Vaccine development for Group A Streptococcus

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The future is optimistic for the development of safe and effective GAS vaccines.
Outline

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

Acute Rheumatic Fever (ARF)

Carditis

Recurrent ARF

Rheumatic Heart Disease (RHD)

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

DEATH
Disease spectrum

Impetigo
Invasive
Pharyngitis

Disease spectrum

ARF

Rheumatic heart disease

APSGN

Chronic kidney disease

Incidence

Age (years)

Burden of disease: Defining the unmet need
**Burden of disease**

- **Pharyngitis**
  - 615 million incident cases

- **Impetigo**
  - 162 million prevalent cases

- **Invasive disease**
  - 660,000 incident cases

- **Acute glomerulonephritis**
  - 470,000 incident cases

- **Acute rheumatic fever**
  - 470,000 incident cases

- **Rheumatic heart disease**
  - 34 million cases

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

Recurrent ARF

Rheumatic Heart Disease (RHD)

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

DEATH

34 million patients
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 to 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%)
- 2\textsuperscript{nd} most common cause of death 5-29 years
- Cost: 0.3% of total GDP

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

Infectious disease

>4.3 million with heart failure

>300,000 deaths p.a.

34 million patients

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

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

USA
- 11,500 cases
- 850 deaths

EU
- 15,000 cases
- 2400 deaths
Invasive Group A *Streptococcus* Infection among Children, Rural Kenya


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


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%)

Incidence < 1 year: 49 per 100,000
All-ages incidence: 10 per 100,000 (CFR 32%)
Burden of disease: mortality

Rheumatic heart disease

Lozano et al. Lancet 2012
Burden of disease: mortality

Rheumatic heart disease and invasive disease

Lozano et al. Lancet 2012
Carapetis, Mulholland, Steer, Weber Lancet ID 2005
Vaccine development: evidence for protective immunity
Evidence for protective immunity

Acquired natural immunity
Evidence for protective immunity

Evidence for protective immunity

Acquired natural immunity

Extensive pre-clinical animal data

Human challenge model
Evidence for protective immunity

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. MAUCKER, and ALBERT DORFMAN

From the La Rabida Children’s Hospital and Research Center, University of Chicago, Chicago, Illinois 60640 and the Department of Medicine, University of Florida, Gainesville, Florida, 32610


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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 with GAS vaccine type M1 n=19
- Volunteers vaccinated with Placebo vaccine n=19

Volunteers vaccinated with GAS vaccine type M1 n=19 → Throat painted with GAS type M1 → 1 patient developed GAS pharyngitis*

Volunteers vaccinated with Placebo vaccine n=19 → Throat painted with GAS type M1 → 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  Immune-mediated disease  Chronic non-communicable disease

Primary prevention

Group A Streptococcal Infection

Susceptible person

Acute Rheumatic Fever (ARF)

Rheumatic Heart Disease (RHD)

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

DEATH
Primary prevention

<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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</thead>
<tbody>
<tr>
<td>Bennike, 1951</td>
<td>0 / 174</td>
<td>0 / 184</td>
<td>-</td>
<td>0.0</td>
<td>Not Estimable</td>
</tr>
<tr>
<td>Brink, 1951</td>
<td>2 / 197</td>
<td>5 / 198</td>
<td>-</td>
<td>7.6</td>
<td>0.40[0.08,2.05]</td>
</tr>
<tr>
<td>Brock, 1953</td>
<td>0 / 262</td>
<td>1 / 97</td>
<td>-</td>
<td>3.4</td>
<td>0.11[0.00,2.71]</td>
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<tr>
<td>Brumfit, 1957</td>
<td>0 / 62</td>
<td>0 / 59</td>
<td>-</td>
<td>0.0</td>
<td>Not Estimable</td>
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<td>Charnowitz, 1954</td>
<td>0 / 132</td>
<td>2 / 109</td>
<td>-</td>
<td>4.2</td>
<td>0.17[0.01,3.41]</td>
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<tr>
<td>Denny, 1950</td>
<td>2 / 798</td>
<td>17 / 804</td>
<td>-</td>
<td>25.8</td>
<td>0.12[0.03,0.51]</td>
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<tr>
<td>Denny, 1953</td>
<td>1 / 53</td>
<td>1 / 50</td>
<td>-</td>
<td>1.6</td>
<td>0.94[0.06,14.68]</td>
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<tr>
<td>Siegel, 1961</td>
<td>0 / 808</td>
<td>2 / 605</td>
<td>-</td>
<td>3.8</td>
<td>0.20[0.01,14.14]</td>
</tr>
<tr>
<td>Wannenmaker, 1961</td>
<td>7 / 1178</td>
<td>35 / 1162</td>
<td>-</td>
<td>53.7</td>
<td>0.20[0.09,0.44]</td>
</tr>
<tr>
<td>Total (95%CI)</td>
<td>12 / 3464</td>
<td>63 / 3238</td>
<td>-</td>
<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

Robertson et al  *BMC Cardiovasc Disord* 2005
Vaccine candidate landscape
Vaccine candidate landscape

M-based designs / non M-based candidates

- 26-valent vaccine
- 30-valent vaccine (223 types)
- J8 vaccine
- StreptInCor

Basis of M / emm typing

VARIABLE REGION

CONSERVED REGION

Steer Curr Op Infect Dis 2009
Vaccine candidate landscape

Non M-protein

- 4-antigen vaccine (“Combo”):
  - CHO, SLO, SpyCEP, Spy0269
- Pilus
- Streptococcal C5a protease
- Fibronectin binding proteins
  - Sfb1, Sfb2, SfbX, Protein F2, FbaB
  - FbaA, Fbp54, GAPDH, shr
- GAS carbohydrate
- Others...
26-valent vaccine (Vaxent)

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
**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>70</td>
</tr>
<tr>
<td>Latin America</td>
<td>60</td>
</tr>
<tr>
<td>Middle East</td>
<td>60</td>
</tr>
<tr>
<td>Asia</td>
<td>50</td>
</tr>
<tr>
<td>Africa</td>
<td>30</td>
</tr>
<tr>
<td>Pacific</td>
<td>20</td>
</tr>
</tbody>
</table>

26-valent $\rightarrow$ 30-valent (StreptAnova)

30-valent vaccine (StreptAnova): 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%)

Slide adapted from Prof Jim Dale
### 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>
</tr>
<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
30-valent vaccine

Phase I trial has started
- Vaxent & Pan-Provincial Vaccine Enterprise Inc. (PREVENT)
- 38 healthy volunteer adults enrolled
- Schedule of 3 vaccinations over 6 months: 0, 30 and 180 days
- 1 year follow-up to assess safety and immune response to the vaccine
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 SpyCEP

-Re-formulation as J8-DT+S2-DT: phase 1 trials planned

Courtesy Prof Michael Good
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: pipeline
Vaccine development: pipeline

M protein

- M protein type specific
  - 26 valent vaccine: Phase I/II completed
  - 30 valent vaccine: Phase I started

- M protein conserved
  - J8-DT: Phase I* completed
  - J8-DT plus rSpyCEP: Phase I shortly to start
  - StreptInCor: Phase I shortly to start
The Jordan Report
20th Anniversary
Accelerated Development of Vaccines 2002

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, but none beyond

HIV vaccine investment 2014: $840 million
TB vaccine investment 2014: $60 million
GAS vaccine investment 2014: <$5 million

WHY?
Vaccine development: pipeline

Pipeline weaknesses
GAS vaccine development is *impeded*
- Limited commercial and NGO interest
- Limited public engagement
- No consensus on PPC / TPP
- No consensus on clinical development plan
- Lack of standardization of immuno-assays
Vaccine development: pipeline

Pipeline strengths

- “Easy” read-out for initial phase III trials (pharyngitis)
- Prevent pharyngitis = prevent ARF and RHD
- Immuno-assays under active development
- 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
-Aim to bring GAS vaccine to Phase III
-Three main areas:
  -1. Strain selection panel
  -2. Economic evaluation
  -3. Assay development
Global investment case

**High-income countries:**
- Prevent strep throat
- Prevent invasive disease
- Reduce health care costs
- Reduce antibiotic use

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

- Very large burden of disease and need: HIC & LMIC
- Protective immunity apparent
- Promising vaccine candidates in Phase 1
- Levers are needed to advance development
With thanks to

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