WHO expert review of Group A Streptococcus vaccines

Hybrid Consultation by IVIR-AC and PDVAC

30 September 2022,
11am-3pm UK time

World Health Organization | IVB

Meeting Objectives

The proposed objectives are to:

1) Review recent advances in GAS Vaccines Research and Development (R&D) and the soon to be published Full Value of Vaccine Assessment (FVVA) for GAS vaccines;

2) Agree on key priorities to ensure the WHO PPC and Vaccine Development Technology Roadmap for GAS vaccines remain current and relevant.

Specifically:
• IVIR-AC is invited to review quantitative methods supporting the development of the GAS FVVA and discuss its relevance and applicability. [CLOSED SESSION]
• PDVAC is invited to review recent progress in GAS Vaccine R&D and to provide recommendations on the need to update the current WHO PPC and R&D Roadmap on GAS vaccines. [CLOSED SESSION]

Chairs: David Kaslow (PDVAC) & Paula Mendes Luz (IVIRAC)
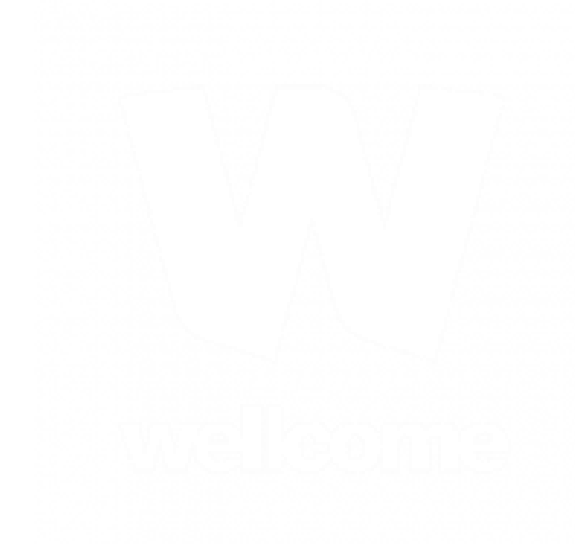
PART I
GAS VACCINE R&D

OPEN SESSION

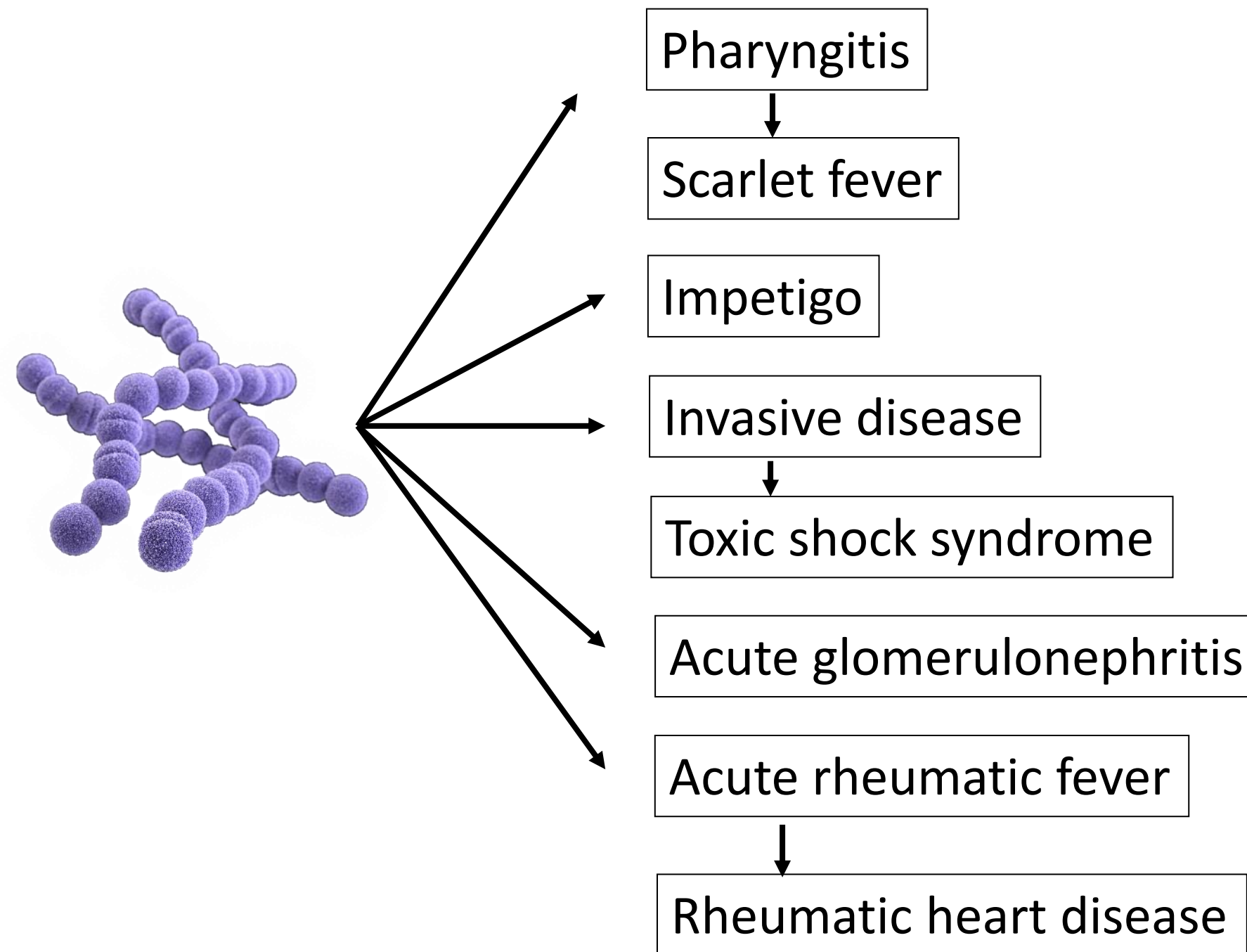World Health Organization | IVB

Strep A vaccine pipeline

With thanks to:

Don Walkinshaw, PhD

A quick primer on Strep A disease burden

Pharyngitis

↓

Scarlet fever

Impetigo

Invasive disease

↓

Toxic shock syndrome

Acute glomerulonephritis

Acute rheumatic fever

↓

Rheumatic heart disease

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Group A Streptococcus

- Scarlet fever has disappeared (like syphilis)

- So has rheumatic fever & heart disease

- Severe invasive GAS is too rare for a vaccine

- Strep throat & impetigo are too mild

- Penicillin always works

- GAS vaccines cause rheumatic fever

Right?

With thanks to Joshua Osowicki

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Group A Streptococcus

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- So has rheumatic fever & heart disease

- Severe invasive GAS is too rare for a vaccine

- Strep throat & impetigo are too mild

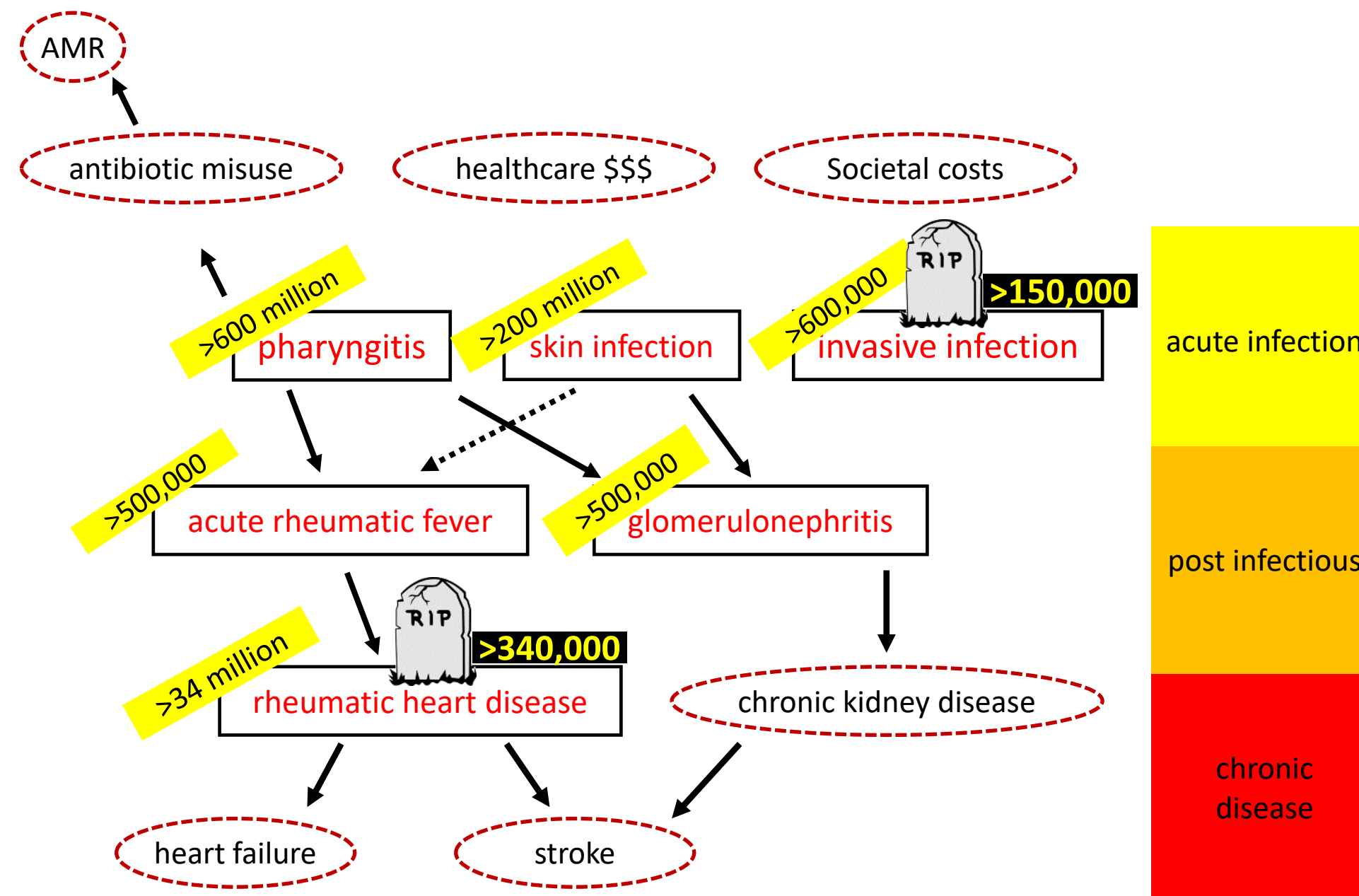- Penicillin always works

- GAS vaccines cause rheumatic fever

Wrong.

With thanks to Joshua Osowicki

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A quick primer on Strep A disease burden

With thanks to Joshua Osowicki

A quick primer on Strep A disease burden

The bacteria we've been ignoring: Why there should be a vaccine for strep A

In first world countries, strep is a stabbing throat ache that is easily remedied with antibiotics. But in many poorer countries, it is a public health catastrophe, says **Emily Sohn**

Friday 22 March 2019 17:17 | comments

Strep A vaccine pipeline

21st Century Group A Streptococcal (GAS) Candidate Vaccines and Antigens.

Candidate Name/Identifier	STAGE OF DEVELOPMENT		
	Preclinical	Phase I	Phase II
M-protein: 6-valent N-terminal	X	X	
M-protein: 26-valent N-terminal	X	X	X
M-protein: 30-valent N-terminal	X	X	
M-related proteins	X		
M-protein: minimal epitope J8	X	X	
P*17: synthetic derivative of J8	X		
M-protein: minimal epitope J14/p145	X		
M-protein: five J14 variants (SV1)	X		
M-protein: divalent N-terminal M1 + M12, with J14	X		
M-protein: 10-valent N-terminal, expressed by live *Lactococcus lactis*	X		
M-protein: C-repeat epitope (StreptInCor)	X		
M-protein: C-repeat epitopes	X		
Three conserved antigens (Combo): SLO, SpyAD, SpyCEP (currently in development with fourth antigen—group A carbohydrate)	X		
Five conserved antigens (Combo5): arginine deiminase, C5a peptidase, streptolysin O, SpyCEP, trigger factor	X		
Seven conserved antigens (Spy7): C5a peptidase, oligopeptide-binding protein, putative pullulanase, nucleoside-binding protein, hypothetical membrane associated protein, cell surface protein, SpyAD	X		
Group A carbohydrate (GAC)	X		
Group A carbohydrate (GAC) defective for GlcNAc side-chain	X		
C5a peptidase (SCPA)	X		
Sortase A (SrtA) + C5a peptidase (SCPA)	X		
Fibronectin-binding protein (FBP)	X		
Streptococcal protective antigen	X		
Serum opacity factor (SOF)	X		
Streptococcal pyrogenic exotoxin A/B/C (SpeA, SpeB, SpeC)	X		
Streptococcal pyrogenic exotoxin (SpeAB) fusion protein	X		
Streptococcal pili (T-antigen)	X		
Serine protease (SpyCEP or S2 subunit)	X		
Nine common antigens	X		

MEMBRANE BOUND

ANCHORLESS

SECRETED

PROTEINS, PEPTIDES, CARBOHYDRATE (and mRNA too!)

MULTIVALENT vs MULTI-COMPONENT

With thanks to Joshua Osowicki

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Strep A vaccine pipeline

- As a prelude to development of the Strep A Vaccine Business Case, Shift Health finalized a Strep A Vaccine Landscape Assessment in May 2020 with updates from several developers in February 2021. I have updated it since then.

- Strep A vaccine pipeline:

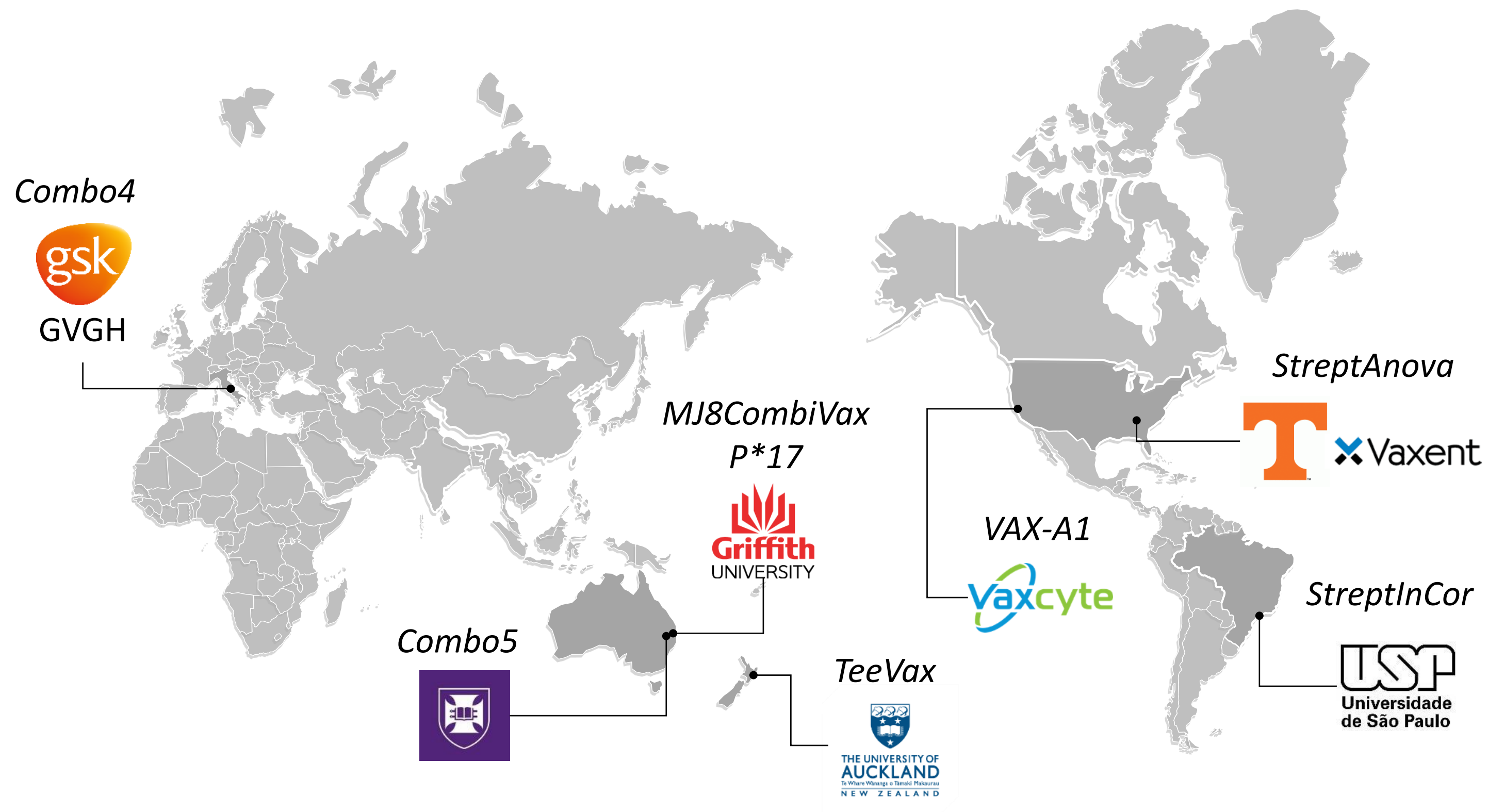|	
Early-Stage	• No program past Phase 1, most yet to enter clinical trials
Growing	• At least 8 active programs with product development focus in addition to a few academic/exploratory programs
Diverse	• Advanced programs evenly split between M and non-M protein candidates with range of antigens employed

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Strep A Vaccine Pipeline Overview

Several other academic/exploratory programs have been or are currently being advanced (e.g. Spy7 in the UK, *Lactococcus Lactis*-based intranasal vaccine in Chile, polyethyleneimine liposome-mediated delivery in Australia).

M Protein Vaccines

Vaccine	StreptAnova	StreptInCor	MJ8CombiVax	P*17
Developer	Vaxent Univ. of Tennessee	Univ. of Sao Paulo Butantan Institute	Griffith Univ.	Griffith Univ.
Design	Type-specific 4 proteins comprising N-terminal subunits from M protein of 30 serotypes + alum	Conserved 55 amino acid peptide from M5 protein conserved regions (C2, C3) with T- and B-cell epitopes + alum	Conserved J8 (C-terminal M proteinpeptide) and modified B-cell epitope from SpyCEP; each conjugated to CRM + alum	Conserved P*17 (C-terminal M protpeptide) and modified B-cell epitope from SpyCEP; each conjugated to CRM + CAF01
Stage	Phase 1 P1a completed in 2020 Plans for P2a, P2b pending funding	Late Preclinical P1 trial start delayed; seeking funding support	Late Preclinical P1 dose-ranging study in 2022	Late Preclinical P1 dose-ranging study in 2021; P1b human challenge study in 2022/2023
Data Highlights	**Humans:** Well-tolerated, no auto-immunity/cross-reactive Abs; significant increase in GMT for 24 of 30 M antigens	**Mice:** High levels of Ag-specific Abs and survival **Minipigs:** Well-tolerated and no harmful effects on heart tissue	**Mice:** Protects against hypervirulent mutant Strep A; OPK ability maintained in presence of human plasma	**Mice:** IM+IN immunization induced high Ab levels in airway mucosa/serum and protects vs. upper respiratory tract + invasive disease in mice

Ag, antigen; CAF01, liposomal adjuvant; CRM (CRM197), non-toxic mutant of diphtheria toxin; GMT, geometric mean titers; IM, intramuscular; IN, intranasal; NHP, non-human primate; OPK, opsonophagocytic killing; SLO, streptolysin O; SpyCEP, Interleukin-8 [IL-8] protease.

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Non-M Protein Vaccines

Vaccine	Combo4	VAX-A1	Combo5	TeeVax
Developer	**GSK Vaccines Institute for Global Health**	**Vaxcyte** (formerly Sutrovax)	**Univ. of Queensland**	**Univ. of Aukland**
Design	3 recombinant proteins (SLO, SpyCEP, SpyAD) + Group A Carbohydrate (native) + alum	Group A Carbohydrate (modified) + undisclosed proteins (possibly SLO, SpyAD, C5a peptidase/ SCPA)	5 recombinant proteins (TF, ADI, SLO, SCPA, SpyCEP) + SMQ	Multivalent protein vaccine with T-antigen domains from pilus of majority of strains + alum
Stage	**Preclinical** Currently aligning on full clinical development Plan; in partnership with ASAVI	**Preclinical** Currently aligning on full clinical development plan	**Preclinical** Planning additional NHP studies and use of human challenge model	**Preclinical** Reformulating with alternative adjuvants (e.g. CAF01); assessing mucosal delivery
Data Highlights	**Mice:** Preclinical efficacy in mouse models and OPK assay **NHP:** Immunogenic and safety demonstrated	**Mice:** Protected against challenge (skin infection and systemic); no cross-reactivity to human heart, brain tissue	**NHP:** Reduced severity of pharyngitis **Mice:** Efficacy vs skin infection and protection against invasive Strep A infection	**Mice:** Protective efficacy against invasive disease **NHP:** Initial model used provided inconclusive results

ADI, arginine deiminase; OPK, opsonophagocytic killing; SCPA, Group A Strep C5a peptidase; SLO, streptolysin O; SMQ, squalene-in-water emulsion containing a TLR4 agonist and QS21; SpyAD, Streptococcus pyogenes Adhesion and Division protein; SpyCEP, Interleukin-8 [IL-8] protease; TF, trigger factor.; ASAVI Australian Strep A Vaccine Initaitive

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M Protein Vaccines

30-valent M type specific (+ alum)
Phase 1a completed 2020
Phase 2 planned, pending funding

Conserved region M5 protein (+ alum)
Phase 1/2a planned in 2021 but withdrawn (COVID vaccines)

J8/K4S2 combivax & P*17/K4S2 combivax (+CRM + alum)
Health Canada approval for phase 1 – commencing 2022
Phase 1b CHIM planned for 2023
(Additional studies being done with mucosal approach CAF01)

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Non-M Protein Vaccines

GSK GVGH
3 recombinant proteins plus GAC (+ alum)
Partnership with ASAVI announced
Planned for phase 1 2022/2023

Vaxcyte
Modified GAC plus recombinant proteins
Clinical development plan under preparation

5 recombinant proteins (+ SMQ)
Clinical plan unclear, but ready for clinical studies

THE UNIVERSITY OF AUCKLAND
3 recombinant T antigens (+ alum)
Clinical plan unclear

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Summary

- Current pipeline has the potential to test human proof-of-concept for a variety of concepts and antigen types, but there are only 8 – more are needed

- Initial preclinical efficacy and safety results and, in some cases, human safety and immunogenicity data, are encouraging.

- Many candidates are expected to have universal coverage of Strep A strains, and even those with lower predicted strain coverage may prove to have broader coverage based on cross-bactericidal activity.

- 2 candidates will reach phase 1 clinical trials in 2022/2023, with an additional candidates that may also reach phase 1 in 2023

- At least 2 candidates have CHIM on their development path

- Funding is currently a limiting factor for some of the programs to move ahead with planned clinical development activities—pointing to the need for continued advocacy and awareness-building.

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Acknowledgements

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THANK YOU

SAVAC
Strep A Vaccine Global Consortium

2018 WHO R&D Roadmap and PPC of GAS vaccines

Pierre Gsell

Technical Officer
WHO/IVB/PDR

30 September 2022

GAS Vaccines - WHO resources

2018 – WHA71.14 Resolution on ARF and RHD

"to facilitate timely, affordable and reliable access to […] new medicines and technologies for prevention and control of rheumatic heart disease by supporting research and development"

2018 – WHO GAS Vaccine Development Technology Roadmap

"provide a strategic framework outlining priority activities for vaccine researchers, funders and product developers, to accelerate the pathway to availability of vaccines in specific priority disease areas, addressing globally unmet medical needs."

2018 – WHO GAS Vaccines Preferred Product Characteristics

"describe preferential attributes pertaining to vaccine indications, target populations, use case(s) and immunization strategies, as well as preliminary consideration of data that should be collected for safety, efficacy and policy evaluation."

Any GAS vaccine that becomes licensed and potentially available will undergo evidence-based assessment for policy recommendations by SAGE.

WHO GAS Vaccine R&D Roadmap & PPC

- Developed in 2018

- Consensus-based Expert, Stakeholder and Public consultation process

- Progress in the field will be monitored, and the document will be updated if there are significant changes impacting the vision, strategic goals or priority activities.

WHO/IVB/18.08

Group A *Streptococcus*
Vaccine Development
Technology
ROADMAP

Priority activities for development, testing, licensure and global availability of Group A *Streptococcus* vaccines

2018

World Health Organization

GROUP A
STREPTOCOCCUS
VACCINE
TECHNOLOGY
ROADMAP

WHO Pre
for Gro
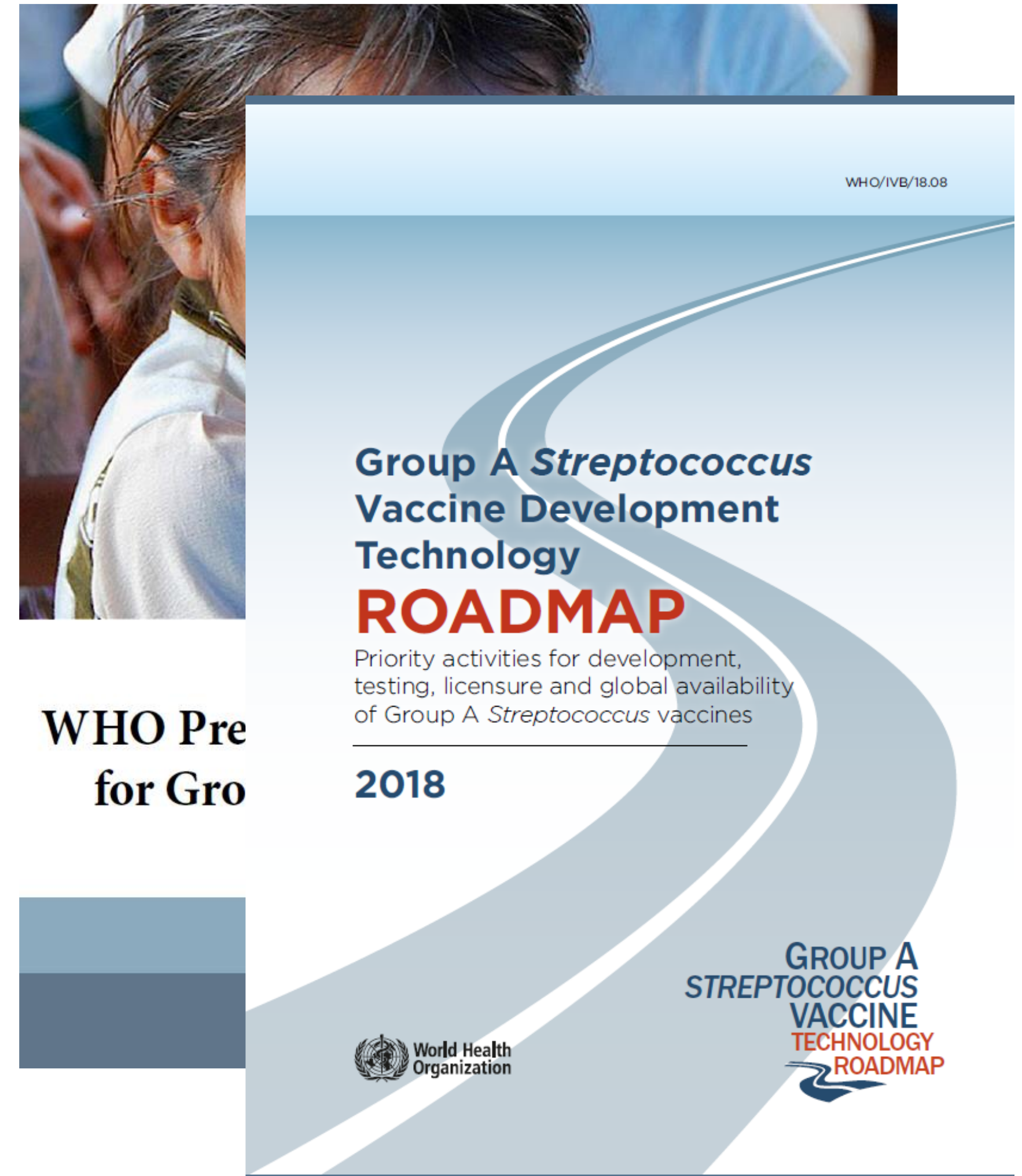
» Vision

A safe, globally effective and affordable GAS vaccine is needed to prevent and potentially eliminate acute GAS infections (pharyngitis, skin infections, cellulitis, invasive disease) and associated antibiotic use, immune-mediated sequelae (kidney disease, rheumatic fever and rheumatic heart disease) and associated mortality.

While the medical need of a GAS vaccine is highest in high endemicity LMIC, the value of a vaccine, primarily for prevention of GAS pharyngitis, skin infections, cellulitis and invasive disease and associated antibiotic use in HIC, is also highlighted.

» Near-term strategic goals

To demonstrate favorable safety and proof of efficacy of a candidate vaccine against GAS pharyngitis and skin infections in children.

» Long-term strategic goal

To develop safe, globally effective and affordable GAS vaccines for prevention of acute infections (pharyngitis, skin infections, cellulitis, invasive disease) and associated antibiotic use, and secondary immune-mediated sequelae (kidney disease, rheumatic fever and rheumatic heart disease) and associated mortality.

WHO/IVB/18.08

Group A *Streptococcus* Vaccine Development Technology

ROADMAP

Priority activities for development, testing, licensure and global availability of Group A *Streptococcus* vaccines

2018

World Health Organization

GROUP A *STREPTOCOCCUS* VACCINE TECHNOLOGY ROADMAP

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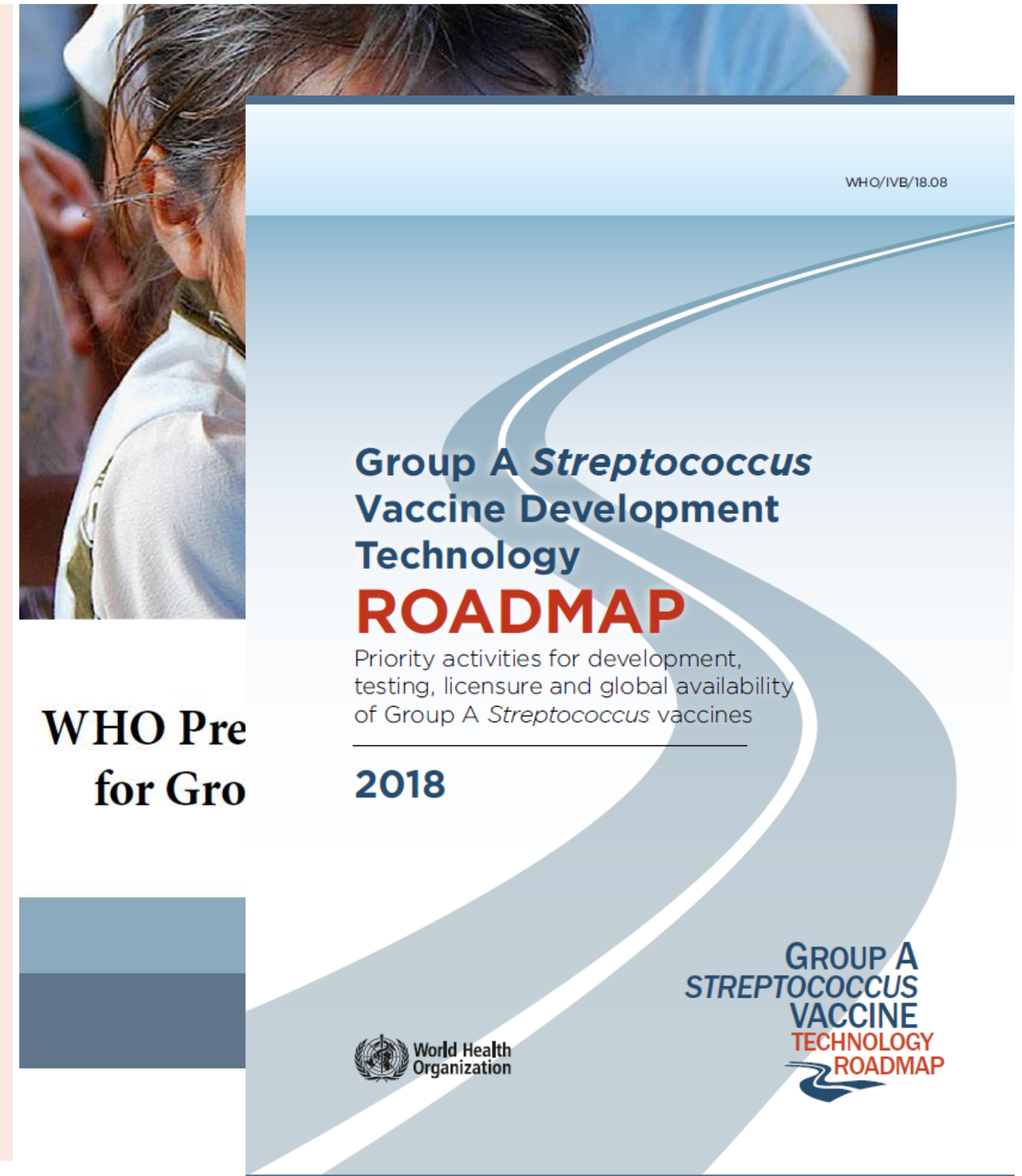
R&D Roadmap - Research Priorities

Improve global estimates of disease burden and better characterize the epidemiology of GAS infection

→ Research is needed to better quantify and characterize the age and geographical distribution of key GAS disease syndromes, and priority should be placed on determining incidence of ARF and onset of new RHD in young people, puerperal and neonatal sepsis, and GAS-attributable mortality. A better understanding of transmission dynamics, the ecological reservoir, genetic diversity and molecular epidemiology is important. Surveillance programs should be developed.

Further describe the spectrum of natural disease history

→ Better estimates of the potential impact of prevention of GAS pharyngitis and skin infection on other severe disease entities would help inform the relative importance of the proposed near-term vaccine development strategic goals. A better quantification of the contribution of GAS infections and PSGN to end-stage kidney disease is needed. The determinants of transmission, including the role of asymptomatic carriage, should be better understood, informing the potential community impact of various vaccine use scenario.

Drive improved understanding of GAS-related secondary immune-mediated diseases

→ A better understanding of the drivers of immune-mediated diseases that occur after natural exposure would help inform vaccine development strategies. The role of repeated infections and the importance of their nature and severity is of particular interest.

Define the consequences of GAS-associated antibiotic use, and estimate the impact of vaccine use on antibiotic use and antimicrobial resistance-related morbidity and mortality

→ Suspected and/or confirmed GAS infections are frequent triggers of antibiotic use, especially in patients presenting with sore throat. Antibiotics are also used for secondary prevention in subjects at risk of complications, in certain cases in household contacts and outbreak management. A GAS vaccine has the potential to reduce overall use of antibiotics, with consequent reductions of selection pressure on pathogenic as well as commensal bacteria. A better characterization of these effects would contribute to more compelling cost-effectiveness and investment case studies. Better estimates of GAS-driven antibiotic use in HIC and LMIC and GAS treatment-related AMR are needed.

R&D Roadmap - Vaccine Development priorities

Pursue antigen discovery efforts, increasing the number of pipeline vaccine candidates.

➡️ Antigen selection and formulation efforts should aim at addressing global GAS antigenic diversity while minimizing product complexity.

Characterize immunological surrogates/correlates of protection

➡️ Collaborative efforts towards the generation of relevant non-clinical assays, using open source reference reagents with international standards of quality may greatly contribute to comparability assessments, generation of a regulatory acceptable correlate of protection, ultimately supporting immune bridging steps, clinical development plan simplification and accelerating the pathway to licensure. Whether cross-strain/serotype immunity can be generated is an important question. The role of reference laboratories is acknowledged.

Develop consensus guidance about the appropriate use of safety monitoring tools in candidate vaccine trials

➡️ The due contribution of the analysis of sequence homology between streptococcal and human antigens, of human tissue and antigen immune reactivity and echocardiography to the assessment of candidate vaccines safety should be defined. A comprehensive review of evidence about past safety data from vaccine studies to inform safety monitoring strategies would be valuable.

Define appropriate pivotal clinical trial design adapted to near-term and long-term strategic goals

➡️ Primary and secondary efficacy endpoint case definitions, adverse events of special interest (AESI) should be defined; standard data collection plans should be developed to support case ascertainment; appropriate trial standards of care should be defined, considering local and WHO recommendations; appropriate trial data dissemination should be ensured.

R&D Roadmap – Key capacities

- Define appropriate use of available and future **animal models** for GAS vaccine safety and efficacy evaluation according to their relevance for human responses

- Develop clinically relevant **human GAS experimental infection model**(s) to support early vaccine proof of concept evaluation

- Establish GAS expert research centres in low- and middle-income countries with Good Clinical Practices (GCP) **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 (cGMP) for late stage development and commercial production

- Develop standardized **immune assay platforms** that meet quality requirements

WHO GAS Vaccine PPC

Parameter	Preferred Characteristic
Indication	Prevention of GAS-related pharyngitis, superficial skin infections, cellulitis, toxin-mediated disease, invasive infections and associated antibiotic use, secondary rheumatic fever, rheumatic heart disease and post-streptococcal glomerulonephritis.
Target population for primary immunization	Primary schedule: infants and/or young children.
Efficacy targets	Preferences for target efficacy differ according to the severity of the target disease syndrome - 80% protection against nonsevere, non-invasive, confirmed GAS disease - 70% protection against confirmed GAS cellulitis and other invasive infections - 50% protection against long-term immune-mediated sequelae
Strain and serotype coverage	Efficacy targets are set irrespectively 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 favourable as current WHO-recommended routine vaccines. The appropriate use of additional safety monitoring tools including human antigen immune reactivity testing and echocardiography should be pre-defined, considering the risk of unspecific, coincidental findings, especially if multiple comparisons are planned.
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 LMIC.
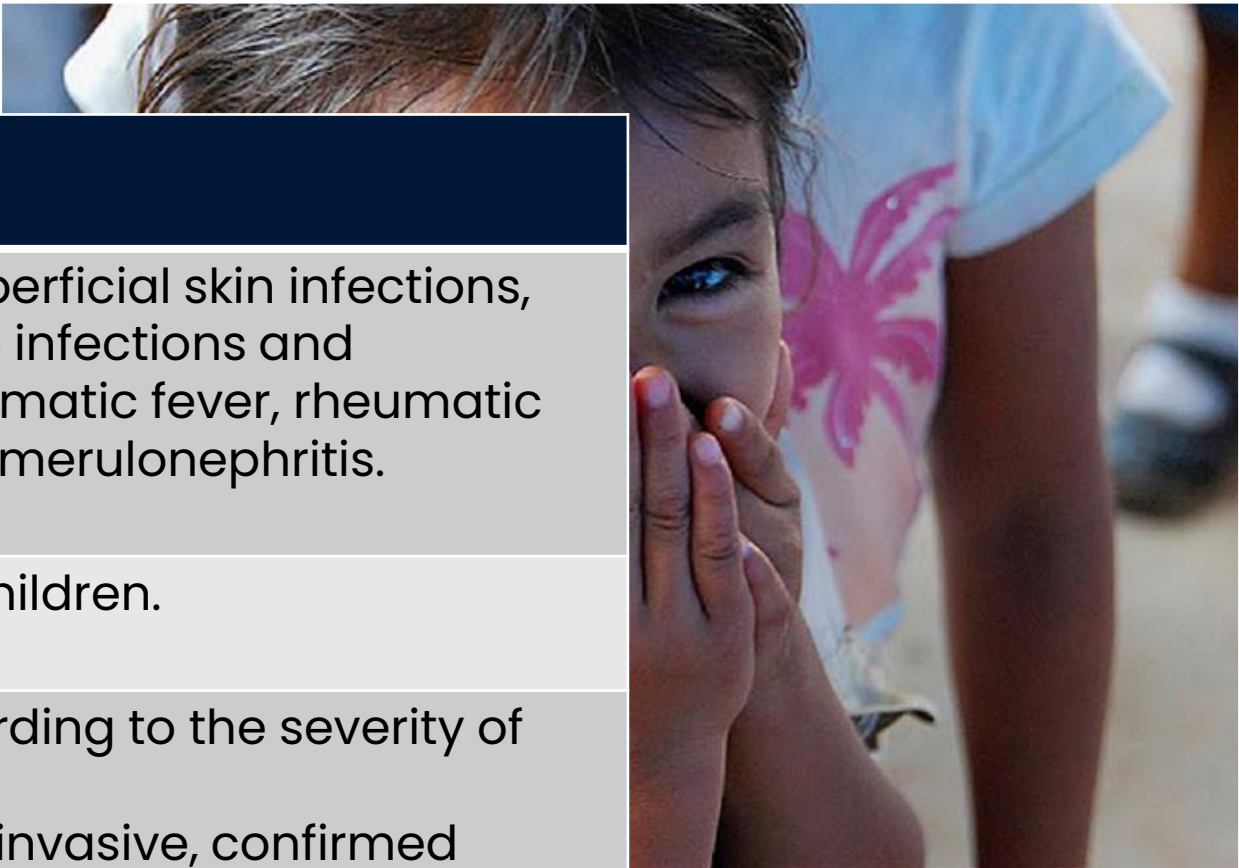
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tococcus Vaccines

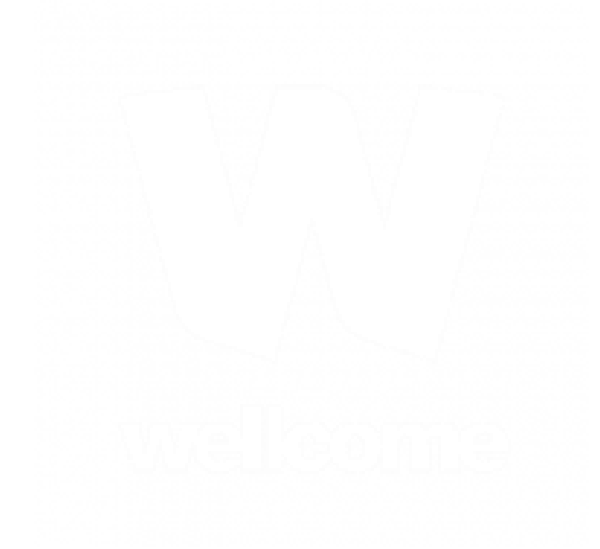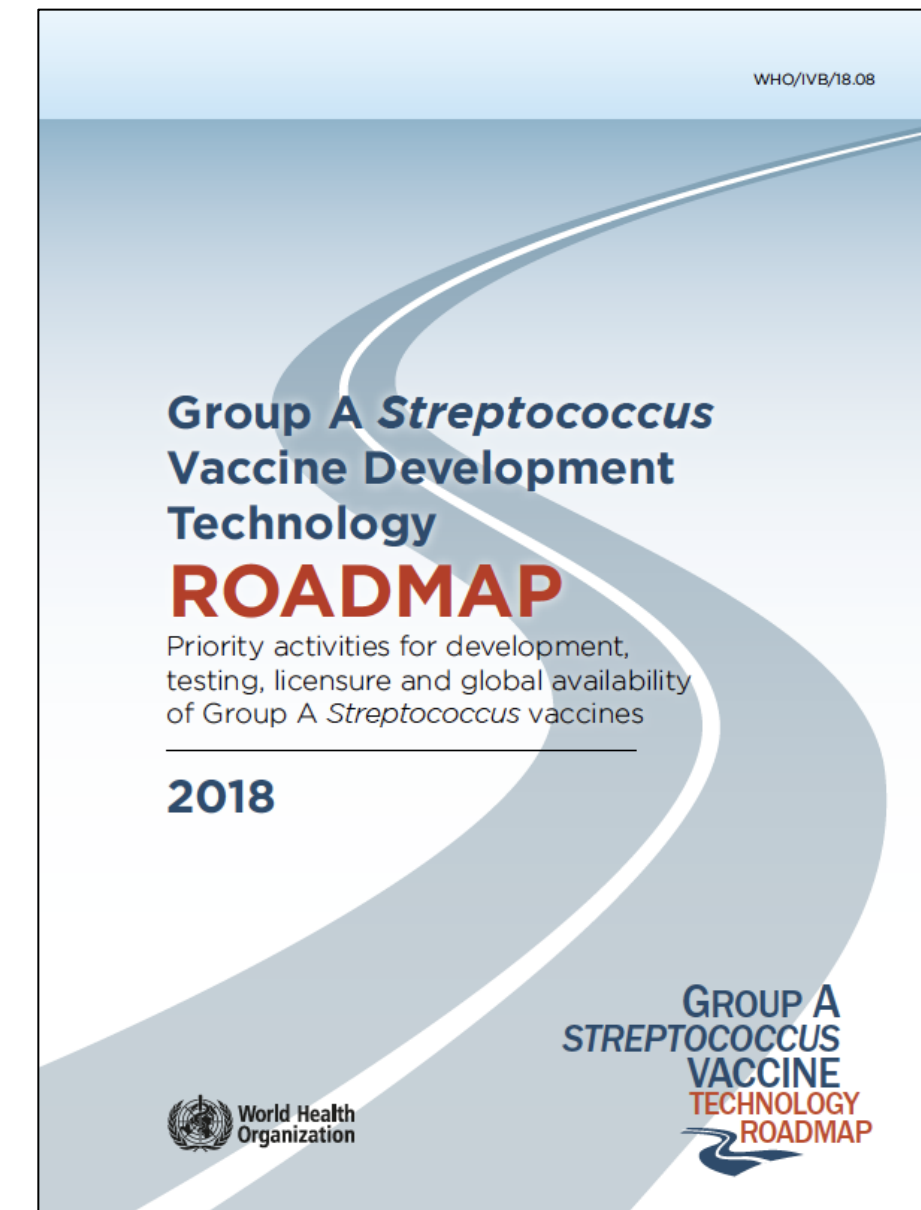# Thank you

Implementing roadmap priorities and progress

My job today

Map progress against the <u>16 priority activities</u>

for testing, licensure and global availability of Strep A vaccines

-Identify successes

-Highlight gaps

JC: Key <u>additional</u> gaps for the roadmap <u>and PPC</u>

JK: <u>Recommendations</u> on elements to be <u>revisited</u> in the roadmap and PPC
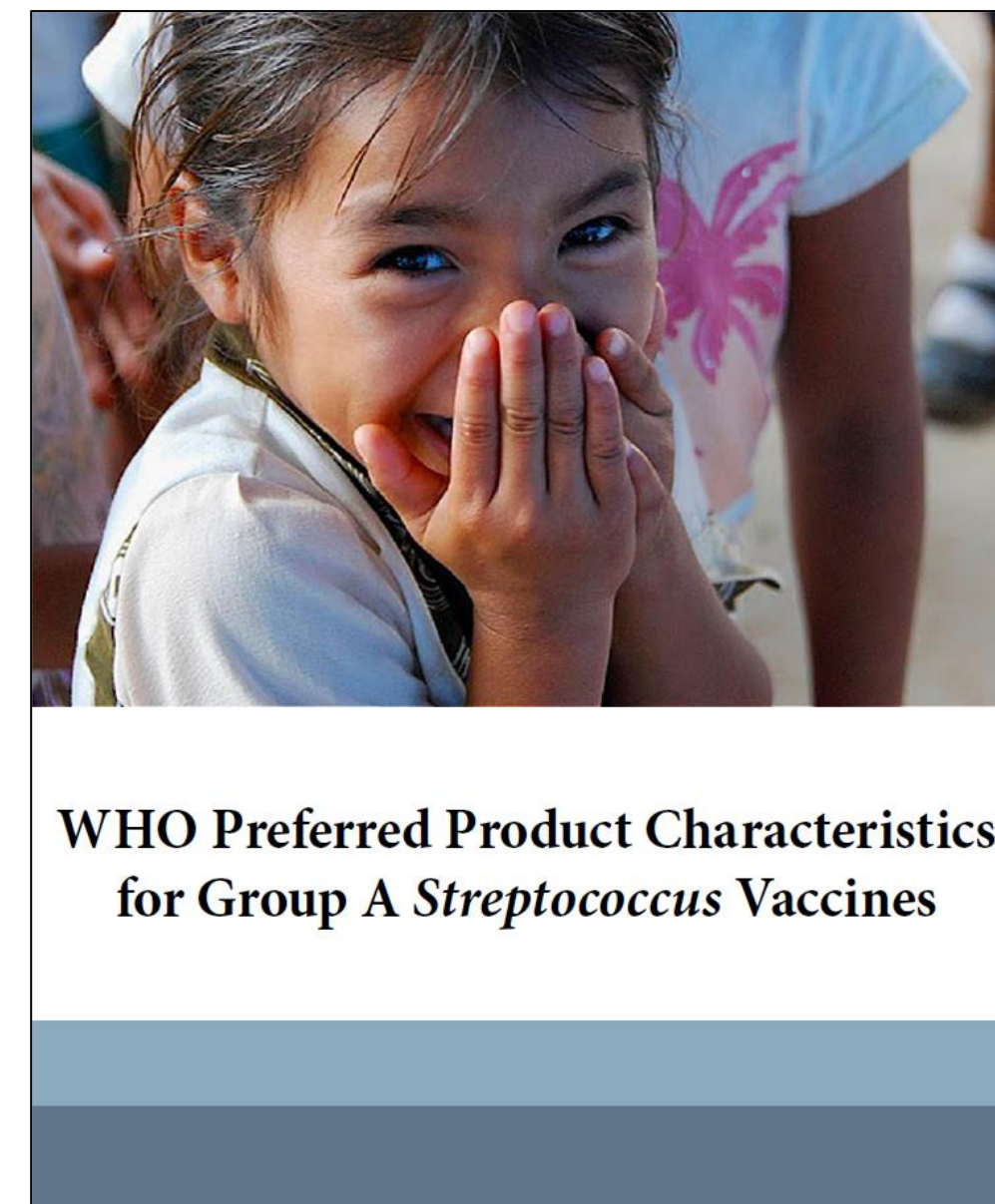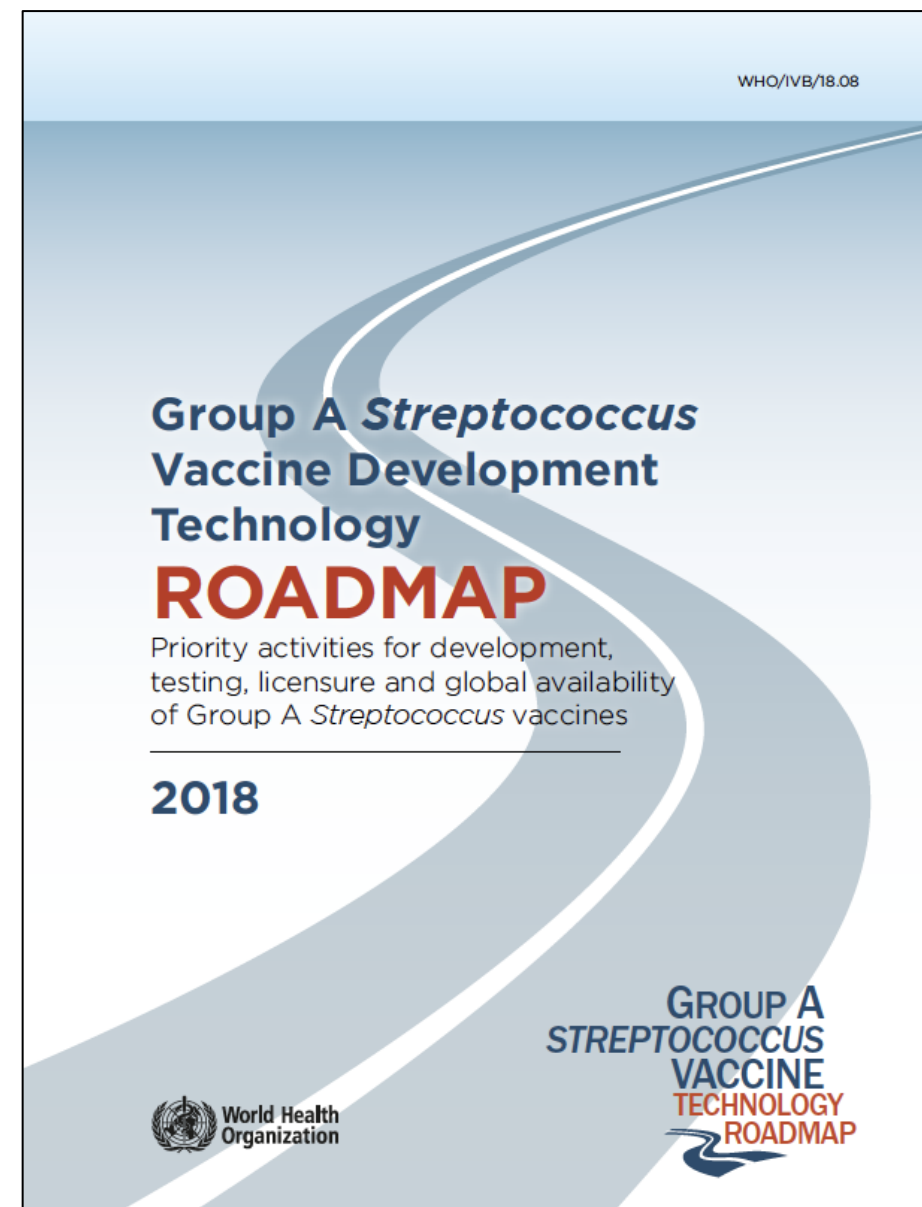
The 16 priority activities

	Key Strategic Areas	Proposed Priority Activities
1	Research	Improve global estimates of disease burden and better characterize the epidemiology of GAS infections
		Further describe the spectrum of natural disease history
	4	Drive improved understanding of GAS-related secondary immune-mediated diseases
		Define the consequences of GAS-associated antibiotic use, and estimate the impact of vaccine use on antibiotic use and antimicrobial resistance–related morbidity and mortality
2	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
	4	Characterize immunological surrogates/correlates of protection
		Define appropriate pivotal clinical trial design adapted to near-term and long-term strategic goals
3	Key capacities	Define appropriate use of available and future animal models for GAS vaccine safety and efficacy evaluation according to their relevance for human responses
		Develop clinically relevant human GAS experimental infection model(s) to support early vaccine proof-of-concept evaluation
	5	Establish GAS 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
4	Policy, commercialization, and delivery 3	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

1. Research

a. Improve global estimates of disease burden and better characterize epidemiology of Strep A infections

b. Further describe the spectrum of natural disease history

c. Drive improved understanding of Strep A related secondary immune-mediated disease

d. Define the consequences of Strep A associated antibiotic use and AMR related morbidity and mortality

SAVAC

1. Research

a. Improve global estimates of disease burden and better characterize epidemiology of Strep A infections
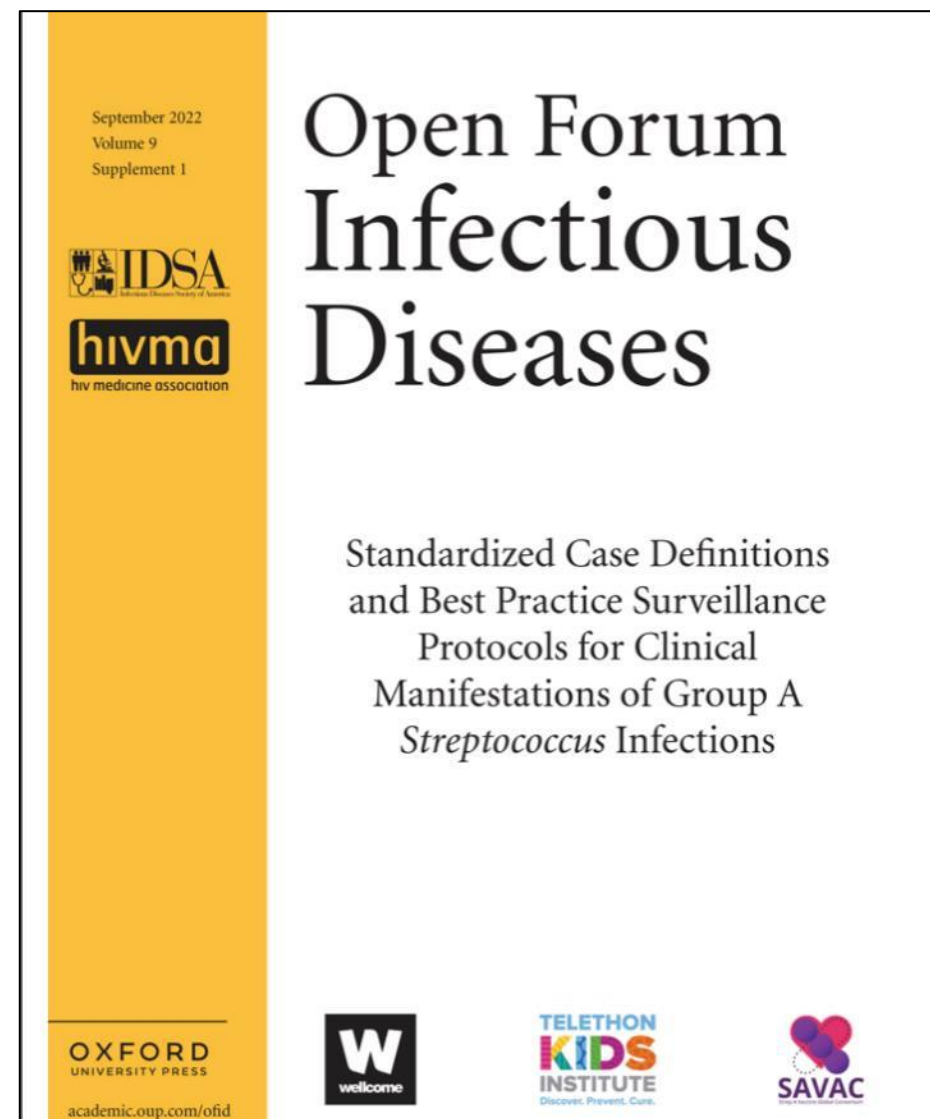
Invasive group A streptococcal disease in pregnant women and young children: a systematic review and meta-analysis

Emma Sherwood, Stefania Vergnano, Isona Kakuchi, Michael G Bruce, Suman Chaurasia, Samara David, Angela Dramowski, Scarlett Georges, Rebecca Guy, Theresa Lamagni, Daniel Levy-Bruhl, Outi Lyytikäinen, Monika Naus, Jennifer Onukwube Okaro, Oddvar Oppegaard, Didrik F Vestrheim, Tammy Zulz, Andrew C Steer, Chris A Van Beneden, Anna C Seale

Lancet Infectious Diseases 2022

Substantial burden, but data lacking from LMICs

1. Research

b. Further describe the spectrum of natural disease history

c. Drive improved understanding of Strep A related secondary immune-mediated disease
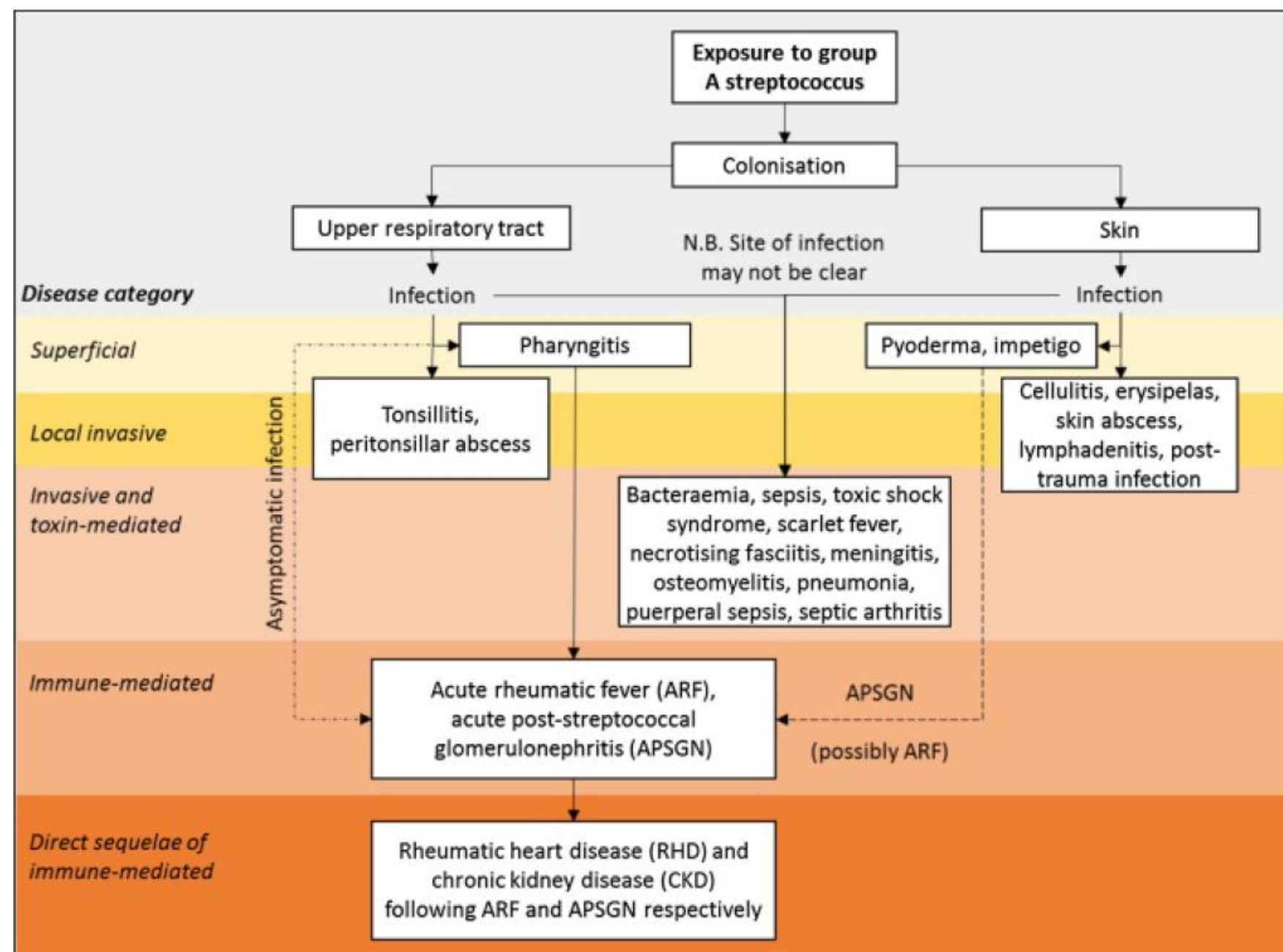
ARF pathogenesis & biomarkers

Strep A immunity & immune correlates

1. Research

d. Define the consequences of Strep A associated antibiotic use and AMR related morbidity and mortality

FVVA*

Adults

Poland
Israel
Japan
Italy
UK
USA

Children

Serbia
Japan
Lithuania
Israel
Italy
USA
Canada
Taiwan
Zambia
UK
Netherlands

Prescriptions per 100 population per year

Sore throat*   Strep throat and/or tonsillitis

SAVAC
Strep A Vaccine Global Consortium
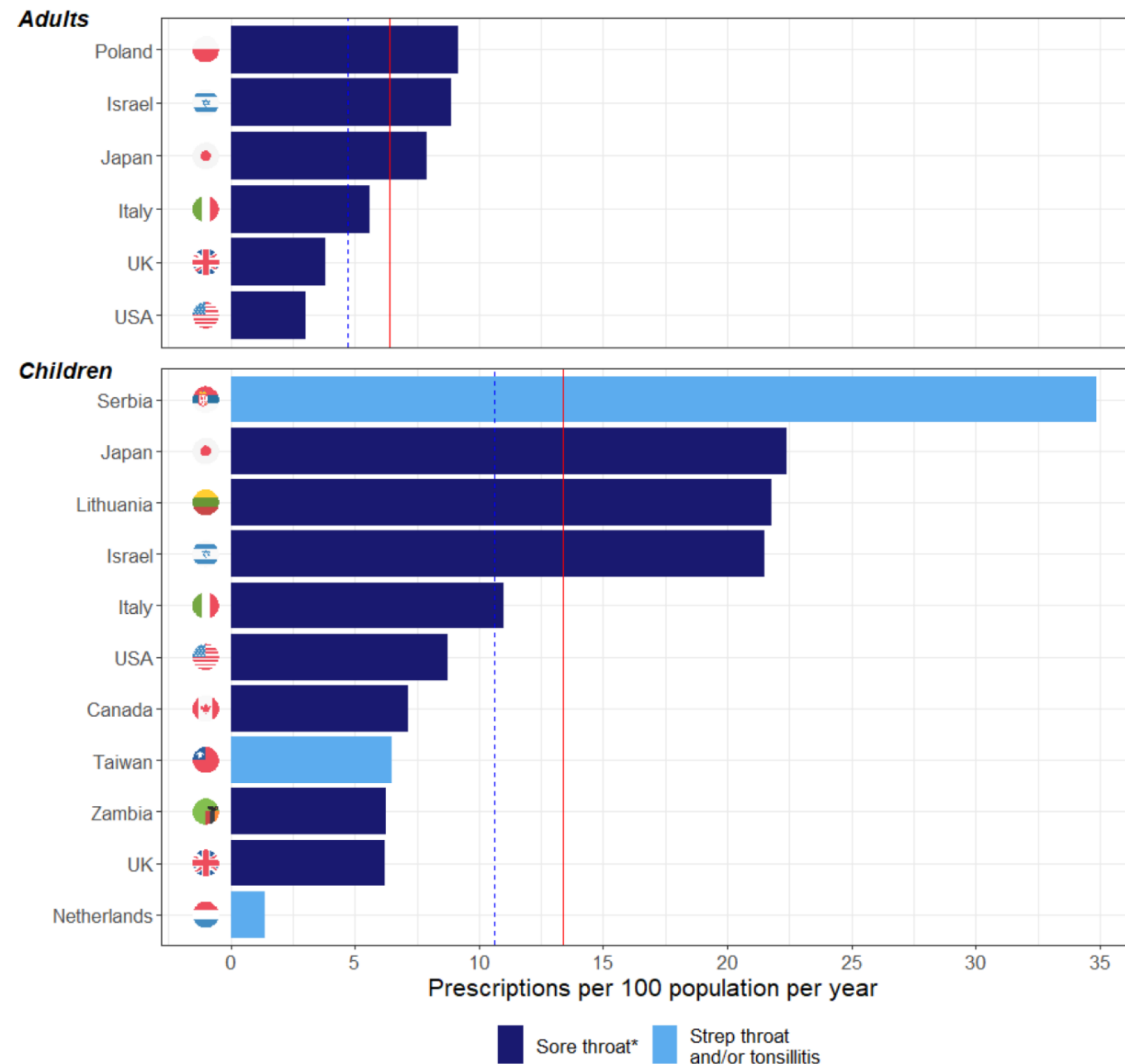
2. Vaccine development

a. Pursue antigen discovery efforts, increasing the number of pipeline vaccine candidates

b. Develop consensus guidelines about the appropriate use of safety monitoring tools in candidate vaccine trials

c. Characterise immunological surrogates/correlates of protection

d. Define appropriate pivotal clinical trial design adapted to near-term and long-term strategic goals

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2. Vaccine development

a. Pursue antigen discovery efforts, increasing the number of pipeline vaccine candidates

Some progress
But more needs to be done
NIH funding

b. Develop consensus guidelines about the appropriate use of safety monitoring tools in candidate vaccine trials

→ Overall guidance

→ Echocardiography working group

→ Screening assays for cross-reactivity

2. Vaccine development

c. Characterise immunological surrogates/correlates of protection

Correlates of immunity to Group A Streptococcus – a pathway to vaccine development

Hannah Frost[1], Jean-Louis Excler[2], Shiranee Sriskandan[3,4]*, Alma Fulurija[5, 6]*

Tiered strategic approach to immunoassay development

ARF pathogenesis & biomarkers
Strep A immunity & immune correlates

Strep A immunity & vaccine candidates

2. Vaccine development

Define appropriate pivotal clinical trial design adapted to near-term and long-term strategic goals

Clinical development strategy for a candidate group A streptococcal vaccine

Florian Schödel [a], Nicole J. Moreland [b], Janet T. Wittes [c], Kim Mulholland [d,e], Ian Frazer [f], Andrew C. Steer [d], John D. Fraser [b], Jonathan Carapetis [g,*]

Vaccine 35 (2017)

IPDP

3. Key capacities

a. Define appropriate use of available and future animal models for Strep A vaccine safety and efficacy evaluation according to their relevance for human response

b. Develop clinically relevant human Strep A experimental models to support early vaccine POC evaluation

c. Establish Strep A expert research centres in LMICs with GCP trial research capacity and appropriate regulatory and ethical oversight; establish baseline rates of efficacy and safety outcomes

d. Access low-cost manufacturing under GMP for late-stage development and commercial production

e. Develop standardised immunoassay platforms that meet quality requirements

3. 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 response

b. Develop clinically relevant human Strep A experimental models to support early vaccine POC evaluation

A controlled human infection model of *Streptococcus pyogenes* pharyngitis (CHIVAS-M75): an observational, dose-finding study

Lancet Microbe 2021

Joshua Osowicki, Kristy I Azzopardi, Loraine Fabri, Hannah R Frost, Tania Rivera-Hernandez, Melanie R Neeland, Alana L Whitcombe, Anneke Grobler, Sarah J Gutman, Ciara Baker, Janet M F Wong, Jason D Lickliter, Claire S Waddington, Manisha Pandey, Tibor Schuster, Allen C Cheng, Andrew J Pollard, James S McCarthy, Michael F Good, James B Dale, Michael Batzloff, Nicole J Moreland, Mark J Walker, Jonathan R Carapetis, Pierre R Smeesters, Andrew C Steer
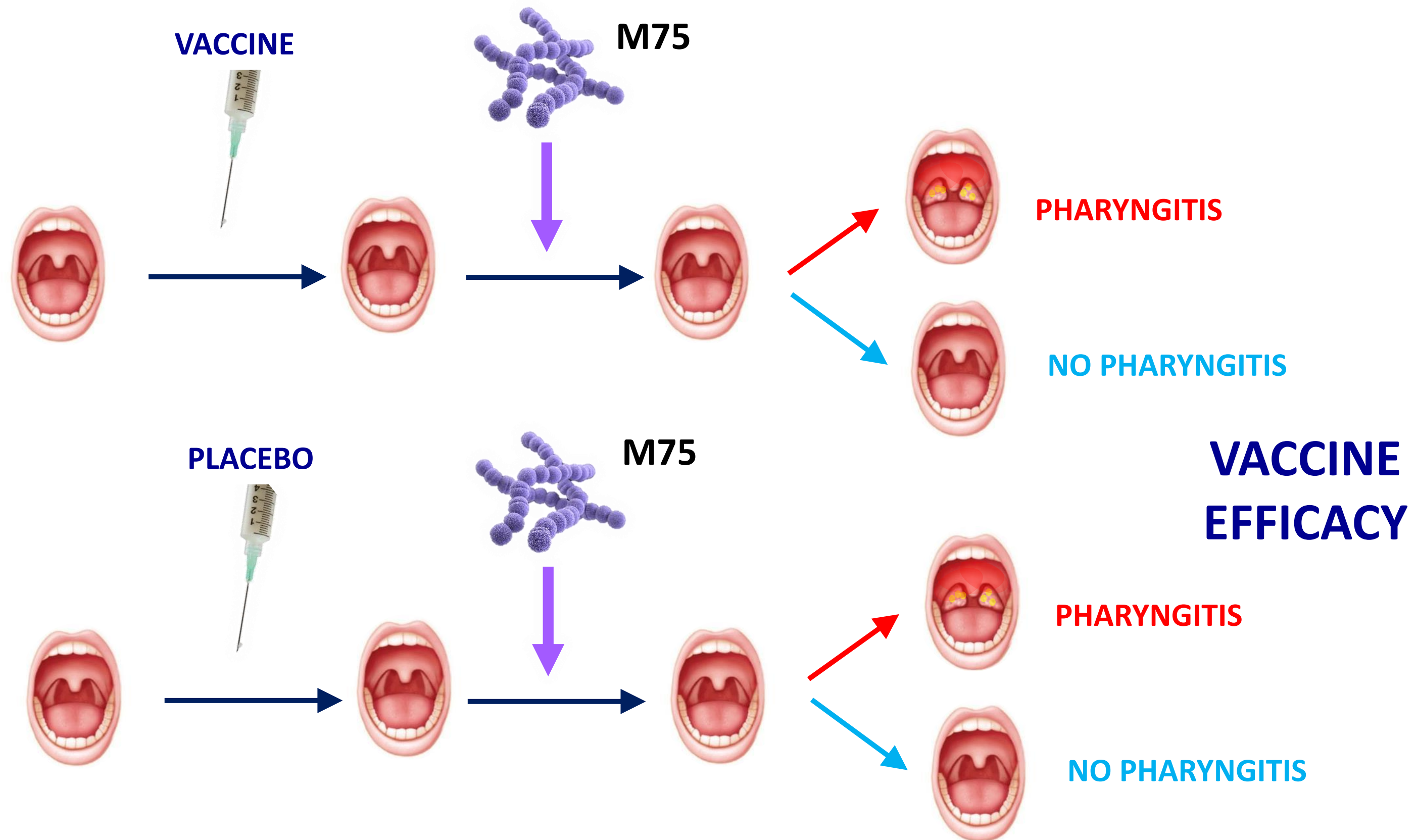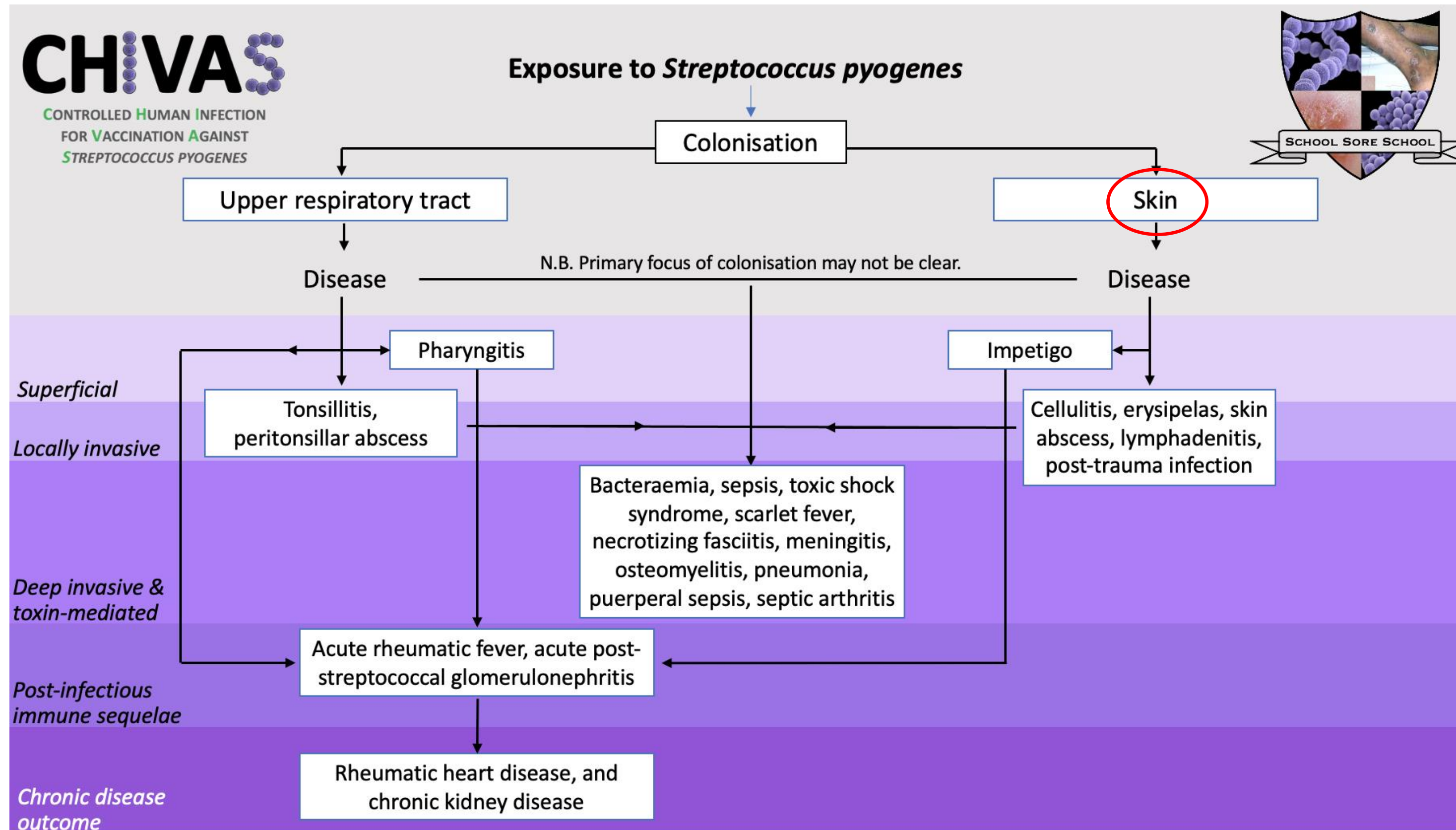
c. Establish Strep A expert research centres in LMICs with GCP trial research capacity and appropriate regulatory and ethical oversight; establish baseline rates of efficacy and safety outcomes

The Gambia

Uganda

Fiji

South Africa

SAVAC
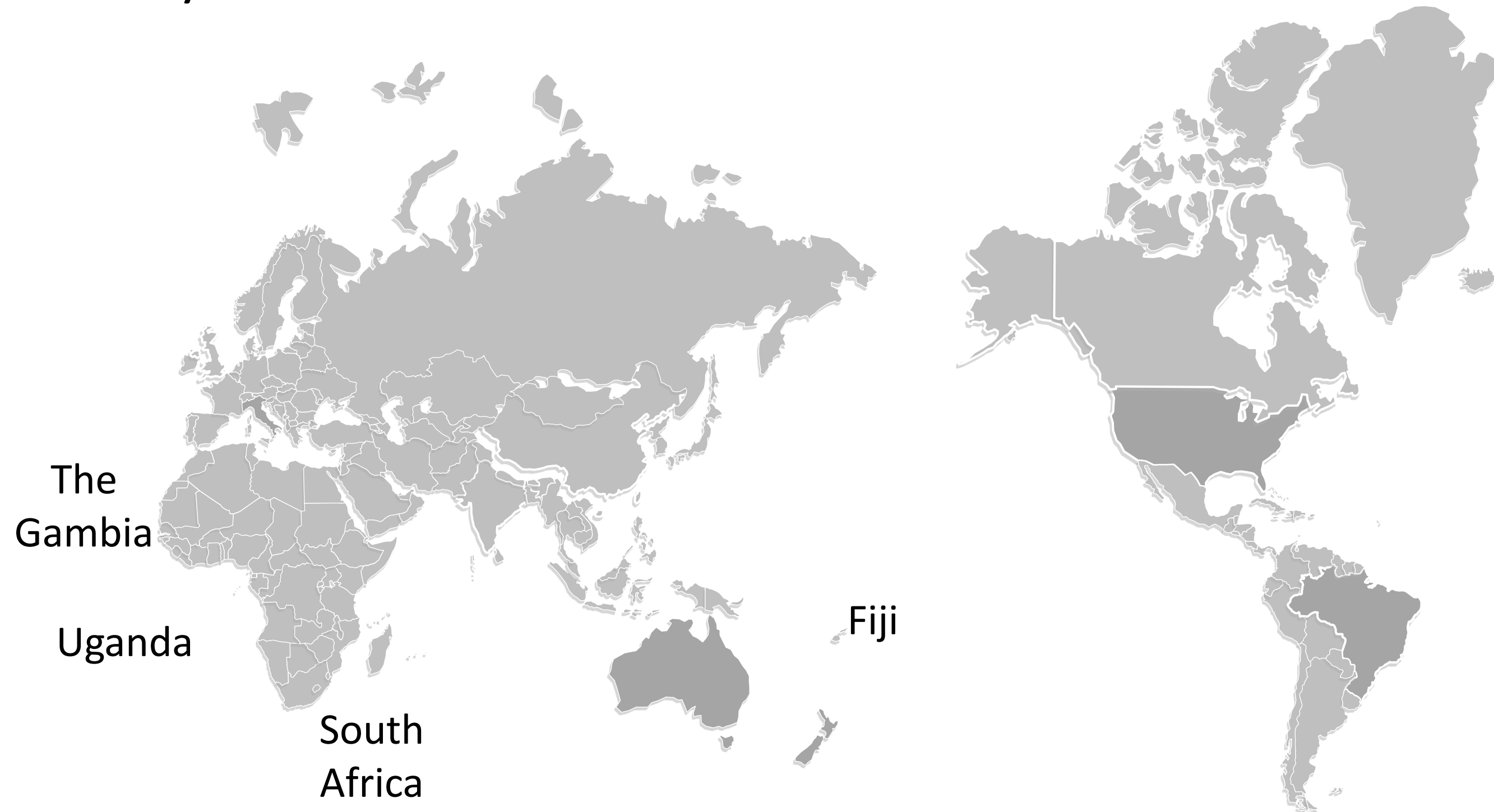
3. Key capacities

d. Access low-cost manufacturing under GMP for late-stage development and commercial production

Not really on the discussion list yet

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3. Key capacities

Develop standardised immunoassay platforms that meet quality requirements

Figure 1. Schematic of 10 plex MSD Serology Assay
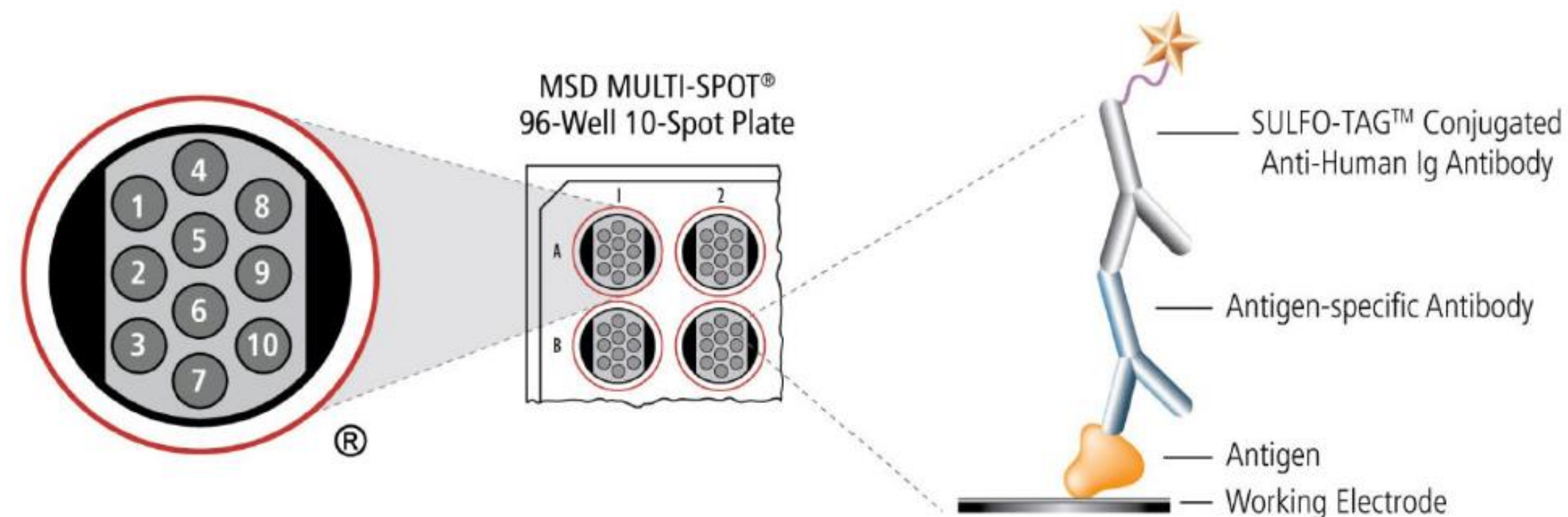
4. Policy, commercialization & delivery

a. Establish cost-effectiveness and develop research and implementation financial investment scenarios to support appropriate funding and policy decision-making at the global and national levels, considering the full scope of costs and benefits

b. Ensure availability, affordability and acceptability of a functional, cost-effective delivery platform for immunization

c. Develop effectiveness and safety vigilance platforms for post-implementation surveillance

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4. Policy, commercialization & delivery

Establish cost-effectiveness and develop research and implementation financial investment scenarios to support appropriate funding and policy decision-making at the global and national levels, considering the full scope of costs and benefits

FVVA*

4. Policy, commercialization & delivery

b. Ensure availability, affordability and acceptability of a functional, cost-effective delivery platform for immunization

Not really on the discussion list yet

c. Develop effectiveness and safety vigilance platforms for post-implementation surveillance

Not really on the discussion list yet

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Summary: successes

Green lights:

-Human challenge

-FVVA

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Amber lights:

-BOD Matrix and BOD surveillance definitions

-Antibiotic use ~ AMR

-Antigen discovery

-Safety guidance

-Correlates of protection

-Trial design

-Research centres in LMICs

-Standardised immunoassays

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Summary: gaps

Red lights:

-Natural history and immune-mediated sequelae

-Optimum use of animal models

-Low-cost manufacturing

-Delivery platforms for immunization

-Safety vigilance platforms

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Conclusions

- The WHO Roadmap has been critical to renewed efforts and increasing momentum in Strep A vaccine development

- The WHO Roadmap has provided consensus goalposts for existing players in the field, and has also provided guidance for new players

- The field has achieved some successes, and is poised for a number of successes in the next couple of years, following Roadmap guidance

- SAVAC has used the existing Roadmap as a template for activities, and SAVAC 2.0 is responding to activity gaps

- The Roadmap was developed in 2018, and is in need of revision

- A revised Roadmap will be critical for future success for a vaccine to meet the unmet need in LMICs, and will be important to guide funders also

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Acknowledgements

- **SAVAC EC, Wellcome Trust**

- **Sushena Krishnaswamy, Michelle Giles (Monash University)**

- **SAVAC EC:**

Name	Affiliation
Jerome Kim	International Vaccine Institute (Co-Chair)
Andrew Steer	Murdoch Children's Research Institute (Co-Chair)
Jonathan Carapetis	Telethon Kids Institute
David Bloom	Harvard School of Public Health
David Kaslow	PATH
Shiranee Sriskandan	Imperial College London
Liesl Zuhlke	University of Cape Town
Edwin Asturias	University of Colorado

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THANK YOU

How can we bring about dramatic acceleration of development and availability of Strep A vaccines, and can the Roadmap and PPC be catalytic to achieving this?

i.e. improvements could be considered in two categories:

1. Incremental

- "Tweaking" to deal with gaps, and new developments

2. Transformational

- Dealing with the major impediments that still remain, and galvanizing the field.

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Gaps

- **Some progress made on most items, but only incremental**

- **Incremental Gaps:**
  - PPC Efficacy targets:
    - Define targets better (e.g. pharyngitis – what is endpoint?)
    - Are efficacy targets appropriate and achievable? e.g.:
      - Pharyngitis
        - Culture pos? Serologically proven? Only symptomatic?
        - Is 80% too high – excluding carriage? Can we prevent 80% of a mucosal infection?
      - No target listed for ARF
      - Have cost benefit analyses been done against any of the endpoints with different efficacy requirements?
        - Have we set the bar too high?
        - We need modelling on minimal criteria for cost-effective vaccine in different settings against different endpoints.
        - For example, the CANVAS Australian estimates:

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An economic case for a vaccine to prevent group A streptococcus skin infections

Jeffrey W. Cannon [a], Susan Jack [b], Yue Wu [a], Jane Zhang [c], Michael G. Baker [c], Elizabeth Geelhoed [d], John Fraser [e], Jonathan R. Carapetis [f,*]
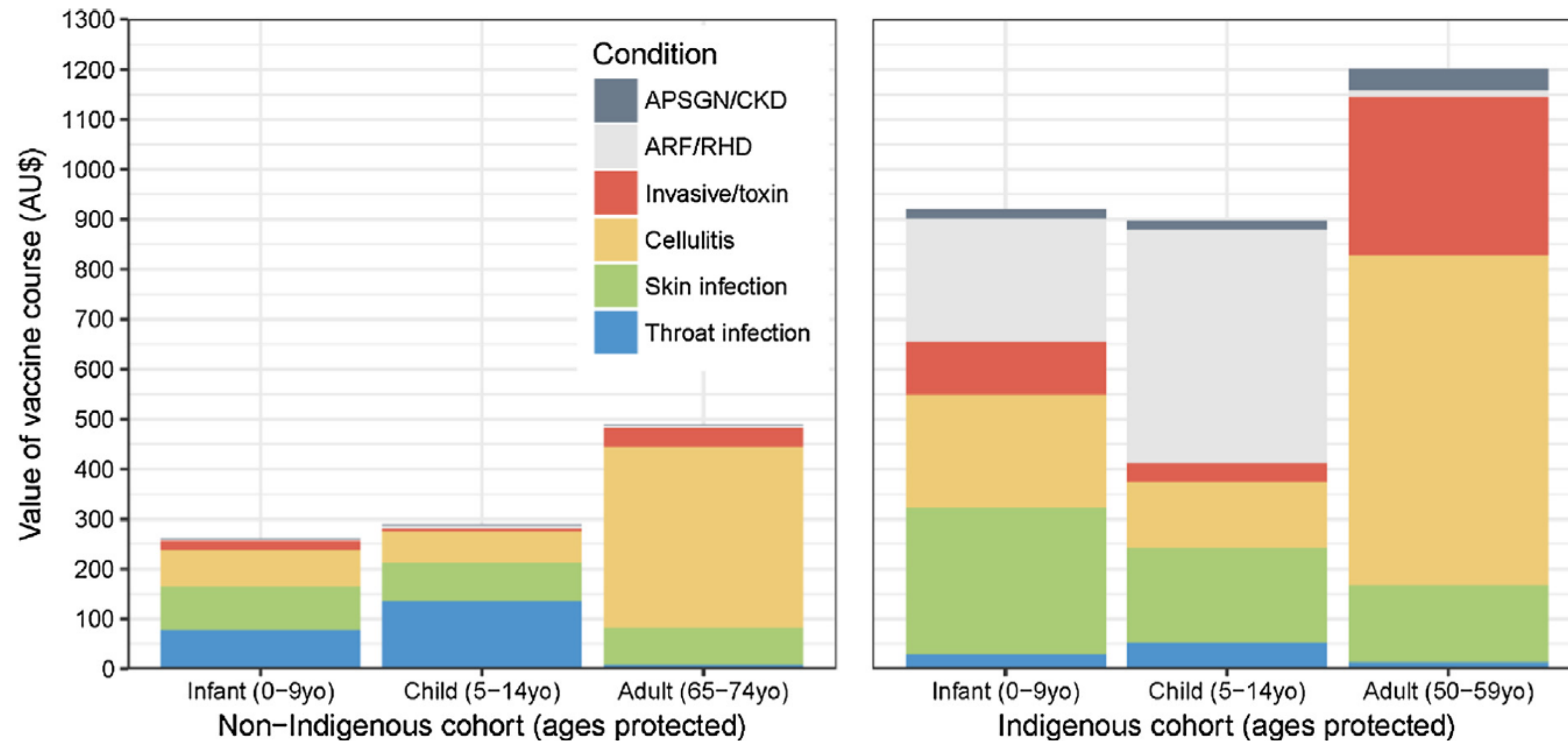
Fig. 3. Estimated value of a vaccine course that prevents 70% of GAS disease for a duration of 10 years.

Table 2.2. *Estimated value of a vaccine with 100% effectiveness over the ages protected (shown in parenthesis) for each strategy.*

Vaccine value in $AU, Non-Indigenous Australian			
Category\Strategy	Infants (0-9y)	Children (5-14y)	Adults (65-74y)	Infants & Adults
Throat	113	194	12	63
Skin	124	109	103	113
Cellulitis	112	96	539	325
Invasive	27	10	59	43
APSGN	1	1	3	2
ARF and RHD	5	10	6	5
Total	382	421	721	552
Vaccine price in $AU, Indigenous Australian			
Category\Strategy	Infants (0-9)	Children (5-14)	Adults (55-64)	Infants & Adults
Throat	42	75	22	32
Skin	420	274	245	333
Cellulitis	418	246	1242	830
Invasive	159	59	495	327
APSGN	32	32	50	41
ARF and RHD	381	735	27	204
Total	1452	1421	2081	1767

Supplementary Report, June 2016

Other incremental gaps

- **Pipeline vaccine candidates**
  - mRNA
  - Mucosal delivery

- **Clinical development pathway**
  - Greater clarity, particularly accelerated pathway from low-risk ARF populations → high-risk ARF populations
  - How to evaluate ARF/RHD as endpoints?

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But what would be transformational?

- **What can we learn from others? E.g. Malaria, GBS?**
- **Gaining attention:**
  - Advocacy and awareness? How do we make people care?
  - Lack of engagement: Industry, Consumers, Countries, Regulators
  - Funders group? (like malaria) Regulatory Advisory Group?
- **Being more strategic/identifying priorities:**
  - Disease burden/epidemiology → "Unmet Need and Potential Impact of Vaccine" (aka GBS)
    - Burden of Disease group:
      - Prioritisation of projects using a "Data Purpose Matrix"
      - Standardising tools - Surveillance protocols
    - Importance of regional and country level estimates, and tools for rapid assessment
  - What are the major gaps that are likely to accelerate the field, and what is not so important?
    - E.g. natural history – how important?
    - Drivers of immune mediated diseases – how important?
    - Potential AMR impact – how important?
  - i.e. do we have too many priorities and should we narrow down to the most important?

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How to deal with the breadth?

- **Strep A:**
  - Lots and lots of endpoints
  - Different burdens in different settings
    - HICs: Pharyngitis, invasive disease, scarlet fever, AMR
    - LICs: Impetigo, ARF, RHD, APSGN, Chronic renal failure, AMR, invasive disease
    - MICs: All of above
  - Commercial v public health vaccine
    - ? De-risk early stage development to make more attractive for industry
    - ? Financing (e.g. Advanced Market Commitments?)

- **Should we consider:**
  - Most rapid pathway to getting a vaccine proven efficacious, safe and effective in practice
    - Australia, NZ, Pacific?
      - This was the motivation for ASAVI
      - Would also be most effective way to test effectiveness for ARF prevention
    - As opposed to a focus on vaccine for the world (Africa) from the start?
  - ? Two roadmaps, and two PPCs:
    - One for HIC/UMICs
    - Another for LICs/LMICs

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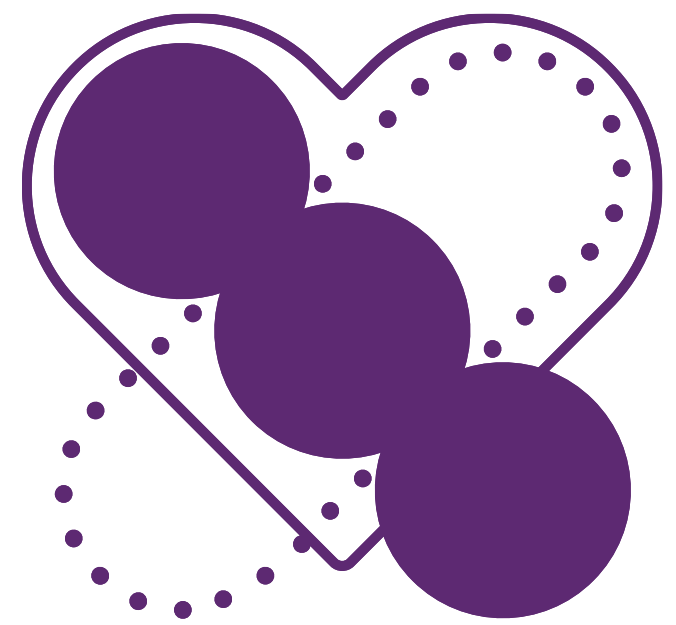
GAS: Preferred Product Characteristics

	CURRENT	COMMENT
INDICATION	Prevention of GAS-related pharyngitis, superficial skin infections, cellulitis, toxin-mediated disease, invasive infections and associated antibiotic use, secondary rheumatic fever, rheumatic heart disease and post-streptococcal glomerulonephritis	• Prioritize for development • HIC vs LMIC indication?
TARGET POPULATION	Primary schedule: infants and/or young children.	• Dislink between HIC and LMIC? • Add in need for booster • Feasibility of school age vaccination vs booster • Other target populations by priority
IMMUNOGENICITY	Established surrogate or correlate of protection based on validated assay	• At least 90% seroconversion in a standardized (qualified, validated) humoral biomarker for GAS infection, immunity • "Establish" a correlate/surrogate
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 LMIC.	• Add in AMR

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GAS Vaccine Technology Roadmap

Key Strategic Areas	Proposed Priority Activities
Research	Improve global estimates of disease burden and better characterize the epidemiology of GAS infections
	Further describe the spectrum of natural disease history
	Drive improved understanding of GAS-related secondary immune-mediated diseases
	Define the consequences of GAS-associated antibiotic use, and estimate the impact of vaccine use on antibiotic use and antimicrobial resistance–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 GAS vaccine safety and efficacy evaluation according to their relevance for human responses
	Develop clinically relevant human GAS experimental infection model(s) to support early vaccine proof-of-concept evaluation
	Establish GAS 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

Abbreviations: GAS, group A *Streptococcus*; LMICs, low- and middle-income countries.

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Research	Improve global estimates of disease burden and better characterize the epidemiology of GAS infections
	Further describe the spectrum of natural disease history
	Drive improved understanding of GAS-related secondary immune-mediated diseases
	Define the consequences of GAS-associated antibiotic use, and estimate the impact of vaccine use on antibiotic use and antimicrobial resistance–related morbidity and mortality

- **Preparation for efficacy trials and effectiveness**
  - Surrogate for ARF/RHD
    - Ethics of untreated prrogression
    - Non-invasive
    - Biomarkers?
  - Understanding colonization, disease transitions, and longer-term outcomes
  - Prioritization of a correlates of protection, progression from natural history studies (also informs Vaccine Dev)
  - Metrics for AMU/AMR

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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

- **Increase candidates in _human_ clinical trials**
- **Collect appropriate samples for correlates analyses**
- **Role of effectiveness studies?**
- **Planning around regulatory strategies for DCVMs and MNC in HIC/LMIC dual market models**
- **Definition / consensus around post efficacy pathway to supply, procurement, implementation (including SAGE, Gavi, R/NITAG) – ie a pathway to policy and implementation**

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Key capacities	Define appropriate use of available and future animal models for GAS vaccine safety and efficacy evaluation according to their relevance for human responses
	Develop clinically relevant human GAS experimental infection model(s) to support early vaccine proof-of-concept evaluation
	Establish GAS 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

- **Prepare for validation and/or recalibration of animal and human experimental challenge systems against human efficacy data**
- **Accommodate dual path vaccine (HIC/LMIC) while ensuring early access to GAS vaccines in early adopter LMIC**
  - Access agreements?
  - Cost effectiveness
  - Preparation of NRAs
  - Safety / pharmacovigilance

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SAVAC (1) primary learnings:

- **The paucity of epidemiologic and economic data from low and middle income countries**
- **Gaps in our understanding of relevant measures of protection against Strep A infection and disease**
- **Favourable cost effectiveness and return on investment of a Strep A vaccine**
- **Challenges, need for standardisation, and parameters of interest for safety surveillance**

Additional accomplishments:

- Advocacy
- Funders
- Neutral convening
- Support for Technical Roadmap and TPP

SAVAC 2.0

- **Preparing for vaccine trials**
- **Preparing industry**
- **Preparing non-industry stakeholders**

- **Preparing for vaccine trials**
  - Gather the epidemiological, economic and societal data that are currently lacking
  - Strengthen surveillance, laboratory and clinical trial capacity through a network of sentinel sites in low and middle income countries.

- **Preparing industry by continuous engagement with vaccine developers and manufacturers to highlight the need for a Strep A vaccine**
  - Discuss and continue to update/improve the favorable business case
  - Understand/anticipate the barriers to vaccine development with a view to accelerating the Strep A vaccine pipeline

- **Preparing non-industry stakeholders to maximize efficient implementation of a future GAS vaccine**
  - WHO, includes updating the Technical Roadmap / TPP
  - Gavi
  - Global funders
  - National policy makers
  - NITAGs
  - Laboratory and safety surveillance

Endpoints, surrogate endpoints
KOL discussions
Early adopter countries?
Pathway to SAGE, PQ, and implementation

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IVIR-AC ad hoc meeting 30 September 2022

Paula Mendes Luz
Chair opening remarks

Full Value of of Group A Streptococcus Vaccine Assessment by SAVAC
(for discussion)

World Health Organization

Background:
- This session serves to discuss preliminary results and way forward of a *Full Value of of Group A Streptococcus Vaccine Assessment* by SAVAC

Session objective :
- Review latest information of Investment cases for prospective Strep A vaccines and Strep A Vaccine Business Case from Developer's Perspective

Expectations to IVIR-AC:
- IVIR-AC is asked to review the results of the value assessment undertaken and comment on/recommend any additional studies that may complement/broaden these initial FVVA analyses of GAS vaccines.
- Does IVIR-AC have feedback on how to communicate the FVVA work to GAS vaccine R&D stakeholders?

Investment cases for prospective Strep A vaccines

Daniel Cadarette
Harvard T. H. Chan School of Public Health

30 September 2022
Presentation to IVIR-AC
Wellcome Trust Headquarters, London

Is increased investment in the development, manufacture, and delivery of Strep A vaccines merited from a:

- Health sector perspective?
- Societal perspective?
- Commercial perspective?

FVVA overview

- Traditional investment case
  - Vaccine impact on disease burden
  - Economic burden per episode
  - Cost-effectiveness analysis

- Global investment case
  - Full societal framework
  - Antibiotic consumption for pharyngitis
  - Global willingness to pay
  - Optimal societal R&D investment

- Commercial investment case
  - Business case from a developer's perspective

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- **Strep A vaccination would plausibly:**
  - Prevent billions of cases of superficial illness and millions of deaths over several decades
  - Be cost-effective at all income levels assuming total costs in line with other new vaccines
  - Produce a wide range of health, economic, and social benefits, including potentially significant AMR mitigation
  - Yield trillions of dollars in global societal benefits
  - Generate full societal returns many times reasonable investment into their development

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Motivation and background

- Strep A is one of the leading causes of infectious disease deaths globally
- Wide range of clinical endpoints
- Broad health, economic, and social burdens
- Burdens concentrated in disadvantaged populations
- Available remedies are imperfect
  - Antibiotics
    - Questionable evidence of ARF/RHD prevention
    - Insufficient access
    - Repeated treatment required
    - Resistance
    - Microbiome disruption

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R&D funding and associated DALYs:
RHD vs. other infectious diseases

McLeod et al. TRSTMH 2019
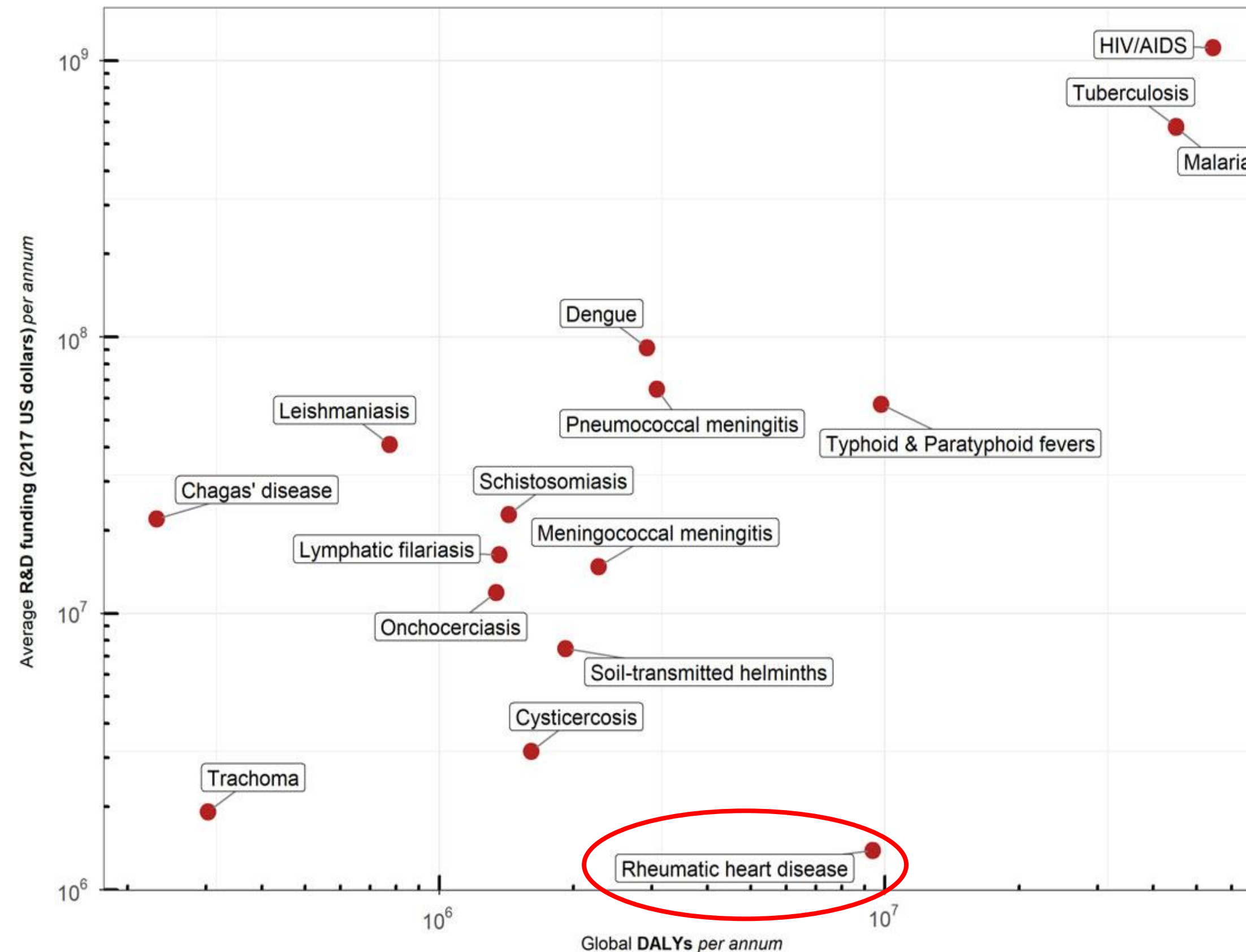
Vaccine impact on disease burden

Methods:

- Static cohort model

- Strep A vaccine profile based on WHO PPC

- Vaccination at age 0 or age 5

- Lifetime impact for 30 birth cohorts (2022-2051):

- Six scenarios with variations in:
  - Country-specific introduction (2022-2034) vs. global introduction in 2022
  - Country-specific max coverage vs. 50% universal coverage
  - Full efficacy for 10 years & null thereafter vs. linear waning over 20 years

Lead authors: Fiona Giannini, Jeffrey Cannon, and Kaja Abbas

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Vaccine impact on disease burden

Range of cases and deaths averted globally over 30 birth cohorts by Strep A manifestation across the six scenarios with vaccination at birth

Manifestation	Cases (deaths) averted
Pharyngitis	1.5-2.5 bil.
Impetigo	195-354 mil.
Cellulitis	14-25 mil.
Invasive disease	750,000-1.4 mil. (46,000-83,000)
Rheumatic heart disease	3.8-8.0 mil. (1.1-2.4 mil.)

Lead authors: Fiona Giannini, Jeffrey Cannon, and Kaja Abbas

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Methods:

- Searched for literature on costs related to Strep A
- Considered direct medical cost (DMC), direct non-medical costs (DNMC), and indirect costs (IC)
- Adjustment factors to overcome data insufficiencies for DMC and DNMC
- IC estimated in terms of productivity loss due to premature mortality
  - Productive years lost multiplied by country minimum wage
- Monte Carlo simulation to estimate 95% CIs

Lead author: Jung Seok Lee

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Economic burden per episode by income group

Lead author: Jung Seok Lee

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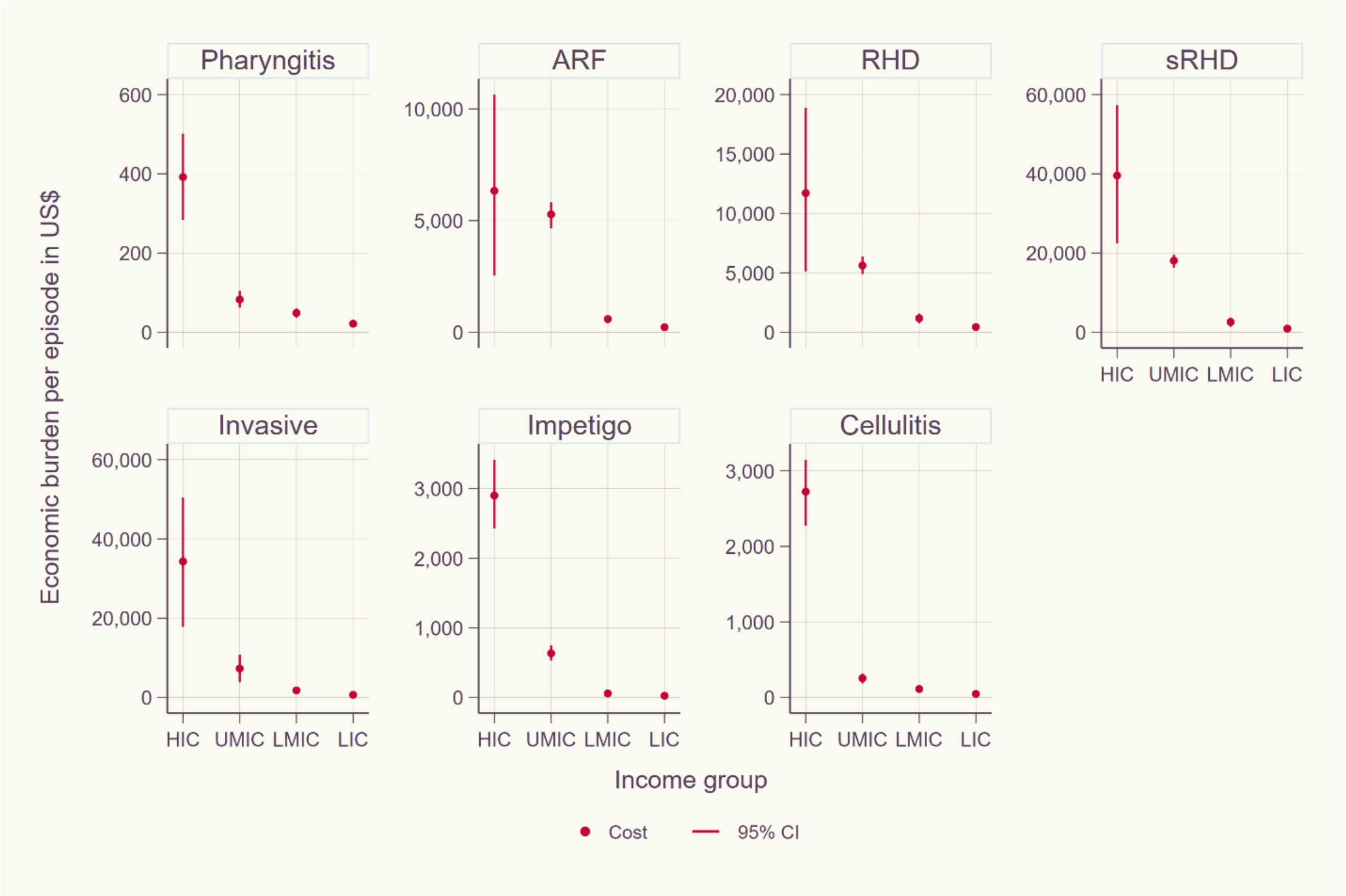
Methods:

- Builds off results of vaccine impact modeling analysis and economic burden analysis
- Maximum cost per fully vaccinated individual to be cost-effective derived for varying threshold costs per DALY averted
- Future costs and health outcomes discounted at 3%
  - Health outcomes with no discounting also considered

Lead author: Jung Seok Lee

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Traditional investment case: Cost-effectiveness analysis

Central estimate of maximum cost per fully vaccinated person to be cost-effective for all manifestations at threshold of 1 x GDP per capita

Country income group	Vaccination at age 0	Vaccination at age 5
Low income	$37	$69
Lower-middle income	$74	$132
Upper-middle income	$213	$312
High income	$385	$489

Lead author: Jung Seok Lee

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Methods:

- Builds off prior valuation frameworks, including:
  - Bärnighausen et al. (2008)
  - Bärnighausen et al. (2014)
  - Jit et al. (2015)
  - Bloom et al. (2017)
  - Mauskopf et al. (2018)
- Expert consultation
- Targeted literature review

Lead author: Daniel Cadarette

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Global societal investment case: Full societal framework

	Vaccination benefits	Distribution			
		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** • Healthcare congestion			✓	✓
	Improved mental health	✓	✓		
Economic benefits	Reduced healthcare costs	✓	✓	✓	
	Reduced caregiving costs	✓	✓	✓	
	Reduced transportation costs	✓	✓		
	Increased labor force participation, hours worked, and income Increase in 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	✓	✓	✓	✓

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Methods:

- Literature review (2000-2021) for studies reporting either:
  - Rate of antibiotic consumption/prescribing for sore throat
  - Proportion of sore throat-related consumption/prescribing for those with diagnostically confirmed Strep A sore throat
- Global antibiotic prescribing rate for sore throat estimated based on countries with available data
- Proportion of prescribing attributable to Strep A also estimated
- Potential prescriptions averted estimated based on results of these analyses for 80% effective vaccine with 10-year duration and 90% coverage among 5-year-olds

Lead authors: Kate Miller and Jeffrey Cannon

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Results:

15% of all antibiotic prescriptions for Strep A sore throat in the countries studied could be directly averted through vaccination

Lead authors: Kate Miller and Jeffrey Cannon

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Methods:

- Based on willingness to pay estimates for general reductions in mortality and morbidity risks
- Value per statistical life year (VSLY) and value per statistical disability (VSD) assumed to be proportional to per-capita income
- For central estimate:
  - VSLY/VSD = three times global GDP per capita (to address equity considerations)
  - Discount rate = 3%
- Builds on results of vaccine impact modeling analysis for 30 birth cohorts

Lead author: Maddalena Ferranna

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Global societal investment case: Willingness to pay

Average total benefits of Strep-A vaccination across the six vaccination scenarios from 2022 to 2051

Lead author: Maddalena Ferranna

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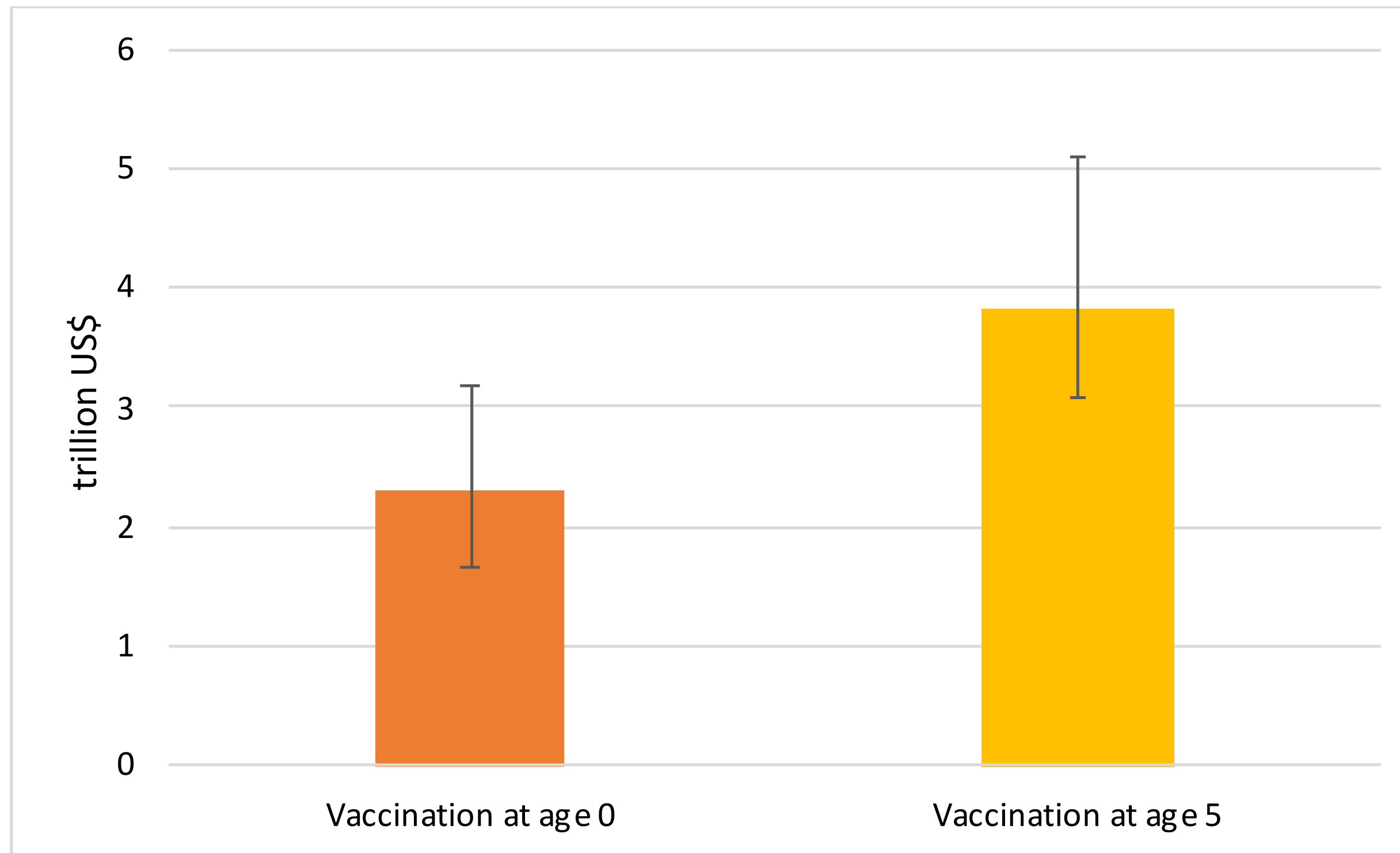
Methods:

- Novel model to estimate socially optimal spending on vaccine R&D and social rate of return on that investment
- Perspective: supranational organization allocating funding across different projects
- Considers the following:
  - Number of available approaches to development (e.g., M protein-based vs. non-M protein-based)
  - Overall likelihood of success of each approach
  - Likelihood of success of any single research project
  - Fraction of remaining harm from Strep A each successive approved vaccine can eliminate
  - Estimated total global harm from Strep A (in dollars)
  - Risk-adjusted cost of developing a successful vaccine
- Calibrated through expert consultation and based on existing literature

Lead author: Daniel Tortorice

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Results:

- Socially optimal to fund 226 Strep A vaccine R&D projects at a cost of $33.9 billion
- This investment generates a social surplus of $1.85 trillion
- 23% annualized social return on investment

Lead author: Daniel Tortorice

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- **Strep A vaccination would plausibly:**
  - Prevent billions of cases of superficial illness and millions of deaths over several decades
  - Be cost-effective at all income levels assuming total costs in line with other new vaccines
  - Produce a wide range of health, economic, and social benefits, including potentially significant AMR mitigation
  - Yield trillions of dollars in global societal benefits
  - Generate full societal returns many times reasonable investment into their development

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- FVVA report
- Planned special issue of *npj Vaccines*
- SAVAC 2.0
  - Collect data related to broad health, economic, and social burdens
  - Estimate full value of Strep-A vaccination using a social welfare function approach
  - Assess allocation of social surplus from vaccination to different stakeholders
  - Dynamic funding model of vaccine research and development
  - Identify financing mechanisms to stimulate simultaneous investment in multiple R&D projects

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Thank you!

dcadarette@hsph.harvard.edu

Business Case for Industry Investment in Strep A Vaccine R&D

Don Walkinshaw
Shift Health

30 September 2022
Presentation to IVIR-AC
Wellcome Trust Headquarters, London

Will there be a viable commercial market for a Strep A vaccine based on the WHO PPCs?

What impact will the following have on commercial viability?
- Big Pharma (MPC) vs DCVM?
- Speed of adoption by HICs?
- Impact of competitive entry?

MPC = multinational pharma company; DCVM = developing country vaccine manufacturer

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Background and motivation

- Very low industry activity in Strep A vaccine R&D

- We hope our results will:
  - Raise awareness of potential commercial viability of Strep A vaccine market
  - Provide a foundation for follow-on work to address uncertainties, explore new scenarios (e.g. adult market) and incorporate additional industry feedback
  - Serve as a resource for companies assessing potential investment in Strep A vaccine R&D

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Overall approach

- Population-based demand forecast with associated revenue and profits
- Investment return analysis using risk-adjusted net-present value (rNPV)
- Scenarios for developer type (MPC, DCVM) and target population (infant, child)
- Strep A vaccine profile based on WHO PPC with pharyngitis and impetigo prevention as indication
- Assume SAGE recommendation and Gavi financing
- Assumptions for public and private market adoption and coverage, prices, COGS, R&D timelines and investments calibrated through expert interviews and literature review
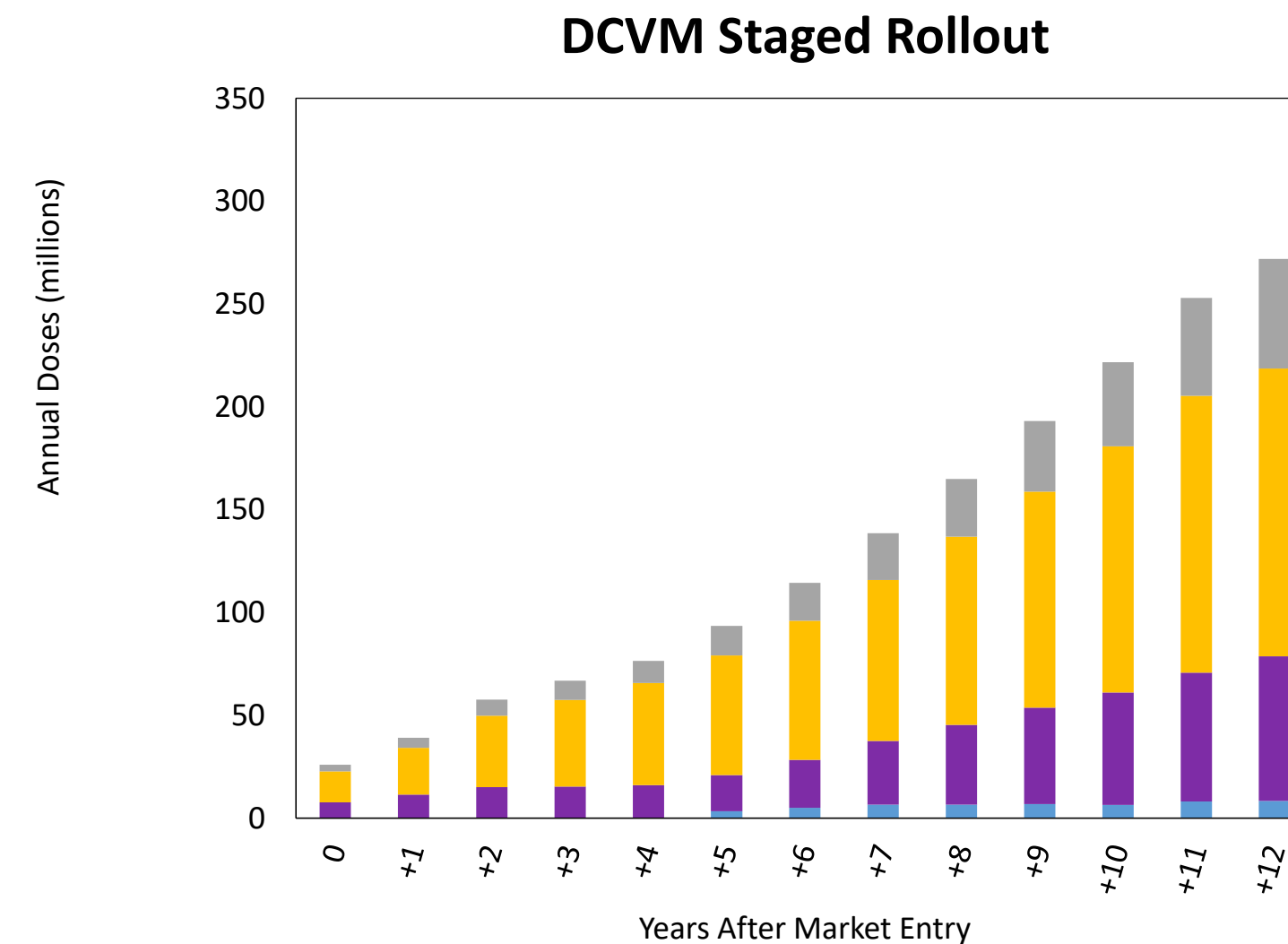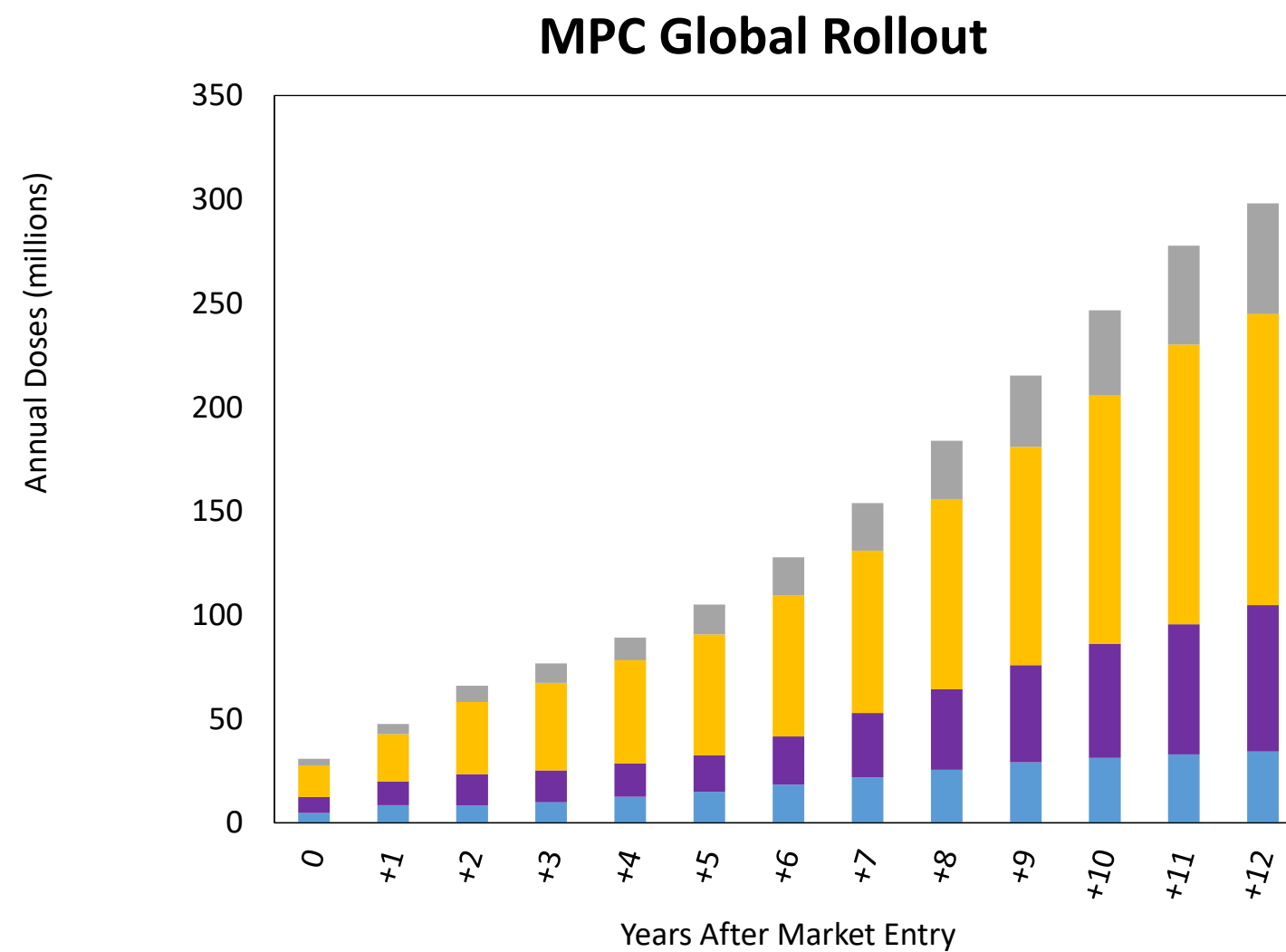
MPC = multinational pharma company; DCVM = developing country vaccine manufacturer

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Demand, revenue, profit forecast

Methods:

- Private market intro in all countries in 2033, public market intro between based on:
  - Disease burden (RHD incidence),
  - History of new vaccine adoption (PCV, Rota, Hib)
  - Vaccine delivery infrastructure (DTP3)
  - MPC and DCVM launch priority considerations

- Linear ramp up to peak vaccine coverage equivalent to DTP3 (infant) or MCV2 (child)

- Price ranged from $3.40 USD per dose (LIC and Gavi) to $53.95 USD per dose (HIC) based on PCV13 2019 prices

- Cost of goods sold: $3.24 USD per dose for 1-dose vial and $3.18 for pre-filled syringe

MPC = multinational pharma company; DCVM = developing country vaccine manufacturer

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Demand forecast

Total annual demand at year 12 is estimated at 298M doses for the MPC global rollout scenario and 272M doses for the DCVM staged rollout scenario.
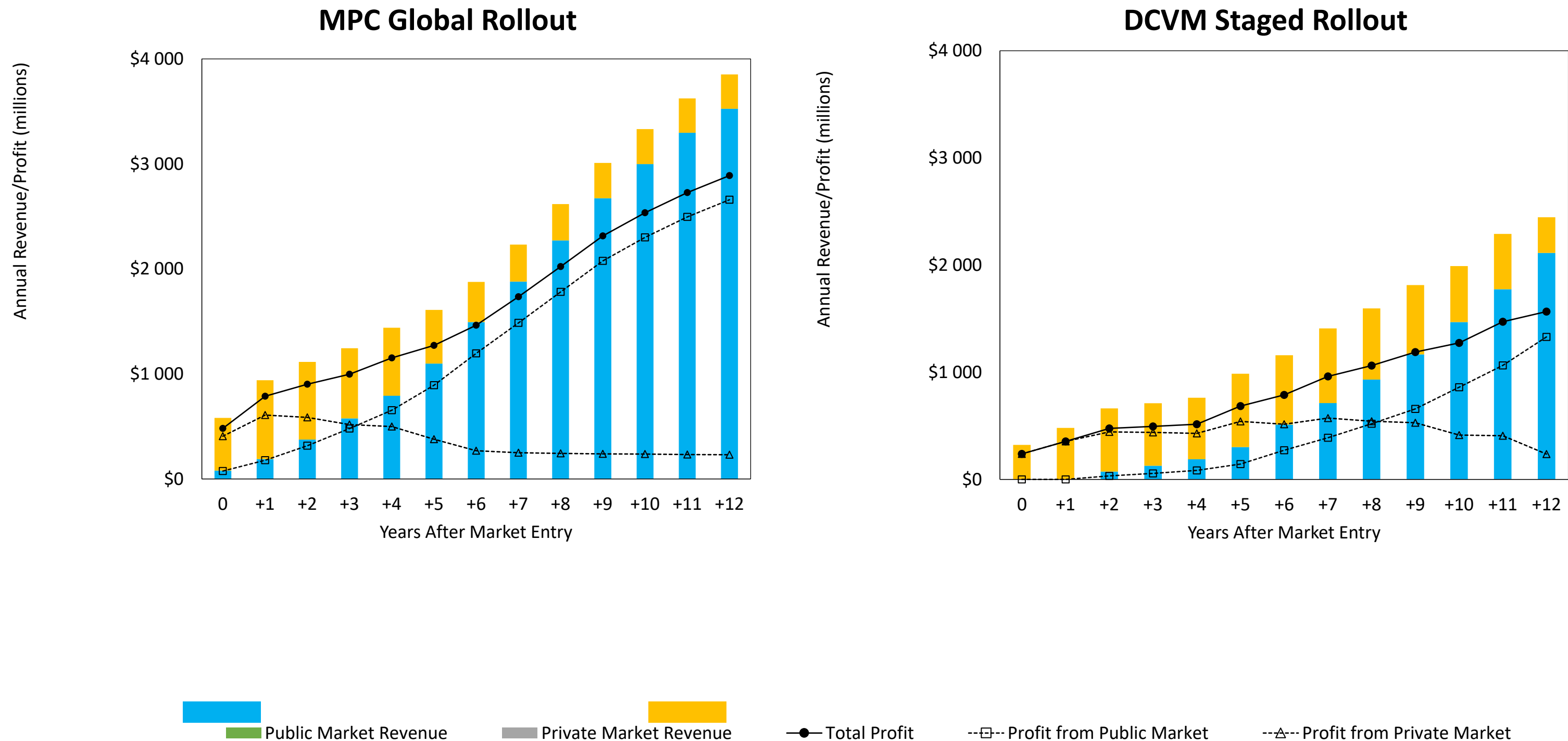

MPC = multinational pharma company; DCVM = developing country vaccine manufacturer

Revenue and profit forecast

Total annual revenue in year 12 is ~$4B for MPC and ~$2.5B for DCVM. By year 12, the public market contributes >85% of total annual profit.

MPC Global Rollout

DCVM Staged Rollout

Legend: Public Market Revenue | Private Market Revenue | Total Profit | Profit from Public Market | Profit from Private Market

MPC = multinational pharma company; DCVM = developing country vaccine manufacturer

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Methods:

- Risk-adjusted NPV (rNPV) calculated using discounted cash flow (DCF) analysis

- 12 years of annual operating profits following 13 years of capital investments (risk-adjusted using probability of success point estimates), discounted back to 2022

- Total risk-adjusted R&D investment: $979M for MPC and $372M for DCVM

- Discount rate: 10% for MPC, 15% for DCVM

MPC = multinational pharma company; DCVM = developing country vaccine manufacturer

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Investment return analysis

rNPV is positive for MPC (even if rollout to HICs is delayed by 5 years) as well as DCVM developer scenarios.

Investment Scenario	rNPV (millions USD)	Average Profit Margin
MPC Global Rollout	$2,460	75%
DCVM Staged Rollout	$307	64%
MPC Staged Rollout	$1,280	71%

rNPV remains positive for several competitor or 'split market' scenarios in which the first developer loses 25% or 50% of profits beginning 3, 5 or 7 years after first rollout of hypothetical Strep A vaccine.

MPC = multinational pharma company; DCVM = developing country vaccine manufacturer

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Conclusions

- Return on investment analysis found a positive rNPV across multiple scenarios, suggesting a viable commercial market for Strep A vaccine

- Primary limitation of this study is the uncertainty associated with forecasting demand of a vaccine 10+ years from market.

- Key assumption that SAVAC and others will continue to: quantify and raise awareness of the burden of Strep A diseases; illuminate the health, economic and social impacts of Strep A vaccination; and define regulatory pathways for a Strep A vaccine.

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Conclusions

- SAVAC 2.0 work may include:
  - Industry engagement to better understand barriers and drivers for Strep A vaccine investment and solicit feedback on business case
  - Strengthening understanding of country-level demand for a Strep A vaccine
  - Business case for adult Strep A vaccination for cellulitis prevention
  - Policy/advocacy narrative and evidence base for stakeholder engagement
  - Updated Strep A vaccine pipeline landscape assessment

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Thank you!

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Full Value of of Group A Streptococcus Vaccine Assessment by SAVAC
(for discussion)

World Health Organization

Background:
- This session serves to discuss preliminary results and way forward of a *Full Value of of Group A Streptococcus Vaccine Assessment* by SAVAC

Session objective :
- Review latest information of Investment cases for prospective Strep A vaccines and Strep A Vaccine Business Case from Developer's Perspective

Expectations to IVIR-AC:
- IVIR-AC is asked to review the results of the value assessment undertaken and comment on/recommend any additional studies that may complement/broaden these initial FVVA analyses of GAS vaccines.
- Does IVIR-AC have feedback on how to communicate the FVVA work to GAS vaccine R&D stakeholders?

PDVAC/IVIRAC ONLY

CLOSED SESSION