Vaccine development for Group A Streptococcus

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Group A Streptococcal Research Group, Murdoch Children’s Research Institute, Melbourne
Department of General Medicine, Royal Children’s Hospital Melbourne, Australia
Outline

1. Pathogen and disease
2. The unmet need
3. Evidence for protective immunity
4. Vaccine candidate landscape
5. Vaccine development pipeline: challenges and potential solutions
Pathogen and disease
The pathogen

A ubiquitous human pathogen
Disease spectrum

- Pharyngitis
  - Scarlet fever
  - Impetigo
  - Invasive disease
    - Toxic shock syndrome
    - Acute glomerulonephritis
    - Acute rheumatic fever
      - Rheumatic heart disease
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) → Rheumatic Heart Disease (RHD) → RHD morbidity (Heart failure, Atrial fibrillation, Infective endocarditis, Stroke) → Death
Disease spectrum

- Pharyngitis
- Impetigo
- Invasive
Disease spectrum

- ARF
- APSGN
- Rheumatic heart disease
- Chronic kidney disease

Incidence vs. Age (years)
Burden of disease: Defining the unmet need
Burden of disease

- Pharyngitis
- Impetigo
- Invasive disease
  - Acute glomerulonephritis
  - Acute rheumatic fever
  - Rheumatic heart disease

615 million incident cases
162 million prevalent cases
660,000 incident cases
470,000 incident cases
470,000 incident cases
30 million cases

Bowen et al. PLoS ONE 2015;10(8):0136789
Rheumatic heart disease

Infectious disease
Immune-mediated disease
Chronic non-communicable disease

~30 million patients

GBD figures 2013 courtesy David Watkins, U Washington
Rheumatic heart disease

The REMEDY study

Registry study of 3343 patients in 25 hospitals in Africa, India, Middle East

Disease of young women
- Median age 28 years
- Two-thirds female

A complicated and progressive chronic disease
- Two-thirds with moderate-severe multi-valve disease
- One-third with heart failure
- One-quarter on oral anti-coagulation therapy

Zuhlke et al. Eur Heart J 2015
Rheumatic heart disease

Case study: Fiji

-2619 patients over 5 years: 378 deaths (14%)
-2nd most common cause of death 5-29 years

Parks T, et al. PLOS NTD 2015
Rheumatic heart disease

~30 million patients

~1 million with heart failure

~300,000 deaths p.a.

GBD figures 2013 courtesy David Watkins, U Washington
Burden of disease: mortality

Rheumatic heart disease

Lozano et al. Lancet 2012
Invasive disease

High-income: 3-5 per 100,000
CFR: ~10-15%

USA
11,500 cases
>1000 deaths

EU
15,000 cases
2400 deaths
Severe community acquired sepsis (after introduction of Nm immunisation)
Invasive disease

**USA**
11,500 cases
850 deaths

**EU**
15,000 cases
2400 deaths

**High-income:** 3-5 per 100,000
**CFR:** ~10-15%
Invasive Group A *Streptococcus* Infection among Children, Rural Kenya


Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 22, No. 2, February 2016

**Kilifi: 1998 – 2011**

Surveillance in children < 5 years:

- Incidence < 5 years: 35 per 100,000
- Incidence < 1 year: 101 per 100,000
- Incidence < 28 days: 0.6 per 1000 (CFR 38%)
Burden of disease: mortality

Rheumatic heart disease

Lozano et al. Lancet 2012
Burden of disease: mortality

Rheumatic heart disease and invasive disease

Deaths (1000's)

- HIV
- TB
- Malaria
- Snp
- Influenza
- Hib
- GAS
- Rotavirus
- Typhoid

Lozano et al. Lancet 2012
Carapetis, Mulholland, Steer, Weber Lancet ID 2005
Pharyngitis

Acute sore throat (USA)
15 million visits per year in adults & children
10-30% are caused by GAS

GAS pharyngitis in children (USA)
10-15% of children per year
$224 - 539 million per year
Pharyngitis

Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis: 2012 Update by the Infectious Diseases Society of America

Stanford T. Shulman,1 Alan L. Bisno,2 Herbert W. Clegg,3 Michael A. Gerber,4 Edward L. Kaplan,5 Grace Lee,6 Judith M. Martin,7 and Chris Van Beneden8

RECOMMENDATIONS FOR THE DIAGNOSIS OF GAS PHARYNGITIS

I. How Should the Diagnosis of GAS Pharyngitis Be Established?

Recommendations

1. Swabbing the throat and testing for GAS pharyngitis by rapid antigen detection test (RADT) and/or culture should be performed because the clinical features alone do not reliably discriminate between GAS and viral pharyngitis except when overt viral features like rhinorrhea, cough, oral ulcers, and/or hoarseness are present. In children and adolescents, negative RADT tests should be backed up by a throat culture (strong, high). Positive RADTs do not necessitate a back-up culture because they are highly specific (strong, high).

RECOMMENDATIONS FOR THE TREATMENT OF PATIENTS WITH GAS PHARYNGITIS

III. What Are the Treatment Recommendations for Patients With a Diagnosis of GAS Pharyngitis?

Recommendations

8. Patients with acute GAS pharyngitis should be treated with an appropriate antibiotic at an appropriate dose for a duration likely to eradicate the organism from the pharynx (usually 10 days). Based on their narrow spectrum of activity, infrequency of adverse reactions, and modest cost, penicillin or amoxicillin is the recommended drug of choice for those non-allergic to these agents (strong, high).
Pharyngitis

Antibiotic Prescribing to Adults with Sore Throat in the United States, 1997–2010

Michael L. Barnett, MD and Jeffrey A. Linder, MD, MPH
Division of General Medicine and Primary Care, Brigham and Women’s Hospital and Harvard Medical School. Both in Boston, Massachusetts

Anthea Dallas, Mieke van Driel, Thea van de Mortel and Parker Magin

Antibiotic prescribing for the future: exploring the attitudes of trainees in general practice

Pharyngitis

In conclusion, despite decades of effort, we found only incremental improvement in antibiotic prescribing for adults making a visit with sore throat. Combining our previous and present analyses, the antibiotic prescribing rate dropped from roughly 80% to 70% around 1993 and dropped again around 2000 to 60%, where it has remained stable. This still far exceeds the 10% prevalence of GAS among adults seeking care for sore throat. The prescription of broader-spectrum, more expensive antibiotics, especially azithromycin, was common. Prescribing of penicillin, which is guideline-recommended, inexpensive, well-tolerated, and to which GAS is universally susceptible, remained infrequent.
Out of 40m people who are given antibiotics for respiratory issues, annually in the US:

- 27m get antibiotics unnecessarily
- 13m who need antibiotics get them

Shapiro et al, JAC 2013
Vaccine development: evidence for protective immunity
Evidence for protective immunity

Acquired natural immunity
Evidence for protective immunity

- Impetigo
- Invasive
- Pharyngitis
Evidence for protective immunity

PERSISTENCE OF TYPE-SPECIFIC ANTIBODIES IN MAN FOLLOWING INFECTION WITH GROUP A STREPTOCOCCI

BY REBECCA C. LANCEFIELD, Ph.D.

(From The Rockefeller Institute)

(Received for publication, April 17, 1959)

Studies on Immunity to Streptococcal Infections in Man. Dr. Lewis W. Wannamaker, Cheyenne, Wyo., Dr. Floyd W. Denny, Dr. William D. Perry, Dr. Alan C. Siegel, and Dr. Charles H. Rammekamp, Jr., Cleveland.

AMA Am J Dis Child 1953;86:347-8
Evidence for protective immunity

Acquired natural immunity

Extensive pre-clinical animal data
Animal data

- Nasal challenge
- Skin challenge
- IP injection
Evidence for protective immunity

Acquired natural immunity

Extensive pre-clinical animal data

Human challenge model
Evidence for protective immunity

The Journal of Clinical Investigation Volume 52 August 1973-1885-1892

Protective Study with a Group A Streptococcal M Protein Vaccine

INFECTIVITY CHALLENGE OF HUMAN VOLUNTEERS

EUGENE N. FOX, ROBERT H. WALDMAN, MASAKO K. WITTNER
ARTHUR A. MAUWER, and ALBERT DORFMAN

From the La Rabida Children’s Hospital and Research Center, University
of Chicago, Chicago, Illinois 60649 and the Department of Medicine,
University of Florida, Gainesville, Florida, 32610


University of Florida College of Medicine, Department of Medicine,
Gainesville, Florida 32610, USA

and

University of Chicago La Rabida Children’s Hospital and Research Center,
Department of Pediatrics, Chicago, Illinois 60649, USA

GROUP A STREPTOCOCCAL M PROTEIN VACCINE:
PROTECTION FOLLOWING IMMUNIZATION
VIA THE RESPIRATORY TRACT

R. H. Waldman, J. D. Lee, S. M. Polly, A. Dorfman and E. N. Fox

THE JOURNAL OF INFECTIOUS DISEASES • VOL. 131, NO. 3 • MARCH 1975
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Protective Studies with a Group A Streptococcal M Protein Vaccine.
II. Challenge of Volunteers after Local Immunization
in the Upper Respiratory Tract

S. M. Polly,* R. H. Waldman,
P. High, M. K. Wittner,
A. Dorfman, and E. N. Fox

From the Department of Medicine, University of
Florida School of Medicine, Gainesville, Florida;
and the La Rabida Children’s Hospital and Research
Center and the Department of Pediatrics,
University of Chicago, Chicago, Illinois
Evidence for protective immunity

Volunteers vaccinated GAS vaccine type M1 n=19

Volunteers vaccinated Placebo vaccine n=19

Throat painted with GAS type M1

1 patient developed GAS pharyngitis*

9 patients developed GAS pharyngitis

*Protective efficacy 89% p<0.01

Fox J Clin Invest 1973
Can a vaccine prevent rheumatic heart disease?

Infectious disease

Primary prevention

Group A Streptococcal Infection

Susceptible person

Acute Rheumatic Fever (ARF)

Immune-mediated disease

Rheumatic Heart Disease (RHD)

Recurrent ARF

Chronic non-communicable disease

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

DEATH
Primary prevention

### Comparison: 02 Penicillin versus control

**Outcome:** 01 Incidence of Rheumatic Fever

<table>
<thead>
<tr>
<th>Study</th>
<th>Penicillin n/N</th>
<th>Control n/N</th>
<th>RR (95%CI Fixed)</th>
<th>Weight %</th>
<th>RR (95%CI Fixed)</th>
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<td>Bennike, 1951</td>
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<td>0 / 164</td>
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<td>5 / 198</td>
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<td>Wannamaker, 1951</td>
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<td>53.7</td>
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<td><strong>Total</strong></td>
<td>12 / 3464</td>
<td>63 / 3238</td>
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<td>100.0</td>
<td>0.20[0.11,0.36]</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=2.57 df=6 p=0.86
Test for overall effect z=-5.39 p=0.00001

**RR 0.20**
Can a vaccine prevent rheumatic heart disease?

Primary prevention

Infectious disease

Immune-mediated disease

Chronic non-communicable disease

Group A Streptococcal Infection

Susceptible person

Acute Rheumatic Fever (ARF)

Rheumatic Heart Disease (RHD)

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

DEATH
Vaccine candidate landscape
Vaccine candidate landscape

M-based designs / non M-based candidates

- 26-valent vaccine
- 30-valent vaccine
- J8 vaccine
- StreptInCor

Basis of M / emm typing

(V223 types)
Vaccine candidate landscape

Non M-protein (active pre-clinical work)

- 4-antigen vaccine (“Combo”):
  - CHO, SLO, SpyCEP, Spy0269
- Pilus
- SpeAB
- F7M5
- Spy469, spy1228, spy1801
- Spy7
Vaccine candidate landscape

Non M-protein (status unclear)

– Streptococcal C5a protease
– Fibronectin binding proteins
  • Sfb1, Sfb2, SfbX, Protein F2, FbaB
  • FbaA, Fbp54, GAPDH, shr
– GAS carbohydrate
– Platelet-Activating Factor Acetylhydrolase SsE
– Others
26-valent vaccine (StreptAvax)

26-valent vaccine clinical trial
- Based on 6-valent vaccine
- Adult volunteers

Safety
- Few systemic side effects
- No tissue cross-reactive antibodies
- No evidence of rheumatogenicity or nephritogenicity observed

Immunogenicity
- Post-vaccination serologic response (≥4-fold) to 20 of 26 epitopes
- Functional opsonic antibodies induced against all vaccine emm types

McNeil Clin Infect Dis 2005
### 30-valent vaccine (StreptAnova)

#### Protein 1

<table>
<thead>
<tr>
<th>Protein</th>
<th>M1</th>
<th>3.1</th>
<th>M6.4</th>
<th>M2</th>
<th>M18</th>
<th>M28</th>
<th>M12</th>
<th>SPA</th>
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#### Protein 2

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<th>M5.14</th>
<th>M11</th>
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<th>M29</th>
<th>M14.3</th>
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<td>(1-25)2</td>
<td>1-50</td>
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<td>(1-25)2</td>
<td>1-45</td>
<td>1-50</td>
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#### Protein 3

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<tr>
<th>Protein</th>
<th>M77</th>
<th>M22</th>
<th>M73</th>
<th>M89</th>
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<th>M118</th>
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</table>

#### Protein 4

<table>
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<th>Protein</th>
<th>M83.1</th>
<th>M82</th>
<th>M81</th>
<th>M87</th>
<th>M49</th>
<th>M92</th>
<th>M114</th>
<th>M83.1</th>
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<tbody>
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<td>1-50</td>
<td>1-50</td>
<td>1-50</td>
<td>1-50</td>
<td>1-50</td>
<td>1-50</td>
</tr>
</tbody>
</table>
30-valent vaccine (StreptAnova)

Phase I trial has completed enrolment

- Vaxent
- 38 healthy volunteer adults enrolled (2:1 vaccine:comparator ratio)
- Schedule of 3 vaccinations over 6 months: 0, 30 and 180 days
- No initial safety issues
- Immunonogenicity available this year
- 1 year safety follow-up
J8 vaccine

-Anti-J8 antibodies increase with age

-Animal studies:
  -Stimulate production of opsonic antibodies
  -Protect against IP challenge (parenteral vaccine)
  -Protect against IN challenge (IN vaccine)

-Phase 1 trial (single dose): safe / immunogenic in 10 volunteers

-New preclinical data with S2 epitope of SpyCEP

Courtesy Prof Michael Good
J8 vaccine

Pandey M et al, J Immunol 2016
J8 vaccine

J8-Crm197 + S2-Crm197:
- adjuvanted with Alum for IM injection
- Australian and Canadian funding
- Phase I trial: multiple doses (x3)

J8-Liposomes.
- intranasal delivery
- IgA induction in mice
- Nasal challenge protection in mice.
Vaccine development: StreptInCor

-Developed in Brazil
-55 amino acids of the C-terminus of M protein
-Immunogenic and protective in animal studies
-GMP production: PolyPeptide Group USA
-Formulation: Butantan Institute Brazil

-Scheduled to enter Phase I/IIa trials in 2016/17

Courtesy Prof Luiza Guilherme
Vaccine development: clinical pipeline

M protein

– M protein type specific
  • 26 valent vaccine
  • 30 valent vaccine
– M protein conserved
  • J8-DT
  • J8-crm197 + S2-crm197
  • StreptInCor

Phase I/II completed
Phase I enrolment complete
Phase I* completed
Phase I shortly to start
Phase I shortly to start
Vaccine development: challenges (and potential solutions)
Challenges

Technical
1. Strain diversity
2. Standardisation of immunoassay
3. Animal model
4. Safety

Impeded pipeline
1. No consensus on PPC / TPP → CDP
2. Limited engagement, limited investment
Challenges

Technical
1. Strain diversity
2. Standardisation of immunoassay
3. Animal model
4. Safety

Impeded pipeline
1. No consensus on PPC / TPP → CDP
2. Limited engagement, limited investment
1. Strain diversity ➔ multivalent vaccine

-Fiji studies: prospective surveillance >400 isolates ➔ 67 emm types

26-valent vaccine

2009 Study: >38,000 isolates from across the globe

% of isolates included in vaccine

<table>
<thead>
<tr>
<th>Region</th>
<th>% of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Income</td>
<td>75</td>
</tr>
<tr>
<td>Latin America</td>
<td>65</td>
</tr>
<tr>
<td>Middle East</td>
<td>60</td>
</tr>
<tr>
<td>Asia</td>
<td>60</td>
</tr>
<tr>
<td>Africa</td>
<td>20</td>
</tr>
<tr>
<td>Pacific</td>
<td>10</td>
</tr>
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</table>
26-valent ➔ 30-valent

30-valent vaccine: the solution?

- More than just addition of further M peptides
- Takes into consideration concept of “cross-opsonization”

Cross-protection experiments
- Bacterial antibodies evoked in rabbits by the 30-valent vaccine
- Antibodies kill both vaccine (VT) and non-vaccine (NVT) emm types

Dale et al, Vaccine 2011
Total *emm*-types tested:
n=117 (30 VT, 87 NVT)

-VT and NVT: Over 50% killing = 99/117 (85%)

-Just NVT: Over 50% killing = 69/87 (79%)
## 30-valent vaccine

<table>
<thead>
<tr>
<th></th>
<th>% Total isolates (cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VT only</td>
</tr>
<tr>
<td>Pharyngitis-US</td>
<td>98</td>
</tr>
<tr>
<td>Invasive Disease-US</td>
<td>90</td>
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<tr>
<td>Invasive Disease-Europe</td>
<td>78</td>
</tr>
<tr>
<td>Pharyngitis-Bamako</td>
<td>40</td>
</tr>
<tr>
<td>Pharyngitis-Cape Town</td>
<td>59</td>
</tr>
</tbody>
</table>

Dale et al Vaccine 2013
Vaccine coverage

>1500 isolates

Regional representation

Clinical representation

All sequenced

All being evaluated for vaccine antigens +/-

Set of 150 core isolates available to developers
Challenges

Technical
1. Strain diversity
2. Standardisation of immunoassay
3. Animal model
4. Safety

Impeded pipeline
1. No consensus on PPC / TPP → CDP
2. Limited engagement, limited investment
2. Immunoassay

<table>
<thead>
<tr>
<th>Immunoassay</th>
<th>Advantages</th>
<th>Disadvantages</th>
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</thead>
<tbody>
<tr>
<td>ELISA</td>
<td>High-throughput</td>
<td>May measure non-functional antibodies</td>
</tr>
<tr>
<td></td>
<td>Easily standardized</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reproducible</td>
<td></td>
</tr>
<tr>
<td>Bactericidal assays</td>
<td>Measures functional antibodies</td>
<td>Labour-intensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inter-assay variability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use of whole human blood imposes two hour time restriction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No controls for DBT</td>
</tr>
</tbody>
</table>

David Goldblatt UCL
-HL-60 assay for *emm1* strain
Challenges

Technical
1. Strain diversity
2. Standardisation of immunoassay
3. Animal model
4. Safety

Impeded pipeline
1. No consensus on PPC / TPP → CDP
2. Limited engagement, limited investment
3. Animal model

Alam F et al. PLoS ONE 2013
Interactome analysis of longitudinal pharyngeal infection of cynomolgus macaques by group A *Streptococcus*

Patrick R. Shea\(^a\), Kimmo Virtaneva\(^b\), John J. Kupko 3rd\(^b\), Stephen F. Porcella\(^b\), William T. Barry\(^c\,1\), Fred A. Wright\(^c\), Scott D. Kobayashi\(^d\), Aaron Carmody\(^b\), Robin M. Ireland\(^d\), Daniel E. Sturdevant\(^b\), Stacy M. Ricklefs\(^b\), Imran Babar\(^b,2\), Claire A. Johnson\(^b\), Morag R. Graham\(^d,3\), Donald J. Gardner\(^e\), John R. Bailey\(^e\), Michael J. Parnell\(^e\), Frank R. DeLeo\(^d\), and James M. Musser\(^a,4\)

The Journal of Clinical Investigation Volume 52 August 1973-1885-1892

Protective Study with a Group A Streptococcal M Protein Vaccine

INFECTIVITY CHALLENGE OF HUMAN VOLUNTEERS

Eugene N. Fox, Robert H. Waldman, Masako K. Wittner

Arthur A. Mauceri, and Albert Dorfman

From the La Rabida Children's Hospital and Research Center, University of Chicago, Chicago, Illinois 60649 and the Department of Medicine, University of Florida, Gainesville, Florida, 32601
Challenges

Technical
1. Strain diversity
2. Standardisation of immunoassay
3. Animal model
4. Safety

Impeded pipeline
1. No consensus on PPC / TPP → CDP
2. Limited engagement, limited investment
4. Safety

21 children who had a sibling with rheumatic fever

Purified M protein vaccine

Vaccinated weekly with increasing concentrations

*For 18 – 33 weeks*

Reduction in number of GAS infections

3* vaccinees developed rheumatic fever

Massell JAMA 1969;207:1115
4. Safety

-Nature of Massell trial

-M protein vaccine studies not consistent

-Over 11,000 GAS vaccine recipients, no signal

-Naturally acquired M protein immunity does not cause ARF

-New M protein vaccines exclude “cross-reactive” sequences
Challenges

Technical
1. Strain diversity
2. Standardisation of immunoassay
3. Animal model
4. Safety

Impeded pipeline
1. No consensus on PPC / TPP $\rightarrow$ CDP
2. Limited engagement, limited investment
1. TPP → Clinical development plan

What is the indication?

- Pharyngitis
  - Scarlet fever
  - Impetigo
  - Invasive disease
    - Toxic shock syndrome
    - Acute glomerulonephritis
    - Acute rheumatic fever
      - Rheumatic heart disease
1. TPP → Clinical development plan

Clinical development plans written:

canvas

Vaxent
1. TPP → Clinical development plan

Phase 1 – safety and tolerability in adults

Phase 2a – step-down dosing

Phase 2b – efficacy against pharyngitis (+/- impetigo)

Phase 3 – efficacy against pharyngitis (final lot)
Challenges

Technical
1. Strain diversity
2. Standardisation of immunoassay
3. Animal model
4. Safety

Impeded pipeline
1. No consensus on PPC / TPP → CDP
2. Limited engagement, limited investment
The future is optimistic for the development of safe and effective GAS vaccines.
Vaccine development: pipeline

Very large burden of disease and unmet need
Vaccines in phase 1 or before, but none beyond

GAS vaccine investment 2014:

<$5 million
<0.1% of NTD global health funding

WHY?
WHY?

- Safety concerns?
- Lack of TPP / CDP?
- Complex trial design?
- Inadequate epi Data?
- Inadequate understanding of biology?
- No POC in humans?
- No confidence in candidates?
- Perception of the market?

HIC
LMIC
Vaccine development: pipeline

Pipeline strengths
- “Easy” read-out for initial phase III trials (pharyngitis)
- Prevent pharyngitis = prevent ARF and RHD
- Potential for role of human challenge
- CANVAS initiative*
- Global investment case: divide drivers*
Vaccine development: pipeline

CANVAS
(Coalition to Advance New Vaccines for GAS)
-New Zealand and Australian governments
-3-year funding period complete end 2016
-Three main areas:
  -1. Strain selection panel
  -2. Economic evaluation
  -3. Assay development
-Next phase unclear
Global investment case

**High-income countries:**
- Prevent strep throat
- Prevent invasive disease (incl. cellulitis)*
- Reduce health care costs
- Reduce antibiotic use

**Low- and middle-income countries:**
- Prevent ARF/RHD
- Prevent invasive disease
- Reduce excess mortality
- +/- impetigo & APSGN
Global GAS vaccine consortium

Emerging consortium of interested partners:
- International Vaccine Institute
- Hilleman
- GSK Vaccines Institute for Global Health
- Others...
Summary

-Very large burden of disease and need: HIC & LMIC
  -HPV-like disease (RHD)
  -Nm-like disease (IGAS)
  -Potential to reduce AMR

-Vaccines in pipeline (but only few)
-Significant other work around vaccine trial readiness

-Levers are needed to advance development
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