SAVAC Stakeholders Meeting Report

Strep A Vaccine Global Consortium

Virtual Meeting organized by

the International Vaccine Institute (IVI)

Seoul, Republic of Korea

11 March 2021

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Welcome Remarks

Dr. Jerome Kim, Director General of IVI, Chair of SAVAC, and Prof. Andrew Steer, co-Chair of SAVAC, from the Murdoch Children's Research Institute, University of Melbourne, Australia

Dr. Jerome Kim, Director General of IVI, Chair of the Strep A Vaccine Global Consortium (SAVAC), introduced his co-Chair Prof. Andrew Steer from the Murdoch Children's Research Institute, University of Melbourne, and welcomed the participants attending this first SAVAC stakeholders meeting.

Dr. Jerome Kim reminded the objectives of the meeting that were to present and review the SAVAC achievements to the scientific community and work in progress that went through an incredible amount of work from leaders of workstreams highlighting very important issues of Strep A vaccine development, and very importantly to discuss, get opinions and seek advice and recommendations from the participants on next steps and gaps to consider, and to increase awareness and interest of funders.

Dr. Jerome Kim thanked the team members organizing the meeting, Ms. Somyoung Cho, Program Manager, Ms. Chloe Sye Lim Hong, Project Administrator, Dr. Jean-Louis Excler, Project Lead, and all the players who made this meeting possible.

Prof. Andrew Steer echoed Dr. Kim in his words of thanks and introduced the major components on the SAVAC workstreams including advocacy, the R&D roadmap priorities and the Full Value of Vaccine Assessment. The first session will focus on R&D roadmap priorities with burden of disease, correlates of protection, safety assessments relevant to vaccines.

The Meeting Agenda and list of speakers are provided in Annex 1 and Annex 2, respectively. The lists of members of the different working groups are provided in Annex 3. Questions and responses raised by participants during or after the presentations are listed in Annex 4.

Epidemiology and Burden of Disease

Prof. Jonathan Carapetis, Telethon Kids Institute, Perth, Australia

Introduction

'Epidemiology and Burden of Disease' is one of the five workstreams of SAVAC. The overall goal is to provide updated estimates of the global burden of group A *Streptococcus* (Strep A) diseases. The Burden of Disease Working Group (BoDWG) comprises 16 members from 7 countries as shown in Annex 3.

The five specific workstream objectives are outlined below:

1. Develop consensus disease case definitions of the different clinical endpoints of Strep A.
2. Identify, maximize and collate existing global data sources.
3. Raise awareness of Strep A burden of disease globally.
4. Identify key stakeholders and regions/jurisdictions who will comprise the Global Burden of Disease Working Group to ensure global collaboration.
5. Develop new funding proposals to assist future burden of disease work.

What is known about Strep A Burden?

Clinical endpoints of Strep A diseases include superficial infections such as pharyngitis and skin infections (impetigo); Other clinical features include locally invasive diseases and invasive diseases such as cellulitis, bacteremia, meningitis, puerperal sepsis, necrotizing fasciitis; immune and toxin-mediated diseases such as scarlet fever and streptococcal toxic shock syndrome; and sequalae of immune-mediated diseases such as acute rheumatic fever, acute post-streptococcal glomerulonephritis, rheumatic heart disease and chronic kidney disease [1]. It was highlighted that as the disease spectrum associated with Strep A disease is wide and complex, understanding and then characterizing the global burden of disease is challenging. Previous attempts to estimate the global burden of Strep A diseases used available data sources, estimates from the World Health Organization (WHO), Global Burden of Disease estimates (e.g., focusing on rheumatic heart disease) and various systematic reviews focusing on particular Strep A clinical endpoints. One of the most recent estimates suggests that Strep A diseases affect approximately 800 million people each year and results in 639,000 deaths, with half of these deaths attributable to rheumatic heart disease and a quarter attributable to invasive infections [2]. Previous attempts to estimate the global burden of Strep A diseases [3] included however few estimates from resource-poor settings where the burden is expected to be highest.

Some meeting attendees discussed the comparison of global burden of Strep A diseases to other major vaccine-preventable diseases (or non-vaccine preventable infectious diseases). It was highlighted that Strep A is likely to be the fifth most lethal global pathogen as measured by mortality (which is mostly driven by rheumatic heart disease and invasive diseases). Based on global mortality figures, Strep A mortality is exceeded by only HIV, *Mycobacterium tuberculosis* (tuberculosis), *Plasmodium falciparum* (malaria) and *Streptococcus pneumoniae*. These estimates were derived by the 2004 World Health Report, publicly available estimates from WHO and the 2005 publication of the global burden of Strep A diseases [3]. There is a paucity of information on other burden measures such as DALYs allowing to compare Strep A disease to other pathogens. An attendee asked why pharyngitis is not listed separately among the Global Burden of Diseases list. It was noted that pharyngitis is encompassed within "upper respiratory infections".

Key activities

The purpose of this meeting was to highlight some of the specific activities to date that have been achieved from the Epidemiology/Burden of Disease workstream. The workstream is led by Prof Jonathan Carapetis from the Telethon Kids Institute, Perth, Western Australia with a core team of five members. A Global Burden of Disease Working Group (BoDWG) has been established to guide and advise on the activities of the workstream. The BoDWG is co-chaired by Prof. Carapetis and Dr Chris Van Beneden, Centers of Disease Control and Prevention, Atlanta, Georgia, USA. Membership of the BoDWG, took into consideration the geographical location, Strep A and non-Strep A knowledge, infectious diseases expertise and gender to ensure a broad and global collaboration.

Surveillance Protocols

Consensus is needed to identify and define the major Strep A endpoints that will drive the use and future evaluation of a Strep A vaccine. In order to provide clear case definitions of the Strep A disease clinical endpoints, this workstream is producing a suite of standardized case definitions and "best practice" surveillance protocols. These have been modified from two original surveillance protocols developed in 2008 by a working group of international Strep A experts and supported by WHO and National Institute of Allergy and Infectious Diseases working group. One protocol comprised "Acute diseases" (pharyngitis, impetigo and invasive diseases), while the other comprised "post-streptococcal sequelae" (acute rheumatic fever, rheumatic heart disease and acute post-streptococcal glomerulonephritis). The revised protocol is divided into seven discrete chapters: pharyngitis, impetigo, invasive infections, cellulitis (new chapter not covered by existing protocols), acute rheumatic fever, rheumatic heart disease and acute post-streptococcal glomerulonephritis. It is planned that scarlet fever, which was not included in the original protocols, will be added as an addendum to the pharyngitis chapter or as a separate chapter. The original protocols have been updated and revised to include contemporary diagnostic methods, in particular molecular methods such as nucleic acid amplifications tests; expanded data sources for disease surveillance; and methods for case ascertainment as they apply to the different Strep A endpoints in both high-income (HIC) and low- and middle-income countries (LMIC) and types of surveillance including the benefits and disadvantages of passive and active surveillance methodologies. These protocols as an essential piece to the Burden of Disease workstream activities, underpin future work of SAVAC to enable collaborators to undertake surveillance in a standardized and harmonized manner.

Core workstream team members are currently updating these protocols to facilitate expert review with BoDWG members and by an additional *ad hoc* expert sub-committee. The stand-alone chapters will be completed by mid-2021. Upon finalization of these protocols, endorsement will be sought from the SAVAC Executive Committee before commencing a dissemination plan that will include hosting on institutional websites and summarizing the protocols in a peer-reviewed manuscript to facilitate further dissemination among the global medical and research community.

Data Purpose Matrix

A key objective of the workstream is to identify, collate and maximize existing data to facilitate estimates of the global burden of Strep A diseases. Through discussions with BoDWG members and connections with the work currently underway for the Full Value of Vaccines Assessment, key questions were raised regarding the types of disease burden data that are needed in order to advance Strep A vaccine development and implementation and who the key audience members are; where the current gaps in knowledge are in terms of global Strep A disease burden; and what existing data can be leveraged to address these needs for a Strep A vaccine. A "data purpose matrix" has been developed to address these questions and provide guiding principles for the Epidemiology/Burden of Disease Workstream. The aim is to identify the priority pieces of data that need to be collected under the mission of SAVAC and what the research priorities are. The matrix addresses four different objectives of vaccine development and evaluation: *advocacy*, *regulatory/licensure*, *policy evaluation*

and post-licensure, and *financing*. Through the lenses of those objectives, the matrix points to different data purposes, key audience members and stakeholder groups and the most appropriate timing of those data needs for the vaccine development pathway. The matrix addresses Strep A diseases overall, and for seven different Strep A clinical endpoints. It also highlights any differences in data requirements between HIC and LMIC for each of the disease endpoints. A manuscript describing the data purpose matrix is in preparation.

Identification of Priority Projects

Using the knowledge created within the Data Purpose Matrix and shared results from other SAVAC activities, a shortlist of priority research areas was created. Nine priority research areas that also include sub-projects within each priority area will be used to streamline the collation of existing data and develop new funding proposals. Members of the BoDWG were asked to rank these projects to refine the list to key areas that need to be further developed. The top listed priority areas include: establishing sentinel surveillance sites for pharyngitis and impetigo – especially in LMIC that may progress to future vaccine trial sites, enhancing data collation activities to better estimate the incidence of invasive Strep A diseases in settings where there is a paucity of published data, understanding the attributable fraction of Strep A to cellulitis and increasing knowledge of cellulitis burden that is most likely under estimated. A further identified priority is obtaining a Strep A-specific estimate from the Global Burden of Disease project through the Institute for Health Metrics and Evaluation (IHME). This is identified as a priority area of interest as there is a lack of global perception of Strep A disease. Aligning disease estimates with other diseases from the Global Burden of Disease project is needed to facilitate comparison, especially between HIC. Other priority areas of interest include multi-country epidemiological record linkage studies of administrative data as they are less resource-intensive compared to prospective data collection studies.

It was acknowledged that while not strictly a burden of disease project, gaining an appreciation on how decisions are made with regards to vaccine development and implementation at the international, regional and country level is important. Knowledge of these areas and the key stakeholders involved will help progress Strep A vaccine development and subsequent implementation. Throughout the meeting, issues regarding the lack of urgency amongst decision makers to advance Strep A vaccines and a lack of investment from large pharmaceutical companies were discussed. This is particularly relevant when considering the unquestionable level of disease burden, despite the gaps in current estimates and paucity of data from LMIC as outlined earlier. This discussion led to the crucial point of understanding on how to communicate decisions both at country, regional and global levels. The fact that a significant burden of disease has not translated into a sense of urgency further points to the importance of understanding vaccine decision-making at multiple jurisdictional levels.

An attendee questioned why the identified priority of establishing sentinel surveillance sites focused on pharyngitis (and impetigo) rather than focusing on surveillance for rheumatic heart disease, especially in LMIC. It was pointed out that in comparison to other Strep A disease endpoints, there are good and accurate data around the prevalence of rheumatic heart disease from a range of LMIC. Furthermore, it was argued that the understanding the prevalence of rheumatic heart disease is best done through systematic echocardiographic surveillance studies. The priority focus on sentinel surveillance sites for pharyngitis and impetigo is directly related to the greater feasibility of conducting vaccine efficacy studies among these common Strep A clinical endpoints as underlined in the WHO Strep A Vaccine R&D Roadmap [4] and Preferred Product Characteristics [5].

The next steps for the Epidemiology/Burden of Disease Workstream are to consolidate the list of priority research projects and identify interested individuals or groups who would be keen to move

the projects forward. The workstream team will be developing concept notes on each of these priority projects with a view of seeking further funding.

Strep A Immunity and Correlates of Protection

Prof. Shiranee Sriskandan, Imperial College, London, United Kingdom

Correlate of Protection Working Group

The aim of the Correlate of Protection Working Group (Annex 3) is to systematically review what is known and what is not known about Strep A immunity, and to summarize the findings in order to guide future research that may benefit to Strep A vaccine development.

Key points addressed

Several key points were addressed and are developed below.

Can you get immunity to Strep A?

The answer is yes.

Humans are capable of developing immunity to Strep A, which is acquired with age.

The frequency of Strep A pharyngitis and scarlet fever peak in childhood, with much lower incidence of these diseases in adulthood. By contrast, invasive infections are seen in both the very young and very old populations associated with naivety in the immune system and immune senescence. This epidemiological data suggest that it will be possible to induce immunity against pharyngitis, if we can replicate what occurs naturally in late adolescence, however the ability to vaccinate against invasive infections may be more complicated.

Strep A immunity research has largely focused on invasive infections and systemic immunity

To date, research has focused on soft tissue infections cellulitis, necrotizing fasciitis and myositis, pneumonia, bacteremia, puerperal sepsis, and toxic shock syndrome. A key reason for this focus is the remarkable ability of Strep A bacteria to grow in non-immune human blood, which forms the basis of the classic Lancefield assay. When non-immune human blood and plasma lacking specific antibodies are combined with live Strep A, the bacteria can survive and grow, due to minimal complement activation and opsonization. By contrast, when plasma contains specific antibodies, the binding of these antibodies and activation of complement lead to phagocytosis and clearance of the bacteria. With advancements in laboratory techniques, the Lancefield assay has been modified using purified neutrophils and fluorescent bacteria. The serum-mediated neutrophil uptake requires both antibody and complement to be effective, indicating the essential roles of these proteins in Strep A immunity.

Intravenous immunoglobulins (IVIg)

IVIg contain the typical IgG antibodies found in the population from which it derives and are often used as a positive control in Strep A immunoassays. When measuring the prevalence of systemic immunity in adults, the vast majority (approximately 90%) have a variable, medium level of immunity when compared to IVIg. Only 5% of the population displays immunity to a similar level of IVIg, and the remaining 5% of adults have no detectable immunity. To determine what comprises Strep A immunity

in the adult population, IVIg were used in a pull-down with purified Strep A cell wall proteins. Immunoproteomic identification revealed ten key cell wall antigens that were recognized by IVIg [6].

The pursuit of Strep A vaccine antigens

The long history in pursuit of Strep A vaccine antigens may have been hindered by fixation on single antigens. Anti-scarlet fever sera were developed and used in the late 1800's to successfully treat Scarlet Fever in children. After determination of the causal agent of scarlet fever, anti-Strep A sera was developed in the 1920's. Rebecca Lancefield first described Strep A M proteins in 1928 [7], determined these proteins to be immunogenic and developed the Strep A serotyping system based on the propensity of M proteins to elicit "type-specific" antibodies [8]. M proteins have been the focus of many vaccine studies, and more recently other non-M cell wall antigens have been evaluated in pre-clinical studies. New technologies including reverse vaccinology [9] and the diverse 'omics have also contributed to possible vaccine antigens.

Invasive infection models

Invasive infection models have been developed for vaccine development and have demonstrated development of systemic immunity. Whole bacteria, single antigens alone and in combination and passive transfer of immunity using antisera and IVIg have all successfully induced immunity in animal models. In these models, intramuscular, subcutaneous, and intranasal vaccination provides protection from invasive intramuscular or subcutaneous challenge with Strep A bacteria.

Non-invasive infections

Non-invasive infections carry the largest burden of Strep A disease and would be the ideal target of vaccination. However, much less is known about sterilizing immunity or inhibiting colonization. During non-invasive infection, there appears to be a temporal sequence of adherence and colonization by the bacteria. The initial "pioneer" cells perform long range adherence and form molecular bridges with host proteins. The following "settler" cells have shorter range adherence with higher affinity and specificity. As the bacterial "society" forms in biofilms there is environmental sensing, extracellular polymeric substance formation and quorum sensing. Finally a "community" is established with cell-to-cell signaling, coaggregation, metabolic synergy and genetic exchange [10]. It is unknown against which stage or stages of colonization an effective immune response must act to inhibit development of infection.

Animal models of nasopharyngeal infection

Animal modes of nasopharyngeal infection have also shown that whole bacteria, single and combinations of antigens and passive immunization are able to induce immunity.

The route of immunization

The route of immunization may also be important to the development of an effective immune response against Strep A. Intranasal vaccination with adjuvanted protein vaccines appear better at preventing lethal intranasal infections. Intranasal vaccines can generate both secretory IgA at the mucosa and serum IgG, and potentially also cell-mediated forms of immunity that are much less characterized [11].

The many unknowns relating to human nasopharyngeal infection

When studying outbreaks of pharyngitis and scarlet fever in children, it has been shown that approximately 50% of children acquire the outbreak strain. Of these children the majority carry the bacteria asymptomatically, some become heavy shedders of the strain, yet only a small number of

children develop scarlet fever and pharyngitis. This may indicate a spectrum of different levels of immunity to different virulence factors in the nasopharynx (**Table 1**) suggesting that a cascade of different gaps in immunity may give rise to scarlet fever.

Table 1. Proposed basis for the spectrum of immunity in nasopharynx

Antibody	Resistant	Colonized	Shedder	Pharyngitis	Scarlet Fever
Attachment	+	-	-	-	-
Opsonic	+	+	-	-	-
Anti-virulence	?	?	+	-	-
Anti-toxin	?	?	+	+	-

No assays to understand mucosal immunity in children

There are no assays to understand mucosal immunity in children despite advances in other diseases. We have a better understanding of systemic immunity, and it has been possible to adapt the neutrophil uptake assay using a neutrophil cell line (HL-60) which is more easily transferrable and reproducible as it does not require primary neutrophil isolation [12]. The classic Lancefield assay with whole blood, the neutrophil uptake assay, the HL-60 assay and assays which measure the inhibition of specific virulence factors are surrogates of immunity for Strep A. These assays provide evidence for the mechanism of immunity, but are often strain dependent, some require fresh human blood or neutrophils, and are difficult to standardize.

Strep A vaccine development requires a correlate of immunity assay

Strep A vaccine development requires a correlate of immunity assay which is easy to standardize and may reflect an interaction of antigen and antibody that is irrelevant to immunity.

The roles of correlates of protection assays are to provide a surrogate indicator of vaccine efficacy in situations where international standards are required; to replace the need for clinical end points in vaccine trials, if they are subject to regulatory acceptance, abrogating the requirement of waiting for disease to develop and to allow for ongoing surveillance of immunity in target populations. Unfortunately, there are many current knowledge gaps hindering development of such an assay for Strep A which need to be addressed to progress the correlate of protection field. These gaps include the identification of key antigens to use in the assay to ensure broad coverage of strains, the comparison to established opsonic or inhibitory assays, the identification of signals in population surveillance, disease samples and vaccinated cohorts, including in the human challenge model developed in Melbourne, assays that measure mucosal secretory IgA may be required to understand mucosal immunity, including which biospecimens to sample, and further investigations to determine the roles of cellular immunity, including T and B lymphocytes, peripheral blood mononuclear cells and cells in the tonsils, as do genetic determinants of susceptibility and the differences between intranasal and intramuscular vaccine-induced immunity. The immune factors associated with post-Streptococcal autoimmune conditions should also be considered.

The Full Value of Strep A Vaccines

Prof. David Bloom, Harvard T.H. Chan School of Public Health, Boston MA, USA

Introduction

The list of members of the SAVAC Full Value of Strep A vaccine Assessment Working Group is provided is Annex 3.

Vaccination can have many sources of value. Such sources of value may include profits for vaccine manufacturers, efficiencies in healthcare spending for health ministers, the inherent and instrumental values of better health for individuals and their families, and in addition to most of those previously stated, the value assigned to any changes in social equity and political stability that may be associated with falls in the incidence and severity of vaccine preventable diseases for society.

The working group for the Full Value of Vaccines Assessment (FVVA) for Strep A vaccines is exploring the potential sources of value of prospective vaccines from multiple perspectives, and incorporating these sources of value into metrics commonly used and understood by different stakeholders. In particular, the FVVA is developing a comprehensive, quantified view of the value of Strep A vaccines through the conduct and consideration of 4 sets of analyses.

The first set of analyses is focused on the burden of Strep A diseases, which is being led by the Telethon Kids Institute. It includes several activities aimed at conceptualizing, modelling, and measuring the consequences of Strep A infection for population health in different epidemiological, social, economic, and health system contexts.

The second set of analyses is focused on a business investment case, which is being led by Shift Health. It includes a vaccine landscape assessment and a report on the return on Investment in the research and development, manufacture, and sale of a Strep A vaccine from a commercial perspective.

The third set of analyses is focused on a traditional health payer-centric investment case, which is being led by the International Vaccine Institute. It includes cost-effectiveness analysis of Strep A vaccination vs. other prevention and control strategies from a health payer perspective.

The fourth set of analyses is focused on a global investment case, which is being led by the Harvard Chan School of Public Health. It looks at the sources and returns on investment in a Strep A vaccine from a societal perspective, encompassing as many of the health, economic, and social benefits of a Strep A vaccine as possible. Insofar as public monies are substantially used to finance Strep A vaccine coverage, it makes sense to know and compare them to the full public benefits that follow from that spend.

Sources of value

The potential sources of value created by the development and delivery of a Strep A vaccine vary in their relevance to the different investment cases. They also vary in terms of the availability of data to meaningfully quantify them. In the absence of data, we can sometimes rely on models calibrated using parameters in existing literature, along with related sensitivity analyses to reflect uncertainty. In other situations, we can merely note a source of value, and reason our way to a determination as to whether it likely makes our results more or less conservative.

Synthesis and summary of existing data

To calibrate our models, we are taking stock, through a series of four systematic reviews, of existing data on the incidence of Strep A clinical endpoints throughout the world and over time, along with its social, economic, and spatial correlates. These systematic reviews will be submitted to academic journals to elicit the benefits of peer review and to save others the time it takes to gather, review, and distill the messages from a sizeable body of literature.

Generating new data

We have been working out a collaboration with the New Zealand's University of Otago. The collaboration seeks to quantify the effect on the microbiome at the individual level and on antibiotic resistance among bystander pathogens at the community level of relying on antibiotics to address Strep A infection.

Economic modeling

We are working on the development of a general, static epidemiological model of Strep A clinical endpoints in collaboration with the London School of Hygiene and Tropical Medicine. Our hope is to use appropriately calibrated versions of the model to anchor our cost-effectiveness and social return on investment analyses. We also hope to work on the development of a disease transmission model to incorporate the indirect effects of a Strep A vaccine on infection and clinical endpoints. Both the static and epidemiological models will be made as user friendly as possible to facilitate use by external stakeholders.

Conclusion

The FVVA has been in operation for a little more than one year. It is no surprise that we've benefited a lot from the generous and constructive guidance received from members of SAVAC's Executive Committee. We've also benefited from a world class Technical Advisory Committee, made up of epidemiologists, health economists, and specialists in medicine, immunology, and global health policy.

Although the past year has been very challenging for all of us, the FVVA team continues to move forward at an accelerating pace toward delivering theoretically sound, quantified investment cases on the development and delivery of Strep A vaccines.

Vaccine Safety Approach to Strep A Vaccine Development

Prof. Edwin J. Asturias, University of Colorado School of Medicine, Colorado School of Public Health

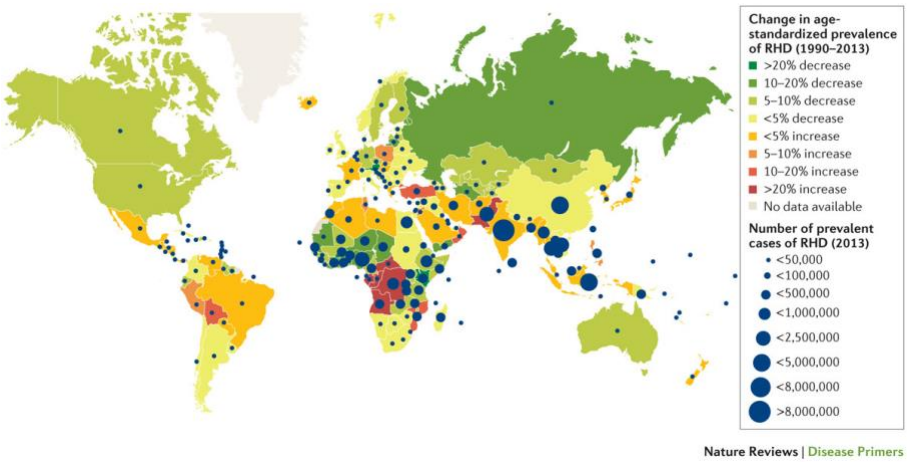
Framework to anticipate and investigate vaccine safety

The list of members of the SAVAC Safety Working Group is provided is Annex 3. Safety of vaccinated individuals and populations is of paramount importance. One important outcome of the SAVAC Safety Working Group was to define a framework of analysis to anticipate and investigate the potential safety issues of the development of Strep A vaccines. It is important we start gathering clues from the natural history of Strep A infections and their complications with background rates in various regions and populations of the world. Ideally, we would like to have biomarkers as signal for disease severity and sequelae that may develop with vaccine-induced immunity or after natural challenge with Strep A in vaccinated people. We also need to gather clues from Strep A Vaccine preclinical studies and learn how the findings might apply to vaccine trials in humans. This would entail the development of methods and causality assessment framework for Strep A vaccine safety assessment during Phase II and III studies. These vaccine safety assessments would benefit of a regulatory framework.

Burden of RHD as background rates for Safety

The natural history of Strep A infection and complications are relatively well described [1]. The burden of Rheumatic Heart Disease (RHD) represents background rate for safety. If ARF/RHD is an efficacy and safety endpoint, background rates are critical. Vaccine studies would likely concentrate in countries with high incidence and prevalence. The map below illustrates how heterogenous the ARF/RHD is across the world. It shows the number of prevalent cases of rheumatic heart disease (RHD) in 2013 by country, as well as the change in age-standardized RHD prevalence from 1990 to 2013 (**Figure 1**) [13]. While the situation has improved in some countries over the years, some are still heavily affected. Vaccine studies would likely concentrate in countries with high incidence and prevalence of Strep A infection. If ARF and RHD are efficacy and safety endpoints, background rates are therefore critical to document.

Figure 1. The global burden of RHD. Number of prevalent cases of rheumatic heart disease (RHD) in2013 by country, as well as the change in age-standardized RHD prevalence from 1990 to 2013.

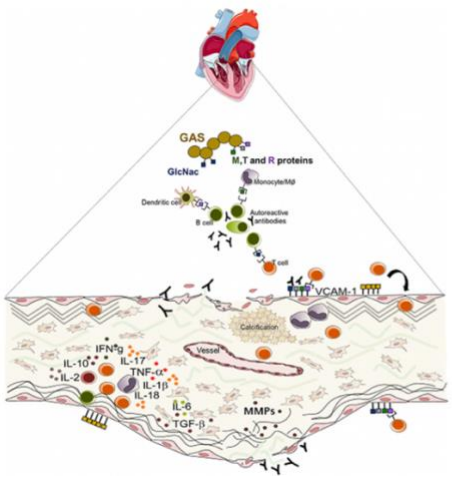


ARF pathogenesis and biomarkers for Strep A vaccine safety

The immunopathogenesis of ARF and RHD is a series of very complex host-pathogen interactions [14]. While we may suspect the implications of carbohydrates and interaction with myosin, we don't have an idea of the window as to when these events occur. We do understand that the minimum window for RHD may be two weeks, more likely 4-6 weeks. If such complication would occur within this time window, this may suggest a link with auto-antibodies induced by the vaccine. As emphasized by Jonathan Carapetis in his presentation, it is therefore critical that studies measuring background rates and endpoints of interest with time of occurrence be implemented as soon as possible.

As all Strep A vaccine developers would welcome the discovery of immune correlates of protection against Strep A, the identification of biomarkers as safety signals would be extremely helpful for the clinical development of Strep A vaccines, whether these signals were present before the vaccine study or developed during the vaccine study. We have listed some potential biomarkers that have been looked at as possibly linked to the Acute Rheumatic Fever (ARF) pathogenesis (**Figure 2**).

Figure 2. Potential biomarkers as possibly linked to the Acute Rheumatic Fever pathogenesis



Process or Marker	Causality component	Immune/non-immune surrogate
Autoimmune reaction B-cells T-cells	Biological plausibility Molecular Koch's postulates	TLR2 (−308A, −238G), FCN2 (G/G/A), MASP2 (371D, 377V, 439R), MBL (A, O) MIF (-173CC), FCγRIIa (393A)
GAS carbohydrate epitope N-acetyl-β- d -glucosamine (GlcNAc)	Biological plausibility Molecular Koch's postulates	
Upregulation of VCAM-1	Biological plausibility Molecular Koch's postulates	
Cardiac myosin Ag	Challenge/ rechallenge Dose responses	T-cell reactivity
Susceptibility to ARF or other autoimmune phenomena		HLA class II genes (several HLA-DR and DQ alleles)

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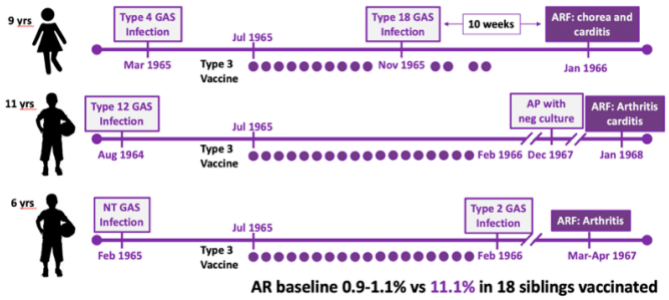
Limitations of biomarkers for Strep A vaccine safety

We must however acknowledge some limitations of biomarkers for Strep A Vaccine Safety. There are no well-defined immune markers that could act as a surrogate for risk of ARF development. There are significant gaps in knowledge of mechanistic correlates of ARF/RHD development and biomarker identification. Natural infection studies are warranted, as well as application of innovative immune-profiling technologies before and during trials. The development of biologic time windows for sequelae of GAS infection may inform vaccine safety assessment. In the meantime, the Jones criteria with echocardiography will be essential for vaccine safety evaluation.

Serious Adverse Events of Strep A M type 3 vaccine study

Much can be learned from the initial vaccine studies in humans that triggered safety concerns with Strep A vaccine development and testing. Massell's study conducted in 1965 tested SAEs of Strep A M type 3 vaccine [15, 16]. The study enrolled 21 children and tested different doses and schedules. Three children who received the vaccine developed ARF (chorea and carditis, arthritis and carditis, or arthritis alone). Although the intervals between vaccination and onset of these serious adverse events varied between these three children (**Figure 3**), the attributable risk was estimated to 11% compared to 0.1% in the unvaccinated population a ten-fold higher risk for those vaccinated This led to the conclusion of the time that these vaccines may be more harmful than beneficial to vaccinated populations.

Figure 3. Massell's study – Serious adverse events and timing



As part of an efficacy review of all Biologicals approved prior to 1972, the US FDA convened a "Panel on Bacterial Vaccines and Bacterial Antigens with No U.S. Standard of Potency." The panel concluded

that uncontrolled use of group A streptococcal antigens in bacterial vaccines with "no U.S. standard of potency" represented unacceptable risks, and the FDA Commissioner, codified this conclusion in "21 CFR 610.19 Status of specific products: Group A Streptococcus", effective 5th January 1979 [17].

A critical Group A Streptococcus Workshop, sponsored by the National Institute of Allergy and Infectious Diseases, NIH, in March 2004, allowed parties interested in developing new group A streptococcal vaccines to voice their opinion about 21 CFR 610.19. perceive the regulation as an impediment, voiced during public meetings and workshops, e.g., the Group A streptococcus workshop sponsored by the National Institute of Allergy and Infectious Diseases, NIH. It was highlighted at this meeting that advances in molecular biological techniques allowed better understanding of the potency and cross reactivity of the group A streptococcus, and therefore, 21 CFR 610.19 may be obsolete [18].

30-valent M protein-based group GAS vaccine in healthy adults

More recently, a 30-valent M protein-based Strep A vaccine was tested in healthy adults It was a Phase I study, enrolling adults 18–50 years of age; 23 received the Strep A vaccine and 13 controls received an active placebo, acellular Pertussis vaccine (2:1 ratio). Each were vaccinated at 0, 30, and 180 days. The thorough safety assessment included frequency and severity of local and systemic adverse events for 7 days. All participants were followed up during 12 months. Cardiac (ECG & echocardiography at day 0 and day 211), neurological and joint examinations were performed. Tissue cross-reactive assays were performed at days 0, 45 and 211).

Some Strep A vaccine participants experienced muscle ache reactions after dose 2 (44.0% vs. 0.0% in controls); p= 0.006). Proteinuria was detected in 3 participants (2 Strep A vaccinees vs. 1 control), very much in the same range of value of the control. Importantly, no cardiac events or tissue cross-reactive antibodies were detected in any of the participants [19].

Proposed Safety Monitoring Phase I, II and III studies

These results let the safety working group to propose some framework of safety evaluation in future Strep A vaccine clinical trials. The proposed Safety Monitoring Phase I, II and III studies are shown in **Table 2**.

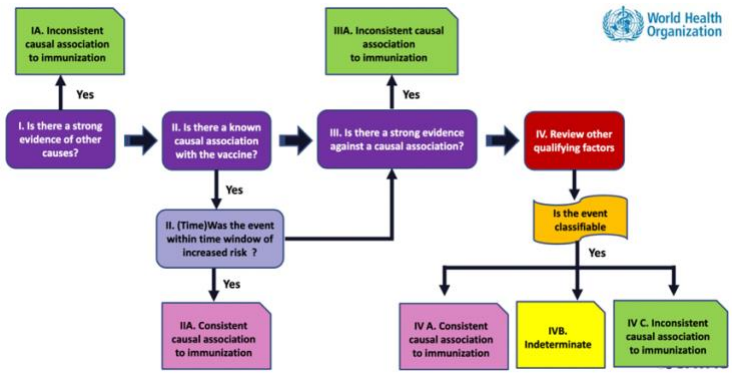
Table 2. Proposed Safety Monitoring for Phase I, II and III studies

Safety Monitoring category	Variables	Frequency
Common Safety	• Clinical exam and vital signs • Immediate local / systemic reactions • Daily local and systemic reactions • Unsolicited adverse reactions • SAE and SUSAR • AESI • Routine lab parameters	Days 1, 7, 14 post each dose 60 minutes Daily up to Day 7 Daily up to Day 28 Duration of the study Duration of the study Days 1, 7, 14 post each dose
Strep A-specific assessments	• Non-specific inflammation parameters: CRP, C3, C4 • Strep A culture monitoring • Anti-DNASe or anti-streptolysin O • Anti-tissue responses (heart, kidney, myelin)	Baseline, Day 14 and every 3 months Baseline and every 3 months
Cardiac function assessment	• ECG • Echocardiogram	Baseline and end of follow-up Baseline, quarterly for 12 months and illness

Use of WHO Causality Assessment Program to evaluate AEFI for Strep A Vaccine

Another important tool is the WHO Causality Assessment Program (CAP) algorithm AP to evaluate Adverse Events Following Immunization (AEFI) adapted to Strep A Vaccine safety assessment, looking at other alternative causes of AEFI and importantly the time window of occurrence of AEFI and evidence investigators may have to associate Strep A vaccination with AEFI (**Figure 4**) [20].

Figure 4. WHO Causality assessment algorithm



Safety parameters required for Causality Assessment

For better causality assessment, we will need the development of additional parameters required for safety assessment. These elements are summarized in **Table 3**, in particular background rates of possible safety signals by studying incidence and prevalence of ARF and RHD and of proteinuria and chronic kidney disease in retrospective studies and prospective surveillance studies, clear case definitions of ARF and RHD, with severity and certainty case definitions for possible AEFI signals with the Brighton Collaboration consensus guidelines, consensus on safety assessment methods such as self-controlled case series methods, immuno-profiling of cases and controls, and minimum incidence rates, and as mentioned earlier, guidelines for causality assessment of Suspected Unexpected Serious Adverse Reactions (SUSAR) and Adverse Events of Special Interest (AESI) with adaptation of WHO AEFI causality assessment guideline, development of work up for alternative causes guide, and laboratory parameters.

Table 3. Development of additional parameters required for safety assessment and better causality assessment

Requirements	Parameters	Sources
Background rates of possible safety signals	• Incidence/prevalence of ARF/RHD • Incidence/prevalence if proteinuria and CKD • Others	• Retrospective studies • Prospective surveillance
Case Definitions	• ARF and RHD • Severity and certainty case definitions for possible AEFI signals	• Consensus guidelines • Brighton Collaboration development
Safety Assessments Methods	• Self-controlled case series methods • Immuno-profiling of cases and controls • Minimum incidence rates	
Guidelines for Causality Assessment of SUSAR, AESI	• Adaptation of WHO AEFI causality assessment guideline • Development of work up for alternative causes guide • Laboratory parameters	

Regulatory framework for Strep A vaccine safety

Importantly, the development of a regulatory framework for Strep A vaccine safety is required. Currently there is no specific regulatory guidance on what constitutes an adequate preclinical assessment of potential vaccine-induced autoimmunity with new GAS vaccines before the first-in-human study.

A regulatory framework and guidance would help the assessment of AESI based on, product-specific mechanism of action, platform and vaccine composition, and preclinical data and the cumulative clinical safety experience should include all severe Strep A-related disease manifestations. This implies the detection of all new-onset Strep A infections that can result in ARF/RHD and an antibiotic treatment regimen of new-onset Strep A infections standardized in vaccine trials. Finally, long term follow-up studies of Strep A vaccine study participants should be designed and implemented with the perspective of post-marketing pharmacovigilance activities looking at identified and potential risks.

Strep A Vaccine Pipeline

Dr. Don Walkinshaw, Shift Health, Toronto, Ontario, Canada

Context

Shift Health's Don Walkinshaw presented an overview of the Strep A Vaccine pipeline at the Strep A Vaccine Global Consortium (SAVAC) 2021 Stakeholder's Meeting. The presentation drew on information from a Strep A Vaccine Landscape Assessment that Shift Health completed in May 2020 and updates via personal communication with several Strep A vaccine developers in February 2021. Shift Health's work on the Landscape Assessment has informed ongoing development of a Strep A Vaccine Business Case which is part of the Full Value of Vaccines Assessment (FVVA) work funded by the Wellcome Trust and coordinated by SAVAC.

Pipeline Overview

Strep A vaccine pipeline is *early-stage*, with only one active program (StreptAnova) having completed a Phase 1 trial and most yet to enter clinical trials; *growing*, with at least 8 active programs with a product development focus; and *diverse*, with advanced programs testing both M and non-M protein candidates and employing a range of antigens and concepts.

Below is an overview of the most advanced, product development-focused programs. Work from other programs with an academic or exploratory research focus will not be described; these include a *Lactococcus lactis*-based intranasal vaccine from Aniela Wozniak's group at Pontificia Universidad Católica de Chile (Chile) [21], the Spy7 candidate from Shiranee Sriskandan's group at Imperial College London (UK) [6], a liposome-mediated intranasal delivery program from Rachel Stephenson's group at The University of Queensland (Australia) [22], a polyglutamic acid-trimethyl chitosan-based intranasal peptide nano-vaccine from Istvan Toth (The University of Queensland; Australia) and colleagues [23] as well as a self-amplifying RNA-based candidate from GSK Vaccines (Italy) [24].

Characterization of Advanced Strep A Vaccine Candidates

M Protein-Based Candidates

StreptAnova, from Jim Dale's group at the University of Tennessee (USA), and commercialization partner Vaxent, is an *emm*-type specific vaccine with four protein subunits comprising the N-terminal regions of M proteins from 30 Strep A serotypes along with alum as adjuvant. This candidate is the farthest along the development path, having completed a Phase 1a trial (in 2020) that demonstrated the vaccine was well-tolerated, had no auto-immunity or cross-reactive antibodies and elicited significant immunogenicity toward most of the targeted antigens [19]. The group has developed plans for future trials with *StreptAnova* and is ready to move into Phase 2 pending funding (James Dale, personal communication).

StreptInCor, from Luiza Guilherme's group at University of Sao Paulo (Brazil), is comprised of a 55-amino acid peptide from M5 protein conserved regions (C2, C3) with B- and T-cell epitopes, adjuvanted with alum. In preclinical studies, StreptInCor has shown high levels of antigen-specific antibodies and survival against Strep A infection challenge in mice as well as a lack of auto-immune reactions [25, 26]. In minipigs, the candidate was well tolerated and displayed no harmful effects on heart tissue [27]. A planned Phase 1 trial (NCT03998592) was recently withdrawn before enrollment began, due to the end of an "agreement between interested parties".

MJ8CombiVax and *P*17*, from Michael Good and collaborators at Griffith University (Australia), both contain the same peptide with a modified B-cell epitope from the IL-8 protease, SpyCEP, combined with one of two versions of a peptide from the M protein C-terminus: J8 for MJ8CombiVax [28] and P*17 for its namesake candidate. Both peptides in each candidate are conjugated to the CRM197 carrier protein and MJ8CombiVax is adjuvanted with alum while P*17 is adjuvanted with CAF01. Both candidates have shown promising activity in animal models, especially P*17. A recent publication [29] showed that intramuscular injections followed by an intranasal dose of P*17 induced high antibody levels in both the airway mucosa and serum as well as protection against upper respiratory tract infection and invasive disease in mice. MJ8CombiVax and P*17 will both be included in a Phase 1 dose-ranging study in Canada in 2021. If successful, P*17 will enter a Phase 1B human challenge study in Australia (Michael Good and Chris Davis, personal communication).

Non-M Protein-Based Candidates

Combo4, from GSK Vaccines Institute for Global Health (GVGH), GSK Vaccines (Italy), contains the native Strep A Group A Carbohydrate (GAC) as well as three recombinant proteins: Streptolysin O (SLO), SpyCEP and SpyAD, adjuvanted with alum. Preclinical studies demonstrated immunoprotection in mouse models and efficacy in opsonophagocytic killing (OPK) assays using sera from immunized rabbits [30, 31]. In non-human primate (NHP) studies, Combo4 was immunogenic and had a favorable safety profile (GVGH, personal communication). GVGH is currently aligning on a clinical development plan and specific plans for a Phase 1 trial have not yet been made public.

Vax-A1, from Vaxcyte (formerly Sutrovax; USA), is based on work from Victor Nizet's group at University of California, San Diego. Like Combo4, Vax-A1 also contains GAC combined with recombinant proteins; however, Vax-A1 employs a modified version of GAC that may lower the risk of cross-immunogenicity. Vaxcyte has not disclosed which recombinant proteins will be included in the final formulation, though a recent publication described a formulation with SLO, SpyAD and SCPA/C5a peptidase together with GAC and adjuvant [32]. That study showed that Vax-A1 protected mice against skin infection and systemic disease following Strep A challenge and showed no cross-reactivity to human heart and brain tissue. Attesting to the potential for Strep A vaccines to benefit efforts to combat antimicrobial resistance, Vaxcyte has received funding for advancing Vax-A1 development from CARB-X (https://carb-x.org/gallery/vaxcyte/).

Combo5, from Mark Walker's group at the University of Queensland (Australia), contains 5 recombinant proteins: SLO, SpyCEP and SCPA as well as trigger factor and arginine deiminase and adjuvanted with SMQ. In NHP studies, Combo5 reduced the severity of pharyngitis [33], and in mice, the candidate protected against skin and invasive infection [34]. Future development plans for Combo5 include additional NHP studies and controlled human challenge studies (Mark Walker, personal communication).

TeeVax, from Thomas Proft and Jocelyn Loe's group at University of Auckland (New Zealand), is a multivalent protein vaccine with T-antigen domains from the pilus of the majority of Strep A strains. TeeVax has shown protective efficacy against invasive disease in mice [35] and its developers are currently working on reformulating the vaccine with alternative adjuvants and assessing mucosal delivery (Thomas Proft and Jocelyn Loe, personal communication).

Conclusion

The current Strep A vaccine pipeline has strong potential to test human proof-of-concept for a variety of concepts and antigen types. Initial preclinical efficacy and safety results and, in some cases, human safety and immunogenicity data are encouraging. Funding is currently a limiting factor for some of the programs to move ahead with planned clinical development activities—pointing to the need for continued advocacy and awareness-building around the urgency and public health value of a Strep A vaccine.

Update on the Business Case for a Strep A Vaccine

Dr. Marni Williams, Shift Health, Toronto, Ontario, Canada

Context

As part of the Full Value of Vaccines Assessment (FVVA) workstream led by the Strep A Global Vaccine Consortium (SAVAC), Shift Health is developing a business case for investment in Strep A vaccine Research & Development (R&D). By estimating the potential demand for, and corresponding revenue and return on investment (ROI) of a vaccine for the prevention of Group A Streptococcus (Strep A), the business case aims to provide vaccine manufacturers with critical information to support investment decision-making related to the R&D and manufacturing of a Strep A vaccine. Together with the other components of the FVVA, the business case will contribute to SAVAC's efforts to assess the potential value of Strep A vaccines from a variety of perspectives.

Model Structure

The business case is being built around a dynamic demand forecasting model of a hypothetical Strep A vaccine. A multistep approach was followed that included: landscape assessment of Strep A vaccine candidates; literature review of vaccine modelling publications; and interviews with infectious disease and vaccine experts, global health funders, in-country vaccine decision-makers, and representatives from multinational pharmaceutical company (MPC) and developing country vaccine manufacturers (DCVMs). Because Strep A vaccine candidates are all at an early clinical development stage, there are no data on vaccine performance or uptake to leverage for the model. Instead, assumptions based on historical proxy vaccines and interviewee insights informed the model inputs.

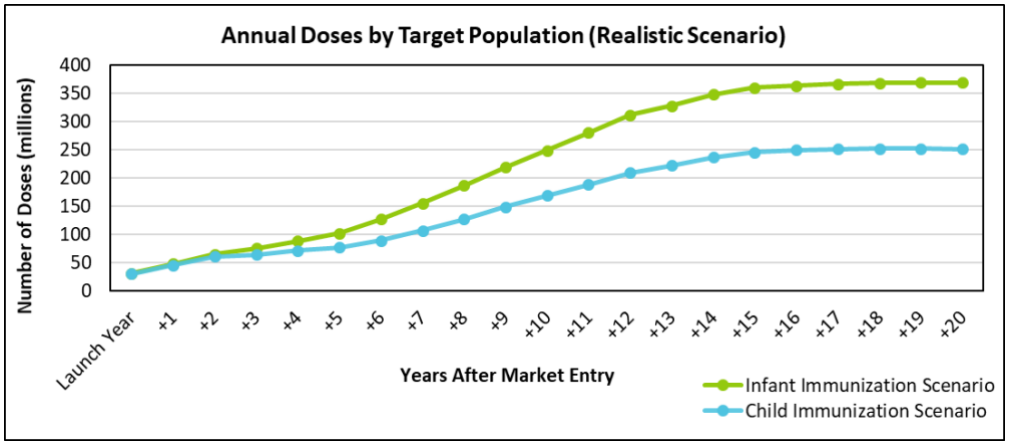
Key features of the model include:

- Employment of a hypothetical Strep A vaccine that aligns with the Preferred Product Characteristics of a Strep A Vaccine [36] put forward by the WHO *(future work could include gathering vaccine decision-maker perspectives on how different PPCs would impact demand)*.
- Inclusion of either infant (<1 year) or young children (aged 4-7) as target populations for the prevention of common Strep A infections (e.g., pharyngitis, scarlet fever, impetigo) and accounting for vaccine access via both public and private markets.
- Assessment of global vaccine demand across optimistic, realistic and conservative scenarios to account for varying timelines for R&D (8 or 13 years), vaccine adoption (8, 15 or 20 years) and ramp-up to peak coverage (5, 10 or 15 years).
- Incorporation of up-to-date, country-level data from relevant proxies to inform:
    - Peak coverage rates—DTP3 and MCV2 for the infant and young child populations, respectively, as these vaccines are assumed to have reached peak coverage rates given their long-standing uptake through national immunization programs and demonstrable value.
    - COGS—cost to manufacture a dose of IPV as detailed cost analysis [37] exists for this vaccine and applying a multiplier to account for relatively more complex Strep A vaccine (~$3.2/dose).
    - Vaccine price—average price per dose of current PCV13 prices by country-income level (i.e., Gavi-eligible, LMIC, UMIC, HIC ranging from ~$3.4 to $30 per dose) as reported in the Market Information for Access to Vaccine (MI4A) Database [38].
- Assessment of the potential ROI for either an MPC (development and manufacturing for global vaccine rollout) or DCVM (rollout to LIC and LMICs only), each with different investment outlays, market access strategies and risk appetites, and additionally accounting for situations where the manufacturer initiates investment at different stages of development (i.e., starting from Phase 1, after completion of Phase 2 or after completion of Phase 3).
- Allowance for modifications to be made to inputs or assumptions in the dynamic forecasting model as new data become available.

Preliminary Results

The preliminary modelling results show that assuming a realistic timeline (i.e., the realistic scenario) for vaccine development (13 years), adoption (15 years across all countries) and ramp-up (10 years), the annual demand peaks at ~360M doses per year for infants (translating into ~120M immunized individuals with the 3-dose regimen) and ~250M doses per year for young children (**Figure 5**) *(N.B. specific outputs should be taken as approximations that may change during refinement and finalization of the model)*. The difference in demand between these two populations reflects the typically higher coverage rates for established infant immunization programs. Approximately 50% of the peak demand is from LMICs, given the higher population sizes of these countries and mirroring what is observed for the global market (MI4A) for other vaccines.

Figure 5. Strep A vaccine demand forecast - Annual Doses by target population (realistic scenario)



The total revenue at peak is estimated at $3.5B and $2.5B per year for the infant and young children immunization programs, respectively (resulting in estimated annual profit of $2.3B and $1.7B, respectively). The private market (with associated higher profit margins) is expected to serve as the major market within the first few years before countries adopt the vaccine as part of their national immunization programs, after which the public market is estimated to contribute up to 90% of the annual profit at peak. The average profit margin across all country-income levels is estimated at ~65% (ranging from~5% in Gavi-eligible countries to ~90% in HICs) with ~60% of the profit originating from vaccine sales in LMICs and UMICs, again reflecting what is observed for the global market broadly. The results for peak demand, revenue and profit are similar across the three scenarios tested; however, the time it takes to reach this peak is 12, 15 and 18 years for the optimistic, realistic and conservative scenarios, respectively.

Lastly, the estimated ROI for all scenarios and levels of investment—with maximum investment from Phase 1 to market launch being $30M for a DCVM and $350M for an MPC—the net present value after 10 years of accumulated profit is positive and significant ($30M and $1.1B for a DCVM and MPC, respectively, for the highest investment level in the realistic scenario for infant immunization).

Conclusion

The development of a dynamic forecasting model for a hypothetical Strep A vaccine estimated the total potential global demand for this vaccine across three scenarios. While model assumptions and inputs continue to be refined and validated by SAVAC, the preliminary results suggest that the Strep A vaccine market may represent an attractive investment for vaccine manufacturers. In combination with the other FVVA workstreams, the business case will serve as an important tool in discussions with private sector companies and potentially other funders to create awareness around the public health urgency to reduce the burden of Strep A and the concomitant commercial opportunity associated with Strep A vaccine R&D.

Concluding Remarks

Dr. Jerome Kim, Director General of IVI, Chair of the meeting, and Prof. Prof. Andrew Steer, co-Chair, from the Murdoch Children's Research Institute, University of Melbourne, Australia

Prof. Andrew Steer wished we would have been together face-to-face. One of the strengths of this community is the interpersonal relationships we have, but more than that is that SAVAC and the funding from the Wellcome Trust has allowed that community to expand outside of Group A "streptococcologists" during this meeting today. The meeting has been outstanding with inspiring work presented that allows to progress in the field, with comments on the importance of understanding the burden of disease, cost and impact of the disease, as part of the advocacy effort. There is a lot more work to be done. You hear more about this work and we will engage more with you will and SAVAC will be reaching out to you over the remainder of the funding period for SAVAC. We really intend and hope that SAVAC will continue as we all think that SAVAC has a key role to play in coordinating the international network around advocacy and advancing the scientific efforts.

Prof. Andrew Steer thanked the speakers, Jonathan Carapetis, Shiranee Sriskandan, Edwin Asturias, David Bloom, Don Walkinshaw, and Marni Williams for their outstanding presentations and the organizers, in particular, Somyoung Cho, Jean-Louis Excler and Chloe Sye Lim Hong. Andrew thanked also the working group members and their enthusiasm and commitment to this field, the members of the Executive Committee (Jerome Kim, Andrew Steer, David Bloom, Shiranee Sriskandan, Leslie Zuhlke, Edwin Asturias, and David Kaslow), most of them unfunded, for their leadership of SAVAC. A big thank to the funder of SAVAC, the Wellcome Trust, to have supported this work. The participants were invited to reach out SAVAC, should they have any additional questions and comments, their contribution being much appreciated to help advance the field further.

Dr. Jerome Kim echoed Andrew's statements. Very importantly, the work Prof. David Bloom on the Full Value of Vaccine Assessment will be one of our strongest point for advocacy and argument to make the companies around the world that this is a major problem and that the investment would not be without benefit for the companies as well as preventing a good portion of the 500,000 deaths occurring annually, linked Strep A infection.

Thank you and wishing you all well.

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Annex 1

The Meeting Agenda

STREP A VACCINE GLOBAL CONSORTIUM

First Stakeholders (Virtual) Meeting

FINAL AGENDA

- **Date:** 11 March 2021
- **Time & City**

KST	EST	GMT	CET
10 PM	8 AM	1 PM	2 PM

The Strep A Vaccine Global Consortium (SAVAC, https://savac.ivi.int/about) is organizing a virtual key stakeholders 2-hour meeting.

Day 1		
Time	**Session/Topic**	**Chair (C) / Presenter(P)**
00:00 - 00:05	**Welcome, Introductions and Objectives**	Jerome Kim, International Vaccine Institute
00:05- 01:00	**(Session 1) Overview of SAVAC key workstreams**	Andrew Steer (C), Murdoch Children's Research Institute
	Burden of Diseases (10min)	Jonathan Carapetis (P), Telethon Kids Institute
	Strep A Immunity and Correlates of Protection (10min)	Shiranee Sriskandan (P), Imperial College, London
	Strep A Vaccine Safety Approach (10min)	Edwin Asturias (P), University of Colorado
	Discussion (25min)	Andrew Steer (C)
01:00- 01:55	**(Session 2) The Full Value of Strep A Vaccines**	David Bloom (C), Harvard School of Public Health (HSPH)
	The Full Value of Vaccines applied to Strep A (15min)	David Bloom (P), HSPH
	Strep A Vaccine Pipeline (5min)	Don Walkinshaw (P), Shift Health
	Update on the business case for a Strep A vaccine (10 min)	Marni Williams (P), Shift Health
	Discussion (25min)	David Bloom (C), HSPH
01:55- 02:00	Closing remarks – Andrew Steer, Murdoch Children's Research Institute	

This meeting will:

- Inform the Strep A community of SAVAC achievements and work in progress
- Discuss critical issues of Strep A vaccine development
- Seek advice and recommendations on next steps
- Increase awareness and interest of funders

SAVAC wishes to receive feedback on Full Value of Vaccine Assessment and the stakeholders' recommendations on next steps.

Annex 2

Speakers

Annex 3

Burden of Disease Working Group Members

- Jonathan Carapetis (Co-Chair), Telethon Kids Institute, Perth, Australia
- Chris Van Beneden (Co-Chair), Centres for Disease Control and Prevention, Atlanta GA, USA
- Hannah Moore, Telethon Kids Institute, Perth, Australia
- Kate Miller, Telethon Kids Institute, Perth, Australia
- Amy Scheel, Emory University, Atlanta GA, USA
- Jeff Cannon, Telethon Kids Institute / Harvard T.H. Chan School of Public Health, Boston MA, USA
- David Kaslow, PATH, Seattle WA, USA
- Thomas Cherian, MM Global Health Consulting, Geneva, Switzerland
- Asha Bowen, Perth Children's Hospital / Telethon Kids Institute, Perth, Australia
- Mark Engel, University of Cape Town, South Africa
- Theresa Lamagni, Public Health England, London, UK
- Anna Seale, London School of Hygiene & Tropical Medicine, London, UK
- Gagandeep Kang, Christian Medical College, Vellore, India
- David Watkins, University of Washington, Seattle WA, USA
- Samuel Kariuki, Kenya Medical Research Institute, Nairobi, Kenya
- Rebecca Trowman, Telethon Kids Institute, Perth, Australia

SAVAC Correlates of Protection Working Group Members

- Shiranee Sriskandan, Imperial College, London, UK
- Alma Fulurija, Telethon Kids Institute, Perth, Australia
- Nina van Sorge, Amsterdam University Medical Center, The Netherlands
- Nikki Moreland, University of Auckland, New Zealand
- Hannah Frost, Murdoch Children's Research Institute, Melbourne, Australia
- Jean-Louis Excler, International Vaccine Institute, Seoul, Republic of Korea

SAVAC Safety Working Group Members

- James Ackland, Global BioSolutions, Melbourne, Australia
- Prof. Edwin Asturias, **Chair,** University of Colorado School of Medicine, Aurora CO, USA
- Adwoa Bentsi-Enchill, World Health Organization, Geneva, Switzerland
- Marco Cavaleri, European Medicines Agency (EMA), Amsterdam, The Netherlands
- James Dale, University of Tennessee Health Science Center, Memphis TN, USA
- Jean-Louis Excler, International Vaccine Institute, Seoul, Republic of Korea
- Alma Fulurija, Telethon Kids Institute, Perth, Australia
- Raj Long, Consultant, Seattle WA, USA
- Mignon McCulloch, Cape Town University, Cape Town, South Africa
- Shiranee Sriskandan, Imperial College, London, UK
- Andrew Steer, **Co-Chair,** Murdoch Children's Research Institute, Melbourne, Australia
- Wellington Sun, Senior Consultant, Vaxcellerant, Silver Spring MA, USA
- Beno Yakubu, National Agency for Food and Drug Administration and Control, Abuja, Nigeria
- Liesl Zuhlke, Cape Town University, Cape Town, South Africa

SAVAC Full Value of Vaccine Assessment Working Group Members

- David Bloom, **Chair,** Harvard T.H. Chan School of Public Health, Boston MA, USA
- Jeff Cannon, Telethon Kids Institute / Harvard T.H. Chan School of Public Health, Boston MA, USA
- Daniel Cadarette, Harvard T.H. Chan School of Public Health, Boston MA, USA
- Don Walkinshaw, Shift Health, Toronto, Ontario, Canada
- Marni Williams, Shift Health, Toronto, Ontario, Canada
- Anne Mullin, Shift Health, Toronto, Ontario, Canada
- Meghan Wright, Shift Health, Toronto, Ontario, Canada
- Ryan Willey, Shift Health, Toronto, Ontario, Canada
- Vittal Mogasale, International Vaccine Institute, Seoul, Republic of Korea
- Junk Seok Lee, International Vaccine Institute, Seoul, Republic of Korea
- Sol Kim, International Vaccine Institute, Seoul, Republic of Korea
- Prerana Parajulee, International Vaccine Institute, Seoul, Republic of Korea

Annex 4

Questions and Responses

No.	Name	Question	Answer	By
1	Danilo Gomes Moriel	Any thoughts why pharyngitis is not among GBD list?	It's bundled up in 'upper respiratory tract infections.'	Jeff Cannon
2	Ravi Ganapathy	Would multiplex-ELISA be then an option as an assay system for this?	There are several groups developing plex-type assays, Luminex, and MSD are in development.	Alma Fulurjia
3	Sushant Sahastrabuddhe	Great presentation! ICP is becoming more elusive goal, even for bacteria which have been studied and for which vaccines have undergone efficacy and human challenge studies. What makes us believe that we will be successful in GAS? Thanks.	Discussion session	Shiranee Sriskandan
4	Mark Sullivan	Do we have the engagement of stringent regulatory authorities in endpoint and assay development discussions when used as evidence for registration purposes? They are the only jurors that matter in determining the adequacy of these measures for registration and SAVAC is ideally placed to engage.	Discussion session	Edwin Asturias
5	Vittal Mogasale	How does burden of Group A streptococcus compared to other major vaccine preventable diseases?	Discussion session	Jonathan Carapetis

6	Jonathan Carapetis	Isn't there a risk of doing sequential echos in trials? There will be subtle changes that may not be of significance but which could raise concerns, because of the difficulties of interpreting echos, and it also adds a lot of expense for Ph 3. And does Edwin think that Ph 3 trials will need to be powered to exclude a risk of increased susceptibility to ARF, and if so is that even feasible?	Discussion session	Edwin Asturias
7	Anna Norrby-Teglund	Functional assays are important, opsonic are good as they measure outcome, while inhibitory assays are often factor-specific (superantigens, proteases, DNases etc). How does the discussion go here?	Discussion session	Shiranee Sriskandan
8	Julie Skinner	How long would you expect long-term follow up for vaccines? What would you recommend to be evaluated?	Often follow up for vaccine safety has been limited to 12 months. However, given the Dengue vaccine experience where AED was a concern and later a signal, 5 years was recommended. This is probably a good timeline for follow up.	Edwin Asturias
9	Jill Gilmour	From immune correlates perspective: Is there enough GAS sequence data globally to know how the bug is evolving. Is there a role for a systems biology approach to identify immune signatures that correlate with clearance, carriage etc.	Discussion session	Shiranee Sriskandan
10	David C. Kaslow	In addition to biomarkers that detect activation of pathways associated with naturally acquired GAS pathology, any thoughts on detection of vaccine-associated enhanced disease not related to natural acquired pathology (e.g., atypical vaccine-related events observed with formalin-inactivated RSV, killed measles vaccine, etc.)? Animal models that might be useful (analogous to cotton rats for RSV)?	Discussion session	Edwin Asturias

11	Charles De Taisne	Can one say that some most-advanced vaccine candidates do not contain antigens that may be linked to auto-immune disorders?	Needs follow up	
12	Vittal Mogasale	Jonathan said establishing sentinel surveillance sites for pharyngitis (and impetigo) is the priority. Why not surveillance for rheumatic heart disease in LMICs?	RHD is one of the conditions we have pretty good data about from a range of LMICs, and is best done through systematic echo surveillance studies. It is not a priority because we have such a good handle on it compared to other Strep A diseases.	Jonathan Carapetis
13	Mark Walker	How to separate identity of protective immunity antigens vs autoimmune triggers in humans? Do we know identity of either?	Discussion session	Shiranee Sriskandan
14	Genevieve Renauld	Are there preclinical data with a mRNA-based vaccine?	1. Not that we are aware of. 2. There has been some work in this area - see this paper published in 2017.	1. Jean-Louis Excler 2. Andrew Steer
15	Ole Olesen	Thanks for the presentation, has any of the 8 vaccine candidates been tested head-to-head?	The short answer is no, as they are too early in development and from different groups. But that may be envisaged in a non-human primate model.	Jean-Louis Excler
16	Julia Lynch	In your model, the vaccine characteristics you chose in your model (derived from PPC) led to the conclusion that there is potential for a commercially viable vaccine of public health value. Sometimes a PPC is general, idealized and may not be fully realistic. Although each developer likely has a more specific target product profile in mind, it might be helpful for this group to put forward a general TPP that would guide toward a useful and feasible product with thresholds for each key characteristic. In particular, I am wondering if the dynamic model can be used to define some of the threshold boundaries such as a minimum level of efficacy, and maximum COGs that would still result in a vaccine of public health value and commercial viability for a manufacturer. This would be very helpful in attracting a commercial	1. Discussion session 2. It is an excellent point Julia, and we need to do precisely what you suggest, given that an 80% efficacy target against pharyngitis may be optimistic.	1. Marni Williams, Don Walkinshaw 2. Jonathan Carapetis

		partner, and guide decision making around trade-offs often required through development.		
17	Mark Walker	The vaccine modelling assumes that a Strep A vaccine is efficacious in humans, I guess? Was there an estimate of the percent vaccine efficacy that was used in the modelling?	Discussion session	Marni Williams
18	James Wassil	Thanks for your extensive forecast. Can you share price assumptions for low, middle, and high-income countries? Also did you take into account affordability, especially at the GAVI-eligible and LMIC countries?	We used current PCV prices based on MI4 data from WHO. And we used prices based on different income level groups as well as Gavi eligibility.	Marni Williams
19	David C. Kaslow	Following Julia's question, given the highly favourable NPV (and robust vaccine pipeline), thoughts on the marketplace response--lack of significant interests by big pharma?	1. Discussion session 2. To address David's question, I think we have heard from Big Pharma that there are multiple overlapping reasons behind their lack of investment. In addition to regulatory obstacles, I do think a major issue is that the disease burden data have not translated into a sense of urgency or demand from countries, hence our statement in disease burden priorities: "Understanding country, regional and international decision-making for vaccines."	1. Marni Williams, Don Walkinshaw 2. Jonathan Carapetis
20	Kaja Abbas	What's the assumed unit price per dose of vaccine in the business investment case analysis?	Based on PCV prices by income level group ranging from ~$3/dose in LICs to $30/dose in HICs.	Marni Williams
21	Charles De Taisne	Slide 11: Why the NPV value of DCVM is much lower despite a lower investment? DCVM vaccine restricted to LMIC markets?	Yes, rollout only to LMICs for DCVMs - resulting in lower demand but also lower profit margin given lower price for the vaccines in LMICs.	Marni Williams