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Strep A Vaccine Industry Forum: Catalyzing Industry Investment In Strep A Vaccine R&D

Forum Report

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In partnership with Shift HEALTH

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Introduction

There is currently limited industry activity and investment in Strep A (*Streptococcus pyogenes*; group A Streptococcus) vaccine development, with two of the field's most advanced vaccine candidates being actively developed by companies. Over the past 5 years, efforts to develop a Strep A vaccine have been re-invigorated and the field has also seen new investments in the development of specific vaccine candidates (e.g., ASAVI[1] and CARB-X) and in characterizing protective immune responses to inform vaccine design (e.g., Leducq Foundation). Nonetheless, the vaccine pipeline for Strep A remains relatively sparse, reinforcing the need to strengthen the commercial case and address barriers to industry prioritization of Strep A vaccine development to enhance the likelihood and speed of development and deployment of a safe and effective Strep A vaccine.

Building on the Strep A vaccine business case generated during SAVAC 1.0[2] and engagement with the biopharmaceutical industry to identify and understand barriers to investment in Strep A vaccine R&D, SAVAC convened an inaugural Strep A Vaccine Industry Forum on April 1st, 2024, as part of the official World Vaccine Congress Washington DC program. The Forum brought together representatives and stakeholders from multinational vaccine manufacturers, small biopharma companies, developing countries vaccine manufacturers (DCVMs), Strep A vaccine developers, government, and non-profit organizations to:

- Provide an overview of the Strep A vaccine pipeline and business case;
- Review findings from interviews with industry on the Strep A vaccine investment opportunity;
- Discuss barriers and enablers relevant to industry engagement in Strep A vaccine development;
- Align on mechanisms to encourage industry prioritization of Strep A vaccine development; and
- Provide an opportunity for networking among Forum participants.

INDUSTRY REPRESENTATION AT THE FORUM

AstraZeneca, BIONTECH, CUREVAC, eubiologics, GSK, moderna, Panacea Biotec (Innovation in support of life), Pfizer, sanofi, uvaxbio, VAXCYTE (protect humankind), VaxForm LLC

[1] The Australian Strep A Vaccine Initiative

[2] Strep A Vaccine Global Consortium

SUMMARY OF OPENING REMARKS AND PRESENTATIONS

The context for the Forum was set by opening remarks and a presentation on the state of the field by the Co-Chairs of the SAVAC Executive Committee, Dr. Jerome Kim (International Vaccine Institute) and Prof. Andrew Steer (Murdoch Children's Research Institute), as well as a presentation on the key findings from industry consultations by Dr. Don Walkinshaw (Shift Health).

Dr. Jerome Kim began by welcoming participants to the inaugural industry Forum for a Strep A vaccine and provided an overview of the Forum objectives and agenda—which included breakout sessions and plenary discussions—and introduced the facilitators of the Forum. Dr. Kim highlighted that the Forum participants represented a diverse group of stakeholders, including government and non-profits, Strep A vaccine developers, multinational vaccine manufacturers and DCVMs, and encouraged participants to share their perspectives on barriers to industry investment in Strep A and recommendations on mechanisms to address those barriers.

Prof. Andrew Steer delivered a presentation on the state of the field, putting a spotlight on the current Strep A vaccine pipeline which includes four M protein-based candidates and eight candidates designed around non-M protein antigens. Prof. Steer highlighted current enablers for the field—SAVAC, ASAVI and the World Health Organization (WHO)—as well as Strep A vaccine development funders including CARB-X, the Right Foundation, NIAID[3] and the Lequcq foundation. Prof. Steer's presentation also drew the participants' attention to publications from SAVAC 1.0 and delved deeper into the Strep A vaccine business case from a developer's perspective, which suggests that there is a viable commercial market for a Strep A vaccine. The business case results show a positive net present value (NPV) for a variety of developer scenarios and target populations, including a global rollout of the vaccine in private and public markets by a multinational pharmaceutical corporation and a staged rollout by a DCVM for both infant and child populations.

Dr. Don Walkinshaw presented key findings from industry consultations aimed at understanding perceptions of the Strep A vaccine market, barriers to investment and activities that can catalyze or enable greater industry investment. Dr. Walkinshaw highlighted that:

- Most interviewees agreed that Strep A is a global health priority and that both high-income countries (HICs) and low- and middle-income countries (LMICs) will be important market segments driving the investment case for a Strep A vaccine.
- Generally, interviewees believed that commercial considerations are the main barrier to greater industry investment, followed by clinical, scientific, and regulatory challenges.
- Interviewees noted several opportunities to de-risk industry investment, ranging from demonstration of vaccine efficacy to guidance from regulatory agencies.
- Actions that interviewees believe SAVAC should (continue to) undertake to support vaccine development include promoting collaboration, enabling evidence generation, and advocating for Strep A vaccine funding and policy prioritization.

In closing, Dr. Walkinshaw encouraged Forum participants to reflect on findings from the industry consultations as they discussed and prioritized barriers during the first breakout session.

[3] National Institute of Allergy and Infectious Diseases / U.S. National Institutes of Health

Barriers to Industry Investment in Strep A

The primary focus of the first breakout session centered on barriers to industry investment in Strep A vaccine R&D. In this breakout, participants discussed barriers with the greatest impact on industry investment. In plenary, participants ranked the barriers in order of perceived impact on industry investment and the results are presented in the figure below.

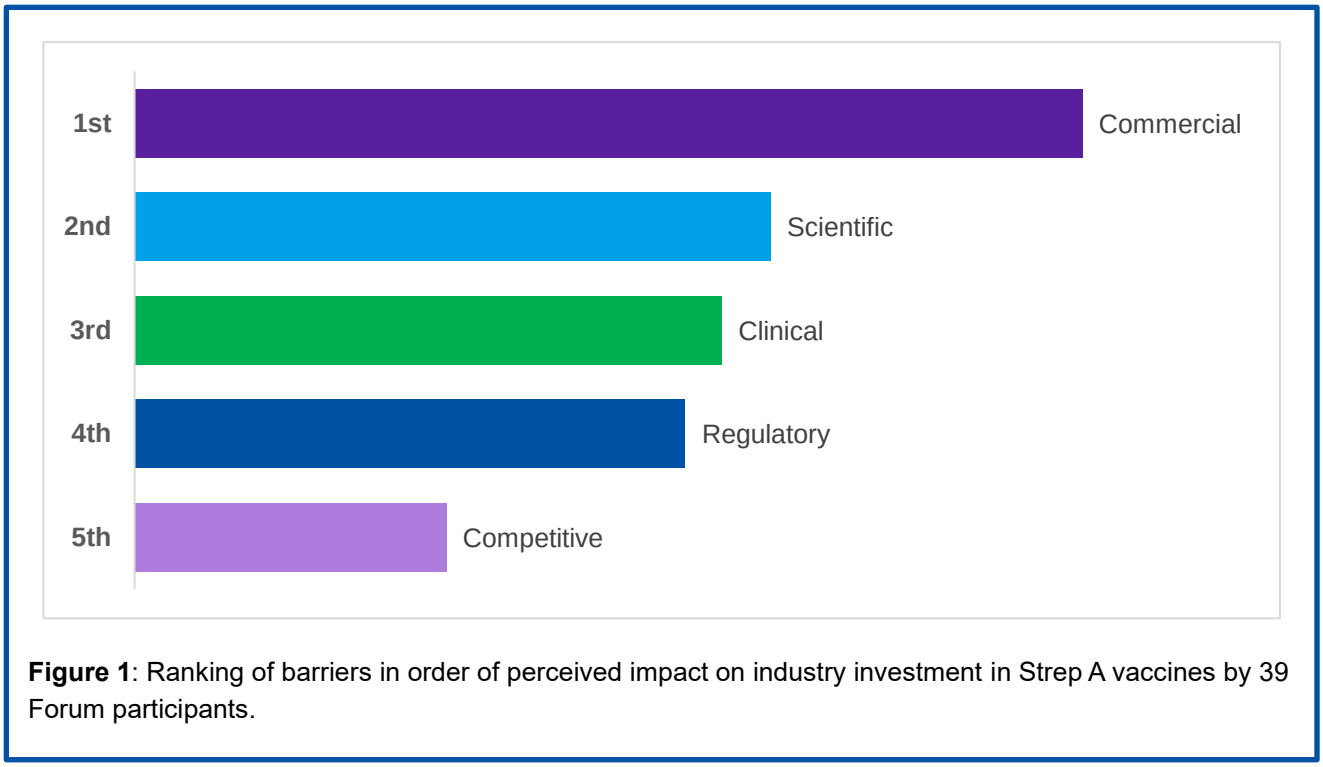

Figure 1: Ranking of barriers in order of perceived impact on industry investment in Strep A vaccines by 39 Forum participants.

While commercial barriers have been ranked as having the highest perceived impact on industry investment, several Forum participants noted that other barriers, such as clinical and regulatory barriers, are also important for the field to address. During the breakout session, Forum participants identified and characterized specific barriers within these five categories; the discussions are summarized below.

COMMERCIAL BARRIERS

- **Lack of certainty in HIC market potential**. Forum participants noted that a universal use recommendation in infants/children from NITAGs[4] (e.g., US Advisory Committee on Immunization Practices; ACIP) would be critical for a robust commercial case in HICs. Some believe that a universal recommendation is possible, citing the potentially compelling health-economic case driven by the high incidence of pharyngitis and the less recognized but growing burden of Strep A invasive disease in HICs and significant indirect costs associated with both diseases (e.g., increased child absenteeism from school and associated decrease in work productivity of their caregivers). However, several factors were cited that could reduce the likelihood of a universal use recommendation, including perceived 'overcrowded' pediatric vaccine schedules, and insufficient recognition of the value of a Strep A vaccine in reducing antimicrobial resistance (AMR) in bystander pathogens. In addition, a Forum participant

[4] National Immunization Technical Advisory Groups

noted that policy support may change over time—in the case of meningitis B vaccines, outbreaks in 2013 drew attention to the unmet medical needs and assurance of a broad use recommendation, but a subsequently declining incidence rate contributed, in part, to ACIP's more restrictive use recommendation in 2015.

- **Unclear demand from LMICs**. Although the recognition of the burden associated with Strep A diseases and long-term sequelae is increasing, participants noted that the perceived priority level of Strep A on global health agendas and with vaccine funders and LMIC governments is unclear compared to other priority pathogens. The lack of comprehensive surveillance data in LMICs adds to the unclear perceived need for the vaccine.

SCIENTIFIC BARRIERS

- **No proven consensus on antigen combination**. Due to the extensive diversity of Strep A *emm* types, optimizing strain coverage and selecting the optimal antigen combination remains a scientific obstacle to vaccine development. The current Strep A vaccine pipeline consists of vaccine candidates with a diverse set of antigens and antigen combinations. The high number of *emm* types also raises concerns about whether a chosen antigen combination would be effective across the spectrum of Strep A diseases, from relatively mild, superficial infections to more severe, systemic and invasive diseases.
- **Inadequate animal models.** While animal models have been developed for various Strep A diseases, these models were noted by Forum participants to have thus far failed to fully reproduce the pathogenesis of human Strep A diseases and provide reliable insights on, and signals for, vaccine efficacy and safety.
- **Lack of standardized, functional assays (e.g., opsonophagocytosis assays, OPAs).** Although several assays that measure protective immunological responses against Strep A have been established, their application is limited to a few strains and assay reproducibility is not yet sufficient.
- **Additional vaccine design challenges.** Additional scientific challenges related to vaccine design were identified: determining the optimal platform (e.g., protein, glycoconjugate, mRNA) for the chosen antigen combination; the suitability of the platform for future combination vaccines; and the lack of clarity on the role of adjuvants in Strep A vaccines.

CLINICAL BARRIERS

- **Need for clarification of appropriate trial endpoints in LMICs.** Due to differences in the predominant Strep A disease manifestations, clinical endpoints may differ between HICs and LMICs. While there is some consensus on the appropriate endpoints beyond considerations as noted in the 2018 WHO Preferred Product Characteristics (PPC), Forum participants recognised the need to review the PPC. For LMICs, the prevention of rheumatic heart disease (RHD) is likely the main value driver, but a trial focusing on longer-term endpoints may not be feasible. As a result, there will likely be a need to show a clear linkage between the prevention of acute Strep A disease manifestations (e.g., pharyngitis) and longer-term autoimmune sequelae (e.g., acute rheumatic fever (ARF) and RHD).
- **High threshold for establishing safety in clinical trials and the need for long-term safety monitoring.** Forum participants agreed that safety concerns represent a barrier to industry investment

due to the historic FDA ban on Strep A vaccine clinical testing that lasted from 1979 to 2005[5]. There will likely be a high bar for demonstrating safety, particularly cardiac safety, possibly through clinical investigation and protocols with long-term follow-up; beyond what is usually required for vaccine safety demonstration — (e.g., tests for human tissue cross-reactive antibodies, echocardiograms, application of the Jones criteria) as there is currently no validated biomarker of probable cardiac tissue damage.

REGULATORY BARRIERS

- **Unclear regulatory expectations for demonstrating vaccine efficacy and safety.** Forum participants agreed that the lack of regulatory guidance and certainty on expectations of efficacy (e.g., accepted levels of efficacy, optimal trial design) and safety (e.g., required length of follow-up period, the need for monitoring via echocardiograms) increases development risks and costs. In addition, participants noted that the field would benefit from updates to the WHO PPC from 2018 for a Strep A vaccine (e.g., refining efficacy targets for different Strep A diseases).

COMPETITIVE BARRIERS

- **Perceived impact of competition as a barrier is currently low but may change**. While the competitive barrier was ranked lower compared to the other barriers, Forum participants acknowledged that competition would increase as the pipeline moves towards later stages of development and more companies invest in the space, which may deter additional industry entrants in the future.

Recommendations on Mechanisms to Address Barriers

The objective of the Forum's second breakout session centered on how to address or minimize the barriers discussed in the first session. Participants focused the discussion on key enabling mechanisms that may help de-risking Strep A vaccine investment. In plenary, a representative from each breakout group provided a summary of their group's key takeaways. Shift Health subsequently facilitated a discussion with Forum participants to reflect on key learnings from the Forum. Recommendations on mechanisms to address barriers and implementation considerations are summarized below.

BUILDING A ROBUST BUSINESS CASE

- **Define the HIC market opportunity.** Given the higher price that the vaccine would be able to command in HICs vs. LMICs and the importance of high demand in HIC markets for large pharmaceutical companies to invest, there is a need to better define the HIC market opportunity. Activities to support this may include understanding healthcare provider (HCP) perceptions of the need and value drivers for a Strep A vaccine, as well as assessing the probability of universal use recommendations from HIC NITAGs (e.g., US CDC's ACIP).
- **Broaden potential target populations to increase volume.** Forum participants noted an opportunity for Strep A vaccine developers to broaden the target population to adults, likely for the prevention of Strep A-induced cellulitis. Expanding beyond the pediatric market segment would in theory offer an opportunity to increase total demand and revenue potential while also potentially decreasing the cost of

[5] Ban enacted in 1979 following 2 definitive and 1 probable ARF case in participants of 1965 Massell study using partially purified M protein extract and no control group. FDA revoked ban in 2005 "because the…requirement is obsolete and perceived to be impeding…development of [GAS] vaccines using purified or characterized streptococcal antigens". No serious safety signals were detected in the 5 Strep A vaccine clinical trials conducted since 2006. Source: Asturias et al. Clin Infect Dis. 2023.

goods sold (COGS) through economies of scale. While the latter will benefit any Strep A vaccine developer, the benefit may be particularly important for DCVMs with lower profit margins.

ESTABLISHING A FAVOURABLE POLICY ENVIRONMENT

- **Engage key stakeholder organizations**. Favourable policies by global (e.g., WHO, GAVI), regional (e.g. Regional Immunization Technical Advisory Group; RITAGs) and country-level stakeholders (e.g., NITAGs) for the uptake of a Strep A vaccine will help increase the certainty of future market demand. There is an opportunity to engage these stakeholders to raise awareness of the unmet policy priorities that need to be addressed to foster Strep A vaccine development, access and implementation. Engaging governments to secure advance market commitments was also noted as a potential mechanism to de-risk industry investment.
- **Substantiate the urgent need for a Strep A vaccine.** Recent outbreaks of invasive Strep A diseases can be leveraged to augment the public health case for a Strep A vaccine. Additional evidence (e.g., HCP and payer perspectives on Strep A pharyngitis and Strep A vaccine candidates, linkage of mild infections to severe sequelae) will help build awareness of the urgency for the vaccine.
- **Prepare policy landscape for integrating evidence into future recommendations.** Evidence linking pharyngitis to RHD is crucial to support the adoption of the Strep A vaccine in LMICs. Understanding the data needs of policymakers (e.g. by leveraging the upcoming SAVAC-WHO joint evidence-to-policy meeting) will inform the field's ongoing evidence-generation activities. This will help to ensure that there is a strong alignment between these data generation activities (e.g. how the studies are designed) and policymaker expectations and data requirements to inform future policy recommendations.
- **Broaden value recognition**. To strengthen cost-effectiveness arguments for a Strep A vaccine, policymakers need to recognize its broader value, which includes the reduction of direct and indirect medical and non-medical costs and the value of reducing AMR in bystander pathogens. Building on the Strep A Full Value of Vaccine Assessment (FVVA) led by SAVAC, there is an opportunity to develop informative communication tools to convey the global health investment case as part of stakeholder engagement efforts targeted at policymakers and vaccine decision-makers.

CATALYZING KEY SCIENTIFIC FINDINGS

- **Accelerate demonstration of clinical efficacy**. While promising data from clinical trials are by nature not fully controllable, Forum participants noted that the demonstration of clinical efficacy would help to address or obviate some of the scientific and clinical barriers and therefore de-risk industry investment. For example, establishing a proof of concept against pharyngitis (e.g. using a controlled human infection model; CHIM) would play a significant role in overcoming or reducing the impact of barriers in HIC markets.
- **Identify correlates of protection**. Building on the work of SAVAC and ASAVI, the establishment of correlates of protection once a Strep A vaccine candidate demonstrates human efficacy will significantly streamline Strep A vaccine development and regulatory approval processes for subsequent vaccines. Identifying common immunological markers across strains and disease manifestations will help overcome the challenge of varying antigens in different vaccine candidates.
- **Standardize immunoassays (e.g., functional assays)**. There is an opportunity for consortia like SAVAC and ASAVI, as well as the WHO, to foster greater collaboration in the field to standardize assays by aligning on and establishing reference standards and ensuring applicability to a variety of Strep A

strains. Efforts and successes by the pneumococcal vaccine field in standardizing OPAs were noted by Forum participants as a source for lessons learned that could inform similar efforts in the Strep A field, although Forum participants noted that application of a single functional assay to different vaccine antigens and vaccine strategies may be challenging.

- **Improve preclinical and clinical models**. Animal models that more accurately reflect human disease and vaccine response will help enable more predictive preclinical signals of vaccine efficacy. Building on the CHIVAS-M75 CHIM, additional CHIMs (e.g., different challenge strains, skin infection model) will be instrumental in efficiently assessing vaccine clinical efficacy and informing further development steps for Strep A vaccine candidates.

CLARIFYING REGULATORY EXPECTATIONS AND PATHWAYS

- **Define optimal efficacy endpoints for licensure in LMICs**. Building on the WHO PPC, clear and specific regulatory guidance on the required efficacy endpoints/evidence, especially for LMICs, will help de-risk industry investment. It was recognized that the evidence generation requirements may differ for different Strep A diseases, populations (e.g. pediatric vs. adults) and target markets/countries.
- **Align on safety endpoints and expectations.** There is a need for consensus in the field on the appropriate laboratory safety assessments (e.g. cross-reactive immune assays) and clinical safety assessments (e.g. echocardiography, rheumatic fever surveillance) for adverse events of special interest, as well as alignment with regulators on the appropriate clinical development pathway for safety (e.g. whether there is a need for a dedicated safety cohort study).
- **Strengthen collaboration with regulators**. Forum participants emphasized that there is a need to strengthen collaboration with regulators through continuous engagement, such as regular meetings organized by SAVAC that involve multiple Strep A vaccine developers and regulatory bodies (e.g. similar to the upcoming SAVAC-WHO joint evidence-to-policy meeting).

BUILDING SURVEILLANCE AND CLINICAL INFRASTRUCTURE

- **Address epidemiology data gaps**: Forum participants affirmed the importance of SAVAC's work in standardizing case definitions of Strep A diseases and the ongoing process of establishing sentinel sites to close surveillance data gaps (e.g., impetigo incidence) in LMICs and monitor incidence rates of Strep A diseases. These initiatives, as well as additional epidemiological surveillance sites/studies in the future, will help de-risk vaccine development by ensuring accurate incidence data is available for trial planning and execution.
- **Disseminate epidemiology data to inform policy decisions**: For NITAGs and other health policy bodies, comprehensive epidemiology data is crucial for securing support and recommendations for vaccine introduction in both HIC and LMIC settings. Disseminating these data will also help influence resource allocation and disease area prioritization decisions within pharmaceutical companies.

SECURING NON-DILUTIVE FUNDING

- **Advocate for non-dilutive funding**[6]. Forum participants agreed that non-dilutive funding (e.g., from global health funders, governments and supranational organizations) will offset costs and risks

[6] Financing that does not require the sale of a company's shares, and hence does not cause dilution of the existing shareholders.

associated with early-stage preclinical and clinical trials of Strep A vaccines. It was noted that non-dilutive funding may be most helpful for small biotech companies.

- **Explore innovative funding models**. There is an opportunity for the field to explore innovative financing models such as Social Impact Bonds specific to Strep A or grouped with other disease areas with substantial impact potential. Forum participants noted that these innovative funding models may be particularly suitable for vaccines that realize their benefits over the longer term, which may be the case for Strep A vaccines.

Closing and Next Steps

Prof. Ruth Karron (Johns Hopkins University), SAVAC Executive Committee Member, closed the forum with a brief summary of key barriers to industry investment in Strep A vaccine R&D and recommendations on mechanisms to address barriers. Prof. Karron emphasized that SAVAC is committed to advancing the field toward developing a safe, effective, and affordable Strep A vaccine to decrease the burden of Strep A disease. Prof. Karron closed by highlighting some critical next steps and solidifying the role that SAVAC can play to encourage Strep A vaccine development, including:

- Finalizing the selection of sentinel sites in LMICs to gather epidemiological, economic and societal data on Strep A diseases and strengthen surveillance, laboratory and potential for clinical trial capacity;
- Building on this inaugural Forum, SAVAC will encourage industry involvement in Strep A vaccine development, update the Strep A Vaccine Business Case and continue engagement with vaccine developers and manufacturers at future meetings (e.g. the 2025 Lancefield Symposium in Brisbane);
- Engaging with relevant non-industry stakeholders (e.g., WHO, global health funders, national policymakers, NITAGs, experts in laboratory and safety surveillance) to address policy-related barriers and enhance implementation efforts for a future Strep A vaccine.

Appendix A—List of Participants

Name*	Affiliation
Alex Bowles	Open Philanthropy
Andrew Steer	SAVAC/MCRI
Annaliesa Anderson	Pfizer
Anne Mullin	Shift Health
Chris Gregory	CDC
Chris Van Beneden	SAVAC/CDC
Christina Dold	Moderna
David Bloom	SAVAC/Harvard SPH
David Kaslow	FDA
David Milan	Leducq Foundation
David Tancredi	Leducq Foundation
Don Walkinshaw	Shift Health
Edwin Asturias	SAVAC/U of Colorado
Elisa Portfilio	Shift Health
Elizabeth Magner	Sanofi Vaccines
Elodie Burlet	VaxForm
Emma Viscidi	Moderna
Francesca Micoli	GSK
Gabrielle Belz	Univ. of Queensland
Garry Morefield	VaxForm
Harshet Jain	Panacea Biotec
Hee Soo Kim	IVI
Helge Dorfmueller	Dundee Univ.
James Wassil	Vaxcyte

Name*	Affiliation
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Jerome Kim	SAVAC/IVI
Jorge Kalil	Univ. of Sao Paulo
Jonsson Liu	Shift Health
Julie Skinner	Pfizer
Kevin O'Neill	UVAXbio
Khalid Ali Syed	Panacea Biotec
Lars Bonefeld	Vaxcyte
Mark Walker	Univ. of Queensland
Megan Lang	Moderna
Meredith Finn	Moderna
Michael Fontaine	Dundee Univ.
Minjeong Kim	EuBiologics
Neeraj Kapoor	Vaxcyte
Ondari Mogeni	IVI
Paul Warrener	AstraZeneca
Rachel Park	EuBiologics
Rekha Rapaka	Moderna
Roxana Rustomjee	BioNTech
Ruth Karron	SAVAC/JHU
Simona Rondini	GSK
Sushant Sahastrabuddhe	IVI
Tania Rivera Hernandez	IMSS
Weila Wang	CureVac

* Alphabetical order by first name

Appendix B—Forum Photos

SAVAC Strep A Vaccine Global Consortium
Shift HEALTH