Research priorities in RHD

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mshr

THE UNIVERSITY OF MELBOURNE

Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

Alvan Feinstein 1926-2001
Founding editor, Journal of Clinical Epidemiology,
'The father of modern clinical epidemiology'

*"Rheumatic fever has a complexity that makes it '**a university of disease**'. It inaugurated my instruction in clinical epidemiology and biostatistics… and it brought me my first academic adventures in controversy""*

Rheumatic heart disease is a disease of poverty that affects 15 million people worldwide and causes at least 250,000 deaths per annum

Aims of this session

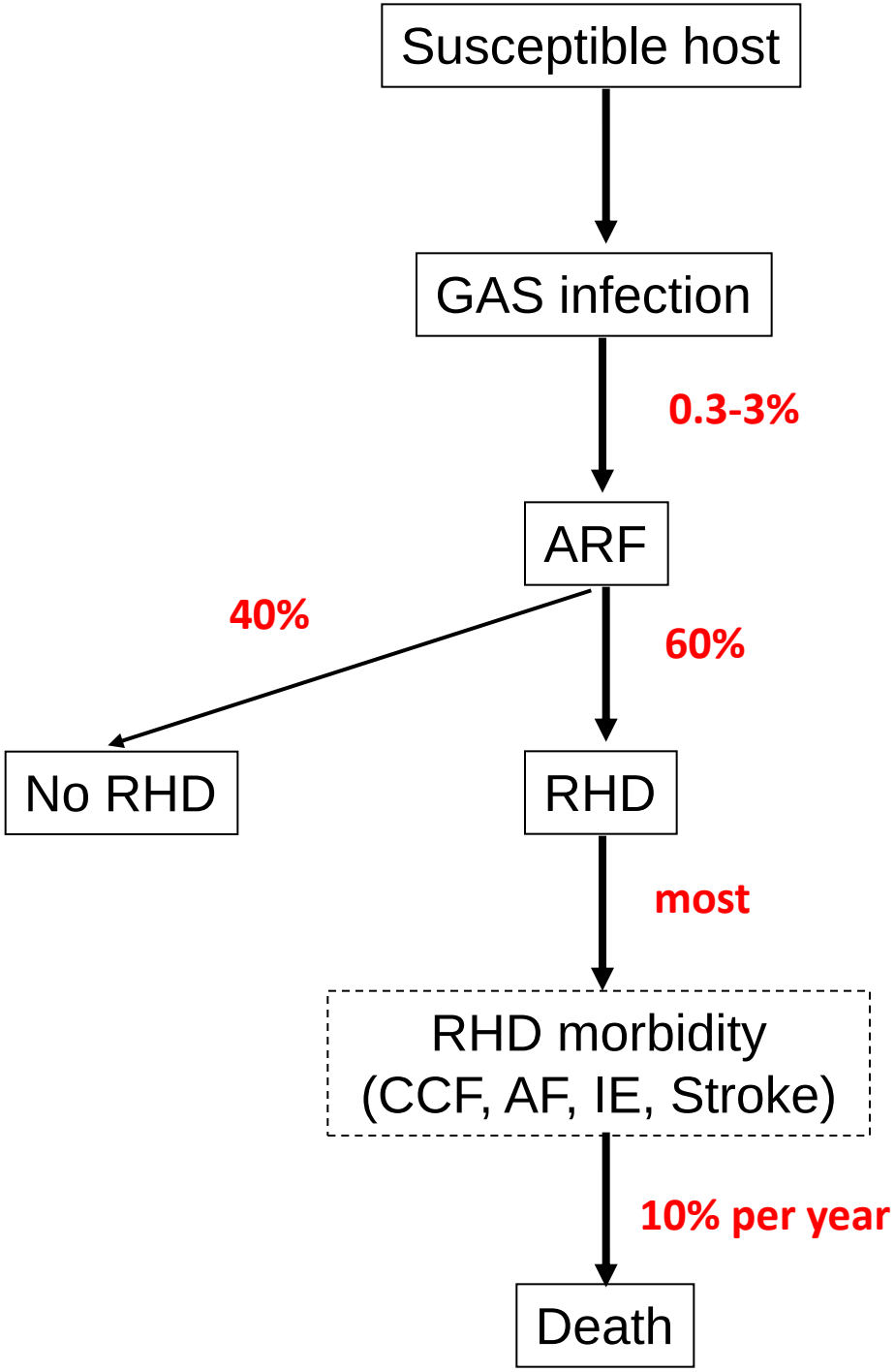
1. To outline research avenues in the RHD field

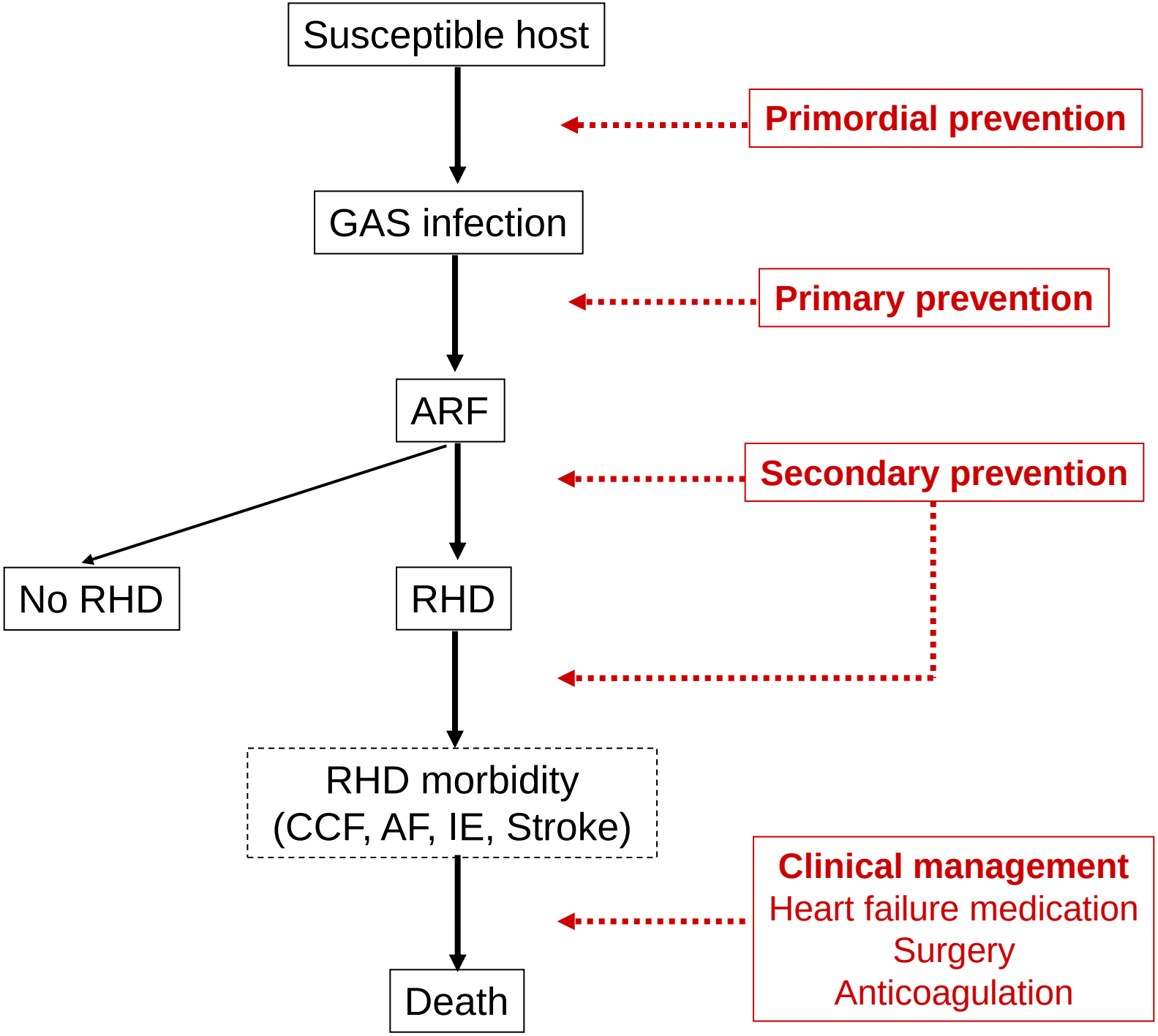
2. To consider what the research priorities are for RHD in the Pacific

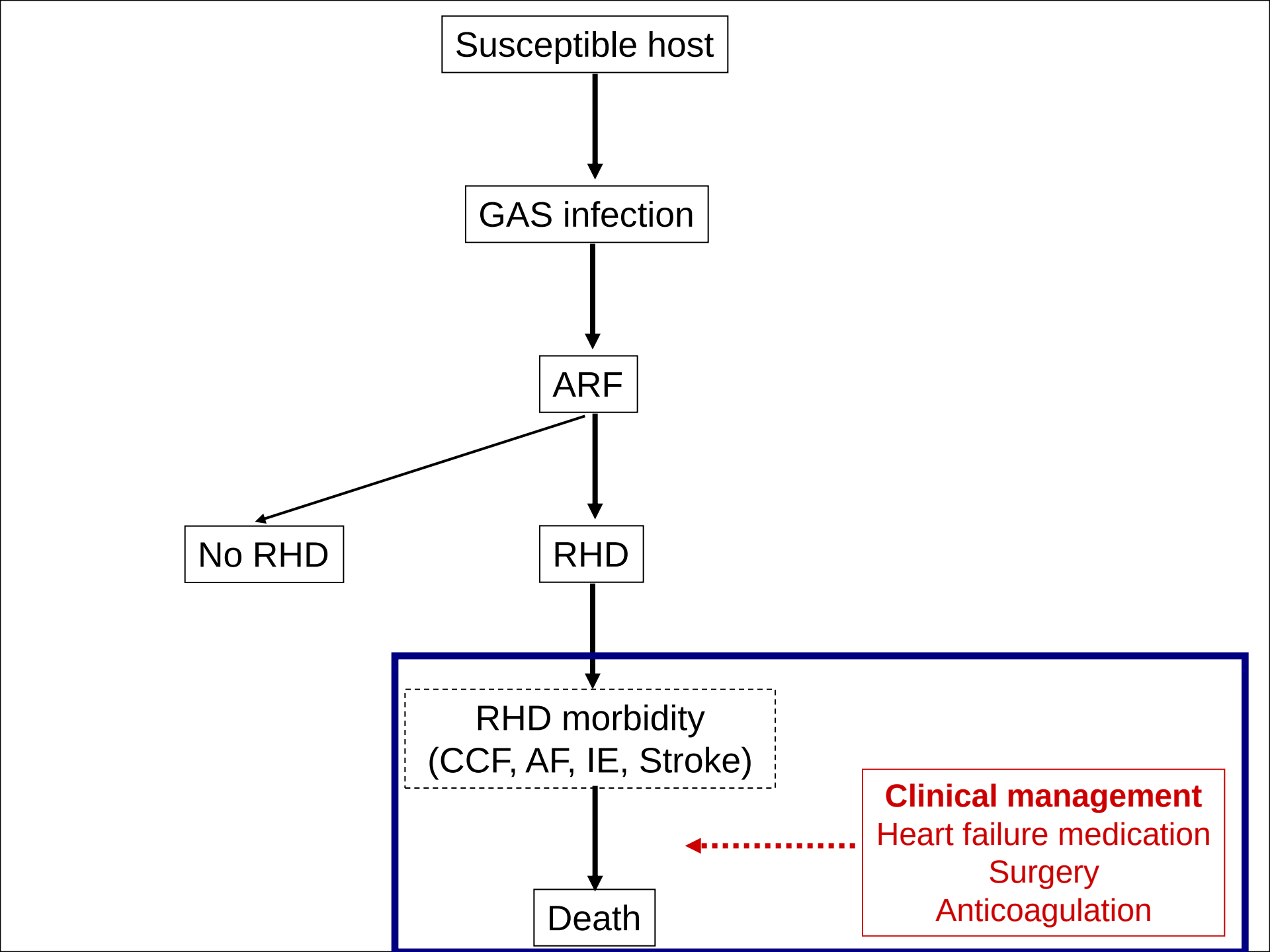
(*And give a little bit of extra information on GAS vaccines)

Frameworks for thinking about RHD research

1. Models of research
    1. Basic science / pre-clinical
    2. Epidemiology and surveillance
    3. Clinical research including clinical trials
    4. Service, programmatic and social research
2. Urgent questions vs. questions of interest
3. The RHD pathogenesis & management model


Susceptible host
GAS infection
0.3-3%
ARF
40%
60%
No RHD
RHD
most
RHD morbidity
(CCF, AF, IE, Stroke)
10% per year
Death


Susceptible host
Primordial prevention
GAS infection
Primary prevention
ARF
Secondary prevention
No RHD
RHD
RHD morbidity
(CCF, AF, IE, Stroke)
Clinical management
Heart failure medication
Surgery
Anticoagulation
Death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ARF
No RHD
RHD
RHD morbidity
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Death
Clinical management
Heart failure medication
Surgery
Anticoagulation

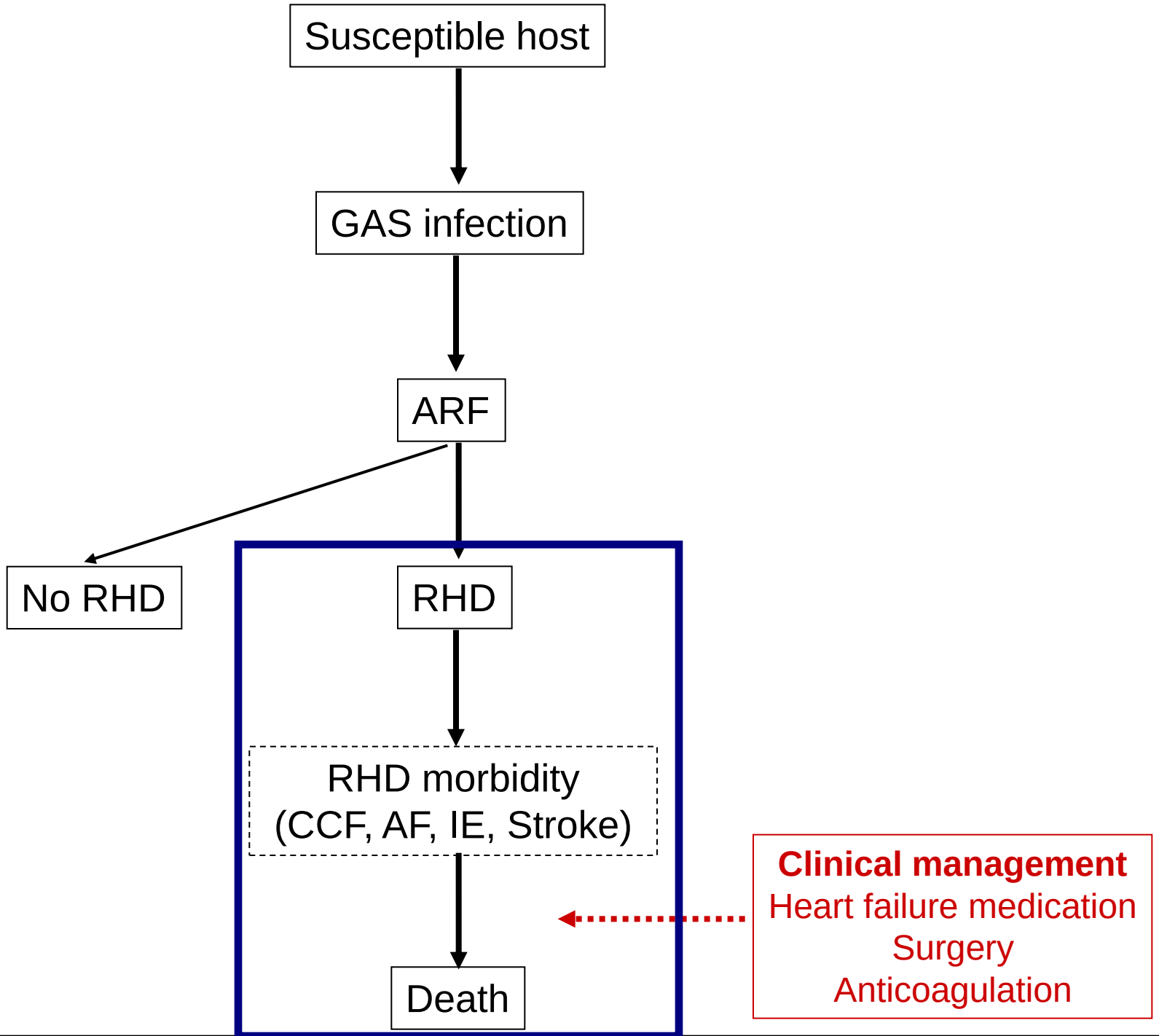
Management of established RHD

What is optimal surgery for RHD valvular disease?

Answer: Prospective clinical studies of repair versus replacement

How can RHD care be improved in the Pacific? (especially remote communities)

Answer: Service delivery research


Susceptible host
GAS infection
ARF
No RHD
RHD
RHD morbidity
(CCF, AF, IE, Stroke)
Death
Clinical management
Heart failure medication
Surgery
Anticoagulation

Established RHD

What is the global prevalence of RHD?

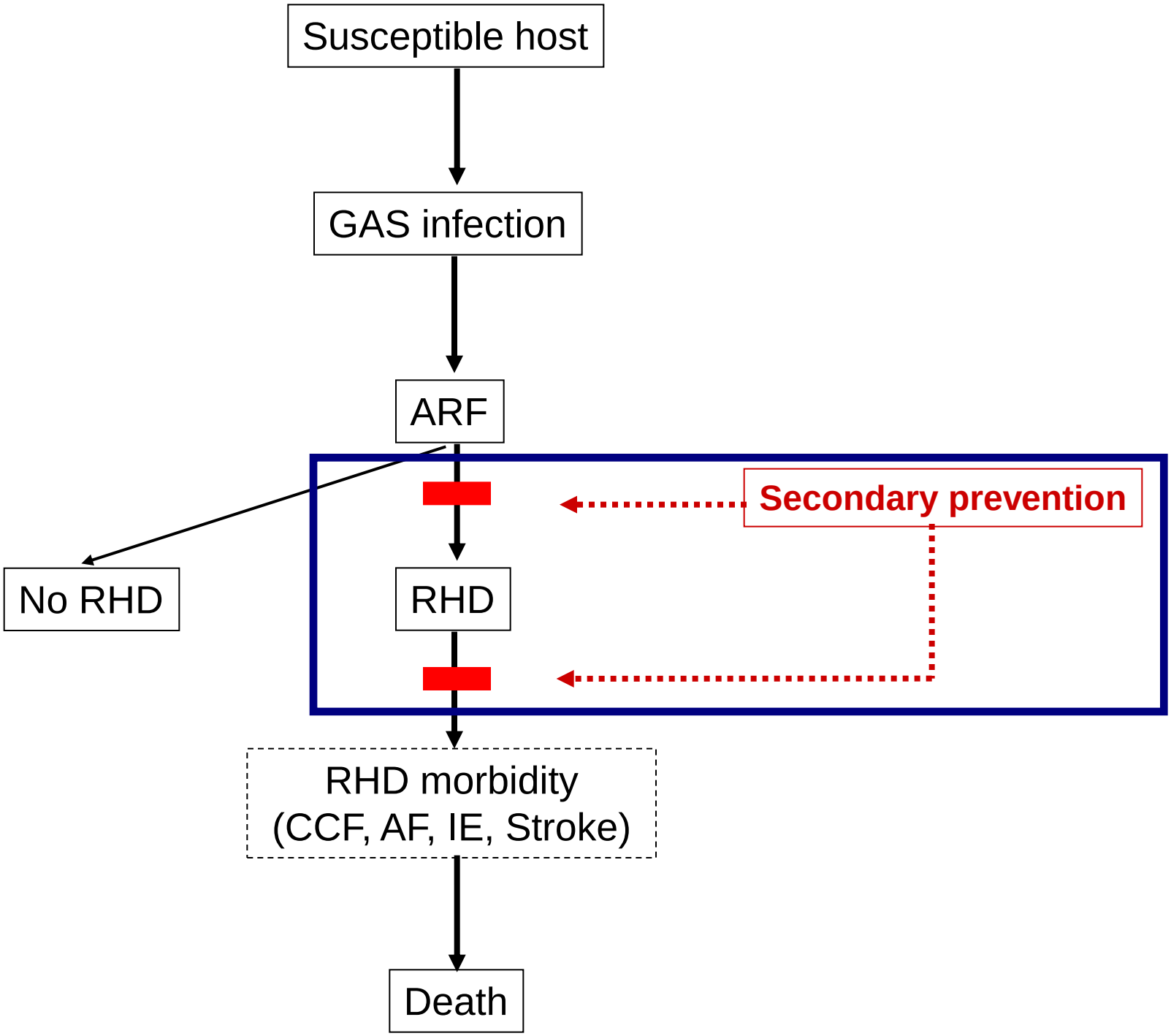
Answer: Systematic review (GBD), newer studies

What is the rate of mortality in patients with RHD?

Answer: Dedicated mortality studies

What is the cost of RHD?

Answer: Systematic economic impact studies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GAS infection
ARF
No RHD
RHD
Secondary prevention
RHD morbidity
(CCF, AF, IE, Stroke)
Death

Prevention of RHD

Are there new ways to deliver secondary prophylaxis?

Answer: depot preparations of long-long acting BPG, BPG pumps

Is the quality of BPG adequate and uniform?

Answer: Audits of BPG quality

Are we successful in increasing adherence? What improves adherence?

Answer: RCT of adherence-enhancing measures

Prevention of RHD: screening

Can we identify people with RHD earlier?

Answer: RHD screening with echocardiography

How do we determine what is normal/abnormal on echocardiogram?

Answer: Compare RHD endemic and non-endemic populations , long term follow up, case-control studies, RCT

How should we manage patients with "borderline" RHD? (or even "mild" definite RHD)

Answer: Case-control study, RCT of penicillin prophylaxis

Prevention of RHD: screening

Is screening clinically effective?

Answer: Follow-up studies of outcomes (no control group)

Is screening for RHD cost-effective?

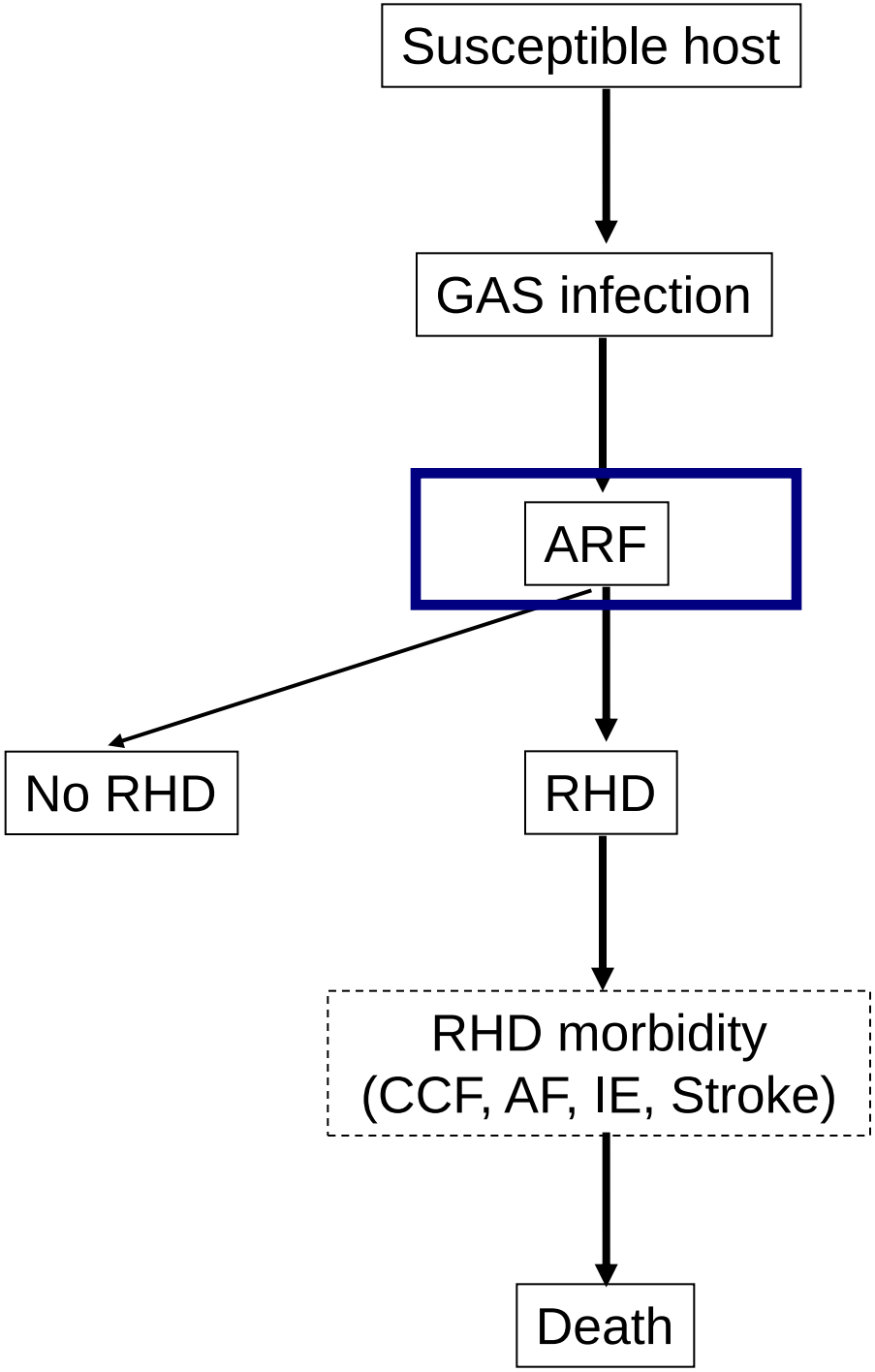
Answer: Detailed cost-effectiveness analysis

Can we create sustainable models for screening?

Answer: nurse-led echocardiography

Can we improve screening efficiency?

Answer: automated echo reading systems


Susceptible host
GAS infection
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Management of ARF

Is the clinical picture of ARF changing?

Answer: Clinical surveillance studies of ARF

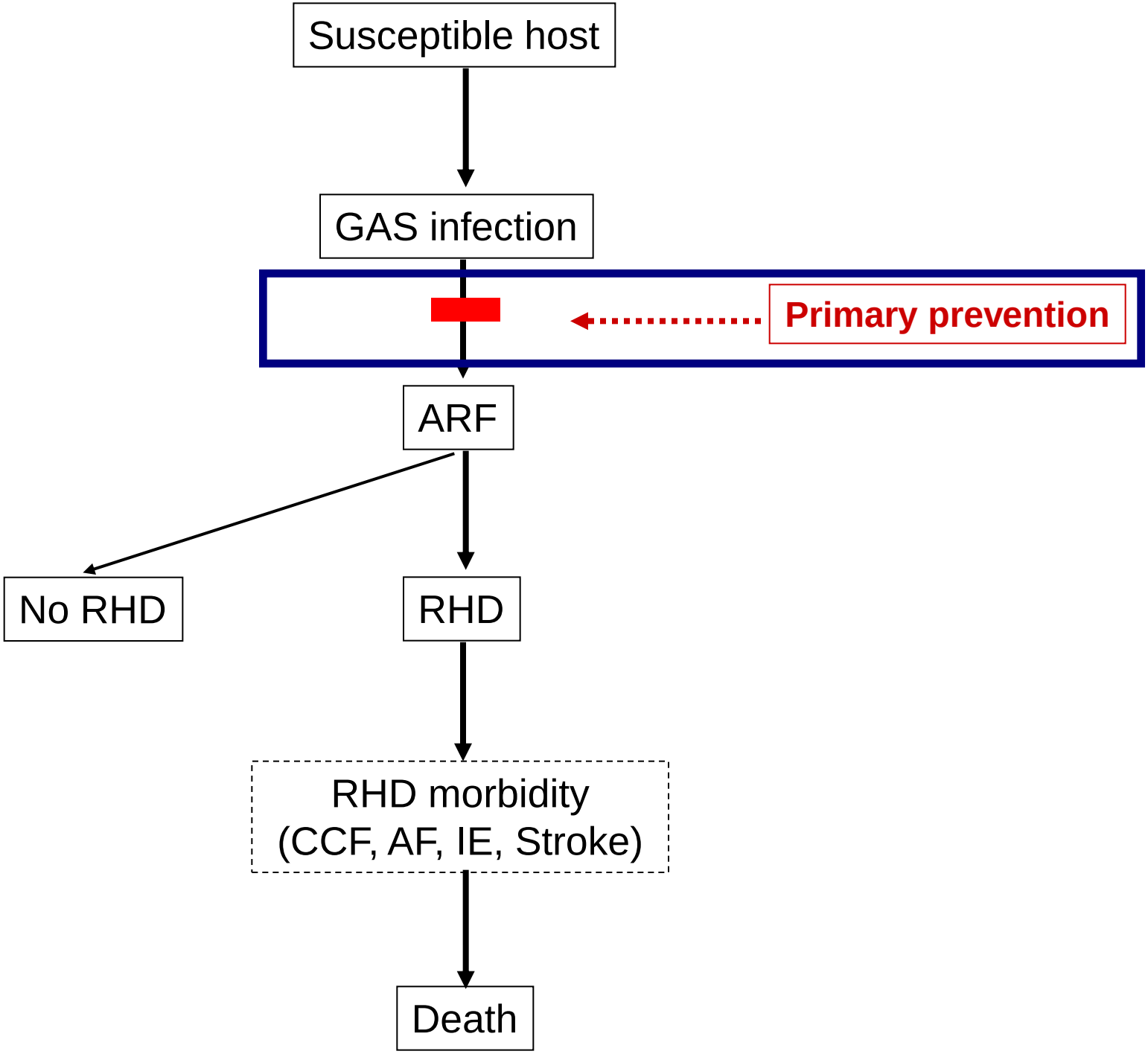
Are there better ways to diagnose ARF?

Answer: Better biomarkers

Are there better ways to manage ARF?

Answer:

- Clinical studies of naproxen
- Clinical studies of TNF-antagonists – eg infliximab, etanercept
- Clinical studies on the management of specific disease manifestations – eg chorea, arthritis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GAS infection
Primary prevention
ARF
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(CCF, AF, IE, Stroke)
Death

Primary prevention of ARF: sore throat

Are antibiotics other than penicillin effective in the prevention of ARF?

Is a comprehensive school-based program of sore throat surveillance and treatment effective in reducing rates of ARF?

What are the best ways to increase awareness of ARF in the community?

Answer: Health promotion research

What is the role of rapid tests in the diagnosis of GAS pharyngitis?

Answer: Diagnostic accuracy studies

Primary prevention of ARF: skin sores

Does control of GAS skin sores lead to a reduction in ARF?

Answer: Difficult. Large studies required: epidemiologic or intervention

Primary prevention of ARF: a vaccine

A work still in progress…

There are 2 vaccines approaching phase 1 trials:

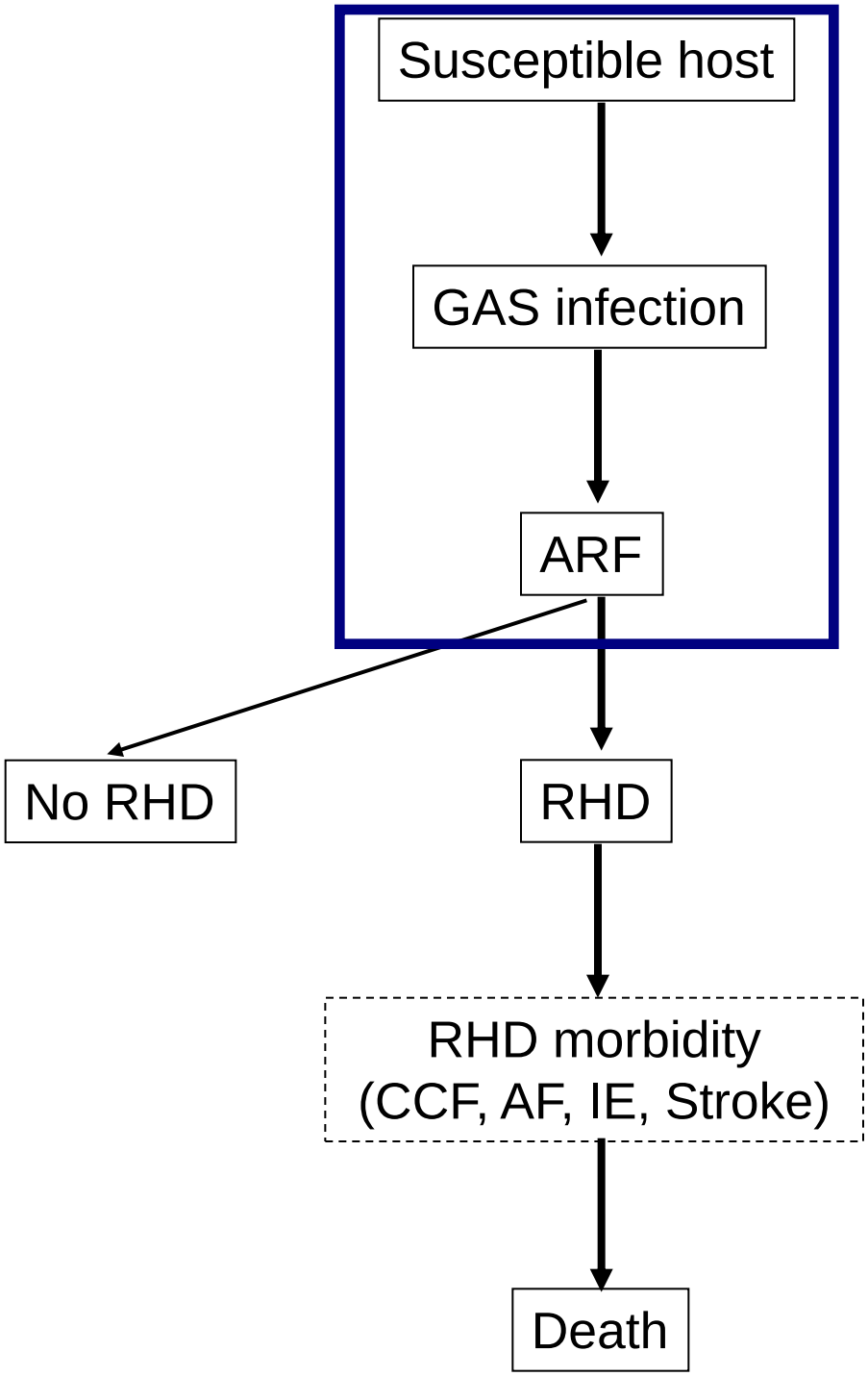
Key questions:

What are the circulating strains of GAS in the Pacific?

What is the incidence of potential outcome measures:

- **ARF**
- **Acute post-streptococcal glomerulonephritis**
- **Pharyngitis**
- **GAS impetigo**

Answer: Detailed epidemiologic studies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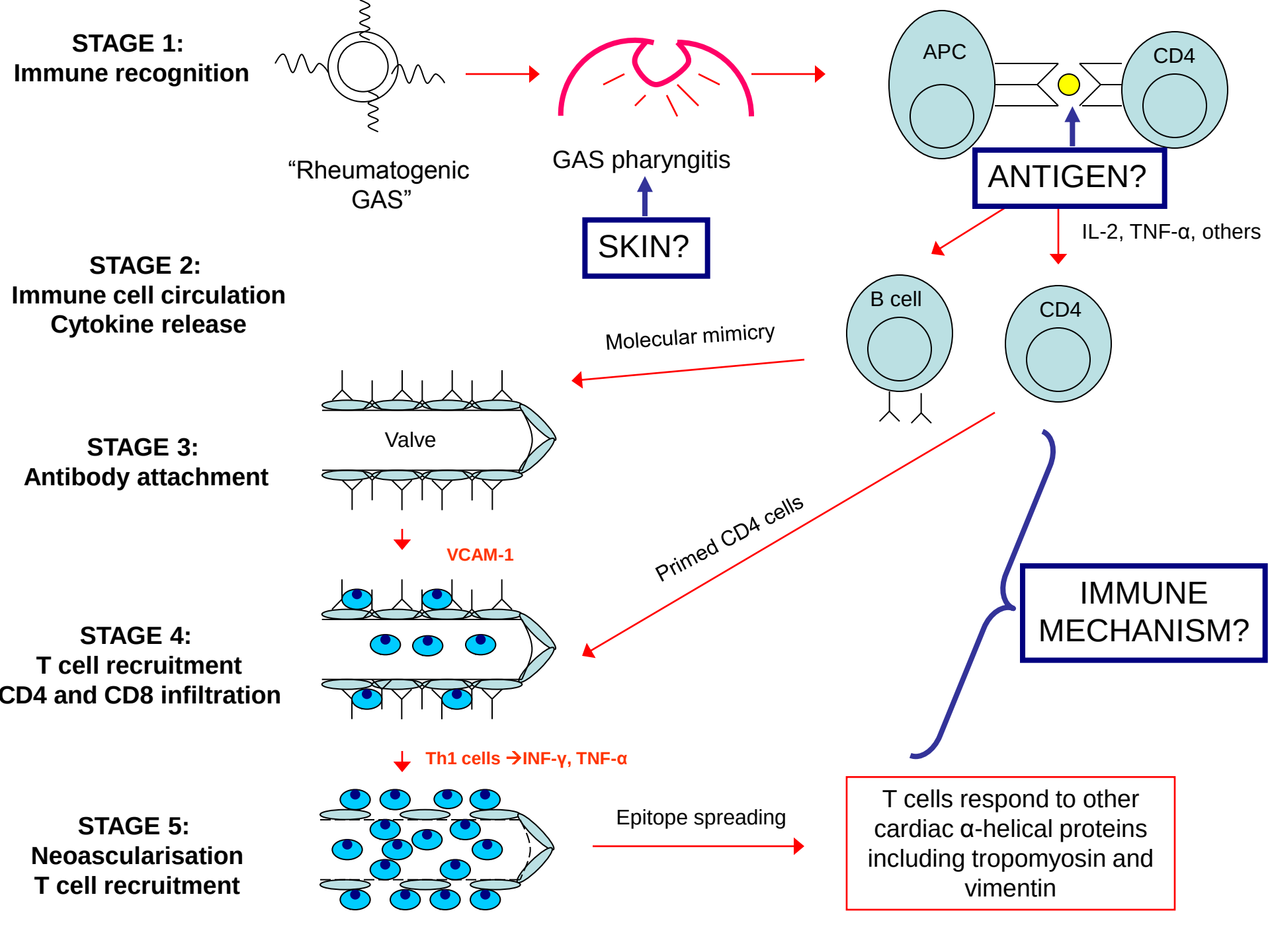
Pathogenesis of rheumatic fever

Another work in progress…


STAGE 1:
Immune recognition
"Rheumatogenic GAS"
GAS pharyngitis
SKIN?
APC
CD4
ANTIGEN?
IL-2, TNF-α, others
STAGE 2:
Immune cell circulation
Cytokine release
B cell
CD4
Molecular mimicry
Valve
STAGE 3:
Antibody attachment
VCAM-1
Primed CD4 cells
IMMUNE MECHANISM?
STAGE 4:
T cell recruitment
CD4 and CD8 infiltration
Th1 cells →INF-γ, TNF-α
STAGE 5:
Neoascularisation
T cell recruitment
Epitope spreading
T cells respond to other cardiac α-helical proteins including tropomyosin and vimentin

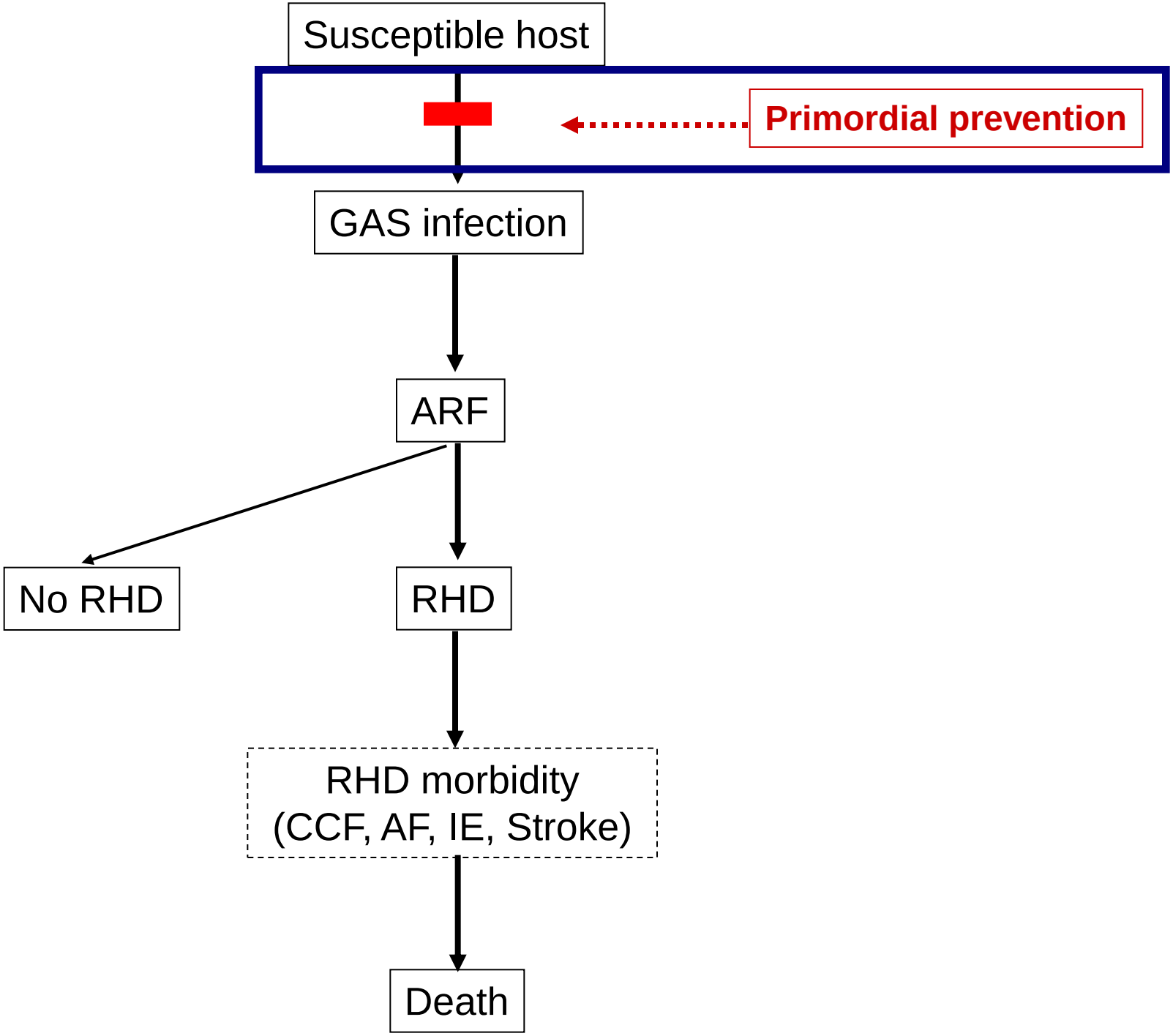
Pathogenesis of rheumatic fever

What is the role of skin infections?

Answer: Epidemiologic studies, intervention studies, basic science approach (homing T-cell studies)

What is the immune mechanism of ARF?

Answer: Animal model of ARF, applying novel technologies to the disease model (proteomics etc.)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Primordial prevention
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RHD
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Social determinants of ARF

What makes particular populations susceptible to ARF and RHD? What can be done about these social determinants?

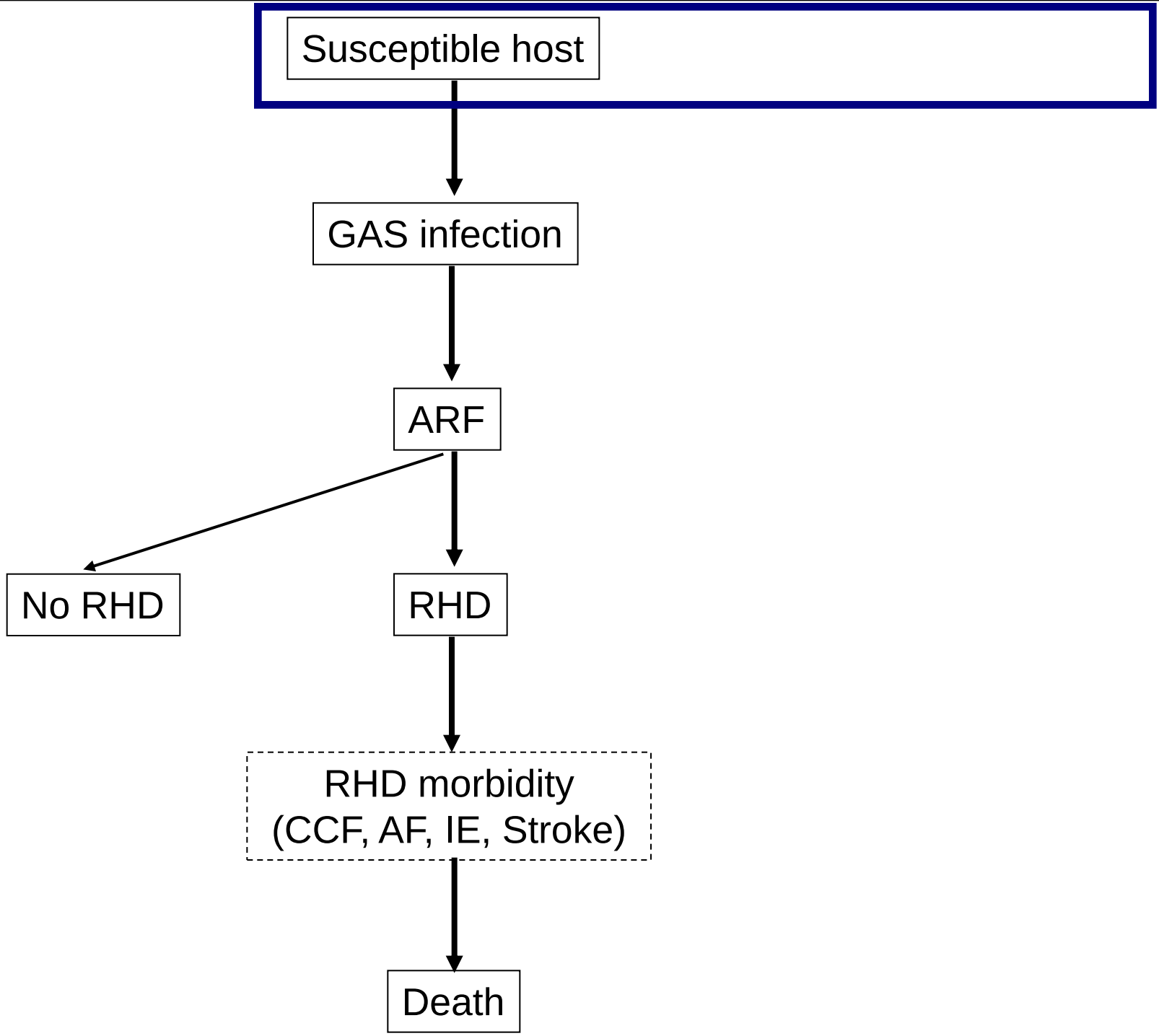
Answer:

- Case-control studies (Leon Gordis)
- Intervention studies (eg healthy housing, impact of social welfare programs on ARF incidence)

Measures of status	Cases ($n = 80$)	Controls ($n = 80$)	Statistical test[a]
Usual mode of transport (%)			
No car	72 (90)	65 (81)	OR 2.5 (95% CI 0.96–6.6)
Car	8 (10)	15 (19)	
Employed in household (%)			
≤1	57 (71)	51 (64)	OR 1.5 (95% CI 0.8–3.0)
>1	23 (29)	29 (36)	
Maternal education			
Primary school	27 (34)	17 (21)	OR 2.0 (95% CI 0.95–4.0)
Secondary school	52 (66)	62 (79)	
Maternal employment			
Not employed	65 (85)	53 (66)	OR 2.6 (95% CI 1.2–5.8)
Employed	12 (15)	23 (34)	
Paternal employment			
Not employed	48 (60)	47 (62)	OR 1.1 (95% CI 0.5–2.1)
Employed	32 (40)	29 (38)	
Mean income household in dollars (SD)	137 (138)	152 (161)	$p = 0.22$

OR odds ratio, *CI* confidence interval

Dobson et al
Pediatr Cardiol
2011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What makes specific people (and populations) particularly susceptible to ARF?

Answer: Novel genetic studies (incl whole genome sequencing)

Of all these questions, what are the priority questions for the Pacific?

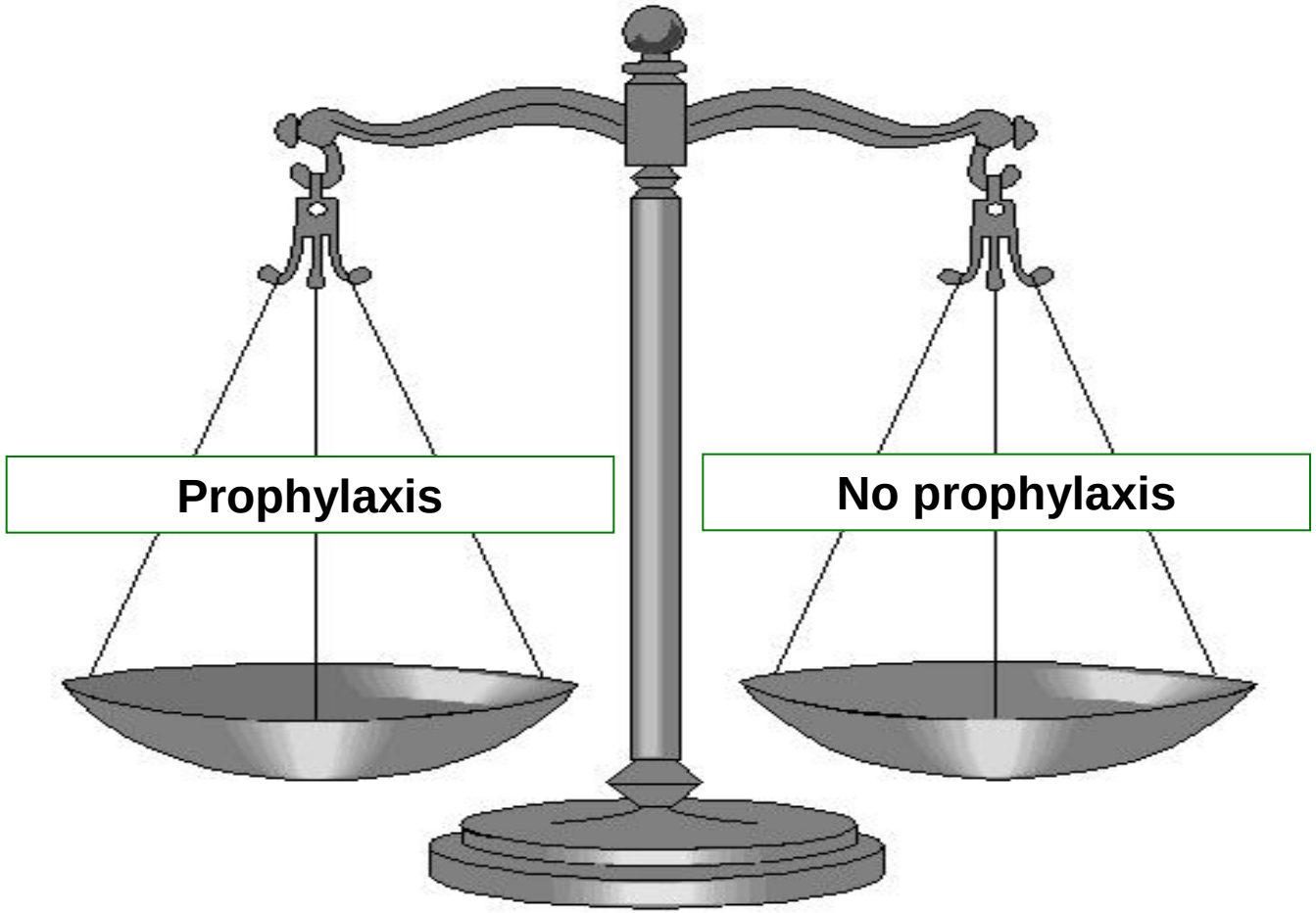
1. Implementation research

- Delivery of RHD care
- Improving secondary prophylaxis adherence
- Primary prevention (incl. rapid tests)

2. Screening research

- Standard case definitions with careful follow-up
- Effectiveness of screening
- Cost-effectiveness
- Borderline cases…

Borderline cases…



A clinical question

Gavin Wheaton, Bangkok, March 2011:

These mild abnormal findings in asymptomatic children…

"Truly a high prevalence of valve abnormalities which are normal and not previously described,

versus

Truly valve abnormalities that are not normal and represent early RHD"

This is a question that requires an URGENT answer if screening is to continue to be conducted

How to answer this question

1) Previous data

2) Observational study:

- Simply observe these cases over time off prophylaxis

3) Case control study

4) RCT of secondary prophylaxis for borderline cases

Design of a RCT
Defining the question…

"In otherwise well children aged 5-15 years with a diagnosis of borderline RHD on echocardiogram, does IM injection of BPG every 28 days reduce the risk of acute rheumatic fever and progression of RHD compared to a control group over a period of 3 years."

Sample size (RHD outcome measure)

Iceberg simulator RCT sample size calculator

Assumptions:
1 year follow-up
CER (RHD progression) = 10% per year
RRR = 50%
IER = 5% per year
Power 80%, alpha 0.05
Loss to follow-up: 10%
Compliance: 80%
Treatment 100% effective

Sample size:
430 in each group → 150 if observed for 3 years
→ 200 if LTFU 10% per annum
→ Compliance…

3. Susceptibility:

- Is it environment?
- Is it genetics

4. Vaccine trials and vaccine epidemiology

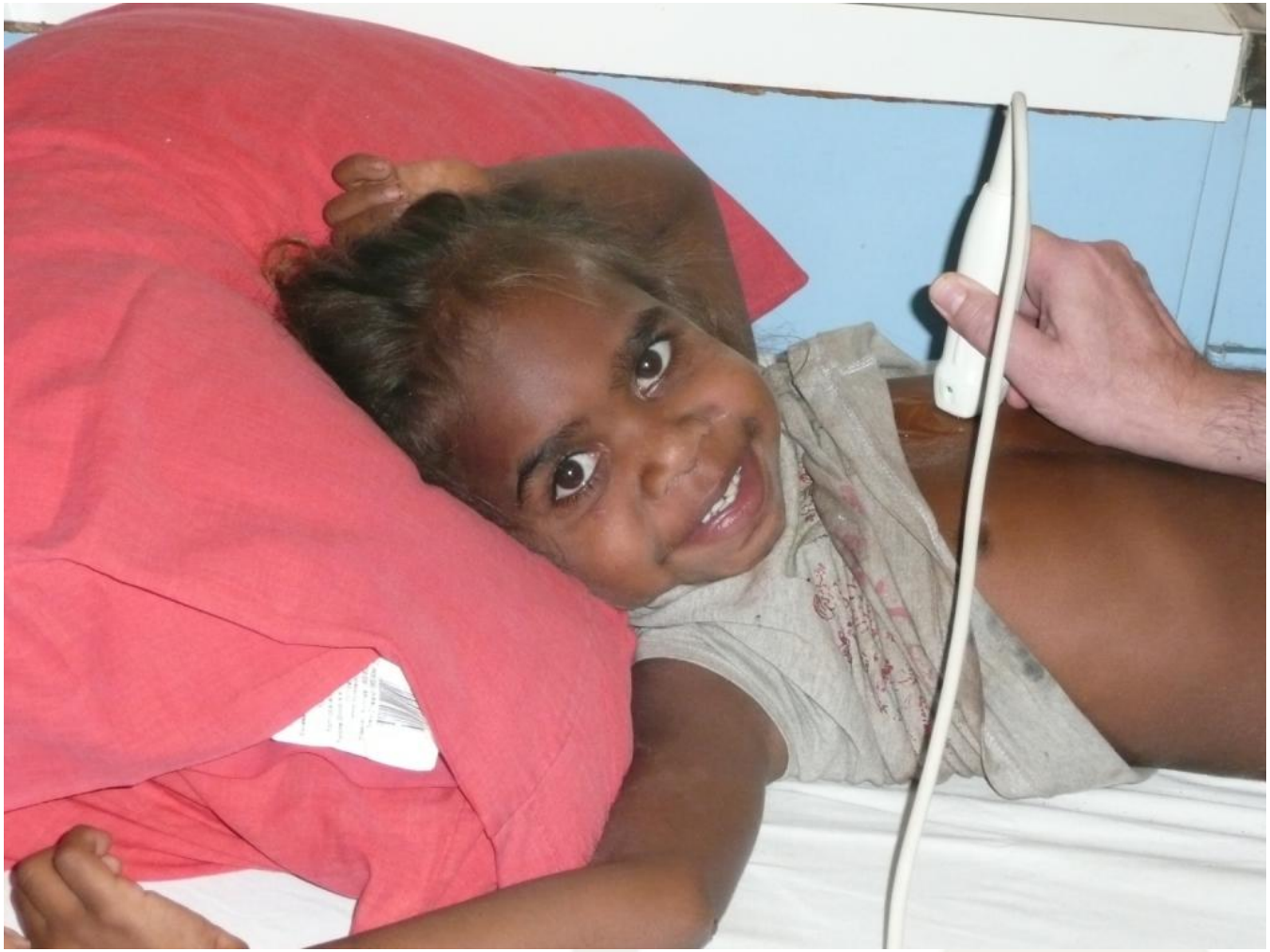
- Molecular epidemiology
- Baseline disease epiemiology

Studies underway by our group

Fiji:	Nurse led echocardiography
	Economic analysis*
	Genetics of RHD*
	Immunopathogenesis of ARF
	Control of skin sores (“RCT”)
	RHD surgery mortality audit
Australia:	gECHO
	RhFFUS
	Genetics of RHD
	RCT for secondary prevention
International:	RHD echocardiographic standardisation

(1) The gECHO study

Population-based echocardiographic screening for Rheumatic Heart Disease in northern Australian children



Methods

Study design	Observational cross-sectional prevalence survey
Population	5000 children aged 5-15 in northern Australia 1000 urban (Darwin and Cairns), 4000 remote 1000 remote Top End 1000 remote Central Australia 1200 remote Far North Queensland 800 remote Kimberly, WA
Sample size	Calculated based on estimated point prevalence of RHD 7.5/1,000 children aged 5-14* Sample size of 4000 gives 95% CI of 5.1-10.7/1000

*Known prevalence of RHD in Central Australia in 2002 according to NT RHD register data

Methods

Screening echocardiogram

- All children (n=5255)
- Abbreviated protocol focusing on MV and AV
- Defined criteria to prompt comprehensive echocardiogram (n=690)
- All comp echos to be reported by service-delivery cardiologist for the region ASAP

Echos performed

	Location	Screens	Comps	(%)
Urban	Darwin	591	63	11
	Cairns	497	44	9
	Total	**1088**	**107**	**10**
Remote	Top End	1015	153	15
	CA	974	111	11
	FNQ	1355	228	17
	WA	823	91	11
	Total	**4167**	**583**	**14**
Total		**5255**	**690**	**13%**

gECHO

- Echos now all read
- Urban (low risk) dataset – analysis complete and presented in Bangkok
- Remote (high risk) dataset – analysis near completion
- In 2012:
  - Publication of results
  - Economic analysis
  - Recommendations for screening in Australia

(2) RhFFUS

RhFFUS

Rheumatic **F**ever
Follow **U**p **S**tudy

Is that echo' normal or not?

RhFFUS

- Follow up of “borderline” cases from gECHO
- Endpoints:
  - Incidence of ARF
  - Progression of RHD
- In NT, WA, Qld
- Due to start in early 2012

(3) Genetics of RHD in Australian Indigenous population

- Main aim – to identify any genetic associations with RHD susceptibility, with a view to unlocking the "Black Box" of ARF pathogenesis
- 500 Indigenous RHD patients, with 1000 healthy controls matched by age and community.
- Currently planning "Immunochip" – may end up doing GWAS if funding adequate.
- Major component looking at informed consent, and governance of samples and information
- First part has begun. NHMRC funding obtained to start in 2012.

Advantages of RHD research

Answer important questions

Provide valuable data to government for informed decision making

Advocacy for RHD (data talks)

Awareness and government buy-in

Establishment of networks

Centre of Excellence

Merci beaucoup pour votre attention.

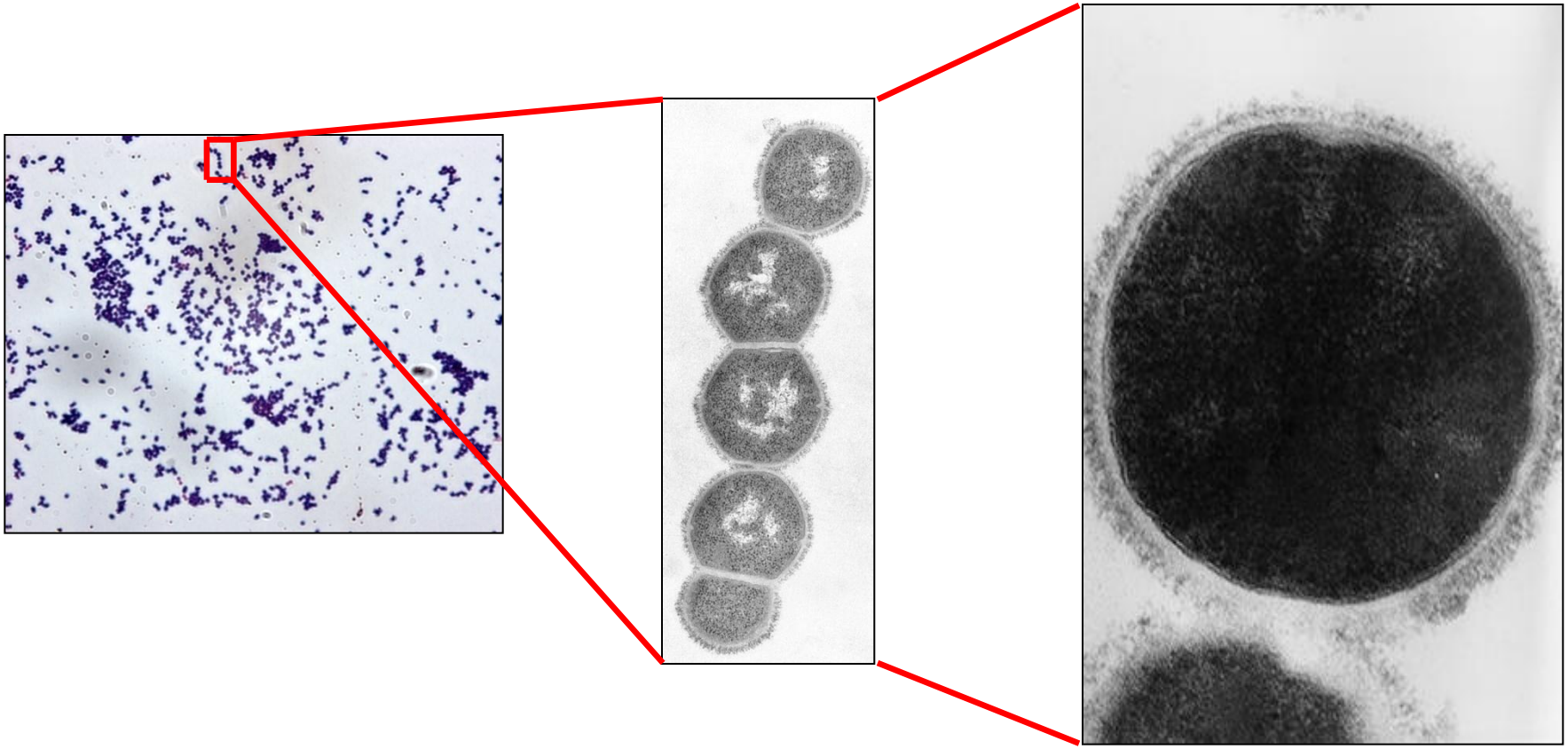
GAS vaccines

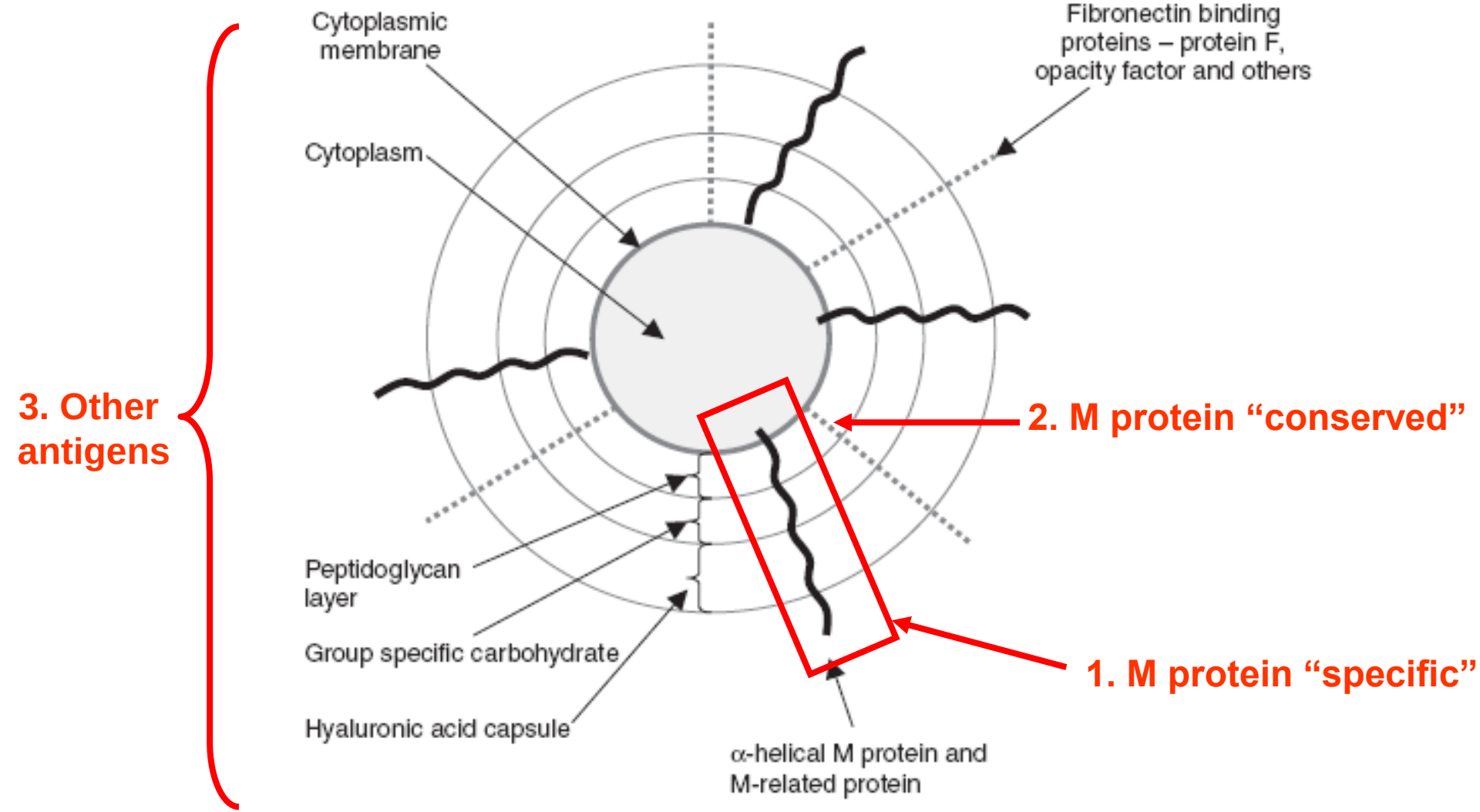
Human GAS immunisation

Year of publication	Antigen
1923	21 strain heat-killed GAS
1930	Heat-killed GAS
1931	Heat-killed GAS
1932	Heat-killed GAS
1933–1943	GAS 'toxin' and GAS tannic acid precipitated 'toxin'
1937–1941	GAS tannic acid precipitated 'toxin'
1946	Heat-killed or ultraviolet-inactivated M17 and M19 GAS
1949	Heat-killed M3 and M17 GAS
1960	Partially purified M19 GAS
1962	Cell wall of M5 and M12 GAS
1963	Cell wall of M14 GAS
1968	Partially purified M protein M3 GAS
1969	Highly purified M protein M12 GAS
1973	Highly purified M protein M1 GAS
1975	Highly purified M protein M1 GAS
1978	Highly purified M protein M3 and M12 GAS
1979	Polypeptide fragment M protein M24 GAS
2004	Six-valent N-terminal M protein fragments M1, M3, M5, M6, M19, M24
2005	Recombinant 26-valent M protein vaccine along with Spa

Steer et al. Curr Opin Infect Dis 2009

Vaccine targets




Cytoplasmic membrane
Cytoplasm
Fibronectin binding proteins – protein F, opacity factor and others
3. Other antigens
2. M protein "conserved"
1. M protein "specific"
Peptidoglycan layer
Group specific carbohydrate
Hyaluronic acid capsule
α-helical M protein and M-related protein

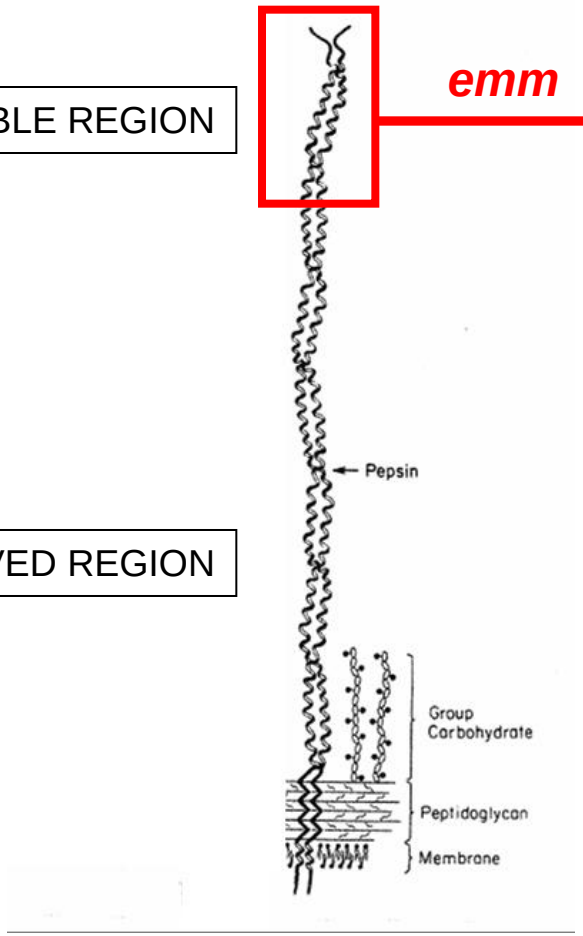
emm-type specific vaccines

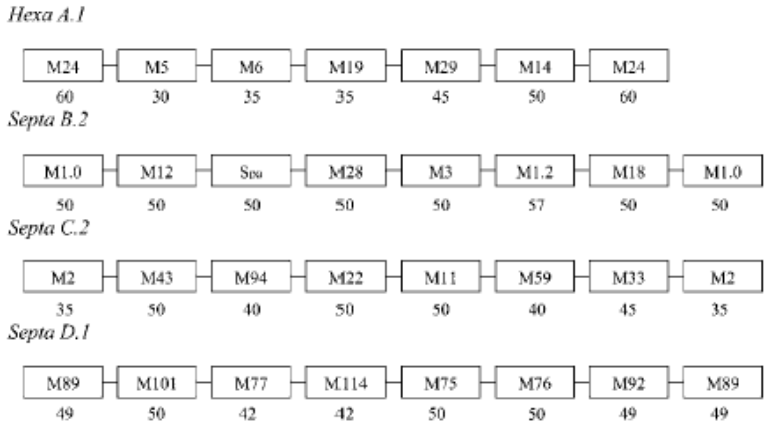
Safety and Immunogenicity of 26-Valent Group A *Streptococcus* Vaccine in Healthy Adult Volunteers

Shelly A. McNeil,[1] Scott A. Halperin,[1] Joanne M. Langley,[1] Bruce Smith,[1] Andrew Warren,[2] Geoffrey P. Sharratt,[2] Darlene M. Baxendale,[1] Mark A. Reddish,[3] Mary C. Hu,[3] Steven D. Stroop,[3] Janine Linden,[3] Louis F. Fries,[3] Peter E. Vink,[3] and James B. Dale[4]

VARIABLE REGION

CONSERVED REGION





Well tolerated
Good immune responses

Choice of *emm* types

26 *emm* types chosen from >150 known *emm* types:

-Most common *emm* types assoc. with ARF

-Most common *emm* types causing invasive GAS

-Most common *emm* types causing pharyngitis

(In the USA and Canada)

The Epidemiology of Invasive Group A Streptococcal Infection and Potential Vaccine Implications: United States, 2000–2004

Rosalyn E. O'Loughlin,[1,2] Angela Roberson,[1] Paul R. Cieslak,[5] Ruth Lynfield,[6] Ken Gershman,[7] Allen Craig,[8] Bernadette A. Albanese,[9] Monica M. Farley,[3,4] Nancy L. Barrett,[10] Nancy L. Spina,[11] Bernard Beall,[1] Lee H. Harrison,[12] Arthur Reingold,[13] and Chris Van Beneden,[1] for the Active Bacterial Core Surveillance Team

The *emm* types in a proposed 26-valent vaccine accounted for 79% of all cases and deaths.

What about *emm* types in Australia and the Pacific where the burden of disease is greatest?

Global *emm* type distribution of group A streptococci: systematic review and implications for vaccine development

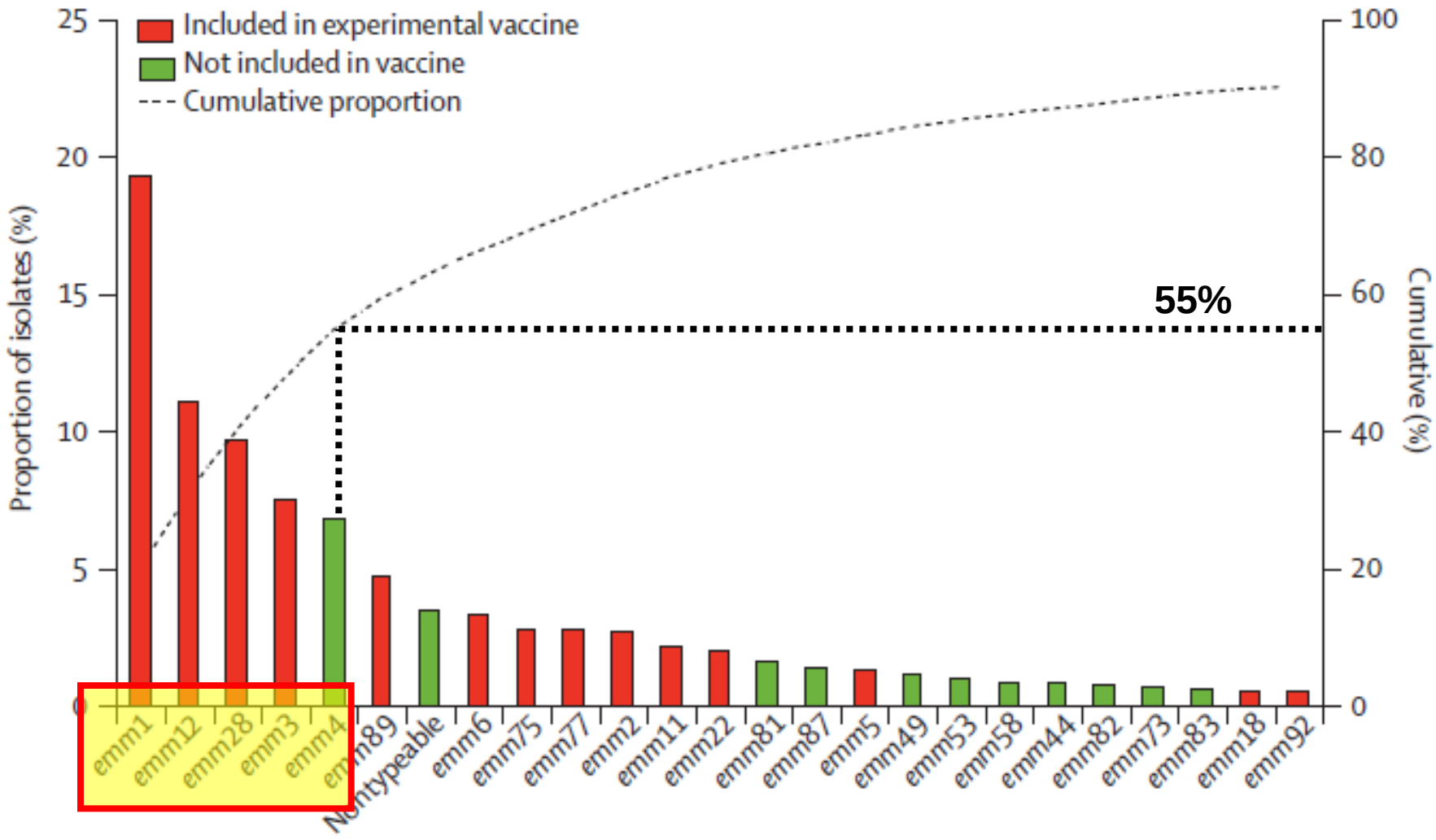
Andrew C Steer, Irwin Law, Laisiana Matatolu, Bernard W Beall, Jonathan R Carapetis

Lancet Infect Dis 2009; 9: 611–16

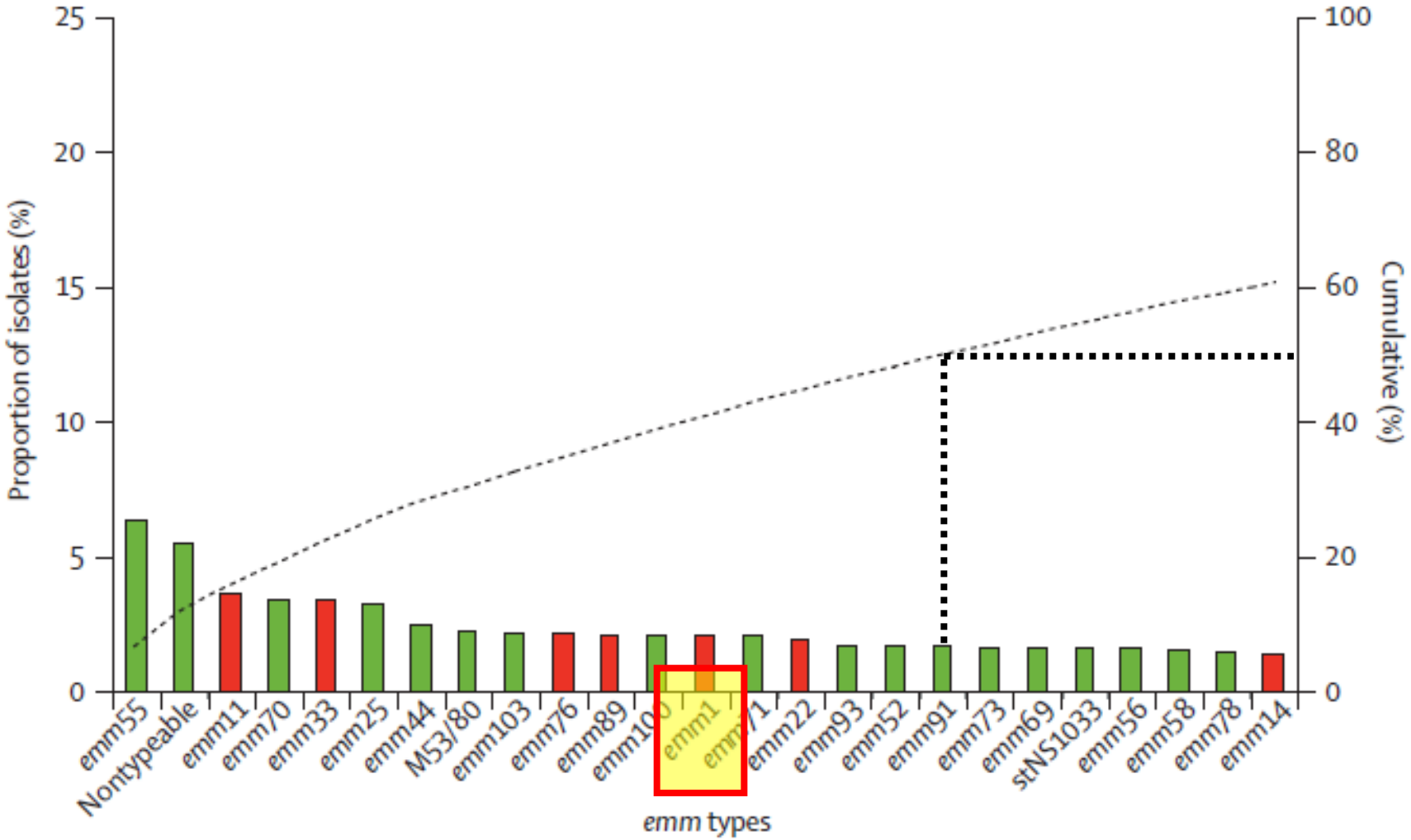
Methods:

- Systematic review
- 1990 – March 2009
- 102 datasets

- Presented data as:
  - *emm* as % of total isolates
  - By region
  - By disease type (invasive, pharyngeal, skin)

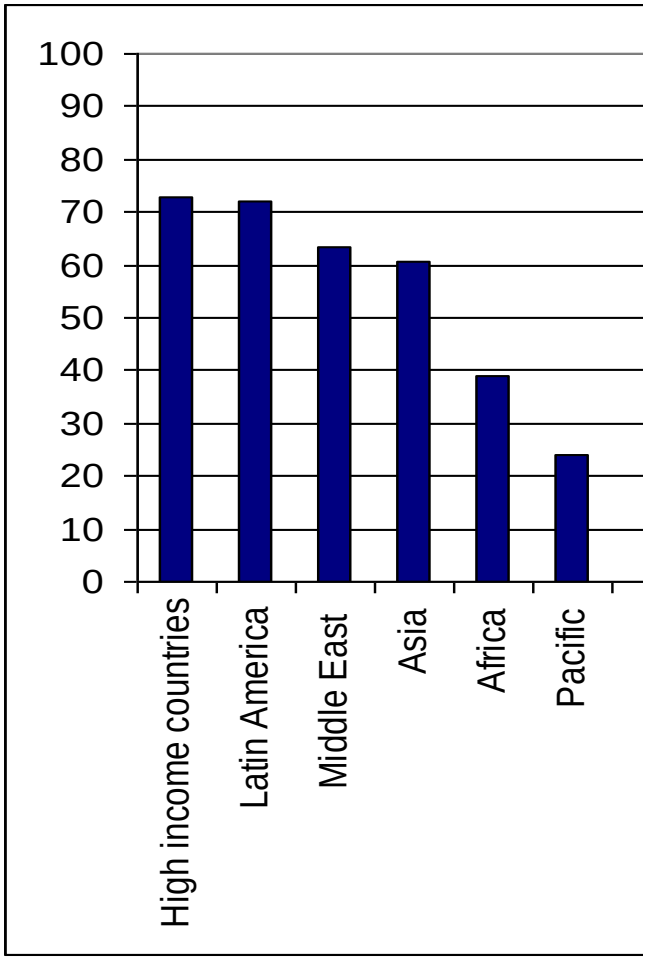


Established market economies



Pacific region

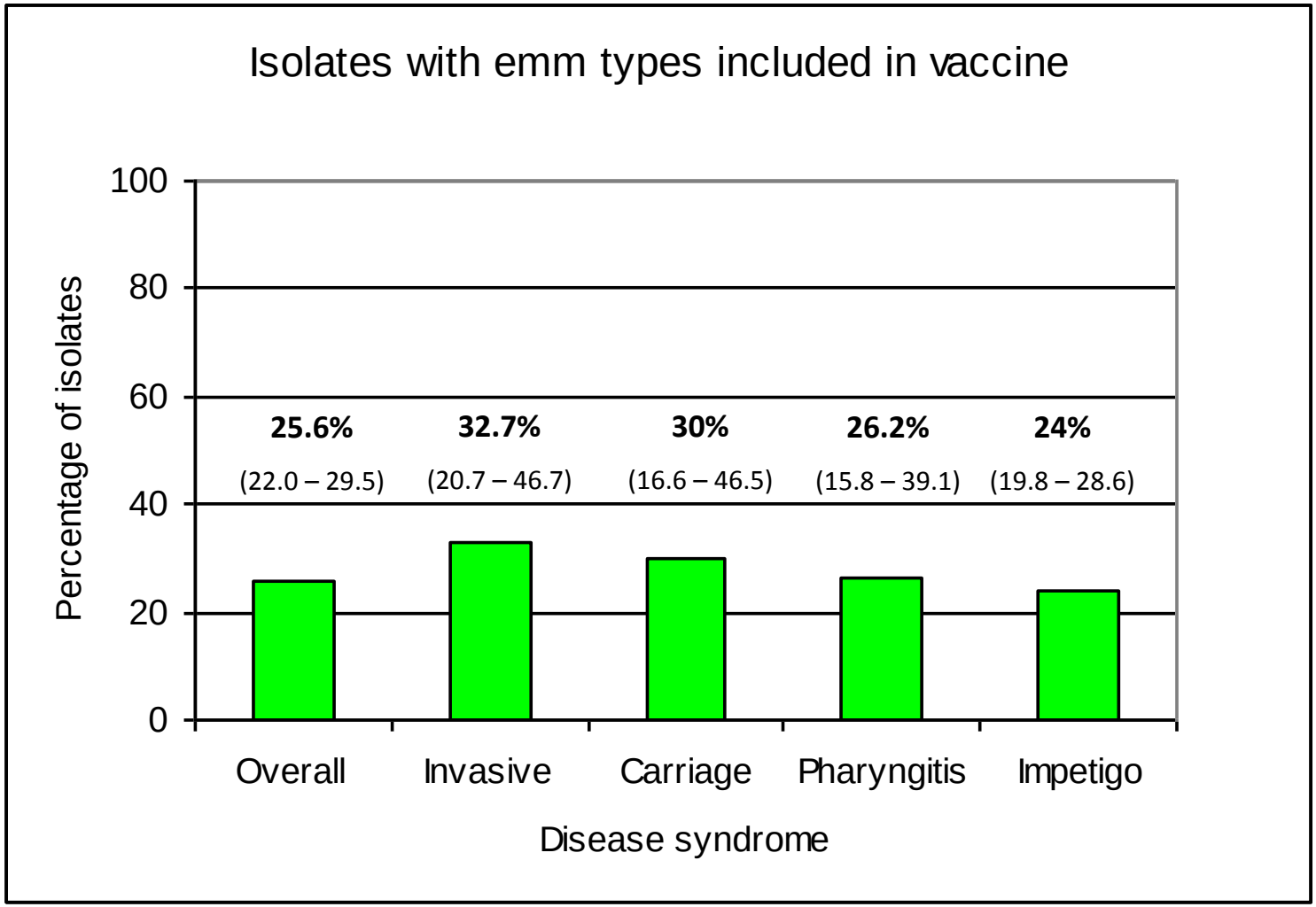
26 valent vaccine - coverage (%)



A good vaccine for temperate countries where pharyngitis is a priority.
A poor vaccine for tropical where disease burden is greatest.

http://www.cdc.gov/ncidod/biotech/strep/emmtype_proportions.htm

26 valent M type vaccine coverage in Fiji

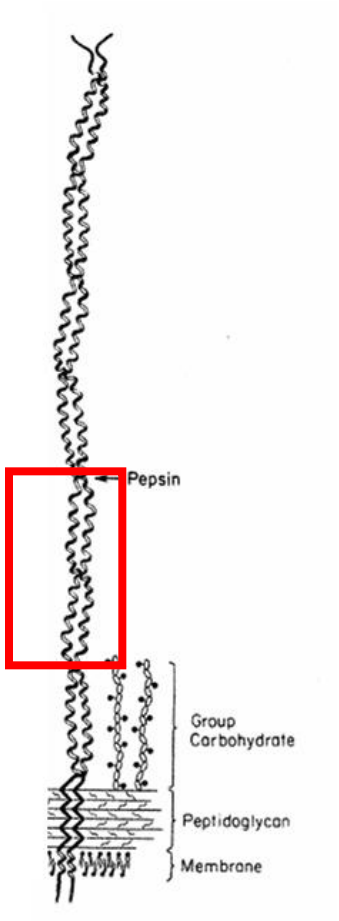


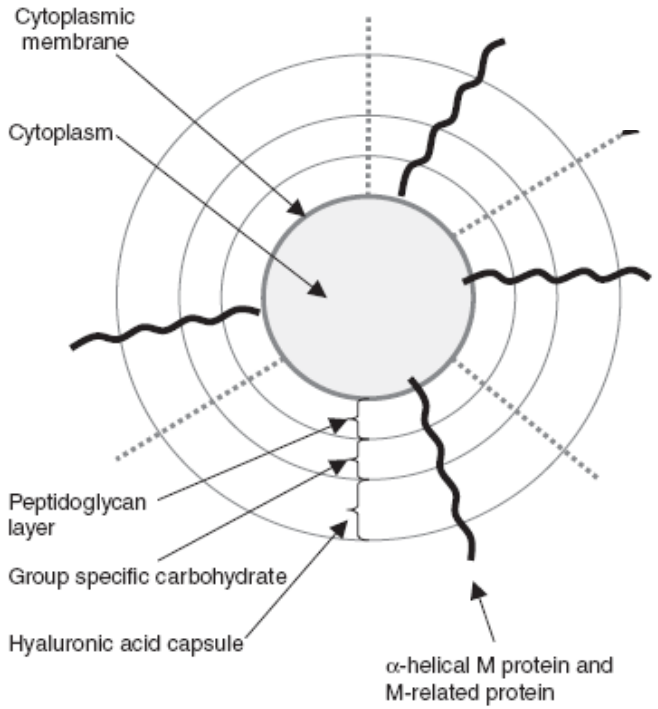
Other vaccine candidates

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

VARIABLE REGION

CONSERVED REGION





New vaccine candidates

Conserved M protein vaccines

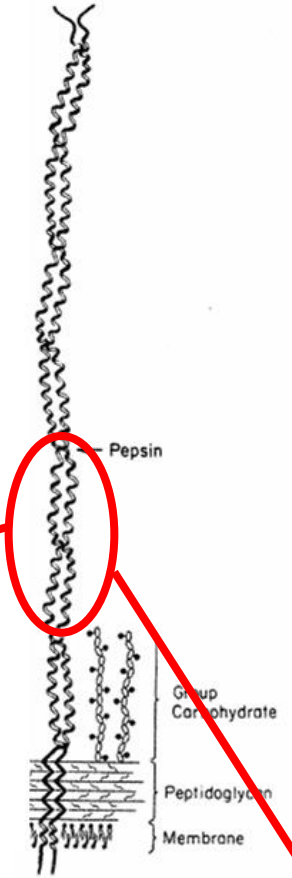
- The “J8” vaccine

Non M protein vaccines

- C35a peptidase
- GAS carbohydrate
- Fibronectin binding proteins
- Cysteine protease
- Streptococcal pili
- Genomic and proteomic “fishing” for vaccines

The J8 vaccine: QIMR/Michael Good

- Animal data encouraging
- Adult vaccine phase I trials to start 2011
- Phase II and III trials planned for developing countries

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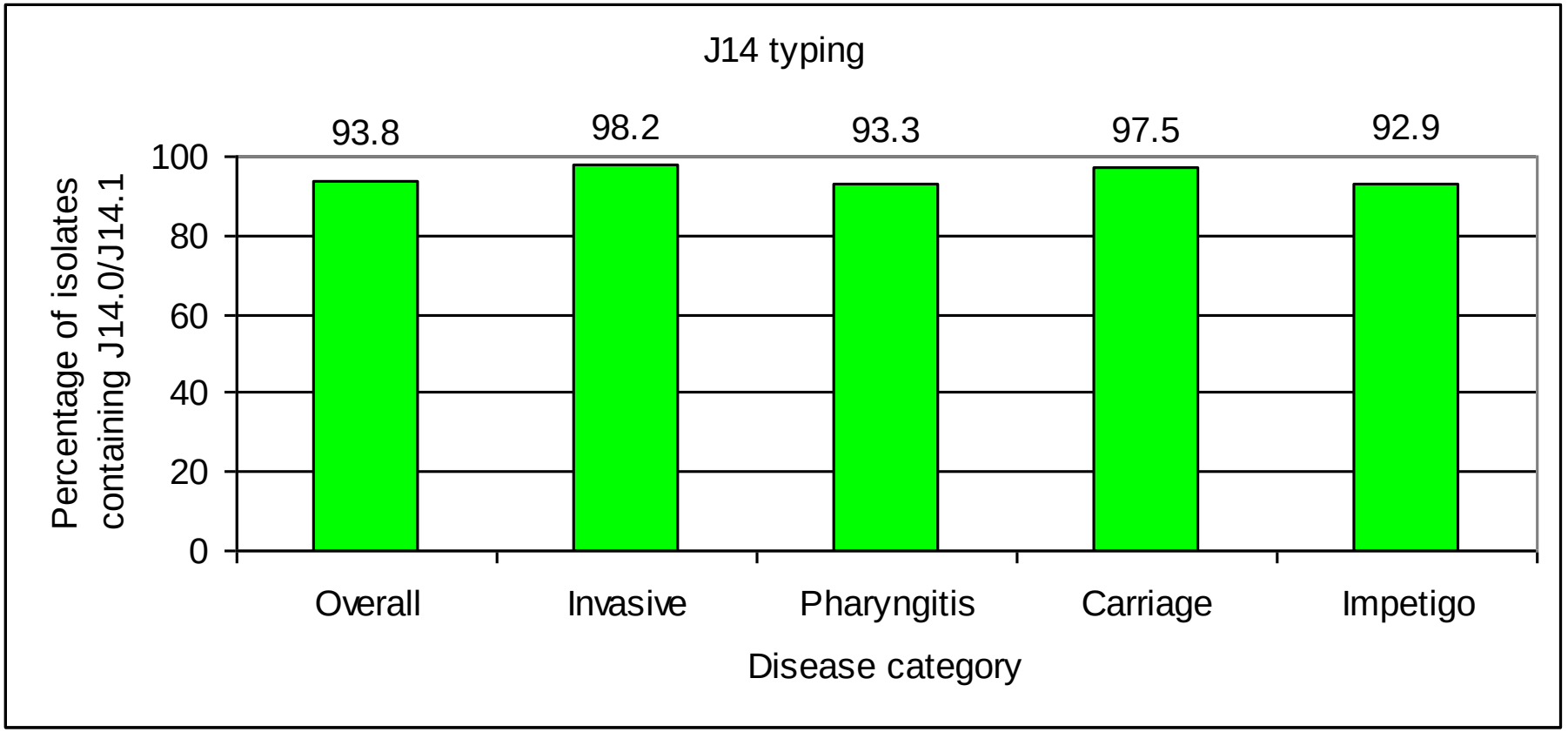
p145 LRRDLDASREAKKQVEKAL
p146          AKKQVEKALEEANSKLAALE
p147                 EANSKLAALEKLNKELEESK
p148                          KLNKELEESKKLTEKEKAEL
p149                                   KLTEKEKAELQAKLEAEAKA
p150                                          QAKLEAEAKALKEQLAKQAE
p151                                                   LKEQLAKQAEELAKLRAGKA
p152                                                            ELAKLRAGKASDSQTPDTKP
p153                                                                     SDSQTPDTKPGNKAVPGKGQ
p154                                                                              GNKAVPGKGQAPQAGTKPNQ.....
```

J8

Courtesy Professor Michael Good, QIMR

Is J8 conserved across GAS isolates?

Results – J14.0* and J14.1 typing in Fiji



***GAS that express J14.0 and J14.1 are protected by antibodies produced against J8**

Therefore a J8 vaccine could theoretically protect against <u>93.8%</u> of isolates in Fiji

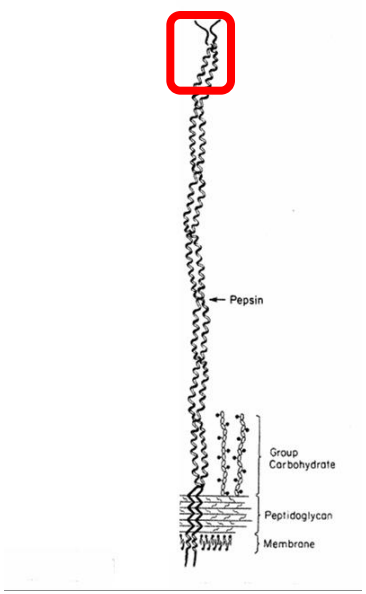
Steer et al. J Clin Microbiol 2009

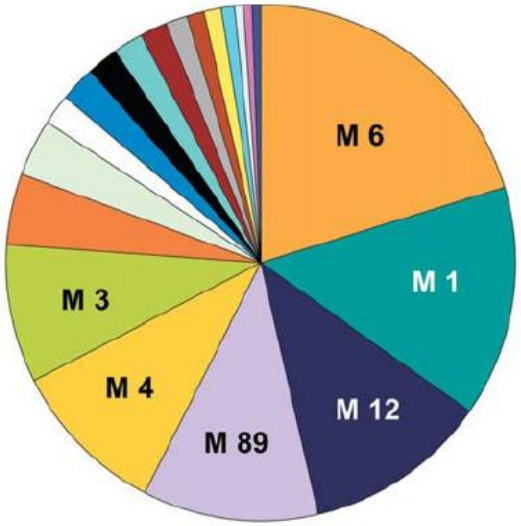
1. More to the type specific story…

Could antibodies to some M proteins
be cross-protective?

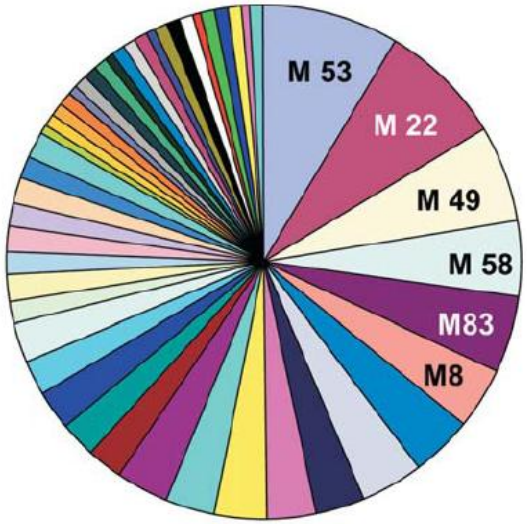
NO for main M proteins in USA (*emm 1,3,6,12,28)*

BUT other M proteins…

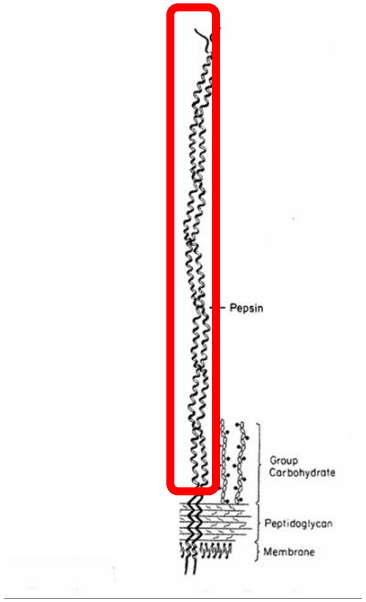




Brussels



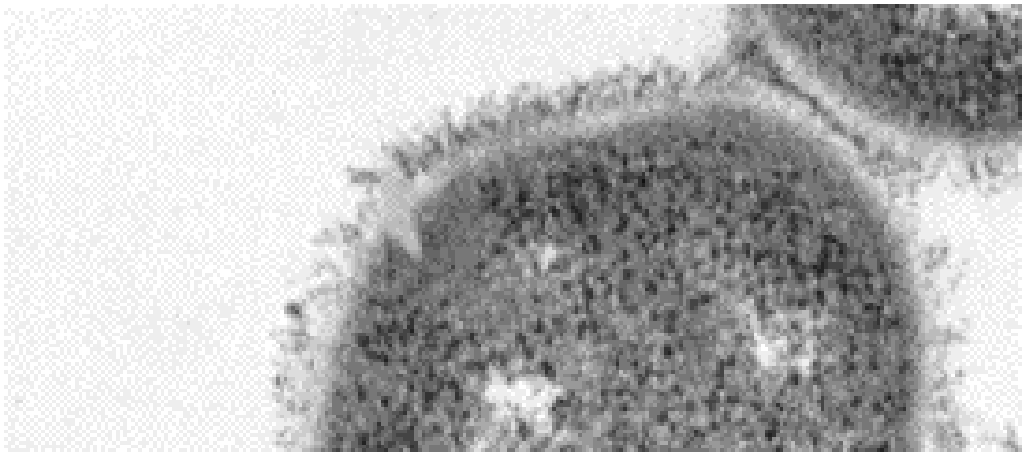
Brasília



More diverse
Fewer clusters

Less diverse
More clusters*

All emm types in one cluster may be cross-protected…



M protein Global survey