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Priorities for sexually transmitted infection vaccine research and development: Results from a survey of global leaders and representatives

Kara M. Plotnikoff [a,b], Robine Donken [a,b,c], Laurie Smith [b,d], Caroline Cameron [e,f], D. Scott LaMontagne [g,h], Julie A. Bettinger [b,c], Manish Sadarangani [c,i], Troy Grennan [j,k], C. Sarai Racey [a,b], Kevin Hybiske [f,h], Monika Naus [a,k], Amanda Monteiro [b,l], Gina S. Ogilvie [a,b,k,*]

[a] School of Population and Public Health, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada
[b] Women's Health Research Institute, British Columbia Women's Hospital and Health Centre, Vancouver, BC, Canada
[c] Vaccine Evaluation Center, BC Children's Hospital Research Institute, Vancouver, BC, Canada
[d] Cancer Control Research, BC Cancer, Vancouver, BC, Canada
[e] Department of Biochemistry and Microbiology, University of Victoria, Victoria, BC, Canada
[f] Division of Allergy and Infectious Diseases, Department of Medicine, University of Washington, Seattle, WA, USA
[g] PATH, Center for Vaccine Innovation & Access, Seattle, WA, USA
[h] Department of Global Health, University of Washington, Seattle, WA, USA
[i] Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada
[j] Division of Infectious Diseases, University of British Columbia, Vancouver, BC, Canada
[k] British Columbia Centre for Disease Control, Vancouver, BC, Canada
[l] Faculty of Health Sciences, Simon Fraser University, Burnaby, BC, Canada

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ABSTRACT

Objective: To determine the sexually transmitted infection (STI) vaccine research priorities of global leaders in STI vaccine research, development, and service provision.
Methods: Global representatives attending the *STI Vaccines: Opportunities for Research, Development, and Implementation* symposium preceding the STI & HIV World Congress in 2019 were invited to complete an electronic survey. We asked participants to rank items by importance/priority for STI vaccine development for the following areas of focus: specific STIs (gonorrhea, chlamydia, syphilis, herpes, and trichomoniasis), broad research domains (basic science, funding, communication, program planning, and vaccine hesitancy), and specific research activities related to these domains. We calculated weighted value scores based on the ranking (e.g., first, second, third) and the total number of responses in order to produce a ranked list of the priorities.
Results: A total of 46 out of 97 (44%) symposium attendees responded to the survey. Gonorrhea was identified as the STI that should be prioritized for vaccine development, followed by syphilis with weighted value scores of 3.82 and 3.37, respectively, out of a maximum of five. Basic science (and vaccine development) was the domain ranked with the highest priority with a weighted value score of 4.78 out of six. Research activities related to basic science and vaccine development (including pre-clinical and clinical trials, and surveillance measures) and increased funding opportunities were the most highly ranked activities in the "STI vaccine development" and "research domains and activities" categories.
Conclusion: Global leaders in attendance at the *STI Vaccines* symposium prioritized continued scientific work in vaccine development and program planning. Gonorrhea was identified as the highest priority infection, followed by syphilis.

* Corresponding author at: Women's Health Research Institute, British Columbia Women's Hospital and Health Centre, 4500 Oak Street, Vancouver, BC V6H 3N1, Canada.
E-mail address: gina.ogilvie@bccdc.ca (G.S. Ogilvie).

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1. Introduction

Sexually transmitted infections (STIs) are prevalent across the globe and contribute to a significant burden of disease for individuals and health care systems, with an estimated one million new STIs acquired globally every day [1,2]. There is also a disproportionate burden in low- and middle-income countries (LMICs) because of limited funding for STI testing, treatment, and surveillance. In turn, this increases the risk of long-term morbidity and complications associated with STIs, which can also exacerbate risk and transmission of human immunodeficiency virus (HIV) [3]. Global cost estimates for STI screening and treatment were previously forecasted to be $4 billion dollars by 2021 (including bacterial STIs and human papillomavirus [HPV], but not HIV). [4] Canadian costs for screening, treatment, and sequalae of chlamydia and gonorrhea infections has been modeled to cost over $178 million (in 2000s CAD; not adjusted for inflation) [5].

Bacterial STIs can lead to varied downstream health consequences, some of which are severe. If left untreated, chlamydia and gonorrhea infections can lead to complications including pelvic inflammatory disease and infertility [3,6,7]. Syphilis infections can affect any organ or tissue, including the nervous system [6]. In addition, congenital syphilis can have long-term health consequences for a newborn, with possible outcomes including low birth weight, neurological complications, and fetal demise [2,8]. If appropriately screened for, detected, and treated, bacterial STIs have traditionally been manageable and curable; however, due to the significant threat of antimicrobial resistance (AMR), particularly in gonorrhea, treatment options are becoming limited [9–11] and new prevention methods are urgently needed. Primary prevention methods like vaccines are also argued to be cost-effective when considering health care costs of repeat or undetected infections [12,13].

Currently, prophylactic vaccines are available against two viral STIs: hepatitis B virus and specific serotypes of HPV. Phase 2 trials for herpes simplex virus (HSV) candidates have been completed but none have been approved for use to date [14,15]. For bacterial STIs, vaccines are in various stages of development. A chlamydia vaccine candidate has completed phase 1 trials [16], which is the bacterial STI vaccine with the most progress thus far. Research involving syphilis vaccine candidates is ongoing, with several pathogen-specific, protein-based subunit vaccine candidates identified and being investigated in pre-clinical studies [17–20]. The meningococcal B vaccine, 4C-MenB is also being investigated for its possible cross-protection for gonorrhea, due to the close relationship between the causative organisms [21–23]. Systematically gathering the perspectives of leaders in STIs and vaccine development to summarize and establish priorities for future research and STI vaccine program implementation and planning can help guide resource allocation and prioritize STI pathogen-specific research.

The need for STI vaccines as a preventive tool in STI management, and to address AMR, catalyzed the assembly of the *Sexually Transmitted Infection Vaccines: Opportunities for Research, Development, and Implementation* symposium preceding the STI & HIV World Congress in Vancouver, Canada, in July 2019. Organized by the Sexually Transmitted Infection Consortium of British Columbia (STRIVEBC), the goal of the symposium was to gather global thought leaders and experts in public health, service delivery, and STI vaccine science to share research updates and open a dialogue about the current landscape and direction of STI vaccine research and development. A full report of the symposium presentations and discussions is available online [24]. The STI vaccine roadmap [25] was a key influence in organizing the symposium and developing the contents of this survey. The objective of this study was to gather key insights from global leaders into STI vaccine research and development priorities that could be beneficial in reducing the global burden of STIs and their sequelae.

2. Methods

2.1. Setting & population

The *STI Vaccines* symposium was held July 14, 2019, in Vancouver, Canada as a pre-conference event prior to the STI & HIV World Congress [26], a joint conference meeting of the International Society for Sexually Transmitted Diseases Research (ISSTDR) and the International Union against Sexually Transmitted Infections (IUSTI). Symposium attendees included international delegates from multidisciplinary roles related to STI and HIV prevention, clinical service provision, vaccinology, and research. Registration for the symposium was open to all registered delegates of the conference.

All registered attendees of the symposium were eligible to participate in the survey and were emailed a link to the survey prior to the symposium. The first page of the survey detailed informed consent, where participants were informed that by completing the survey, they were consenting for their responses to be used in data analysis. This study was approved by the University of British Columbia Research Ethics Board (H19-0141).

2.2. Survey distribution & data collection

All study data were collected and managed using REDCap electronic data capture tools hosted at the University of British Columbia [27,28]. We received contact information from the conference secretariat for registrants who consented to receive pre-conference communications. The initial survey invitation was sent out via email on July 11, 2019. Reminders were sent to non-responders one and two weeks later. A link to the survey was available during the symposium, shared via handouts and on a projected slide during breaks. Accessing the survey via this link did not require participants to enter any personal information, including email addresses. This link was available for those who did not consent to pre-conference communications or late registrants. This link was also used to send the survey to symposium presenters and STRIVEBC members, with reminders sent two and three weeks after the symposium. The link was used for the presenters and consortium members so that no email addresses were connected to responses from these groups.

2.3. Survey contents

After completing demographic information (age, gender, occupation, region and setting of work), participants ranked specific STIs (gonorrhea, chlamydia, syphilis, herpes, and trichomoniasis), broader domains of research, and specific activities related to each domain. The content of the survey was derived from the content areas in the STI vaccine roadmap developed by the World Health Organization (WHO) [25], and supplemented by input from key researchers in the field who were part of the study team. Participants were then asked to rank the top three specific activities they thought should receive priority in basic science, pre-clinical and clinical development (including activities around vaccine development, dosing, target product profiles, clinical trials, and surveillance and screening), funding (research grants, cost to the public, government subsidies, fundraising), program planning (immunization schedules, treatment protocols, health economics modelling, optimal and efficient vaccine program rollout, determining which governmental sector STI vaccines fall under [STI prevention and control vs. immunization]), communication (information dissemi-

nation, public vs. health care providers, the impact of social media), and vaccine hesitancy (understanding of, the impact of, and strategies to address vaccine hesitancy). Broad domains were ranked in order of importance and all activities within the domains were ranked. For specific activities, the top three items in each category were ranked, so that only the items within each category were rated in comparison to each other, and not across all activities presented. All questions included the opportunity for participants to include comments for additional domains or activities. We asked participants to consider the infections listed and exclude HIV from their considerations in this activity, which aligns with the WHO STI priorities [3]. A copy of the survey is available in Supplementary File 1.

2.4. Data analysis

Identifying information (email addresses, location metadata) was removed before exporting the study data from the REDCap online platform. All data cleaning and analyses were performed in SAS version 9.4 (SAS Institute, Cary NC). Demographic characteristics were analyzed using descriptive statistics. We performed weighted value calculations to generate scores for each ranked survey item. These were grouped into STI infections, broad research domains, and specific research activities. The weighted value calculation is:

$$(x_1w_1 + x_2w_2 + \cdots + x_nw_n)/(\text{total response count})$$

where x is the response count for the survey item (e.g., each infection) and w is the weight for the ranked position (counted in the inverse of the ranked position; e.g., if a participant ranked an infection as their first choice, it was assigned the weighted value of five to give that score the highest value in comparison to the other infections. Their second and third choices would be assigned a weighted value of four and three, respectively). The total response count is the number of responses per line (this is because in the activities section, there were more options than ranks available to be assigned, so that each item has a different total frequency of responses) [29]. The weighted value calculation was used to account for the varied number of responses per research activity, as participants were forced to choose their top three, and therefore, the total count per line (i.e., activity) is not consistent through all activities.

3. Results

We sent 97 survey invitations and received 46 responses for a response rate of 44%. Comparison between respondents and non-respondents is not available, as all survey responses were anonymized, with email addresses and date stamps removed before analyses, and we did not have access to additional demographic data for symposium registrants. Descriptive results of survey respondents are presented in Table 1. Most participants identified as female, and worked as public health professionals, clinicians, or researchers in high income settings (Europe, North America).

3.1. Infection priorities

Gonorrhea ranked highest as the primary infection to be prioritized for STI vaccine research with a weighted value score of 3.82 out of 5.00. Syphilis and herpes followed, with scores of 3.37 and 3.17, respectively (Fig. 1). The proportions of respondents who ranked the infections as their first priority were 37.8% for gonorrhea, 18.6% for syphilis, 19.0% for herpes, 14.0% for chlamydia, and 7.5% for trichomoniasis.

Table 1
Characteristics of survey respondents (n = 46).

Category	n (%)
Occupation	
Public health professionals and clinicians	17 (37.0)
Academic researchers and professionals	15 (32.6)
Trainees, post-docs, or students	8 (17.4)
Government, granting, or non-profit affiliations or funding agencies, government affiliations	4 (8.7)
Pharmaceutical industry leaders and researchers	2 (4.4)
Age	
18–29 years old	7 (15.2)
30–39 years old	15 (32.6)
40–49 years old	9 (19.6)
50–59 years old	9 (19.6)
60 + years old	6 (13.0)
Gender	
Female	34 (73.9)
Male	12 (26.1)
Region of work	
North America, Europe, Australia	35 (76.1)
South America, Middle East, Northern Africa, West/Central Africa, South/East Africa	6 (13.0)
Asia, South Asia, Pacific Islands	5 (10.9)
Income setting of work[a]	
High income settings	23 (50.0)
Upper-middle income settings	5 (10.1)
Lower-middle income settings	11 (23.9)
Low income settings	7 (15.2)

[a] Income setting for work locations are as defined by the World Bank and World Health Organization.

3.2. STI development domains and activities

Out of the five broad categories presented, participants were asked to rank the categories presented in Fig. 2. The categories "basic science and, pre-clinical and clinical development", followed by "funding" were identified as top priorities.

Following the ranking of these research domains, participants ranked the top three individual activities within each domain. The top five overall research activities are presented in Fig. 3. The full table of all ranked activities can be found in the Supplementary File 2. Basic science, pre-clinical and clinical development activities, including trials for vaccine development, were ranked as the highest priority activity, followed by increasing funding opportunities specific to STI vaccine research. Other key activities identified as priorities were to develop interventions that address vaccine hesitancy and to make reports and evidence available to governments to encourage STI vaccine program implementation (Fig. 3).

4. Discussion

Vaccinations against STIs offer real promise on the road to control and ultimately eradicate STIs. Understanding the priorities of scientists and policy makers can help catalyze action, funding, and policy in this dynamic field. The results of this survey, completed by experts in the field of STIs and vaccines, indicate that gonorrhea is the disease that should receive priority for primary prevention via an STI vaccine when compared to other infections. This aligns with messaging from other groups of health researchers and policy makers who advocate for gonococcal vaccine development due to increasing AMR, and repeat infections [11,30]. Despite decades of research, an effective vaccine to prevent gonococcal infections has not yet been developed. This is in part attributed to mutations of the organism and its protein structures, which impacts a vaccines effectiveness when components of the vaccine are developed to target specific protein complexes that then mutate, rendering the vaccine less or ineffective against the patho-

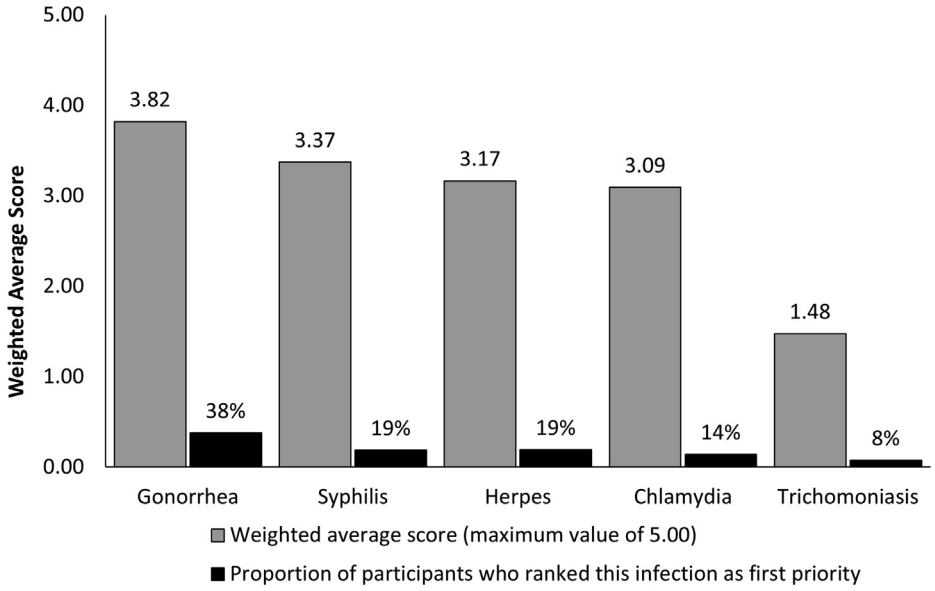

Fig. 1. Weighted value scores of ranked infections compared with the proportion of participants who ranked each infection as their first priority.

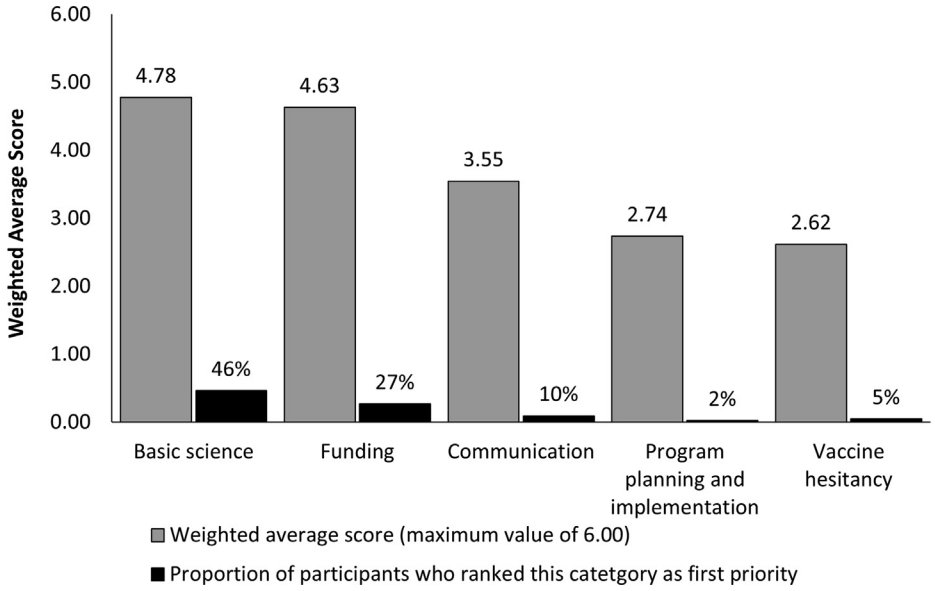

Fig. 2. Weighted value scores for general domains related to STI vaccine research and development compared with the proportion of participants who ranked each domain as their first priority.

gen [31]. This is further complicated by the inability of the human immune system to generate natural immunity to the pathogen, leading to repeat infections of the same strain of bacteria [31]. Mouse models have provided some insights into pathogenicity, but long-term human trials to investigate long term gonorrhea infections are not ethically possible [31]. Current research is looking at the possibility of cross-protection for gonorrhea via the meningococcal B vaccine, 4C-MenB. Two observational studies have reported decreased gonorrhea rates in the general population after campaigns of 4C-MenB vaccine, which was an unexpected outcome of the 4C-MenB vaccination program [21,22]. The potential for cross-protection arises because of the close relationship between *Neisseria gonorrhoeae* (the causative agent of gonorrhea) and *Neisseria meningitidis*, including the presence of some of the 4C-MenB vaccine proteins in *N. gonorrhoeae* [23]. Due to the findings of these observational studies, clinical trials in the United States have begun at the University of North Carolina [32], and National Institutes of Health funding has been announced for a second clinical trial to be conducted by the University of Alabama [33] in order to investigate the efficacy of using the 4C-MenB vaccine as a preventive vaccine for gonorrhea infections.

This survey assessed priorities across five broad research and development domains and activities. The results spanning these different domains demonstrate that concurrent research and planning efforts across several areas of STI vaccine development is necessary to drive STI vaccine development forward. The results of our survey illustrated that several areas of STI vaccine development, including continued pre-clinical and clinical work, increasing funding opportunities, and communication with government will need to be considered synchronously. Although these scores do not vary greatly, and are not necessarily surprising, the results illustrate there is a need across all domains to further advance STI vaccine

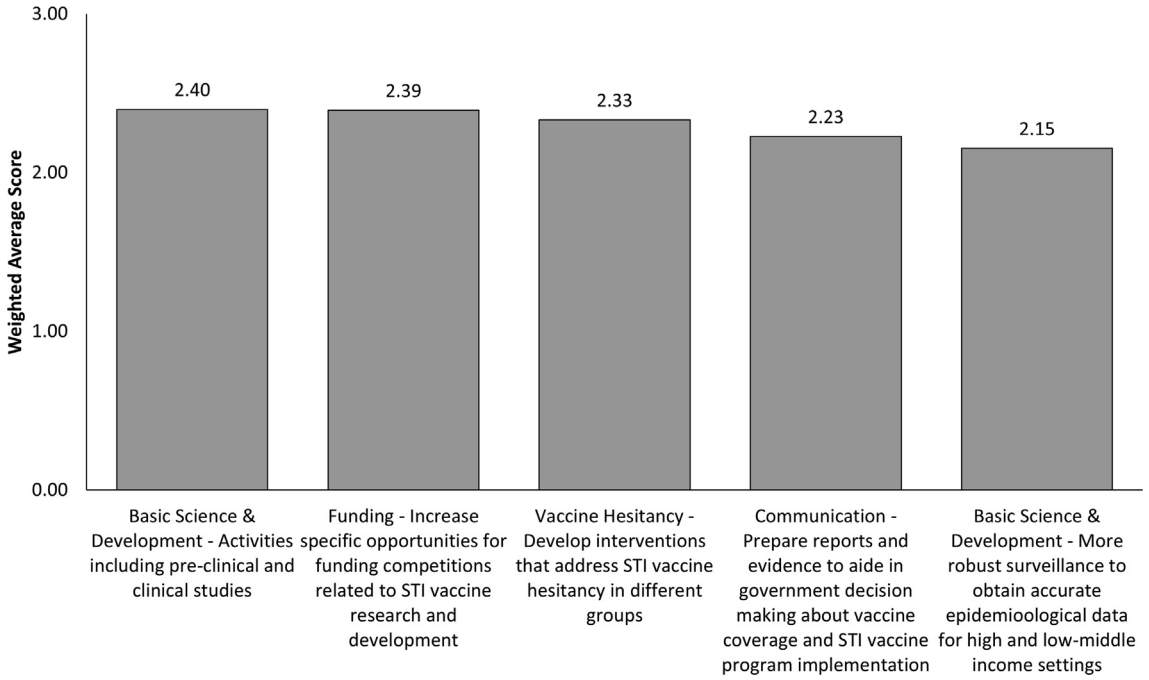

Fig. 3. Weighted value scores of specific STI vaccine research and development activities (top five overall activities).

research for development and implementation. The COVID-19 pandemic has clearly demonstrated that when there is a perceived and wide-reaching need for vaccinations, research and development through clinical trials is catalyzed. An influx of funding fueled clinical trials through their stages, leading to a marketable vaccine within one year of the pandemic's emergence [34].

Respondents identified continued scientific efforts to develop STI vaccines and increasing opportunities for STI vaccine-specific funding as the top two activities (Fig. 2). However, the scores across research domains and more specific activities indicate that there was not one clear area identified by the respondents that should be focused upon as a priority. Instead, our findings indicate these elements of STI vaccine development may need to be concurrently explored. Two pathogens that provide context to the importance of continued dedication in these areas are syphilis and HSV. Currently, there are several syphilis vaccine candidates in the pre-clinical stage of development [17–20]. Continued funding is needed to ensure that vaccine candidates showing promise in pre-clinical studies progress to a phase 1 clinical trial. This is especially vital with so few researchers working on developing a vaccine for this pathogen. For HSV, therapeutic vaccines (for those who have already been infected) have shown promising effects on the reduction of viral shedding, symptoms, and transmission between partners in phase 1 and 2 trials [14,15,35]. WHO preferred product characteristics for both therapeutic and preventive HSV vaccines were released in 2019 [36], but continued funding support is needed to progress the clinical development of these vaccines.

In addition to the support for basic science and increased funding to further research on promising STI vaccine candidates, survey respondents identified the need to understand and address vaccine hesitancy, specifically the development of interventions to address vaccine hesitancy in different populations as the third highest ranked research activity (Fig. 3). Highlighting the urgency of this issue, the WHO named vaccine hesitancy as one of the top threats to global health in 2019 [37]. Understanding what fuels and drives vaccine hesitancy is critical: vaccine hesitancy is a complex issue, and reasons for vaccine hesitancy are heterogeneous within and across populations. Based on experience with hepatitis B and HPV vaccines, there will likely be barriers to other STI vaccine programs, and addressing these will be of critical importance [38]. A message well received with the HPV vaccine was cancer prevention [39]. Future STI vaccines could use messaging that highlights the benefits of STI immunization to overall sexual and reproductive health, as well as fertility, and the decreased need for frequent diagnostic screening and medication to treat repeat infections. It is essential that communication and public engagement occur before vaccine implementation to increase acceptance and uptake. Communication strategies used should also address the spread of misinformation in the media by using engaging and factual scientific communication. Our results demonstrate that experts working in STI vaccine development see the importance of addressing STI vaccine implementation considerations during all stages of the vaccine development timeline.

4.1. Limitations

While these results include the input of international leaders from different organizations, this was a convenience sample of those attending the symposium. There are other researchers contributing to this work globally who were not present. Less than half of invited participants completed the survey, but as we did not have information beyond contact emails for those who did not complete the survey, we are unable to compare the characteristics of the symposium attendees who participated in the survey and those who did not. Additionally, the public link used to collect responses on the day of the symposium does not allow us to compare the demographics of those who were present, but chose not to complete the survey (as the symposium was open to all Congress attendees, regardless if they were previously registered or not). Half of the respondents indicated that they work in high-income settings, so further discussions in LMICs are necessary to ensure that any STI vaccine and associated implementation program developed is done with that region's specific needs and capacity in mind. Unequal attendance at academic conferences has been documented. A recent systematic review by Velin and colleagues

demonstrated that those from LMICs looking to attend global health conferences faced inequities related to cost, visas, and limited speaking opportunities that were less commonly encountered by attendees from HICs [40]. Given these limitations, the generalizability of the results may be limited.

The sample size of the survey was small, limiting the available power for further statistical analysis. The opinions and priorities of this group of experts may not be representative of a broader network who are involved in STI vaccine research. The weighted value scoring of the specific activities was completed in comparison with other activities in those categories (i.e., all basic science activities were initially compared with other basic science activities to produce the score provided). It is possible that if all research activities were presented in one list, and then subsequently ranked, the resulting scores would be different based on participant's perceptions of the activities related to one another.

5. Conclusion

Despite available screening and treatment options, there are still one million new STIs every day around the world [1]. Vaccines as a primary prevention method for STIs are a promising tool to help control the spread of these infections, reduce the burden of disease, and reduce costs associated with subsequent treatment. Dedicated efforts and funding are needed to continue advancing the science and the associated program planning and development for STI vaccines. Experts in clinical sciences, program implementation, and knowledge translation will benefit from continued collaboration in this growing and important field. Dedicated symposia and working groups are valuable tools to continue moving this critical research forward. The priorities presented here, as identified by this group of leading researchers, policy makers, and service providers, should be noted by other public health leaders, funding bodies, and governments. Coordinated efforts and planning should be maintained to prepare for the use of these vaccines as they become available. Overall, these findings contribute broadly to STI vaccine development and can be used to elevate research priorities going forward.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: GO, LWS, RD, CC, JAB, MS, CSR, TG, MN are members of the STRIVEBC consortium. The core team who completed the data analysis and interpretation of results (KP, RD, LS, GO) did not complete the survey. MS is supported via salary awards from the BC Children's Hospital Foundation, the Canadian Child Health Clinician Scientist Program and the Michael Smith Foundation for Health Research. MS has been an investigator on projects funded by Pfizer, Merck, VBI Vaccines, Seqirus, Sanofi-Pasteur and GlaxoSmithKline. All funds have been paid to his institute, and he has not received any personal payments. RD has received fellowships from the Canadian Immunization Research Network and Michael Smith Foundation for Health Research. CSR received a fellowship from Michael Smith Foundation for Health Research. All other authors have no competing interests.

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Contributions

GO conceived the study. All authors provided feedback on the survey used. KP and AM prepared the surveys for administration and data collection. KP and RD performed the data analysis. KP wrote the first draft of the manuscript. All authors provided critical revisions.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2021.100107.

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