Vaccine development for Group A Streptococcus

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With thanks to

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-Jim Dale, University of Tennessee, USA
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-Allan Saul, GSK
-Florian Schodel, MedImmune Inc
-Pierre Smeesters, Belgium
Outline

1. Pathogen, disease and the unmet need
2. Evidence for why a vaccine should work
3. Possible antigenic targets
4. Most advanced candidate
5. Other candidates
6. Vaccine development pipeline
7. Assessment and role of WHO
Pathogen, disease and defining the unmet medical need
Pathogen, disease and defining the unmet medical need

- Pharyngitis
  - Scarlet fever
  - Impetigo
- Invasive disease
  - Acute glomerulonephritis
  - Acute rheumatic fever
- Rheumatic heart disease
Pathogen, disease and defining the unmet medical need

Pharyngitis: 615 million new cases
Impetigo: 162 million cases*
Invasive disease: 660,000 new cases
Kidney disease: 470,000 new cases
Acute rheumatic fever: 470,000 new cases
Rheumatic heart disease: 34 million cases

Carapetis et al. Lancet ID 2005
Bowen et al. PLoS ONE 2015
Pathogen, disease and defining the unmet medical need
Pathogen, disease and defining the unmet medical need

Rheumatic heart disease

<table>
<thead>
<tr>
<th></th>
<th>2010 (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>34.2</td>
</tr>
<tr>
<td>YLL</td>
<td>8.7</td>
</tr>
<tr>
<td>YLD</td>
<td>1.4</td>
</tr>
<tr>
<td>DALY</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Lozano et al. Lancet 2012
Pathogen, disease and defining the unmet medical need

Rheumatic heart disease – the REMEDY study

Registry study of 3343 patients
25 hospitals in Africa, India, Yemen

Disease of young women
-Median age 28 years and two-thirds were female

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

Zuhlke et al. Eur Heart J 2015
Pathogen, disease and defining the unmet medical need

Rheumatic heart disease

<table>
<thead>
<tr>
<th></th>
<th>2010 (millions)</th>
<th>2015</th>
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<tr>
<td>Prevalence</td>
<td>34.2</td>
<td></td>
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<tr>
<td>YLL</td>
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<td></td>
</tr>
<tr>
<td>DALY</td>
<td>10.1</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>345,110*</td>
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</tbody>
</table>

Lozano et al. Lancet 2012
Pathogen, disease and defining the unmet medical need

Rheumatic heart disease – case study Fiji

- 2619 patients over 5 years: 378 deaths
- 2.6-fold difference in the death rate cf. GBD
- 2nd most common cause of death 5-29 years
- Cost: 0.3% of total GDP

Pathogen, disease and defining the unmet medical need

Invasive group A streptococcal disease

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Incidence per 100,000</th>
<th>CFR</th>
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</thead>
<tbody>
<tr>
<td>US</td>
<td>2000 – 04</td>
<td>3.5</td>
<td>14%</td>
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<tr>
<td>Canada</td>
<td>2000 – 02</td>
<td>3.8</td>
<td>11%</td>
</tr>
<tr>
<td>Australia</td>
<td>2002-04</td>
<td>2.7</td>
<td>8%</td>
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<th>Country</th>
<th>Year</th>
<th>Incidence per 100,000</th>
<th>CFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiji</td>
<td>2000 – 04</td>
<td>10.4</td>
<td>32%</td>
</tr>
<tr>
<td>Kenya</td>
<td>2000 – 02</td>
<td>13</td>
<td>25%</td>
</tr>
</tbody>
</table>
Pathogen, disease and defining the unmet medical need

UK: direct maternal death rate: 4.67 per 100,000

Sepsis: 1.13 per 100,000

50% of sepsis due to GAS

Brit J Obstet Gynaecol 2011
Pathogen, disease and defining the unmet medical need

Lozano et al. Lancet 2012
Pathogen, disease and defining the unmet medical need

Rheumatic heart disease and invasive disease

Lozano et al. Lancet 2012
Pathogen, disease and defining the unmet medical need

What are the key gaps?

Data from LMICs (the population at highest risk)

Rheumatic heart disease:
- Burden of established RHD
- Mortality data (including contribution of RHD to stroke deaths)
- Economic impact

Invasive GAS disease:
- Puerperal and neonatal sepsis
- Bacteremia in LMIC esp. Africa, including CFR

Kidney disease – role of PSGN in ESRF
Pathogen, disease and defining the unmet medical need

Preventative strategies

Pharyngitis (and scarlet fever)
- treatment available
- no prevention

Impetigo
- treatment available
- prevention may involve control of triggers (e.g. scabies)

Invasive disease (and toxic shock syndrome)
- treatment available but high mortality
- no prevention
Pathogen, disease and defining the unmet medical need

Preventative strategies

**Kidney disease**
- possible prevention if pharyngitis and impetigo treated

**Rheumatic fever**
- "primary prevention"

**Rheumatic heart disease**
- "secondary prevention"
Pathogen, disease and defining the unmet medical need

Primary prevention

Group A Streptococcal Infection
(e.g. Streptococcal pharyngitis ("Strep throat")

Susceptible person

Acute Rheumatic Fever (ARF)

Carditis

Rheumatic Heart Disease (RHD)

Recurrent ARF

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

DEATH
Pathogen, disease and defining the unmet medical need

Primary prevention

**RR 0.20 (95% CI 0.11 – 0.36)**

Robertson et al  *BMC Cardiovasc Disord* 2005
Pathogen, disease and defining the unmet medical need

Primary prevention: not that simple

Multiple individual level barriers to prevention:
- 25% of patients with ARF report prior GAS infection
- Potential role of GAS impetigo in ARF
- Attendance for clinical care in LMICs
- Adherence to treatment

Multiple health care systems issues
- Access to health care centres
- Quality and staffing of health care facilities, training of health care staff
- Availability and reliability of diagnostic tests
- Stocking and supply of antibiotics
Pathogen, disease and defining the unmet medical need

Primary prevention

Secondary prevention

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
Pathogen, disease and defining the unmet medical need

Secondary prevention

Highly effective in preventing recurrent ARF
- Can prevent progression of RHD
- Able to be implemented as public health initiative

But does not prevent RHD in the first place
Pathogen, disease and defining the unmet medical need

Target indications/populations in LMICs

Prevention of ARF and RHD
- Prevent pharyngitis
- Pre-school dosing schedule

Prevention of invasive disease
- Prevent maternal / infant disease
- Maternal or infant dosing schedule

Combined approach for all GAS disease
- Infant schedule with school entry booster
Vaccine development: evidence for why a vaccine should work
Vaccine development: evidence for why a vaccine should work

Acquired immunity
- disease frequency reduces with age
- prospective studies of protection following natural infection (protection up to 30 years) – serotype ($emm$ type) specific

Preclinical POC data
- Multiple studies showing protection of vaccinated animals against challenge infection (IP, IN, SC challenge)
- Passive transfer of antibody studies

Human challenge data
Vaccine development: evidence for why a vaccine should work

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 60640 and the Department of Medicine, University of Florida, Gainesville, Florida, 32601


University of Florida College of Medicine, Department of Medicine,
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University of Chicago La Rabida Children's Hospital and Research Center,
Department of Pediatrics, Chicago, Illinois 60649, USA

GROUP A STEPTOCOCCAL 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
Vaccine development: evidence for why a vaccine should work

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
Possible antigenic targets
Possible antigenic targets

M-based designs / non M-based candidates

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

Steer Curr Op Infect Dis 2009
Possible antigenic targets

Non M-protein

– 4-antigen vaccine (“Combo”):
  • SLO, SpyCEP, Spy0269

– Pilus

– Streptococcal C5a protease

– Fibronectin binding proteins
  • Sfb1, Sfb2, SfbX, Protein F2, FbaB
  • FbaA, Fbp54, GAPDH, shr

– GAS carbohydrate

– Others…
Vaccine development: most advanced candidate (Vaxent)
Vaccine development: most advanced candidate (Vaxent)

26-valent vaccine clinical trial
- Based on 6-valent vaccine
- 120 adult volunteers

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

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

*McNeil Clin Infect Dis 2005*
Vaccine development: most advanced candidate (Vaxent)

26-valent vaccine: disadvantage
- Concerns re: “coverage”

Established market economies

Steer Lancet Infect Dis 2009
Vaccine development: most advanced candidate (Vaxent)

26-valent vaccine: disadvantage

- Concerns re: “coverage”

Pacific region

Steer Lancet Infect Dis 2009
Vaccine development: most advanced candidate (Vaxent)

26-valent vaccine: disadvantage

- Concerns re: “coverage”

% of isolates included in vaccine

<table>
<thead>
<tr>
<th>Region</th>
<th>% of isolates included in vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Income countries</td>
<td>70</td>
</tr>
<tr>
<td>Latin America</td>
<td>70</td>
</tr>
<tr>
<td>Middle East</td>
<td>60</td>
</tr>
<tr>
<td>Asia</td>
<td>60</td>
</tr>
<tr>
<td>Africa</td>
<td>30</td>
</tr>
<tr>
<td>Pacific</td>
<td>20</td>
</tr>
</tbody>
</table>

Steer Lancet Infect Dis 2009
Vaccine development: most advanced candidate (Vaxent)

30-valent vaccine (StreptAnova): the solution?

- More than just addition of further emm types
- Takes into consideration concept of “cross-opsonization” between emm types

Cross-protection experiments
- Bacterial antibodies evoked in rabbits by the 30-valent vaccine kill both GAS of vaccine (VT) and non-vaccine (NVT) emm types
Vaccine development: most advanced candidate (Vaxent)

30-valent vaccine (StreptAnova): the solution?

<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
Vaccine development: most advanced candidate (Vaxent)

30-valent vaccine (StreptAnova): the solution?

A Systematic and Functional Classification of Streptococcus pyogenes That Serves as a New Tool for Molecular Typing and Vaccine Development

Martina Sanderson-Smith,1 David M. P. De Oliveira,1,2 Julien Guglielmini,2,3,4 David J. McMillan,4,5 Therese Vu,4,6 Jessica K. Holien,7 Anna Henningham,8 Andrew C. Steer,9,10,11 Debra E. Bessen,12 James B. Dale,13,14,15 Nigel Curtis,9,16,17 Bernard W. Beall,18 Mark J. Walker,8 Michael W. Parker,7,19 Jonathan R. Carapetis,20 Laurence Van Melderen,6 Kadaba S. Sriprakash,4 and Pierre R. Smeesters,6,9 The M Protein Study Group

Sanderson-Smith J Infect Dis 2014
Vaccine development: most advanced candidate (Vaxent)

30-valent vaccine (StreptAnova): the solution?

Phase I trial has started
-Vaxent & Pan-Provincial Vaccine Enterprise Inc. (PREVENT)
-45 healthy volunteer adults
-Schedule of 3 vaccinations over 6 months
-1 year follow-up to assess safety and immune response to the vaccine

Clinical development pathway beyond Phase I trial
-May move to safety/immunogenicity in adolescents and pre-school children
-Possibly then to phase III trial with GAS pharyngitis as endpoint
Other vaccine candidates
Vaccine development: J8

J8 vaccine

- Anti-J8 antibodies increase with age
- Stimulate production of opsonic antibodies (mice)
- Protect against IP challenge (parenteral vaccine)
- Protect against IN challenge (IN vaccine)

- Phase 1 trial of single dose - safe / immunogenic

- Re-formulation with a CXC chemokine protease – protection against impetigo in murine model
Vaccine development: StreptInCor

StreptInCor

- Developed in Brazil
- 55 amino acids of the C-terminus of M protein
- Immunogenic and protective in animal studies

- Scheduled to enter Phase I trials in 2015
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
  - pepVac StreptInCor
    - Phase I shortly to start
Vaccine development: pipeline

Pipeline weaknesses
GAS vaccine development is *impeded*

- Limited commercial and NGO interest
- Limited public engagement
- No consensus on TPP
- No consensus on clinical development plan
- Lack of standardization of immuno-assays
Vaccine development: pipeline

Pipeline strengths
- Substantial vaccine-preventable disease burden
- Relatively easily measurable outcome measure for initial phase III trials (GAS pharyngitis)
- Prevent pharyngitis = prevent ARF
- Immuno-assays under active development
- Potential for role of human challenge
- CANVAS initiative*
- Initial efforts of development of roadmap*
Vaccine development: pipeline

CANVAS (Coalition to Advance New Vaccines for GAS)
-New Zealand and Australian governments
-Aim to bring GAS vaccine to Phase III
-Four main areas initially:
  -Strain selection panel
  -Economic evaluation
  -Assay development
  -Development of clinical plan
Conference report

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

Vaccine development: pipeline

Group A streptococcal vaccines: Paving a path for accelerated development

James B. Dale, Vincent A. Fischetti, Jonathan R. Carapetis, Andrew C. Steer, Samba Sow, Rajesh Kumar, Bongani M. Mayosi, Fran A. Rubin, Kim Mulholland, Joachim Maria Hombach, Florian Schödel, Ana Maria Henao-Restrepo

- Define immune correlates of protection
- Develop high throughput serologic and bactericidal assays
- Standardize epidemiologic protocols
- Establish clinical trial sites in GAS endemic countries
- Harmonize clinical trial design and safety protocols
- Propose GAS pharyngitis as the endpoint for phase III trials
- Establish collaboration b/w academia, industry and public health institutions
Assessment and role of WHO
Assessment and role of WHO

Potential role for WHO IVR

- Prioritize of prevention of GAS disease at global level
- Engage NGOs re: the burden of disease
- Co-ordinate disease burden documentation
- Promote vaccine pipeline / engage industry
- Lead development of standardized assays
- Lead clinical development pathway / PPC evaluation
- Lead/endorse a roadmap for vaccine development
Assessment and role of WHO

Potential role for WHO IVR

Documentation of disease burden
- Endorse further disease burden research
- Disease burden assessment protocols
- Targeted key areas (disease type, geographic)
- Establish sentinel sites
Assessment and role of WHO

Potential role for WHO IVR

Standardization of immuno-assays
- Antigen and serum standards
- New functional assay development
- Policy re: integration of assays into clinical development
Assessment and role of WHO

Potential role for WHO IVR

Clinical development pathway
- Engage key stakeholders
- Draft PPC
- Meeting to develop consensus for clinical development plan for a vaccine for LMICs
Assessment and role of WHO

Potential role for WHO IVR

A vaccine development roadmap
-Bring together these elements
-Comprehensive consensus document
-Engagement with KOLs and stakeholders
Thank you