Vaccine development for Group A Streptococcus

A/Prof Andrew Steer
Centre for International Child Health, University of Melbourne
Group A Streptococcal Research Group, Murdoch Children's Research Institute, Melbourne
Department of General Medicine, Royal Children's Hospital Melbourne, Australia

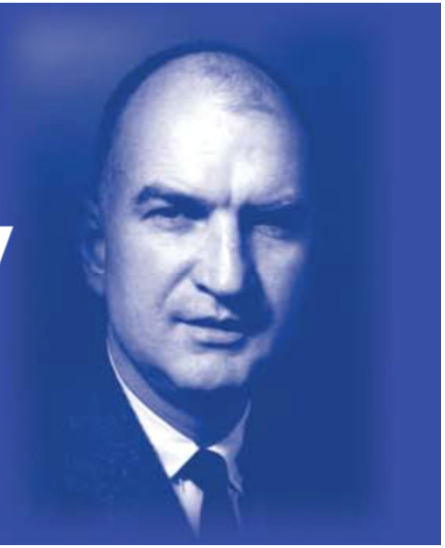
GVRIF Johannesburg March 2016

Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

The Jordan Report

20th Anniversary

Accelerated Development of Vaccines 2002



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

Melbourne Children's
Excellence in clinical care, research and education

The Royal Children's Hospital Melbourne
Murdoch Childrens Research Institute
The University of Melbourne

Outline

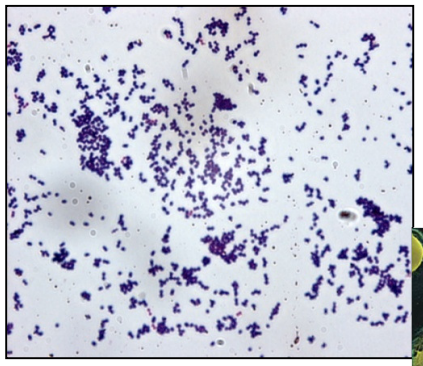
1. Pathogen and disease
2. The unmet need
3. Evidence for protective immunity
4. Vaccine candidate landscape
5. Vaccine development pipeline

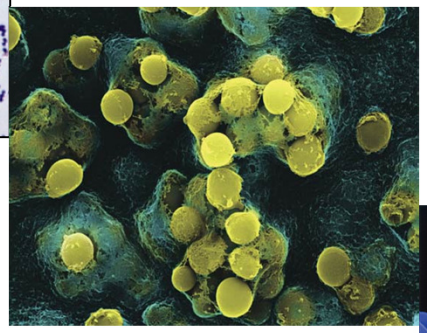
Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

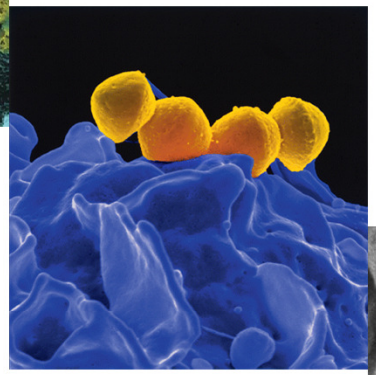
Pathogen and disease

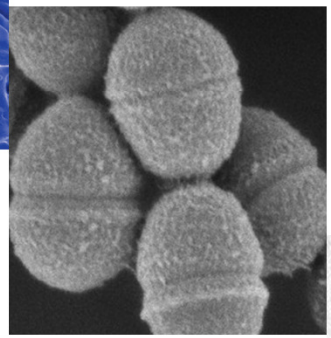
Melbourne Children's
Excellence in clinical care, research and education

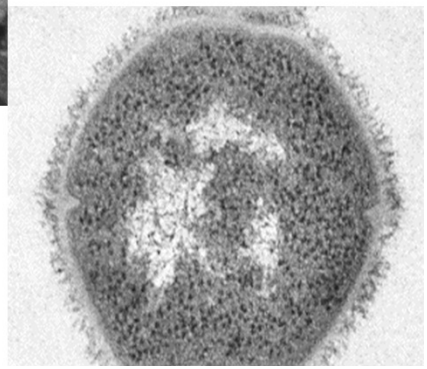
The pathogen





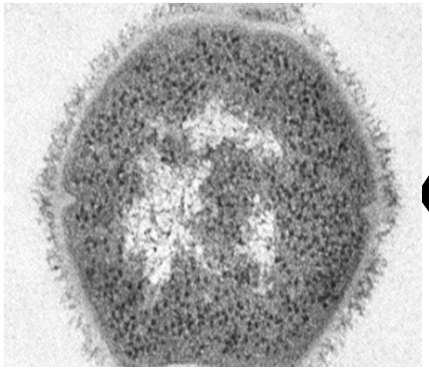




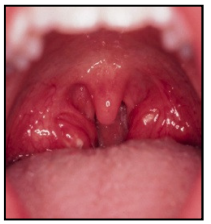


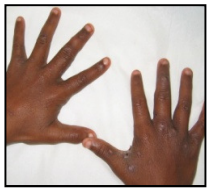
A ubiquitous human pathogen

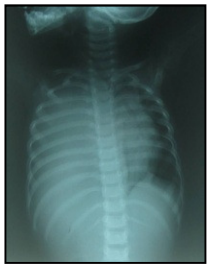
Disease spectrum

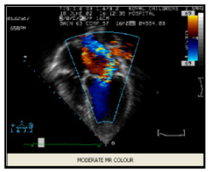


- Pharyngitis
  - Scarlet fever
- Impetigo
- Invasive disease
  - Toxic shock syndrome
- Acute glomerulonephritis
- Acute rheumatic fever
  - Rheumatic heart disease







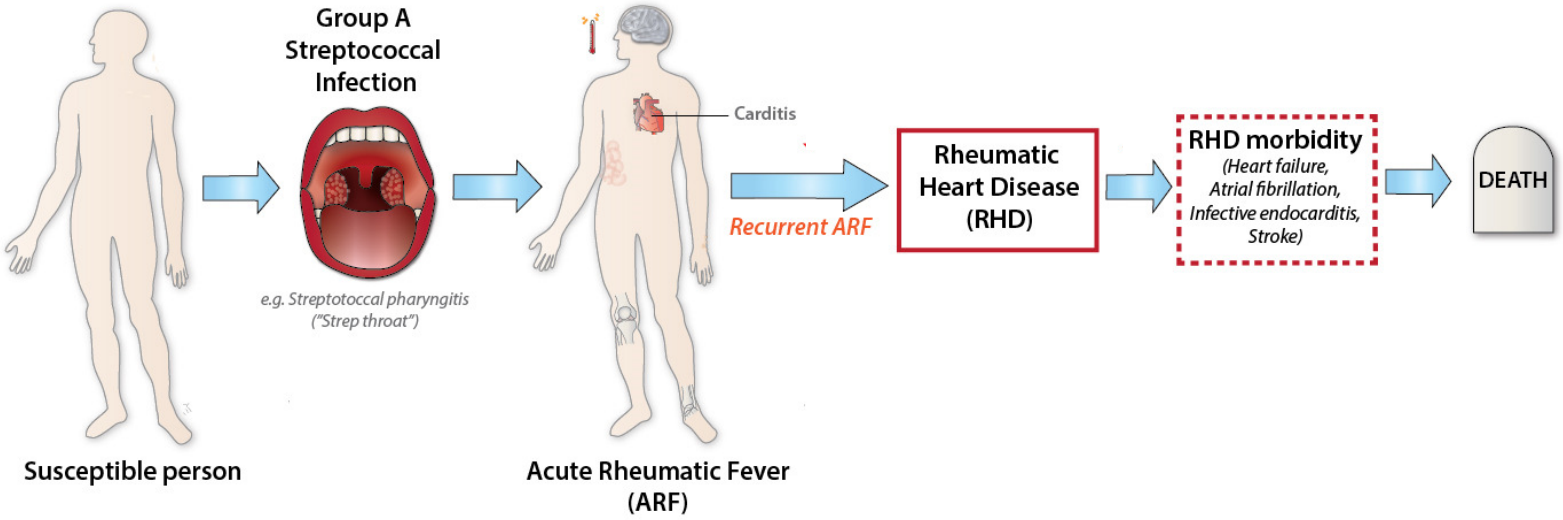


Rheumatic fever and rheumatic heart disease

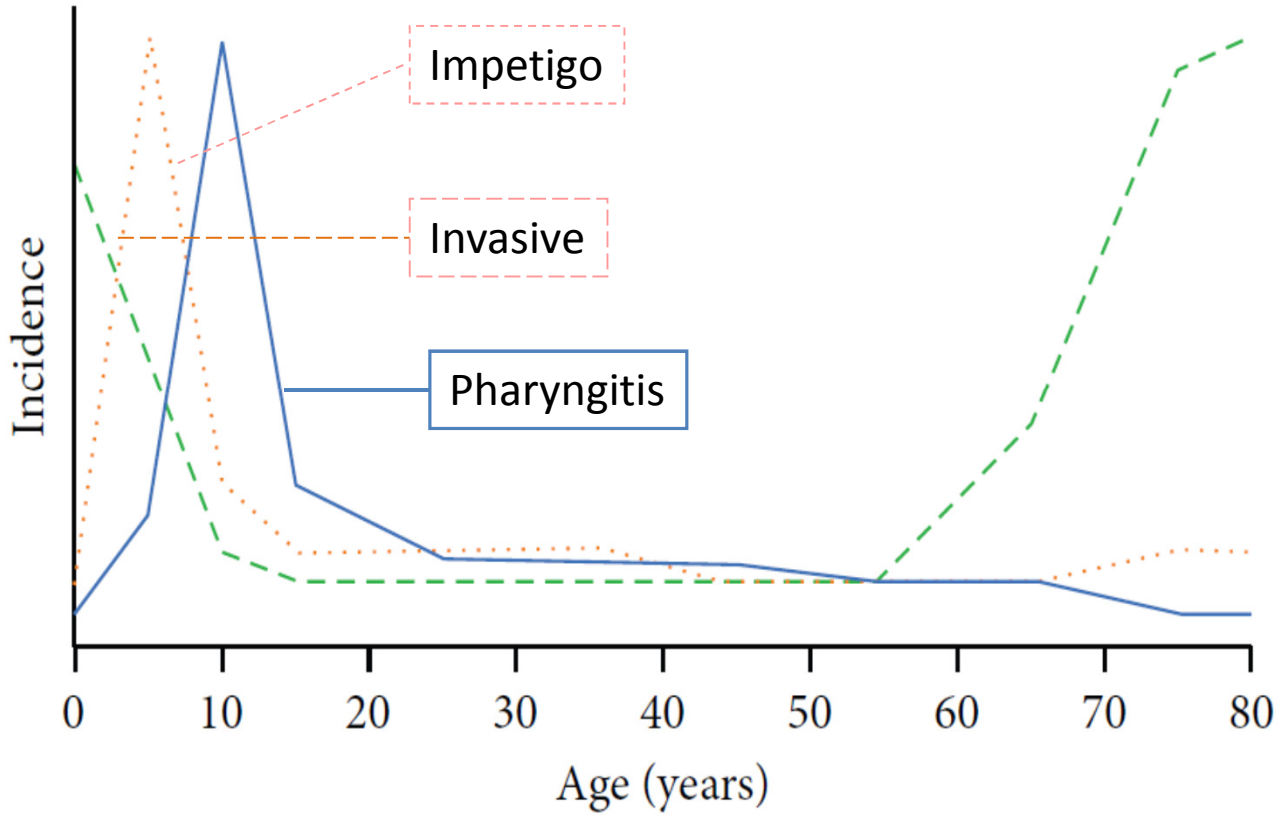
Infectious disease

Immune-mediated disease

Chronic non-communicable disease

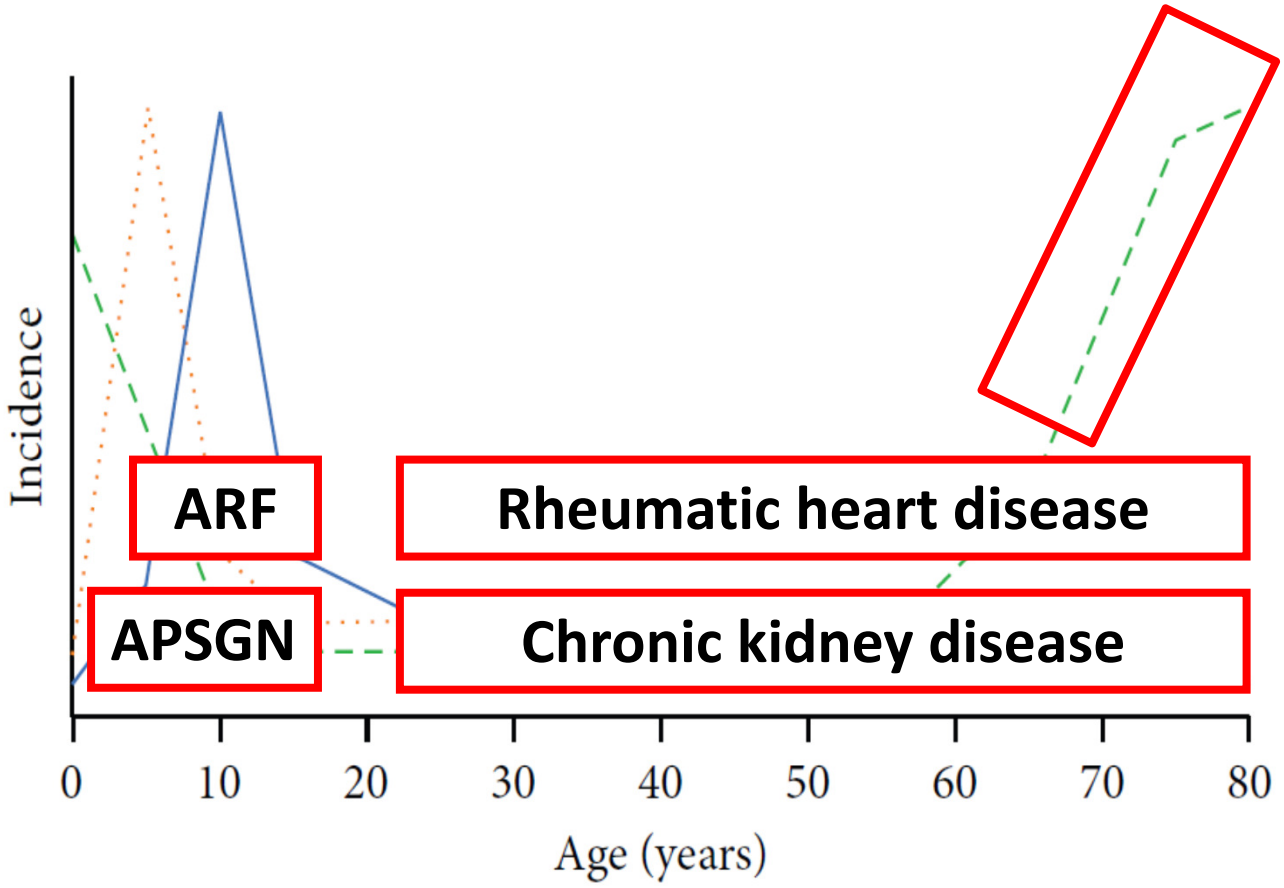


Disease spectrum



Tsoi et al. J Immunol Res 2015

Disease spectrum



Tsoi et al. J Immunol Res 2015

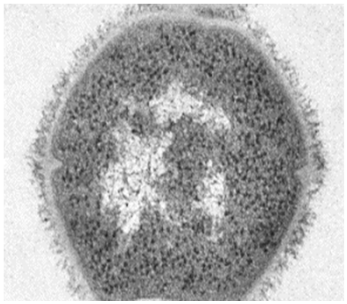
Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

Burden of disease: Defining the unmet need

Melbourne Children's
Excellence in clinical care, research and education

The Royal Children's Hospital Melbourne
Murdoch Childrens Research Institute
The University of Melbourne

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**

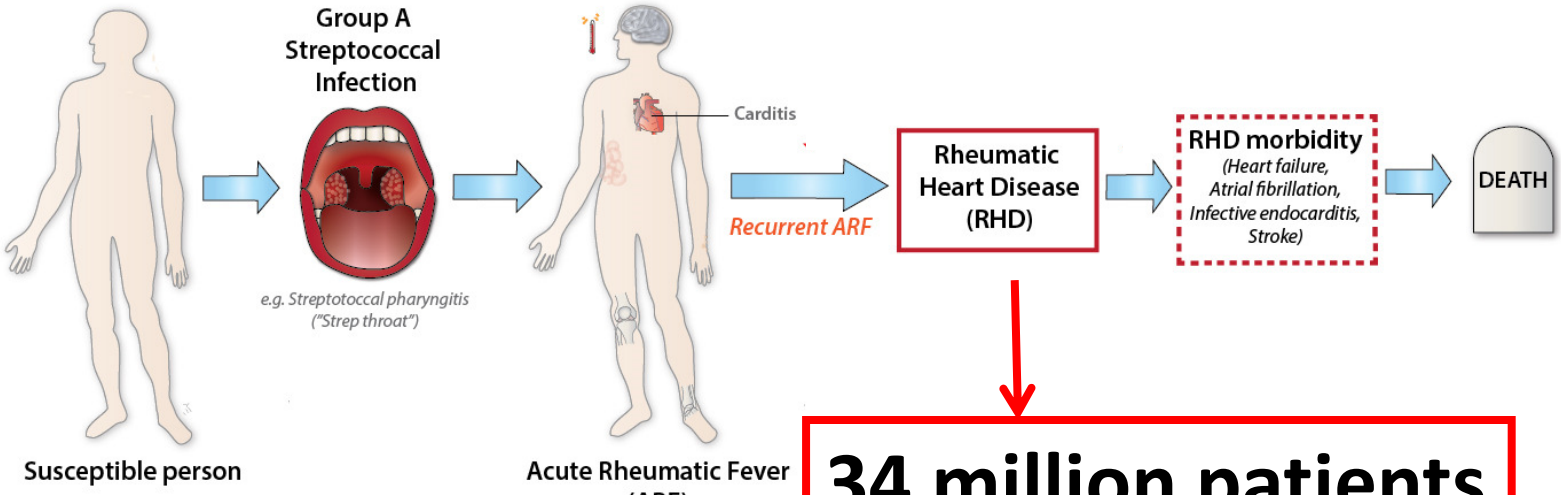
Carapetis JR, Steer AC, et al. Lancet Infect Dis 2005;5:685-94
Bowen et al. PLoS ONE 2015;10(8):0136789

Rheumatic heart disease

Infectious disease

Immune-mediated disease

Chronic non-communicable disease



34 million patients

Rheumatic heart disease

The REMEDY study

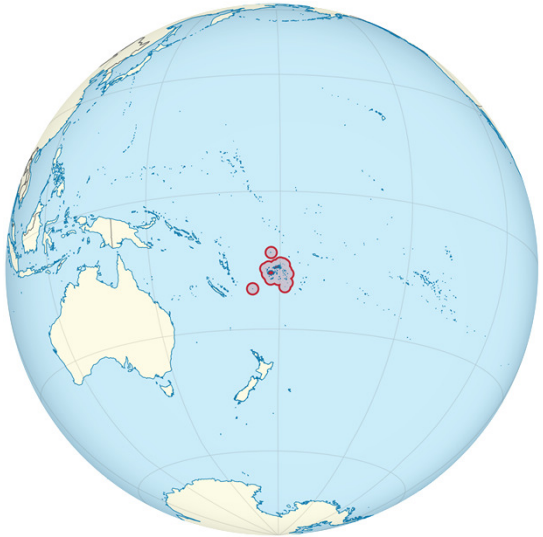
Registry study of 3343 patients in 25 hospitals in Africa, India, Middle East

<u>Disease of young women</u>
-Median age 28 years
-Two-thirds female

<u>A complicated and progressive chronic disease</u>
-Two-thirds with moderate to severe multi-valve disea
-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%)

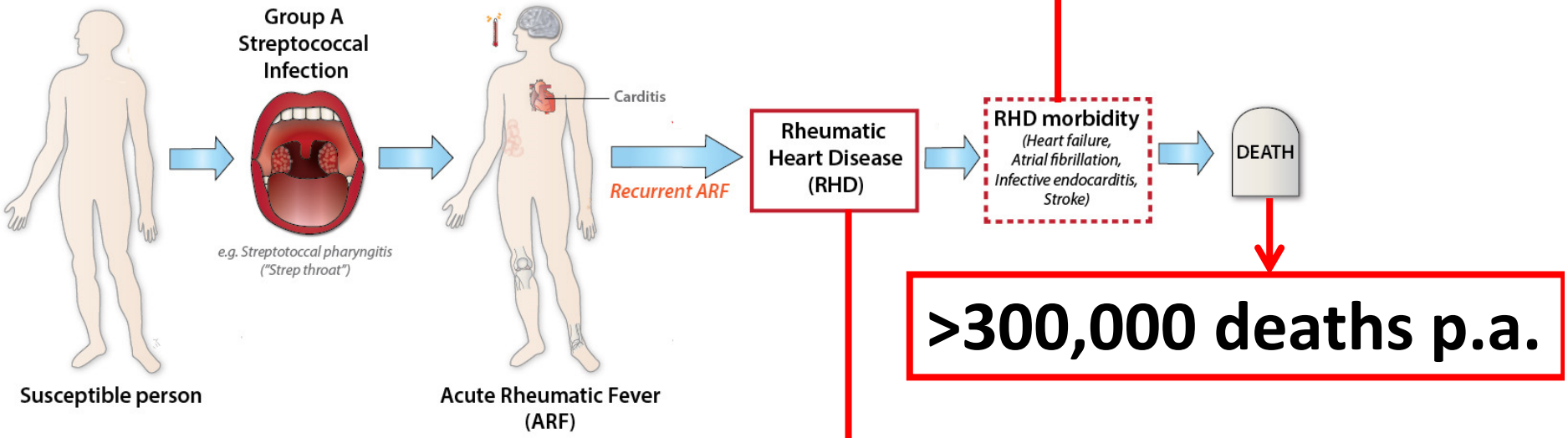
-2nd most common cause of death 5-29 years

-Cost: 0.3% of total GDP

Parks T, et al. PLOS NTD 2015

Rheumatic heart disease

Infectious disease



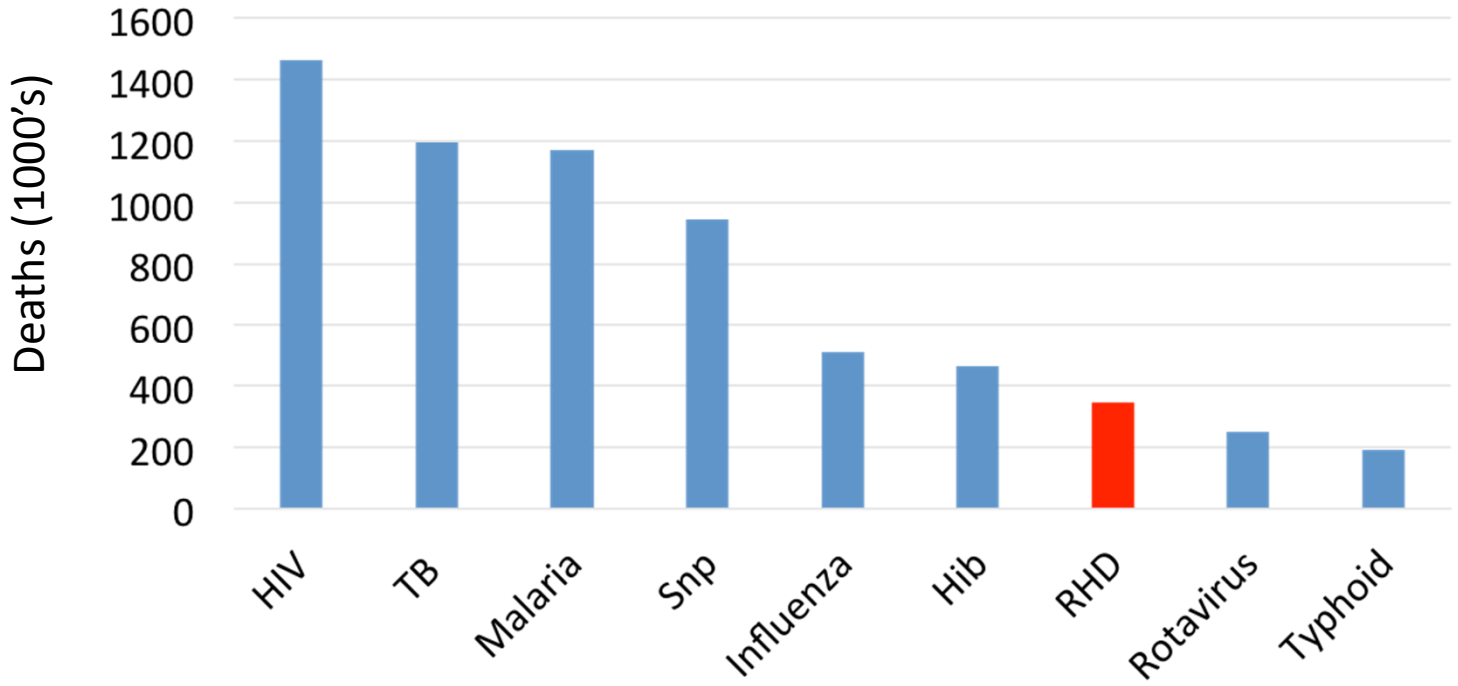
>4.3 million with heart failure

>300,000 deaths p.a.

34 million patients

Burden of disease: mortality

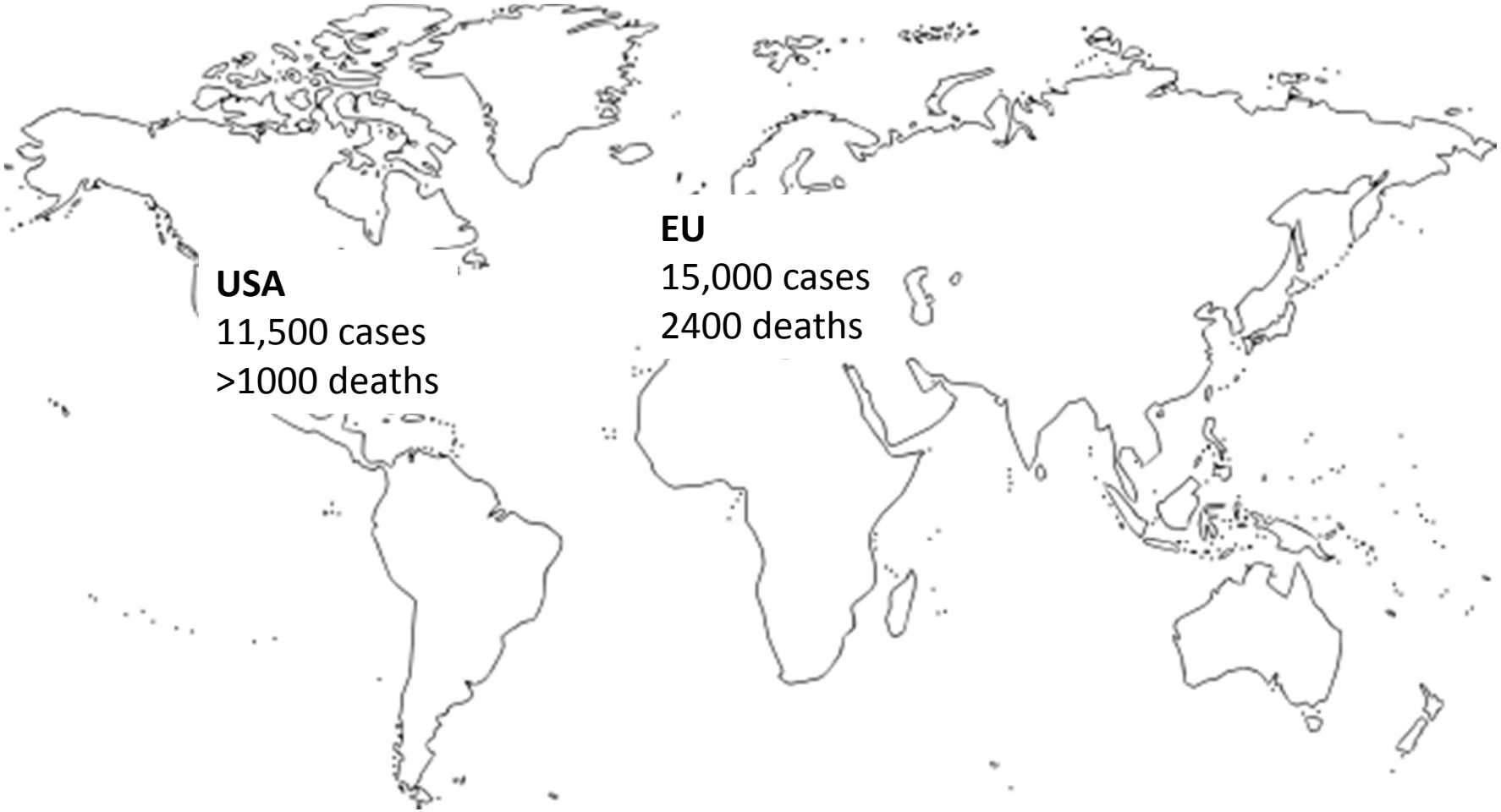
Rheumatic heart disease



Lozano et al. Lancet 2012

Invasive disease

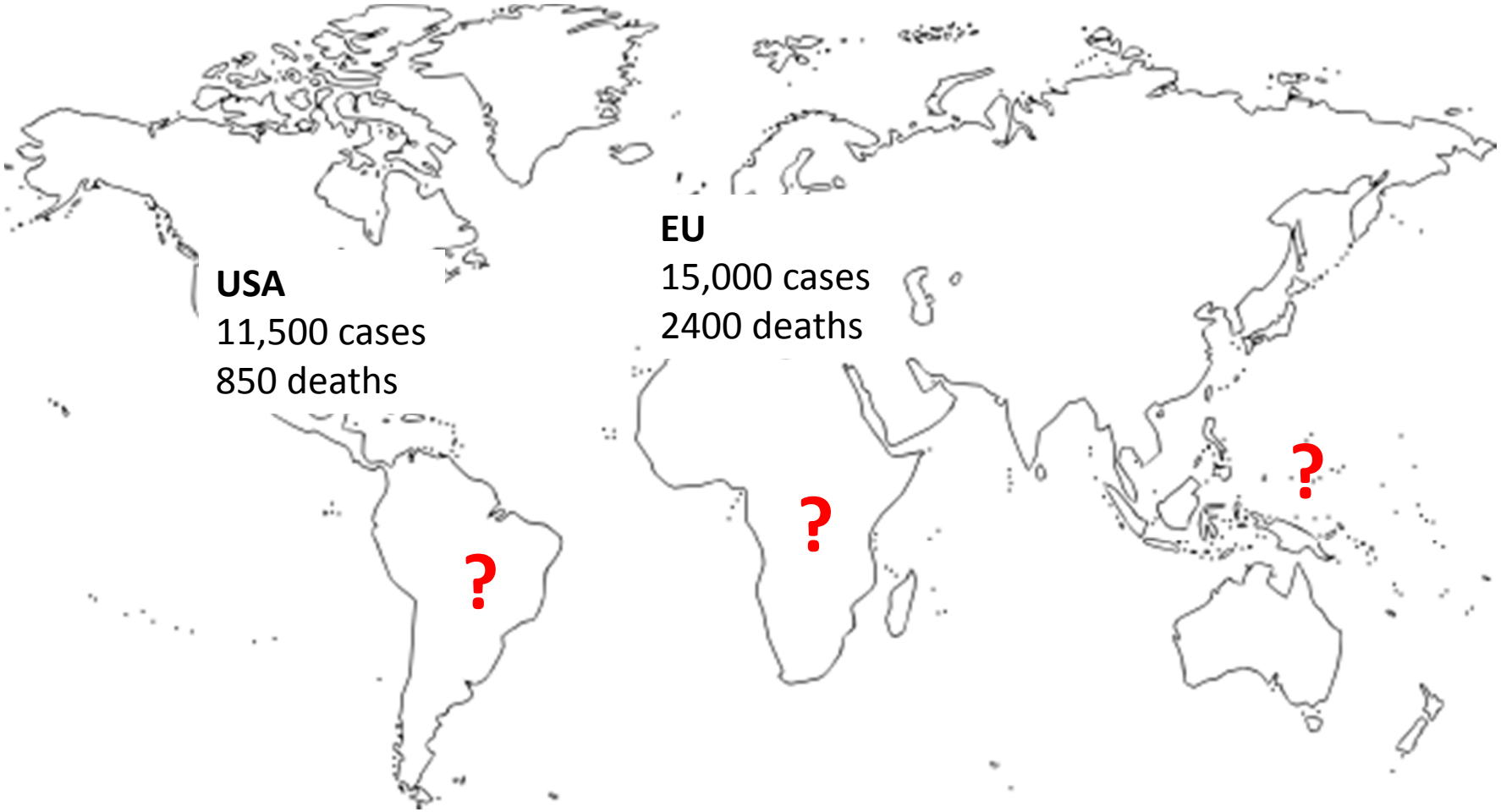
High-income: **3-5 per 100,000**
CFR: ~10-15%



Severe community acquired sepsis (after introduction of Nm immunisation)

Invasive disease

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



Invasive Group A *Streptococcus* Infection among Children, Rural Kenya

Anna C. Seale, Mark R. Davies, Kirimi Anampiu, Susan C. Morpeth, Sammy Nyongesa, Salim Mwarumba, Pierre R. Smeesters, Androulla Efstratiou, Rosylene Karugutu, Neema Mturi, Thomas N. Williams, J. Anthony G. Scott, Samuel Kariuki, Gordon Dougan, James A. Berkley

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%)

Prospective Surveillance of Invasive Group A Streptococcal Disease, Fiji, 2005–2007

Andrew C. Steer, Adam Jenney, Joseph Kado, Michael F. Good, Michael Batzloff, Lepani Waqatakirewa, E. Kim Mullholland, and Jonathan R. Carapetis

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 15, No. 2, February 2009

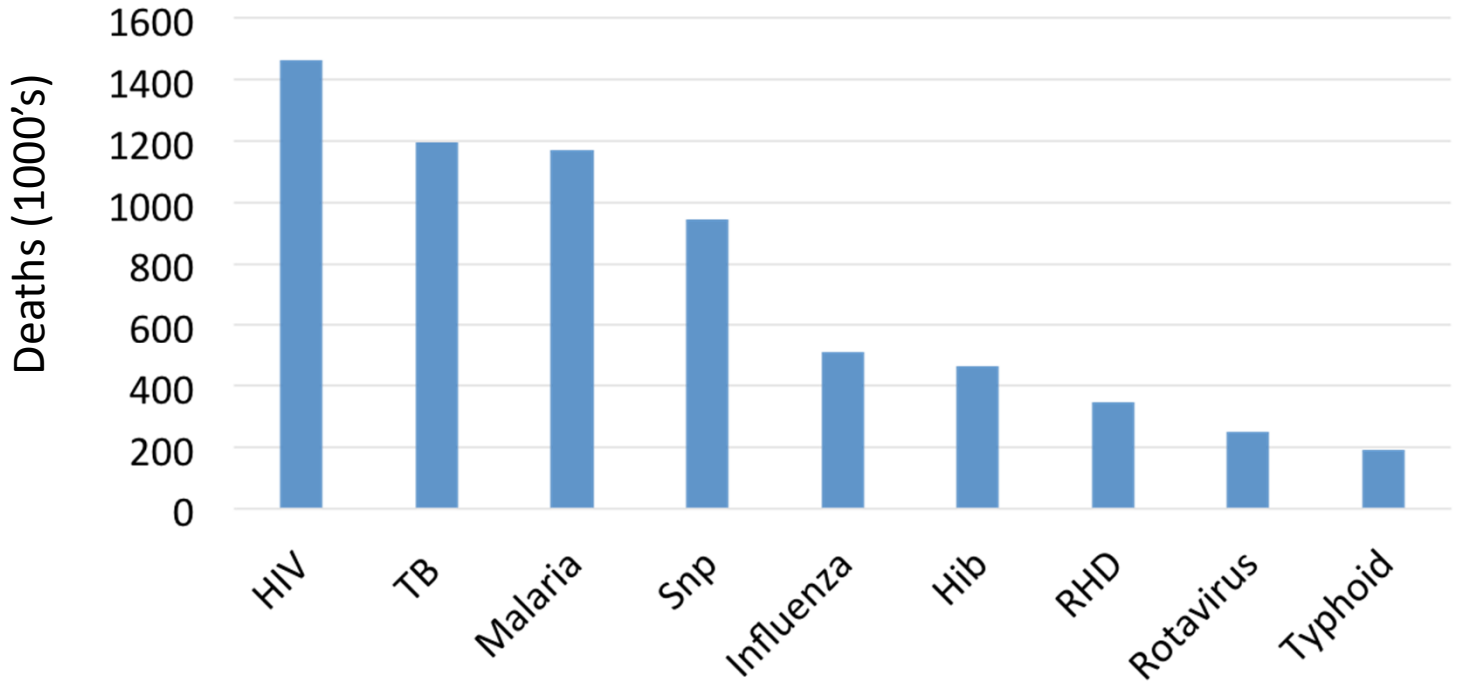
Fiji: 2005 – 2007

Incidence < 1 year: 49 per 100,000

All-ages incidence: 10 per 100,000 (CFR 32%)

Burden of disease: mortality

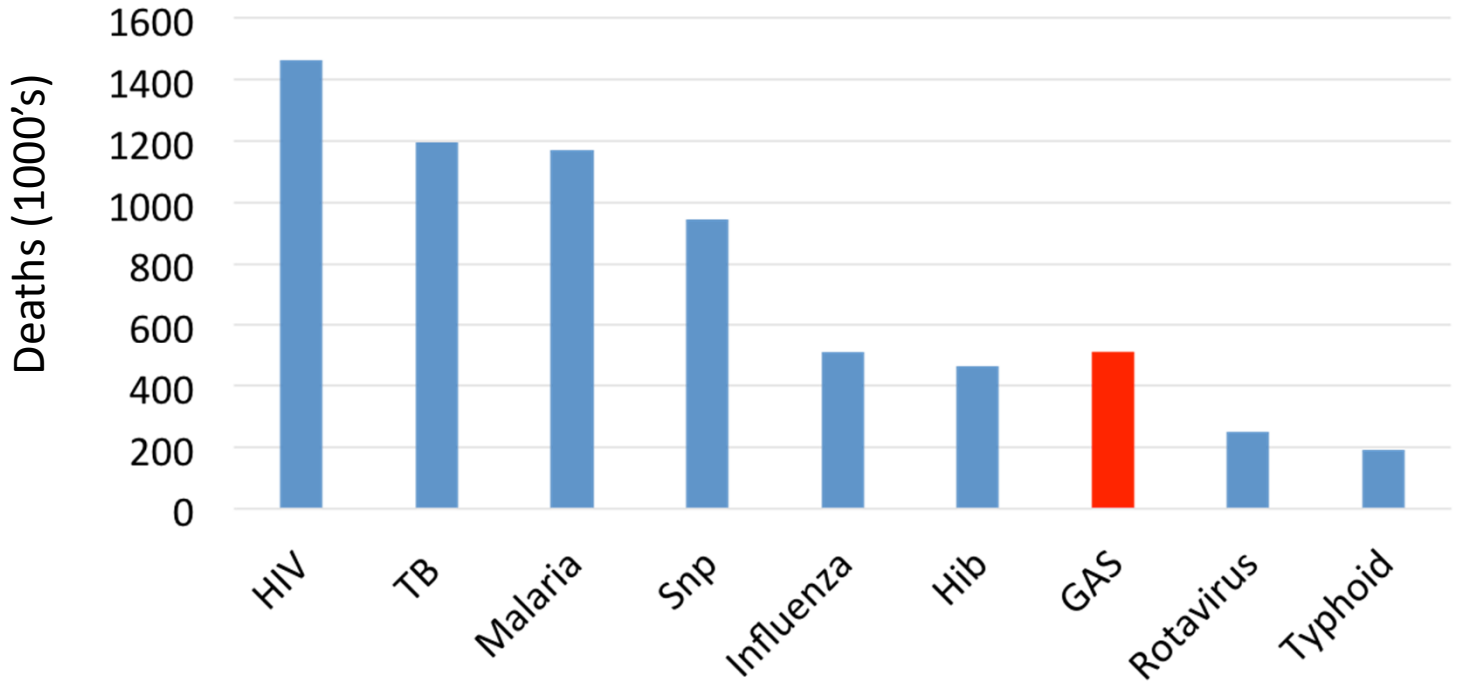
Rheumatic heart disease



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

Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

Vaccine development: evidence for protective immunity

Melbourne Children's
Excellence in clinical care, research and education

The Royal Children's Hospital Melbourne

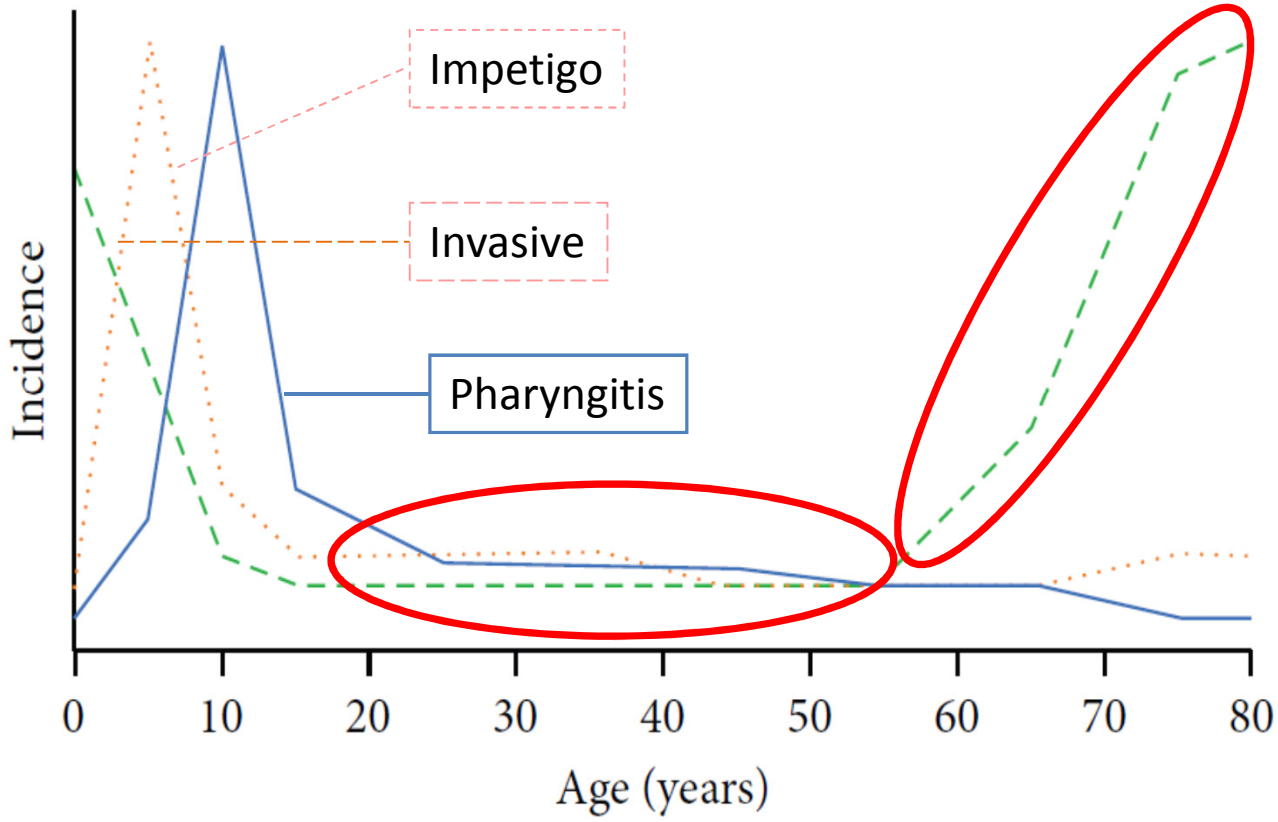
Murdoch Childrens Research Institute

The University of Melbourne

Evidence for protective immunity

Acquired natural immunity

Evidence for protective immunity



Tsoi et al. J Immunol Res 2015

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. 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

London 1974. Develop. biol. Standard., vol. 28, pp. 429-434 (Karger, Basel 1975).

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

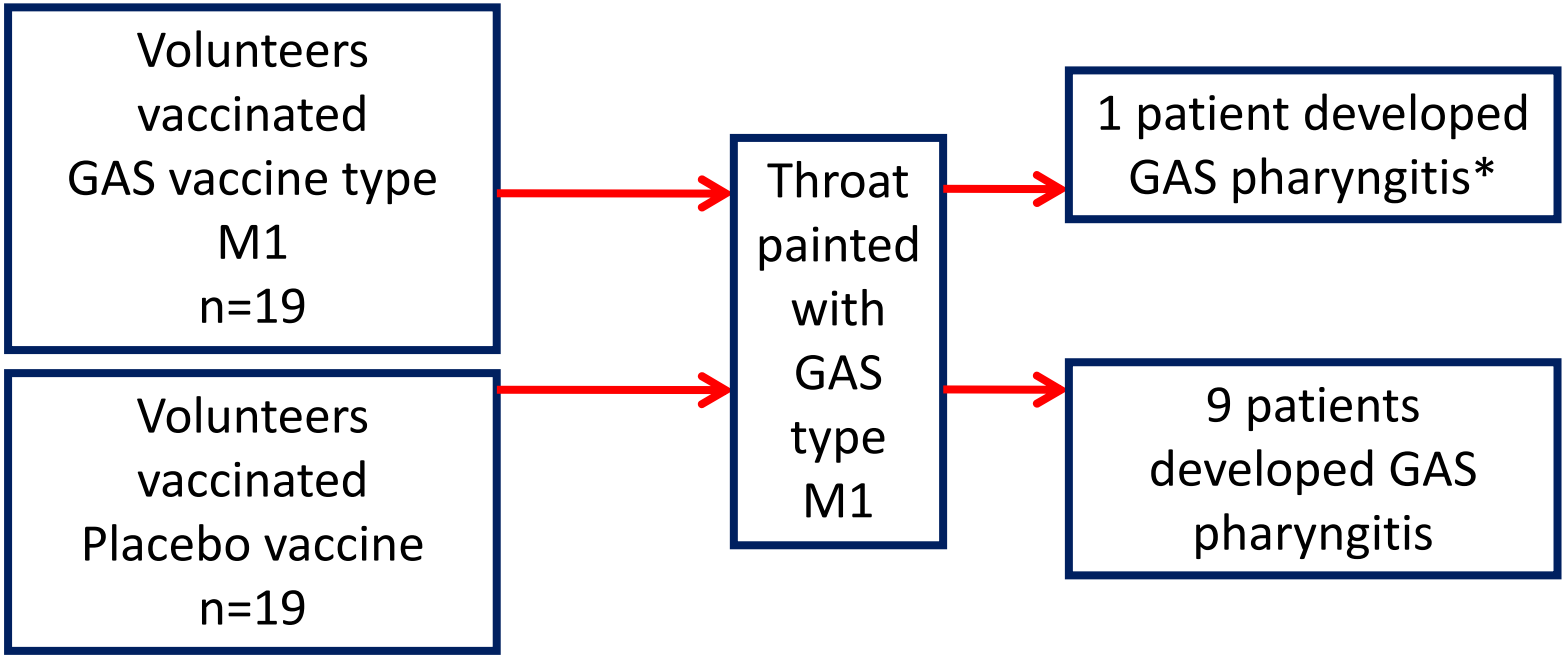
THE JOURNAL OF INFECTIOUS DISEASES • VOL. 131, NO. 3 • MARCH 1975

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



*Protective efficacy 89% p<0.01

Fox J Clin Invest 1973

Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

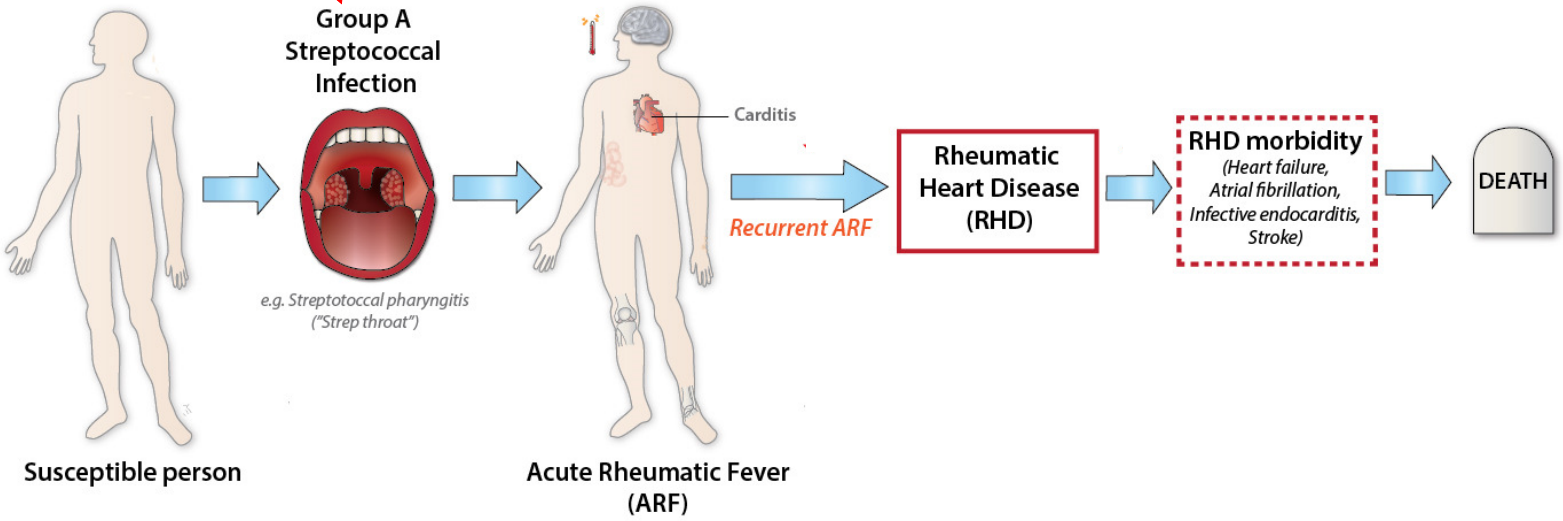
Can a vaccine prevent rheumatic heart disease?

Infectious disease

Immune-mediated disease

Chronic non-communicable disease

Primary prevention



Primary prevention

Comparison: 02 Penicillin versus control
Outcome: 01 Incidence of Rheumatic Fever

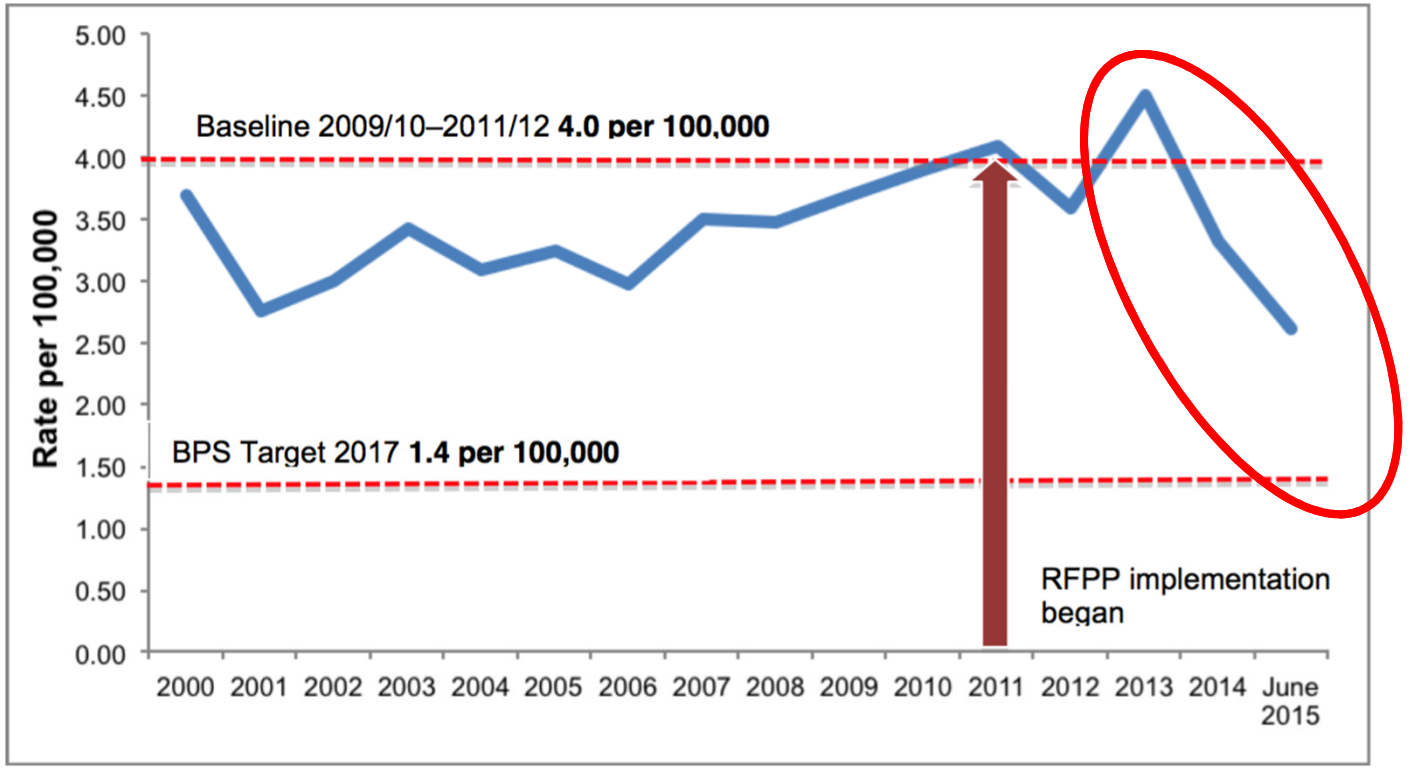
Study	Penicillin n/N	Control n/N	RR (95%CI Fixed)	Weight %	RR (95%CI Fixed)
× Bennike, 1951	0 / 174	0 / 164		0.0	Not Estimable
Brink, 1951	2 / 197	5 / 198		7.6	0.40[0.08,2.05]
Brock, 1953	0 / 262	1 / 87		3.4	0.11[0.00,2.71]
× Brumfitt, 1957	0 / 62	0 / 59		0.0	Not Estimable
Chamovitz, 1954	0 / 132	2 / 109		4.2	0.17[0.01,3.41]
Denny 1950	2 / 798	17 / 804		25.8	0.12[0.03,0.51]
Denny 1953	1 / 53	1 / 50		1.6	0.94[0.06,14.68]
Siegel, 1961	0 / 608	2 / 605		3.8	0.20[0.01,4.14]
Wannamaker, 1951	7 / 1178	35 / 1162		53.7	0.20[0.09,0.44]
Total(95%CI)	12 / 3464	63 / 3238		100.0	0.20[0.11,0.36]

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

1 5 10
Favours control

Robertson et al *BMC Cardiovasc Disord* 2005


5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Rate per 100,000
Baseline 2009/10–2011/12 4.0 per 100,000
BPS Target 2017 1.4 per 100,000
RFPP implementation began
2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 June 2015

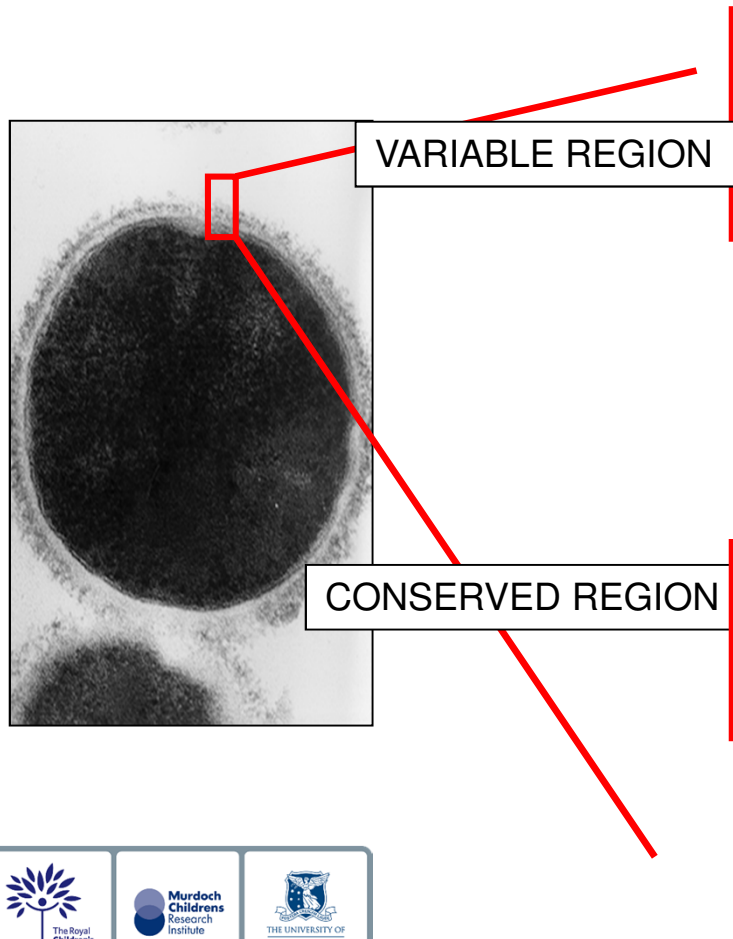
Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

Vaccine candidate landscape

Melbourne Children's
Excellence in clinical care, research and education

Vaccine candidate landscape

M-based designs / non M-based candidates



Basis of
M / *emm*
typing
(223 types)

- **26-valent vaccine**
- **30-valent vaccine**

- **J8 vaccine**
- **StreptInCor**

Steer Curr Op Infect Dis 2009

Vaccine candidate landscape

Non M-protein

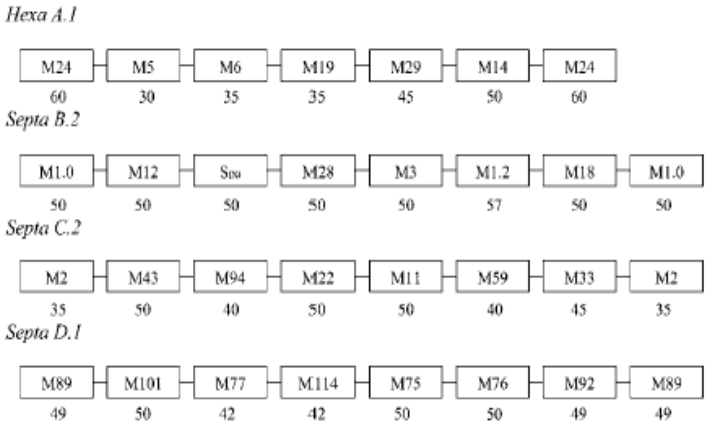
- 4-antigen vaccine ("Combo"):
  - CHO, SLO, SpyCEP, Spy0269
- Pilus
- Streptococcal C5a protease
- Fibronectin binding proteins
  - Sfb1, Sfb2, SfbX, Protein F2, FbaB
  - FbaA, Fbp54, GAPDH, shr
- GAS carbohydrate
- Others…

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

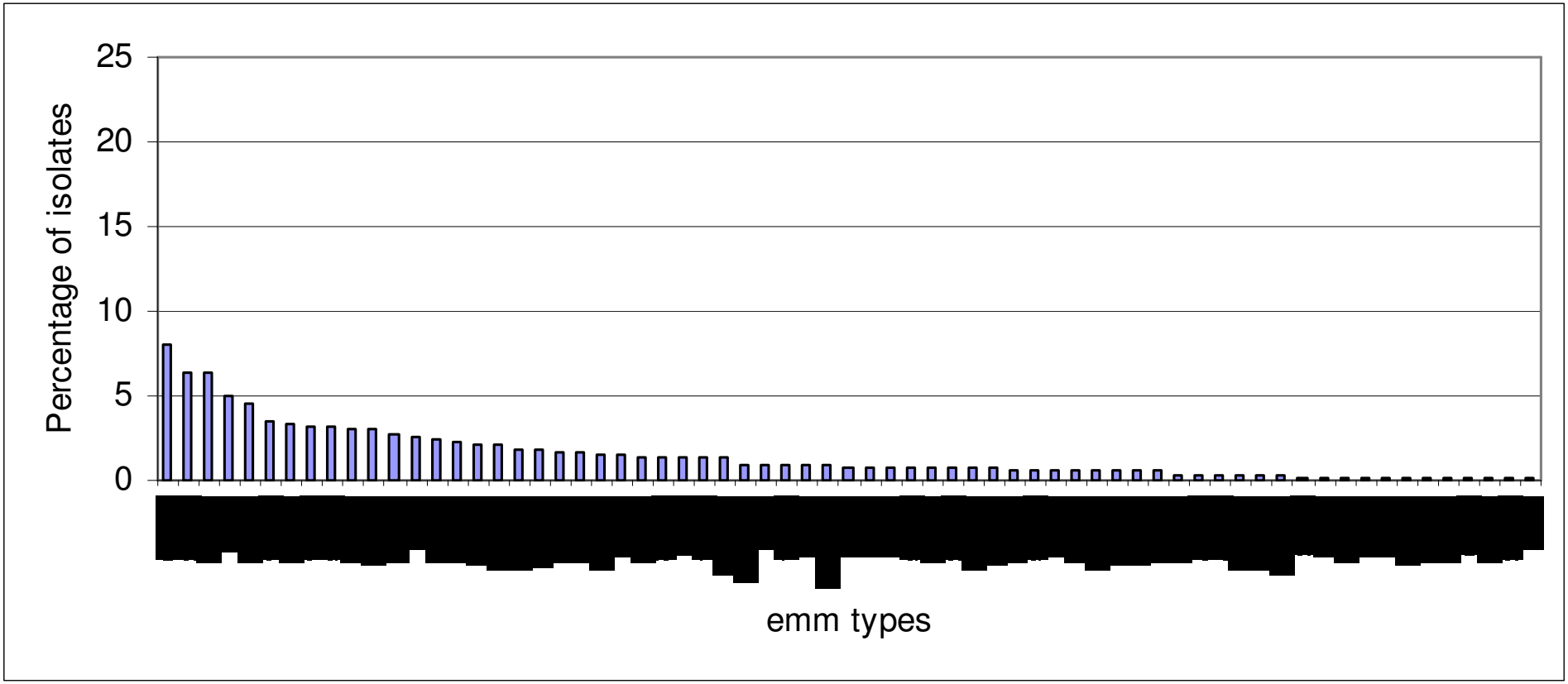
Immunogenicity

-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

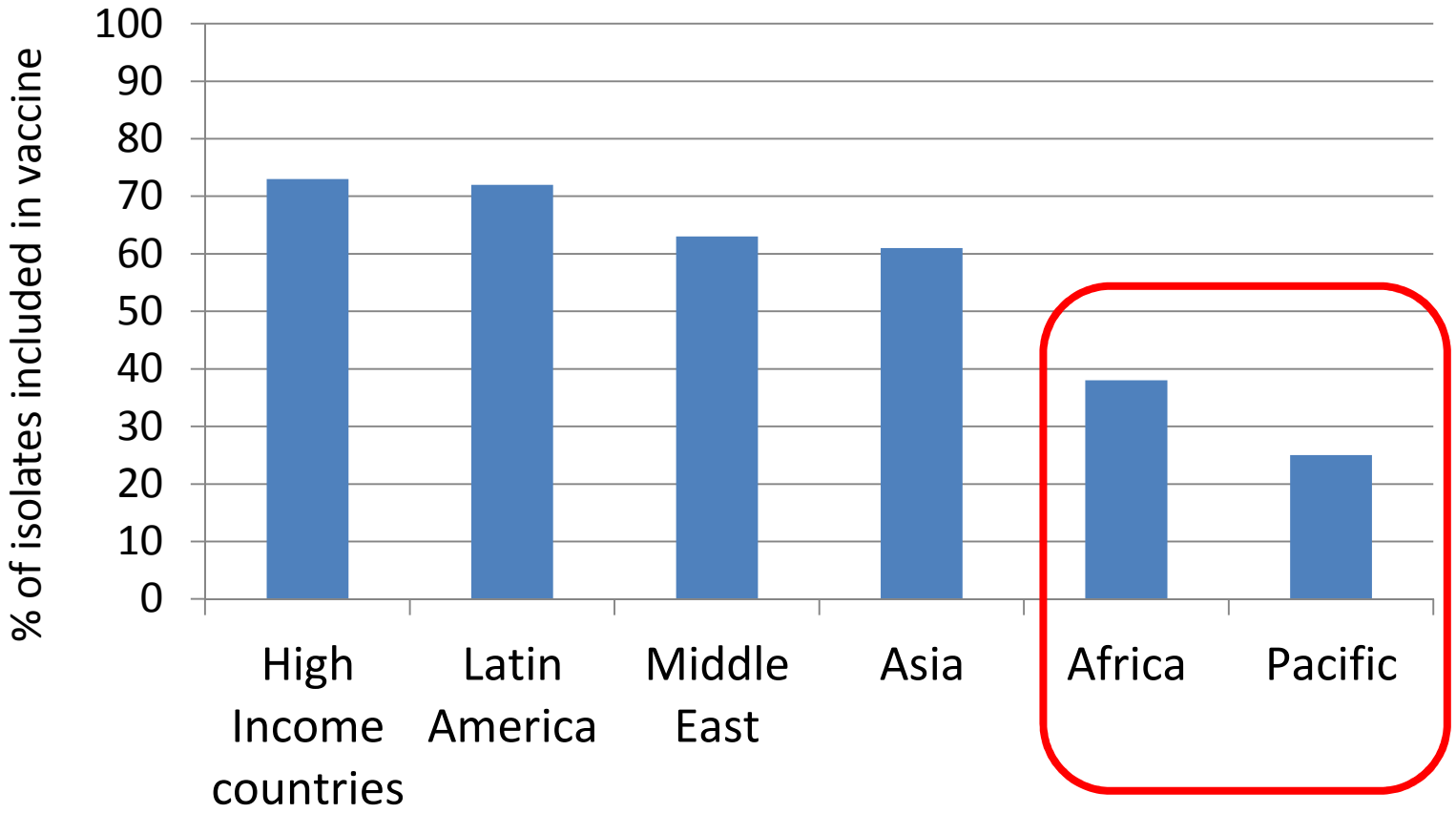
-Fiji studies: prospective surveillance >400 isolates → 67 *emm* types



Steer AC et al, J Clin Microbiol 2009;47(8):2502–2509

26-valent vaccine

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



Steer AC et al, Lancet Infect Dis 2009; 9(10):611-616

26-valent → 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

	% Total isolates (cases)	
	VT only	VT + NVT (cross-opsonized)
Pharyngitis-US	98	98
Invasive Disease-US	90	93
Invasive Disease-Europe	78	97
Pharyngitis-Bamako	40	**84**
Pharyngitis-Cape Town	59	**90**

Dale et al Vaccine 2013

30-valent vaccine

Phase I trial has started

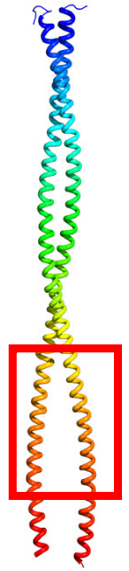
-Vaxent & Pan-Provincial Vaccine Enterprise Inc. (PREVENT)

-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)

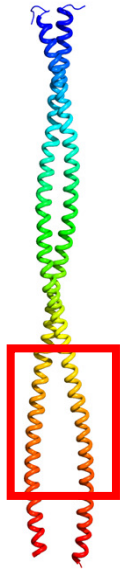
-Phase 1 trial (single dose): safe / immunogenic in 10 volunteers

-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

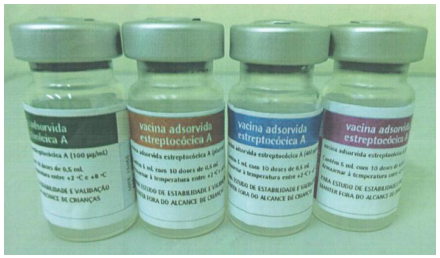
-55 amino acids of the C-terminus of M protein

-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

Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

Vaccine development: pipeline

Melbourne Children's
Excellence in clinical care, research and education

The Royal Children's Hospital Melbourne

Murdoch Childrens Research Institute

The University of Melbourne

Vaccine development: pipeline

M protein

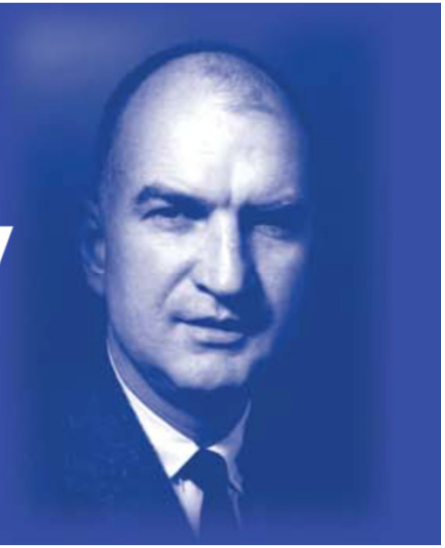
- M protein type specific
  - 26 valent vaccine — **Phase I/II completed**
  - 30 valent vaccine — **Phase I started**
- M protein conserved
  - J8-DT — **Phase I* completed**
  - J8-DT plus rSpyCEP — **Phase I shortly to start**
  - StreptInCor — **Phase I shortly to start**

Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

The Jordan Report

20th Anniversary

Accelerated Development of Vaccines 2002



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

Melbourne Children's
Excellence in clinical care, research and education

The Royal Children's Hospital Melbourne

Murdoch Childrens Research Institute

The University of Melbourne

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

<u>High-income countries</u>:

Prevent strep throat

Prevent invasive disease

Reduce health care costs

Reduce antibiotic use

<u>Low- and middle-income countries</u>:

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

Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

With thanks to

-Jim Dale, University of Tennessee, USA
-Michael Good, Griffith University, Australia
-Luiza Guilherme, Brazil
-Allan Saul, GSK
-David Kaslow, PD-VAC
-Pierre Smeesters, Belgium
-Jonathan Carapetis, Telethon Institute, Australia
-John Fraser, Auckland University, NZ
-Nicole Moreland, Auckland University, NZ
-Kim Mulholland, MCRI, Australia
-Florian Schodel, MedImmune Inc
-Jeff Cannon, Telethon Institute, Australia

Melbourne Children's
Excellence in clinical care, research and education
The Royal Children's Hospital Melbourne
Murdoch Childrens Research Institute
The University of Melbourne

Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

Thank you

Melbourne Children's
Excellence in clinical care, research and education

The Royal Children's Hospital Melbourne

Murdoch Childrens Research Institute

The University of Melbourne