Group A Streptococcus: Full Value of Vaccine Assessment (FVVA) Report

Executive Summary

Background and Context

Group A *Streptococcus* (Strep A) causes a wide range of non-invasive (e.g., pharyngitis and impetigo), invasive (e.g., sepsis) and toxin-mediated (e.g., scarlet fever) diseases, as well as autoimmune sequelae such as acute rheumatic fever (ARF), a precursor to rheumatic heart disease (RHD) as well as acute post-streptococcal glomerulonephritis. Strep A is among the deadliest pathogens worldwide, with an estimated 639,000 deaths due to RHD and other severe clinical manifestations of Strep A in 2019. The economic cost of Strep A clinical disease and premature mortality is also significant. The cost of Strep A pharyngitis among children in the US was previously estimated to range between $224 to $539 million per year in a 2005/2006 study (2006 prices). Using 2022 prices, this cost range would be $329 to $792 million.

Antibiotics form the basis of the principal biomedical response to Strep A; however, they are an imperfect remedy, particularly in low- and middle-income countries (LICs, MICs), where they are often difficult to access and where supply chain and quality control issues can also surface. Further, the effectiveness of antibiotic treatment of Strep A sore throat as a means to prevent ARF and, by extension, RHD is unclear, and antibiotic resistance in bystander pathogens and microbiome disruption are persistent concerns. Absence of awareness and diagnostic capabilities further limit the use of antibiotics in LICs and MICs.

Given the high health and economic burden of Strep A diseases globally, greater investment in the development and delivery of safe and effective Strep A vaccines is warranted. Fortunately, there is evidence that a preventive vaccine against Strep A infection is possible, with several Strep A vaccine candidates demonstrating promising immunogenicity and efficacy results in pre-clinical studies and some also demonstrating immunogenicity and safety in early-stage human trials. Building on these promising results and in conjunction with the World Health Organization (WHO), the Strep A Vaccine Global Consortium (SAVAC) brings together stakeholders to ensure that safe, effective and affordable Strep A vaccines are available and implemented to decrease the burden of Strep A disease, particularly in the countries and regions where the burden of disease is greatest.

Purpose of this Report

SAVAC has led the development of this Full Value of Vaccines Assessment (FVVA) Report to provide an objective assessment of the value of a Strep A vaccine from multiple stakeholder perspectives. This FVVA Report has been developed using the WHO FVVA framework and aims to assess and communicate the full value of vaccination against Strep A infection, particularly in LICs and MICs—accounting for not only the individual health benefits but also indirect and broader socioeconomic impacts. The FVVA report also aims to foster alignment among key stakeholders and inform decision-making around investment in vaccine development, policy, procurement and delivery.

Major Chapter Summaries

Burden of Strep A Diseases—This chapter presents new and contemporary analyses and estimates of the global burden of Strep A pharyngitis and invasive infections based on independent systematic reviews and meta-analyses. Pooled incidence rates (IRs) were 22.1 episodes of Strep A sore throat per

100 child-years and 2.21 episodes of invasive infection per 100,000 person-years. For invasive disease, age-specific incidence rates showed a U-shaped trend, with IRs highest among infants (0-12 months) and those aged 70 years and over. The pooled case-fatality rate (CFR) from invasive Strep A infection was 11.0%, with country-specific CFRs ranging from 3.33% in New Caledonia to 30.56% in Fiji. Future research directions include gaining a better understanding of Strep A disease burden in LICs and MICs, including a more complete picture of the frequency of invasive infections and resultant mortality as well as incidence of ARF and rate of progression to RHD.

Vaccine Impact on Disease Burden—A static cohort model was developed to estimate the projected health impact of Strep A vaccination using a hypothetical Strep A vaccine profile based on the WHO Preferred Product Characteristics (PPCs). Vaccination during the first year of life for 30 birth cohorts born between 2022-2051 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 6 million cases of RHD during the vaccinated cohorts' lifetime. Total cases averted are highest in Sub-Saharan Africa and lower-middle-income countries (LMICs) for pharyngitis, impetigo, invasive disease, cellulitis, and RHD. Per 1,000 vaccinated individuals, the impact is highest in North America for cellulitis and in Sub-Saharan Africa for RHD. Future updates to the model may include the incorporation of immune-mediated sequelae of Strep A infection, including ARF and kidney disease, as well as indirect (herd) effects of vaccination.

Traditional Investment Case—Modelling was undertaken to estimate the economic burden associated with Strep A diseases and to evaluate the cost-effectiveness of a hypothetical Strep A vaccine. The economic burden per episode of Strep A disease ranged from $22 to $390 for pharyngitis, $231 to $6,332 for ARF, $449 to $11,717 for RHD, $949 to $39,560 for severe RHD, $662 to $34,330 for invasive infections, $25 to $2,903 for impetigo, and $47 to $2,725 for cellulitis. For Strep A vaccination to be cost-effective at the threshold of 1 x GDP per capita, the maximum vaccination cost per fully vaccinated person was $385 in high-income countries (HICs), $213 in upper-middle-income countries (UMICs), $74 in LMICs, and $37 in LICs for all disease states combined. Future research is needed to fill data gaps, particularly related to LIC settings.

Full Societal Benefits—Strep A vaccination is likely to confer significant benefits beyond direct reductions in morbidity, mortality, and healthcare costs. These broader societal benefits include: decreased antibiotic consumption (3.1 million courses of antibiotics could be averted by Strep A vaccination in a set of 9 high-income countries alone); positive impacts on educational attainment, school attendance, and cognitive function in children; mitigation of losses in labor force participation, productivity, and income for adults; and greater social equity, given Strep A's disproportionate burden on low-income and otherwise disadvantaged populations. Overall, the full lifetime value for 30 birth cohorts of reducing deaths and disabilities directly associated with Strep A vaccination with waning effectiveness is estimated to range from $1.7 to $3.2 trillion USD if the vaccine is administered at birth, and from $3.1 to $5.1 trillion USD if the vaccine is administered at age 5, according to a value-per-statistical-life approach. There are several avenues open for future research into the broad benefits of Strep A vaccines, including the incorporation of the value of preventing antibiotic resistance and quantification of the distributional impacts and potential equity implications.

Business Case from a Developer's Perspective—A demand and return on investment forecast model was developed to estimate the potential demand for a hypothetical Strep A vaccine globally, support

associated revenue and profit forecasts, and enable a risk-adjusted net-present value (NPV) analysis of return on investments required for the development, licensure and manufacturing of a Strep A vaccine. Assuming a risk-adjusted total R&D investment of $979 million (which assumes an aggregate probability of technical and regulatory success of 13%) by a hypothetical multinational pharmaceutical company supplying a global market with first market entry in 2033, the risk-adjusted NPV is approximately $2.5 billion USD. In the case of a developing-country vaccine manufacturer (DCVM) that conducts a staged rollout wherein LICs and MICs are initially targeted (starting in 2033) before rollout in HICs several years later (starting in 2038), and assuming a risk-adjusted total R&D investment of $372 million, the risk-adjusted NPV is ~$310 million USD. These results suggest there will be a viable commercial market for a Strep A vaccine. It is hoped that this work will help to address the perceived lack of commercial opportunity for a Strep A vaccine and mitigate challenges that have impeded commercial investment in Strep A vaccine R&D, including relatively low levels of overall R&D funding, safety concerns stemming from vaccine candidate testing in children in the 1960s as well as unanswered scientific questions and a lack of regulatory clarity.

Optimal Spending on Strep A Vaccine R&D—This chapter estimates the optimal global spending on R&D for a Strep A vaccine from the perspective of a supranational organization that can allocate funding for a portfolio of Strep A vaccine R&D projects. In the model, the hypothetical organization considers the available Strep A vaccine 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. Results indicate that optimal spending for Strep A vaccine R&D is estimated to be in the tens of billions of USD; benefits of this R&D spending (in the range of $1.6 to $3.3 trillion USD) would be more than 50 times greater than investments, including R&D, manufacturing, and related regulatory costs. Returns on investment range from 18% to 29% per year for 30 years. These returns, which point to gross global societal underinvestment in R&D of Strep A vaccines, are large even compared to other social interventions that have received considerable support. These results call for both national and international policy to prioritize, fund and promote development of Strep A vaccines.

Key Findings, Evidence and Recommendations At-A-Glance

KEY FINDING	EVIDENCE	RECOMMENDATION
New meta-analysis data of pharyngitis and invasive infections substantiate the high burden of Strep A-mediated diseases globally	The pooled IR for Strep A sore throat was 22.1 episodes per 100 child-years. The pooled IR for invasive Strep A infections was 2.21 episodes per 100,000 person-years, with U-shaped age distribution showing highest in infants and adults aged 70+.	Enhance country-level surveillance programs, particularly in LMICs, and particularly to monitor rates of Strep A invasive disease as well as acute rheumatic fever (ARF).
New estimates of economic burden per case of different Strep A diseases indicate a significant economic burden globally	The estimated economic burden ranged from $22 to $392 for pharyngitis, $231 to $6,332 for ARF, $449 to $11,717 for rheumatic heart disease (RHD) $949 to $39,560 for severe RHD, $662 to $34,330 for invasive infections, $25 to $2,903 for impetigo, and $47 to $2,725 for cellulitis (lower end of range is for low-income	Prioritize collection and use of data to fill knowledge gaps and improve accuracy of economic burden estimates, particularly in UMICs, LMICs, and LICs. Revisit cost-effectiveness analysis (CEA) outcomes as characteristics of vaccines advancing through clinical trials are known.

	countries (LICs), higher end for high income countries (HICs). Productivity loss due to premature death from RHD and invasive infections ranged from $9,637 and $17,830, respectively, in LICs to $72,097 and $50,484, respectively, in HICs.	
A Strep A vaccine could substantially reduce global morbidity and mortality due to Strep A diseases	Globally, a Strep A vaccine could avert 82 million cases of pharyngitis, 11.8 million cases of impetigo, 45,000 cases of invasive disease, 805,000 cases of cellulitis and 210,000 cases of RHD per birth cohort.	Global policy makers and global health organizations should recommend and work with funders and countries to prioritize investments in Strep A vaccine development and implementation.
A Strep A vaccine is likely to be a cost-effective intervention in all country income groups when considering total spectrum of Strep A diseases	For Strep A vaccination (routine vaccination for infants at birth) to be cost-effective at the threshold of 1 x Gross Domestic Product (GDP) per capita, the maximum vaccination cost per fully vaccinated person was $385 in HICs, $213 in UMICs, $74 in LMICs, and $37 in LICs for all disease states combined.	Local governments and global health funders should work together to determine expected delivery costs associated with Strep A vaccine implementation.
Strep A vaccination is likely to confer significant broad socioeconomic benefits beyond direct reductions in morbidity, mortality, and healthcare costs	Significant broad benefits of Strep A vaccination include reduced antibiotic use and resistance, gains in schooling and labor, and improved social equity. Based on a value-per-statistical-life approach, the full global societal lifetime value for 30 birth cohorts of Strep A vaccination is estimated to range from $1.7 to $3.2 trillion United States dollar (USD) if the vaccine is administered at birth, and from $3.1 to $5.1 trillion USD if the vaccine is administered at age 5.	Funders should support further study of the broad socioeconomic benefits of Strep A vaccination—including, for example, incorporating the value of preventing antibiotic resistance—and governments should better incorporate the full socioeconomic value of vaccines into R&D prioritization and vaccine implementation decisions.
The market for private sector investment in Strep A vaccine development and manufacturing is financially sustainable with base case forecasts indicating likely profitability.	The net present value (NPV) for development and manufacturing of a Strep A vaccine in the scenario where a multinational pharmaceutical company completes a global roll-out is ~$2.5 billion USD for an infant immunization schedule scenario and ~$2.0 billion USD for a child immunization schedule scenario.	Companies should be engaged to understand current barriers to R&D investment and cross-sector solutions to incentivize industry prioritization of Strep A R&D investment should be explored.
Optimal spending on the development of Strep A vaccines is measured in the billions of dollars, but this spending may be expected to unlock trillions of dollars in value.	Base case optimal spending for Strep A vaccine R&D is estimated at $33.0 billion USD with resulting social surplus benefits 50-fold higher, in the range of $1.6 to $3.3 trillion USD. Returns on investment range from 18% to 29% per year for 30 years. These returns are large even compared to other social interventions that have received considerable support. For	Governments should analyze options (e.g., debt financing, bond funding) and align on a preferred approach for achieving optimal R&D spending on Strep A vaccine development.

	example, estimates of the return to increased years of education range from 9-10% per year.	HIC governments should donate funds through international organizations to ensure equitable vaccine implementation.

Conclusion

Strep A infections lead to multiple diseases that collectively pose a substantial health, economic and social burden globally. This burden is disproportionately carried by LICs/MICs and disadvantaged communities, but there is also significant burden in HICs. Current preventive and treatment options for Strep A have major limitations. This FVVA report provides new evidence that an effective and safe vaccine for Strep A could avert millions of cases of Strep A disease and prevent a significant amount of the morbidity and mortality caused by the pathogen. It could also alleviate much of the economic burden associated with direct and indirect medical costs. But the impact of a Strep A vaccine would likely extend far beyond traditional benefits. Vaccination to prevent Strep A infections and associated diseases could reduce reliance on antibiotics; lead to gains in education, cognition, labor force participation, productivity, and income; and promote equity, improve quality of life, and reduce stigma. The bottom line of this report is that traditional thresholds for cost-effectiveness will plausibly be satisfied by a Strep A vaccine and more so when one accounts for full societal benefits above and beyond morbidity and mortality reductions.

Strep A vaccine R&D has historically been underfunded by governments and global health funders, and few pharmaceutical companies have invested in Strep A vaccines throughout the development pipeline. It is postulated that a major impediment to industry investment has been uncertainty around the market for a Strep A vaccine. Importantly, the FVVA findings suggest that pharmaceutical companies will find a viable market for investing in Strep A vaccine R&D and that the public sector could support tens of billions of dollars in Strep A vaccine R&D and still achieve a strong return on investment. Through this evidence, it is hoped that the FVVA heightens awareness of both the need for and value of Strep A vaccination and informs decision-making and policies that support greater prioritization of investment in Strep A vaccine R&D as a vital public health tool and commercially viable product.

Acknowledgements

This report presents research authored by teams at College of the Holy Cross (Worcester MA, USA), the Harvard T.H. Chan School of Public Health (HSPH, Boston MA, USA), the International Vaccine Institute (IVI, Seoul, Republic of Korea), London School of Hygiene and Tropical Medicine (LSHTM, London, UK), Shift Health (Toronto, Canada), and Telethon Kids Institute (TKI, Perth, Australia), as part of ongoing work by the Strep A Vaccine Global Consortium (SAVAC), a global effort to drive the development of public health vaccines for Strep A diseases. SAVAC is funded by a grant from the Wellcome Trust.

Authors include: David Bloom, Daniel Cadarette and Maddalena Ferranna (HSPH); Daniel Tortorice (Holy Cross); Jean-Louis Excler, Vittal Mogasale, Jung Seok Lee, and Sol Kim (IVI); Kaja Abbas (LSHTM); Ryan Wiley, Anne Mullin, Donald Walkinshaw, Marni Williams, Tanya Scarapicchia and Meghan Wright (Shift Health); and Jeffrey Cannon, Kate Miller and Fiona Giannini (TKI).

The authors would like to acknowledge the leadership and support of the SAVAC Executive Committee, including: Jerome H. Kim, Chair, (IVI); Andrew Steer, Co-Chair, (Murdoch Children's Research Institute); David Bloom (HSPH); Jonathan Carapetis (TKI); David Kaslow (PATH); Edwin Asturias (University of Colorado); Shiranee Sriskandan (Imperial College); and Liesl Zühlke (University of Cape Town).

The authors would also like to acknowledge the support of a Technical Advisory Committee (TAC), including (in alphabetical order by last name): Ijeoma Edoka (University of the Witwatersrand, Johannesburg, South Africa); Birgitte Giersing (WHO, Geneva, Switzerland); Raymond Hutubessy (WHO); and Mark Jit (LSHTM).

Finally, the authors wish to extend a sincere thank you to Deborah King, Elizabeth Klemm and Charlie Weller from the Wellcome Trust for support of this work.

Additional acknowledgements are included in the Appendix.

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List of Abbreviations

ADI	Arginine Deiminase
AMR	Antimicrobial Resistance
ARF	Acute Rheumatic Fever
ASAVI	Australian Strep A Vaccine Initiative
CANVAS	Coalition to Advance Vaccines Against Group A Streptococcus
CEA	Cost-Effectiveness Analysis
CFR	Case-fatality rate
CHIM	Controlled Human Infection Model
CHIVAS	Controlled Human Infection for Vaccination against Streptococcus pyogenes
CHOICE	CHOosing Interventions that are Cost-Effective
DALY	Disability-Adjusted Life Year
DCVM	Developing Countries Vaccine Manufacturer
DMC	Direct Medical Cost
DNMC	Direct Non-Medical Cost
DTP3	Diphtheria, Tetanus, Pertussis Vaccine by Third Dose
FDA	Food and Drug Administration
FVVA	Full Value of Vaccine Assessment
GAC	Group A Carbohydrate
GBD	Global Burden of Disease
GDP	Gross Domestic Product
GVGH	GSK Vaccines Institute for Global Health
HIC	High-Income Country
HPV	Human Papillomavirus Vaccine
IC	Indirect Cost
ICER	Incremental Cost-Effectiveness Ratio
IM	Intramuscular
IPV	Inactivated Polio Vaccine
IR	Incidence Rate
LIC	Low-Income Country
LMIC	Lower-Middle-Income Country
MB	Marginal Benefit
MC	Marginal Cost
MCV	Measles-Containing Vaccine
MDB	Multilateral Development Banks
MI4A	Market Information for Access to Vaccines Database
MIC	Middle-Income Country
MPC	Multinational Pharmaceutical Company
NGO	Non-governmental Organization
NHP	Non-Human Primate
NIP	National Immunization Program
NPV	Net Present Value
OPK	Opsonophagocytic Killing

PCV	Pneumococcal Conjugate Vaccine
PPC	Preferred Product Characteristics
R&D	Research and Development
RHD	Rheumatic Heart Disease
RT0	Routine vaccination for Infants at birth
RT5	Routine vaccination for Infants at age 5 years
SC	Subcutaneous
SCPA	Streptococcal C5a Peptidase
SLO	Streptolysin O
SAVAC	Strep A Vaccine Global Consortium
SpyAD	Putative Surface Exclusion Protein
SpyCEP	Streptococcal Interleukin-8 Protease
STSS	Streptococcal Toxic Shock Syndrome
TF	Trigger Factor
TPP	Target Product Profile
VSL	Value-per-Statistical-Life
VSLY	Value-per-Statistical-Life-Year
USA	United States of America
USD	United States Dollar
UMIC	Upper-Middle-Income Country
WHO	World Health Organization
YLD	Years Lived with Disability

1 Purpose of the FVVA Report

1.1 Objectives of a full value of vaccines assessment

The Full Value of Vaccines Assessment (FVVA) is a framework developed by the World Health Organization (WHO) (1) to guide the assessment and communication of the value of a vaccine intended for use in LICs and MICs, particularly where HIC developers are insufficiently incentivized to invest. By communicating the full value of a vaccine, the FVVA aims to foster alignment among key stakeholders and inform decision-making around investment in vaccine development, policy, procurement and introduction (1). Focusing on considerations across the full continuum of development of a preventive Strep A vaccine (Figure 1-1), this FVVA report combines results from three primary analyses to describe the health, economic, and societal value of Strep A vaccination for a range of stakeholders:

- **The Traditional Investment Case** (Chapters 6-8) uses standard economic evaluations to define the individual, direct health burden, and related costs associated with Strep A infections. It also estimates the cost-effectiveness of a safe and effective Strep A vaccine and provides an overview of the findings from a systematic literature review on existing Cost-Effectiveness Analysis (CEA) models. The primary analysis applies the WHO Preferred Product Characteristics (PPC) of a Strep A vaccine. The outcomes and findings drawn from the Traditional Investment Case can be used to inform the decisions made by government policymakers, funders, and manufacturers to develop, introduce, and invest in a vaccine for Strep A.
- **The Global Investment Case** (Chapter 9) aims to identify the full societal value of Strep A vaccination at the population level. It comprises a conceptual framework that catalogs potential health, economic, and social benefits of vaccination and their distribution across stakeholder types, a literature review of the societal benefits of vaccine-related interventions, analyses regarding the potential impact of a Strep A vaccine on antimicrobial use and antimicrobial resistance (AMR), and value-per-statistical-life (VSL) estimates of the global value of vaccination. The Global Investment Case intends to provide evidence of the global health benefits of Strep A vaccination to national and international policymakers, funding agencies, philanthropic organizations, and procurement agencies. Further, Chapter 11 provides an assessment of the number of Strep A vaccine R&D projects that would be worth investing in by a hypothetical supranational funder based on the overall health, societal, and economic benefits likely to result from Strep A vaccination.
- **The Commercial Investment Case** (Chapter 10) aims to make the case for vaccine manufacturers to invest in Strep A vaccine development. The Business Case includes a demand forecast, a revenue and profit forecast, and an analysis of the return on investment in a Strep A vaccine under different Strep A vaccine research and development (R&D) scenarios.

Ultimately, this work aims to provide investors, donors, developers and policymakers with key information to enable more accurate prioritization of available resources to avoid unnecessary delays in access to new vaccines that prevent Strep A diseases. An overview of the analyses presented in the FVVA is presented in Figure 1-2.

Figure 1-1. The continuum of vaccine development.*

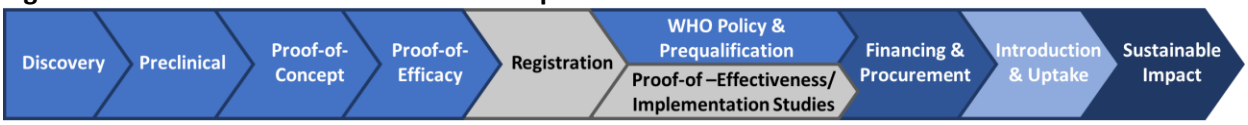

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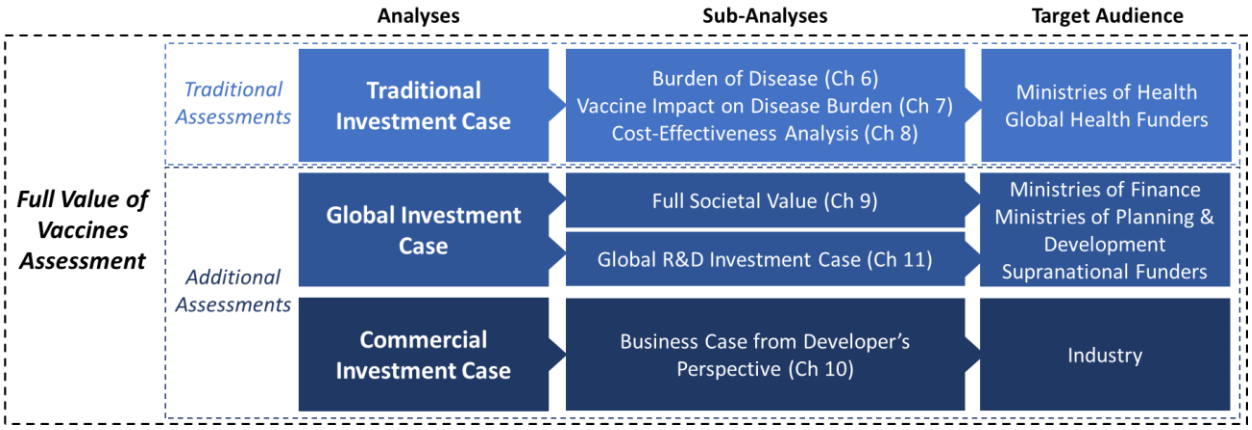
Figure 1-2. Overview of analyses included in the Full Value of Vaccines Assessment (FVVA).



1.2 Target audiences

While each chapter may have specific implications and relevance to different stakeholders, generally speaking, the target audiences for the FVVA include:

- Funders/Investors
  - Donor governments
  - Multilateral organizations
  - MDBs (Multilateral Development Banks)
  - Private foundations
  - Philanthropies
  - Investors
- Policy decision-makers
  - Global (including WHO)
  - Regional (including RITAGs – Regional Immunization Technical Advisory Groups)
  - National (including NITAGs – National Immunization Technical Advisory Groups, and national/sub-national Ministries of Health, Ministries of Finance, Ministries of Planning & Development)
- Vaccine researchers
  - Academic institutions
  - Biotech & pharmaceutical companies
  - Product Development Partnerships (PDPs)
- Vaccine manufacturers
  - MPC (Multinational Pharmaceutical Company)
  - DCVM (Developing Countries Vaccine Manufacturer)
- Gavi, UNICEF, non-governmental organizations (NGOs)

- Vaccine recipients, parents/caregivers, healthcare workers, community leaders, civil societies

2 Background and context for this report

2.1 Description of SAVAC and EC members

The Strep A Vaccine Global Consortium (SAVAC) brings together representatives from the health sector to ensure that safe, effective, and affordable Strep A vaccines are available and implemented to decrease the burden of Strep A disease in the most in need. With funding from the Wellcome Trust, SAVAC's work focuses on disseminating and applying the WHO Strep A research and development (R&D) Roadmap and Preferred Product Characteristics (PPCs; see Chapter 4 for additional details), investigating the potential value of prospective Strep A vaccination through this Full Value of Vaccines Assessment (FVVA) report and supporting activities coordinated through dedicated working groups (e.g. Vaccine Safety Working Group, Global Burden of Disease Working Group, FVVA Working Group). SAVAC's multi-stakeholder activities are led by an Executive Committee comprised of the following infectious disease, vaccine development, and public health experts:

Dr. Jerome H. Kim, Chair, International Vaccine Institute, Seoul, Republic of Korea

Prof. Andrew Steer, Co-Chair, Murdoch Children's Research Institute, Melbourne, Australia

Prof. Jonathan Carapetis, Telethon Kids Institute, University of Western Australia, Perth, Australia

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

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Prof. Liesl Zühlke, University of Cape Town, South Africa

Prof. Edwin J. Asturias, University of Colorado, Aurora CO, USA

Prof. Balram Bhargava, Indian Council of Medical Research & National Technical Advisory Group on Immunisation, New Delhi, India

2.2 Description of disease and economic burden

2.2.1 Group A Streptococcus

Group A *Streptococcus* (Strep A) or *Streptococcus pyogenes* is a β-hemolytic, Gram-positive bacterium. It typically colonizes on mucous membranes in the upper respiratory tract. Strep A can also colonize on human skin, but it is not considered to be a normal commensal organism of healthy skin. It can be transmitted from human to human by droplet and by direct contact. Nasopharyngeal carriage and asymptomatic infection are also possible and may facilitate Strep A transmission.

Strep A rarely infects animals, is considered to be pathogenic only in humans, and is associated with possibly the most diverse range of clinical conditions compared to any other pathogen (Table 2-1). Superficial throat and skin diseases include those resulting from Strep A infections of the upper respiratory tract and the outer layer of skin, and most commonly occur in childhood. More severe throat and skin diseases can arise from infections of the deeper layers of skin, soft tissue, and lymph nodes. When Strep A invades a normally sterile body site, the disease is characterized as invasive Strep A

infection, which can manifest as pneumonia, sepsis, postpartum sepsis, bacteremia, meningitis, streptococcal toxic shock syndrome (STSS), or necrotizing fasciitis.

While severe diseases are less frequent than those arising from superficial infection, they are much more likely to result in fatal outcomes. For example, almost one in two patients with Strep A toxic shock syndrome will die from the condition (2). In some circumstances, immune-mediated diseases may result from an abnormal auto-immune response following Strep A infection and one or more episodes of immune-mediated disease, such as acute rheumatic fever (ARF) or Acute Poststreptococcal Glomerulonephritis (APSGN), can result in chronic, long-term conditions (e.g., rheumatic heart disease [RHD] and chronic kidney disease) and premature mortality (3).

Table 2-1. Common infection sites and associated clinical diseases and conditions.

INFECTION SITE	CLINICAL DISEASES/CONDITIONS
Upper Respiratory Tract	Pharyngitis, tonsillitis, otitis media, *scarlet fever**
Outer Skin	Impetigo
Deeper Skin and Soft Tissue and Lymph Nodes	Erysipelas, cellulitis, lymphadenitis
Invasive Infection of Sterile Sites (e.g., blood, bone, organs)	Sepsis (including maternal sepsis), *toxic shock syndrome**, *necrotizing fasciitis**, meningitis, pneumonia, septic arthritis
Post-Infection, Auto-Immune Sequelae	Acute rheumatic fever and rheumatic heart disease
	Acute poststreptococcal glomerulonephritis and chronic kidney disease

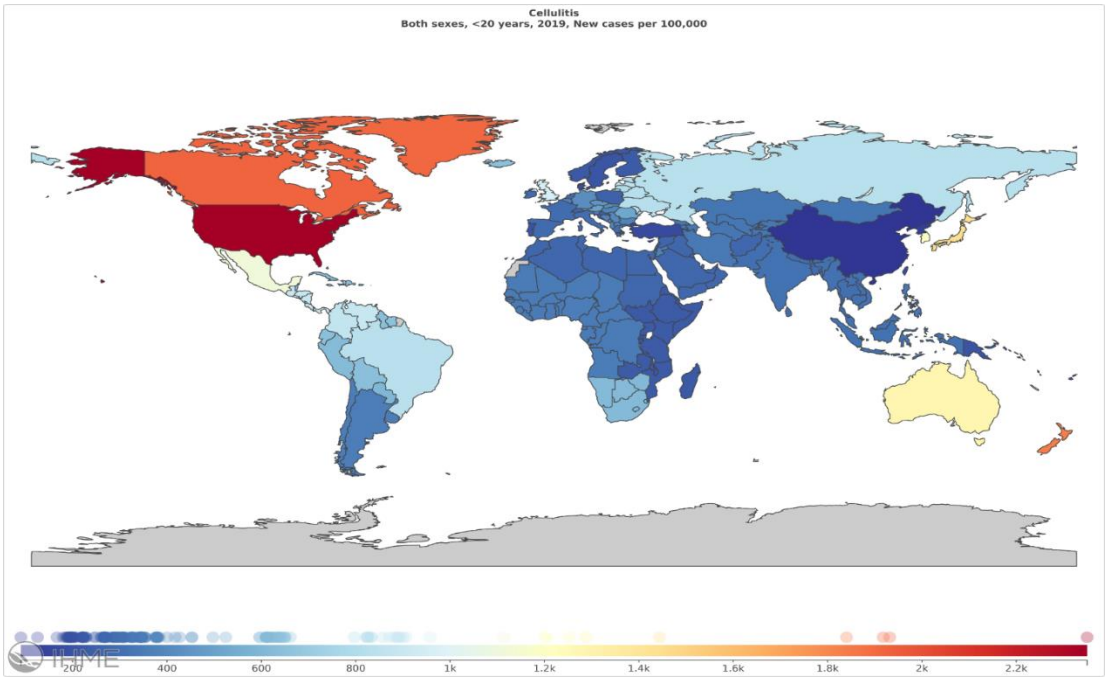
** Toxin-mediated diseases*

2.2.2 Disease Burden

A contemporary estimate for the global burden of Strep A infection that includes all acute clinical endpoints and sequelae is lacking. In a 2005 publication, Strep A was estimated to cause 517,000 deaths each year (4). Updated with more recent data for RHD-related deaths, the 2005 estimate was revised to 639,000 deaths due to all Strep A diseases each year in 2019 (5). In that update, RHD-related deaths accounted for 467,000 (73%) of all deaths due to Strep A infection, while deaths due to invasive infection accounted for 163,000 (25%) of Strep A deaths. Moreover, unlike many diseases for which treatments are available, RHD-related deaths were forecasted to remain nearly unchanged between 2016 and 2040, underscoring the importance of thinking in terms of health system strengthening and not simply antibiotics as the most valuable strategies (6).

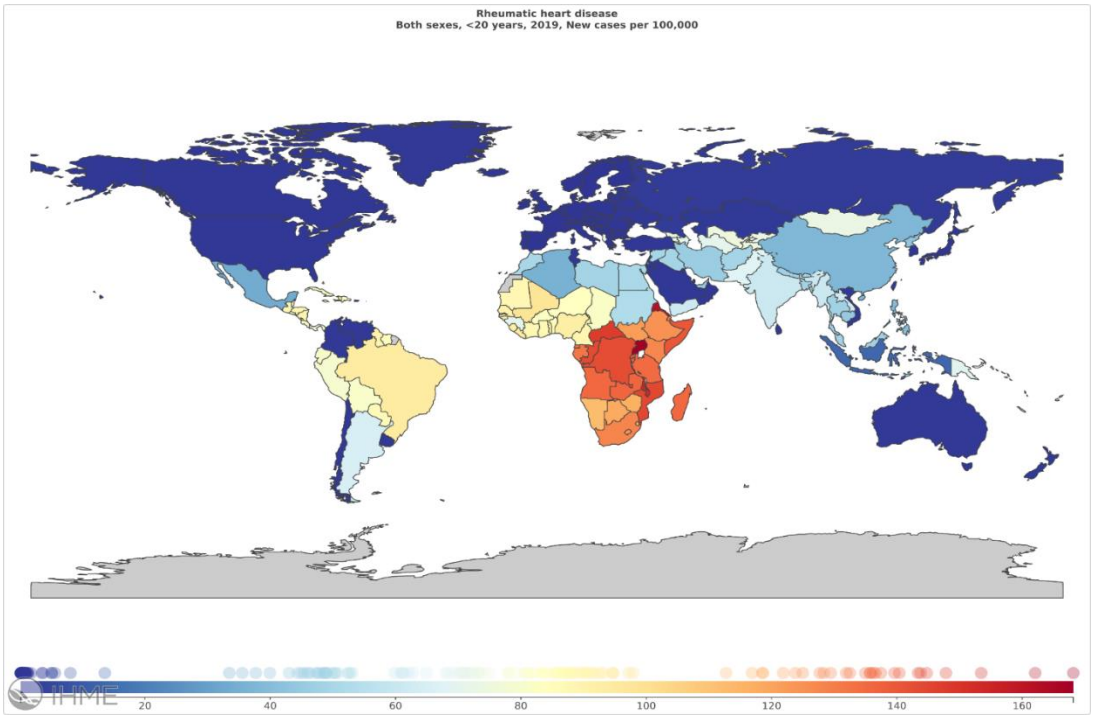
Country- and age-specific incidence rates for cellulitis, impetigo, and RHD are available from the Global Burden of Disease project (7), but impetigo and cellulitis incidence rates are for any pathogen, not Strep A specifically. Incidence rates for cellulitis and RHD among people <20 years of age are shown in Figures 2-1**Error! Reference source not found.** and 2-2**Error! Reference source not found.**.

Figure 22-1. Cellulitis Global Burden of Disease (GBD) 2019 incidence rates per 100k.*



Adapted from (7, 8)

Figure 22-2. Rheumatic heart disease GBD 2019 incidence rates per 100k.*



Adapted from (7, 8)

2.2.3 Economic Burden

Strep A clinical disease and premature mortality also have a significant economic impact. At the population level, healthcare-related costs due to superficial infection can be higher than those due to severe disease (4). However, healthcare-related costs constitute an equivalent or lower economic burden compared to other costs (e.g., productivity loss, non-medical costs such as travel). In Fiji, RHD in 2008-2012 was estimated to cost approximately $47.7 million (2010 price levels), of which productivity losses from premature mortality accounted for more than two-thirds of that cost (9). Similarly, non-medical costs comprised almost half of the total cost of diagnosed Strep A pharyngitis, with the total cost of Strep A pharyngitis among children in the United States of America (USA) estimated to range between $224 to $539 million per year in a 2005/2006 study (2006 prices) (10). Yet, there are likely further economic and social consequences that have yet to be fully qualified (see Chapter 8).

3 Strategies to address Strep A infection

3.1 Antibiotics and other potential interventions

Whether investment in Strep A vaccines is justified depends, in part, on the availability and effectiveness of alternative strategies to prevent or treat Strep A diseases (11). In this section, we briefly describe the primary strategies currently available to address Strep A diseases, summarizing their strengths and limitations.

3.1.1 Antibiotics

Antibiotics are the foundation of the principal biomedical response to Strep A and are the fastest and sometimes only strategy to prevent or limit the pathogen's adverse effects. Penicillins are the antibiotic class of choice for superficial infections, but other antibiotic classes are sometimes used, including in patients with penicillin allergies. Treatment of sore throat is a major driver of antibiotic prescriptions in many countries. Penicillin V and amoxicillin, administered orally over ten days, are typically used to treat Strep A pharyngitis or tonsillitis patients in high-income countries. Benzathine penicillin G (BPG), administered as a single intramuscular injection, can be used in patients at risk of low compliance to the ten-day oral course and is recommended in many low- and middle-income countries. Repeated BPG injections, typically 4-weekly, are used as a prophylactic measure against recurrent Strep A infections and acute rheumatic fever (ARF) among patients with a first episode of ARF or diagnosed rheumatic heart disease (RHD). Penicillin can be used for Strep A impetigo, but because other pathogens (mainly *Staphylococcus aureus*) may also be involved, broader spectrum antibiotics may be used – trimethoprim-sulphamethoxazole has been shown to be a cheap, widely available and effective antibiotic for impetigo. For invasive infections, penicillin is also typically the first treatment choice once Strep A is the confirmed pathogen and is administered intravenously; however, clindamycin or intravenous immunoglobulin treatment may be used in addition or as an alternative to penicillin, and expensive, broader spectrum antibiotics are often used in very sick patients (12).

Reliance on antibiotics for treatment and prevention of Strep A diseases presents several challenges. Access to antibiotics may be limited in some resource-constrained settings. Among LICs and MICs, there have been supply chain and quality issues for BPG (13). In addition, out-of-pocket drug costs, as well as time and transportation costs associated with seeking diagnosis and treatment, may represent a substantial burden to low-income patients and their parents/caregivers, especially for those facing repeated infections (14). In addition, Strep A is a major driver of overuse of antibiotics; pharyngitis is one of the most common diagnoses among patients prescribed antibiotics (15-18).

Even where access and cost are not major concerns, antibiotics are an imperfect remedy. For instance, the effectiveness of antibiotic treatment of sore throat as a means to prevent ARF and, by extension, RHD has come under question. For example, while a systematic review and meta-analysis of clinical trials conducted in the middle of the 20th century showed a 68% reduction in risk of ARF following penicillin treatment (19), it also found that the studies were generally of poor methodological quality, that only one study comprised children (all others were in military personnel), and that the study involving children did not show a significant effect. Moreover, nine of the ten studies analyzed were based on the effect of penicillin administered through intramuscular injection, whereas oral treatment of sore throat is standard in the 21st century. And none of these studies accounted for the high proportion of ARF cases that either do not follow a sore throat or a sore throat sufficiently severe to

lead to a healthcare presentation. More recently, a large-scale, population-based implementation study from New Zealand, a high-income country that has invested heavily in reducing ARF over the past decade, found that penicillin treatment of Strep A sore throat, when administered through a combination of school, pharmacy, and GP-based sore throat clinics, did not significantly reduce the risk of ARF among children with Strep A infection. There may have been a significant impact in a region with particularly high ARF incidence (but even then, less than one-third of ARF cases were prevented) (20). This approach was very expensive and logistically complex, such that the same approach would be difficult to contemplate in low- and middle-income countries, and it has since been abandoned in NZ.

Further, a traditional focus on the treatment of Strep A pharyngitis may miss ARF caused by skin infection. Strep A skin infection has been posited as a risk factor for ARF since the mid-2000s (21), and this hypothesis has been strengthened by recent evidence from New Zealand (20). Yet, skin infections frequently go untreated in many populations, such as Indigenous Australian communities (22).

Even with adequate access to antibiotic treatment, the mortality rate among patients with invasive infections is high. A study of invasive Strep A infections among European countries found that almost one in two patients with toxic shock syndrome died within seven days of hospitalization (2).

Over the long term, microbiome disruption (at the individual level) and antibiotic resistance (at the population level) present additional concerns with overreliance on antibiotics to address Strep A (15-18). Disruption of the microbiome may occur in individual patients when antibiotics are consumed, with repeated consumption being especially problematic. This disruption may have negative and lasting effects on the immune system, nutritional health, and metabolic function (23). Regarding antibiotic resistance in the population, Strep A remains completely susceptible to penicillin antibiotics; however, resistance among other classes of antibiotics sometimes used for treatment has been observed (24). The development of resistance in bystander pathogens incidentally exposed to antibiotics during treatment of Strep A (including with penicillin) is also a concern. Antibiotic resistance is discussed in more detail in Chapter 9.

3.1.2 Other healthcare-related strategies

Other healthcare-related strategies—which are largely relevant to the management of RHD —include early detection of disease through screening and the prevention of death through surgical intervention. Community-based echocardiographic screening for latent or early-stage RHD is increasingly becoming a practical and affordable strategy globally. Field research studies have demonstrated high levels of diagnostic accuracy when using hand-held portable screening devices among non-expert operators (25). Surgical interventions include valve surgery among RHD patients with advanced disease and extensive skin debridement or amputation among necrotizing fasciitis patients.

Notwithstanding recent improvements, issues of equitable access and cost are even more of a concern for these other healthcare-related strategies than they are for antibiotics. Indeed, many LICs and MICs lack the capacity to conduct valve surgeries for RHD patients (13). In addition, patients have already suffered significant adverse effects of Strep A infection by the time some of these interventions are implemented. Prevention of Strep A infection through vaccination (or early treatment of infection) is therefore far more desirable.

3.1.3 Public health and socioeconomic strategies

Before the start of the antibiotic era (around 1940), large reductions in the incidence of maternal sepsis, scarlet fever, ARF, and RHD were achieved in correlation with improvements in public health knowledge and practices (26). Important advances included improvements in hygienic and sanitary infrastructure and practices (e.g., wastewater management and hand washing before medical interventions and before preparing and eating meals) and in social conditions (e.g., reduced household crowding and social contact/mixing). Socioeconomic improvements have also contributed, as access to medical care and treatment has expanded with rising incomes. Holistic programs that included public health campaigns, health worker education and training, and general socioeconomic improvements have demonstrated success in eliminating ARF and RHD (27).

Strategies to improve socioeconomic conditions are generally more expensive and take longer to achieve compared to medical interventions. These strategies may be financially prohibitive in many LICs and LMICs.

3.1.4 Conclusion

Multiple strategies are available to address the negative health, economic, and social consequences of Strep A infections (11). In particular, early treatment of Strep A infection with antibiotics can prevent or mitigate Strep A's worst impacts. However, the effectiveness of antibiotics and other countermeasures is imperfect and depends largely on broad, equitable access – the New Zealand experience tells us that even in the most sophisticated and affluent settings, effective prevention of Strep A diseases at the population level is not possible with current tools. It is questionable whether the challenges facing existing strategies can be addressed in the near term. Given the high burden of Strep A diseases globally, greater investment in existing strategies and greater investment in the development, manufacture, and delivery of safe and effective Strep A vaccines are likely both warranted. Thoughtful integration of Strep A vaccination into the existing portfolio of strategies is likely to be the most prudent path forward.

3.2 Vaccines

3.2.1 Rationale for feasibility of Strep A vaccine development

There is clear evidence that a preventive vaccine against Strep A infection is possible. Strep A pharyngitis and skin infections are common in school-age children but become rare in early adulthood, indicating that immunity to infection develops with age and repeated exposure. Longitudinal serological studies have also shown that infection with a single strain of Strep A leads to the generation of strain-specific antibodies against M protein that can persist for a long time (up to 30 years), providing protection against homologous strains (but not against others) (28). This FVVA report provides an overview of the eight most advanced Strep A vaccine candidates in development (see Chapter 5): StreptAnova, StreptInCor, MJ8CombiVax, P*17, Combo4, VaxA1, Combo5 and TeeVax, most of which have demonstrated promising immunogenicity and efficacy results in pre-clinical studies in a range of animal models, further supporting the feasibility of a Strep A vaccine for humans (see Chapter 5 for details) (29, 30).

Key to the development of a Strep A vaccine is the availability and ongoing improvement of enabling technologies and/or research platforms. For example, Strep A infections can be mimicked in non-human primates as an infection model for pharyngitis and tonsillitis (31), and mice and rabbits have been used

as infection models in extensive preclinical vaccine studies. Further, controlled human infection models (CHIMs) have a long history of contributing to Strep A vaccine development, and the field is getting closer to having a standardized model (32, 33).

3.2.2 Constraints and limitations of Strep A vaccine development

Despite promising evidence supporting the feasibility of a Strep A vaccine, development is hampered by several (potentially interacting) scientific, programmatic, and funding constraints and limitations (29). Enabling coordinated and effective solutions will benefit from building a shared understanding of key constraints.

3.2.2.1 Scientific constraints

3.2.2.1.1 Global burden of Strep A diseases

An accurate assessment of the global burden of Strep A diseases is critically important to vaccine development and implementation decisions, but it is challenging due to the wide and complex spectrum of diseases associated with Strep A infection and shortcomings in surveillance and data collection. Previous attempts to estimate the global burden of Strep A diseases have used available data sources, estimates from the WHO, Global Burden of Disease estimates (e.g., focusing on RHD), and various systematic reviews focusing on particular Strep A clinical endpoints (4, 34). These estimates may be incomplete as few studies include data from many low- and middle-income countries where the burden of Strep A diseases is expected to be highest.

In order to help identify global burden of disease data gaps and potential uses, an innovative systematic framework—or data purpose matrix—has been proposed (35) that associates advocacy, regulatory oversight and licensure, policy and post-licensure evaluation objectives with specific stakeholders and burden of disease data requirements. This framework has been applied to Strep A, providing examples for eight clinical endpoints and considerations for both high- and lower-income settings (35).

Alignment is needed on the major Strep A clinical endpoints that will drive the surveillance, use, and future evaluation of a Strep A vaccine. To provide clear case definitions of the Strep A disease clinical endpoints, SAVAC's Burden of Disease Working Group is producing a suite of standardized case-definition and 'best practice' surveillance protocols (36-43).

3.2.2.1.2 Immune response to infection and correlates of protection

A human immune correlate of protection provides a surrogate indicator of vaccine efficacy in situations where international standards are required. Subject to regulatory acceptance, detection of a recognized correlate of protection can also replace the need to reach clinical endpoints in vaccine trials and support ongoing surveillance of immunity in target populations (44, 45).

Identifying a correlate of protection for Strep A disease and developing an associated assay requires several scientific gaps to be addressed. These gaps include: identifying key antigens to use in the assay to ensure broad coverage of strains; comparing results from proposed correlates of protection assays with established opsonic or inhibitory assays; and validating proposed correlates of protection in population surveillance, disease samples and vaccinated cohorts—including in the human challenge model developed in Melbourne (20, 45).

Further, several opportunities exist to support Strep A vaccine development by building a more comprehensive understanding of the immune response to Strep A. First, there is an opportunity to

better understand mucosal immunity through assays that measure mucosal secretory IgA (46), including which biospecimens to sample. Further, there are no assays to understand mucosal immunity in children despite advances in other diseases. Investigations to determine the protective roles of cellular immunity, including T and B lymphocytes, peripheral blood mononuclear cells, and mucosal cells in the tonsils are also needed. The genetic determinants of susceptibility to Strep A and the differences between intranasal and intramuscular vaccine-induced immunity also remain incompletely understood. To date, Strep A immunity research has largely focused on invasive infections and systemic immunity. Although non-invasive infections carry the largest burden of Strep A disease and would be the ideal target of vaccination, much less is known about sterilizing immunity or inhibition of colonization.

3.2.2.1.3 Vaccine pipeline and clinical development

Strep A vaccine research and development (R&D) efforts began as early as 1923 when the first recorded vaccine clinical trials against Strep A occurred. However, to date, only four candidate vaccines have reached Phase 1 clinical trials and just one has reached Phase 2 trials for the prevention of Strep A infection (28, 29). This is, in part, due to the challenge of designing a vaccine that addresses the broad genetic diversity of Strep A from extant and emerging strains (47), but it has also been heavily influenced by a ban placed by the Food and Drug Administration (FDA) in 1979 (and not lifted until 2006) preventing the testing of Strep A vaccines in humans after two study volunteers—siblings of rheumatic fever patients—developed rheumatic fever in the years following the administration of crude M protein antigens (48-51). There is a continued, perceived risk of autoimmune complications (52); with vaccine safety a perennial priority, the absence of consensus safety biological markers following vaccination has led to assessment of autoimmune markers and clinical assessments, in particular cardiologic assessments by echocardiography (53).

Second, models and assays to compare and assess vaccine candidates are currently suboptimal: the predictive value of preclinical models is subject to debate; human immune correlates of protection (see 3.3.1.2) and relevant functional assays are still elusive. Responding to this challenge is Controlled Human Infection for Vaccination against Streptococcus *pyogenes* (CHIVAS), an Australian National Health and Medical Research Council initiative aimed at establishing a new Strep A pharyngitis human infection model as a safe and reliable platform for vaccine evaluation and pathogenesis research (32). Nevertheless, determining vaccine efficacy will require clinical endpoint-driven clinical efficacy trials. The definition and incidence of clinical endpoints in various settings are therefore critical. Although the main killer, RHD, is a remote event in the cascade of Strep A infection disease expression, pharyngitis and impetigo are currently the preferred proxy clinical endpoints for ARF and RHD for efficacy trials in children (and cellulitis in adults). Indeed, the demonstration that a vaccine candidate can protect against pharyngitis would be a tremendous advance.

Initiatives aimed at guiding the Strep A vaccine development pathway are also underway. In anticipation of regulatory and policy requirements and to help define the value proposition for Strep A vaccines in development, the WHO identified Preferred Product Characteristics and also developed a Research and Development Technology Roadmap to guide the clinical development of a Strep A vaccine (see Chapter 4) (48).

3.2.2.1.4 Regulatory framework

Regulators have not yet aligned on the pathway to licensure for a Strep A vaccine. Evidence to support licensure based on immunogenicity studies and correlates of protection is a priority and much work in

this area is ongoing (54). Importantly, the development of a regulatory framework for Strep A vaccine safety is required, particularly given the history of Strep A vaccine safety concerns and the importance of minimizing adverse events for the health of recipients of future Strep A vaccines and to avoid potential 'spillover' effects that safety issues may have on uptake of other vaccines (55). Currently, there is no specific regulatory guidance on what constitutes an adequate preclinical assessment of potential vaccine-induced autoimmunity with new Strep A vaccine before first-in-human studies. A regulatory framework and guidance would assess adverse events of special interest based on product-specific mechanism of action, platform, and vaccine composition. Preclinical data and the cumulative clinical safety experience should capture all severe Strep A-related disease manifestations. This implies the detection of all new-onset Strep A infections that can result in ARF/RHD, and an antibiotic treatment regimen for new-onset Strep A infections need to be standardized in vaccine trials. Finally, long-term follow-up studies of Strep A vaccine study participants should be designed and implemented with consideration for post-marketing pharmacovigilance activities to monitor for recognized and potential risks as well as effectiveness against rare disease endpoints. SAVAC's Safety Working Group has recently proposed key regulatory considerations for Strep A vaccine development related to preclinical safety, pre-licensure clinical safety, post-licensure safety, as well as regulatory considerations in low- and middle-income countries (56). SAVAC's Safety Working Group has recently proposed key regulatory considerations for Strep A vaccine development related to preclinical safety, pre-licensure clinical safety, post-licensure safety, as well as regulatory considerations in low- and middle-income countries (56).

3.2.2.2 Programmatic and funding constraints

To date, Strep A vaccine development has not been strongly prioritized by global vaccine decision-makers or funders or large pharmaceutical companies. The fact that a significant burden of disease has not yet translated into a sense of urgency points to the importance of understanding vaccine decision-making at multiple jurisdictional levels and underscores the need for a comprehensive advocacy agenda. Jointly with WHO, SAVAC has a critical role to play in generating and consolidating the evidence base required to encourage prioritization, investment, development, and introduction of Strep A vaccines optimized for use in resource-poor settings.

There has been insufficient evidence of the commercial potential of a Strep A vaccine, and R&D for Strep A-related diseases is severely underfunded relative to the burden of disease (57). Consequently, several Strep A vaccine candidates that are ready to move beyond preclinical or even beyond Phase 1 clinical development have not yet obtained the necessary funding for next steps. This again points to the need for continued advocacy and awareness-building—including via this FVVA report—around the need and public health value of a Strep A vaccine. Nevertheless, recent large investments from government and not-for-profits signal renewed interest in the development of a Strep A vaccine. Building on the outcomes of the Australian- and New Zealand-funded Coalition to Advance Vaccines Against Group A Streptococcus (CANVAS), the Australian Strep A Vaccine Initiative (ASAVI) is advancing Strep A vaccine research with the goal of accelerating at least one vaccine candidate into a Phase 1 clinical trial for the prevention of Strep-A associated diseases. In 2019, CARB-X, an international non-profit partnership of private, academic, and government institutions, awarded up to $15 million to Vaxcyte Inc. (United States of America (USA)) to develop a universal vaccine for Strep A, and up to $12.4 million to the GSK Vaccines Institute for Global Health for their Strep A vaccine which is in development (58). Finally, in July 2022, The Leducq Foundation, an international grant-making organization focused on combatting cardiovascular disease and stroke, announced $5 million to be awarded to a research network focused

on characterizing the protective immune response to Strep A infection in order to inform vaccine development efforts (59).

4 WHO PPC and R&D roadmap for vaccines

At the 71st World Health Assembly in 2018, prioritization of a Strep A vaccine was recommended as an intervention toward the pursuit of the Sustainable Development Goals to end poverty and achieve universal health coverage. Further, this recommendation is consistent with the WHO Constitution and priority work areas, given that such a vaccine would effectively reduce the burden of rheumatic heart disease (RHD) – a preventable disease of poverty (60).

The WHO and partners developed WHO Preferred Product Characteristics (PPC; an early development stage precursor to class- or product-specific target product profiles) and a research and development (R&D) technology roadmap for a Strep A vaccine, summarized here in Table 4-1 and

Table 4-2, respectively (originally presented in (48)). These considerations and characteristics aimed to anticipate requirements for regulatory and policy recommendations and to help define the value proposition for Strep A vaccines in development. As such, they have informed the work of the Full Value of Vaccines Assessment (FVVA) presented in this report.

Table 4-1. WHO PPC summary.*

PARAMETER	PREFERRED PRODUCT CHARACTERISTICS
Indication	Prevention of Strep A-related pharyngitis, superficial skin infections, cellulitis, toxin-mediated disease, invasive infections and associated antibiotic use, secondary rheumatic fever, RHD, and poststreptococcal glomerulonephritis
Target population	Primary schedule: infants and/or young children
Schedule of primary immunization	No more than 3 doses required for primary immunization
Efficacy targets	• 80% protection against non-severe, noninvasive, confirmed Strep A disease • 70% protection against confirmed Strep A cellulitis and other invasive infections • 50% protection against long-term immune-mediated sequelae
Strain and serotype coverage	Efficacy targets are set irrespective of strain/serotype considerations. The vaccine composition should ensure that a vast majority (preference for at least 90%) of the current disease-causing isolates from the region targeted for use are prevented
Safety	Safety and reactogenicity profile at least as favorable as current WHO-recommended routine vaccines
Adjuvant requirement	Evidence should be generated to justify adjuvant inclusion in the formulation
Immunogenicity	Established correlate/surrogate of protection based on a validated assay measuring immune effector levels/functionality
Non-interference	Demonstration of favourable safety and immunologic noninterference upon coadministration with recommended other vaccines if used in the same target population

Route of administration	Injectable (intramuscular (IM) or subcutaneous (SC)) using standard volumes for injection as specified in programmatic suitability for prequalification or needle-free delivery
Registration, prequalification, and programmatic suitability	The vaccine should be prequalified according to the process outlined in procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies. WHO-defined criteria for programmatic suitability of vaccines should be met
Value proposition	Dosage, regimen, and cost of goods amenable to affordable supply. The vaccine should be cost-effective, and price should not be a barrier to access including in LMICs.

**Adapted from (48)*

Table 4-2. Priority activities as expressed in the Vaccine Development Technology Roadmap for Strep A Vaccines.*

KEY STRATEGIC AREAS	PROPOSED PRIORITY ACTIVITIES
Research	• Improve global estimates of disease burden and better characterize the epidemiology of Strep A infections • Further describe the spectrum of natural disease history • Drive improved understanding of Strep A-related secondary immune-mediated diseases • Define the consequences of Strep A-associated antibiotic use, and estimate the impact of vaccine use on antibiotic use and antimicrobial resistance (AMR)–related morbidity and mortality
Vaccine development	• Pursue antigen discovery efforts, increasing the number of pipeline vaccine candidates • Develop consensus guidance about the appropriate use of safety monitoring tools in candidate vaccine trials • Characterize immunological surrogates/correlates of protection • Define appropriate pivotal clinical trial design adapted to near-term and long-term strategic goals
Key capacities	• Define appropriate use of available and future animal models for Strep A vaccine safety and efficacy evaluation according to their relevance for human responses • Develop clinically relevant human Strep A experimental infection model(s) to support early vaccine proof-of-concept evaluation • Establish Strep A expert research centers in LMICs with Good Clinical Practices trial research capacity and appropriate regulatory and ethical oversight; establish baseline rates of efficacy and safety outcomes • Access low-cost vaccine manufacturing under current Good Manufacturing Practices for late-stage development and commercial production • Develop standardized immunoassay platforms that meet quality requirements

Policy, commercialization, and delivery	• Establish cost-effectiveness and develop research and implementation financial investment scenario(s) to support appropriate funding and policy decision making at the global and national levels, considering the full scope of costs and benefits • Ensure availability, affordability, and acceptability of a functional, cost-effective delivery platform for immunization • Develop effectiveness and safety vigilance platforms for postimplementation surveillance

**Adapted from (48)*

5 Vaccine landscape analysis

5.1 Pipeline Overview

The current pipeline of Strep A vaccine candidates on a product development track includes at least 8 programs testing both M protein-based concepts and non-M protein antigens (summarized in Other, earlier-stage Strep A vaccine research with less clearly defined product development focus is described elsewhere (63-68).

Table 5-1) (29, 30, 61, 62). Other, earlier-stage Strep A vaccine research with less clearly defined product development focus is described elsewhere (63-68).

Table 5-1. Strep A vaccine development pipeline: Overview of the most advanced, product development-focused programs.

CONCEPT	CANDIDATE	DEVELOPER	DEVELOPMENT PHASE	ANTIGENS
M-Based	**StreptAnova** (30-valent)	University of Tennessee/Vaxent	Phase 1a Completed 2020	N-terminal subunits from the M protein of 30 serotypes of Strep A
	J8/S2 combivax	Griffith University/ University of Alberta	Phase 1/2 Active, not recruiting as of 2025 February	J8 peptide from the M protein C-terminus combined with a 20-mer B-cell epitope (K4S2) from SpyCEP
	P*17/S2 combivax	Griffith University/ University of Alberta	Phase 1/2 Active, not recruiting as of 2025 February	P*17 peptide from the M protein C-terminus combined with a 20-mer B-cell epitope (K4S2) from SpyCEP
	StreptInCor	University of São Paulo/Butantan Institute Brazil	Preclinical	55-amino acid sequence peptide from the M5 protein conserved regions (C2 and C3 regions)
Non-M-Based	**Combo4**	GSK/ GSK Vaccines Institute for Global Health (GVGH)	Preclinical	SpyCEP, SLO and SpyAD recombinant proteins and native GAC conjugated to CRM197 carrier protein
	Vax-A1	Vaxcyte	Preclinical	SLO and SCPA recombinant proteins and modified GAC (Polyrhamnose) conjugated to SpyAD disease-specific carrier protein
	Combo5	University of Queensland	Preclinical	Trigger factor (TF), inactivated versions of arginine deiminase (ADI), SLO, SpyCEP and SCPA
	TeeVax	University of Auckland	Preclinical	Multiple T-antigen domains from the pilus of the majority of Strep A strains

Abbreviations: SpyCEP = streptococcal interleukin-8 protease; SLO = streptolysin O, SpyAD = putative surface exclusion protein, Spy0269, SCPA = streptococcal C5a peptidase

5.2 Characterization of the most advanced Strep A vaccine candidates

5.2.1 M protein-based candidates

Building on the long history of M protein-based vaccine research, several current Strep A vaccine candidates have been designed around various M protein antigens. Given the high number of *emm* types and the hypervariability of M protein N-terminal regions, the only current vaccine candidate targeting N-terminal epitopes employs a multivalent approach (i.e., the 30-valent StreptAnova). Other M protein-based vaccines incorporate peptides from the more conserved C-terminus, and two of these (MJ8CombiVax and P*17) combine a non-M protein (i.e., peptide from SpyCEP) in their formulation.

StreptAnova, developed by Dale et al. at the University of Tennessee (USA) with commercialization partner Vaxent, is an *emm*-type specific, adjuvanted (alum) vaccine with four protein subunits comprising the N-terminal regions of M proteins from 30 *S. pyogenes* serotypes. This candidate is the farthest along the development pathway, having completed a Phase 1a trial (in 2020) that demonstrated significant immunogenicity towards most of the targeted antigens (53). Moreover, the trial showed that StreptAnova was well-tolerated and did not elicit autoimmune or cross-reactive antibodies (53). Additional clinical trials for StreptAnova are planned, including a Phase 2 efficacy study, pending funding (69).

*J8/S2 combivax and P*17/S2 combivax* are related vaccines in development by Good et al. at Griffith University (Australia) and University of Alberta (Canada). Both vaccine candidates contain K4S2, a peptide with a modified B-cell epitope from *S. pyogenes* cell envelope proteinase (SpyCEP), combined with one of two versions of the p145 peptide from the M protein C-terminus: J8 for J8/S2 combivax (70) and P*17 for its namesake candidate (71). Both peptides in each candidate are conjugated to the CRM197 carrier protein. In mouse studies J8/S2 combivax and P*17/S2 combivax, formulated with alum, protected against skin and systemic infection from hypervirulent CovR/S strains of *S. pyogenes* (70). Using the CAF01 adjuvant, intramuscular injections followed by an intranasal dose of P*17 induced high antibody levels in both the airway mucosa and serum, as well as protection against upper respiratory tract infection and invasive disease in mice (72). Approval has been requested from Health Canada (the Canadian Regulator) to undertake a Phase 1a trial of J8/S2 combivax and P*17/S2 combivax. Upon success of the Phase 1a trial, the developers are planning to undertake a Phase 1b with human challenge study in Australia in late 2022 or early 2023 (73).

StreptInCor, from Guilherme et al. at the University of Sao Paulo (Brazil), is comprised of a 55-amino acid peptide from the M5 protein conserved regions (C2, C3) with B- and T-cell epitopes, adjuvanted with alum (74). In preclinical studies, StreptInCor has shown high levels of antigen-specific antibodies and survival against *S. pyogenes* infection challenge in mice as well as a lack of auto-immune reactions (74, 75). In minipigs, the candidate was well tolerated and displayed no harmful effects on heart tissue (76). Studies in Wistar rats showed no evidence of toxicity after repeated intramuscular injections (77). A planned Phase 1/2a trial was withdrawn in early 2021 before enrollment began (78) when the sponsoring institution prioritized COVID-19 vaccine development (79).

5.2.2 Non-M protein-based candidates

Given the potential, but unproven, safety concerns of M protein-based vaccines, several *S. pyogenes* vaccine candidates are being designed around other antigens that provide broad coverage across *S. pyogenes* strains, and which have lower potential for cross-reactivity to host tissues. One of these antigens is Group A Carbohydrate (GAC), a surface polysaccharide comprising a polyrhamnose backbone with an N-acetylglucosamine (GlcNAc) side chain. GAC is highly conserved and expressed in all *S. pyogenes* isolates (80). Two groups have a vaccine candidate featuring GAC, but each is using a different version of GAC and have conjugated their respective GAC antigens to different carrier proteins (see below for details). Several *S. pyogenes* protein antigens are also targeted by vaccine candidates. These proteins are highly conserved, being found in 95-99% of all characterized *S. pyogenes* isolates across the world (81), and include: streptolysin O, SpyCEP, SpyAD, group A streptococcal C5a peptidase (SCPA), trigger factor (TF), arginine deiminase (ADI), and T antigen proteins from the *S. pyogenes* pilus.

Combo4, from GSK Vaccines Institute for Global Health (GVGH), GSK Vaccines (Italy), contains the native *S. pyogenes* GAC conjugated to the CRM_{197} carrier protein, SLO, SpyCEP and SpyAD (81). GVGH has presented data indicating that the native GAC can induce a higher anti-GAC IgG response than polyrhamnose and greater binding of anti-GAC antibodies compared to anti-polyrhamnose antibodies to a panel of Strep A strains (82). Preclinical studies of Combo4 adjuvanted with alum demonstrated immunoprotection in mouse models and efficacy in opsonophagocytic killing assays using sera from immunized rabbits (83, 84). GVGH is currently conducting GMP manufacturing and toxicity studies with Combo4 and is planning a Phase 1 dose-escalation study in Australia (85).

VAX-A1, from Vaxcyte (USA), is based on work from the Nizet group at University of California, San Diego. VAX-A1 contains GAC^{PR}, a modified version of GAC in which the GlcNAc side chain is removed, leaving the polyrhamnose core (86). GAC^{PR} may lower the risk of cross-immunogenicity compared to native GAC since the GlcNAc side chain on GAC has been implicated in provoking auto-immune cross-reactivity in RHD (86). Moreover, the GAC^{PR} in Vax-A1 is conjugated to the *S. pyogenes* virulence factor SpyAD, and this SpyAD-GAC^{PR} conjugate is combined with recombinant SLO and SPCA proteins and adjuvanted with alum (86). Immunization of mice with VAX-A1 protected against *S. pyogenes* challenge in both a systemic infection model and localized skin infection model, with no observed signs of cross-reactivity to human heart or brain tissue epitopes (86). Having initiated IND-enabling activities in late 2021, Vaxcyte is planning to provide guidance on expected timing for an IND application submission in the second half of 2022 (87).

Combo5, from Walker et al. at the University of Queensland (Australia), contains five recombinant proteins: SLO, SpyCEP, SCPA, TF, and ADI, adjuvanted with SMQ (a squalene-in-water emulsion containing a toll-like receptor 4 agonist and QS21) (88). In addition to offering broad coverage across *S. pyogenes* strains (88), the vaccine candidate was designed to exclude *S. pyogenes* antigens potentially linked to autoimmune complications (31). In earlier studies using alum as adjuvant, Combo5 reduced the severity of pharyngitis and tonsillitis but did not protect against colonization in NHP (31); in mice, the candidate protected against superficial skin infections but not invasive disease (88, 89). In contrast, adjuvanting Combo5 with SMQ conferred protection against invasive challenge in mice, potentially owing to a more balanced Th1/Th2 immune response compared to Combo5 adjuvanted with alum, which produced a Th2-biased response (88). Interestingly, Combo5/SMQ protected mice against invasive challenge in the absence of opsonizing antibodies, suggesting that an opsonizing antibody response may not be a correlate of protection for non-M protein vaccines (88).

TeeVax, from Thomas Proft and Jacelyn Loh's group at University of Auckland (New Zealand), is a multivalent vaccine targeting T-antigens, the major protein component of the surface-exposed *S. pyogenes* pili (90, 91). This candidate is comprised of three recombinant proteins (TeeVax1, TeeVax2, and TeeVax3), each consisting of a fusion of 6 unique T-antigen domains (91). Combination of all three proteins (TeeVax1-3) elicited a robust antibody response in rabbits that was reactive to all 18 T-antigens included in the three proteins and was cross-reactive to the three remaining sub-types not included in any of the proteins (91). Immunization of humanized plasminogen transgenic mice with TeeVax1 adjuvanted with alum produced opsonophagocytic antibodies in rabbits and conferred protective efficacy in mice against invasive disease (91). The developers are currently testing TeeVax with different adjuvants and plan to conduct analyses of humoral and cellular immune responses to TeeVax to gain further knowledge about correlates of protection (92).

5.3 Conclusion

The current Strep A vaccine pipeline has strong potential to test a variety of concepts and antigen types in human proof-of-concept studies. Initial preclinical efficacy and safety results and, in some cases, human safety and immunogenicity data are encouraging. While some programs have resources to support their next clinical development steps (including Vaxcyte and GVGH, which have garnered up to $15 million and ~$12.4 million, respectively, from CARB-X (58)), funding is currently a limiting factor for some of the other programs to move ahead with planned clinical development activities. These resource gaps point to the need for continued advocacy and awareness-building around the urgency and public health value of a Strep A vaccine and the potential commercial opportunity for industry. The following chapters present findings of new analyses from SAVAC that will strengthen the case for prioritization of and investment in Strep A vaccine R&D.

6 Burden of disease

6.1 Context and Rationale

This chapter describes new epidemiological analyses to estimate the global burden of Strep A pharyngitis and invasive infections. Strep A pharyngitis incidence rates, invasive infection incidence rates, and case-fatality rates were obtained from systematic reviews and meta-analyses completed during this project.

6.2 Methods

We conducted two independent systematic reviews and meta-analyses to estimate the incidence of Strep A pharyngitis and the incidence and mortality rates of invasive Strep A infection.

6.2.1 Pharyngitis

A systematic review and meta-analysis were conducted to provide contemporary estimates of the global incidence of sore throat and Strep A sore throat (93). Literature was searched via Clarivate Analytics' Web of Science for studies published between 2000 and 2021. Studies were eligible if: 1) incidence rates or cumulative incidence could be calculated for sore throat or Strep A sore throat (both outcomes including pharyngitis, tonsillitis, or tonsillopharyngitis) and 2) participants were recruited from settings that captured a representative sample of the general population. Studies were excluded if the population denominator could not be determined; incidence rates were modeled, rather than observed; episodes of sore throat were limited to those caused solely by a pathogen other than Strep A (e.g., studies of only episodes of group C or G *Streptococcus* pharyngitis); or episodes of sore throat resulting from endotracheal intubation. We also excluded studies based on healthcare presentations for sore throat as they are biased toward people accessing care and, therefore, are not representative of all people who experience a sore throat in a population.

Random-effects meta-analyses were used to pool sore throat and Strep A sore throat incidence. Meta-analyses were limited to children, due to the limited availability of data for adults, and studies for which surveillance was conducted for six months or more to account for the seasonal nature of Strep A sore throat.

6.2.2 Invasive infection

The global burden of disease estimates for invasive Strep A infections was estimated from a systematic review and meta-analysis of studies published between 1980 and 2019 (94).

Invasive Strep A infections were defined as patients with *S. pyogenes* isolated from a normally sterile site or isolation of Strep A from a nonsterile site in combination with clinical signs of streptococcal toxic shock syndrome and/or necrotizing fasciitis.

Eligible studies included those that provided data on Strep A invasive infections. Studies were excluded if: the population denominator could not be determined; primary data were not provided (such as systematic reviews or narrative reviews); incidence rates were modeled rather than observed; or episodes of invasive disease were limited to those caused solely by a pathogen other than Strep A.

Due to the significant between-study heterogeneity, random-effects meta-analysis with log-transformed incidence rates as the effect size was conducted to estimate the pooled incidence rate (IR) across

studies. Meta-regression models were fitted to population-level and age-specific incidence rates and hospital case-fatality rates (CFRs).

6.3 Results

6.3.1 Pharyngitis

The pharyngitis review found 12, 11, and 14 studies for sore throat incidence rates, sore throat cumulative incidence, and Strep A sore throat incidence rates, respectively. Of the 14 studies with Strep A sore throat incidence rates, nine qualified for inclusion in a meta-analysis. Those nine studies were conducted in Australia, Fiji, the U.S., China, New Zealand, and India (4 studies). The pooled IR was 22.1 episodes of Strep A sore throat per 100 child-years. Strep A pharyngitis incidence rates were not statistically different between county income levels (high-income country (HIC) vs. lower-middle income country (LMIC)), but there was high statistical (I^2=98%) and methodological heterogeneity between the studies.

6.3.2 Invasive infection

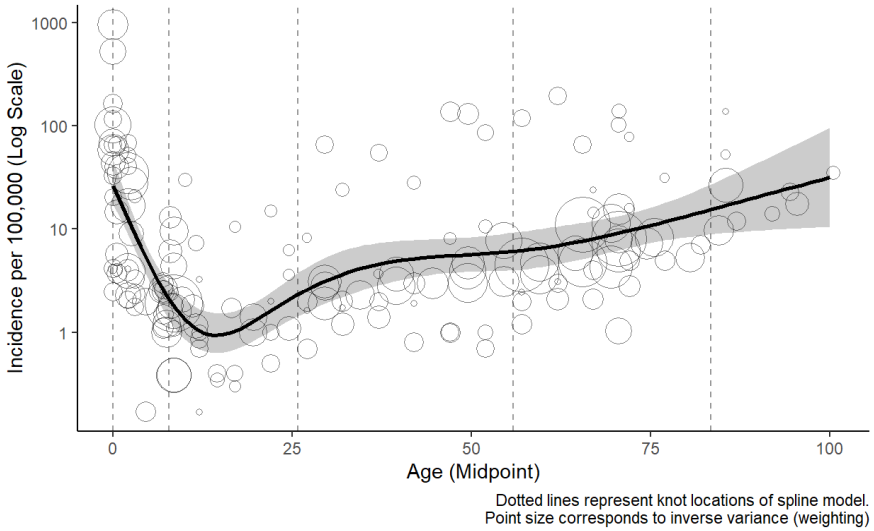
Seventy-nine studies met the eligibility criteria and were included in at least one meta-regression (population-level or age-specific). Studies spanned 6 continents and 27 countries, with the majority taking place in either North America or Europe. Notably, there was a distinct lack of studies from LICs and LMICs (3). Invasive Strep A infections were a notifiable disease in 26 studies. Surveillance duration ranged from 9 months to 13 years.

The pooled IR for invasive Strep A infections was 2.21 episodes per 100,000 person-years (95%CI 1.65, 2.96). Significant heterogeneity was present among those studies (I^2=99.93%, p<0.001). Overall, there was no statistical evidence of differences in the pooled IRs of HICs and LMICs. Age-specific incidence rates (0-99 years) showed a U-shaped trend, with IRs highest among infants (0-12 months) and those aged 70 years and over (

Figure 6-1).

Forty-eight studies included data to determine the case-fatality rate associated with Strep A infections. The pooled case-fatality rate from invasive Strep A infection was 11.0% (95% CI 9.0% -13.0%). The CFR ranged from 3.33% (95% CI 1.10% - 10.14%) in New Caledonia to 30.56% (95% CI 22.57% - 41.39%) in Fiji. Age-specific CFRs were available in 30 of the studies. The CFR increased linearly with age, from 5.7% (95% CI 3.4% - 9.3%) among those aged < 1yrs to 50.8% (9% CI 25.5% - 100%) among those aged 90-99 years.

Figure 6-1. Estimates of Strep A invasive infection by age.*



**Adapted from (94)*

6.4 Conclusions and Limitations

This chapter presents new and contemporary analyses and estimates for the global burden of Strep A pharyngitis and invasive infections, building on burden estimates for impetigo, cellulitis, and rheumatic heart disease (RHD) from the Global Burden of Disease project (Chapter 2.2.2) (7).

While we aimed to obtain epidemiological data for all the major Strep A clinical manifestations, data on the epidemiology of acute rheumatic fever (ARF), including incidence and rate of progression to RHD, are limited. The first population-based study to estimate the incidence of ARF in sub-Saharan Africa highlights not only a lack of data but also the challenges of disease surveillance in LMICs, among numerous other challenges (95).

Limited surveillance data from LMICs was also apparent for Strep A invasive infection. A more complete picture of the frequency and mortality caused by invasive infection is possibly more important than corresponding data for ARF in the short term. Given the incidence of RHD, the sequel to ARF, rates of ARF could be approximated through mathematical modeling. Invasive infection, on the other hand, has no proxy disease to interpolate incidence rates and may or may not have a higher mortality rate in low-resource settings (3).

7 Vaccine impact on disease burden: model-based projections

7.1 Context and Rationale

Understanding the potential impact of Strep A vaccination on alleviating disease burden is important to informing vaccine development efforts, building the case for research and development (R&D) funding, and informing future decision-making around adoption and implementation of a Strep A vaccine. In this chapter, we describe the development and application of a vaccine impact model that simulates the health benefits of Strep A vaccination (96). The model was designed to be transparent and accessible by using the R statistical software (97). The program code and data for the vaccine impact model are available at https://github.com/fionagi/GASImpactModel, and the model can be run as a user-friendly (R Shiny) web application to explore different vaccination scenarios. Further information on model development and application are described elsewhere (96).

7.2 Methods

A static cohort model was developed to estimate the projected health impact of Strep A vaccination at the global, regional, national, and income levels. Vaccination impact is estimated in terms of reductions in episodes of acute Strep A pharyngitis, impetigo, invasive infection, and cellulitis; cases of rheumatic heart disease (RHD); deaths due to Strep A invasive infection and RHD, and disability-adjusted life years (DALYs) due to each Strep A disease. The reductions in burden are in direct proportion to vaccine efficacy, vaccine coverage, and vaccine-derived immunity (based on duration of protection and waning dynamics). Indirect (herd) effects are excluded; therefore, the estimated health benefits of Strep A vaccination are conservative if Strep A vaccination prevents population transmission.

7.2.1 Data inputs

Pre-vaccination disease incidence rates are projected from data from the Global Burden of Disease (GBD) project for impetigo, cellulitis, and RHD (7) and the data and analyses described in Chapter 6 for pharyngitis and invasive infection. As impetigo and cellulitis incidence rates from the GBD project are not specific to Strep A as the causative pathogen, we assumed that 27% of cellulitis episodes are attributable to Strep A based on a review by Chira and Miller (94) and 50% of impetigo episodes are attributable to Strep A based on expert opinion. However, these attributable fractions are likely to vary by region (e.g., 90% of impetigo cases among Indigenous Australians are caused by Strep A infection (98)). Further, as rates for impetigo were not available for download, they were estimated from plots produced by the Epi Visualization app (8). As the app displays rates by sex, we assumed a global 51:49 male:female ratio to estimate age- but not gender-specific rates. Additionally, we used the global impetigo rate, rather than approximating age-specific rates for each country individually. Projecting forward, country- and age-specific rates of Strep A burden were assumed to remain constant in the future.

Mortality rates due to Strep A invasive infections were estimated from the age-specific case-fatality rates presented in Chapter 6 and were assumed consistent across all countries. Mortality rates among RHD cases from LMICs were extrapolated from data presented by the REMEDY study (99), assuming a cumulative mortality rate between RHD diagnosis and 10 years of follow-up of 30%. Mortality rates among cases occurring in high-income countries (HICs) were based on an analysis of Indigenous patients from the Northern Territory of Australia, which reported a cumulative mortality rate between diagnosis and 10 years of follow-up of 3% (100).

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 (101).

Vaccine efficacy assumptions are based on the WHO Preferred Product Characteristics (PPCs) for a Strep A vaccine (Table 7-1) (48). The waning dynamics of vaccine-derived immunity are modeled in two ways: 1) vaccine-induced immune protection at maximum efficacy for 10 years and null thereafter; 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). For the sake of demonstration, the year of vaccine introduction is arbitrarily assumed to be 2022 or country-specific, ranging from 2022 to 2034, with initial coverage at 10% of maximum coverage. Country-specific coverage rates were based on estimates outlined in Chapter 10 (i.e., drawing on each modeled country's diphtheria, tetanus, pertussis vaccine third dose (DTP3)). Specifically, six potential scenarios were analyzed for varied years of vaccine introduction, coverage, and waning dynamics (Table 7-2).

Table 7-1. Vaccine efficacy. The vaccine efficacy assumptions are based on the WHO Preferred Product Characteristics for a Strep A vaccine.

GROUP A STREPTOCOCCUS DISEASE STATE/SEQUELAE	VACCINE EFFICACY (%)
Pharyngitis	80
Impetigo	80
Invasive disease	70
Cellulitis	70
Rheumatic heart disease	50

Table 7-2. Vaccination scenarios. Potential vaccination scenarios for varying years of vaccine introduction, coverage, and vaccine-derived immunity dynamics.

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

7.2.2 Modelled outcomes

The model was used to estimate the lifetime health benefits of vaccination for 30 birth cohorts born between 2022-2051 on Strep A disease burden 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 (102), 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

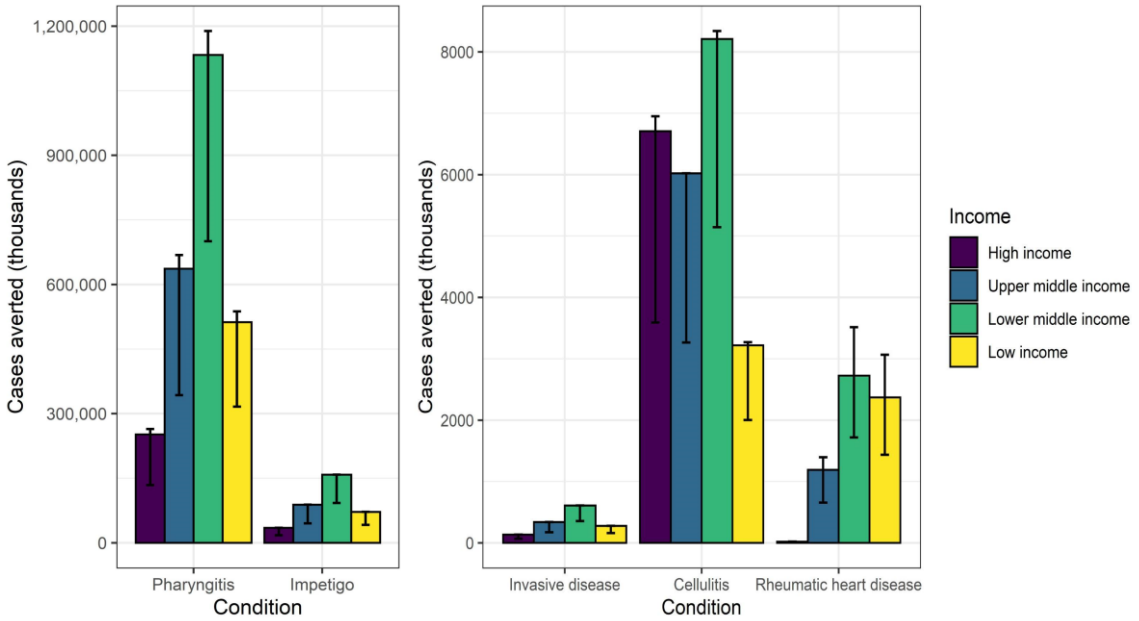
respectively, based on the GBD reported prevalence divided by incidence (7). The duration for RHD was assumed for the remaining life expectancy since the onset of the condition.

7.3 Results

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 7-3 and Figure 7-1. Vaccine impact at the country-income levels.

The vaccine impact on cases averted 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 of 2022-2051 on Strep A disease burden (pharyngitis, impetigo, invasive disease, cellulitis, and rheumatic heart disease). 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 rheumatic heart disease).



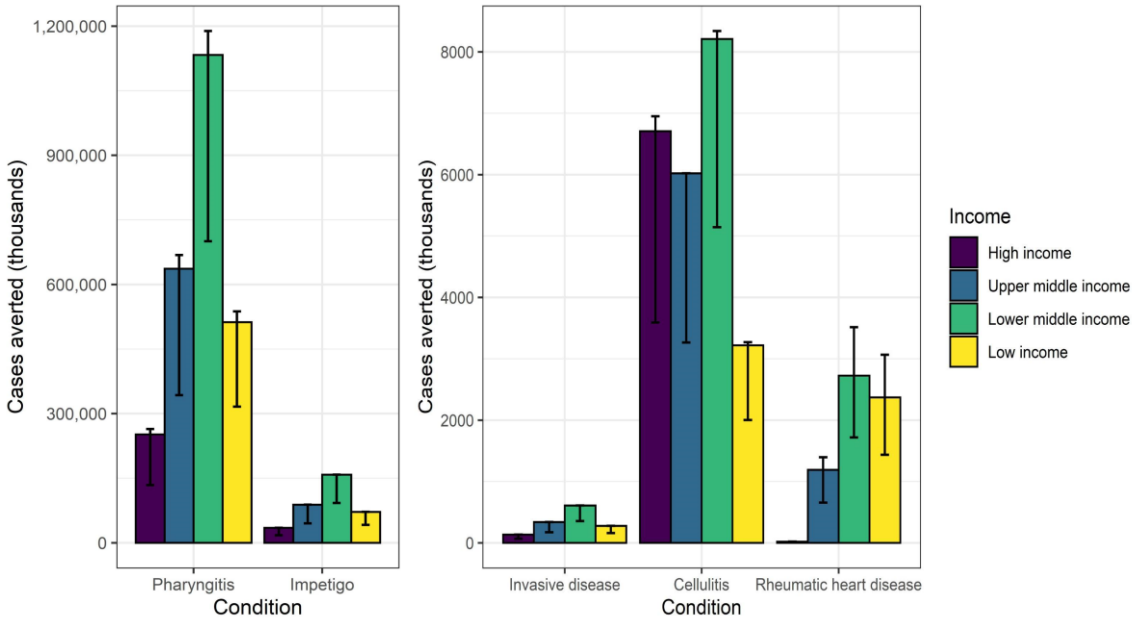
, **Error! Reference source not found.**, and**Error! Reference source not found.**. Vaccination in first year of life for 30 birth cohorts born between 2022-2051 under Scenario 1 can avert 2.5 billion episodes of pharyngitis, 354 million episodes of impetigo, 1.4 million episodes of invasive disease, 24 million episodes of cellulitis, and 6 million cases of rheumatic heart disease during their lifetime (see

Table 7-3 for scenario 1). This translates 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 7-3) and lower-middle-income countries (see Figure 7-1. Vaccine impact at the country-income levels.

The vaccine impact on cases averted 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

of 2022-2051 on Strep A disease burden (pharyngitis, impetigo, invasive disease, cellulitis, and rheumatic heart disease). 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 rheumatic heart disease).



) for pharyngitis, impetigo, invasive disease, cellulitis, and RHD.

Vaccination impact in terms of cases averted per 1,000 vaccinated individuals is relatively higher in North America for cellulitis and in Sub-Saharan Africa for rheumatic heart disease (see **Error! Reference source not found.**). The vaccine impact metric of disease burden averted per 1,000 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.

Table 7-3. 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, based on the lifetime health impact of vaccination at first year of life for 30 birth cohorts of 2022-2051 on Strep A disease burden (pharyngitis, impetigo, invasive disease, cellulitis, and rheumatic heart disease).*

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 7-1. Vaccine impact at the country-income levels.

The vaccine impact on cases averted 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 of 2022-2051 on Strep A disease burden (pharyngitis, impetigo, invasive disease, cellulitis, and rheumatic heart disease). 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 rheumatic heart disease).

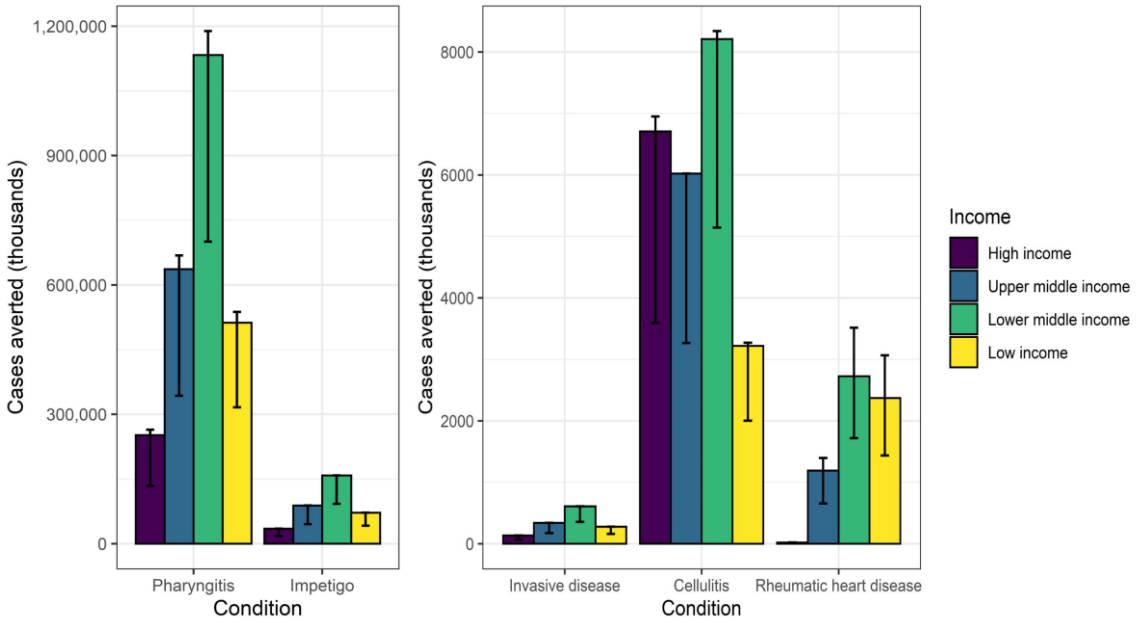


Figure 7-2. Vaccine impact at the regional and global levels.

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 of 2022-2051 on group A streptococcus disease burden (pharyngitis, impetigo, invasive disease, cellulitis, and rheumatic heart disease). 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).

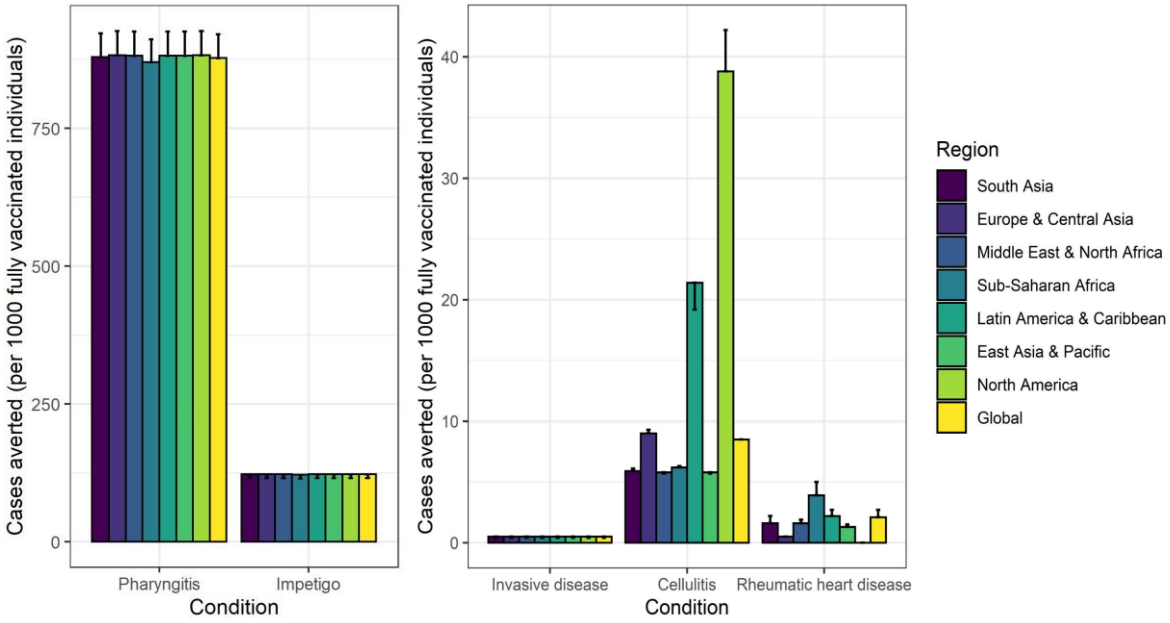
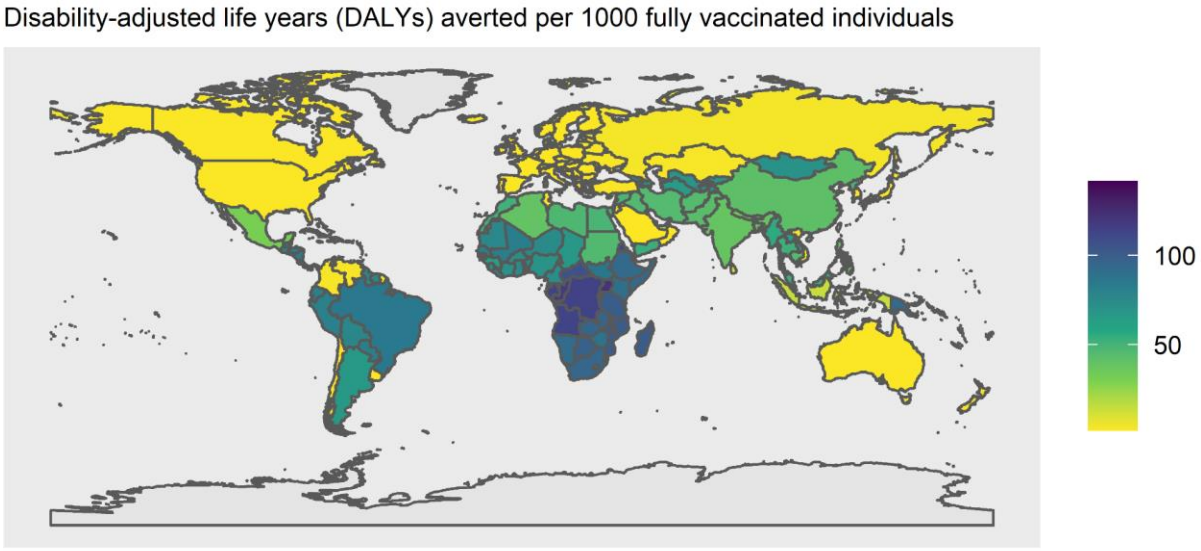


Figure 7-*3*. Vaccine impact at the national level.

The vaccine impact on 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 of 2022-2051 on Strep A disease burden (pharyngitis, impetigo, invasive disease, cellulitis, and rheumatic heart disease).



7.4 Conclusions and Limitations

The Strep A vaccine impact model estimates the health benefits of vaccination in terms of averted infections, sequelae, and DALYs at the global, regional, national, and income levels. Globally, the Strep A vaccine could avert 82 million cases of pharyngitis, 11.8 million cases of impetigo, 45,000 cases of invasive disease, 805,000 cases of cellulitis, and 210,000 cases of RHD per birth cohort. The results suggest that 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. However, those results are contingent on epidemiological and vaccination assumptions.

The vaccine impact projections are based on a hypothetical vaccine that meets the criteria of the WHO PPCs (48) and that fulfills several vaccination scenarios. However, coverage and scale-up of future Strep A vaccines may differ, as well as a duration of protection and waning dynamics of vaccine-derived immunity.

The Strep A vaccine impact model can be updated to include the immune-mediated sequelae of Strep A infection, including acute rheumatic fever (ARF) and kidney disease, and estimate the added health benefits of averting morbidity and mortality attributable to these conditions. The health benefits of Strep A vaccines 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 in estimating 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 modeling 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 (103).

8 Traditional vaccine investment case: cost-effectiveness analysis

8.1 Context and Rationale

This section aims to estimate the economic burden of Strep A infections and conduct a cost-effectiveness analysis for a hypothetical Strep A vaccine (104, 105). A systematic literature review was first conducted to identify existing cost-effectiveness analyses (CEAs) on Strep A disease states and to understand current knowledge gaps (4, 11, 106-108).

Of a total of 321 articles, 44 met the criteria for inclusion. The majority of studies (93%) were done in countries classified as high-income (HICs) or upper-middle-income (UMICs) by the World Bank. There were only three studies carried out in lower-middle-income (LMICs) or low-income countries (LICs): two studies from Africa (109, 110) and one study from India (111). Overall, existing CEA models typically each only considered a limited set of disease manifestations caused by Strep A. About 25% of the studies (n = 11) solely considered superficial diseases such as throat or skin infections. Among those 11 studies, 6 of them were not Strep A-specific but more general, resulting in only 5 studies with a specific focus on Strep A. Another 34% of the studies (n = 15) included immune-mediated (i.e., acute rheumatic fever (ARF)) or locally invasive diseases (i.e., peritonsillar abscess) in addition to superficial diseases. Strep A causes severe cardiac failures as well. Five studies looked at disease sequelae (i.e., rheumatic heart disease (RHD)) along with superficial and immune-mediated diseases, and 2 studies further included locally invasive diseases.

While some studies conducted CEAs alongside (randomized) clinical trials (n = 7) or simple comparisons between costs and benefits (n = 8), the majority of the studies (66%) used decision analytic models. Among the studies with decision analytic models, 72% of them (n = 21) adopted decision tree models, and 8 studies employed Markov models. None of the existing studies identified through this review took into account the indirect benefits from reducing Strep A transmission (108).

8.2 Methods

8.3.1 Economic burden per episode for Group A Streptococcus infections

A literature search was conducted to identify any costs associated with *S. pyogenes* and to extract further details including healthcare descriptions, treatment items, and the unit of measure if available. Given the insufficient number of existing studies, adjustment factors for direct medical cost (DMC) and direct non-medical cost (DNMC) were generated by comparing with the WHO-CHOICE (CHOosing Interventions that are Cost-Effective) unit cost database (112) and Gross Domestic Product (GDP) per capita, respectively. For the DMC estimation, the number of outpatient visits and the duration of hospital stays were estimated by evaluating longitudinal datasets available for a 10-year period from the healthcare big data hub system (113). The final DMC and DNMC values were estimated by applying the adjustment factors to the crude DMC and DNMC values for all countries. To consider productivity losses due to Strep A infections, indirect cost (IC) was estimated by multiplying minimum wage by the average duration of illness by income group and disease type. Productivity loss due to premature death from RHD and invasive infections was also taken into account (8). The final costs were expressed both in 2018 United States dollars (USDs) and in 2018 International dollars (I$).

A probabilistic multivariate sensitivity analysis was extensively carried out (114). A Monte Carlo simulation was conducted based on 5,000 random draws for input parameters to estimate 95% confidence intervals of the economic burden for each of the seven disease types.

8.3.2 Economic burden per episode for Group A Streptococcus infections

A static cohort model is used to estimate vaccination impacts for six scenarios as described in Chapter 7 (104). Table 8-1 shows a list of health economic parameters. Future costs and health outcomes are discounted at a rate of 3%, but health outcomes with no discounting are also considered following the WHO guideline (115). Both vaccine procurement and delivery costs are unknown since there is no vaccine available against Strep A infections. Instead of setting up additional assumptions on vaccination costs, a range ($0 - $300) of the total cost per fully vaccinated person is applied (116, 117), and the maximum cost per fully vaccinated person to be cost-effective is derived at varying threshold costs per disability-adjusted life years (DALYs) averted. Given that the conventional threshold approach (i.e., 3 times GDP per capita) has been criticized and discouraged by the WHO (118, 119), population weighted cost per DALYs averted which takes into account marginal productivity of healthcare expenditure (health opportunity cost) is considered in addition to the conventional threshold per DALYs averted (1 x GDP per capita) (120).

Table 8-1. Health economic parameters.

ITEM	ASSUMPTION
GEOGRAPHICAL PRESENTATION	World Bank income groups (HIC, UMIC, LMIC, LIC)
VACCINE DOSES	3 doses
VACCINATION STRATEGIES	Routine at age 0 year; routine at age 5 years
COST PER FULLY VACCINATED PERSON	$0 - $300
DISCOUNTING	3% discounting for costs and health outcomes (default); 0% discounting for health outcomes (sensitivity analysis)
WASTAGE FACTOR DURING VACCINATION CAMPAIGNS	10% (default); 5% and 20% (sensitivity analysis)
ECONOMIC BURDEN	Point estimates (default); 95% confidence intervals (sensitivity analysis); societal perspective
COST-EFFECTIVENESS THRESHOLD	1 x GDP per capita (default); health opportunity costs (conservative)

8.4 Economic burden of Strep A infections

The economic burden per episode is shown in Figure 8-1 for the seven disease types by income group. The estimated economic burden ranged from $22 to $392 for pharyngitis, $231 to $6,332 for ARF, $449 to $11,717 for RHD, $949 to $39,560 for severe RHD, $662 to $34,330 for invasive infections, $25 to $2,903 for impetigo, and $47 to $2,725 for cellulitis. Productivity loss due to premature death from RHD and invasive infections is shown in

Figure 8-2. For both RHD and invasive infections, while productive years lost were the lowest in HICs given the weighted average age of death being the highest, the cost due to early death was the greatest in HICs and the lowest in LICs. This is mainly because patients in HICs are expected to earn more than those in lower-income groups.

Figure 8-1. Economic burden per episode for Strep A infections by income group. Cost of illness per episode shown in this figure includes DMC, DNMC, and IC (excluding costs due to premature death). Please note that scales on the Y-axes vary to improve the readability across diseases and income groups. HICs: High Income Countries, UMICs: Upper-Middle Income countries, LMICs: Lower-Middle Income countries, LICs: Low Income countries, sRHD: severe RHD.

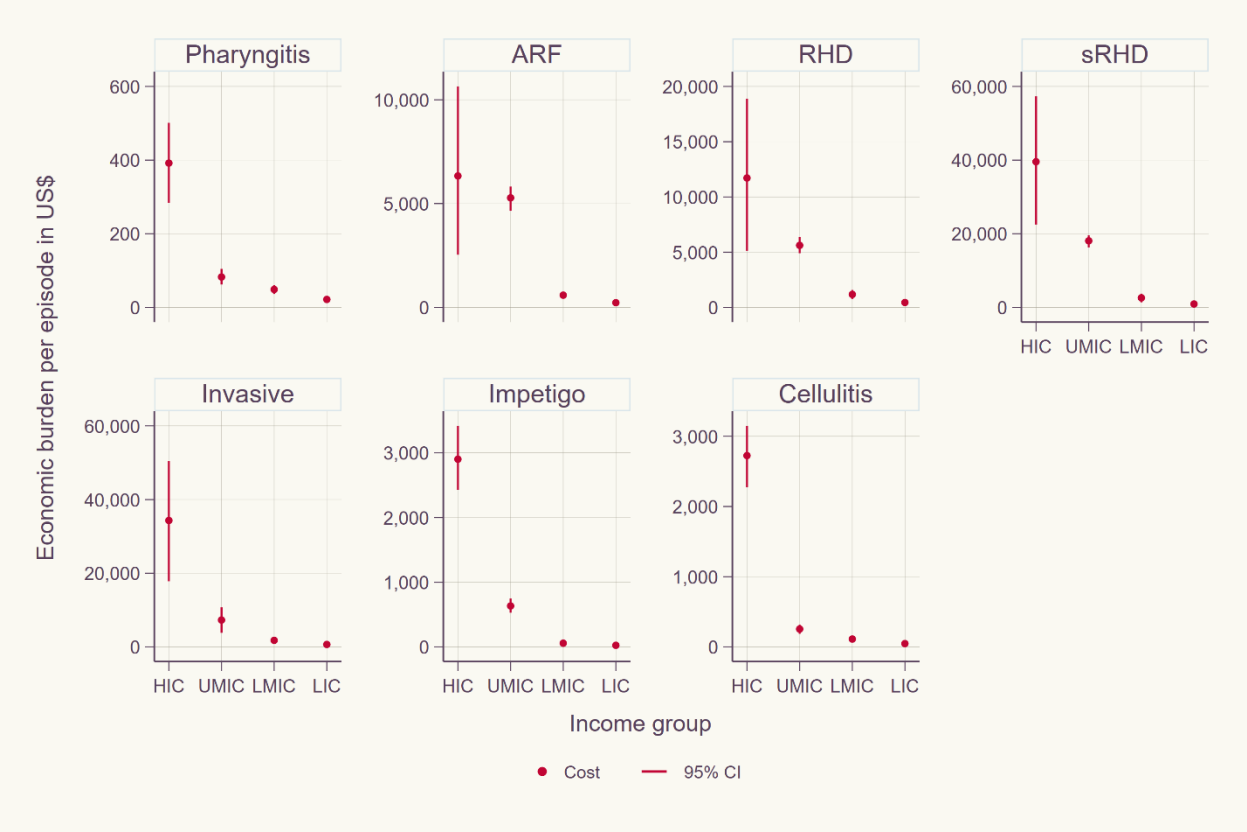


Figure 8-2. Productivity loss due to premature death by income group.

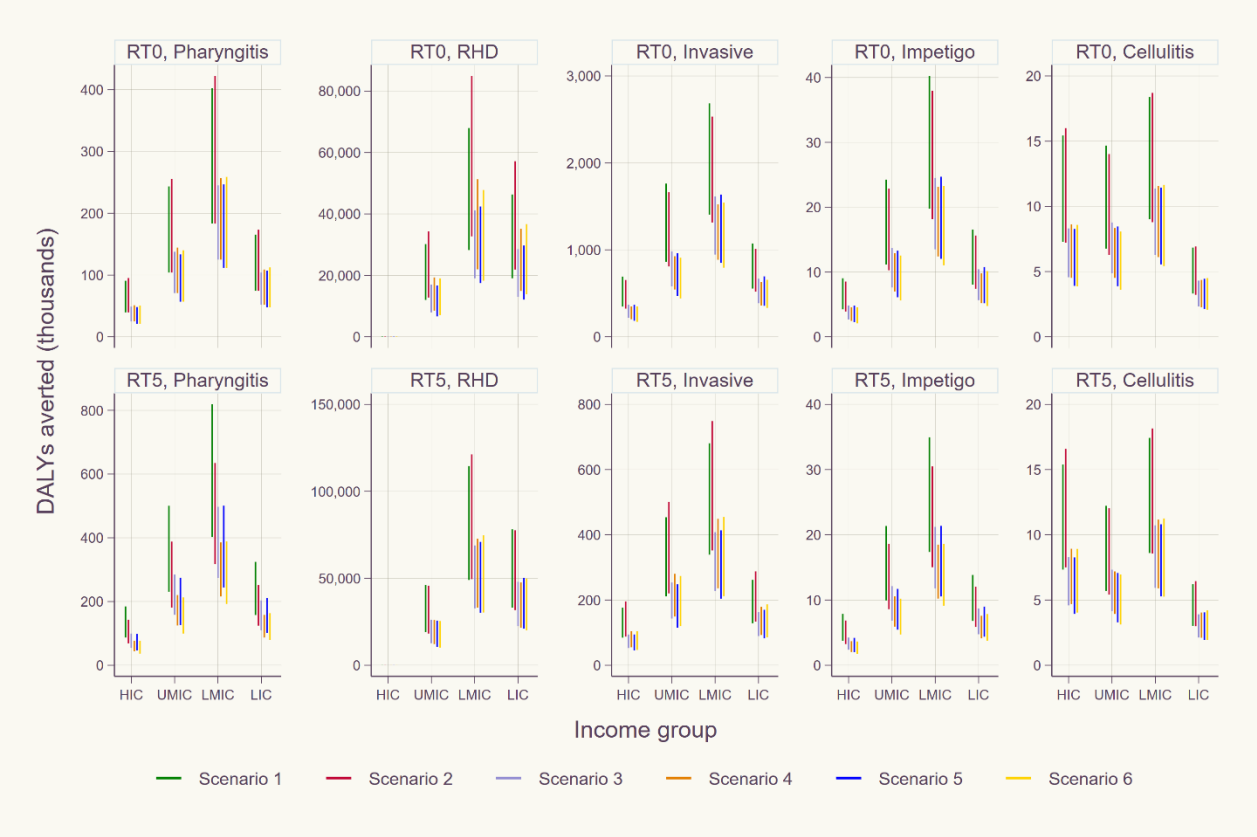
8.5 Cost-effectiveness of a hypothetical Strep A vaccine

DALYs saved due to vaccination are shown in

Figure 8-3. The number of cases averted for pharyngitis and skin infections is far greater than for more severe illnesses such as RHD or invasive infections. However, the number of DALYs saved is higher for the severe illnesses than for superficial infections due to the longer duration of illness and higher disability weights, as well as premature deaths from more severe illnesses. As expected, vaccination scenarios with higher coverage rates such as scenarios 1 and 2 resulted in a greater number of averted DALYs than the rest of the scenarios where the peak coverage rates were identically assumed to be 50% across countries. By income group, the highest number of DALYs averted is observed in LMICs regardless of the target age cohorts for routine vaccination.

Figure 8-3. Averted DALYs by Strep A vaccination scenario and disease type by income group.

RT0: routine vaccination for infants (at birth), RT5: routine vaccination at age 5 years. The upper bound of each bar shows health outcomes with no discounting (0%), whereas the lower bound estimates are based on the discount rate of 3%. Please note that scales on the Y-axes vary to improve the readability across diseases.

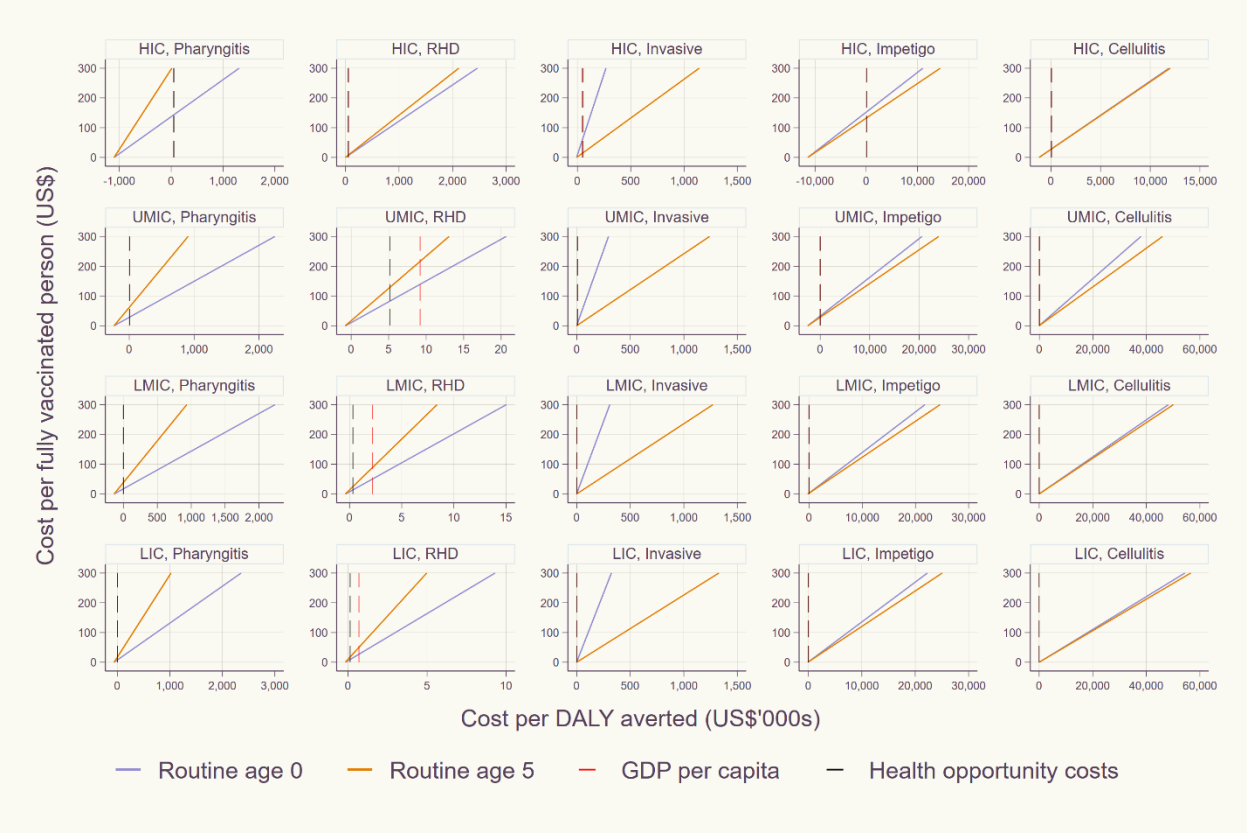


The incremental cost-effectiveness ratios (ICERs) of the two routine vaccination strategies are shown by disease manifestation and income group in

Figure 8-4. While vaccinating the age cohort of 5 years old is more cost-effective than vaccinating infants for pharyngitis and RHD, this is the opposite for invasive infections. This is because the burden of pharyngitis was assumed to be more common in children 5-15 years old, and the incidence rate of RHD was also higher for children and adults (5-24 years old) than the cohorts younger than 5 years old (see Chapter 6). Thus, vaccinating the cohort of 5 years old averts a higher number of cases than vaccinating infants for pharyngitis and RHD. On the other hand, the incidence rate for invasive infections was estimated to be the highest among infants (0-12 months as shown in Chapter 6), making the infant routine vaccination more cost-effective. For impetigo and cellulitis, marginal differences are observed between the two routine vaccination strategies since the incidence rates of the two infections appeared to be quite consistent among the age cohorts affected by vaccination.

Figure 8-4. Incremental cost-effectiveness ratios by income group under scenario 1.

Interventions are considered to be cost-effective if the total cost per fully vaccinated person is located on the left side of varying threshold costs per DALY averted.



Overall, vaccination would be cost-effective if the total cost per fully vaccinated person were set properly as shown in

Figure 8-5. In order for Strep A vaccination to be cost-effective at the threshold of 1 x GDP per capita, the maximum vaccination cost per fully vaccinated person ranges from $8 to $308 for pharyngitis, $6 to $216 for RHD, $0.2 to $56 for invasive infections, $1 to $153 for impetigo, $0.1 to $28 for cellulitis, and $37 to $489 for all disease states combined. In general, vaccination is more cost-effective in HICs for all disease types except RHD, for which the maximum cost per fully vaccination person is the highest in UMICs. It should be noted that the total vaccination cost per person needs to be set around $0.1 to $3 when only considering skin and invasive infections to be cost-effective in LMICs and LICs. However, the threshold cost per person is higher for pharyngitis and RHD, as well as for all disease states combined in LMICs and LICs.

Figure 8-5. Threshold cost per fully vaccinated person to be cost-effective by disease manifestation and income group under scenario 1.

The lower bounds are for the least favorable scenario: 20% wastage rate, lower bound of economic burden, and 3% discounting of health outcomes. The upper bounds are based on the most favorable scenario: 5% wastage rate, upper bound of economic burden, and 0% discounting of health outcomes. Please note that scales on the Y-axes vary to improve the readability across diseases.

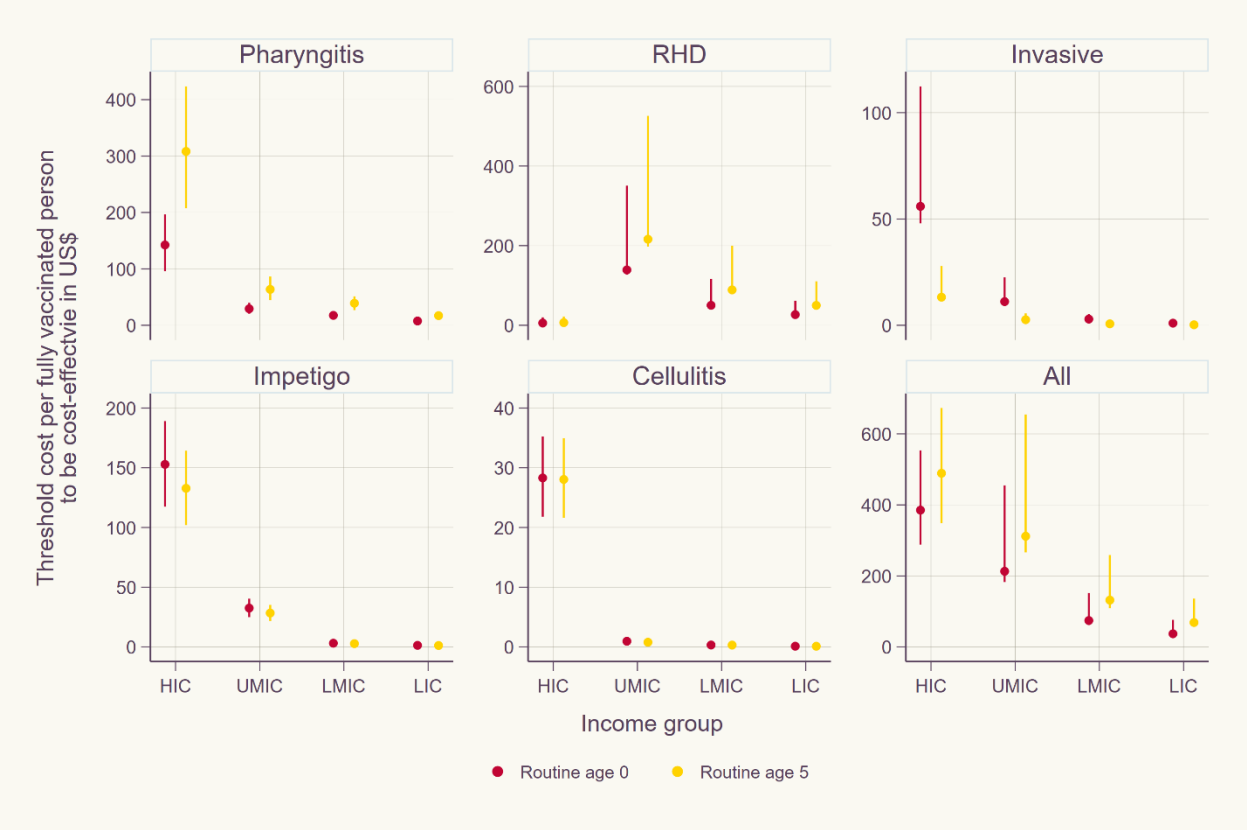
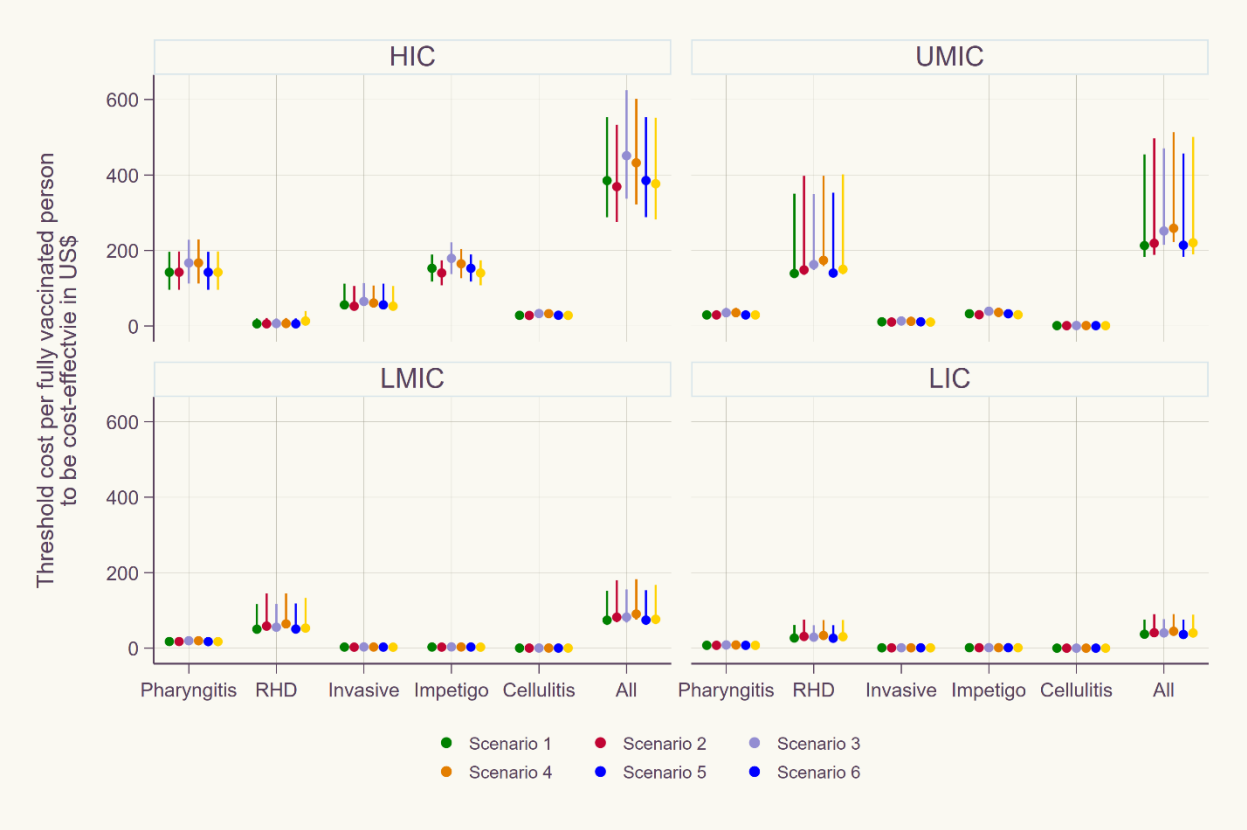


Figure 8-6 compares the threshold costs per fully vaccinated person among the six scenarios. Given the nature of a static model, the reduction in disease burden is linearly associated with vaccine efficacy, duration, and coverage rates. Thus, variations in ICERs would not be expected among the six scenarios. If any, marginal differences could be observed mainly due to the background demographic information (i.e., varying mortality rates by year).

Figure 8-6. Threshold cost per fully vaccinated person to be cost-effective by income group and scenario.

The lower bounds are based on the least favorable scenario: 20% wastage rate, lower bound of economic burden, and 3% discounting of health outcomes. The upper bounds are for the most favorable scenario: 5% wastage rate, upper bound of economic burden, and 0% discounting of health outcomes.



8.6 Conclusions and limitations

Across income groups, the estimated economic burden ranged from $22 to $392 for pharyngitis, $231 to $6,332 for ARF, $449 to $11,717 for RHD, $949 to $39,560 for severe RHD, $662 to $34,330 for invasive infections, $25 to $2,903 for impetigo, and $47 to $2,725 for cellulitis. For Strep A vaccination (RT0) to be cost-effective at the threshold of 1 x GDP per capita, the maximum vaccination cost per fully vaccinated person was $385 in HICs, $213 in UMICs, $74 in LMICs, and $37 in LICs for all disease states combined (104).

Overall, existing studies that reported cost of illness for Strep A-induced disease manifestations were scarce. Among the few studies available, most of them reported the costs from the same HICs such as Australia and the United States. The number of available studies was disproportionately lower in UMICs, LMICs and LICs. Some of the DMC and DNMC adjustment factors particularly in LICs were not directly estimated due to the absence of data, thus the adjustment factors from similar income groups were applied. Moreover, there were fewer studies available for invasive infections, impetigo, and cellulitis. While extensive sensitivity analyses were carried out with a Monte Carlo simulation of 5,000 random draws, future research is needed to fill existing knowledge gaps and reduce a large degree of uncertainties particularly in low-income group settings. The CEA outcomes are sensitive to vaccine

characteristics such as efficacy, waning rates, and respective duration, etc (105). While the WHO Preferred Product Characteristics (PPCs) were employed for the current study, hypothetical Strep A vaccine characteristics will need to be updated as clinical trials for potential vaccine candidates advance.

9 Full societal benefit

9.1 Context and Rationale

In recent decades, many researchers and policymakers have come to understand that good population health has beneficial impacts on other forms of wellbeing (121-124). Healthier populations, for instance, tend to have stronger income growth and economic development than their less healthy counterparts. To the extent that good population health has instrumental value, health-promoting technologies are liable to provide societal benefits beyond the limited set of health benefits typically captured in traditional economic evaluations (e.g., the direct prevention of cases, deaths, and future treatment costs often captured in health sector-centric cost-effectiveness analysis). When the aim of an economic evaluation is to inform the rational and fair allocation of public funds, the full societal health, economic, and social impacts of the health technology in question—as well as their distribution—should be assessed (125).

In this chapter, we do the following: 1) present a taxonomy of vaccination's full health, economic, and social impacts in general; 2) discuss several impacts likely to be especially significant for Strep A vaccination; 3) summarize a set of analyses of the relationship between Strep A infection, antibiotic consumption, and vaccination; and 4) present the results of an exercise to assess the full value of reducing deaths and disabilities associated with Strep-A vaccination using a value-per-statistical-life approach.

9.2 Methods

9.2.1 Conceptual framework of the full societal benefits of vaccination

Table 9-1 summarizes potential health, economic, and social impacts of vaccination and describes their distribution throughout levels of society—from the individual to society as a whole (126). This taxonomy builds on previous work, and we employed qualitative research to identify benefits likely to be especially impactful for prospective Strep A vaccination.

Table 9-1. Health, economic, and social benefits of vaccination and their distribution.

		Distribution			
	Vaccination benefits	**Individual**	**Family/ household**	**Society (health sector)**	**Society (general)**
Health benefits	Direct health effects • Reduced morbidity & mortality due to target pathogen • Adverse effects of vaccination (negative benefit)	✓			
	Prevention of secondary individual (physical) health effects • Off-target pathogens • Aggravation of comorbidities • Nosocomial infections • Microbiome disruption	✓			
	Mitigation of secondary population-level health effects • Disease transmission • Antimicrobial resistance (AMR) • Healthcare congestion			✓	✓
	Improved mental health	✓	✓		
Economic benefits	Reduced healthcare costs	✓	✓	✓	
	Reduced caregiving costs	✓	✓	✓	
	Reduced transportation costs	✓	✓		
	Increased labour force participation, hours worked, and income	✓	✓		✓
	Increased productive non-market activities	✓	✓		✓
	Improved educational attainment, school attendance, and cognition	✓			✓
	Fiscal impact • Increased tax receipts • Reduced public health spending			✓	✓
	Increased wealth/savings	✓	✓		
	Reduced risk and severity of impoverishment	✓	✓		✓
	Reduced risk of economically disruptive outbreaks			✓	✓
Social benefits	Improved social equity				✓
	Intergenerational benefits		✓		
	General risk reduction	✓	✓	✓	✓
	Improved quality of life	✓	✓		✓
	Reduced stigma	✓	✓	✓	✓

9.2.2 The potential impact of Strep A vaccination on antibiotic consumption for sore throat

We reviewed the literature for studies describing rates of antibiotic treatment for sore throat or pathology outcomes among those treated. We abstracted and analyzed the data from eligible studies to estimate global antibiotic consumption rates for sore throat and Strep A sore throat. We then extrapolated from these analyses to explore the potential reduction in antibiotic consumption for sore throat due to Strep A vaccination. The methods employed in each analysis are summarized below and described further elsewhere (127).

To estimate the global rate of antibiotic consumption for sore throat and Strep A sore throat, we conducted a systematic review of the literature for studies published between January 2000 and Feb 2022 that reported either:

- The rate of antibiotic doses or courses consumed or prescribed for the treatment of sore throat per person in a defined population or
- The proportion of consumed or prescribed antibiotics for sore throat for patients with diagnostically confirmed Strep A sore throat.

Prescribing rates from countries with available data were used to estimate the global rate of antibiotic prescribing for sore throat in two ways: first, by calculating an arithmetic mean prescribing rate, and second, by calculating a population-weighted mean prescribing rate. For countries with more than one study, the most recent and nationally representative available prescribing rate was used. Only one study reported sufficient data to directly calculate the prescribing rate for confirmed Strep A sore throat.

To estimate the proportion of prescriptions attributable to Strep A, a random-effects meta-analysis was conducted to determine the proportion of prescriptions for sore throat that were diagnostically confirmed by laboratory or point-of-care test as Strep A. In addition, a sub-group meta-analysis by age group (children or adults) at treatment was conducted.

Subsequently, a back-of-the-envelope estimate of prescriptions averted due to Strep A vaccination was generated by multiplying together the results of the previous two analyses with the potential population impact of a prospective Strep A vaccine administered to 5-year-old children. The population impact reflected the following assumptions: vaccine effectiveness of 80% against Strep A pharyngitis (based on the WHO's Preferred Product Characteristics for Strep A vaccines), 90% vaccine coverage in the eligible population, and vaccine durability of 10 years with no waning during that period.

9.2.3 Estimation of the full benefits of prospective Strep A vaccines

To assess the full value of reducing deaths and disabilities associated with Strep A vaccination, we rely on the concept of the value-per-statistical-life-year (VSLY). VSLY is obtained by dividing the population-average value-per-statistical-life (VSL) by the average remaining life expectancy (128). In turn, 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.[1] VSL and VSLY are thought to capture both the intrinsic and internalized

[1] For example, if individuals in a group are each willing to pay $1,000 to reduce their risk of death by 0.1%, the value per statistical life in this group is equal to $1,000,000. This does not mean that each individual would pay $1,000,000 to guarantee their own survival. Rather, it means that each would agree to pay an equal share of $1,000,000 (i.e., $1,000) to fund a project that reduces the expected number of fatalities in the group by one.

instrumental value of living longer and in better health. Thus, they can be considered appropriate monetary proxies for some of the broader impacts of vaccination.

VSL estimates are based on individuals' reported preferences or on individuals' consumption and work behaviors, and they typically vary by income, baseline risk, and age. Based on the relevant literature (129), we assumed that: 1) VSLY (and VSL) is proportional to income; 2) the monetary value of benefits experienced by future generations is discounted at a constant yearly rate r; 3) the value of preventing a year lived with disability is also equal to VSLY. Estimates of VSLY are typically between one and five times per-capita income.

The dependence of VSL on income can have unacceptable ethical implications. In particular, since a well-off individual may be willing to pay a larger amount of money than a less well-off individual for the same change in risk of death, the use of individual- and country-specific VSL estimates implies that the lives and interests of the well-off count more than those of the less well-off (130). To avoid undervaluation of benefits experienced by lower-income countries, we adopt a single global estimate of VSLY to be applied to all countries and assume that it is equal to one to five times global Gross Domestic Product (GDP) per-capita. We also vary the yearly discount rate r from 1% to 5%.

9.3 Results

9.3.1 Broad benefits of Strep A vaccination

Many, if not all, of the vaccination impacts enumerated in Table 9-1 have relevance to prospective Strep A vaccines. In this sub-section, we briefly describe examples of health, economic, and social benefits likely to have a substantial impact in determining the magnitude of net benefits conferred by Strep A vaccination and provide the conceptual rationale for this assessment. In the following section, we report on new empirical research into one of these potential benefits (reduced antibiotic consumption and resistance).

9.3.1.1 Broad health benefits: reduced antibiotic consumption and resistance

Beyond direct prevention of morbidity and mortality, highly effective and widely distributed Strep A vaccines could plausibly yield significant indirect health benefits by virtue of decreasing antibiotic consumption and, potentially, resistance.

High amounts of antibiotics are consumed globally to treat Strep A diseases, with penicillin representing the first-line antibiotic of choice for treating superficial infections. To date, no significant resistance to penicillin has been detected in Strep A. However, Strep A resistance to other antibiotics sometimes used as treatments (e.g., erythromycin) has been detected (24), and consumption of penicillin may engender resistance in bystander pathogens for which penicillin is also a clinically relevant treatment (131).

9.3.1.2 Broad economic benefits: gains in education, cognition, labor force participation, productivity, and income

Beyond direct healthcare cost savings, broader economic benefits of vaccination are often ignored in economic analyses. Among the economic benefits of vaccination enumerated in Table 9-1, Strep A vaccination is likely to have an outsized positive impact on educational attainment, school attendance, and cognitive function—all of which have been demonstrated for other vaccines (123)—due to the disproportionate burden the pathogen places on children. The high incidence of pharyngitis and

impetigo in children (coupled with the transmissible nature of Step A) leads to frequent absences among schoolchildren. And given the relatively early age of onset for severe manifestations, such as rheumatic heart disease (RHD), more significant educational disruptions, related to ongoing health impacts and disease management, are possible.

In adults, Strep A can diminish labor force participation, productivity, and income. This is true both for adults directly affected by RHD and other severe Strep A diseases and for adults who serve as caretakers of children suffering from illness. In addition, premature mortality from Strep A diseases removes individuals from the labor force entirely. These economic impacts of Strep A—and the benefits that would result from preventing them via vaccination—are likely to be of particular importance in low-income settings where social safety nets are often lacking, and an individual's labor is typically their greatest asset.

9.3.1.3 Broad social impacts: improved equity, better quality of life, and reduced stigma

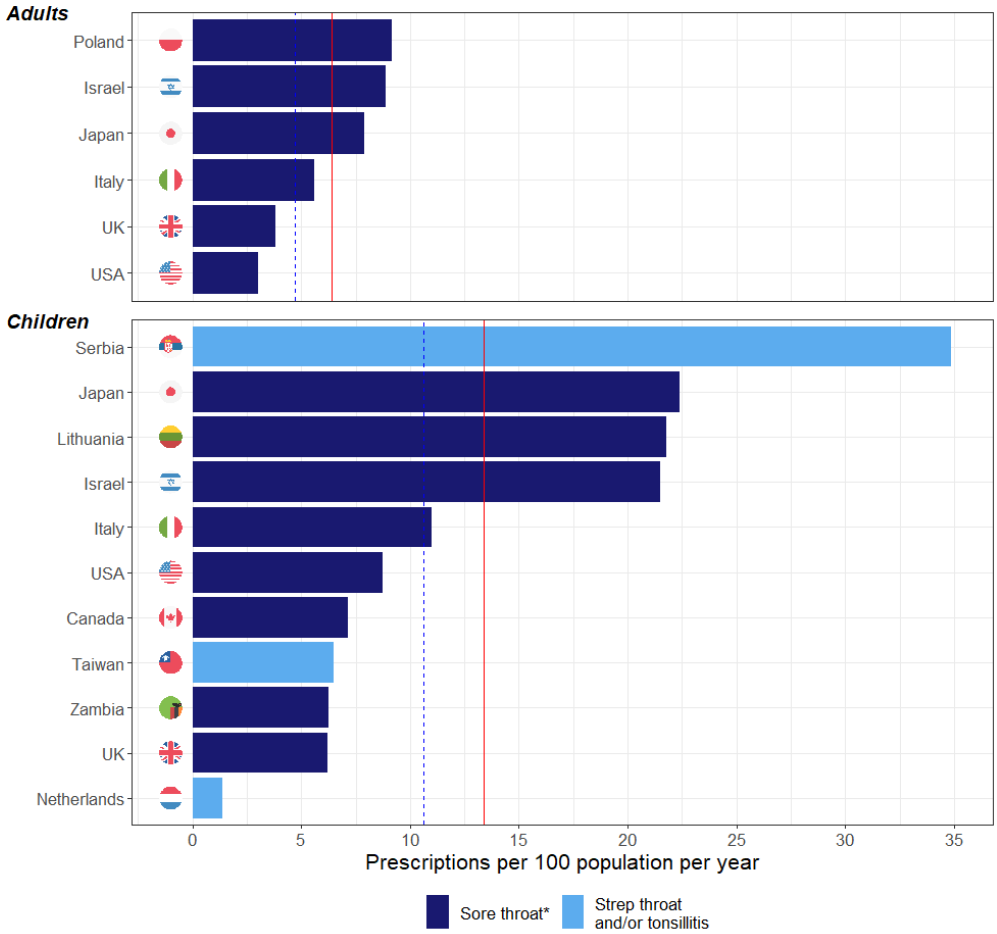
Finally, Strep A vaccination is also likely to have several positive social impacts. Prevention of Strep A diseases could lead to substantial improvements in social equity both across and within populations. That is because the global distribution of Strep A's health and economic burdens falls disproportionately on LICs and MICs, and within countries the burden typically falls disproportionately on low-income and otherwise disadvantaged groups, such as indigenous communities in Australia and New Zealand. In practice, any equity improvements a Strep A vaccine may promise are contingent on widespread access that is not predicated on ability to pay for vaccination.

Strep A vaccination may confer additional social benefits. These include better quality of life—beyond improved health status—for individuals who would otherwise suffer long-term effects from Strep A diseases. As one concrete example, women suffering from RHD sometimes refrain from having children due to their disease status. Social benefits of vaccination may also include reduced stigma among RHD patients in populations where the disease is not well understood.

9.3.2 Global antibiotic consumption for sore throat and the potential effect of prospective Strep A vaccination

The review identified 44 studies from 19 countries that described antibiotic prescribing rates for sore throat. Eleven studies focused on children, six evaluated adults, and 27 assessed all ages (with six reporting age-specific rates). Mean and population-weighted mean rates of antibiotic courses prescribed for children with sore throat were 13.4 and 10.6, respectively, per 100 population per year (Figure 9-1). For adults, the respective rates were 6.4 and 4.8 per 100 population per year.

Figure 9-1. Rates of antibiotic prescribing for sore throat by adults and children.* [+]Sore throat comprises "sore throat" or pharyngitis with or without tonsilitis.



**Adapted from (127)*

Nineteen studies that reported prescriptions for sore throat attributable to Strep A were identified across nine countries. All these studies were conducted in high-income countries, 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. Rapid antigen detection was the most common microbiological testing method used to test for Strep A. The proportion of antibiotics prescribed for sore throat attributable to Strep A was 55% (95% CI 42%-67%) among children and 45% (95% CI 36%-55%) among adults.

Based on 2020 population counts, the countries reviewed represent 9% of the global population for all age groups and 6% of children aged 5-14 years. For the countries reviewed, it is estimated that annually 8 million antibiotic courses are prescribed for sore throat among children and 37.4 million among all ages. Of those, 4.3 million and 20.7 million courses are prescribed for Strep A sore throat annually among each respective age group.

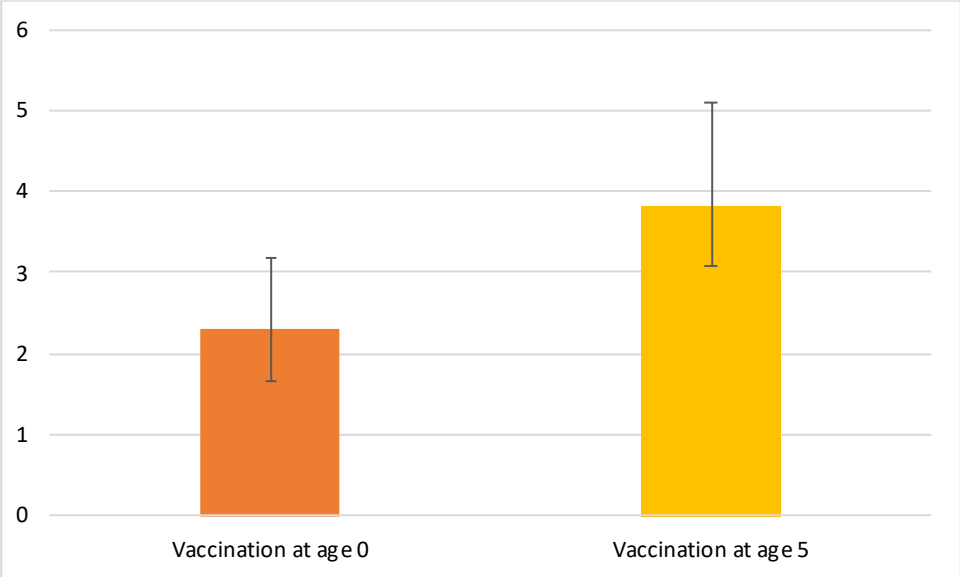
We estimate that 3.1 million courses of antibiotics could be averted based on 2020 population counts in the countries reviewed if vaccination was administered according to the stated assumptions. This reduction represents 15% of all antibiotic prescriptions for Strep A sore throat in those countries.

9.3.3 Estimation of the full benefits of prospective Strep-A vaccines

We consider the six vaccination scenarios presented in Chapter 7 and the associated health benefits in terms of averted years of life lost and years lived with disability. When the discount rate is equal to 3% and the VSLY is equal to three times global GDP per capita, the expected benefits across the six scenarios of a prospective Strep A vaccine amount to $2.3 trillion if the vaccine is administered at birth ($1.7 to $3.2 trillion), and to $3.8 trillion if the vaccine is administered at age five ($3.1 to $5.1 trillion) (Figure 9-2). These figures are equivalent to 2.7% and 4.4%, respectively, of global income in 2021.[2] Ninety-four percent of the benefits are due to the prevention of deaths associated with Strep A diseases (Table 9-2).

The chosen normative assumptions play a fundamental role in the estimation of the value of Strep A vaccination (126). With more favorable normative assumptions (discount rate of 1% and VSLY equal to five times global GDP per capita), the average benefits of Strep A vaccination increase to $6.96 trillion for infant vaccination and $11.46 trillion for childhood vaccination (Table 9-2).

Figure 9-2. Expected total benefits of Strep A vaccination from 2022 to 2051 (in trillions of USD).



Assumptions: 3% discount rate and VSLY evaluated at three times global GDP per capita. Global GDP per capita is equal to $11,000 (constant 2015 USD). The colored columns represent the average benefits across the six scenarios, while the black bars represent the variation in benefits across the different scenarios.

[2] Global Gross Domestic Product in 2020 was 84.7 trillion (US$) (https://data.worldbank.org/indicator/NY.GDP.MKTP.CD).

Table 9-2. Benefits of Strep A vaccination by scenario, metric, and normative assumptions (in billions of USD).

SCENARIO	VACCINATION AT AGE 0			VACCINATION AT AGE 5		
	Low value	Baseline	High value	Low value	Baseline	High value
SCENARIO 1	0.55	2.73	8.08	1.00	5.07	15.32
SCENARIO 2	0.61	3.19	9.92	0.97	5.08	15.80
SCENARIO 3	0.42	2.03	5.77	0.69	3.27	9.17
SCENARIO 4	0.47	2.36	7.06	0.67	3.26	9.44
SCENARIO 5	0.33	1.65	4.90	0.61	3.10	9.39
SCENARIO 6	0.37	1.93	6.02	0.59	3.09	9.66
AVERAGE	**0.46**	**2.32**	**6.96**	**0.75**	**3.81**	**11.46**

Baseline: 3% discount rate; VSLY is equal to three times global GDP per capita
Low value: 5% discount rate; VSLY is equal to global GDP per capita
High value: 1% discount rate; VSLY is equal to five times GDP per capita
GDP per capita is equal to $11,000.

9.4 Conclusions and limitations

Strep A vaccination is likely to confer significant benefits beyond direct reductions in morbidity, mortality, and healthcare costs. Considering the scenarios described in Chapter 7, the full value of reducing deaths and disabilities directly associated with Strep A vaccination is estimated to range from $1.7 to $3.2 trillion if the vaccine is administered at birth, and from $3.1 to $5.1 trillion if the vaccine is administered in early childhood.

There are several open avenues for future research into the broad benefits of Strep A vaccines. These include further exploration of the sensitivity of the VSLY-based results to underlying assumptions, the incorporation of the value of preventing antibiotic resistance into these results, and formal quantification of vaccination's distributional impacts and potential equity implications.

10 Business case from a developer perspective

10.1 Context and rationale

Quantifying the potential demand and market for a 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—whether multinational pharmaceutical companies (MPCs) or developing country vaccine manufacturers (DCVMs). The current study advances a novel Strep A vaccine demand and return on investment forecast model that provides an estimate for the potential demand for a hypothetical Strep A vaccine globally, associated revenue and profit forecasts as well as a net-present value (NPV) analysis of return on investments required for the development, licensure and manufacturing of a Strep A vaccine. It is hoped that the results of this study will help to inform industry decision-making and drive increased prioritization of Strep A vaccine development as a viable commercial opportunity for industry.

10.2 Methodology

The Strep A vaccine demand and investment return forecast model leverages traditional methodological approaches (132-134), a landscape assessment of Strep A vaccines in development (Chapter 5), information from proxy vaccines sourced from the WHO vaccine-preventable diseases monitoring system (135) and the Market Information for Access to Vaccines database (MI4A) (136), as well interviews with infectious disease and vaccine experts, global health funders, in-country vaccine decision-makers, and representatives from MPCs and DCVMs.

The following is an overview of the key inputs and assumptions used in the demand and investment forecast model. Detailed methodologies are presented in (137).

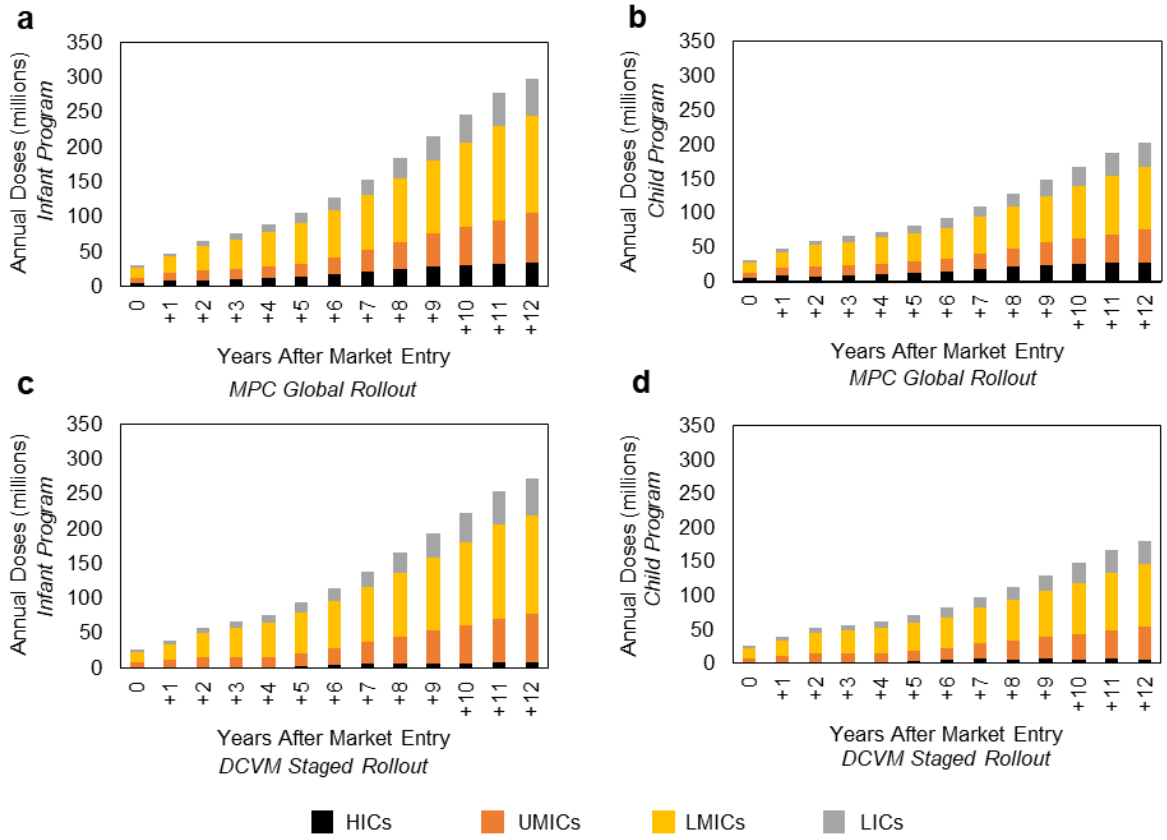
- **Hypothetical Target Product Profile:** The forecast model is centered on a hypothetical Strep A vaccine Target Product Profile (TPP) based on the WHO Preferred Product Characteristics for a Strep A vaccine (48) as well as common characteristics of the most advanced current Strep A vaccine candidates (80). The model assumes that the vaccine will protect against Strep A-induced pharyngitis, impetigo and scarlet fever, diseases that will likely serve as the clinical endpoints for efficacy trials. The analysis includes two different target population scenarios: infants (less than 1 year) or young children (4-7 years).
- **Market Launch:** Based on typical R&D timelines (138, 139) and validated through expert interviews, the year of market entry for the hypothetical Strep A vaccine is assumed to be 2033.
- **Timing of Introduction:** It is assumed that countries would introduce the vaccine in their national immunization program (NIP) over a period of up to 15 years following the first market launch, based on historical examples (135). Country-specific year of introduction was determined via a scoring system based on country-level data across the following 3 parameters: rheumatic heart disease (RHD) incidence (8) as a proxy for Strep A disease burden, new vaccine adoption history, and vaccine delivery infrastructure as well as degree to which the MPC or DCVM would prioritize launching in certain countries based on commercial capacity and vaccine market dynamics. In certain cases, information from subject matter interviews and/or the literature also informed a country's year of introduction.

- **Developer Scenarios:** Two different vaccine developer scenarios are presented herein: 1) Global rollout by an MPC starting in 2033, and 2) Staged rollout by a DCVM starting in 2033 (all countries except high-income countries [HICs]) and 2038 (HIC markets).
- **Market Segments and Coverage Rates:** Both public (NIP) and private markets are modeled. Country income group segments include low-income countries (LICs), lower middle-income countries (LMICs), upper middle-income countries (UMICs) and high-income countries (HICs). The estimated size and peak coverage rate of the private vs. public market is informed by expert interviews. The 2019 coverage rate of each country's diphtheria, tetanus, pertussis vaccine third dose (DTP3) is used as the peak coverage rate for the infant immunization program. The second dose of each country's measles-containing vaccine (MCV) 2019 coverage rate is used as the peak coverage rate for the child immunization program (135). For countries without an MCV childhood immunization program, a maximum coverage rate of 50% is assumed.
- **Vaccine Presentation, Cost and Price:** The vaccine presentation and price assumptions for the public market are based on historical vaccine procurement data from the WHO MI4A database using pneumococcal conjugate vaccine (PCV) 13, human papillomavirus vaccine (HPV) 2/4 and Rota as proxy vaccines (140). A wastage rate for both vaccine presentations of 5% was also assumed (141, 142). The cost per dose of vaccine (or cost of goods sold, COGS) is estimated based on detailed reported costs of the inactivated polio vaccine (IPV) – adjusted to account for the relatively more complex manufacturing requirements expected for a Strep A vaccine (142). Cost estimates were validated during interviews with industry expects including representatives from DCVMs.
- **Investment Costs:** Research and development (R&D) investment for both an MPC and DCVM investor scenario are estimated based on published literature and interviews with industry experts (138, 143, 144). These investment estimates are risk-adjusted according to assumed probability of success (POS) for advancing past each stage of development (60% POS for preclinical development, 75% POS for Phase 1, 40% POS for Phase 2, 80% POS for Phase 3 and 90% POS for all post-clinical development activities; resulting in a 13% aggregate probability of regulatory and technical success) (138, 143, 145, 146). The NPV was calculated from 12 years of annual operating profits using a 10% discount rate for the MPC and 15% for the DCVM (due to the higher risk associated with smaller companies versus MPCs with a global footprint).

10.3 Vaccine demand forecast

Model results indicate that the total annual demand at year 12 for the MPC Global Rollout developer scenario is estimated at 298 million doses for the infant immunization program scenario and 202 million doses for child immunization (Figure 10-1a and b, respectively). Annual demand at year 12 for the DCVM Staged Rollout scenario is 272 million doses for the infant immunization program scenario and 180 million for child immunization (Figure 10-1c and d, respectively). While immunizing infants would result in higher peak demand due to the relatively higher uptake of vaccines in the infant schedule compared to school-aged immunization programs, ensuring protection to peak years for pharyngitis incidence (approximately 5 - 15 years) would depend on greater vaccine durability than for the child immunization scenario.

Figure 10-1. Annual doses in millions delivered throughout the forecast period segmented by country income-level group for (a) the MPC Global Rollout infant immunization program scenario, (b) the MPC Global Rollout child immunization program scenario, (c) the DCVM Staged Rollout infant immunization program scenario, and (d) the DCVM Staged Rollout child immunization program.



10.4 Investment return

The estimated investment return for the development of a Strep A vaccine is summarized in

Table 10-1 expressed as the risk-adjusted net present value (NPV) of investment in development of a hypothetical Strep A vaccine. The risk-adjusted NPV represents 12 years of profits discounted to today's dollars minus the risk-adjusted capital investment required to bring a Strep A vaccine to market, also discounted to today's dollars. With a risk-adjusted total development investment of $979 million for the MPC Global Rollout scenario, the NPV at year 12 is approximately $2.5 billion and $2.0 billion for the infant and child immunization program scenarios, respectively. With a risk-adjusted investment of $372 million by a DCVM for the complete development and manufacturing of the vaccine, the year 12 NPV is approximately $310 million and $210 million for the infant and child immunization programs, respectively. In addition to a higher NPV, the MPC Global Rollout scenario has a greater gross profit margin (profit margin before selling, general & administrative costs). This is due to the higher proportion of revenue from high-profit, HIC markets in this scenario. The gross profit margin at year 12 for the child immunization program is slightly higher than for the infant immunization program in both the MPC Global Rollout and DCVM Staged Rollout scenarios, due to the relative proportion of private market versus public market at year 12, which is greater for the child program than for the infant program.

Table 10-1. Year 12 average profit margin and NPV for MPC global rollout and DCVM staged rollout scenarios.

	INFANT PROGRAM SCENARIO YEAR 12 FINANCIAL ANALYSIS		CHILD PROGRAM SCENARIO YEAR 12 FINANCIAL ANALYSIS	
INVESTMENT SCENARIO	**NPV (millions USD)**	**Gross Profit Margin**	**NPV (millions USD)**	**Gross Profit Margin**
MPC GLOBAL ROLLOUT	$2,460	75%	$1,990	77%
DCVM STAGED ROLLOUT	$307	64%	$210	66%

10.5 Conclusions and limitations

The outcomes of this study suggest there is a viable commercial market for private sector investment in Strep A vaccine development. Return on investment analysis found a positive NPV for investment in Strep A vaccine development across multiple scenarios, including: 1) different types of vaccine developer (i.e., MPC global rollout, DCVM staged rollout); 2) different target populations for the vaccine (i.e., infant or child immunization program scenarios). It is hoped that this demonstration of commercial viability will contribute to an increase in the number of biopharmaceutical companies investing in Strep A vaccine development programs. As detailed in Chapter 2 and 5, there is currently little industry investment or prioritization of Strep A vaccine development. Both GVGH and Vaxcyte have programs, but it is noteworthy that GSK is investing through its non-commercial, global health-focused entity (GVGH) and both GVGH and Vaxcyte programs have thus far been subsidized by the global health funder, CARB-X (58).

Limitations of the current study center on the degree to which the model accurately predicts adoption of a Strep A vaccine for market entry in specific countries. Interviews with vaccine decision-makers in a subset of countries revealed that for many countries, Strep A is an underappreciated public health threat in large part due to a lack of disease registries and active surveillance systems as well as underreporting of cases—particularly in low- and middle-income countries (48). However, given the known high global burden of Strep A disease, it is likely that the current effort as well as continued advocacy efforts through groups such as the Strep A Vaccine Global Consortium (SAVAC) will increase demand for a Strep A vaccine by the time one is ready for the market. Future work aimed at more precisely forecasting country-level demand and likely year of adoption will be important to undertake.

11 Optimal R&D spending on research and development for Strep A vaccines

11.1 Context and Rationale

In this chapter optimal global spending on research and development (R&D) for a Strep A vaccine is calculated (147). The perspective of a supranational organization that can allocate funding for Strep A vaccine development projects is taken.

The key question is: how many projects the organization should fund, and the amount needed to fund all these projects? The total global expected benefit of this funding, based on the expected reduction of harm from Strep A disease, and the social rate of return on this investment are calculated.

11.2 Methodology

The model further generalizes a framework previously applied to COVID-19 vaccine supply (148). In the model, the hypothetical supranational organization considers a list of vaccine R&D projects to fund. The projects are organized under different approaches and then numbered sequentially. One role of the approaches is to allow correlation in the likelihood that a project produces an approved vaccine. With some probability, the approach will fail and none of funded projects will succeed in producing an approved vaccine. Otherwise, conditional on the approach succeeding, the likelihood of success of any project under the approach is independent of the success of any other project. Moreover, the likelihood one approach can succeed is independent of the likelihood another approach can succeed. The other role of the approaches is to partition harm. We assume that the first approach can address only a fraction 1/N of the total harm caused by Strep A where N is the total number of available approaches.

The organization considers 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. It then 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 is found, and multiplying by the cost per project, optimal funding is calculated.

The model requires various parameters. There are two approaches to develop a Strep A vaccine, the M-protein approach and a catch-all other approach (28, 29). Based on consultations with industry experts, the probability that an approach can possibly succeed is calibrated at 90%. A single research project has an estimated 15% chance of resulting in an approved vaccine (149, 150). Based on the literature, and consultation with experts, the fraction of Strep A harm that a single approved vaccine can eliminate is 30% (151). For mathematical convenience, subsequent successes reduce remaining harm by the same fraction. Using estimates for Australia, total global harm caused by Strep A is $1.85 trillion (this and

subsequent dollar amounts are in 2020 United States dollar (USD))[3] (151). Finally, the cost of developing a successful vaccine, inclusive of failures, is $1 billion (138, 152). We use sensitivity analysis to show that the basic conclusions are robust to alternative assumptions for these parameters.

11.3 Results

Figure 11-1 illustrates the calibrated model. The orange line 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 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 as 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.

As long as the marginal benefit (MB) line is above the marginal cost (MC) line, the organization should continue to fund projects as the expected benefit of doing so is larger than the cost. The organization will continue funding projects until it reaches the 221st project. At this point, enough harm from Strep A is expected to be reduced that it is no longer cost effective to fund additional projects as the amount of remaining harm that could be expected to be reduced is very small.

Figure 11-1Figure 11-1. Calibrated Model.

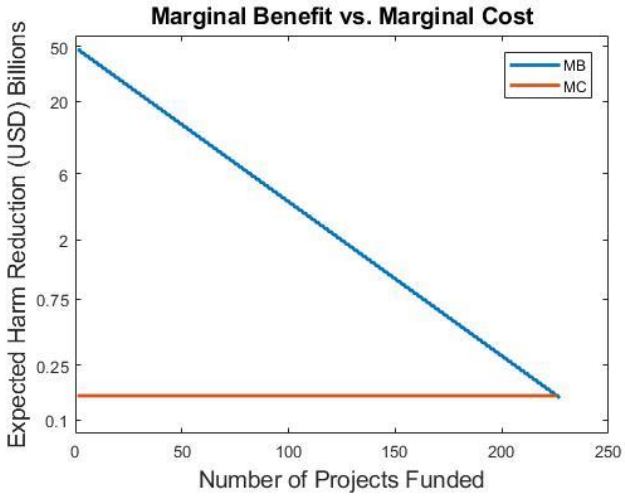


Table 11-1 provides numerical results. Under the parameters above, it is optimal to fund 220 projects at a cost of $33.0 billion. Social surplus generated by this investment is $1.63 trillion. Calculating a rate of return on this investment assuming the benefits accrue over a 30-year period beginning 10 years after the initial investment, leads to a return on investment of 22.3% per year.

If it is assumed that a successful vaccine will reduce 70% of the harm instead of 30% then less spending would be required ($15.9 billion), however social surplus remains almost unchanged. The rate of return on this investment increases to 28.5%.

[3] Other estimates of Strep A harm are even larger. For example, using the epidemiological model of Chapter 7 of the current report, and using the VSL methods of Chapter 9, the global burden of Strep A for the 2022–2051 birth cohorts is estimated at USD 42.2 trillion. With this harm estimate optimal spending is USD 51.3 billion with a rate of return equal to 48.2%.

If projects are less likely to result in a successful vaccine (a 5% probability versus a 15% probability), then more projects need to be funded. The rate of return on investment, in this case, is 20.7%.

A doubling of the harm caused by Strep A increases the number of projects funded and spending rises, though by a smaller factor than the increase in estimated harm. However, the benefits of the spending double and the returns to investment rise to 27.1%.

Finally, the case in which four approaches are required to address all the harm associated with Strep A is examined. Here, we should fund almost 400 projects at a cost of almost $60 billion. Social surplus differs little from the baseline case. The return to investment falls to a still quite substantial 18.0% per year for 30 years.

Table 11-1. Optimal Spending.

BASELINE CALIBRATION	PROJECTS FUNDED	OPTIMAL SPENDING	SOCIAL SURPLUS	INTERNAL RATE OF RETURN
	220	$33.0 billion	$1.63 trillion	22.3%
Sensitivity				
Harm Reduction = 70%	106	$15.9 billion	$1.65 trillion	28.5%
Success Probability = 5%	272	$40.8 billion	$1.62 trillion	20.7%
Total Strep A Harm 2x	248	$37.2 billion	$3.29 trillion	27.1%
Require 4 Approaches	388	$58.2 billion	$1.60 trillion	18.0%

Internal Rate Return (IRR) calculated assuming 10-year delay before harm reduction begins and assuming harm reduction spread out evenly over 30 years. All monetary values in 2020 USD

11.4 Potential Funding Mechanisms

For multiple reasons, private sector investment in Strep A R&D will not reach the optimal amount. First, some components of R&D, like basic research, are hard to patent and unlikely to provide an adequate return on investment. Second, the high rate of return required by pharmaceutical companies will discourage investment in all but the most promising projects. Third, the probability of success of an individual project is small, resulting in returns that may not be sufficiently high to justify the risk.

While Chapter 10 characterizes scenarios in which investment in Strep A vaccine R&D by pharmaceutical companies can result in a positive net-present value, companies will often have investment opportunities with a higher potential return and/or clearer path to market. In contrast to single Strep A vaccine projects, a large portfolio of diversified projects—which would necessitate public sector involvement—will greatly reduce the risk of not developing a viable product.

The public sector can play an important role in moving overall global investment towards the optimal amount, calculated above through direct funding for Strep A vaccine R&D. Done on a large scale, this mechanism of funding greatly reduces the risk of vaccine R&D by diversifying across many projects. To raise funds for such an investment, governments have a variety of approaches: increasing taxes, reducing other government spending, and debt financing. We view debt, when available, as appealing to better align costs and benefits. Any vaccine R&D project will see its benefits many years into the future. Debt allows a government to borrow money and pay back the principal in the future after benefits from the R&D efforts materialize.

An alternative, which would stimulate funding by private sector organizations, would be the government encouraging a bond fund for private sector investment in vaccine R&D. With this approach, many

private investors would pool capital and fund many vaccine R&D projects simultaneously (153). Profits from successful projects would provide a return to bond holders. The government could facilitate the development of such a fund with a government guarantee on the principal investment. Such an approach would help reduce the risk of vaccine R&D while providing a substantial role for both the public and private sector.

11.5 Conclusions and limitations

Optimal spending for Strep A vaccine R&D is large, estimated to be in the tens of billions of USD. More importantly, the benefits are more than 50 times larger than investments, in the range of $1.6 to $3.3 trillion. Returns on investment range from 18% to 29% per year for 30 years. These returns are large even compared to other social interventions that have received considerable support. For example, estimates of the return on increased years of education range from 9-10% per year (154, 155). These results call for both national and international policy to fund and promote accelerated development of Strep A vaccines.

Finally, the full benefits of vaccine development will not be achieved without a plan to ensure equitable access to the vaccine. This plan is especially important with regard to Strep A, as most of the associated deaths are in low-income countries where affordable antibiotics are less accessible. High income countries should support donations to international organizations to support the purchase of vaccines for low-income countries. Such a policy would not be purely altruistic. Overuse of antibiotics is likely to lead to increased antimicrobial resistance (AMR). Ensuring global access to an effective Strep A vaccine can be a potent defense against the development of such super strains.

12 Conclusions and recommendations

Studies conducted as part of this Full Value of Vaccines Assessment (FVVA) work have revealed important new findings related to the health, economic, and social burden of Strep A globally, as well as the potential public health impact and return on investment in research and development (R&D) spending on a Strep A vaccine. Below, we summarize key findings and supporting data, along with recommended next steps.

Key Finding #1: New meta-analysis data of pharyngitis and invasive infections substantiate the high burden of Strep A-mediated diseases globally.

Evidence: The pooled IR for Strep A sore throat was 22.1 episodes per 100 child-years. The pooled IR for invasive Strep A infections was 2.21 episodes per 100,000 person-years, with U-shaped age distribution showing highest in infants and adults aged 70+.

Recommendation: Enhance country-level surveillance programs, particularly in LMICs, and particularly to monitor rates of Strep A invasive disease as well as acute rheumatic fever (ARF).

Key Finding #2: New estimates of economic burden per case of different Strep A diseases indicate a significant economic burden globally.

Evidence: The estimated economic burden ranged from $22 to $392 for pharyngitis, $231 to $6,332 for ARF, $449 to $11,717 for rheumatic heart disease (RHD) $949 to $39,560 for severe RHD, $662 to $34,330 for invasive infections, $25 to $2,903 for impetigo, and $47 to $2,725 for cellulitis (lower end of range is for low-income countries (LICs), higher end for high income countries (HICs). Productivity loss due to premature death from RHD and invasive infections ranged from $9,637 and $17,830, respectively, in LICs to $72,097 and $50,484, respectively, in HICs.

Recommendation: Prioritize collection and use of data to fill knowledge gaps and improve accuracy of economic burden estimates, particularly in UMICs, LMICs, and LICs. Revisit cost-effectiveness analysis (CEA) outcomes as characteristics of vaccines advancing through clinical trials are known.

Key Finding #3: A Strep A vaccine could substantially reduce global morbidity and mortality due to Strep A diseases.

Evidence: Globally, a Strep A vaccine could avert 82 million cases of pharyngitis, 11.8 million cases of impetigo, 45,000 cases of invasive disease, 805,000 cases of cellulitis and 210,000 cases of RHD per birth cohort.

Recommendation: Global policy makers and global health organizations should recommend and work with funders and countries to prioritize investments in Strep A vaccine development and implementation.

Key Finding #4: A Strep A vaccine is likely to be a cost-effective intervention in all country income groups when considering total spectrum of Strep A diseases.

Evidence: For Strep A vaccination (routine vaccination for infants at birth) to be cost-effective at the threshold of 1 x Gross Domestic Product (GDP) per capita, the maximum vaccination cost per fully vaccinated person was $385 in HICs, $213 in UMICs, $74 in LMICs, and $37 in LICs for all disease states combined.

Recommendation: Local governments and global health funders should work together to determine expected delivery costs associated with Strep A vaccine implementation.

Key Finding #5: Strep A vaccination is likely to confer significant broad socioeconomic benefits beyond direct reductions in morbidity, mortality, and healthcare costs.

Evidence: Significant broad benefits of Strep A vaccination include reduced antibiotic use and resistance, gains in schooling and labor, and improved social equity. Based on a value-per-statistical-life approach, the full global societal lifetime value for 30 birth cohorts of Strep A vaccination is estimated to range from $1.7 to $3.2 trillion United States dollar (USD) if the vaccine is administered at birth, and from $3.1 to $5.1 trillion USD if the vaccine is administered at age 5.

Recommendation: Funders should support further study of the broad socioeconomic benefits of Strep A vaccination—including, for example, incorporating the value of preventing antibiotic resistance—and governments should better incorporate the full socioeconomic value of vaccines into R&D prioritization and vaccine implementation decisions.

Key Finding #6: The market for private sector investment in Strep A vaccine development and manufacturing is financially sustainable with base case forecasts indicating likely profitability.

Evidence: The net present value (NPV) for development and manufacturing of a Strep A vaccine in the scenario where a multinational pharmaceutical company completes a global roll-out is ~$2.5 billion USD for an infant immunization schedule scenario and ~$2.0 billion USD for a child immunization schedule scenario.

Recommendation: Companies should be engaged to understand current barriers to R&D investment and cross-sector solutions to incentivize industry prioritization of Strep A R&D investment should be explored.

Key Finding #7: Optimal spending on the development of Strep A vaccines is measured in the billions of dollars, but this spending may be expected to unlock trillions of dollars in value.

Evidence: Base case optimal spending for Strep A vaccine R&D is estimated at $33.0 billion USD with resulting social surplus benefits 50-fold higher, in the range of $1.6 to $3.3 trillion USD. Returns on investment range from 18% to 29% per year for 30 years. These returns are large even compared to other social interventions that have received considerable support. For example, estimates of the return to increased years of education range from 9-10% per year.

Recommendation: Governments should analyze options (e.g., debt financing, bond funding) and align on a preferred approach for achieving optimal R&D spending on Strep A vaccine development. HIC governments should donate funds through international organizations to ensure equitable vaccine implementation.

In summary, it is clear that Strep A infections lead to multiple diseases that collectively pose a substantial health, economic and social burden globally. This burden is disproportionately carried by LICs/MICs and disadvantaged communities, but there is also significant burden in HICs. Current preventive and treatment options for Strep A have major limitations. This FVVA report provides new evidence that an effective and safe vaccine for Strep A would avert millions of cases of Strep A disease and prevent a significant amount of the morbidity and mortality caused by the pathogen. It could also

alleviate much of the economic burden associated with direct and indirect medical costs. But the impact of a Strep A vaccine would likely extend far beyond traditional benefits. Vaccination to prevent Strep A infections and associated diseases could reduce reliance on antibiotics; lead to gains in education, cognition, labor force participation, productivity, and income; and promote equity, improve quality of life, and reduce stigma. The bottom line of this report is that traditional thresholds for cost-effectiveness will plausibly be satisfied by a Strep A vaccine and more so when one accounts for full societal benefits above and beyond morbidity and mortality reductions.

Strep A vaccine R&D has historically been underfunded by governments and global health funders, and few pharmaceutical companies have invested in Strep A vaccines throughout the development pipeline. It is postulated that a major impediment to industry investment has been uncertainty around the market for a Strep A vaccine. Importantly, the FVVA findings suggest that pharmaceutical companies will find a viable market for investing in Strep A vaccine R&D and that the public sector could support tens of billions of dollars in Strep A vaccine R&D and still achieve a strong return on investment. Through this evidence, it is hoped that the FVVA heightens awareness of both the need for and value of Strep A vaccination and informs decision-making and policies that support greater prioritization of investment in Strep A vaccine R&D as a vital public health tool and commercially viable product.

Appendix

Further Acknowledgements

List of Interviewees for Chapter 5 (Vaccine landscape analysis)

Interviewee	Affiliation
Andrew Steer	Professor, Murdoch Children's Research Institute (Melbourne, Australia)
Andrew Wong	Vice-President of Business Development, Walvax Biotechnology (Kunming, China)
Anonymous	Former Global Market Access for Vaccines, Top-5 Pharma; Former Regional Market Access Lead, Top-5 Pharma
Anonymous	Former Executive Director, Vaccine Strategy and Implementation, Top-5 Pharma
Anonymous	Former Associate Medical Director, International Vaccine Agency
Anonymous	Former Vice President, Vaccine Company (India); Former Senior General Manager, Therapeutics Company (India); Former Business Head, Pharma Company (India)
Danilo Gomes Moriel	Project Leader, GSK Vaccines Institute for Global Health (Sienna, Italy)
Jacelyn Loh	Senior Research Fellow, University of Auckland (Auckland, New Zealand)
James Dale	University of Tennessee Health Science Center (Memphis, USA)
James Wassil	Chief Operating Officer, Vaxcyte (Foster City, USA)
Jin S. Park	Head of Global Business Development, SK Bioscience (Seongnam-si, Republic of Korea)
Johan Vekemans	Former Medical Officer, Initiative for Vaccine Research, WHO (Geneva, Switzerland)
Jonathan Carapetis	Professor, Telethon Kids Institute (Nedlands, Australia)
Krishna Mohan	Executive Director, Bharat Biotech (Hyderabad, India)
Luiza Guilherme	Professor, University of Sao Paulo (Sao Paulo, Brazil)
Madhu Kapoor	Former Deputy Director QC and Regulatory Affairs, Serum Institute (Delhi, India)

Mark Walker	Professor, University of Queensland (Brisbane, Australia)
Michael Good	Griffith University (Brisbane, Australia)
Nikki Moreland	Senior Lecturer, University of Auckland (Auckland, New Zealand)
Patrick Tippoo	Head of Science and Innovations, Biovac (Cape Town, Africa)
Rachel Park	Business Director, EuBiologics (Seoul, Republic of Korea)
Rino Rappuoli	Chief Scientist, GSK (London, England)
Shiranee Sriskandan	Professor, Imperial College London (London, England)
Thomas Proft	Associate Professor, University of Auckland (Auckland, New Zealand)
Weidan (Wendy) Huang	Assistant to General Manager, Innovax (Xiamen, China)

List of Interviewees for Chapter 10 (Business case from a developer perspective)

Global Vaccine Groups

Interviewee	Title and Affiliation
Dr. Alejandro Cravioto	Chair of WHO SAGE / Faculty of Medicine of the Universidad Nacional Autónoma de México
Alexa Reynolds	Senior Country Manager (PNG and Solomon Islands), Gavi, the Vaccine Alliance
Carmen Tull	Deputy Director, Office of Maternal and Child Health and Nutrition, USAID
Deepali Patel	Senior Program Officer, Policy, Gavi, the Vaccine Alliance
Folake Olayinka	Team Leader, Office of Maternal and Child Health and Nutrition, USAID
Lois Privor-Dumm	Director, Policy, Advocacy & Communications, the International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health

In-Country Vaccine Decision-Makers

Country Income Level	Region	Country	Interviewee	Title and Affiliation
LIC	Sub-Saharan Africa	**Mozambique**	Dr. Ana Mocumbi	Head, Non-Communicable Diseases Division at National Health Institute
	South Asia	**Nepal**	Dr. Jhalak Gautam	Chief, Child Health and Immunisation Section, Ministry of Health & Population
	Caribbean	**Haiti**	Dr. Vanessa Rouzier	Chief, Pediatrics at GHESKIO and advisor on vaccines to Ministry of Health
LMIC	South Asia	**India**	Dr. Satinder Aneja Dr. Rose Winsley	Chair, National Technical Advisory Group on Immunisation Pediatrician, Department of Child Health Unit, Christian Medical College Vellore
	South Asia	**Bangladesh**	Dr. Chowdhury Kawser	Chair, National Committee of Immunisation Practices
	Pacific	**Papua New Guinea**	Dr. Mathias Bauri Dr. Edward Waramin	Acting National EPI Manager, NDOH Acting Manager, Public Health Division, NDOH
UMIC	South East Asia	**Thailand**	Dr. Nakorn Premsri	Director, National Vaccine Institute
	Pacific	**Fiji**	Litiana Volavola	Coordinator, National EPI Program
	Sub-Saharan Africa	**South Africa**	Dr. Anne von Gottberg Dr. Sibongile Walaza	Deputy Chair, National Advisory Group on Immunisation Senior Epidemiologist at the NICD Centre for Meningitis and Respiratory Diseases
HIC	Europe	**Germany**	Dr. Ole Wichmann	Director, Immunization Unit at the Robert Koch Institute

	Europe	**France**	Dr. Judith Mueller	Member, Commission Technique des Vaccinations
	Europe	**UK**	Dr. David Salisbury	Former Director, Immunisation at the Department of Health
	Pacific	**Australia**	Dr. Chris Blyth	Member, Australian Technical Advisory Group on Immunisation
	Pacific	**New Zealand**	Dr. Tony Walls	Member, Pharmacology & Therapeutics Advisory Committee

Additional Acknowledgements for Chapter 11 (Optimal R&D spending on research and development for Strep A vaccines)

- Steven Black (Emeritus Professor of Pediatrics, University of Cincinnati and Children's Hospital)
- David Kaslow (Chief Scientific Officer, PATH)
- Bill Hausdorff (Lead, Vaccines Public Health Value Proposition, PATH)
- Andrew Steer (Professor and Pediatric Infectious Diseases Physician, Department of General Medicine, Royal Children's Hospital Melbourne)
- Jim Wassil (Chief Operating Officer, Vaxcyte)
- The Value of Vaccination Research Network (VoVRN)
- Participants at the 2021 Palio Meeting "Planning a new era in vaccinology" for helpful comments and suggestions

While these experts and groups were consulted to support the development of the model, responsibility for the content of this report is the authors' alone.

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