Working towards a vaccine for Strep A

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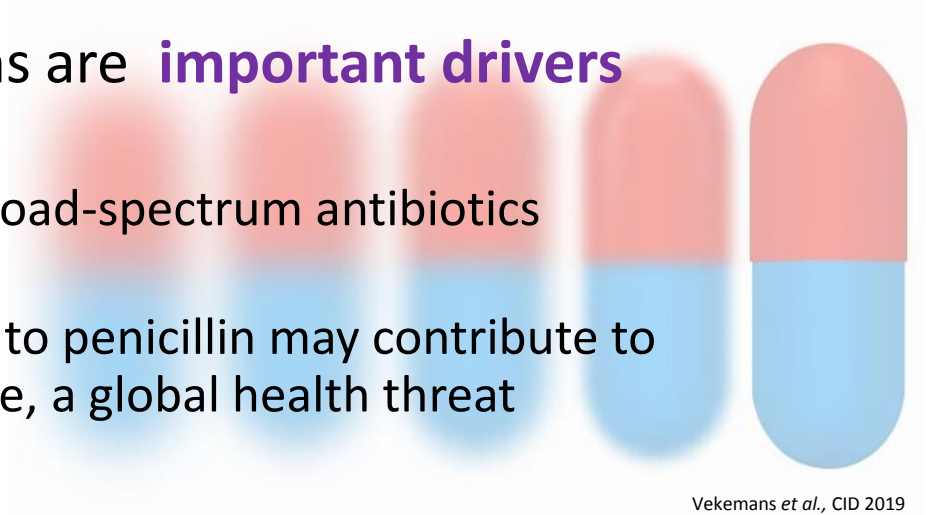
The case for a StrepA Vaccine
Disease Burden

- StrepA is a leading cause of infectious disease burden
  - **~600 million** incident cases of pharyngitis and **~160 million** cases of impetigo each year
  - **18 million** new cases of **severe disease** each year
  - **>30 million** people living with RHD
  - StrepA disease causes **500,000** annual deaths
- Disease burden is not limited to LMIC or high social deprivation
  - UK witnessing huge surge in **scarlett fever outbreaks**
  - Invasive disease **increasing** in UK, US, Canada and NZ

Carapetis et al., Lancet 2005
Watkins et al., NEJM, 2017
Moreland et al., Vaccine 2014
Vekemans *et al.,* CID 2019

The case for a StrepA Vaccine
Penicillin and AMR

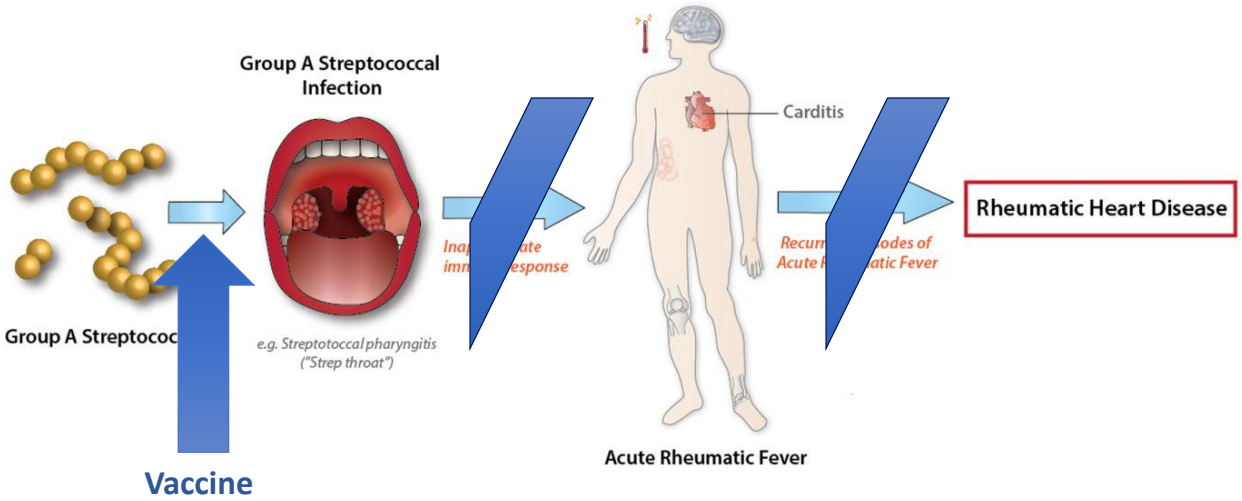
- StrepA is sensitive to **penicillin**, yet the burden of GAS diseases remains high
  - Delivery and access to care difficult in LMIC settings
  - Delay in recognizing severity and initiating treatment
- StrepA skin and throat infections are **important drivers** of antibiotic use
  - Many sore throats are viral yet broad-spectrum antibiotics prescribed
  - Exposure of the commensal flora to penicillin may contribute to emergence of antibiotic resistance, a global health threat



Vekemans *et al.*, CID 2019
Dooling KL et al., JAMA Pediatr, 2014

Are StrepA diseases vaccine preventable?

- StrepA skin and throat infections are more common in children than in adults suggesting **exposure generates immunity**
  - Adults have higher levels of anti-StrepA antibodies than children

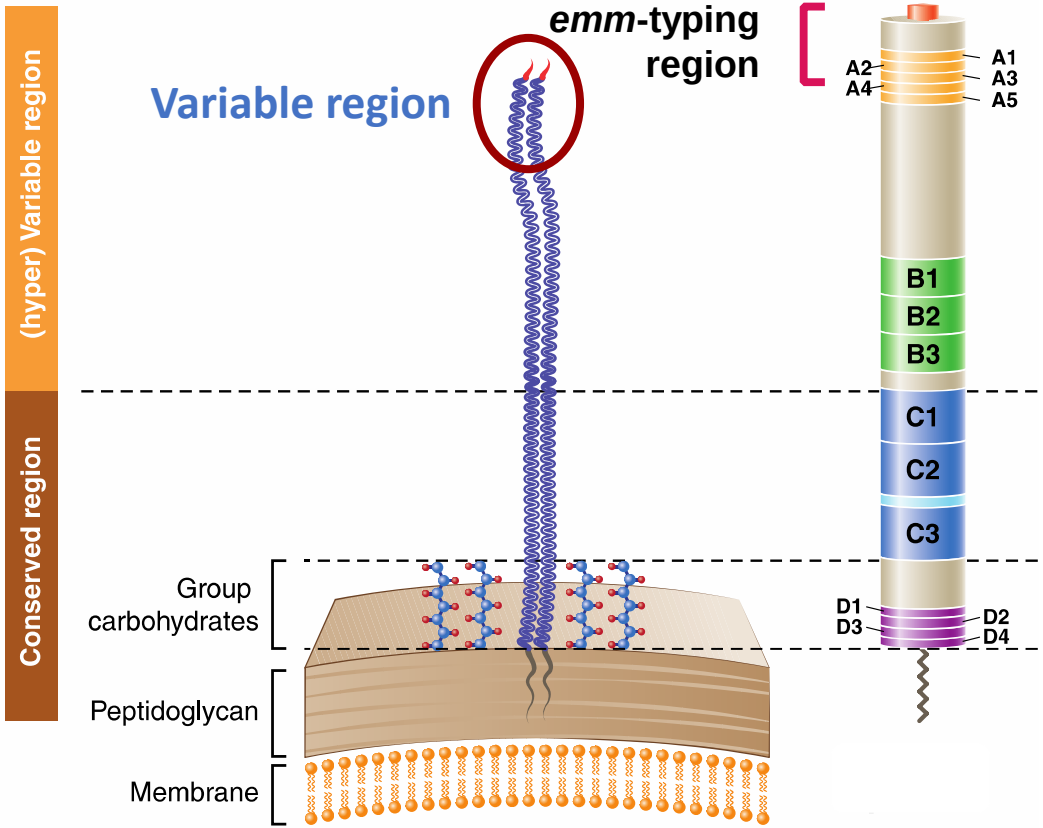


[Image: Steer, J PCH, 2015]

Vekemans *et al.,* CID 2019
Tsoi SK *et al.,* J Immunol Res, 2015
Brandt ER *et al.,* Immunology, 1996
Mortensen R *et al.,* J Immunol, 2015

The Vaccine Pipeline I: M protein

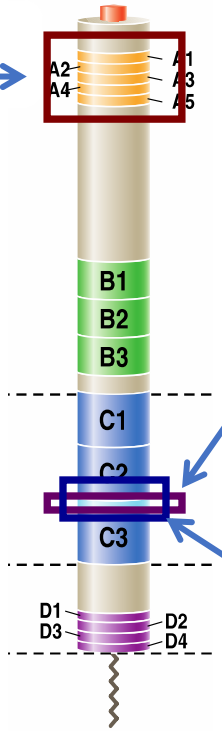
- The most **“clinically advanced”** vaccine candidates are based on the M-protein
  - Antibodies that bind the N-terminal HVR are type specific & protective
  - Antibodies that bind conserved C-repeats are less protective but cross-reactive



M protein based vaccines

30-Valent Vaccine: Jim Dale/PREVENT
Phase I, 2017, Canada
Based on 30 most prevalent strains in US/Europe

Coverage estimates (NZ ARF)
Williamson *et al.,* JCM 2015
- 31% strains in the vaccine
- 70% theoretical protection with *in vitro* cross-opsonisation



J8-DT Vaccine: Michael Good/UQ
12 AA peptide from C-repeat region
Phase I, 2014, Australia; safe and well tolerated, now being reformulated with peptide from SpyCEP

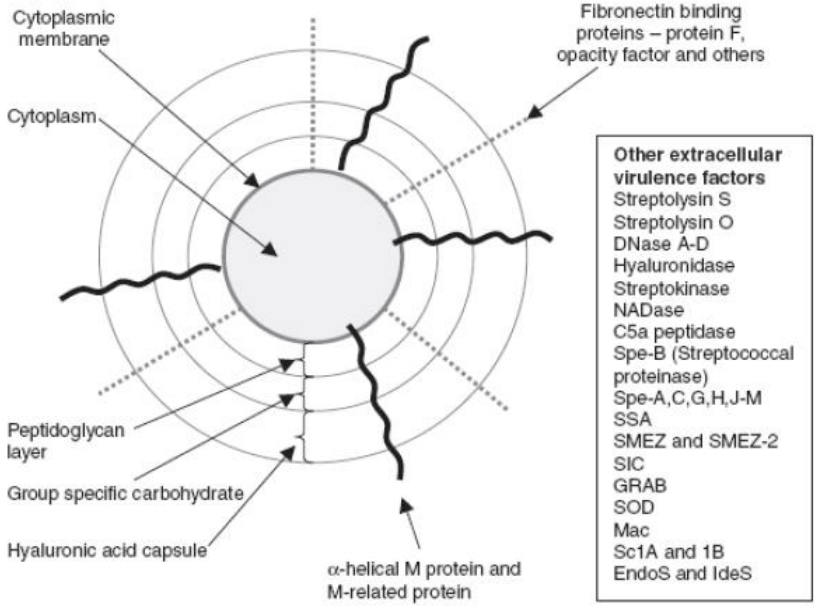
StreptinCor: Luiza Guilherme/InCor
Phase I planned, Brazil
55 AA (discontinuous) peptide from C-repeat region

Dale JB et al., (2011) Vaccine
Good MF et al., (2013) HVI
Pandey et al., (2015) JI
Sekuloski et al., (2018) PloS One
Guilherme et al., (2011) JBC

The Vaccine Pipeline II: Conserved

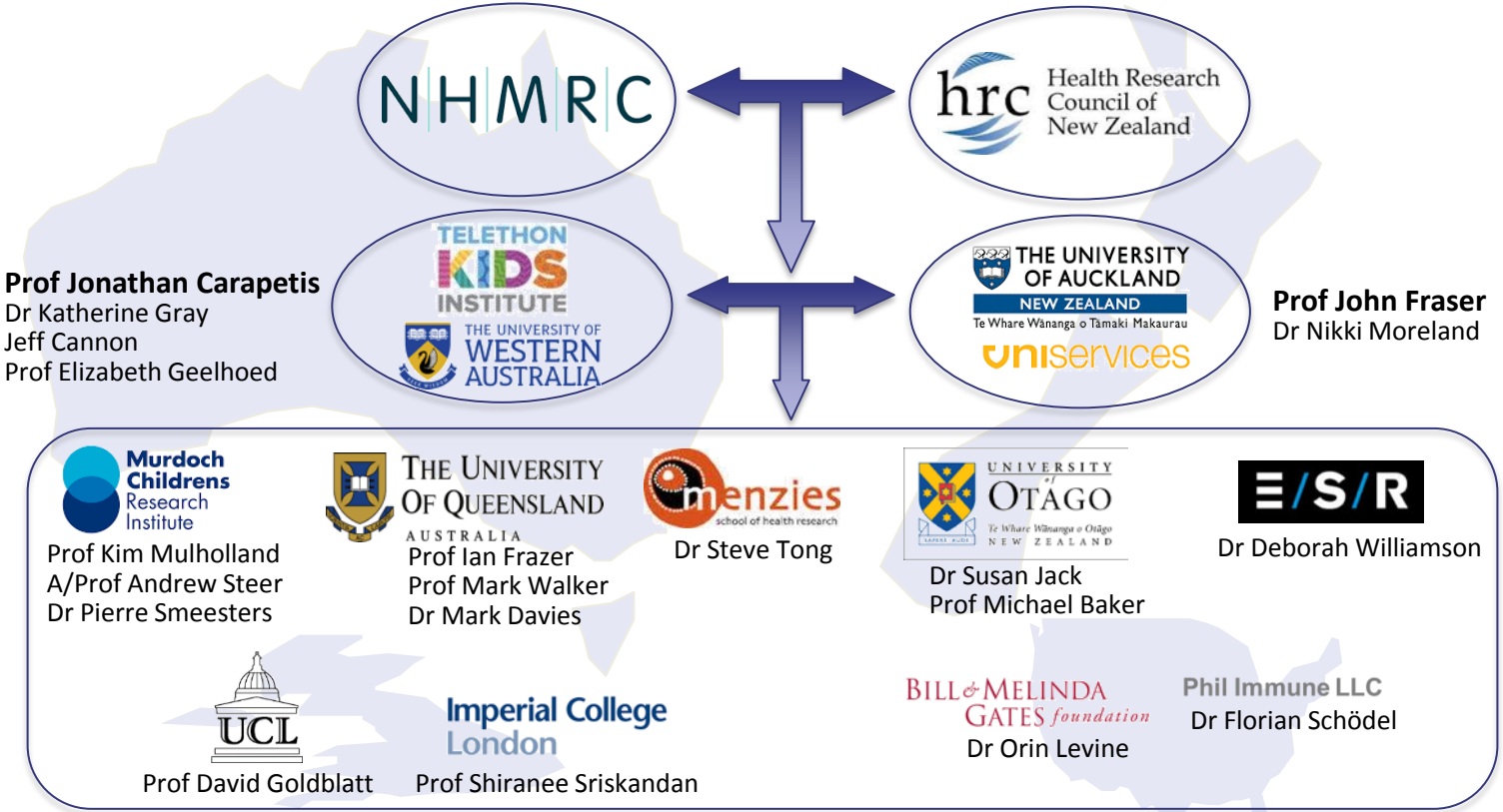
Conserved multi-antigen Vaccines

- GSK “Combo”
  - SLO, SpyAD, SpyCEP and GAC
- Other “Combo” vaccines
  - Walker Lab (UQ), Combo5
  - Sriskandan Lab (London), Spy7



Bensi *et al.,* Mol Cell Proteomics, 2011
Rivera-Hernandez *et al.,* mBio, 2016
Reglinski et al., JI, 2016

CANVAS: international collaboration to accelerate development of a GAS vaccine (2014-2017)



Preparing for a GAS vaccine: 3 key deliverables

1

GAS strain repository

- Comprehensive assessment of regional GAS strain epidemiology (*emm*-typing, whole genome sequencing)

2

GAS assay development

- Development of a robust assay to assess GAS vaccine efficacy

3

Economic evaluation

- Health economics analysis of GAS vaccine cost

Clinical development strategy for GAS vaccine candidate

canvas

Preparing for a GAS vaccine: Outputs

1

GAS strain repository

- Repository of StrepA strains that represents global disease
- GWAS (>1500 strains) for deep exploration of antigen variation

Mark Davies

2

GAS assay development

- OPKA developed for GAS

3

Economic evaluation

- GAS vaccines are cost effective compared to current options
- Cannon *et al.,* Vaccine 2018

Jeffery Cannon

Clinical development strategy for GAS vaccine

- Pivotal phase 2b in pharyngitis (Schodel et al., Vaccine 2017)

canvas

GAS Assay Development: Deliverable II

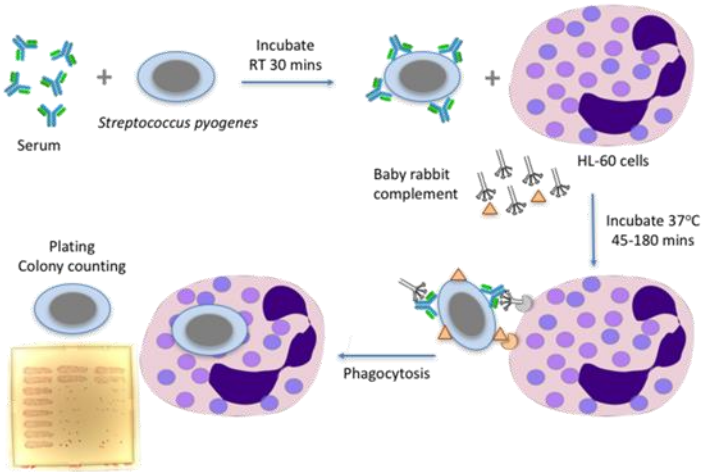
- Critical lack of robust bactericidal assays to measure protective immunity in vaccine antisera
- Indirect bactericidal test (Lancefield assay) is most frequently used
  - Uses human donor whole blood
  - Not amenable to high throughput analysis
  - Relies on single serum dilution

GAS assay development

Deliverable II

- Opsonophagocytic killing assays using HL-60 cells
  - Neutrophil cell line, not whole blood
- Robust assessment of killing
  - Generate titration curve
  - Calculate opsonisation index (OI)
  - Colony counter and 96-well plate format enables high throughput

Overview of StrepA HL-60 assay



David Goldblatt

OPKA for GAS Established in London and Auckland

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Development of an opsonophagocytic killing assay for group a streptococcus

Scott Jones [a,*], Nicole J. Moreland [b], Marta Zancolli [a,1], Jeremy Raynes [b], Jacelyn M.S. Loh [b], Pierre R. Smeesters [c,d], Shiranee Sriskandan [e], Jonathan R. Carapetis [f], John D. Fraser [b], David Goldblatt [a]

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Reuben McGregor
Auckland OPKA

Obstacles

- Safety concerns
- Incomplete understanding of immune protection in humans
- Lack of reliable disease models
- Inadequate epidemiological data
- Minimal development of combination antigen vaccines
- ? Market
- Competing priorities

Reluctance of Big Pharma to invest

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Vaccine 34 (2016) 2953–2958

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Status of research and development of vaccines for *Streptococcus pyogenes*

Andrew C. Steer[a,b,*], Jonathan R. Carapetis[c], James B. Dale[d], John D. Fraser[e], Michael F. Good[f], Luiza Guilherme[g], Nicole J. Moreland[h], E. Kim Mulholland[i,j], Florian Schodel[k], Pierre R. Smeesters[a,b,l]

Expert Review of Vaccines

ISSN: 1476-0584 (Print) 1744-8395 (Online) Journal homepage: http://www.tandfonline.com/loi/ierv20

Development of Group A streptococcal vaccines: an unmet global health need

Meru Sheel, Nicole J Moreland, John D Fraser & Jonathan Carapetis

ESPID Reports and Reviews

Progress Toward a Global Group A Streptococcal Vaccine

Andrew C. Steer, PhD, James B. Dale, PhD,† and Jonathan R. Carapetis PhD‡*

Vaccine 31S (2013) B216–B222

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Group A streptococcal vaccines: Paving a path for accelerated development

James B. Dale[a,*], Vincent A. Fischetti[b], Jonathan R. Carapetis[c], Andrew C. Steer[d], Samba Sow[e], Rajesh Kumar[f], Bongani M. Mayosi[g], Fran A. Rubin[h], Kim Mulholland[i], Joachim Maria Hombach[j], Florian Schödel[k], Ana Maria Henao-Restrepo[j]

Vaccine 32 (2014) 3713–3720

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Conference report

Working towards a Group A Streptococcal vaccine: Report of a collaborative Trans-Tasman workshop

Opportunities

- WHO re-prioritization
  - Preferred Product Characteristics
  - Technical R&D roadmap
- WHO workshops
  - Seoul Dec 2016, London May 2018
- WHO Global Resolution on RF/RHD
  - May 2018

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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 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
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 level, 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 post-implementation surveillance.

http://dx.doi.org/10.1093/cid/ciy1143

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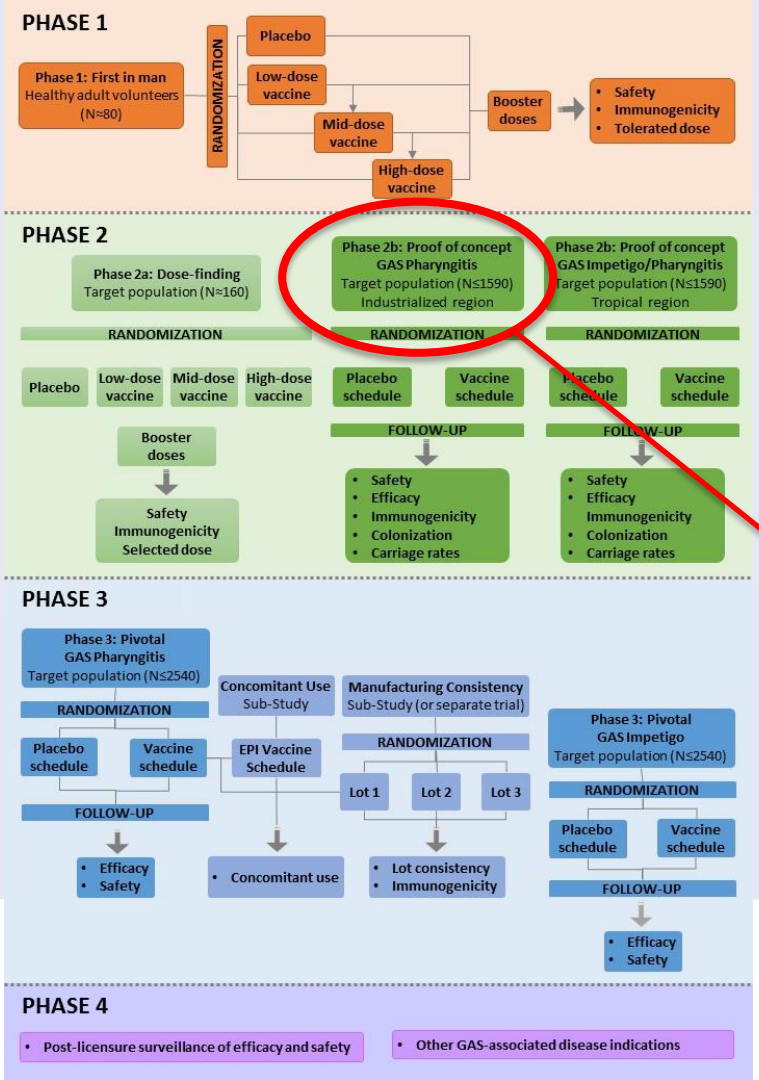

Clinical development schematic

The phases of development required for registration of a candidate GAS vaccine indicated for GAS pharyngitis, GAS impetigo and other GAS-associated diseases

Proof of Concept Phase 2B – pharyngitis
- Critical study to demonstrate safety and efficacy

Shodel et al., Vaccine 2017