SAVAC Second Stakeholders Meeting Report

Strep A Vaccine Global Consortium

In-person and virtual meeting organized by
the International Vaccine Institute (IVI)
Seoul, Republic of Korea
6 June 2022

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Introduction

The Strep A Vaccine Global Consortium (SAVAC) Second Stakeholders' Meeting took place on 6 June 2022, in Stockholm, Sweden. The meeting was organized by the SAVAC Executive Committee chaired by Dr. Jerome Kim, Director General of IVI, and co-chaired by Professor Andrew Steer, Murdoch Children's Research Institute (MCRI), and by the IVI Secretariat. Participants contributed both in-person and virtually. The meeting followed on from the SAVAC First Stakeholders' meeting on 11 March 2021, which reviewed work in progress, discussed critical issues of Strep A vaccine development, and made recommendations on next steps.

The second SAVAC meeting shared and reviewed the latest SAVAC progress and achievements, and gaps identified since the first meeting, with the aim of widening the knowledge of vaccine development for *Streptococcus* A vaccine stakeholders. SAVAC working groups – including on the burden of disease, vaccine safety considerations, immunity and correlates of protection, and full value of vaccine assessment – presented their work to, and sought input from stake-holders in academia, the pharmaceutical industry, policy decision-makers, and funders. The SAVAC recommendations gathered from participants are a catalyst for 'SAVAC 2.0': a continuation aimed at filling the gaps and translating into action the development of Strep A vaccines to ensure that safe, effective, and affordable vaccines are available.

The full list of presenters was (see Annex D for the meeting agenda):
1. Jonathan Carapetis. A strategic approach to understand strep A disease burden.
2. Shiranee Sriskandan. Immunologic protection and correlates.
3. Edwin Asturias. A Vaccine Safety Considerations and Guidance during Development.
4. Kaja Abbas. Potential impact of prospective Strep A vaccines on the global burden of disease model-based analysis.
5. Jung-Seok Lee. Global economic burden for Strep A infections and cost effectiveness analysis for a hypothetical Strep A vaccine.
6. Dan Cadarette. The full health economic social benefits of vaccination conceptual framework and application to Strep A vaccines.
7. Jeff Cannon. The Effect of a Prospective Vaccine Against Group A Streptococcus on Global Antibiotic Consumption for Sore Throat.
8. Maddalena Ferranna. Global health and economic benefits.
9. Don Walkinshaw. Business Case for Industry Investment in Strep A Vaccine R&D.
10. Dan Tortorice. Optimal Global Spending for Group A Streptococcus Vaccine Research and Development.
11. Sushena Krishnaswamy. SAVAC 2.0.

The mission of SAVAC is to ensure that safe, effective and affordable Strep A vaccines are available and implemented to decrease the burden of Strep A disease for the most in need. SAVAC is funded by the Wellcome Trust.

Welcome remarks

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

Dr. Jerome Kim, Director General of IVI and Chair of SAVAC welcomed and thanked participants. Dr Kim noted the work that has been done and how it has positioned the consortia for the next stage, SAVAC 2.0. Dr Kim thanked the Wellcome Trust (Dr Charlie Weller, Dr Elizabeth Clem, and Dr Debbie King) for their support; and the Executive Committee for their commitment and time. Following a description of the meeting agenda, highlighting some of the key presentations, Dr Kim further thanked the moderators, Liesl Zuhlke (University of Cape Town) and David Kaslow (PATH), Dr Jean-Louis Excler (Project Lead), and the IVI organisers, Ms Somyoung Cho (Program Manager) and Ms Chloe Sye Lim Hong (Project Administrator). Finally, Dr Kim thanked and introduced the SAVAC co-Chair, Professor Andrew Steer (Murdoch Children's Research Institute, University of Melbourne).

Prof. Steer reiterated the thanks for the Executive Committee and IVI organisers, and thanked Dr Kim, and the funders, the Wellcome Trust. He highlighted how exciting it is to look back at the work that has been done, whilst also acknowledging that COVID-19 had created some challenges. Prof. Steer encouraged participants to consider what had been achieved during SAVAC 1.0, and also what can be further achieved in the future with SAVAV 2.0. He alluded to a proposal to be highlighted later in the meeting, for feedback from participants. Prof Steer, Dr Kim and the Executive Committee were in agreement that much had been achieved under SAVAC 1.0, but this was only the start, with much more to be done. Prof Steer introduced the first presenter.

1 Epidemiology and Burden of Disease workstream

Presented by Professor Jonathan Carapetis, and Associate Professor Hannah Moore and Dr Jeffrey Cannon, Telethon Kids Institute, Perth, Australia

1.1. Introduction

The overall goal of the workstream was to provide updated estimates of the global burden of diseases due to Group A *Streptococcus* (Strep A). Activities conducted under this workstream complement that of the Full Value of Vaccines Assessment (FVVA) workstream, in particular, providing estimates of the global burden of disease for specific Strep A endpoints required as inputs into economic models.

Updates to the global burden

There are many clinical endpoints of Strep A diseases including superficial infections such as pharyngitis and skin infections (impetigo); locally invasive diseases and invasive diseases such as cellulitis, bacteraemia, meningitis, puerperal sepsis, necrotising fasciitis; immune and toxin-mediated diseases such as scarlet fever and toxic shock syndrome; and sequalae of immune-mediated diseases such as acute rheumatic fever (ARF), acute post-streptococcal glomerulonephritis (APSGN), rheumatic heart disease (RHD) and chronic kidney disease [1]. It has been highlighted that as the disease spectrum associated with Strep A disease is wide and complex, understanding and then enumerating the global burden of disease is challenging. There have been previous attempts to estimate the burden using available data sources,

estimates from the World Health Organization (WHO), Global Burden of Disease (GBD) estimates (e.g., focusing on RHD) and systematic reviews focusing on particular Strep A endpoints. A recent estimate 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 RHD and a quarter to invasive infections [2]. Previous attempts to estimate the global burden of Strep A diseases[3] included few estimates from resource-poor settings where the burden is expected to be highest. Prior to COVID-19, Strep A had been highlighted as the fifth most lethal global pathogen as measured by mortality; following 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].

Systematic reviews have been conducted to better estimate the global burden of Strep A sore throat and invasive disease, whilst estimates for RHD, impetigo, and cellulitis are attainable from the GBD project. In the global literature review of Strep A sore throat incidence rates, only nine studies published since the year 2000 were identified with data suitable for a meta-analysis, which indicated a pooled incidence rate among children approximately 5-14 years-old of 22.1 episodes of Strep A sore throat per 100 child-years (95% CI 14.7–33.1) [4]. The review found significant methodological heterogeneity between the studies, which will need to be standardised to analyse and evaluate impact of Strep A vaccines post-introduction into policy. In the global systematic review of Strep A invasive infection incidence and case-fatality rates, 81 studies were identified from 29 countries, however, only four countries were low-or middle-income countries (LMICs). Preliminary meta-regression models indicate that invasive infection incidence rates peak in infants and older adults, while case-fatality rates increase linearly with age (Cannon *et al*, manuscript under preparation).

1.2. Key activities of the workstream

Specific activities that have been conducted through the workstream include:

- Establishing a Burden of Disease Working Group
- Developing standardised case definitions and surveillance protocols
- Formation of a systematic data purpose matrix
- Identification of priority projects to fill knowledge gaps

Burden of Disease Working Group

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. Jonathan Carapetis and Dr Chris Van Beneden, Centers of Disease Control, Atlanta, Georgia, USA and has been managed and coordinated by A/Prof. Hannah Moore. In identifying and selecting the membership of the BoDWG, considerations of geographical location, Strep A and non-Strep A knowledge, infectious diseases expertise and gender were considered, to ensure global collaboration and breadth. The BoDWG comprises 13 members from seven countries (see Annex A). The group has met periodically online for over two years, with the SAVAC Second Stakeholder meeting in Stockholm, the first opportunity for group members to meet in person.

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. As part of providing clear case definitions of the endpoints, a suite of standardised case definitions and “best practice” surveillance protocols was produced: modified from two original surveillance protocols developed in 2008 by a working group from the WHO and the National Institute of Allergy and Infectious Diseases. One protocol comprised ‘Acute diseases’ (pharyngitis,

impetigo and invasive infections), and the other comprised 'Autoimmune sequalae' (ARF, RHD and APSGN). These protocols have been separated into seven discrete chapters: pharyngitis (also including scarlet fever which was not previously captured), impetigo, invasive infections, cellulitis (new chapter not covered by existing protocols), ARF, RHD and APSGN.

The protocols have been revised and updated to achieve a common structure across all protocols and to include contemporary diagnostic methods (inclusion of molecular methods such as nucleic acid amplifications tests), expanded data sources for disease surveillance and minimal requirements for surveillance. Core workstream members have updated these protocols and facilitated expert review with BoDWG members and an additional *ad-hoc* expert sub-committee for each Strep A endpoint. The protocols will form a dedicated supplement in *Open Forum Infectious Disease,* consisting of an introduction commentary article and the seven stand-alone protocols. All except one article (protocol for acute PSGN) have been accepted by the journal and proofs have been edited. It is expected to have all articles accepted by the end-of-July with the supplement published in September 2022. A dissemination plan aims to ensure maximum exposure of the protocols to ensure their utility, including posting on websites, twitter, societal newsletters utilising BoDWG member's networks, and Two-page factsheets summarizing each protocol which are being developed. The protocols form an essential component of the Burden of Disease workstream activities, underpinning future work of SAVAC to enable collaborators to undertake surveillance in a standardised and harmonised way.

Data purpose matrix

A key objective of the workstream was to identify, collate and maximise existing data to facilitate estimates of the global burden of Strep A diseases. Through discussions with BoDWG members and connections with work conducted under the Full Value of Vaccines Assessment, key questions were posed regarding the types of disease burden data that are needed 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 systematic 'Data purpose matrix' was developed to address these questions and provide guiding principles for the types of burden of disease that are needed and to prioritise future research activities. The matrix addresses four different objectives of vaccine development and evaluation: advocacy; regulatory/licensure; policy evaluation/post-licensure; and post-licensure financing. Through the lenses of those objectives, the matrix points to key elements and requirements of burden of disease data, key audience members and stakeholder groups and the most appropriate timing of those data needs on the vaccine development pathway. The matrix addresses Strep A diseases overall, and for eight different Strep A clinical endpoints (acute: pharyngitis, impetigo, invasive disease, cellulitis, scarlet fever; immune-mediated sequalae: ARF, RHD and APSGN). It also highlights any differences in data requirements between high-income countries (HICs) and LMICs for each disease endpoint. The matrix was recently published in *Clinical Infectious Diseases* [5].

Identification of priority projects

The matrix enabled a shortlist of priority research areas to be identified. BoDWG members then ranked projects within those areas to refine the list, and define a consolidated list of priority projects:

1. Establishing sentinel surveillance sites for pharyngitis and impetigo – especially in LMICs that may progress to future vaccine trial sites. This priority focus is directly related to those Strep A conditions being the clinical target endpoints on the WHO Strep A Vaccine roadmap [6] and Preferred Product Characteristics [7].

2. Enhancing data collation activities to better estimate the incidence of invasive Strep A diseases, especially in jurisdictions where there is a paucity of published data, for example: LMICs where there is a lack of robust data on incidence, despite their being a presumed high burden.
3. Understanding the attributable fraction of Strep A to cellulitis and increasing knowledge of cellulitis burden that is most likely under-appreciated.
4. Obtaining a Strep A specific estimate from the GBD project through the Institute for Health Metrics and Evaluation (IHME). This was identified as a priority area of interest as there is a lack of global perception of Strep A disease, and aligning disease estimates with other diseases from the GBD project is needed to facilitate comparison, especially between HICs. Whilst this project is a long-term goal, this would aid in the advocacy objective to contextualise the burden of Strep A amongst other global, regional and national public health goals.
5. Multi-country epidemiological record linkage studies of administrative data to describe the age-specific incidence rates of acute Strep A disease endpoints. Record linkage studies are less resource intensive compared to prospective data collection studies, although are likely to be limited to middle- and high-income countries.

Other identified project areas include: gaining an appreciation for how decisions are made with regard to vaccine development and implementation at the international, regional and country level; better understanding of the burden of maternal sepsis; quantifying the use of antibiotics; and exploring the incidence of burden and ARF through transmission modelling.

1.3. Next steps

Each priority project needs to be developed into a funding proposal that can be either packaged individually or as a suite of activities that can be funded under one umbrella. Another key step is the transitioning of BoDWG into a scientific advisory group to provide scientific and intellectual guidance to the priority projects, and ensuring the surveillance protocols are disseminated widely.

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2 Strep A vaccines. Immunological protection and correlates – an update

Dr Shiranee Sriskandan, Imperial College, London, United Kingdom

2.1. Introduction

Immunity to sore throats

One of the key observations that provides a basis for the possibility of vaccinating against Group A *Streptococcus* (Strep A), is the natural immunity that humans develop during childhood. Children get strep sore throats fairly frequently, but adults do not. Incidence of symptomatic throat infections, including scarlet fever, increases fairly sharply around the age of four years of age: this could be due to expansion of tonsil tissue allowing greater access for strep A, increased exposure through mixing with other children, or simply an artefact of school-aged children being able to articulate throat pain. Towards the end of childhood, frequency of strep sore throats diminishes markedly. The mechanisms that confer resistance in the throat (or the skin) are not known, but might include one, some or all of the following:

- Opsonophagocytic killing of bacteria with antibody or complement
- Inhibition of directly acting virulence factors
- Prevention of bacterial adhesion

- Inhibition of factors that would otherwise impede development of immunity
- Cellular immunity

Immunity to systemic infection

Resistance to systemic infection is better understood in terms of opsonophagocytosis in human blood, albeit that this is likely to be a marker of resistance to invasive infection. New assays have developed on the classical Lancefield whole blood assay – which is otherwise cumbersome and hard to standardize – to use a cell line, HL60, as a model for human neutrophils. This can demonstrate the opsonic activity of donor serum in an experimentally tractable system, measuring bacterial survival at the end of the assay, similar to the system used for *pneumococcus*. The assay requires an overnight incubation and works well with certain bacterial strains.

2.2. More tractable correlates of immunity

Finding an easier method of detecting anti-Strep A antibodies would be useful. There are a number of Strep A antigens that are already known to act as targets of antibodies that either promote opsonophagocytosis or inhibit virulence factors. Some are already in vaccines being developed, while others have been identified in protective preparations of human immunoglobulin. Being able to detect antibodies to such antigens would be useful for a number of reasons. If testing vaccines, these antibodies might indicate that a vaccinee has made a response. In order to differentiate vaccine-induced immunity from natural immunity, one could look for antibodies to the other Strep A antigens that are not in the vaccine (similar to DIVA capability). Such antibodies might be a marker of recent infection, so might have a further use diagnostically and in surveillance. One assay can detect eight different Strep A antigens through use of magnetic beads that are coated in individual Strep A antigens and carry unique fluorescent tags: this enables responses to multiple individual antigens to be detected from a single, small serum sample. Using a similar principle, a mesoscale assay has also been devised that can specifically detect antibodies reacting with up to 10 Strep A antigens in a single well. Such assays are agnostic to the function of the antibodies they detect: the purpose is to enable large-scale screening using a readily transferrable assay that can be done in less than a few hours.

What is needed now for the tractable assays?

Having developed such assays it is important to establish the most effective way to use them, including optimized positive and negative controls that are readily available in all locations using the assays. At present, in the absence of any commercial vaccine, the best positive control is human-pooled intravenous immunoglobulin (IVIG), whilst the best current negative control appears to be IgG-depleted serum. Secondly, we need to understand whether the antibodies detected by such assays are functional and whether the levels correlate with functional immunity. Thirdly, we need to optimize the assays to detect antibodies from different types of samples, including oral fluids, soft tissue infection, and finger prick blood tests.

2.3. Conclusion: understanding what happens in natural immunity

The obvious way to understand how natural immunity develops is to study children in early years settings. As demonstrated by classrooms of children who are all the same age and are exposed to the same dose of Strep A exposure from classmates with scarlet fever, there are a wide range of outcomes. Even though over one-in-four children acquire the outbreak strain and carry it, only a very small percentage get scarlet fever or severe tonsillitis. Understanding differences in oral fluid content of immunoglobulins directed against different Strep A antigens would be highly valuable in such a setting and, learning from COVID-19 studies it should be possible to detect such antibodies in crevicular (oral) fluid, thereby avoiding the need

for blood samples. Studying adults provides further insight into what happens when an adult encounters Strep A for probably the first time. This was achieved by the 'CHIVAS-M75' model where healthy adults were infected with an M75 Strep A: most, but not all developed sore throats. The experiment paves the way for future studies that compare antibody levels in those who were resistant to the challenge and those who were susceptible.

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3 Vaccine safety considerations and guidance

Professor Edwin Asturias, University of Colorado School of Medicine, United States

3.1. Introduction

The aim of the safety working group is to review the safety issues regarding Group A *Streptococcus* (Strep A) vaccine, look at the pathways and opportunities for vaccine safety evaluation, including current Strep A vaccines in development, factors that have prevented development of a Strep A vaccine, and to utilize experiences from other vaccines in terms of safety concerns.

Strep A vaccines started almost at the moment that Group A Strep was identified as a bacterium. There have been 135 different human *S. pyogenes* vaccine trials during 1796 and 2019, and an estimated 320,000 subjects vaccinated with investigational vaccines, with particular activity between the 1920s and 1960s. In the 1970s, safety fears reduced vaccine trial activity, due to review of the safety issues. There has subsequently been a revival since 2004. In the 1920s, mostly in the USA, children were inoculated with the 'Dick toxin', particularly for scarlet fever. Safety reporting was simple, and research papers showed that there was no serious reaction in those children (although it was later discovered that some children developed a 'Scarlatiniform' rash and fever.

During 1965-1967, the Massell GAS type 3 M-protein vaccine study took place at Harvard Medical School. The trial involved 21 healthy siblings randomly selected from 106 patients with rheumatic fever (weekly injections for up to 18 to 33 weeks, and continuous exposure to M-protein type 3 antigens, with a 30-month observation). During that period there were 18 episodes of *S. pyogenes* pharyngitis (none due to type 3). In the comparison group, observed over 15 years, there were 447 episodes of *S. pyogenes* pharyngitis and five cases of rheumatic fever (1%). Ultimately there were three cases of children (out of 21) deemed to have developed acute rheumatic fever (ARF) during the trial: 11%, compared to 0.9 to 1.1% in the historical trials. This data led to the interruption of the Strep A vaccine investigation: the United States Food and Drug Administration (FDA) convened a 'Panel on Bacterial Vaccines and Bacterial Antigens with No U.S. Standard of Potency' in the 1970s, which concluded that group A Strep antigens in bacterial vaccines were an unacceptable risk. Such trials and data would be unlikely to withstand epidemiological scrutiny nowadays.

3.2. Methods

Vaccine safety evaluation traditionally has a pathway: from toxicity studies to clinical trials, i.e., Phase I, II and III, and an extended Phase IV trial now considered as part of the safety evaluation (as many adverse events may not appear until thousands or even millions of people are being vaccinated. In terms of developing a vaccine safety framework, it is important to use clues from historical studies of Strep A as there are important issues in relation to the background rates, and complications rates, which vary across

regions and populations. There can also be an important contribution from biomarkers for disease severity if available, together with clues from pre-clinical studies and recent Phase 1 studies.

In relation to the immune-pathogenesis of ARF, one of the most feared sequelae of Strep A, and potentially of using a Step vaccine: when there is an infection with Strep A, traditionally there is an immune response mounted which may lead to cross-reactivity of antibodies to human proteins, therefore leading to immune phenomena, such as AFR. If those responses are triggered through an M-protein or any other carbohydrate, this can induce the same cross-reactivity, leading to a potential safety effect. The problem is the lack of good biomarkers for Strep A safety. If the biomarker is linked to an event, it needs to be put through the causality pathway. There have been multiple investigations on the immune reaction of B and T cells, and if they go through the pathway of being the causality of these events. Work has also been done on Strep A carbohydrates, epitopes and how they will be potentially plausible as an explanation of cross-reactivity; and the cardiac myosin which has been looked at most frequently as thought to be one of those processes.

There is also the issue of genetics: are populations more susceptible to such health immune phenomena? Genetics plays an important role potentially in Strep A infection and sequelae, which must be further explored and understood.

There is no well-defined immune marker that would act as a surrogate for risk of ARF development. There are gaps in the knowledge of mechanistic correlate of ARF and rheumatic heart disease (RHD) development and identification and the right biomarkers for identification. Natural infection studies are also needed, that may provide additional knowledge. For vaccine safety and especially for causality attribution, the biological time windows are needed, i.e., the timeframe for expressions of safety signals.

Burden of disease

The burden of disease is crucial to understand the background rates of diseases. In high-endemic countries, when the vaccine is rolled-out, if ARF occurs and the background rate in that country is not understood, an increase in the identification of ARF might be seen, even though it may already have been there.

Strep A is a seasonal disease, and the burden of disease is not over one time-period: several years of understanding are needed in relation to the incidence of disease and the different expressions. In terms of safety, of ARF and RHD, estimations of the incidence and prevalence of disease are necessary. The metric of ARF incidence estimation is resource-intensive and not feasible for low-income countries (LICs). This could be done through clinical criteria but this method is not entirely reliable. There have been efforts at echocardiographic screening as a way of looking into the incidence in the population, which not only identifies clinical disease, but sub-clinical disease. Hence, it is a pragmatic surrogate for ARF incidence and trends, and which easily measured, repeatable and less costly. There are also community survey and hospital-based systems, and the administrative databases, and registration systems: these are poor surrogates, but can monitor long-term trends in ARF incidence. Echo-cardiographic screening is more powerful at detecting potential RHD cases than clinical ascertainment. The importance is in simplifying a protocol in LICs where the vaccine will be most used. The problem is that there is no gold standard criterion for subclinical RHD.

Recent Strep A vaccine trials

There have been five clinical trials for Strep A vaccines in development enrolling a total of 195 subjects. All are M-protein based vaccines. Most did not have a control group at the beginning, but more recently

trials have used Hep A or other vaccines as controls. Most trials were open label at the beginning then subsequently randomized. Safety assessments included: reactogenicity (7 to 14 days); cardiac and neurologic clinical examination (at 6/12 months, or 7/14 days after each dose); Echocardiogram/ECG screening for potential side effects in the cardiac anatomy (after 6/12 months, or baseline, and 1 month after 3rd dose); routine clinical labs, troponin-I, C3, CRP looking at inflammation (baseline screening, and after 1/6/9/12 months in one case); human tissue cross-reactive antibodies by IFA to understand more about what was happening after administration of each dose; and a long-term adverse events assessment follow up after 12 months.

3.3. Discussion

The outcomes were that most had mild local reactions; none had echocardiographic/ECG changes of concerns (although the trial samples were small); most had no associated side effects of concern. But most are in Phase I (only one was in Phase II), hence the safety assessment is relatively limited.

The next steps are Phase II and Phase III trials. The development of Dengue vaccine is relevant as it is similar to Strep A: caused by different serotypes; seasonal and inter-year variability; variability of incidence among populations; and cross protection is important, but also a risk for more serious disease expression. The latter prolonged the studies for up to five years, and the same type of follow-up may apply to Strep A vaccines. With the dengue vaccine, there was a difference between those who had been exposed to the virus before (seropositive), and those not (seronegative): in the first case protection was good, but in the second, there was increased hospitalisation, especially in children aged 2-to-8 years, phenomena which was seen at year 2 or 3 of the vaccine but not before.

Proposed safety monitoring for Phase II/III includes: initial reactivity of the vaccine; daily follow-up of local and systemic reactivity looking at severe adverse events (AE) throughout the study. Also, routine laboratory testing during that period; Strep A specific assessments, such as non-specific inflammation parameters, CRP, C3, C4; GAS culture monitoring; anti-tissue responses; cardiac function assessment.

The working group defined two expert meetings that should be convened to look at the following:

1. Echocardiography:
    - Pre-trial validity of criteria and age/illness standards
    - Optimal times for measurement (baseline? Post-dose?)
    - Instrument standardization

2. Screening assays for cross-reactive proteins (ELISA-based):
    - Possible CR antigens:
        - Identical amino acid sequences in different proteins
        - Similar protein structures shared among different proteins
        - Diverse molecules such as DNA, carbohydrates, and proteins
    - Predefined normal ranges across pre- and post-immune sample differences

Another important aspect is the use of the WHO assessment tool to evaluate AEFI/causality for Strep A vaccine. This requires data on:

- Background rates and possible safety signals, including from previous trials
- Case definition for ARF/RHD and possible AEFI signals (using the Brighton Collaboration)
- Safety assessment methods: self-controlled methods? Immune-profiling of cases and controls? Minimum incidence rates?

- Guidelines for causality assessment: adaptation of WHO AEFI causality, for example, to define alternative causes unrelated to the vaccine; and what laboratory parameters are needed for each case to be investigated.

Robust databases of safety information are important to support licensure of vaccines, and expected by regulators (i.e., FDA, European Medicines Agency [EMA]). They should be established at the end of Phase II or earlier. Rare adverse events following immunization (AEFI) require large sample sizes in trials, and this requires strong administrative data. The complexity of new vaccines present challengers to national regulatory authorities:

- New technologies used in product development
- Quality and process validation concerns
- Evaluation of non-clinical and clinical data for novel vaccines
- Testing capacity
- Risk benefit assessment as part of product evaluation
- Specific form of pharmacovigilance commitment, including for Phase IV studies

For Group A Strep safety in particular, it will be important to look at:

- Adverse events of special interest based on:
  - Product-specific mechanism of action
  - Platform and vaccine composition
  - Preclinical data and cumulative clinical safety experience
- Detecting all new-onset Strep A infections that can result in ARF/RHD
- Antibiotic treatment regimen of new-onset Strep A infections standardisation in vaccine trials
- Long-term follow up of Strep A vaccine study participants

3.4. Conclusion

- New complex vaccine with partial protection and concerns for immune-related adverse events pose a challenge for develops/regulators:
  - However, technological advances could provide solutions
  - Definitions of public health outcomes of interest, and background of adverse event of special interest (AESI) to facilitate that process
- New development Phases IIb and III need consensus during the next 2 years:
  - For validity and usability of echocardiography and cross-reactive testing for ARF
  - Framework of vaccine safety assessment including the duration of the follow-up
- Safety of Strep A vaccines should not be a barrier to development (other vaccines are overcoming similar obstacles, e.g., rotavirus, dengue, zika, COVID-19)

Introduction of the value of vaccines – Welcome address

David Bloom, Harvard T.H Chan School of Public Health, US

David Bloom introduced the next session and welcomed in-person and online participants. He also thanked the IVI team for their organization and arrangements. He described the focus for the following session as being on the value of prospective Strep A vaccines and vaccinations under SAVAC, and progress made. The essential focus has been on identifying, understanding and measuring the economic burden of

Strep A diseases, which also define the benefits of vaccination. Major challenges relate to the wide range of clinical endpoints that Strep A can manifest, including pharyngitis, scarlet fever and RHD. Challenges also relate to the fact that the data available is highly imperfect, in terms of availability and quality, and the signals that they contain. Moreover, the tools and models employed in the absence of sufficient data are in some cases limited, or are in flux or in development. Hence there is model uncertainty and parameter uncertainty: which translates into uncertainty in policy-relevant results. He described SAVAC's work as characterizing and reducing the sources of uncertainty. David Bloom introduced the presentations to follow.

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4 Potential impact of prospective Strep A vaccines on the global burden of disease: model-based analysis

Dr Kaja Abbas, London School of Hygiene and Tropical Medicine, UK; Dr Fiona Giannini and Dr Jeffrey Cannon, Telethon Kids Institute, Perth, Australia

4.1. Methods: Group A *Streptococcus* vaccine impact model

A static cohort model was developed to estimate the projected health impact of Group A *Streptococcus* (Strep A) vaccination at the global, regional, national, and income levels. Vaccination impact is estimated in terms of reduction in the burden of several major Strep A disease states and sequelae. Burden estimation comprised of episodes of acute Strep A disease (pharyngitis, impetigo, invasive disease, and cellulitis) and cases of rheumatic heart disease (RHD), deaths due to severe Strep A disease (invasive disease and RHD), and disability-adjusted life years (DALYs) due to each Strep A disease. The reduction in disease burden is in direct proportion to vaccine efficacy, vaccine coverage, and vaccine-derived immunity (based on duration of protection and waning dynamics). Direct effects of vaccination are included, and indirect (herd) effects are excluded: therefore, the estimated health benefits of Strep A vaccination are conservative (if Strep A vaccination prevents population transmission).

Data inputs

The pre-vaccination disease burden is based on country- and age-specific incidence rates for cellulitis and RHD, and global age-specific prevalence for impetigo from the 2019 GBD study [1]. It is also based on global age-specific rates for pharyngitis and invasive disease from systematic reviews conducted as part of this project and described in Chapter 8. Mortality risk was limited to 28 days from hospitalisation for invasive disease and to 10 years from disease onset for RHD, using rates described in Chapter 8. Country and age-specific rates of Strep A burden were assumed to remain constant in the future. Demography estimates for country, year, and age-specific population, all-cause mortality rates, and remaining life expectancy are based on the 2019 UN World Population Prospects [2].

The vaccine efficacy assumptions are based on the WHO preferred product characteristics for Strep A vaccine (see Annex B. Table 1) [3]. The waning dynamics of vaccine-derived immunity is modelled in two ways: (1) vaccine-induced immune protection at maximum efficacy for 10 years and null thereafter and (2) waning linearly with annual reduction in efficacy equivalent to 5% of maximum efficacy for 20 years and null thereafter (i.e., waning to 50% of maximum efficacy after 10 years). The year of vaccine introduction is assumed to be 2022 or country-specific ranging from 2022 to 2034, with initial coverage at 10% of maximum coverage. The vaccine coverage is assumed to scale-up linearly during the first 10

years post-introduction to reach either a maximum of 50% coverage for all countries or a country-specific coverage level ranging from 9% to 99%. Specifically, six potential scenarios were analysed for varied years of vaccine introduction, coverage, and waning dynamics (see Annex B. Table 2), with vaccination in the first year of life (at birth).

The model was used to estimate the lifetime health benefits of vaccination for 30 birth cohorts from year of vaccine introduction on Strep A disease burden (pharyngitis, impetigo, invasive disease, cellulitis, and RHD) in terms of episodes/cases, deaths, and disability-adjusted life years (DALYs) averted by vaccination. Disability weights used for calculation of years lived with disability (YLD) are from the GBD study [4], and YLD was attributed to the years of prevalence. The duration for pharyngitis, impetigo, invasive disease, and cellulitis were estimated to be 5 days, 15.5 days, 10 days, and 16.4 days respectively, based on the GBD reported prevalence divided by incidence [1]. The duration for RHD was assumed for the remaining life expectancy since the onset of the condition.

4.2. Results: modelled outcomes

The model was used to estimate the lifetime health benefits of vaccination for 30 birth cohorts of 2022-2051 on Strep A disease burden (pharyngitis, impetigo, invasive disease, cellulitis, and RHD) in terms of episodes/cases, deaths, and DALYs averted by vaccination. Disability weights used for calculation of years lived with disability (YLD) are from the GBD study [4], and YLD was attributed to the years of prevalence. The duration for pharyngitis, impetigo, invasive disease, and cellulitis were estimated to be 5 days, 15.5 days, 10 days, and 16.4 days respectively, based on the GBD reported prevalence divided by incidence [1]. The duration for RHD was assumed for the remaining life expectancy since the onset of the condition.

The Strep A vaccine impact model was developed using the R statistical software [5], and includes a user-friendly (R Shiny) web application. The program code and data for the vaccine impact model is available at https://github.com/fionagi/GASImpactModel. The vaccine impact model is flexible to estimate the health benefits of vaccination by calendar year, birth year, and year of vaccination [6].

Estimated vaccine impact on disease burden

The vaccine impact on disease burden averted among the vaccinated cohorts during their lifetime at the global, regional, national, and income levels is presented in Table 3 and Figures 1–3 (see Annex B. Table 3 and Figures 1-3). Vaccination at first year of life for 30 birth cohorts born between 2022-2051 under Scenario 1 can avert 2.5 billion episodes of pharyngitis, 354 million episodes of impetigo, 1.4 million episodes of invasive disease, 24 million episodes of cellulitis, and six million cases of RHD during their lifetime (see Annex B. Table 3 for scenario 1). This relates to an average of 82 million, 11.8 million, 45,000, 805,000, and 210,000 cases averted per birth cohort during their lifetime for pharyngitis, impetigo, invasive disease, cellulitis, and rheumatic heart disease respectively. Vaccination impact in terms of total cases averted is relatively higher in Sub-Saharan Africa (see Table 3) and lower-middle-income countries (see Annex B. Figure 1) for pharyngitis, impetigo, invasive disease, cellulitis, and RHD.

Vaccination impact in terms of cases averted per 1000 vaccinated individuals is relatively higher in North America for cellulitis and in Sub-Saharan Africa for RHD (see Annex B. Figure 2). The vaccine impact metric of disease burden averted per 1000 vaccinated individuals remains the same for any vaccination coverage in each scenario, with the caveat that the Strep A vaccine impact model includes only the direct effects of vaccination and excludes indirect herd effects.

Major gaps in knowledge or research evidence

The Strep A vaccine impact model can be updated to include the immune-mediated sequelae of acute rheumatic fever (ARF) and kidney disease, and estimate added health benefits of vaccination on averting morbidity and mortality attributable to these conditions. The health benefits of the Strep A vaccine on reducing Strep A infections are expected to lower the corresponding antibiotic use (to treat Strep A infections), and the model could capture this feature with availability of quality data.

Evidence on natural history of disease dynamics will be beneficial to simulate disease prognosis using a Markov model and estimate the vaccination impact. Evidence on Strep A transmission dynamics will be valuable to develop a transmission dynamic model for estimating the direct and indirect effects of vaccination. Instead of endogenous modelling of transmission dynamics, the current static cohort model can be extrapolated to include the indirect (herd) effects by specifying a basic multiplier of the direct effect [7].

The vaccine impact projections are based on a hypothetical vaccine that meets the criteria of the WHO preferred product characteristics [3], and Strep A vaccines that attain licensure may have varied characteristics. The vaccine coverage assumptions are based on past coverage trends for the pentavalent vaccine (diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenzae* type B), and coverage and scale-up of future Strep A vaccines may differ. Also, assumptions for duration of protection and waning dynamics of vaccine-derived immunity may differ from future evidence generated from clinical trials and effectiveness studies.

4.3. Conclusion

The Strep A vaccine impact model estimates the added health benefits of vaccination in terms of Strep A disease burden averted for pharyngitis, impetigo, invasive disease, cellulitis, and RHD at the global, regional, national, and income levels. Vaccination impact in terms of burden averted per fully vaccinated individual is relatively higher in North America for cellulitis and in Sub-Saharan Africa for RHD.

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5 Global economic burden for Strep A infections and cost-effectiveness analysis for a hypothetical Strep A vaccine

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5.1. Introduction

Group A *Streptococcus* (Strep A) causes a wide spectrum of clinical manifestations ranging from mild infections such as pharyngitis to more severe illnesses including rheumatic heart disease (RHD). Currently, there is no vaccine available against Strep A infections. There is also a lack of standardized surveillance programs and economic evaluations. During the study, it was observed that available studies were disproportionately lower in low-income countries (LICs) than in high-income countries (HICs). As a part of the SAVAC consortium, the International Vaccine Institute (IVI) carried out the traditional investment case component comprising a literature review on existing cost-effectiveness analysis, global economic burden estimation, and cost-effectiveness analyses (CEA) for a hypothetical Strep A vaccine.

5.2. Methods

In order to estimate economic burden of Strep A infections, an initial search was conducted by the Telethon Kids Institute (TKI) to identify any costs associated with Strep A. As existing costs were reported in various formats, they were manually reviewed and categorized into three cost categories: direct medical costs (DMC), direct non-medical costs (DNMC), and indirect costs (IC). The search outcomes indicated that there was an insufficient number of existing studies by income group (as classified by the World Bank), as well as by disease manifestation. Thus, there were a significantly lower number of studies available in non-HICs and a disproportionately low number or absence of economic burden data for multiple disease manifestations. Given the lack of available resources, the study focused on the following disease outcomes for the economic burden estimation: pharyngitis, acute rheumatic fever (ARF), RHD, severe RHD, invasive infections, impetigo, and cellulitis.

Adjustment factors were created to overcome related data insufficiency by using the WHO-CHOICE unit cost database, the healthcare big data hub system, and GDP per capita [1, 2]. Productivity loss due to premature death was also considered. It was assumed that it is more likely that death is triggered from more severe illnesses such as RHD and invasive diseases than minor infections including pharyngitis. Thus, the weighted average age of death was first estimated based on the IHME dataset for each of RHD and invasive infections [3]. Then productivity years lost was multiplied by minimum wage which was discounted at the rate of 3%. Given a large degree of uncertainty on input parameters, extensive sensitivity analyses were conducted including a probabilistic multivariate sensitivity analysis with a Monte Carlo simulation and generated 95% confidence intervals for the point estimates.

For the CEA, the same static cohort model was adopted and six vaccination scenarios which were set up by the TKI team. As there is no vaccine available at the time of this research, the WHO Preferred Product Characteristics (PPC) were followed for a Strep A vaccine, where efficacy rates were assumed to be variable depending upon disease outcomes. The study outcomes were presented by income group as classified by the World Bank. Following the WHO PPC, the number of doses were assumed to be three doses. As previously defined in the vaccination impact model by the TKI, there were two vaccination strategies considered: routine at birth, and routine at 5 years of age. Given the absence of Strep A vaccines, both vaccine procurement and delivery costs are unknown. Instead of setting up additional assumptions on vaccination costs, a range of the total cost per fully vaccinated person (US$0 - US$300) was applied, and the maximum cost per fully vaccinated person to be cost-effective was derived at varying threshold costs per DALY averted [4, 5]. Future costs and health outcomes were discounted at the rate of 3%, but health outcomes with no discounting were also considered following the WHO guideline [6]. A 10% wastage factor was applied as the default, but 5% and 20% wastage factors were additionally considered as a part of the sensitivity analysis. Given that the conventional CEA threshold (i.e., 3 X GDP per capita) had been widely discouraged [7, 8], 1 X GDP per capita (default) was used in addition to health opportunity costs which take into account marginal productivity of healthcare expenditure [9]. Both univariate and multivariate sensitivity analyses for the CEA was also conducted.

5.3. Results

The economic burden per episode for Strep A infections was higher in HICs than in LICs (see Annex C. Figure 1). As expected, the economic burden was greater for more severe illnesses than for mild infections. For example, in the HIC setting, the economic burden per episode was US$392 for pharyngitis, UD$6,32 for ARF, and over US$11,000 for RHD. Productivity loss due to premature death – shown in productivity years lost – was lowest in HICs; the cost due to early death was highest in HIC and lowest in LICs (see Annex C. Figure 2). This is mainly because we would expect patients in higher-income groups to

earn more than patients in lower-income groups. Incremental cost-effectiveness ratios (ICERs) highlight that whilst vaccinating the age cohort of 5 years was more cost effective than vaccinating infants for pharyngitis and RHD, this was the opposite for invasive infections (see Annex C. Figure 3). This is because the burden of pharyngitis was assumed to be more common in children aged 5-15 years-old, and the incidence rate of RHD was also higher among children and adults (5-24 years-old) than the cohorts younger than 5 years old. In the case of impetigo and cellulitis, marginal differences were observed between the two vaccination strategies given that the incidence rates for the two infections were fairly consistent across the age cohorts affected by vaccination. The maximum cost per fully vaccinated person – at the threshold of 1 X GDP per capita – ranged from US$8-US$308 for pharyngitis, US$6-US$216 for RHD, US$0.2-US$56 for invasive infections, US$1-US$153 for impetigo, and US$0.1-US$28 for cellulitis (see Annex C. Figure 4). For all disease states combined, the maximum cost per fully vaccinated person to be cost effective ranged from US$37 to US$489.

5.4. Conclusion

The study indicated that the economic burden for Strep A infections could be substantial, and vaccination with the current hypothetical vaccine could be potentially cost-effective if a threshold cost per fully vaccinated person were properly set. Nonetheless, it should be noted that the study outcomes are sensitive to vaccine characteristics such as efficacy, waning, and the duration of protection. Given the absence of Strep A vaccines, the WHO PPC was utilized, but updates are required as clinical trials for potential vaccine candidates advance. We would like to emphasize that there is a scarcity of existing studies on both economic and disease burden for multiple disease outcomes caused by Strep A. Thus, future research is needed to increase a number of primary data points such as surveillance programs, and field-based economic burden studies, paying special attention to the lack of evidence in lower-and middle-income countries (LMICs) and LICs.

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6 The full health economic social benefits of vaccination: conceptual framework and application to Strep A vaccines

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6.1. Introduction

Vaccination yields an array of health, economic, and social benefits beyond those typically captured in health sector-centric economic analyses (e.g., traditional cost-effectiveness analysis). Several previous efforts have been made to catalogue and categorize vaccination's "broad" health, economic, and social impacts. Notable examples of prior valuation frameworks include those set forth by Bärnighausen *et al*. in 2008 [1], Jit *et al*. in 2015 [2], Mauskopf *et al*. in 2018 [3], and Lakdawalla *et al*. in 2018 [4].

Bärnighausen *et al*. divided vaccination's impacts into narrow and broad benefits, with the narrow benefits representing a subset of the broad ones. According to this framework, narrow benefits include healthcare cost savings, health gains, and care-related productivity gains, while broad benefits also encompass outcome-related productivity gains, behavior-related output gains, and community externalities. This framework was later updated in 2014 [5] and 2017 [6].

Jit *et al*. identified 13 vaccination impacts grouped into the four major categories of health-related individual impacts, productivity-related individual impacts, community/system-level impacts, and broader

macroeconomic impacts. They also mapped out causal pathways among vaccination's impacts and attempted to appraise the strength of evidence backing the inclusion of each impact in the valuation framework.

Mauskopf *et al*. emerged out of the 2018 Economic Evaluation of Vaccines Designed to Prevent Infectious Disease: Good Practices Task Force from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). As in the Bärnighausen *et al*. framework, vaccination impacts were divided into narrow and broad factors. Mauskopf *et al*. identified more finely delineated direct health benefits than those included in other frameworks, such as potential vaccination-induced shifting of the severity or age profile of cases and serotype replacement. The Lakdawalla *et al*. framework emerged out of another ISPOR task force and was not specific to vaccination. This framework incorporates a number of 'elements of value'—including quality-adjusted life years (QALYs) gained, productivity, insurance value, scientific spillover, and the value of hope—into a 'value flower' for health technologies.

6.2. Methods

As part of the research conducted under SAVAC's Full Value of Vaccines Assessment (FVVA) working group, a novel framework was developed of vaccination's benefits, that updates and expands on previous work [7]. It is a general framework for the full societal value of vaccination. Impacts are organized according to whether they are primarily health, economic, or social in nature and are expressed in language that is easy for policymakers and other interested stakeholders to understand.

The framework includes an expanded set of benefits in comparison with prior versions, including impact on off-target pathogens observed for some vaccines, reduced healthcare congestion, several categories of reduced risk, intergenerational benefits, and improved quality of life. The framework also attempts to capture the distribution of benefits throughout different social strata, from the individual to all of society. We have applied this framework to prospective Strep A vaccination by identifying sources of value—beyond direct reduction of morbidity and mortality and direct healthcare savings—that are likely to be significant.

6.3. Results

Noteworthy health benefits of Strep A vaccination include avoidance or mitigation of microbiome disruption and antimicrobial resistance (AMR). Microbiome disruption may lead to future infections or contribute to chronic ill health and is likely particularly an issue for those who are treated repeatedly for Strep A, especially for those treated with broad-spectrum antibiotics. AMR is a concern because it tends to lead to higher treatment costs and worse outcomes for patients than antibiotic-susceptible infections. Vaccines can counter resistance directly by preventing resistant cases of the target pathogen and indirectly by preventing both appropriate and inappropriate consumption of antibiotics, which creates evolutionary pressure towards development of resistance in the target and bystander pathogens. Given that Strep A remains largely susceptible to penicillin, pressure towards resistance in bystander pathogens is the major relevant concern.

Noteworthy economic benefits of Strep A vaccination include increased labor force participation, hours worked, and income in adults, and improved educational attainment, school attendance, and cognition in children. These impacts are likely to be especially salient for severe manifestations, such as rheumatic heart disease (RHD).

The noteworthy social benefits of Strep A vaccination include potential equity improvements. The potential for improved equity stems in part from the fact that the disease burden of Strep A is highly heterogeneous, with individuals in low- and middle-income countries (LMICs) and in disadvantaged communities in high-income countries (HICs) much more likely to suffer the worst outcomes than those who are better off. Inadequate sanitation, crowded living conditions, and poor access to treatment as well as basic healthcare all contribute to the high burden in underserved populations. Inequity is also driven by the fact that, all other things equal, the consequences of infection tend to be greater for those who are worse off due to higher costs of infection relative to income and lower access to social safety nets. Equity improvements from Strep A vaccination are conditional on widespread access that is not predicated on ability to pay. The equity benefits of Strep A vaccination can be captured through distributionally sensitive benefit-cost analysis.

In applying the framework to Strep A vaccination, there are several important considerations. First, this application is to a prospective vaccine as opposed to an existing vaccine. Second, Strep A infection results in a wide range of diseases of varying severity. Certain benefits may be more relevant to some manifestations than to others. For example, preventing cases of RHD is likely to yield disproportionately high productivity-related benefits, since RHD can limit an individual's ability to work or result in premature mortality. On the other hand, reducing the incidence of Strep A pharyngitis is likely to have a disproportionately high impact on AMR because of the high frequency of related antibiotic treatment. Third, alternative countermeasures to Strep A infection (e.g., effective treatment) are available, and valuation of Strep A vaccination must account for the existence of potential substitutes. Reliance on treatment comes with several drawbacks, however, including AMR, microbiome disruption, and access issues. Finally, the potential for adverse outcomes from vaccination should be considered when assessing the expected value of a new vaccine, especially since such outcomes can result in negative spillovers onto immunization programs generally. Recent experience with the introduction of dengue vaccine in the Philippines provides a good case study. After it was discovered that vaccination of dengue-naïve individuals can worsen the impact of subsequent infection, uptake of other vaccines (e.g., measles) decreased, and outbreaks of previously contained pathogens occurred consequently.

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7 The Effect of a prospective vaccine against Group A *Streptococcus* on global antibiotic consumption for sore throat

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7.1. Introduction

Vaccines could play a valuable role in reducing antibiotic consumption. Reducing consumption may reduce the unintended consequences of antibiotic treatment, which include antimicrobial resistance (AMR) among both target and off-target, or bystander pathogens and the adverse effects of microbiome disruption. Reducing consumption would apply to the vaccines against Group A *Streptococcus* (Strep A) under development. However, the impact that Strep A vaccines could have on consumption is unknown and hinders our understanding of the full value of Strep A vaccination.

Of all diseases caused by Strep A, sore throat is by far the most common, and whether caused by Strep A or presumed to be caused by Strep A, is the second most common reason for antibiotic consumption

among European adults and the third most common reason among the US population. In fact, unnecessary and excessive treatment of sore throats is a common target for antimicrobial stewardship campaigns.

The aims of this work were to:

1. Estimate how many antibiotic courses are consumed globally in the treatment of sore throat and what proportion is attributable to Strep A; and
2. Explore the potential impact of Strep A vaccination on global antibiotic consumption.

7.2. Methods

For the first aim, a systematic review of the literature published after the year 2000 was conducted to collate all studies related to sore throat and antibiotics. From those studies, analysis studies that described the population rate of antibiotic prescribing for sore throat were included: from which the arithmetic and the population-weighted mean prescribing rates for sore throat from the most recent and nationally representative data were calculated.

A separate analysis included studies describing the proportion of prescriptions due to Strep A sore throat among all prescriptions for sore throat. From those studies, a random-effects meta-analysis was conducted to estimate the pooled proportion of prescriptions for sore throat that was attributable to Strep A based on linked diagnostic testing (e.g., point-of-care or laboratory tests). Finally, the number of antibiotics prescribed for the treatment of sore throat based on the 2020 global population count were estimated, as well as the number of prescriptions attributable to Strep A.

For the second aim, we explored the potential impact of Strep A vaccination on global antibiotic consumption under three scenarios related to possible changes to prescribing practices. These were:

Scenario 1: No change in prescribing practices (minimum estimate of averted prescriptions).
Scenario 2: A change in prescribing practices in high-income countries (reduced to the prescribing rate observed in the Netherlands) and no change in low- and middle-income countries (LMICs).
Scenario 3: A global change in prescribing practices (maximum estimate of averted prescriptions)

Based on prescribing rates, the effect of vaccination was estimated to comprise an 80% reduction in Strep A sore throat episodes over a 10-year efficacity period, with no waning, among children vaccinated at 5 years of age at 90% coverage.

7.3. Results

The review identified 46 studies from 19 countries that described antibiotic prescribing rates for sore throat. Thirteen studies focused on children, six evaluated adults, and 27 assessed all ages (with five reporting age-specific rates). Of the 19 countries with prescribing rates, 12 countries reported rates for all ages, 11 countries reported rates among children, and six countries reported rates among adults. Country-level antibiotic consumption for sore throat was estimated to range between 1% and 17% of all antibiotic consumption.

Another 18 studies from nine countries were identified describing prescriptions for sore throat with linked diagnostic outcomes. All those studies were conducted in high-income countries (HICs), with seven conducted in the U.S., four in Sweden and two in Spain. Seven studies reported diagnostic results for all age groups (but one study did not report counts), six focused on children, and five focused on adults. Office-based, rapid antigen detection was the most common microbiological testing method used to test

for Strep A. Just over one in two antibiotics prescribed for sore throat among children was attributable to Strep A.

Based on 2020 population counts, the countries included in the analysis of prescribing rates represent almost 10% of the global population for all age groups and 6% of global children aged 5-14 years. For the countries reviewed, it was estimated that almost nine million antibiotic courses are prescribed for sore throat among children and 35 million courses among all ages. Approximately five million and 20 million annual courses prescribed to treat sore throat are attributable to Strep A in each respective age group.

An estimated three million courses of antibiotics could be averted based on 2020 population counts in the countries reviewed if there were no changes to prescribing practices (Scenario 1) and with vaccination under the stated assumptions. This equals approximately 10% of all antibiotics prescribed for sore throat among the reviewed population. Corresponding results for Scenarios 2 and 3 are 27 million (78% of all prescribing for sore throat) and 35 million (all prescribing) courses averted for the countries reviewed.

7.4. Conclusion

This work shows that a significant amount of antibiotics is consumed for the treatment of sore throat. A vaccine that prevents infection and is administered to five-year-old children could avert approximately 10% of all antibiotic prescriptions for sore throat in the reviewed population without changes to prescribing behaviour. The reduction increases substantially if an effective vaccine and vaccination campaign has a significant impact on prescribing practices.

There were several limitations to the above estimates. First, the majority of studies reporting prescribing rates for sore throat and all studies with prescriptions linked to diagnostic outcomes were from HICs. These data are unlikely to represent that of LMICs, and therefore, the results described were based only on the countries with data and not the global population. Second, the majority of studies report data for prescribing rather than consumption: although, a study with linked data reported that 84% of prescriptions were dispensed. Third, there was a range of case definitions for sore throat: sore throat, pharyngitis, tonsillitis, tonsillopharyngitis, and (unconfirmed) *streptococcal* pharyngitis, as well as upper respiratory tract infection with symptoms of sore throat. It is likely that the latter definition most accurately captures prescribing rates for the treatment of sore throat, while the others underestimate rates, but it is rarely used. Lastly, more reliable estimates of a vaccine's effectiveness in reducing infection and its impact on prescribing will not be known until better vaccine efficacy data becomes available.

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8 Global health and economic benefits of prospective Strep A vaccines

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8.1. Background

- There is an increasing amount of evidence that vaccination yields broad health and socioeconomic benefits well beyond the direct health benefits for the immunized (e.g., the number of avoided deaths or disability-adjusted-life-years) and the healthcare cost savings.
- These broad benefits include, for instance, herd protection, increased work hours and productivity, and enhanced cognitive function among healthy children.

- Traditional health-centric cost-effectiveness analysis fails to capture the full value of vaccination.
- The full value of prospective Strep A vaccines is estimated using a societal-perspective benefit-cost approach.

8.2. Methodology

- The results of a static cohort model are taken that projects the country-specific number of cases, deaths and DALYs averted over time under six different Strep A vaccination scenarios.
- The concept of value-per-statistical-life (VSL) is used to assess the full value of vaccination.
- VSL is derived from the rate at which individuals are willing to trade off small changes in income for small changes in risk of death.
- VSL captures both the intrinsic and the instrumental value of being alive (i.e., any averted earnings or income loss).
- VSL is typically estimated based on individuals' reported preferences or based on workplace or consumption behaviours (e.g., bike helmet purchase, wage premium for risky jobs).
- There are three main issues with the concept and use of VSL estimates:
    - VSL estimates are mostly from high-income countries; estimates for lower-income countries are derived by interpolation.
    - VSL estimates typically increase with income. This can have unacceptable ethical consequences in global analyses since the interests of the well-off tend to count more than the interests of the worse-off.
    - VSL refers to fatal risks; the literature on the willingness to trade off changes in income with changes in nonfatal risks is less developed.
- In assessing the full value of vaccination, the following key assumptions are made:
    - The monetary value of being alive for an additional year is equal to the value-per-statistical-life-year (VSLY), which is found by dividing VSL by the population average life expectancy.
    - VSL is proportional to income.
    - The monetary value of future health benefits is discounted at a constant yearly rate.
    - The value of preventing a year with disability is also equal to VSLY.
    - To avoid ethically objectional consequences, the same VSLY is applied to all countries independently of their current income.

8.3. Results

- In the baseline scenario, it is assumed that: VSLY is evaluated at three times global gross-domestic-product (GDP) per-capita (US$11,000); GDP grows at a 2% annual rate; the annual discount rate is 3%.
- In the baseline scenario, the average total benefits of Strep A vaccines for the 2022-2051 birth cohorts across the six vaccination scenarios amount to US$1.44 trillion if the vaccine is administered at birth (1.7% of global income in 2020), and to US$2.41 if the vaccine is administered at age 5 (2.8% of global income in 2020).
- Vaccination at age 5 leads to more benefits than vaccination at birth due to the age distribution of Strep A infections.
- The chosen normative assumptions (i.e., discount rate and VSLY level) play a fundamental role in the estimation of the benefits of prospective Strep A vaccines.
    - Under less favourable normative assumptions (e.g., 5% discount rate and VSLY at one time GDP per-capita), the average total benefits of vaccination at age 5 for the 2022-2051 birth cohorts across the six vaccination scenarios amount to US$0.5 trillion.

- Under more favourable normative assumptions (e.g., 1% discount rate and VSLY at five times GDP per-capita), the average total benefits of vaccination at age 5 for the 2022-2051 birth cohorts across the six vaccination scenarios amount to US$6.2 trillion.

8.4. Conclusion

- Preliminary estimates suggest that Strep A vaccination is likely to confer significant socioeconomic benefits.
- These benefits are likely to be larger than the costs of developing, procuring, and distributing vaccines.
- Rational and fair allocation of public funds requires information on the full value of vaccination. This information can be used in comparing different uses of a fixed health budget, as well as the relative benefits of health and non-health interventions.

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9 Business case for industry investment in Strep A vaccine R&D

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9.1. Context

Quantifying the market and commercial potential for a Group A *Streptococcus* (Strep A) vaccine is important to inform industry investment decisions, particularly as Strep A vaccine development has yet to garner significant funding and activity from biopharmaceutical companies**.** The study aims to demonstrate the potential demand, revenue and return on investment (ROI) in development and manufacturing of a hypothetical Strep A vaccine. It is hoped that the results will help to drive increased prioritization of Strep A vaccine development as a viable commercial opportunity for industry.

9.2. Demand forecast and NPV analysis methodology

The model employs a hypothetical Strep A vaccine Target Product Profile (TPP; **Table 1**) based on WHO Preferred Product Characteristics (PPC) for a Strep A vaccine. Additional assumptions for the TPP were derived from a literature review, expert interviews, proxy vaccine information and discussions with SAVAC FVVA Working Group and Technical Advisory Committee members.

Table 1: Hypothetical Strep A Vaccine Profile

Parameter	**Characteristics**
Vaccine Type	Multivalent adjuvanted vaccine
Indication	Prevention of pharyngitis and superficial skin infections
Target Population	Infants (<1 year) or young children (~4-7 years)
Regimen	3 doses; no booster
Presentation	Single-dose vial (LIC, LMIC, UMIC-Public) or pre-filled syringe (UMIC-Private, HIC)
Price Per Dose	Range from US$3.40 (LIC) to US$54 (HIC)
COGS	~US$3 per dose
Wastage Rate	5%

It was assumed that the hypothetical Strep A vaccine would enter clinical trials in 2022, and enter public and private markets in 2035. Based on historical examples, a spread of 12 years beyond 2035 (to 2047) was assumed from earliest adopting countries to latest adopting countries in terms of adding the vaccine to their national immunization program (NIP): either the infant or school-age program. To determine where a country would fall on this range, a composite score was created based on: Strep A burden (using rheumatic heart disease [RHD] incidence as a proxy); degree to which recent vaccines had been adopted (PCV, Rota, Hib); and overall vaccine delivery infrastructure (using DTP3 coverage rate).

The vaccine was assumed to be available in all countries' private markets in 2035 with differing sizes for the private market and peak coverage rates in private markets assumed based on country income group level. For public markets, once the vaccine was added to the NIP, a linear 10-year ramp-up was assumed to a peak coverage level equal to the country's DTP3 coverage rate for the infant program scenario and 2nd dose of measles-containing vaccine (MCV2) for the child program. For the private market, for both infant and child program scenarios, a linear 3-year ramp-up was assumed from 0% coverage to peak coverage levels of: 30% for low-income countries (LICs) and low- and middle-income countries (LMICs), 15% for upper middle-income countries (UMICs), and 10% for high-income countries (HICs).

The net-present value (NPV) was assessed for industry investment in Strep A vaccine R&D for two developer profiles: a multinational pharmaceutical company (MPC) with a global market and a developing country vaccine manufacturer (DCVM) with a target market of LICs, LMICs and UMICs. Given the need for the developer to take the Strep A vaccine candidate through clinical trials, navigate regulatory activities and build manufacturing capacity, costs were assigned for each of stage in an attrition-adjusted manner (i.e., incorporating the cost of potential failures based on historical probability of success estimates) as follows: US$700 million for the MPC and US$196 million for the DCVM. The NPV was calculated using 12 years of annual operating profits and a discount rate of 10% for the MPC and 20% for the DCVM.

9.3. Results

Total annual demand at year 12 is estimated at 312 million doses for the infant immunization program scenario and 210 million doses for the child immunization program scenario (N.B. specific outputs should be taken as approximations that may change during refinement and finalization of the model). The difference in demand between the two target populations reflects the typically higher coverage rates for infant immunization programs. Approximately 50% of the peak demand is from LMICs, given the higher population sizes and high RHD burden of these countries. The total, peak annual revenue is estimated at US$3.5 billion and US$2.5 billion for the infant/child immunization programs respectively (resulting in estimated annual profit in year 12 of US$2.5 billion and US$2.0 billion, 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 NIPs, after which the public market is expected to contribute up to 90% of the annual profit at peak. The average profit margin across all country-income levels is estimated at ~70%.

The ROI calculations demonstrated a positive NPV for the MPC and DCVM investment scenarios for both the infant and child program scenarios (**Table 2),** assuming the developer bears the full cost of development, from Phase 1 through manufacturing, regulatory activities, capacity building and post-market activities. The NPV is higher if costs of earlier development stages are subsidized through global health funding. NPV was also calculated under various competitive scenarios in which profits were assumed to be either 25% or 50% lower beginning either three, five or seven years after market entry. In all but the most extreme competitive scenario (50% profit loss after three years for the DCVM child

program scenario), the NPV remained positive, albeit at a lower value than the scenarios without a competitive event.

Table 2: NPV Analysis Results

Developer Type	Target Markets	R&D Costs (millions US$)	Infant Program Scenario		Child Program Scenario	
			Average Profit Margin	NPV (millions US$)	Average Profit Margin	NPV (millions US$)
MPC	All markets	700	71%	1,120	74%	930
DCVM	UMIC, LMIC, LIC markets	196	55%	33	60%	28

9.4. Conclusion

The ROI analysis found a positive NPV for investment in Strep A vaccine development across multiple scenarios, including different types of vaccine developer (i.e., MPC targeting all countries, DCVM targeting LICs, LMICs and UMICs); different target populations for the vaccine (i.e., infant or child immunization program scenarios); and most competitive event scenarios modeled. The primary limitation of this study is the uncertainty associated with forecasting demand of a vaccine 10+ years from market. A key assumption underpinning the model is that the work of SAVAC and others will continue to raise awareness of the burden of Strep A diseases, illuminate the health, economic and social impacts of Strep A vaccination and define appropriate regulatory pathways for a Strep A vaccine.

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10 Optimal global spending for Group A Streptococcus vaccine research and development

Dr Daniel Tortorice, College of the Holy Cross, Harvard University, US

10.1. Introduction and key takeaway

Optimal spending on the development of *Streptococcus* A vaccines is measured in the billions of dollars, but this spending can be expected to unlock trillions of dollars in value. The presentation answered the following question: How much money should a supranational organization allocate to fund research and development (R&D) for a Group A *Streptococcus* (Strep A) vaccine?

10.2. Method

A model was presented where the organization considers a list of vaccine R&D projects to fund. The projects are organized under different approaches and then numbered sequentially. The organization considers all the available projects and calculates the benefits of funding each project as a product of the expected amount of harm remaining from Strep A, the fraction of harm the new project's success would alleviate, and the probability the newly funded project will succeed in producing an approved vaccine. The organization then funds the highest benefit project if the benefit of that project exceeds its cost, which is taken as known and constant across projects. The organisation repeats these calculations again with the remaining projects. Importantly, the benefit of funding a project falls the more projects that have

already been funded, because it is likely one of these projects will succeed and there will be less remaining harm from Step A to be addressed. The organization again funds the highest benefit project if the benefit of that project exceeds its cost. The organization continues in this manner until the benefit of funding the next project is less than its cost. At this point the optimal number of projects to fund has been identified and multiplying by the costs per project, the total optimal amount of funding can be calculated. The model takes as inputs various parameters summarized in **Table 3** below:

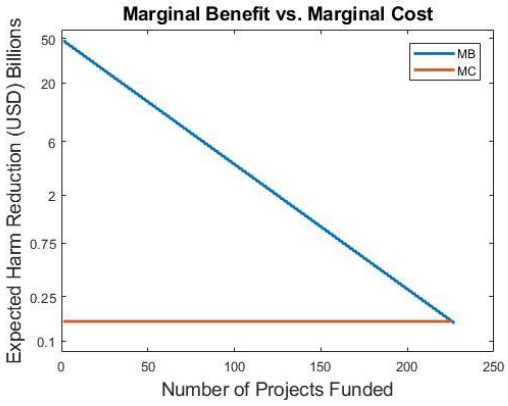
Table 3. Optimal funding model parameters

Approaches		Value
	Number of approaches	2
	Fraction of harm each approach can alleviate	1/2
Probability project succeeds		
	Approach	90%
	Overall	15%
Fraction of harm success alleviates		30%
Total US Dollar value of harm		2.1 trillion
Development cost of success inclusive of failures		1 billion

10.3. Results

Figure 1 illustrates a version of the model calibrated as described in the previous sub-section. The orange line (MC) represents the cost of funding a project. This cost is constant and does not depend on the number of projects funded. In contrast, the blue line (MB) represents the benefit of funding the next highest value project given the number of projects that have been funded in the past. This line slopes downward since the more projects that have been funded the more likely a successful vaccine will be developed. As a result, we expect there to be less harm from Strep A remaining and therefore, an additional project is less beneficial. However, as long as the MB line is above the MC line, the organization should continue to fund projects as the expected benefit of doing so is larger than the cost.

Figure 1: Calibrated Model



The numerical results from the model are presented in **Table 4** below.

Table 4. Numerical results from the model

Baseline calibration		Projects funded	Optimal spending (US$ billions)	Social surplus (US$ trillions)	Internal rate of return
		226	33.9	1.85	23%
Sensitivity					
	Harm reduction = 70%	108	16.2	1.87	29.4%
	Success probability = 5%	278	41.7	1.84	21.5%
	Total Strep A harm 2x	252	37.8	3.74	28.1%
	Require 4 approaches	396	59.4	1.82	18.8%

10.4. Conclusion

A Strep A vaccine represents a very high return on investment for public funds and with a call for both national and international policy to fund and promote accelerated development of Strep A vaccines.

Discussion/Q&A

Dr David Kaslow, PATH Centre for Vaccine Innovation and Access, US

Dr David Kaslow moderated a discussion and Q and A following the presentations, and included:

- Gaps between the value of Strep A vaccine development and the business case and the lack of investment from both public and private sectors: for example, a difference of opinion or judgement in terms of the probability of technical and regulatory successes between experts and those making funding decisions.
- Certainty, biological feasibility, viability, proof of efficacy, and risk (including financial and commercial risk, and vaccine safety).
- Health outcomes, economic/financial outcomes, and the narrative for social value.
- Global mapping for policy-makers, donors, and manufacturers.
- Pricing structures for manufacturing: in low-income and high-income countries.
- Involvement of pharmaceutical countries.

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11 SAVAC 2.0 Preparing for a Strep A vaccine

Dr Sushena Krishnaswamy, Monash University, Australia, Professor Andrew Steer, Murdoch Children's Research Institute, University of Melbourne, Australia and Dr Michelle Giles, Monash University and University of Melbourne, Australia.

The focus of SAVAC 2.0 is to build on the large body of work and achievements of SAVAC 1.0 summarised in this report. The vision of SAVAC 2.0 is to progress on three key priority areas in readiness for clinical trials when a Group A *Streptococcus* (Strep A) vaccine becomes available. Research groups that have contributed to SAVAC 1.0 have different priorities based on their expertise and interest. In the proposal for SAVAC 2.0 we have attempted to bring these together in an integrated way to negotiate the path forward.

Developing the SAVAC 2.0 proposal was a collaborative and iterative process. The first step was a series of meetings with key members of each of the working groups (burden of disease, correlates of protection, vaccine safety, and the various groups doing work towards the FVVA [cost effectiveness analysis, business case and full societal value framework]) to understand their key achievements and outputs over the preceding three years; and the key priorities that they have identified for the next three to five years. These ideas were synthesised into a cohesive proposal that seeks to integrate the ideas and to ensure that the work of SAVAC 2.0 lays the groundwork for a potential vaccine to enter Stage 3 clinical trials. The proposal was refined through feedback from many individuals – including Dr Jerome Kim, Prof. Andrew Steer, and Dr Jean-Louis Excler – prior to presentation at the Second stakeholders meeting.

With the overarching theme of 'preparedness for a Strep A vaccine', the proposal encompasses three work streams: preparing for vaccine trials, preparing industry, and preparing non-industry stakeholders. The first stream seeks to fill the current data gaps with a focus on LMICs, whilst simultaneously building capacity for surveillance, laboratory work and potential vaccine trial sites. The second and third streams seek to engage with stakeholder groups in vaccine development, implementation, and funding. The aim is to align these stakeholders to pave the way for a smooth transition from early stage to later stage clinical trials and eventually programmatic implementation.

We would like to take this opportunity to thank the Executive Committee for inviting us to be involved in preparing the proposal, and also all members of the working groups who have met and corresponded with us to develop this proposal. Lastly, we'd particularly like to thank Andrew, Jerome and Jean-Louis for their invaluable input and feedback into this work.

A discussion followed the presentation including sentinel sites, time scale and funding for developing a vaccine, engagement with vaccine developers, availability of burden of disease data.

Prof Andrew Steer thanked the presenters.

Closing remarks

Dr Jerome Kim, IVI, Seoul, Republic of Korea

Dr Kim stressed that vaccine development had to move from need to impact. The different working groups in their presentations identified the needs: the need for better data on burden; the need for more information on the correlates of protection; and the need for understanding mechanisms for monitoring safety; and the information developed by the FVVA workstream. Dr Kim thanked the working groups for their work, stressing that there had been solutions, but the solutions are partial and there is still work that needs to be done.

SAVAC 2.0 is a continuation of work to fill the gaps and to prepare for a test of a safe and efficacious Strep A vaccine. The SAVAC 2.0 presentation shown at the meeting will be modified with additional discussion around the new concept; together with further discussions with funders around what they can support, in the period of time available. Dr Kim stressed that global health vaccine development requires patience. A lot of progress has been made, and we are in a much better position than we were before SAVAC 1 started. As we move forward with the revised SAVAC 2.0, we will get to a place where we are able to fill the gaps.

Dr Kim thanked the team that set the meeting up and thanked participants and presenters.

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Presented by Professor Jonathan Carapetis, and Associate Professor Hannah Moore and Dr Jeffrey Cannon, Telethon Kids Institute, Perth, Australia

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From 4. Potential impact of prospective Strep A vaccines on the global burden of disease: model-based analysis

Dr Kaja Abbas, London School of Hygiene and Tropical Medicine, Dr Fiona Giannini and Dr Jeffrey Cannon, Telethon Kids Institute, Perth, Australia

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From 5. Global economic burden for Strep A infections and cost-effectiveness analysis for a hypothetical Strep A vaccine

Dr Jung-Seok Lee, International Vaccine Institute, Seoul, Republic of Korea

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From 6. The full health economic social benefits of vaccination: conceptual framework and application to Strep A vaccines

Daniel Cadarette, Harvard T.H Chan School of Public Health, United States

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Annex 1. From: 1. Prof. Jonathan Carapetis. A strategic approach to understand strep A disease burden

Burden of Disease Working Group Members

Name	Affiliation, Country
Jonathan Carapetis (Co-Chair)	Telethon Kids Institute, Australia
Chris Van Beneden (Co-Chair)	Centres for Disease Control and Prevention, USA
Hannah Moore	Telethon Kids Institute, Australia
Jeff Cannon	Telethon Kids Institute / Harvard University, USA
David Kaslow	PATH, USA
Thomas Cherian	MM Global Health Consulting, Switzerland
Asha Bowen	Perth Children's Hospital / Telethon Kids Institute, Australia
Mark Engel	University of Cape Town, South Africa
Theresa Lamagni	Public Health England, UK
Anna Seale	London School of Hygiene & Tropical Medicine, UK
Gagandeep Kang	Christian Medical College, India
David Watkins	University of Washington, USA
Sam Kariuki	Kenya Medical Research Institute, Kenya

Annex 2. From 4: Dr Kaja Abbas. Potential impact of prospective Strep A vaccines on the global burden of disease: model-based analysis

Table 1. Vaccine efficacy**.** The vaccine efficacy assumptions are based on the WHO Preferred Product Characteristics for the Group A *Streptococcus* vaccine.

Group A streptococcus disease state/sequelae	**Vaccine efficacy (%)**
Pharyngitis	80
Impetigo	80
Invasive disease	70
Cellulitis	70
Rheumatic heart disease	50

Table 2. Vaccination scenarios**.** Potential vaccination scenarios for varying years of vaccine introduction, coverage, vaccine-derived immunity dynamics, and age of vaccination (first year of life or 5 years of age).

Scenario	**Year of vaccine introduction**	**Maximum coverage**	**Durability of vaccine-derived immunity**
1	Country-specific (2022 - 2034)	Country-specific (9 - 99%)	Full efficacy for 10 years
2	Country-specific (2022 - 2034)	Country-specific (9 - 99%)	Linear waning over 20 years
3	2022	50%	Full efficacy for 10 years
4	2022	50%	Linear waning over 20 years
5	Country-specific (2022 - 2034)	50%	Full efficacy for 10 years
6	Country-specific (2022 - 2034)	50%	Linear waning over 20 years

Table 3. Vaccine impact at the regional and global levels**.** The vaccine impact on cases averted is presented at the regional (UN regions) and global levels for different scenarios (estimate for scenario 1 and range across the 6 scenarios), based on the lifetime health impact of vaccination at first year of life for 30 birth cohorts from year of vaccine introduction on Group A *Streptococcus* disease burden (pharyngitis, impetigo, invasive disease, cellulitis, and RHD).

UN regions	Scenarios	Fully vaccinated individuals (millions)	Cases averted through vaccination (thousands) (range for scenarios 1-2 and 3-6)				
			Pharyngitis	Impetigo	Invasive disease	Cellulitis	Rheumatic heart disease
South Asia	1-2*	657	(578,344, 606,913)	(76,156, 80,716)	(291, 310)	(3,880, 3,992)	(1,041, 1,466)
	3-6	(381, 388)	(334,999, 357,905)	(44,117, 47,620)	(169, 183)	(2,246, 2,352)	(608, 870)
Europe & Central Asia	1-2*	226	(199,636, 209,585)	(26,231, 27,796)	(100, 106)	(2,027, 2,104)	(102, 120)
	3-6	(122, 124)	(107,661, 114,573)	(14,146, 15,197)	(54, 58)	(1,115, 1,171)	(53, 62)
Middle East & North Africa	1-2*	218	(192,160, 201,701)	(25,266, 26,776)	(96, 102)	(1,253, 1,258)	(348, 407)
	3-6	(121, 122)	(106,638, 112,917)	(14,025, 14,991)	(53, 57)	(693, 701)	(196, 232)
Sub-Saharan Africa	1-2*	918	(799,501, 838,027)	(105,671, 112,075)	(407, 433)	(5,548, 5,635)	(3,635, 4,633)
	3-6	(583, 607)	(505,846, 553,384)	(62,933, 74,061)	(258, 286)	(3,562, 3,777)	(2,285, 3,030)
Latin America & Caribbean	1-2*	184	(162,482, 170,555)	(21,361, 22,637)	(81, 87)	(3,544, 3,949)	(413, 501)
	3-6	(109, 113)	(95,898, 104,796)	(12,608, 13,913)	(48, 53)	(2,091, 2,435)	(244, 306)
East Asia & Pacific	1-2*	575	(507,378, 532,590)	(66,695, 70,679)	(254, 270)	(3,261, 3,354)	(763, 860)
	3-6	(317, 329)	(279,857, 304,513)	(36,790, 40,426)	(140, 155)	(1,837, 1,954)	(414, 483)
North America	1-2*	107	(94,334, 99,039)	(12,395, 13,134)	(47, 50)	(4,145, 4,506)	(4, 4)
	3-6	(58, 58)	(51,094, 53,879)	(6,714, 7,145)	(26, 27)	(2,245, 2,451)	(2, 2)

Global	1-2*	2,886	(2,533,834, 2,658,410)	(333,775, 353,814)	(1,277, 1,359)	(23,657, 24,797)	(6,306, 7,991)
	3-6	(1,690, 1,741)	(1,481,995, 1,601,967)	(195,332, 213,353)	(748, 820)	(13,789, 14,843)	(3,802, 4,985)

* Same number of fully vaccinated individuals for scenarios 1 and 2.

Figure 1. Vaccine impact at the country-income levels. The vaccine impact on cases averted (in thousands) is stratified by income levels of countries (World Bank income classification), based on the lifetime health impact of vaccination at first year of life for 30 birth cohorts from year of vaccine introduction on Group A *Streptococcus* disease burden (pharyngitis, impetigo, invasive disease, cellulitis, and RHD). The vertical bars show the estimates for scenario 1, and the error bars show the range across scenarios 1-6. Note the differences in scale between the left panel (pharyngitis and impetigo) and the right panel (invasive, cellulitis and RHD).

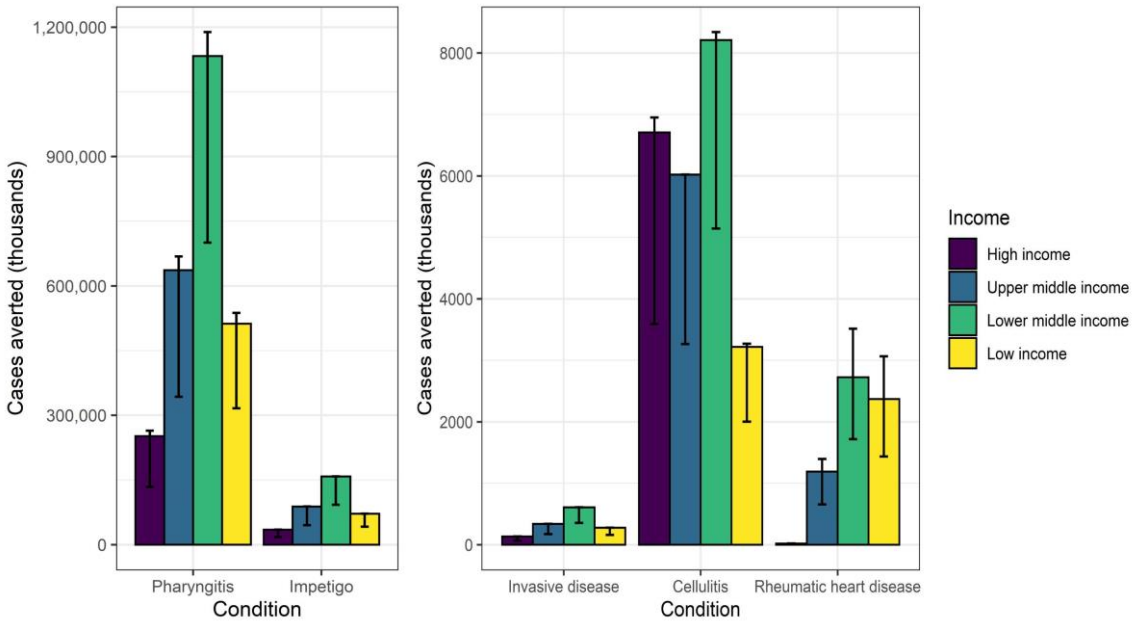


Figure 2. Vaccine impact at the regional and global levels. The vaccine impact on cases averted per 1000 fully vaccinated individuals is stratified at the regional (UN regions) and global levels for different scenarios (estimate for scenario 1 and range across the 6 scenarios), based on the lifetime health impact of vaccination at first year of life for 30 birth cohorts from year of vaccine introduction on Group A *Streptococcus* disease burden (pharyngitis, impetigo, invasive disease, cellulitis, and RHD). The vertical bars show the estimates for scenarios 1, 3, and 5 (which are equal), and the error bars show the estimates for scenarios 2, 4, and 6 (which are equal).

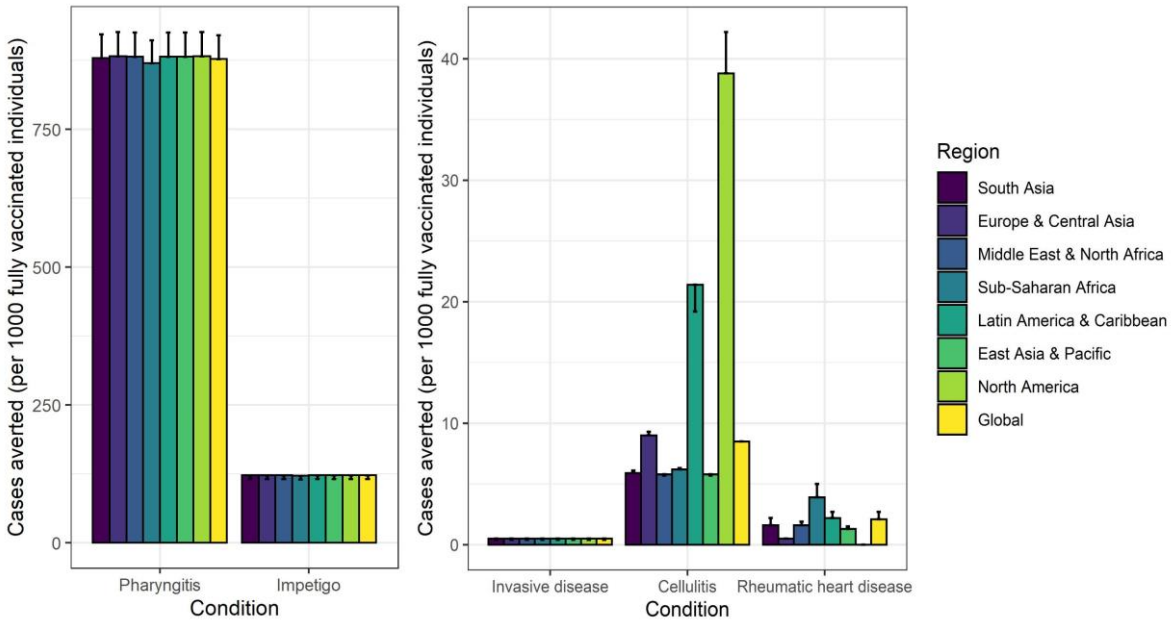
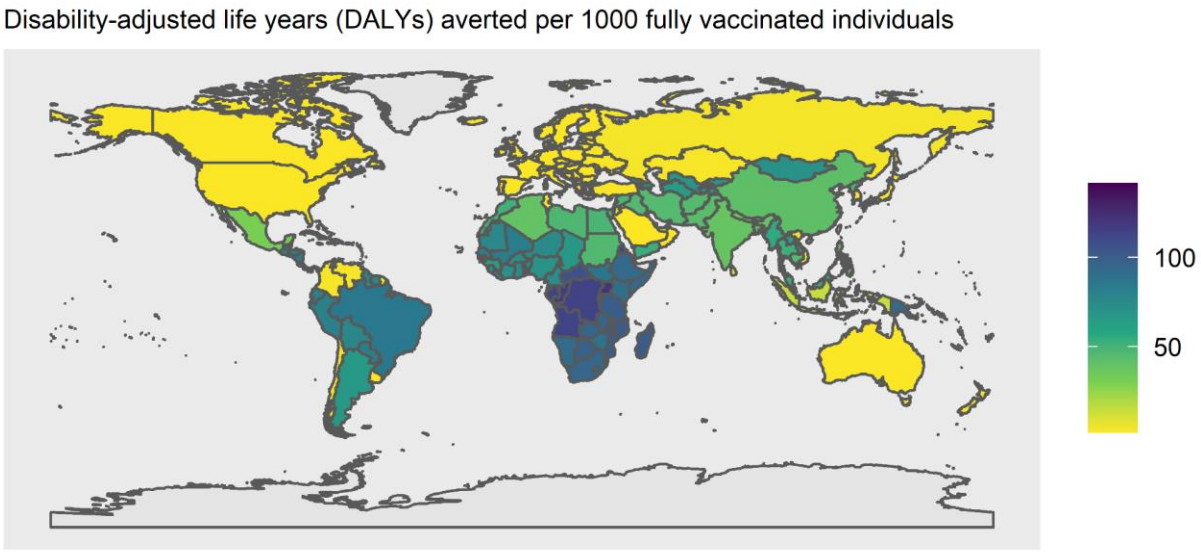


Figure 3. Vaccine impact at the national level**.** The vaccine impact on disability-adjusted life years (DALYs) averted per 1000 fully vaccinated individuals is shown for 183 countries, based on the lifetime health impact of vaccination at first year of life for 30 birth cohorts on Group A *Streptococcus* disease burden (pharyngitis, impetigo, invasive disease, cellulitis, and RHD) using scenario 1 estimates.



Annex 3. From 5: Dr Jung-Seok Lee. Global economic burden for Strep A infections and cost-effectiveness analysis for a hypothetical Strep A vaccine.

Figure 1. Economic burden per episode for Strep A infections by income group

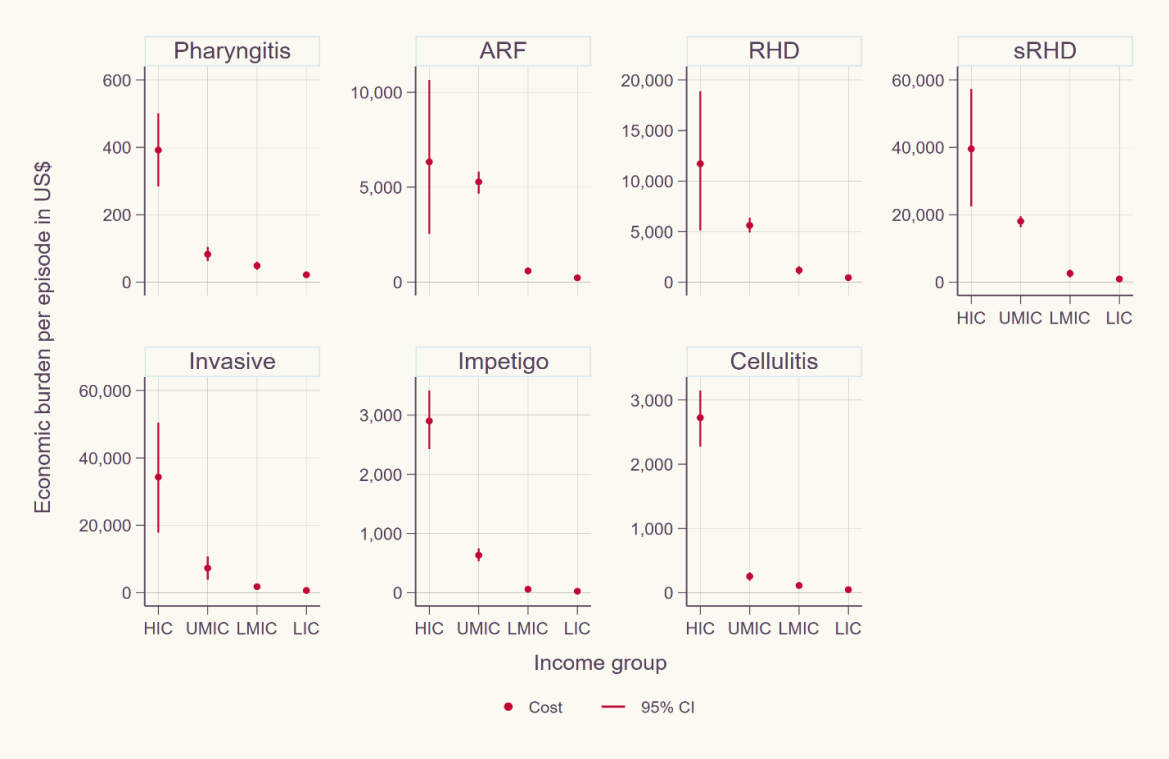


Figure 2. Productivity loss due to premature death by income group

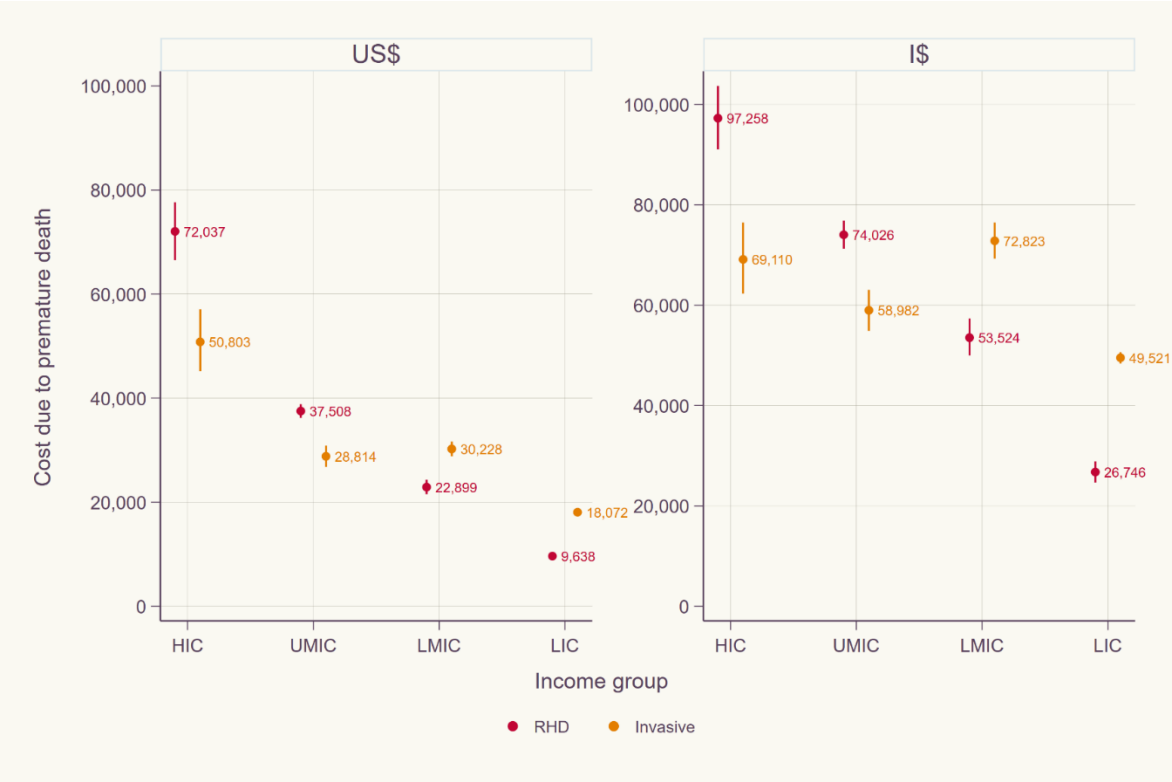


Figure 3. Incremental cost-effectiveness ratios by income group under scenario 1

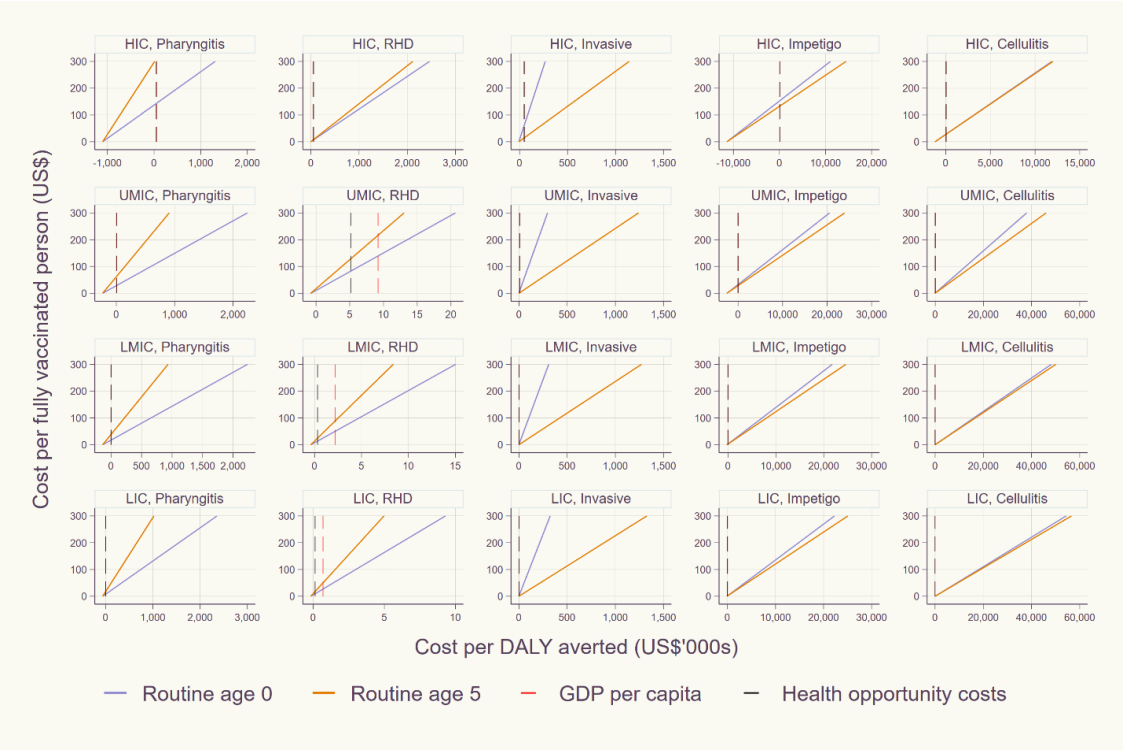
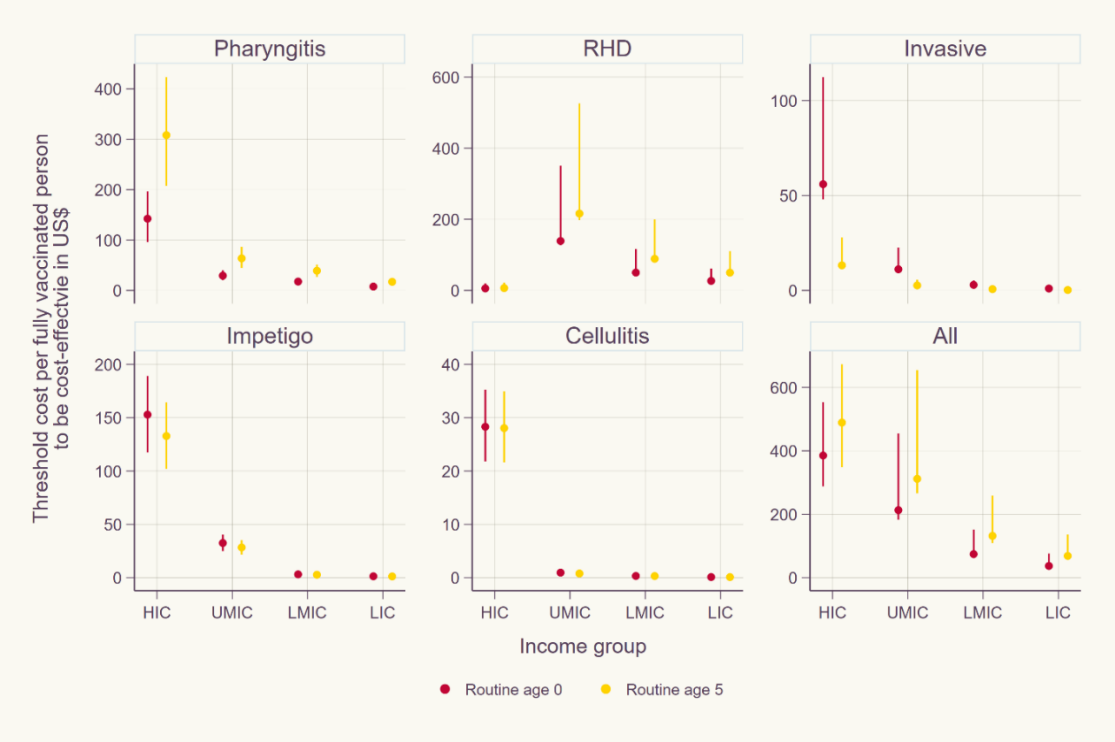


Figure 4. Maximum cost per fully vaccinated person to be cost-effective by income group under scenario 1



Annex 4. Meeting Agenda

Clarion Hotel Sign, Stockholm, Sweden/ 6 June 2022 9am – 5pm CET

Time	Session/Topic	Chair/Presenter
8:00 - 9:00	*Registration (in-person) / Standby (virtual)*	
9:00 - 9:10	Welcome, Introductions and Objectives - Jerome Kim (IVI) and Andrew Steer (MCRI)	
9:10 - 10:10	A strategic approach to understanding Strep A disease burden Jonathan Carapetis, Jeff Cannon and Hannah Moore, Telethon Kids Institute	
10:10 - 10:40	Immunologic protection and correlates - Shiranee Sriskandan, Imperial College	
10:40 - 11:00	*Tea Break*	
11:00 - 11:40	Vaccine safety considerations and guidance - Edwin Asturias, University of Colorado	
11:40 - 12:00	Q&A/Discussion - Liesl Zuhlke, University of Cape Town	
12:00 - 13:00	*Lunch*	
13:00 - 14:50	**Valuing Strep A vaccines/vaccination** • Introduction on the Value of Vaccines and Welcome Address - David Bloom, Harvard T.H. Chan School of Public Health ○ The potential impact of prospective Strep A vaccines on the global burden of disease: A model-based analysis - Kaja Abbas, London School of Hygiene & Tropical Medicine ○ Global economic burden for Strep A infections and cost-effectiveness analysis for a hypothetical Strep A vaccine - Jung Seok Lee, International Vaccine Institute ○ The full health, economic, and social benefits of vaccination: conceptual framework and application to Strep A vaccines - Daniel Cadarette, Harvard T.H. Chan School of Public Health ○ Global antibiotic consumption for sore throat and the potential effect of Strep A vaccines - Jeffrey Cannon, Telethon Kids Institute ○ Global health and economic benefits of Strep A vaccines - Maddalena Ferranna, Harvard T.H. Chan School of Public Health ○ Business Case for Industry Investment in Strep A Vaccine R&D - Don Walkinshaw, Shift Health ○ Optimal Global Spending for Group A Streptococcus Vaccine Research and Development - Daniel Tortorice, College of the Holy Cross • Wrap up – David Bloom	
14:50 - 15:25	Q&A/Discussion - David Kaslow, PATH	
15:25 - 15:45	*Tea Break*	
15:45 - 16:30	**SAVAC 2.0**	

	• Andrew Steer, Murdoch Children's Research Institute (MCRI) ○ Sushena Krishnaswamy, Monash University ○ Michelle Giles, Monash University and Doherty Institute, University of Melbourne
16:30 - 16:40	Wrap up and Closing remarks - Jerome Kim (IVI) and Andrew Steer (MCRI)
16:40 - 17:00	*Photo Session*

Annex 5. List of participants

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