning into discussions with government, Dr. Bonnie Henry (Provincial Health Officer of British Columbia) illustrated the example of when the HPV vaccine was implemented in Canada, and how the rapid implementation timeline from the federal level surprised the provincial governments¹, and in turn, the public health system. The rapid implementation of the HPV vaccine program created some doubts and mistrust within the public, as this seen as an industry driven program, rather than as a public health good. Alluding to Dr. Dobson’s presentation at the beginning of the day, uptake of the HPV vaccine is still low across the country. Because provincial governments in Canada have jurisdiction over health care, the vaccination programs also differ across provinces. Dr. Henry emphasized that it is important that forums like these are occurring now, early in vaccine development, so that all stakeholders are on the same page as the science and program planning progresses for other STI vaccines.

All agreed that starting this conversation now will benefit the entire field working towards STI vaccine development and implementation. Early discussions and planning will prepare all stakeholders, including government, public health officials, and others imperative to the policy making process in both HIC and LMIC settings. A key message suggested by Dr. Gottlieb and Dr. Henry when implementing an STI vaccine program could include that an STI vaccine (and STI prevention more broadly) is an important part of sexual and reproductive health for all. Panelists also warned about focusing solely on adolescent girls as the population eligible for vaccinations in the future, where adolescent boys are brought into the program at a later date. This tiered system of roll-out may confuse some groups about the importance of an STI vaccine and could create mistrust in the motives behind the program.

¹ The provincial governments in Canada are responsible for the provision of health care services in Canada but do receive funding from the federal government to allocate within their budgets.
Dr. Dull’s parting advice was to also be opportunistic – to capitalize on current events and subsequent interest and funding to move research along. This is another reason why it is important to have the quantifiable data about the burden of these infections readily available.

Conclusions

Dr. Gina Ogilvie and Dr. Manish Sadarangani closed the workshop with various reflections of the afternoon, concluding that the robust discussions indicated a call to action - that the people in the room possessed both the desire and the talent to work together as a community and catalyze the move towards elimination of STIs.

As a consortium, STRIVEBC hopes that these forums continue to occur, and that sharing the discussions allowed for a continuous conversation with scientists and stakeholders around the globe embedded in different aspects of STI vaccine research, policy, and health care delivery. This topic is complex but combining multiple perspectives in one room gives the disciple an advantage, as research in this multifaceted and interdisciplinary field continues.

Symposium attendees were fortunate to hear from key representatives in this industry who will champion progress in this field. As a community of practicing professionals engaged in different aspects of the STI vaccine development and implementation pathway, this network should continue to highlight the important work being accomplished by their peers. STRIVEBC urges clinicians, researchers, and policy makers to continue telling their stories, sharing their data, and make the case as to why STI vaccines are a valuable public health tool to improve the lives of populations globally. You can keep up to date on STRIVEBCs research and activities by visiting www.strivebc.org.
Acknowledgements

STRIVEBC would like to thank all the speakers and panelists for their invaluable contributions to this session, the organizing committee for the STI & HIV 2019 World Congress for the meeting time and venue, and to CIHR for a Meeting Dissemination Grant which helped make the session possible. Finally, thanks to all the attendees for their attention, engagement, and participation.

Disclaimer

The views and opinions expressed in this report are those of the authors and do not necessarily represent the viewpoints of any other institutions, affiliations, or employers.
References


# Appendix A - Reported Conflicts of Interest

<table>
<thead>
<tr>
<th>Speaker</th>
<th>Affiliations</th>
<th>COI</th>
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<tbody>
<tr>
<td>Caroline Cameron</td>
<td>University of Victoria</td>
<td>None to report.</td>
</tr>
<tr>
<td>Carolyn Deal</td>
<td>National Institute of Allergy and Infectious Diseases</td>
<td>None to report.</td>
</tr>
<tr>
<td>Simon Dobson</td>
<td>Sidra Medicine</td>
<td>SD has carried out vaccine trials for Merck, GSK, Novartis, Sanofi Pasteur, and Dynavax. He has been on Advisory Boards for GSK and Merck. He has been on the Canadian National Advisory Committee on Immunization.</td>
</tr>
<tr>
<td>Peter Dull</td>
<td>Bill &amp; Melinda Gates Foundation</td>
<td>None to report.</td>
</tr>
<tr>
<td>Sami Gottlieb</td>
<td>World Health Organization</td>
<td>None to report.</td>
</tr>
<tr>
<td>Troy Grennan</td>
<td>University of British Columbia BC Centre for Disease Control</td>
<td>TG is a site investigator for studies funded by Gilead and Merck.</td>
</tr>
<tr>
<td>Bonnie Henry</td>
<td>Government of British Columbia</td>
<td>None to report.</td>
</tr>
<tr>
<td>Kevin Hybiske</td>
<td>University of Washington</td>
<td>None to report.</td>
</tr>
<tr>
<td>Charu Kaushic</td>
<td>Canadian Institutes of Health Research McMaster University</td>
<td>None to report.</td>
</tr>
<tr>
<td>D. Scott LaMontagne</td>
<td>PATH</td>
<td>None to report.</td>
</tr>
<tr>
<td>Gina Ogilvie</td>
<td>University of British Columbia BC Centre for Disease Control Women’s Health Research Institute</td>
<td>GO has not has not received industry grants, funds or honoraria. However, co-investigators have received contract funding paid to their institution, to compare the accuracy of different manufacturer's HPV assays as adjunct studies to the main HPV FOCAL trial.</td>
</tr>
<tr>
<td>Rino Rappuoli</td>
<td>GlaxoSmithKline Inc.</td>
<td>RR is a full-time employee of the GSK group of companies.</td>
</tr>
<tr>
<td>Manish Sadarangani</td>
<td>University of British Columbia Vaccine Evaluation Center</td>
<td>MS has been an investigator on studies funded by Pfizer, Merck, VBI Vaccines and GlaxoSmithKline. All funds have been paid to his institute, and he</td>
</tr>
<tr>
<td>Anna Wald</td>
<td>University of Washington</td>
<td>has not received any personal payments.</td>
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