Vaccines against Strep A

Prof Andrew Steer
Group A Streptococcal Research Group, Murdoch Children’s Research Institute, Australia

Prof Jerome Kim
International Vaccine Institute, Seoul, Korea

Geneva June 27th 2018
Last year

Key updates
1. Pathogen
2. Disease burden updates
3. Vaccine candidate landscape
4. Global antigen data
5. Controlled infection models
6. Plans for PPC, Roadmap
This year: outline

PART A: Building momentum (Andrew Steer)
1. Pathogen, disease burden, candidates, infection models
2. WHO Resolution on Rheumatic Heart Disease
3. London meeting May 2018
4. WHO Roadmap
5. WHO PPC

PART B: Strep A Vaccine Enterprise (Jerome Kim)
PART A: Building momentum
1. Pathogen

Disease burden

Candidates

Models
The pathogen

A ubiquitous human pathogen
Tertiary prevention
Surgical/medical

Primary prevention
Antibiotic treatment

Secondary prevention
Antibiotic prophylaxis

ACUTE INFECTIONS

Cellulitis

Pharyngitis

Impetigo

Invasive infections

>20 million?

>600 million

>160 million

>600,000

>150,000

>500,000

>300,000

>34 million

>300,000

POST-INFECTIONOUS/IMMUNE

Premature cardiovascula...
Rheumatic fever and rheumatic heart disease

1. Infectious disease
   - Group A Streptococcal Infection
     - e.g. Streptococcal pharyngitis ("Strep throat")

2. Immune-mediated disease
   - Carditis
   - Recurrent ARF

3. Chronic non-communicable disease
   - Rheumatic Heart Disease (RHD)
     - RHD morbidity (Heart failure, Atrial fibrillation, Infective endocarditis, Stroke)

   - DEATH
Rheumatic fever and rheumatic heart disease

Infectious disease

Immune-mediated disease

Chronic non-communicable disease

33 million PLWRHD

11.5 million DALYs

Susceptible person

Group A Streptococcal Infection

e.g. Streptococcal pharyngitis ("Strep throat")

Acute Rheumatic Fever (ARF)

Recurrent ARF

Carditis

Rheumatic Heart Disease (RHD)

RHD morbidity (Heart failure, Atrial fibrillation, Infective endocarditis, Stroke)

DEATH

Watkins et al. NEJM 2015
Rheumatic fever and rheumatic heart disease

Infectious disease | Immune-mediated disease | Chronic non-communicable disease

Susceptible person → Group A Streptococcal Infection (e.g., Streptococcal pharyngitis, "Strep throat") → Acute Rheumatic Fever (ARF) → Carditis → Rheumatic Heart Disease (RHD) → RHD morbidity (Heart failure, Atrial fibrillation, Infective endocarditis, Stroke) → DEATH

305,000 deaths p.a.

Watkins et al. NEJM 2015
# Vaccine candidates

<table>
<thead>
<tr>
<th>Vaccine Candidates</th>
<th>M Protein/Peptide</th>
<th>Researcher/Development</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-valent vaccine (StreptAnova)</td>
<td>M protein (HVR region)</td>
<td>Jim Dale, PREVENT, USA</td>
<td>Phase 1 complete (awaiting results)</td>
</tr>
<tr>
<td>J8 vaccine</td>
<td>M protein (C-terminal peptide)</td>
<td>Michael Good, Australia</td>
<td>Phase 1 of reformulated vaccine (planned)</td>
</tr>
<tr>
<td>StreptinCor</td>
<td>M protein (C-terminal peptide)</td>
<td>Luiza Guilherme, Brazil</td>
<td>Phase 1 (planned)</td>
</tr>
<tr>
<td>“Combo”</td>
<td>Non-M protein multi-antigen</td>
<td>Novartis/GSK</td>
<td>Under development</td>
</tr>
</tbody>
</table>
Rammelkamp CH, 1956

Slide courtesy Joshua Osowicki
'73 N=44

SC M1-alum
n=19

SC alum
n=25

M1 GAS $10^6$ CFU

<table>
<thead>
<tr>
<th></th>
<th>pharyngitis</th>
<th>no pharyngitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1-alum</td>
<td>1 (5%)</td>
<td>18</td>
</tr>
<tr>
<td>alum</td>
<td>12 (48%)</td>
<td>13</td>
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</table>

P = 0.026

VE = 89% (22.9 - 98.4)

Fox EN et al, 1973

Slide courtesy Joshua Osowicki
<table>
<thead>
<tr>
<th></th>
<th>pharyngitis</th>
<th>no pharyngitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>mucosal M1</td>
<td>5 (24%)</td>
<td>16</td>
</tr>
<tr>
<td>placebo</td>
<td>17 (74%)</td>
<td>6</td>
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</tbody>
</table>

VE = 68% (28.1 – 85.6)

N = 44

P = 0.006

Polly SM et al, 1973
### '78 Study:

- **N=84**

<table>
<thead>
<tr>
<th></th>
<th>Pharyngitis</th>
<th>No Pharyngitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Controls</strong></td>
<td>15 (42%)</td>
<td>21</td>
</tr>
<tr>
<td><strong>All Vaccinees</strong></td>
<td>15 (31%)</td>
<td>33</td>
</tr>
<tr>
<td><strong>All Parenteral</strong></td>
<td>9 (45%)</td>
<td>11</td>
</tr>
<tr>
<td><strong>All Mucosal</strong></td>
<td>6 (21%)</td>
<td>22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>SC M3-Alum</th>
<th>Mucosal M3</th>
<th>SC M12-Alum</th>
<th>Mucosal M12</th>
</tr>
</thead>
<tbody>
<tr>
<td>M3 GAS 10^6 CFU</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>M12 GAS 10^6 CFU</td>
<td>6</td>
<td>9</td>
<td>3</td>
<td>13</td>
</tr>
</tbody>
</table>

D’ Alessandri R et al, 1978
<table>
<thead>
<tr>
<th></th>
<th>Pharyngitis</th>
<th>No pharyngitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All vaccinees</strong></td>
<td>21 (24%)</td>
<td>67</td>
</tr>
<tr>
<td><strong>All controls</strong></td>
<td>44 (52%)</td>
<td>40</td>
</tr>
</tbody>
</table>

P = 0.0003

VE = 54% (30.3 - 70.2)

*We have a proof of concept of vaccine efficacy from CHIM*
Conclusions from experimental induction of GAS pharyngitis in humans

- Proof of concept of efficacy
- Safe
- Can generate efficacy data for candidate GAS vaccines
- Can be used to explore immune responses to GAS pharyngitis
- May ‘spotlight’ candidate correlates of protection
CONTROLLED HUMAN INFECTION FOR VACCINES AGAINST STREPTOCOCCUS PYOGENES
Observational sequential dose-escalation inpatient study aiming to develop a safe controlled human infection model of GAS pharyngitis in healthy adults, establishing the dose of \textit{emm75} GAS required to achieve a reproducible attack rate of $\geq 60\%$ within 5 days of direct oropharyngeal inoculation.
PHARYNGITIS

NO PHARYNGITIS

LEARNING

Dose escalation
Pathogenesis
Immune response
Correlate(s) of protection
Transmission

TESTING

Vaccines
Therapies
Diagnostics

SCREENING

6 DAY INPATIENT ADMISSION

6 MONTH PERIODIC OUTPATIENT FOLLOW-UP

CHIVAS
CONTROLLED HUMAN INFECTION
FOR VACCINES AGAINST STREPTOCOCCUS PYOGENES
<table>
<thead>
<tr>
<th>Feature</th>
<th>Ideal GAS pharyngitis CHIM strain</th>
<th>emm75 GAS</th>
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</thead>
<tbody>
<tr>
<td>Causes pharyngitis</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>Causes skin infection</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>Limited pre-existing immunity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncommon cause of iGAS</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>Uncommon cause of ARF and PSGN</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>Antibiotic susceptible</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>Whole genome sequence available</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>Predictable and limited virulence</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>Wide array of candidate vaccine antigens</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>Reliable growth in an animal-free medium</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>Not subject to repeated passage</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>Suitable for use in animal models</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>Compatible with laboratory assays</td>
<td>YES</td>
<td></td>
</tr>
</tbody>
</table>
**Step 1:** Challenge 1 volunteer at starting dose

- Safety check

**Step 2:** Challenge 4 volunteers (5 volunteers for the next dose)

- Move to next dose and go to step 2
- Yes: Step 3: Challenge further 5 volunteers
- No: Move to next dose and go to step 2

**Step 3:** Challenge further 5 volunteers

- Yes: Step 4: Challenge further 10 volunteers
- No: Move to next dose and go to step 2

**Step 4:** Challenge further 10 volunteers

- Yes: Dose confirmed
- No: Move to next dose and go to step 2

### GAS M75 dose

<table>
<thead>
<tr>
<th>Starting dose</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 x 10^5 CFU/mL</td>
<td>≥ 2/5 develop pharyngitis</td>
<td>≥ 7/10</td>
<td>≥ 15/20</td>
</tr>
<tr>
<td>1-3 x 10^6 CFU/mL</td>
<td>≥ 2/5</td>
<td>≥ 7/10</td>
<td>≥ 14/20</td>
</tr>
<tr>
<td>1-3 x 10^7 CFU/mL</td>
<td>≥ 2/5</td>
<td>≥ 6/10</td>
<td>≥ 13/20</td>
</tr>
<tr>
<td>1-3 x 10^8 CFU/mL</td>
<td>≥ 2/5</td>
<td>≥ 6/10</td>
<td>≥ 12/20</td>
</tr>
</tbody>
</table>
SCREENING

6 DAY INPATIENT ADMISSION

6 MONTH PERIODIC OUTPATIENT FOLLOW-UP

Microbiology

Mucosal immunity (saliva)

Humoral immunity (serum, saliva)

Cellular immunity (PBMC)

Proteomics (serum, plasma, saliva)

Transcriptomics (RNA): host, GAS

Genomics (DNA): host, GAS, microbiome
2. WHO Resolution on Rheumatic Heart Disease
Member States of the World Health Organization unanimously adopted a “Global Resolution on Rheumatic Fever and Rheumatic Heart Disease”

The Resolution was co-sponsored by countries from all six WHO regions.

The government of New Zealand, which led the drafting process to develop the Resolution, stated: ‘the facts and figures are clear’.

This argument was reinforced by the delegation of Namibia, who noted that the number of people living with RHD around the world was comparable to those living with HIV.
15. Potential future research areas may include: better understanding of disease epidemiology and case detection; further elucidation of the pathogenic mechanisms of disease, aiming to identify new pathways amenable to therapeutic intervention and to inform vaccine development and application; development of a safe and effective group A streptococcal vaccine; and development of a long-acting formulation of penicillin that might improve adherence to secondary prophylactic regimens. New tools for primary prevention including vaccines may improve the prospect for a global reduction in incidence of all syndromes related to group A streptococci, including cellulitis and sepsis, maternal and infantile morbidity, and of rheumatic heart disease, and reduce the use of antibiotics for sore throats (an important concern in the context of growing antimicrobial resistance resulting from antibiotic exposure).
“Research:… development of a safe and effective vaccine”

“...vaccines may improve the prospect for a global reduction in incidence of all syndromes related to group A streptococci, including cellulitis and sepsis, maternal and infantile morbidity, and of rheumatic heart disease, and reduce the use of antibiotics for sore throats (an important concern in the context of growing antimicrobial resistance resulting from antibiotic exposure).”
3. London Meeting
May 2018
WHO/IVI Global Stakeholder Consultation on Group A Streptococcal Vaccine Development
12-13th December, 2016, Sheraton Seoul Palace Gangnam Hotel, Seoul, Korea
Supported by: Shinil Corporation, CANVAS, RHD Action, MCRI
Defining the gaps and needs in:

(1) Global GAS epidemiology and diversity, burden of disease
(2) Immunology and pathophysiology
(3) Pre-clinical vaccine development
(4) Clinical vaccine development
(5) Licensure pathway, policy recommendations, commercialization & delivery
WHO IVR Consultation on GAS vaccine R&D
16-17th May 2018
Wellcome Trust, London, UK
Objectives

• Review the present status of GAS vaccine R&D, and identify bottlenecks
• Build consensus on priority R&D pathways including establishment of proof of concept, safety guards, stage gates, case definitions
• Review evidence gaps related to medical need and potential value of vaccines
• Promote GAS vaccine R&D investments and stakeholder engagement
• Strengthen the institutional framework incl. research capacity in LMICs
• Provide vaccine stakeholders with guidance on priority activities:
  – WHO GAS vaccine technical R&D roadmap
  – WHO preferred product characteristics
• Promote implementation of the WHO roadmap *
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  - WHO GAS vaccine technical R&D roadmap
  - WHO preferred product characteristics
- Promote implementation of the WHO roadmap

Finalize WHO Roadmap

Finalize WHO Preferred Product Characteristics
4. WHO Roadmap for Strep A Vaccines
Strep A Vaccine Roadmap and PPC

WHO GAS Vaccine Advisory Group draft

Expert stakeholder review of draft

Public Consultation

London meeting

Final document
Roadmap 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.”
Roadmap goals

Near-term strategic goal: To demonstrate favourable safety and proof of efficacy of a candidate vaccine against GAS pharyngitis and skin infection in children.

Long-term strategic goal: To develop a safe, globally effective and affordable GAS vaccine 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.
Research

Global burden of disease estimates and epidemiology

Spectrum of natural disease history, esp. post-infectious diseases

Antibiotic use, and impact of a vaccine on AMR
Vaccine development

Antigen discovery - more candidates

Consensus on safety monitoring

Immunological surrogates / correlates of protection

Pivotal clinical trial design (near and long-term goals)
Key capacities

Define role of animal models, including NHP

Develop CHIM for early POC

Establish expert research centres in LMICs

Access low-cost cGMP manufacturing

Develop standardised quality immune assay platforms
Policy, commercialization and delivery

Vaccine value proposition - full scope of costs and benefits

Functional, cost-effective immunisation delivery platform

Post-implementation surveillance platforms
5. WHO
Preferred Product Characteristics
for Strep A Vaccines
WHO PPC: bridging development, licensure, policy, financing, use

High level requirements:
Address a true public health need
Favourable value proposition

Implementation
Financing
Informing GAVI Vaccine Investment Strategy
Country interest
INTRODUCTION

I. Background and purpose

II. Public health need for GAS vaccines

III. WHO strategic goals for GAS vaccines
   I. Near-term goals
   II. Long-term goals

IV. Clinical research and development considerations
   I. Vaccine construct, antigen target
   II. Target population
   III. Efficacy evaluation
   IV. Safety evaluation
   V. Value proposition

PREFERRED PRODUCT CHARACTERISTICS: Parameters
Preferred Product Characteristics: parameters

1. Indication
2. Target population for primary immunization
3. Schedule, primary immunization and boosting
4. Efficacy targets
5. Strain and serotype coverage
6. Safety
7. Adjuvant requirement
8. Immunogenicity
9. Non-interference
10. Route of administration
11. Registration, prequalification and programmatic suitability
12. Value proposition
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preferred Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Target population for primary immunization</strong></td>
<td>Primary schedule: infants and/or young children.</td>
</tr>
<tr>
<td><strong>Schedule, primary immunization and boosting</strong></td>
<td>No more than three doses required for primary immunization</td>
</tr>
<tr>
<td><strong>Efficacy targets</strong></td>
<td>Preferences for target efficacy differ according to the severity of the target disease syndrome.</td>
</tr>
<tr>
<td></td>
<td>- 80% protection against non-severe, non-invasive, confirmed GAS disease</td>
</tr>
<tr>
<td></td>
<td>- 70% protection against confirmed GAS cellulitis and other invasive infections</td>
</tr>
<tr>
<td></td>
<td>- 50% protection against long term immune-mediated sequelae</td>
</tr>
<tr>
<td><strong>Strain and serotype coverage</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Safety and reactogenicity profile at least as favourable as current WHO-recommended routine vaccines.</td>
</tr>
<tr>
<td><strong>Adjuvant requirement</strong></td>
<td>Preference for the absence of an adjuvant. Evidence should be generate to justify adjuvant inclusion in the formulation.</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Established correlate/surrogate of protection based on a validated assay measuring immune effector levels/functionality.</td>
</tr>
<tr>
<td><strong>Non-interference</strong></td>
<td>Demonstration of favourable safety and immunologic non-interference upon co-administration with recommended other vaccines if used in the same target population.</td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td>Injectable (IM, ID, or SC) using standard volumes for injection as specified in programmatic suitability for PQ or needle-free delivery.</td>
</tr>
<tr>
<td><strong>Registration, prequalification and programmatic suitability</strong></td>
<td>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 (Appendix 1).</td>
</tr>
<tr>
<td><strong>Value proposition</strong></td>
<td>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 low and middle income countries.</td>
</tr>
</tbody>
</table>
Near-term strategic goals:

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

- required
- highly desired / required
Long-term strategic goals

Primary prevention
Antibiotic treatment

Secondary prevention
Antibiotic prophylaxis

Tertiary prevention
Surgical/medical

VACCINE

Cellulitis
Pharyngitis
Impetigo
Invasive infections

ACUTE INFECTIONS

Superficial infections

Primary prevention
Antibiotic treatment

Secondary prevention
Antibiotic prophylaxis

Tertiary prevention
Surgical/medical

POST-INFECTIONOUS/IMMUNE

Non-communicable

Rheumatic Heart Disease
Chronic renal failure

Accelerated cardiovascular disease
Renal replacement therapy

Heart failure
Stroke
2. Target population

- Primary schedule: infants and/or young children.

**Research Notes:**

- Which? Early infancy, or early childhood
- Booster?
- Special circumstances:
  - Secondary prevention in subjects at increased risk of RHD
  - Immunization of adults at increased risk of cellulitis or severe invasive disease
  - Women
  - Campaigns for outbreaks
4. Efficacy targets

- Targets differ according to the severity of target disease:
  - 80% against non-severe, non-invasive, confirmed GAS disease
  - 70% against confirmed GAS cellulitis and other invasive infections
  - 50% against long-term immune-mediated sequelae
Research Notes:

• Stage-gate criteria:
  • CHIM may be valuable
  • Early proof of concept focusing on pharyngitis
  • Cellulitis and invasive infections will require larger sample size
  • Pilot implementation or post-licensure studies for less frequent endpoints

• Vaccine development informed by epidemiological characterization.
  • Comprehensive characterization of causal pathways leading to RHD
  • An evidence-based determination of the reduction in RHD to be expected from a vaccine-mediated prevention of pharyngitis would be highly valuable.
5. Strain and serotype coverage

• Vast majority (preference >90%) of the current disease-causing isolates from the region targeted for use are prevented.

Research Notes:

• Immune assays to infer strain/serotype specificity of protection.

• The role of variation over time and potential for bacterial population replacement should be characterized.
6. Safety

- Safety and reactogenicity profile at least as favourable as current WHO-recommended routine vaccines
Research Notes:

• A stage-gate vaccine development strategy should be developed to minimize subject exposure to a vaccine-derived risk of immune sequelae.

• The role of sequence homology analysis, pre-clinical animal models, human tissue reactivity, and human antigen screening should be defined.

• The intensity of safety investigations should be tailored to the amount of accrued evidence about the safety profile.

• Safety endpoints of interest should be protocol defined. The role of special investigations such as echocardiography and autoimmune antibodies should be defined.
12. 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.

Research Notes:

- Reduction of antibiotic use in routine practice of high added value.
- The vaccine impact on health systems, economic impact and other aspects of implementation science should be evaluated in large trials, pre- or post-approval, as practicable.
Acknowledgements

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Mark Walker

Jerome Kim

Jonathan Carapetis

Nikki Moreland
John Fraser
PART B: Strep A Vaccine Enterprise
(Jerome Kim)
A Strep A Vaccine Enterprise?

Stakeholder Engagement, Collaborative Partnerships, Institutional Framework

Dr Jerome Kim
27 June 2018
GAS mortality is substantial

Mortality by year (GBD)

Deaths

- RHD
- Pyoderma
- Cellulitis

Year: 1990 to 2015

Number of deaths: 0 to 400,000

Source: JS Lee using IHME estimates
# Work in Progress: Spending on Vaccine R&D, 2016

<table>
<thead>
<tr>
<th>Disease Area</th>
<th>Basic Research</th>
<th>Vaccine Spending</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV/AIDS</td>
<td>166.87</td>
<td>72.4 M</td>
</tr>
<tr>
<td>Malaria</td>
<td>136.90</td>
<td>20.11</td>
</tr>
<tr>
<td>P. falciparum</td>
<td>68.76</td>
<td>89.75</td>
</tr>
<tr>
<td>P. vivax</td>
<td>9.73</td>
<td>6.49</td>
</tr>
<tr>
<td>Other malaria strains</td>
<td>60.40</td>
<td>65.07</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>151.84</td>
<td>265.19</td>
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<tr>
<td>Diarrhoeal diseases</td>
<td>34.14</td>
<td>8.83</td>
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<tr>
<td>Rotavirus</td>
<td>5.67</td>
<td>0.42</td>
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<tr>
<td>Shigellosis</td>
<td>15.19</td>
<td>0.54</td>
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<tr>
<td>Cholera</td>
<td>5.24</td>
<td>7.43</td>
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<tr>
<td>Cryptosporidium</td>
<td>8.24</td>
<td>1.01</td>
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<tr>
<td>Enterotoxigenic E. coli (ETEC)</td>
<td>3.41</td>
<td>0.16</td>
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<tr>
<td>Enterohemorrhagic E. coli (EagEC)</td>
<td>1.09</td>
<td></td>
</tr>
<tr>
<td>Giardia</td>
<td>7.04</td>
<td>0.12</td>
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<tr>
<td>Multiple diarrhoeal diseases</td>
<td>50.30</td>
<td>51.10</td>
</tr>
<tr>
<td>Kinetoplastis</td>
<td>16.51</td>
<td>4.91</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>15.81</td>
<td>14.35</td>
</tr>
<tr>
<td>Sleeping sickness (HAT)</td>
<td>10.00</td>
<td>13.86</td>
</tr>
<tr>
<td>Chagas' disease</td>
<td>13.07</td>
<td>7.85</td>
</tr>
<tr>
<td>Multiple kinetoplastis diseases</td>
<td>3.45</td>
<td>25.02</td>
</tr>
<tr>
<td>Dengue</td>
<td>49.92</td>
<td>28.45</td>
</tr>
<tr>
<td>Bacterial pneumonia &amp; meningitis</td>
<td>9.20</td>
<td>61.29</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>7.52</td>
<td>57.87</td>
</tr>
<tr>
<td>N. meningitidis</td>
<td>0.98</td>
<td>23.52</td>
</tr>
<tr>
<td>Both S. pneumoniae and N. meningitidis</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Salmonella infections</td>
<td>45.49</td>
<td>37.56</td>
</tr>
<tr>
<td>Typhoid and paratyphoid fever (S. Typhi, S. Paratyphi A)</td>
<td>31.13</td>
<td>2.96</td>
</tr>
<tr>
<td>Non-typhoidal S. enterica (NTS)</td>
<td>2.95</td>
<td>0.46</td>
</tr>
<tr>
<td>Multiple Salmonella infections</td>
<td>11.40</td>
<td>0.30</td>
</tr>
<tr>
<td>Helminth infections (worms &amp; flukes)</td>
<td>28.49</td>
<td>30.00</td>
</tr>
<tr>
<td>Schistosomiasis (bilharziasis)</td>
<td>10.13</td>
<td>2.90</td>
</tr>
<tr>
<td>Lymphatic filariasis (elephantiasis)</td>
<td>5.64</td>
<td>7.27</td>
</tr>
<tr>
<td>Onchocerciasis (river blindness)</td>
<td>1.31</td>
<td>7.38</td>
</tr>
<tr>
<td>Hookworm (anisakiasis &amp; necatoriasis)</td>
<td>0.27</td>
<td>0.25</td>
</tr>
<tr>
<td>Tapeworm (cestodes/cysticercosis)</td>
<td>1.76</td>
<td>1.68</td>
</tr>
<tr>
<td>Whiteworm (trichuriasis)</td>
<td>0.87</td>
<td>0.94</td>
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<tr>
<td>Strongylodiasis &amp; other intestinal roundworms</td>
<td>0.68</td>
<td>0.47</td>
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<tr>
<td>Roundworm (ascaris)</td>
<td>0.83</td>
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<tr>
<td>Multiple helminth infections</td>
<td>7.01</td>
<td>8.82</td>
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<tr>
<td>Hepatitis C (genotypes 4, 5, &amp; 6)</td>
<td>11.92</td>
<td>3.47</td>
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<tr>
<td>Leprosy</td>
<td>6.57</td>
<td>0.13</td>
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<tr>
<td>Cryptococcal meningitis</td>
<td>5.64</td>
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<td>Buruli ulcer</td>
<td>1.05</td>
<td>1.17</td>
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<tr>
<td>Leptospirosis</td>
<td>1.90</td>
<td>1.18</td>
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<tr>
<td>Trachoma</td>
<td>1.19</td>
<td></td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>1.18</td>
<td></td>
</tr>
</tbody>
</table>

- **HIV Vaccines**: $724 M
- **TB Vaccines**: $73 M
- **Shigella Vaccines**: $18 M
- **NTS vaccines**: $0.4 M
- **Schisto vaccines**: $2.3 M
- **GAS vaccines**: $1.2 M

Minimal current funding for GAS vaccine R&D.

*G-finder Report, 2017*
Newly Approved Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Company</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue (Dengvaxia®)</td>
<td>Sanofi</td>
<td>COFEPRIS, Dec 2015</td>
</tr>
<tr>
<td>DTPHibHepiPV (Vaxelis®)</td>
<td>Merck &amp; Co., Inc, Sanofi</td>
<td>EMA, Feb 2016</td>
</tr>
<tr>
<td>HPV (Gardasil 9®)</td>
<td>Merck &amp; Co., Inc.</td>
<td>FDA, Dec 2014</td>
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<tr>
<td>HPV (Gardasil®) Controlled Temperature Chain</td>
<td>Merck &amp; Co., Inc.</td>
<td>EMA</td>
</tr>
<tr>
<td>Meningococcal A (MenAfriVac®) 5 µg dose</td>
<td>Serum Institute of India</td>
<td>WHO, Dec 2014</td>
</tr>
<tr>
<td>for children under one year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal B (Trumenba®)</td>
<td>Pfizer</td>
<td>FDA, Oct 2014</td>
</tr>
<tr>
<td>Pneumococcal (Prevenar 13®) four-dose vial</td>
<td>Pfizer</td>
<td>EMA, Apr 2016</td>
</tr>
<tr>
<td>Rabies</td>
<td>Serum Institute of India</td>
<td>CDSCO, Jun 2016</td>
</tr>
<tr>
<td>Seasonal influenza (VaxiGripTetra™)</td>
<td>Sanofi</td>
<td>UK, Jul 2016</td>
</tr>
</tbody>
</table>

• 1/3 of R&D covers new vaccine targets
• At least 32 diseases have no vaccines from companies in review
• Cost
  ▪ $500M less complex vaccine
  ▪ $1 B more complex vaccine
• Failure rate
  ▪ Only 7% of vaccines reaching preclinical development are licensed
  ▪ Hi Risk, no Incentive – why spend $1 B with a high risk of failure and a low ROI if successful?

Diseases without vaccine R&D

- Adenovirus
- Amoebiasis
- Balantidiasis
- Buruli ulcer
- Campylobacter enteritis
- Chagas disease
- Cryptosporidiosis
- Cytomegalovirus (CMV)
- Dracunculiasis
- Echinococcosis
- Food-borne trematodiasis
- Giardiasis
- Hantavirus pneumonia
- Human African trypanosomiasis
- Human metapneumovirus
- Human monkeypox
- Isosporiasis
- Klebsiella pneumoniae
- Lassa fever
- Leishmaniasis
- Leprosy
- Lymphatic filariasis
- Onchocerciasis
- Parainfluenza
- Pneumocystis jiroveci
- Schistosomiasis
- Severe Acute Respiratory Syndrome (SARS)
- Soil-transmitted helminthiasis
- Taeniais/cysticercosis
- Trachoma
- Yaws
- Yersinia enterocolitica

Diseases that don’t make the list of diseases without vaccine R&D
- Group A Strep?
- Hepatitis E?
- Non typhoidal Salmonella?
- Shigella?

Access to Vaccines Index 2017
Do we need another “Initiative, Consortium...”?

Yes.

- The burden of GAS is substantial
- It is a disease that has minimal funding
- It is a disease for which no major vaccine company has an active funded program

What would a consortium do?

- Enact/enable the R&D Roadmap
  - Advocacy >> Engage stakeholders
  - Push technical workstreams
- Create the Public Health Value Proposition with WHO
  - Full Public Health Value Proposition
    - Business Case
    - Investment Case (Direct and Indirect benefits)
A Strep A Vaccine Enterprise (SAVE)?
What makes partnerships successful?

Advocacy

Vaccine Development Pathway
- Preclinical: 1-3 years
- Clinical: 6-7 years
- Registration: 1-1.5 years
- Launch: Life cycle management

Programs
- Preclinical, Animal, Toxicology Proof of Concept, Process Development
- Tech Transfer, Trial Sites, Project Management, Trial Execution, Data Management
- Host Country NRA Strengthening & Coordination, WHO Prequalification
- Uptake, Access Health Economics, Vaccination Campaigns

Science
- Discovery
- Development
- Delivery
- Epidemiology, Disease Burden Research

Funding
- Commitment
- Funding
- Vaccine candidate
- Clinical Development plan
- Plan for use/delivery
A Consortium is a part of the beginning

- WHO PPC and R&D Roadmap complete
- There is a World Health Assembly call to action
- Needs
  - Strep A vaccine consortium
  - Roadmap driven increases in funding, prioritization, and coordination
  - Public health value proposition: Business case, Investment case
  - Manufacturer(s)
  - End-to-end thinking (integrated product development plan through implementation)
Short term goals

- Make the issue known to potential stakeholders
- 1 or more manufacturers / DCVMN
- Commitments to funding GAS vaccine development
- Commitment to advance workstream funding
- FPHVP
  - Business case
  - Investment case
Questions and discussion