Preventing RF through vaccination

Jonathan Carapetis

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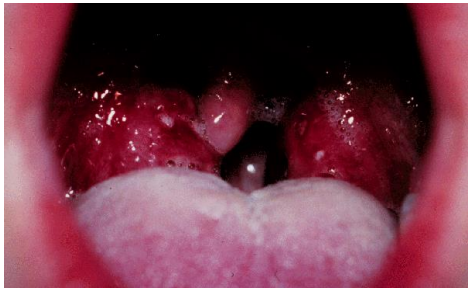
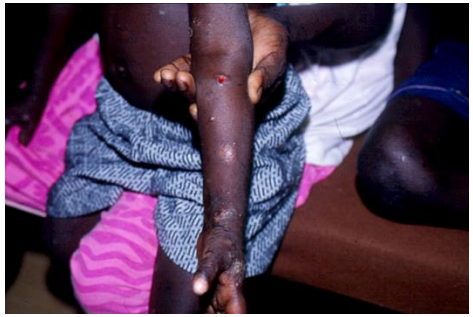
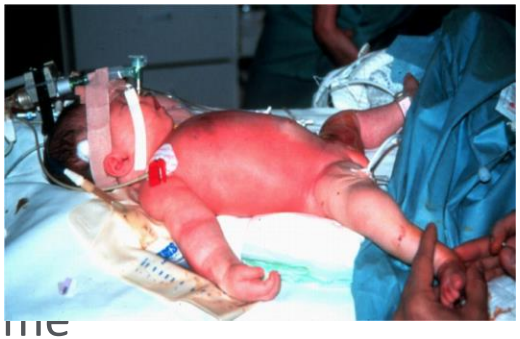
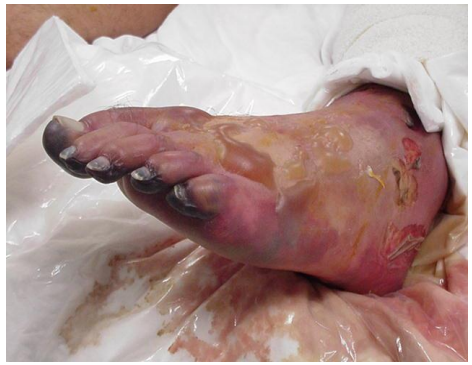
Group A streptococcal diseases

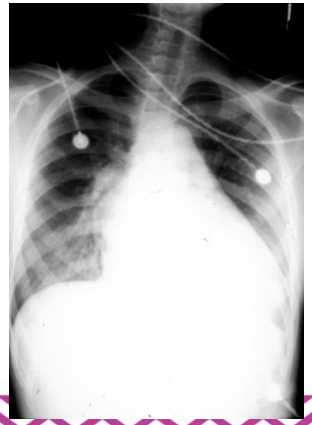
- Superficial infection
  - Pharyngitis
  - Pyoderma
- Invasive diseases
  - Septicaemia
  - Pneumonia, osteomyelitis…
  - Necrotising fasciitis
- Toxin mediated diseases
  - Scarlet fever
  - Streptococcal toxic shock syndrome
- Post-streptococcal autoimmune sequelae
  - Acute rheumatic fever / rheumatic heart disease
  - Post-streptococcal glomerulonephritis

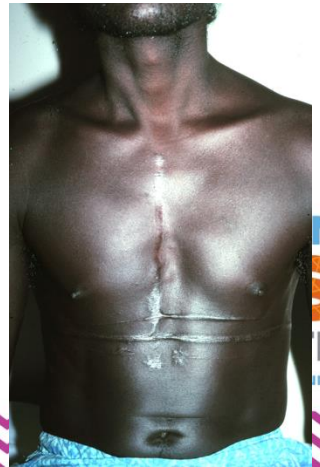




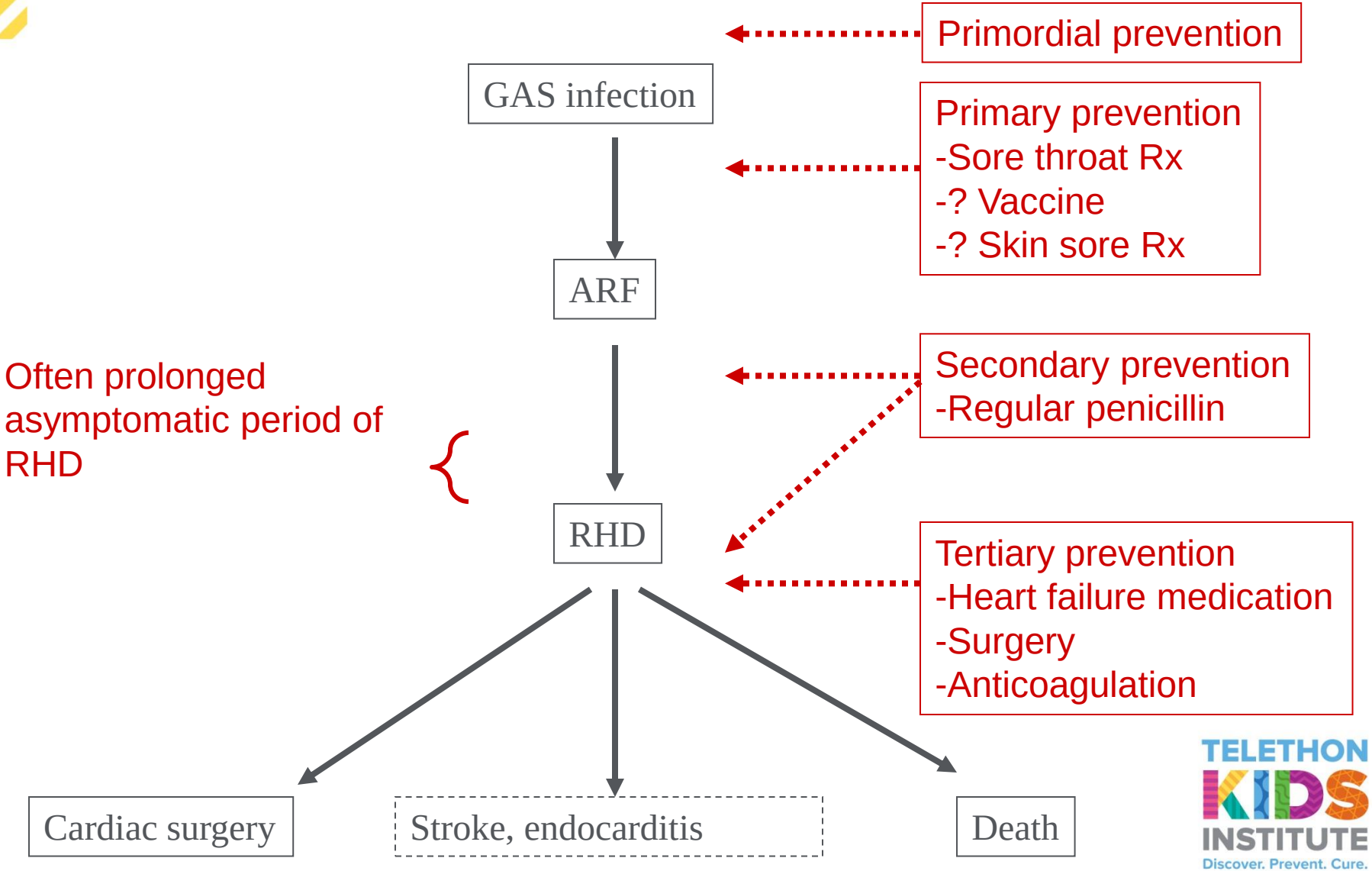








Preventing RHD



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Preventing RHD

Only proven effective, and cost-effective intervention for preventing/controlling RHD

GAS infection

ARF

RHD

Cardiac surgery

Stroke, endocarditis

Death

Often prolonged asymptomatic period of RHD

Primordial prevention

Primary prevention
-Sore throat Rx
-? Vaccine
-? Skin sore Rx

Secondary prevention
-Regular penicillin

Tertiary prevention
-Heart failure medication
-Surgery
-Anticoagulation

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Preventing RHD

No proven effective way of preventing first episodes of ARF at population/community level

GAS infection

ARF

RHD

Cardiac surgery

Stroke, endocarditis

Death

Often prolonged asymptomatic period of RHD

Primordial prevention

Primary prevention
-Sore throat Rx
-? **Vaccine**
-? Skin sore Rx

Secondary prevention
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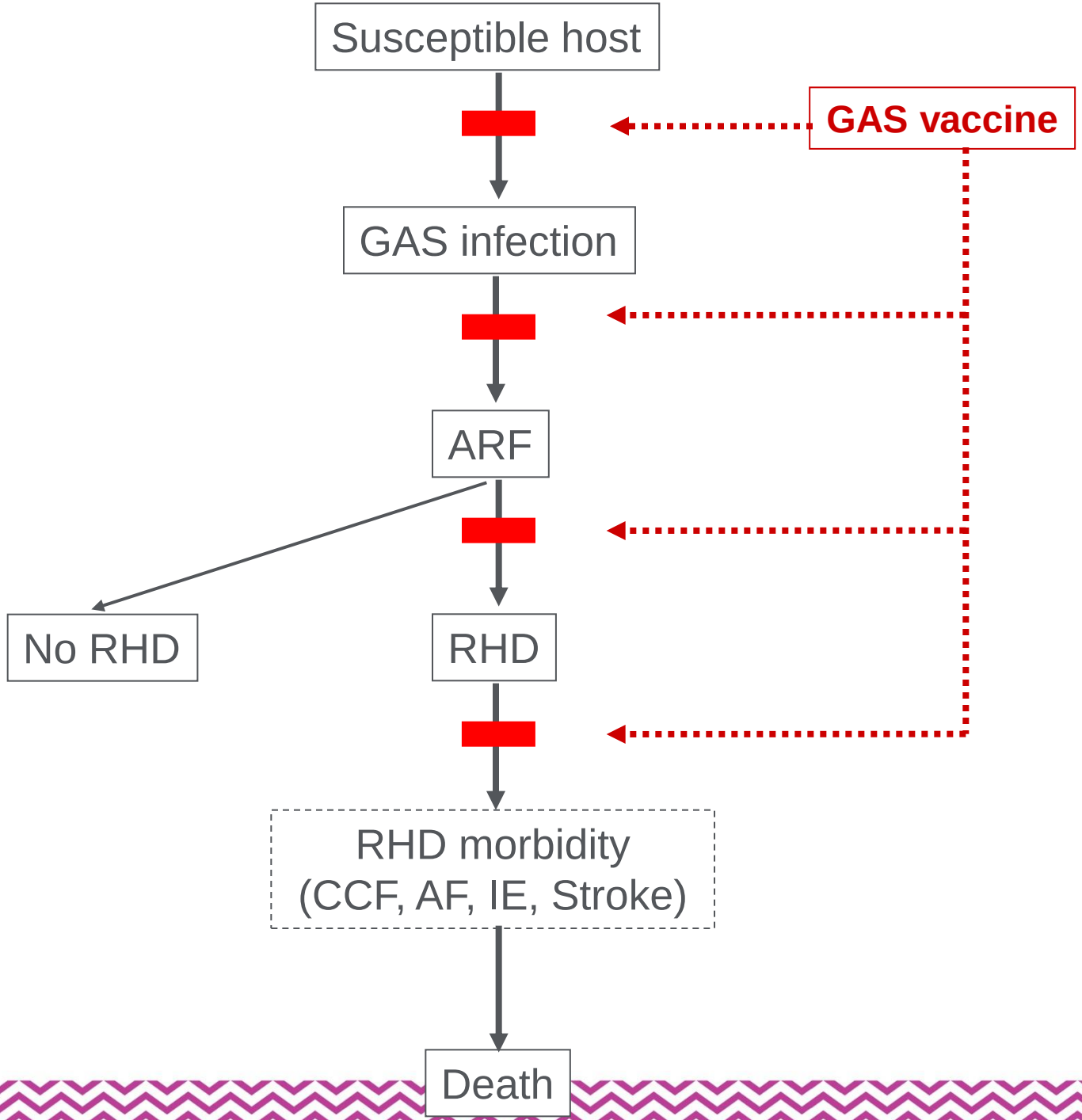

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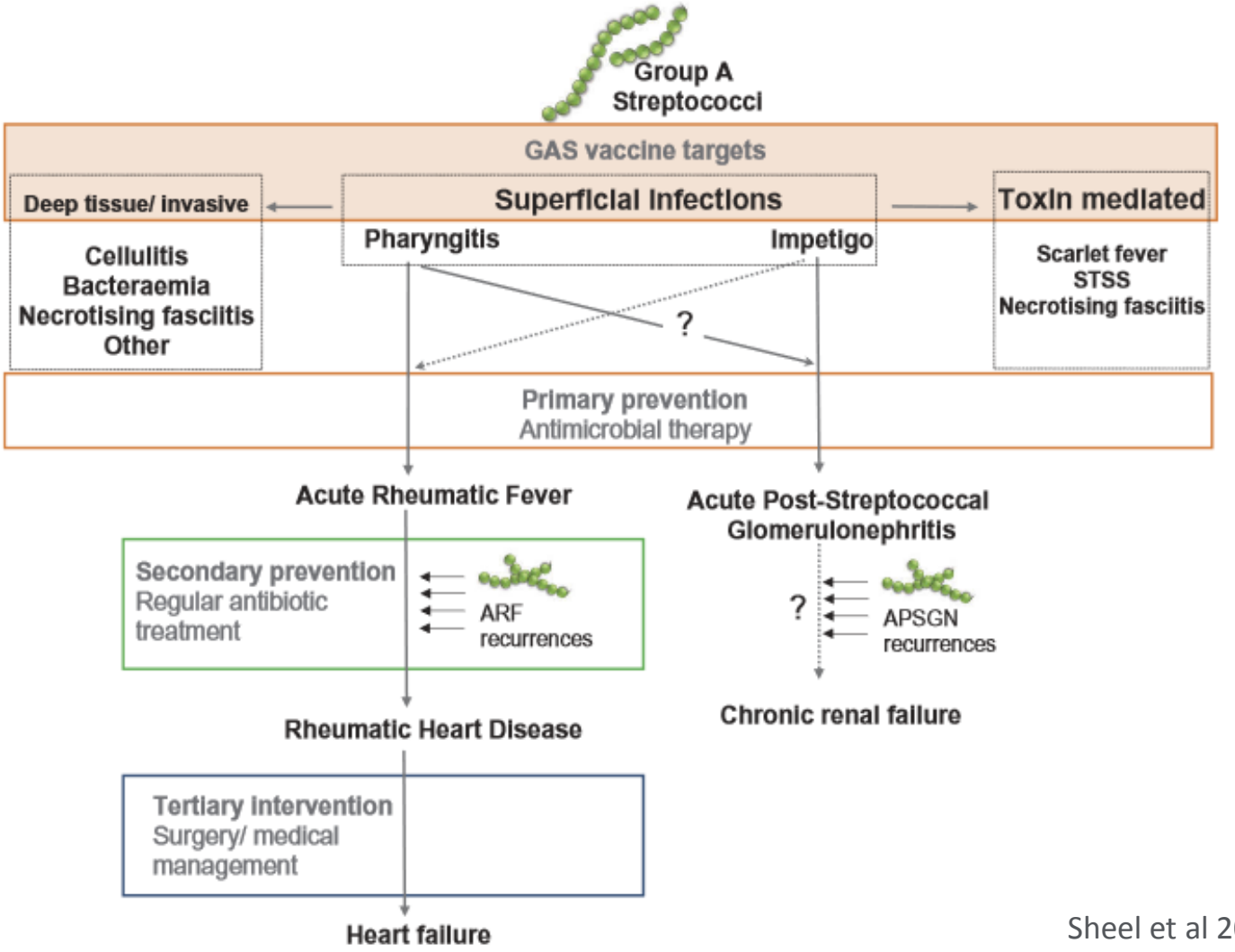
Other GAS vaccine targets



Sheel et al 2016

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Human clinical trials of GAS vaccines

(courtesy A Steer, adapted from Curr Opin Infect Dis. 2009 Dec;22(6):544-52)

YEAR	AUTHOR	ANTIGEN	Vaccinated adults	Vaccinated children	Controls
1923	Bloomfield	21 strain polyvalent vaccine	35	-	55
1931	Wilson	Heat killed Q33 strain given IV at least 9 doses	-	80 (history of ARF)	92
1932	Collis	Heat killed 'Carter' or 'autogenic' strain given IV	-	47	-
1937	Veldee	Tannic acid precipitated toxin	-	3208	?
1938	Wasson	Ny5 strain heat killed GAS toxin (>15 injections)	-	34 (history of ARF)	66
1940	Wasson	Ny5 strain heat killed GAS toxin	-	32 (history of ARF)	80
1940	Veldee	Tannic acid precipitated toxin	-	3797	?
1942	Wasson	Tannic acid precipitated (5 doses)	-	42 (history of ARF)	38
1946	Young	Heat killed or UV-inactivated M17 and/or M19 GAS (Navy recruits) UV type 19 Heat type 19 Heat type 17/19 Total	 381 308 +1452 1393 3534	-	 373 1542 1528 3443
1949	Rantz	Heat killed type3/17	43	-	-
1960	Schmidt	Partially purified M protein type 19	12	22	-
1962	Potter	Type 5/12 cell wall vaccine	18	30	-
1963	Wolfe	Type 14 cell wall/M	69	2	-
1968	Massell	Partially purified M3 protein	-	21	-
1969	Fox	Highly purified M protein type 12	-	50	13
1973	Fox	Highly purified M protein type 1 subcut (Challenge study)	19	-	19
1975	Polly	Highly purified M protein type 1 Intranasal (Challenge study)	21	-	23
1978	D'Alessandri	M3 and M12 Intranasal and subcut (Challenge study) M3 vaccine M12 vaccine	 37 47	-	 * *
1979	Beachey	Purified pep M fragments M24/M6	12	-	
2004	Kotloff	6-valent N-terminal fragments M1, M3, M5, M6, M19, M24	28	-	-
2005	McNeil	Recombinant multivalent vaccine 26 antigens	30		
TOTAL			3905	7365	3829

Total 3905 vaccinated adults, 7365 vaccinated children

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The Massell study

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

? Real risk of ARF following M protein vaccination

- Many problems with Massell study
- Multiple other studies with no reported cases

- HOWEVER

- Led to FDA 21 CFR 610.19 in 1979
- "Group A streptococcus organisms and derivatives **are prohibited** from bacterial vaccines and bacterial antigens"

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Revocation of 21 CFR Part 610

- February 15 2006
- "The Food and Drug Administration (FDA) is **removing the regulation** applicable to the status of specific products; Group A streptococcus."

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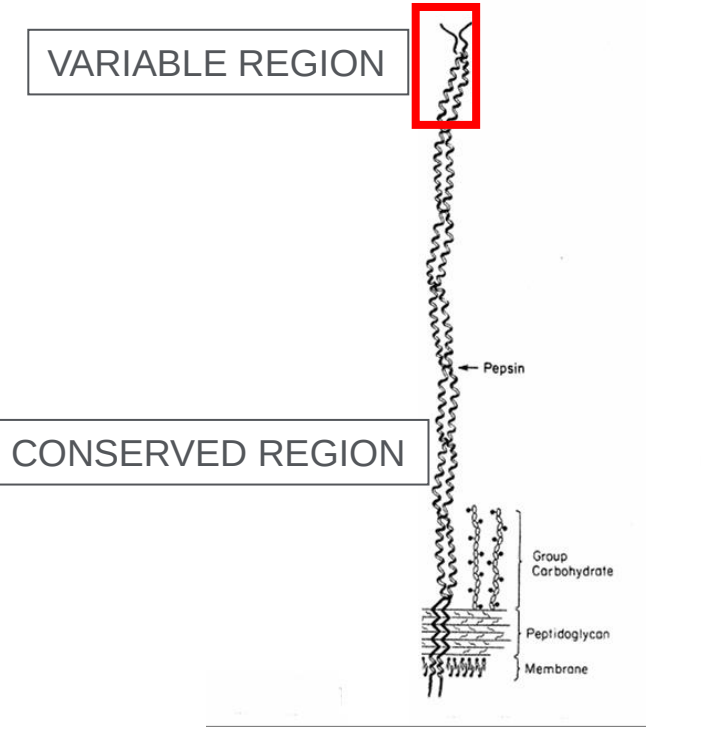
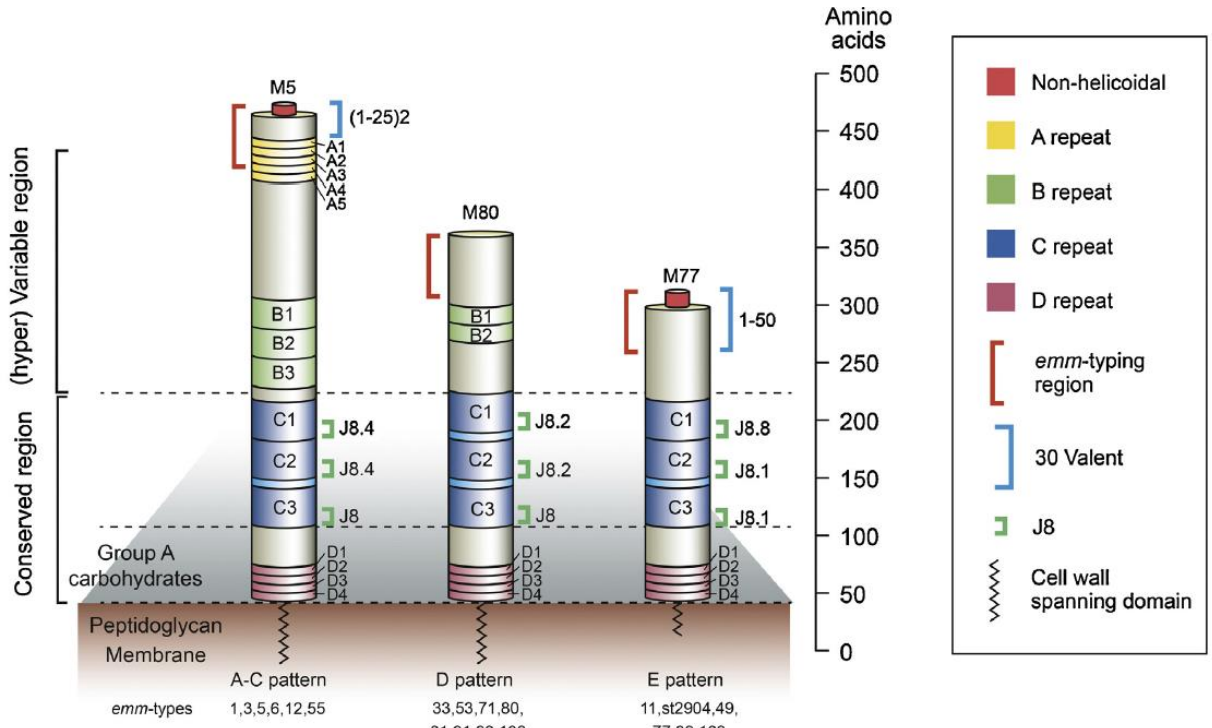
Types of vaccines

- M protein based vaccine
- Multi-valent M protein vaccine



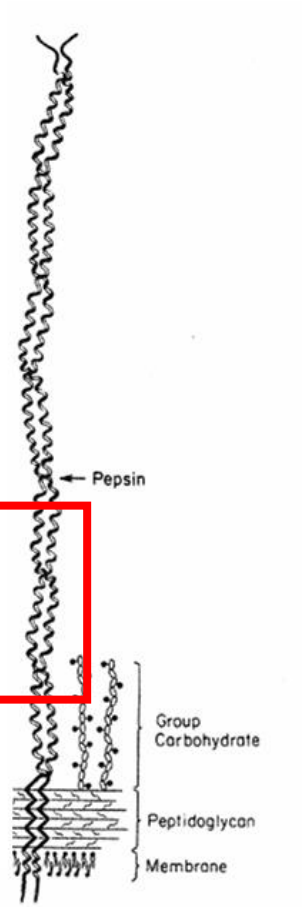


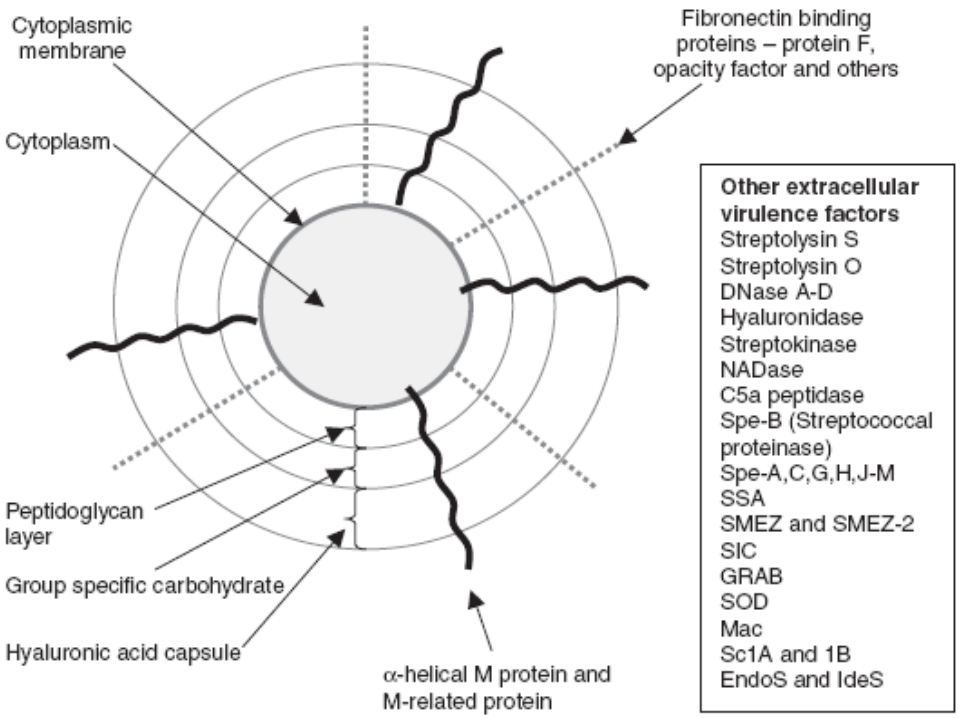
Other vaccine types

Conserved region M protein vaccines **OR** **Non M protein vaccines**

VARIABLE REGION

CONSERVED REGION





Current leading vaccine candidates

Griffith University J8-DT/Alum
Conserved M protein vaccine
(Brisbane, Australia)
PI: Michael Good

StreptInCor
C-terminal portion of M protein
(Heart Institute, São Paulo)
PI: Luiza Guilherme

PREVENT 30-Valent M protein based Vaccine
(Tennessee, USA
Saskatchewan, Canada)
PI: James Dale

GSK 4-component non M protein vaccine
(Siena, Italy, now GSK)

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30-Valent Vaccine

Protein 1

M1	3.1	M6.4	M2	M18	M28	M12	SPA	M1
1-50	32-81	(1-25)2	(1-25)2	1-50	1-50	1-50	1-50	1-50

Protein 2

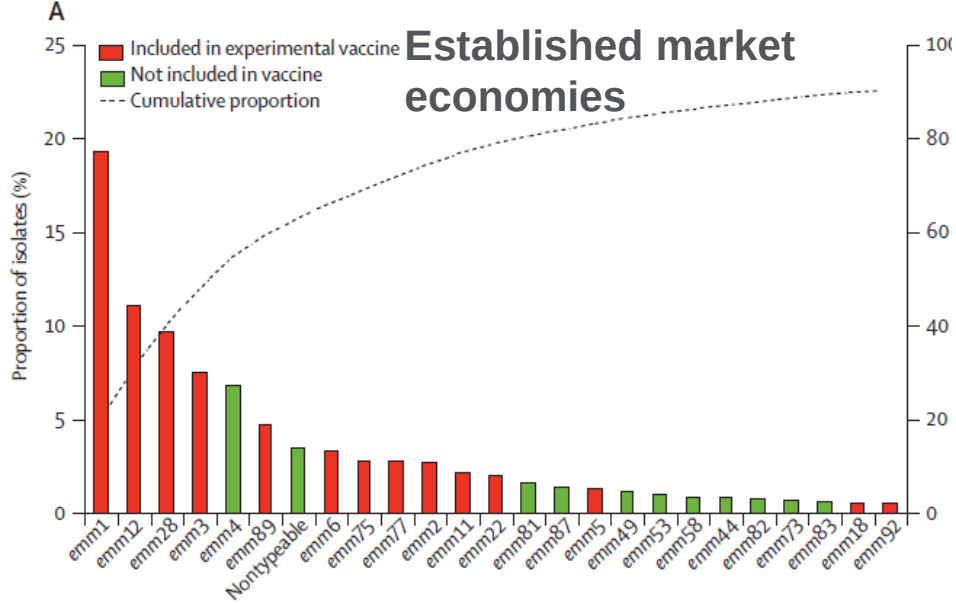
M4	M5.14	M11	M75	M19	M29	M14.3	M24	M4
1-50	(1-25)2	1-50	1-50	(1-25)2	1-45	1-50	1-50	1-50

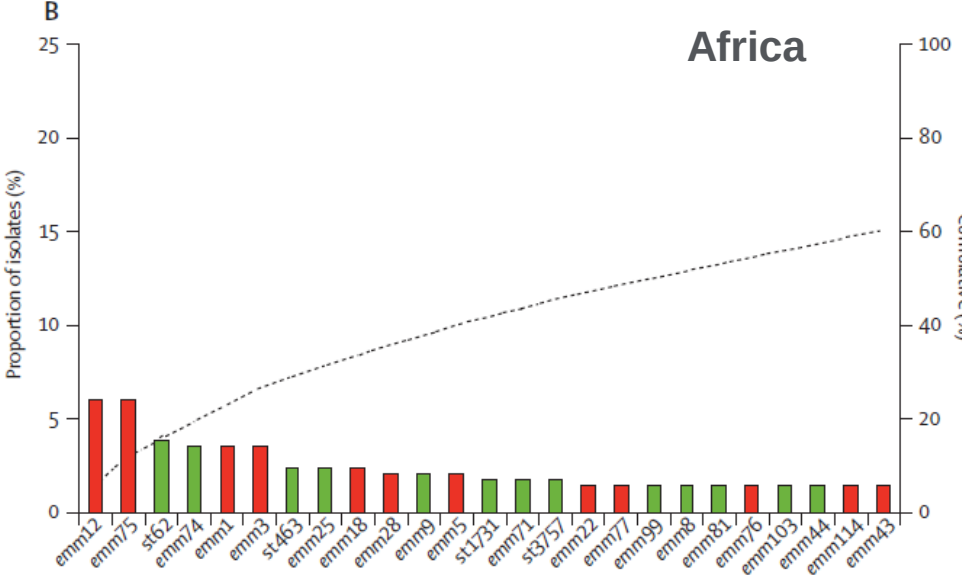
Protein 3

M77	M22	M73	M89	M58	M44	M78	M118	M77
1-50	1-50	1-50	1-50	1-50	1-50	1-50	1-50	1-50

Protein 4

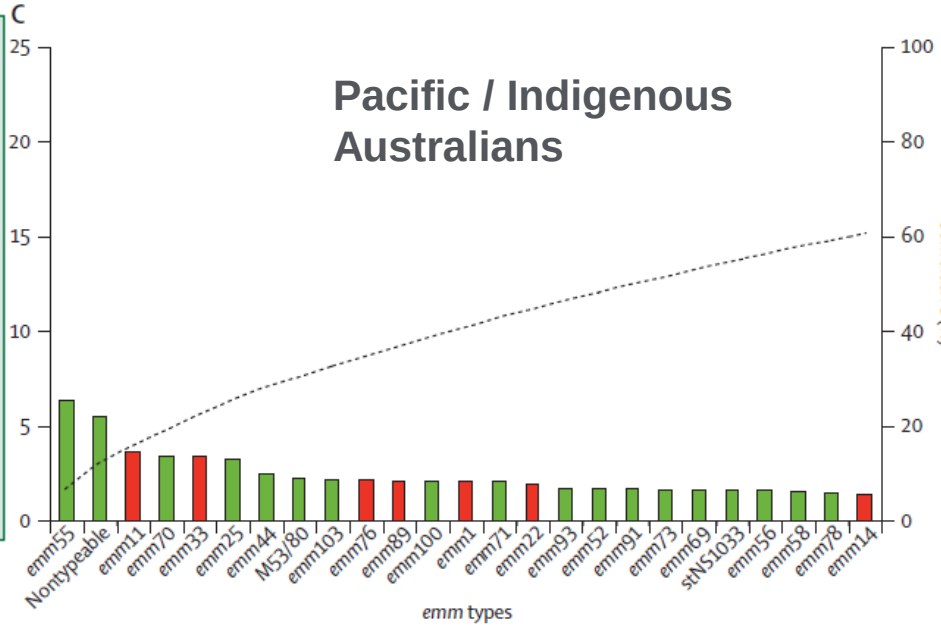
M83.1	M82	M81	M87	M49	M92	M114	M83.1
1-50	1-50	1-50	1-50	1-50	1-50	1-50	1-50





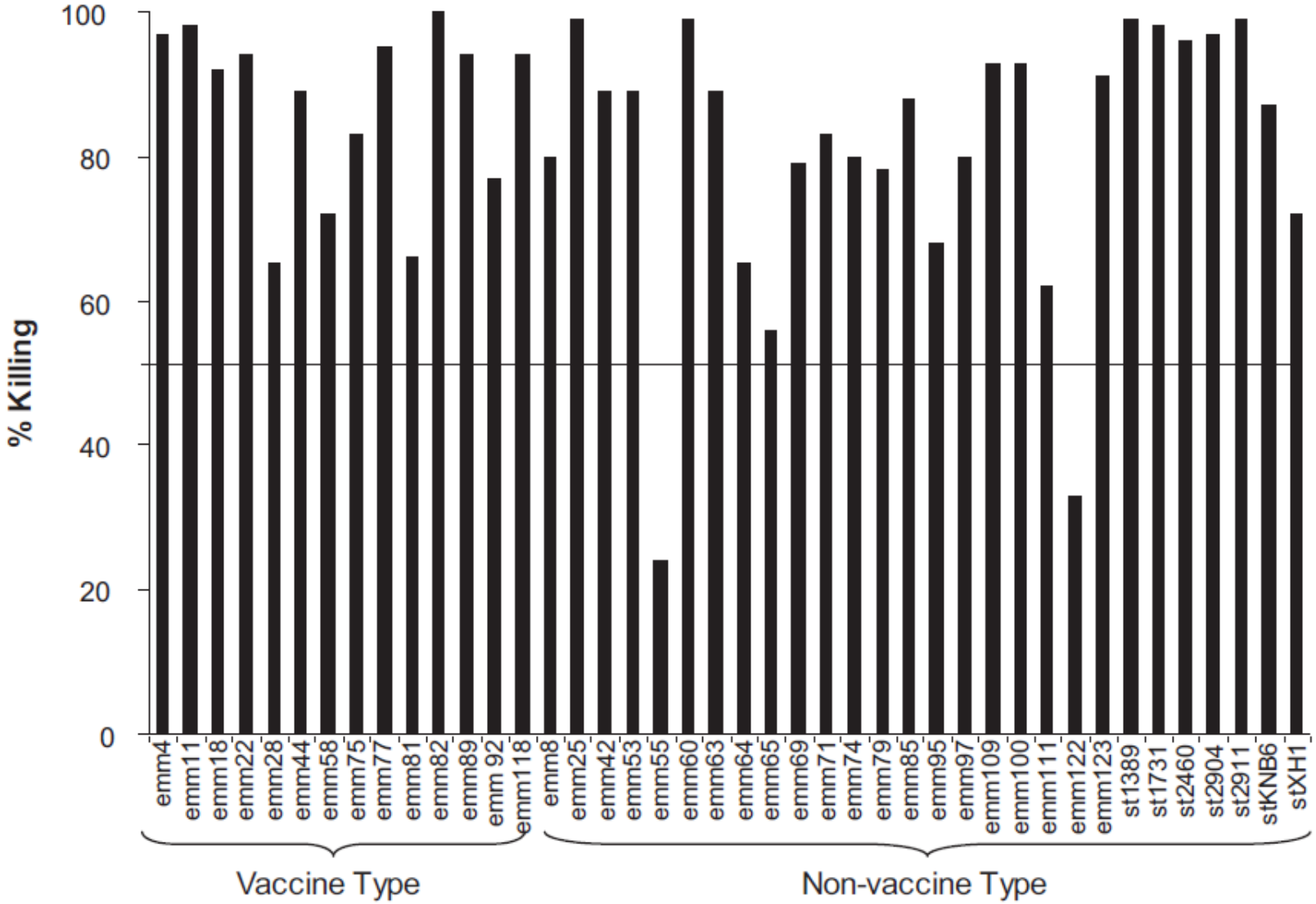
	Simpson's index of diversity[22] (% [95% CI])
Africa	98·1% (97·7–98·5)
Asia	88·7% (88·0–89·4)
Latin America	93·2% (92·4–94·1)
Middle East	93·0% (92·4–93·5)
Pacific region	97·9% (97·7–98·1)
High-income countries	92·1% (92·0–92·3)
Combined	92·8% (92·7–92·9)

Table 1: **Diversity of *emm* types by global region**



Lancet Infect Dis 2009; 9: 611–16

Bactericidal Antibodies Evoked by 30-Valent Vaccine Against Non-Vaccine Serotypes of GAS



Dale, Vaccine 2013

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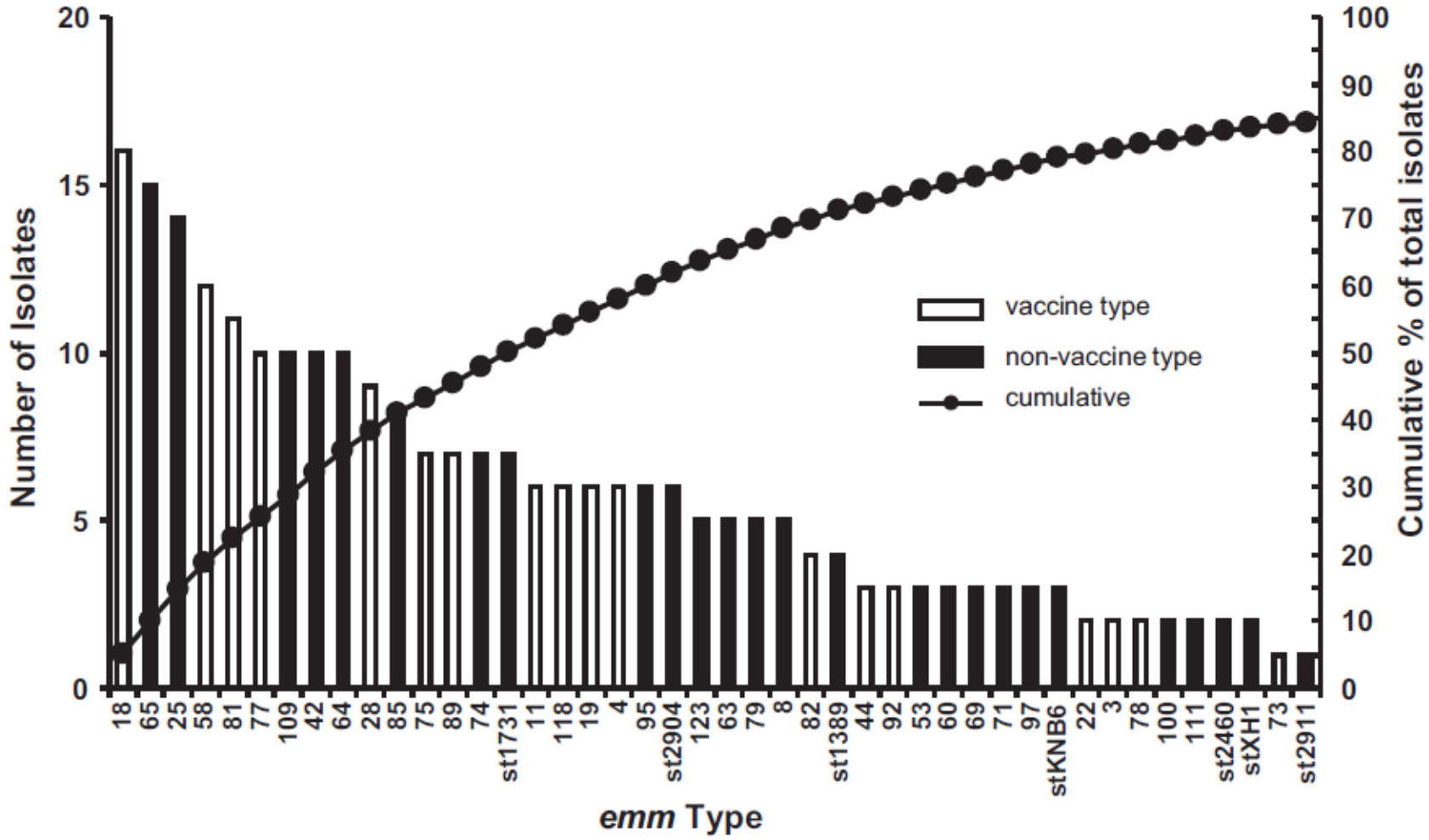

Dale, Vaccine 2013

Big pharma

- Wyeth / Pfizer
- Merck
- GSK
- Novartis
- Intercell

What are the obstacles?
- Safety?
- Market?
-Technical?
- Other?

- Risk/profit balance

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Vaccine 32 (2014) 3713–3720

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Conference report

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

- ? Safety requirements for licensure
- Correlates of protection
  - Lack of acceptable animal models
  - Lack of agreed and practical functional assays
  - ? Agreed assay, non-human primate models, human challenge studies

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Coalition to Advance New Vaccines for Group A Streptococcus

A trans-Tasman initiative to combat rheumatic fever

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Conversation between Prime Minister John Key and Dean of Auckland Medical School, Professor John Fraser

Prime Ministers of NZL and AUS investigate possible joint support towards a program

Partnership with Professor Jonathan Carapetis, Director of Telethon Kids Institute

Government's Chief Science Advisors oversee proposal development and initial peer review

Discussions with vaccine developers, local and international experts, stakeholders

Program commissioned through Australian NHMRC and NZ HRC

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Te Whare Wānanga o Tāmaki Makaurau

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CANVAS Stage 1

- Selection of representative panel of GAS strains
- Evaluation of potential protection against the panel
  - Develop immunological assay
- Economic analysis
  - Making the case for investment in a GAS vaccine in Aust/NZ

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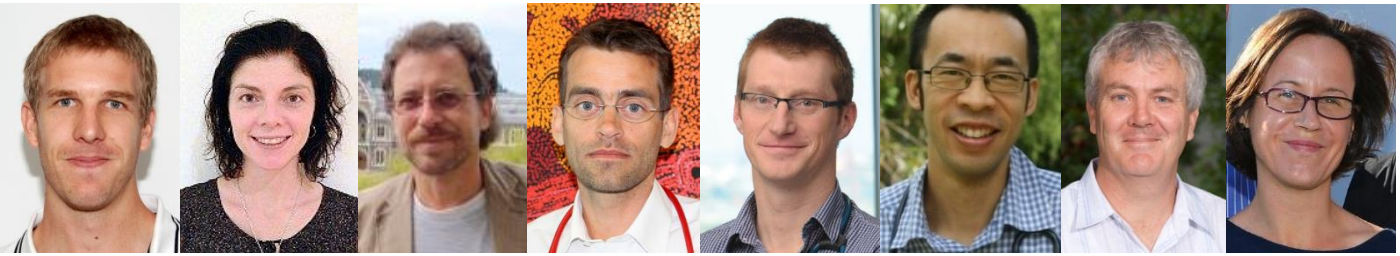
Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

Strain selection, bioinformatics and lead candidate selection

Andrew Steer, Pierre Smeesters, Deborah Williamson, Steven Tong, Mark Davies, Nikki Moreland, Mark Walker, Thomas Proft



Melbourne Children's
Excellence in clinical care, research and education
The Royal Children's Hospital Melbourne
Murdoch Childrens Research Institute
THE UNIVERSITY OF MELBOURNE

Aims and desired Outcomes

"Tackle GAS disease burden in ANZ, the Pacific and the world by vaccination"

=> Evaluation of lead vaccine candidates

1. Collate a representative Australia, New Zealand and Pacific GAS strain panel with global relevance
2. Convene a strain selection group
    a. Criteria for strain selection
    b. Report on strain selection: rationale, gaps and representativeness
3. Strains genome sequencing and bioinformatics
    a. Collate existing data
    b. Dispatch strains not yet sequenced to the Sanger
    c. Bioinformatic analysis with focus on vaccine antigen

Development of candidate evaluation assays

- For assessing the efficacy of GAS vaccine candidates
- Current “gold standard” - Lancefield bactericidal assay
- Methodology established decades ago and unsuitable for use in contemporary clinical trials
  - Uses whole blood from human donors
    - Whole blood causes large variance between experiments
    - Some GAS strains do not grown in whole human blood
  - Relies on data from a single serum dilution (1:5)
  - 50% killing considered ‘protective’

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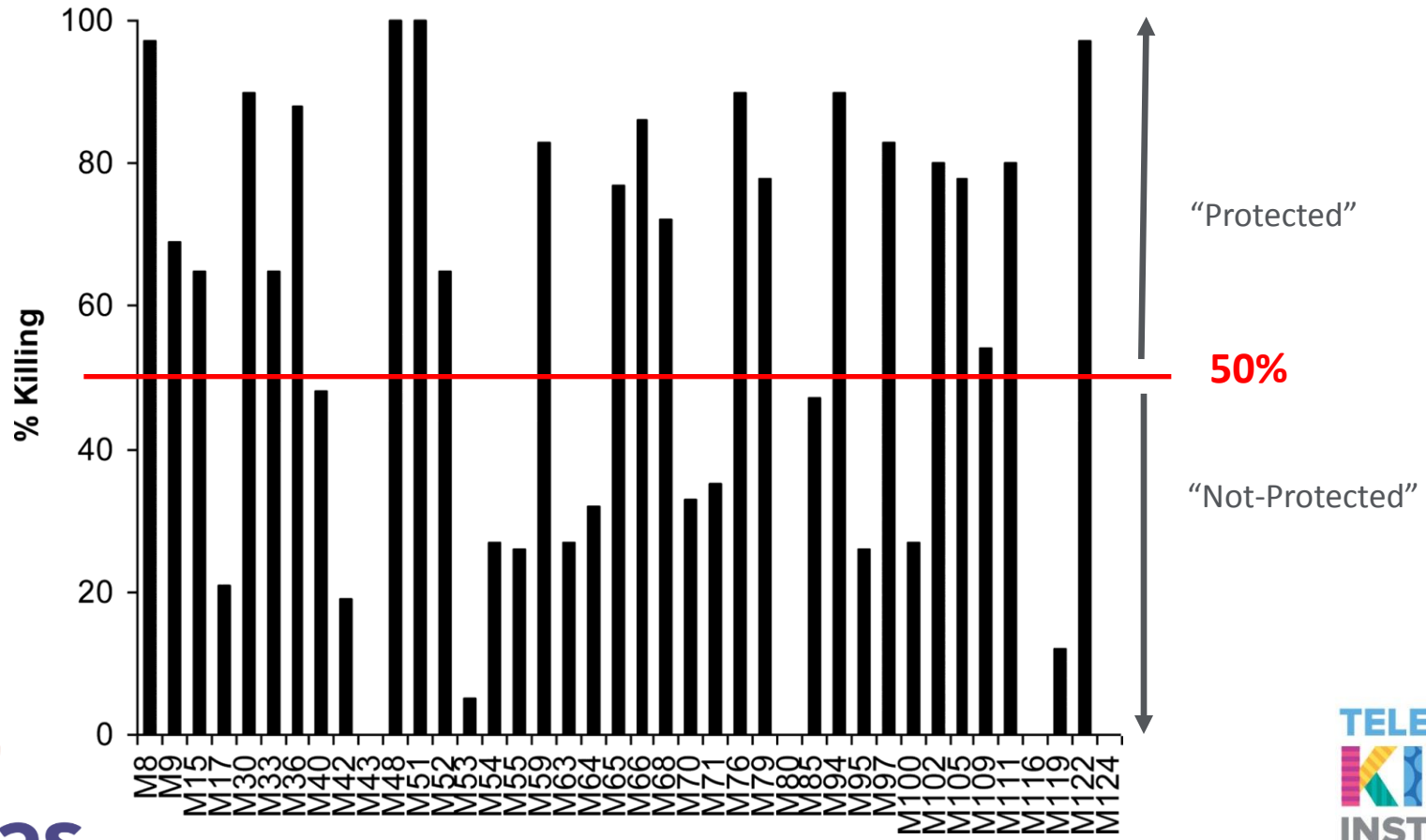
Lancefield Assay – Data Example

30-valent antisera against non-Vaccine M-types (Dale JB et al., (2011) Vaccine)



Group A Strep OPK

Modelled opsonisation killing assays (OPK) from assays developed for *S. Pneumo*

- Use HL60 cells (neutrophil cell line), not whole blood
- Robust assessment of killing; generate titration curve and calculate opsonisation index (OI)

Goldblatt Laboratory, University College London

- WHO reference laboratory for Pneumococcal serology
- Leading expertise in HL60 cell differentiation and OPK methodology

David Goldblatt

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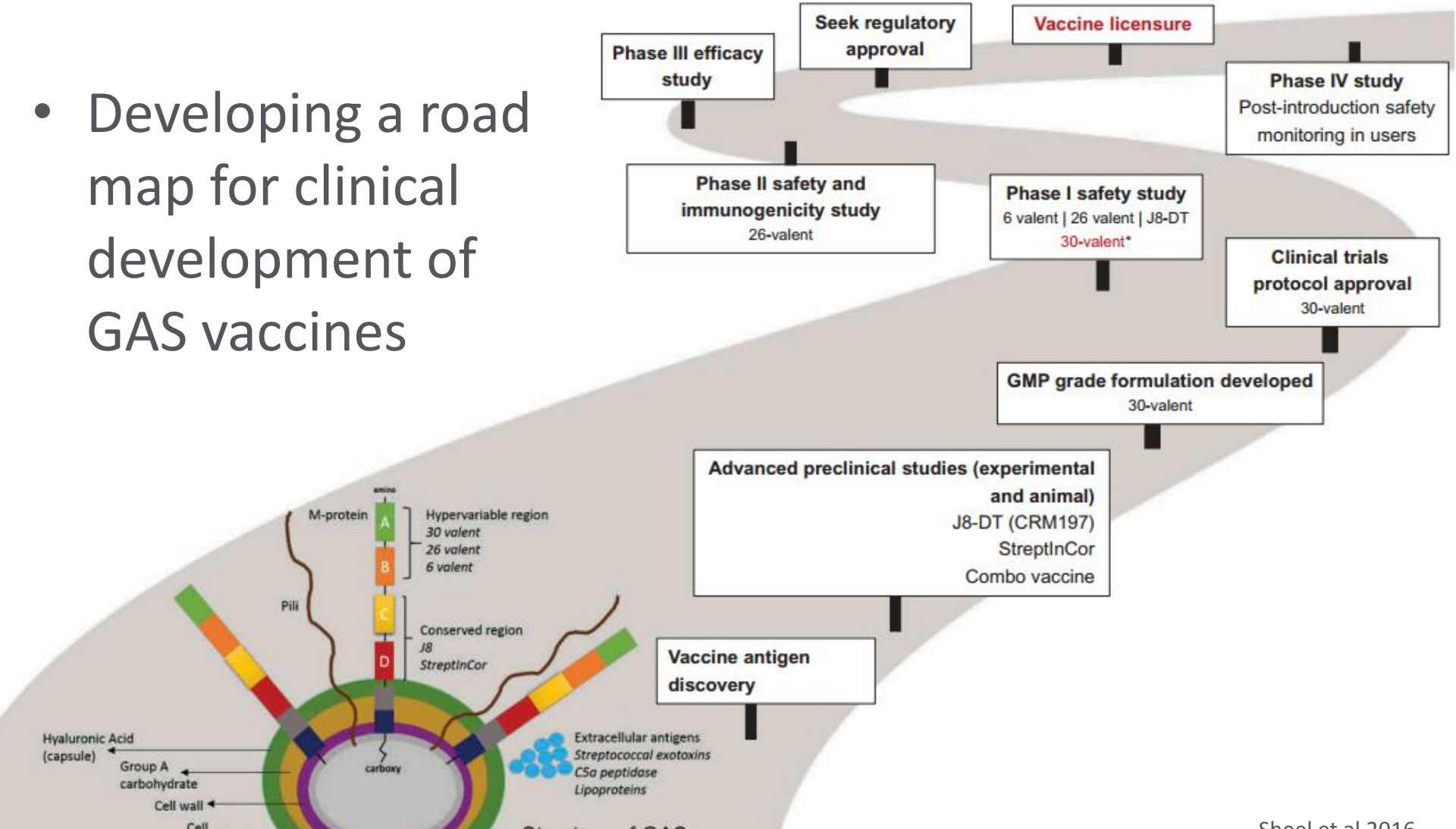
Clinical Development Plan

- Developing a road map for clinical development of GAS vaccines



Sheel et al 2016

Summary

- Major technical and safety challenges to GAS vaccine development are surmountable
- CANVAS initiative should “de-risk” early stage clinical development
- An RF vaccine is a realistic possibility in the medium term

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