RHD Research and Global Perspective

Jonathan Carapetis

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RhEACH
RHEUMATIC HEART DISEASE
EVIDENCE · ADVOCACY · COMMUNICATION · HOPE

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Proudly supported by the people of Western Australia through Channel 7's Telethon

RF mortality, USA

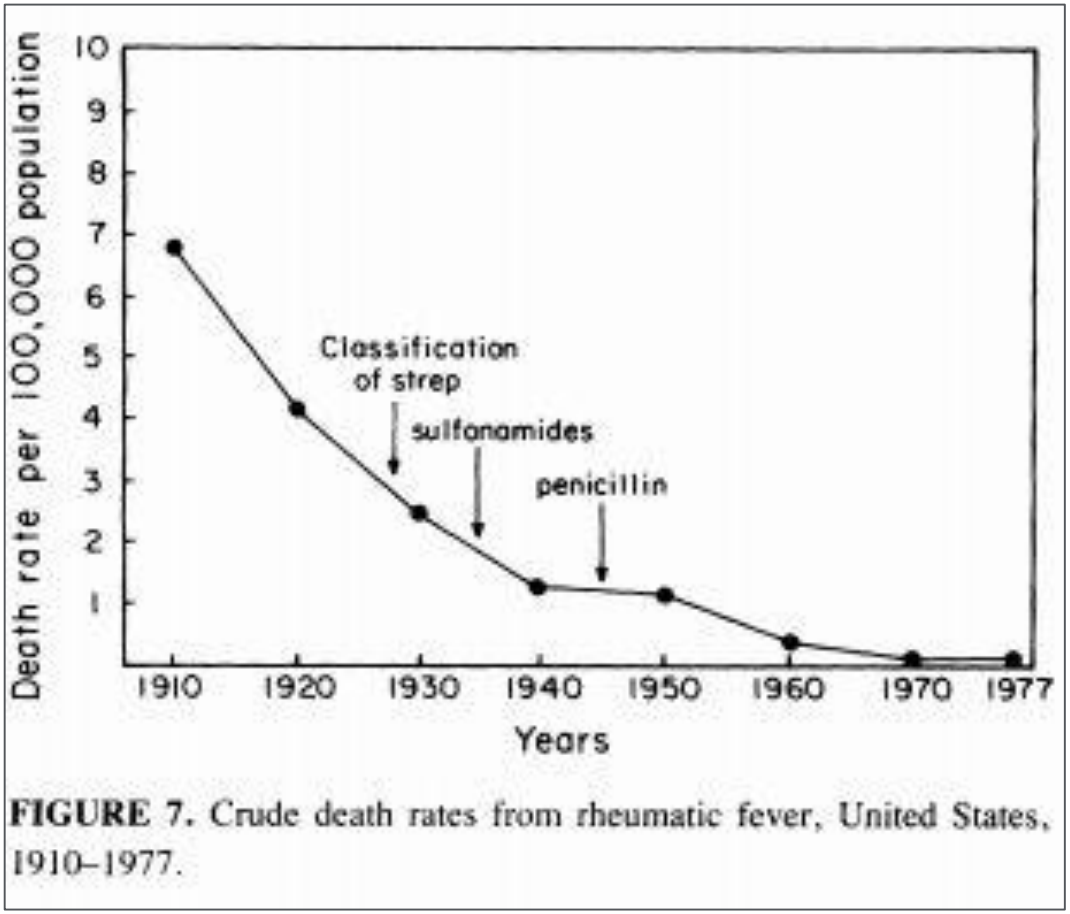

FIGURE 7. Crude death rates from rheumatic fever, United States, 1910–1977.

Gordis L. The virtual disappearance of rheumatic fever in the United States: lessons in the rise and fall of disease. T Duckett Jones Memorial Lecture. Circulation (1985) 72:1155-1162

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THE GLOBAL BURDEN OF DISEASES, INJURIES, AND RISK FACTORS STUDY

HARVARD UNIVERSITY
~
INSTITUTE FOR HEALTH METRICS AND EVALUATION AT THE UNIVERSITY OF WASHINGTON
~
JOHNS HOPKINS UNIVERSITY
~
UNIVERSITY OF QUEENSLAND
~
WORLD HEALTH ORGANIZATION

Global RHD burden: GBD estimates

	1990	2015	% change
Prevalence	30,344,900	33,438,800	+10.2%
DALYs	12,720,900	10,513,200	-17.4%
Deaths	347,500	319,400	- 8.1%

Watkins et al, New Engl J Med, in press 2017

Unpublished

The bleak reality of RHD in low income countries: The REMEDY study

Table 2. Clinical Outcomes at 2 Years of Follow-Up in 2960 Children and Adults With Rheumatic Heart Disease

	Low-Income Countries (n=964)	Lower-Middle-Income Countries (n=1158)	Upper-Middle-Income Countries (n=838)	*P* Value
Death, n (%)	200 (20.8)	195 (16.8)	105 (12.5)	<0.001
Congestive heart failure, n (%)	87 (9.0)	66 (5.7)	51 (6.1)	0.006
Stroke or transient ischemic attack, n (%)	14 (1.5)	12 (1.0)	20 (2.4)	0.053
Recurrence of acute rheumatic fever, n (%)	4 (0.4)	11 (1.0)	4 (0.5)	0.244
Infective endocarditis, n (%)	1 (0.1)	13 (1.1)	6 (0.7)	0.18
Atrial fibrillation	28 (2.9)	14 (1.2)	14 (1.7)	0.013
Prosthetic valve thrombosis	0 (0)	2 (0.1)	7 (1.0)	0.003
Surgery	30 (3.1)	84 (7.3)	109 (13.0)	<0.001
Death, congestive heart failure, or acute rheumatic fever, n (%)	251 (26.0)	228 (19.7)	143 (17.1)	<0.001
Death, stroke, systemic embolism, or major bleeding, n (%)	209 (21.7)	203 (17.5)	129 (15.4)	0.002

Zuhlke et at, Circulation 2016

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Acute Rheumatic Fever and Rheumatic Heart Disease

Incidence and Progression in the Northern Territory of Australia, 1997 to 2010

Joanna G. Lawrence, BHB, MBCHB, FRACP; Jonathan R. Carapetis, MBBS, FRACP, PhD; Kalinda Griffiths, BBMSci, MPH; Keith Edwards, MBBS, DCH, FRCP(Edin), FRCPCH FRACP; John R. Condon, FAFPHM, PhD

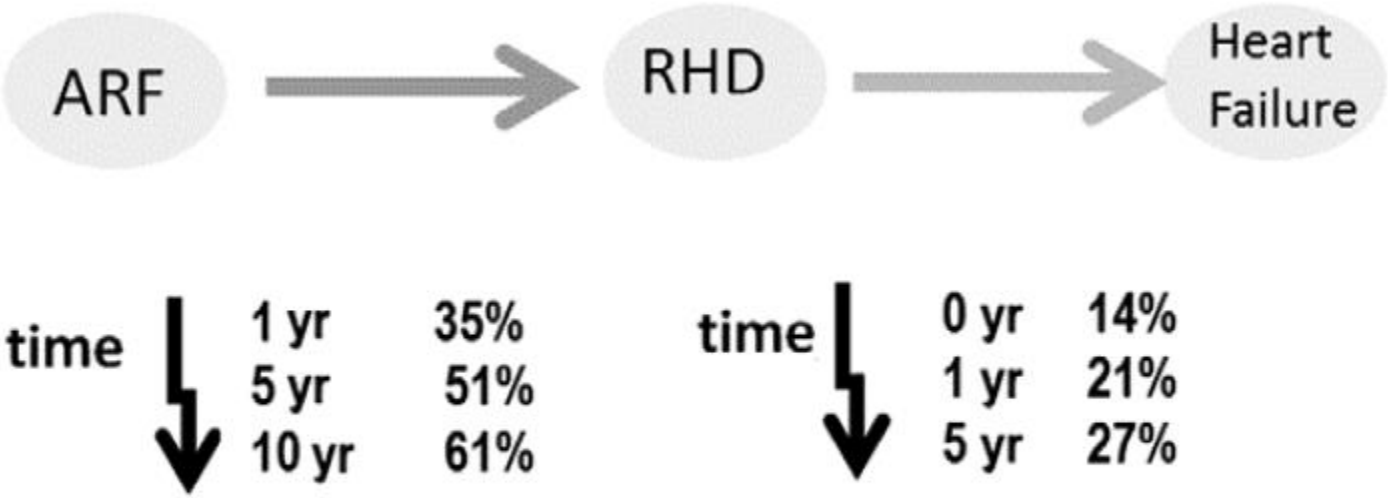

Figure 6. Progression of acute rheumatic fever (ARF) to rheumatic heart disease (RHD) and cardiac failure among Indigenous subjects.

(*Circulation*. 2013;128:492-501.)

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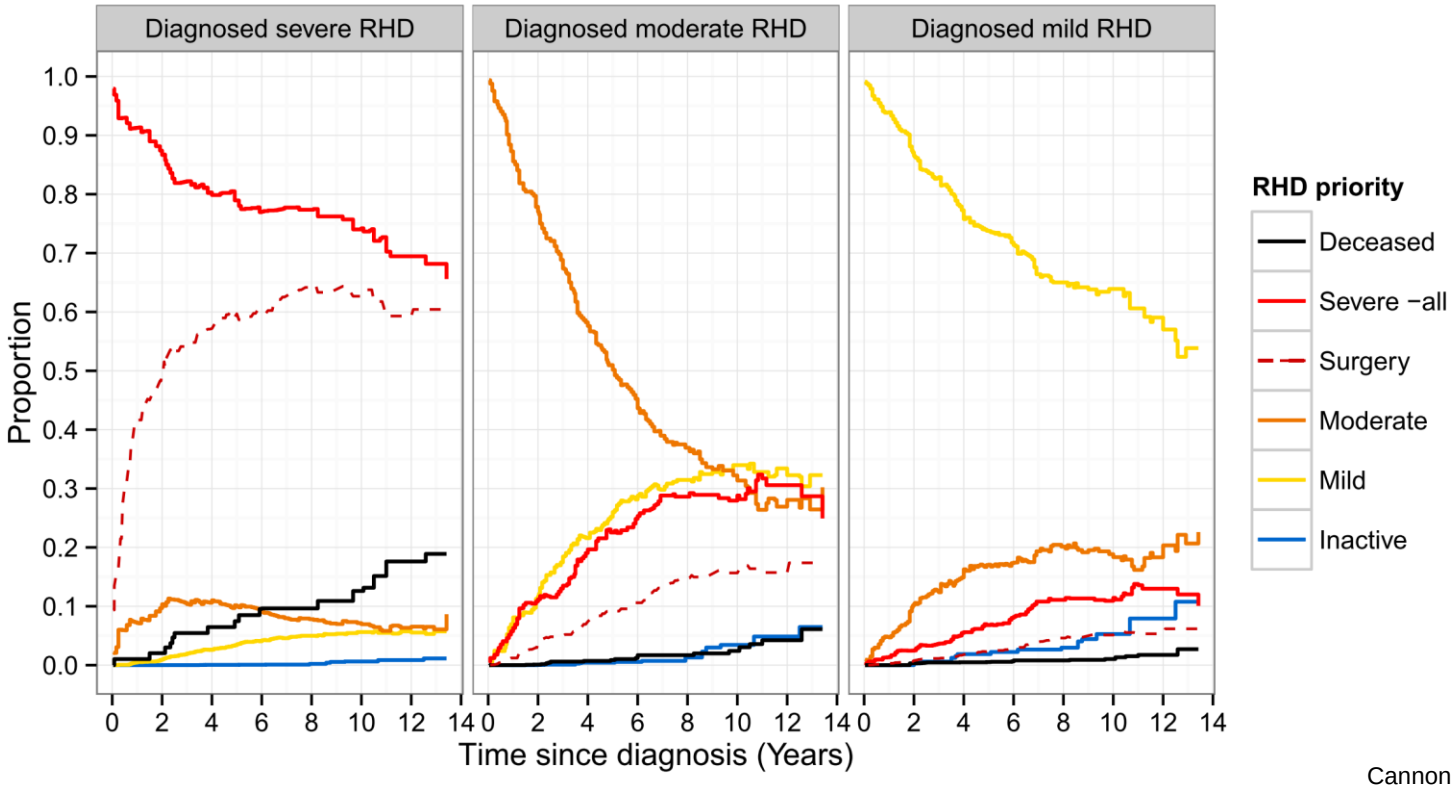
Progression of RHD diagnosed in Indigenous Australian children, NT 1999-2012.



- At diagnosis, 16.2% were severe, 27.2% moderate and 56.6% mild.
- **Severe**; 50% had surgery within 2 years, and 10% were dead within 6 years of their diagnosis.
- **Moderate**; 29% progressed to severe within 10 years, comprising 15% requiring surgery.
- **Mild**: 10% progressed to severe within 10 years.

Cannon et al. Rheumatic Heart Disease Severity, Progression and Outcomes: A Multi-State Model. JAHA. 2017;6:e003498

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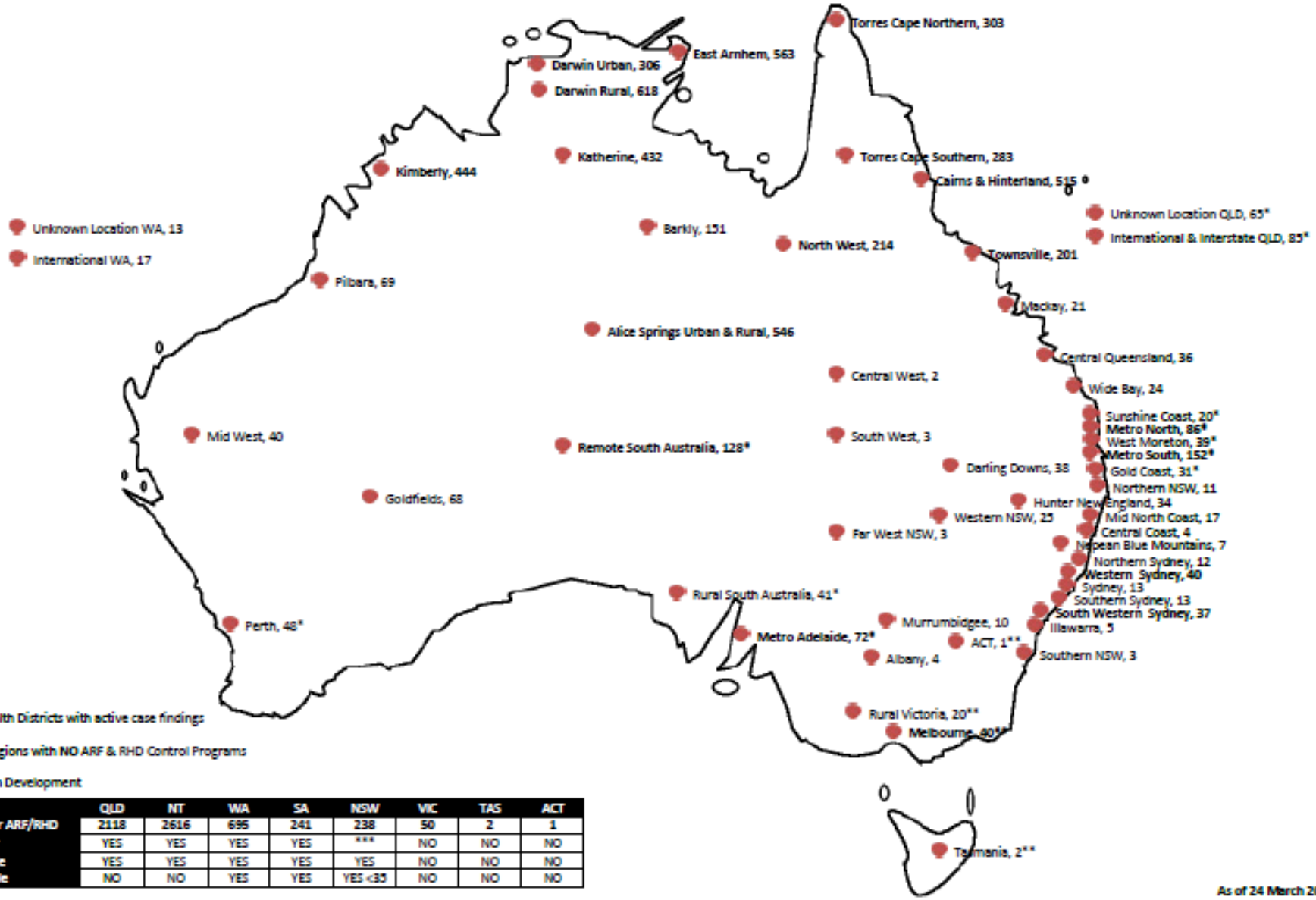
Number of **known** patients with ARF and RHD in Australia by Health Districts

RHD Australia



* Health Districts with active case findings

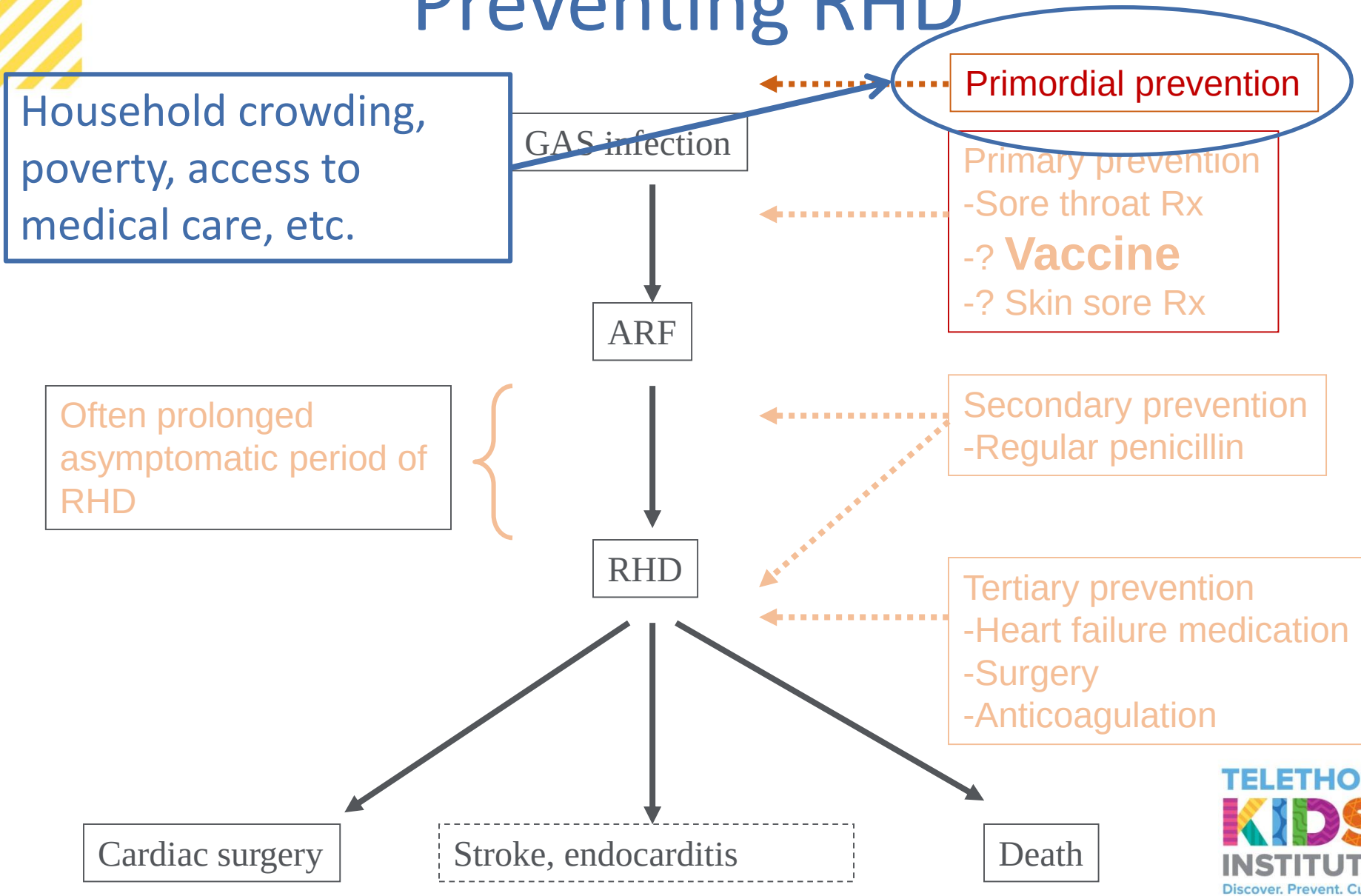
** Regions with NO ARF & RHD Control Programs

*** In Development

	QLD	NT	WA	SA	NSW	VIC	TAS	ACT
Total Number ARF/RHD	2118	2616	695	241	238	50	2	1
RHD Register	YES	YES	YES	YES	***	NO	NO	NO
ARF Notifiable	YES	YES	YES	YES	YES	NO	NO	NO
RHD Notifiable	NO	NO	YES	YES	YES <35	NO	NO	NO

As of 24 March 2016

Preventing RHD



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Acute Rheumatic Fever Associated With Household Crowding in a Developed Country

Richard Jaine, MB CHB, MPH, Michael Baker, MB CHB, DCH, and Kamalesh Venugopal, PhD

(*Pediatr Infect Dis J* 2011;30: 315–319)

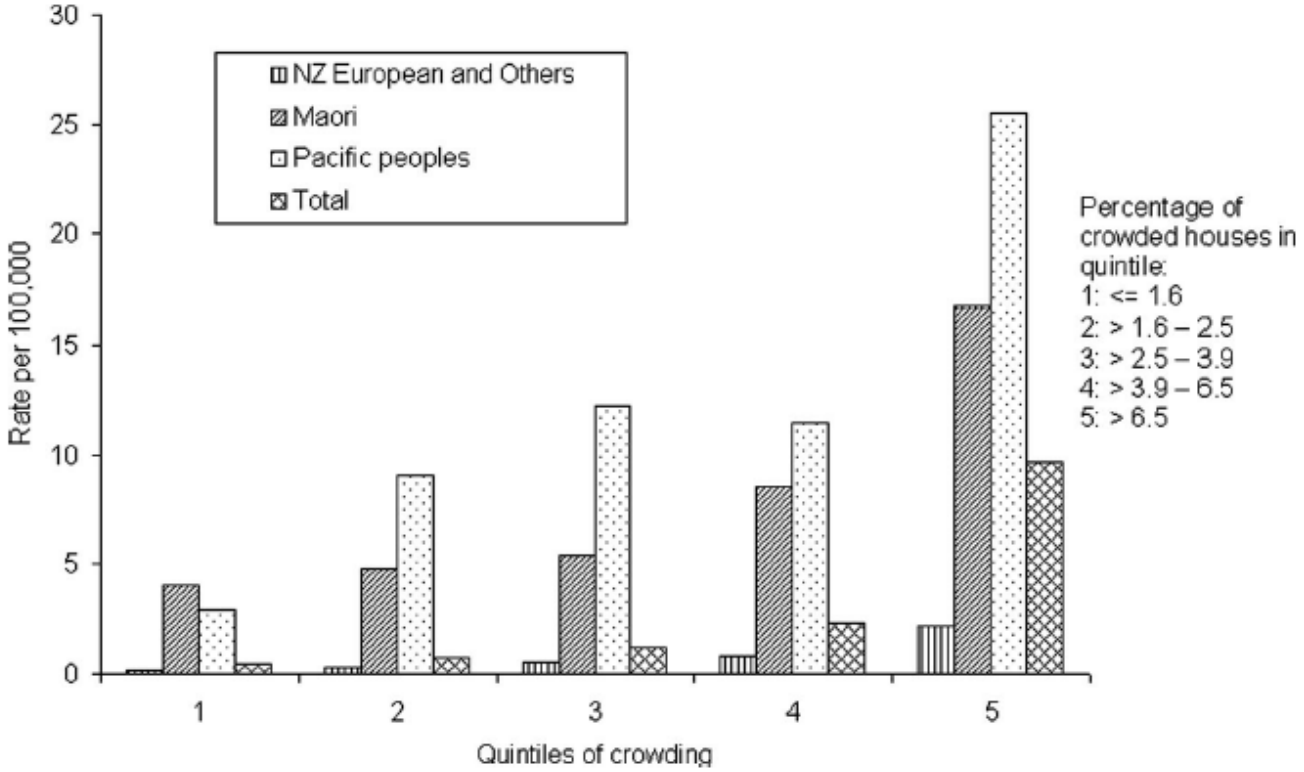
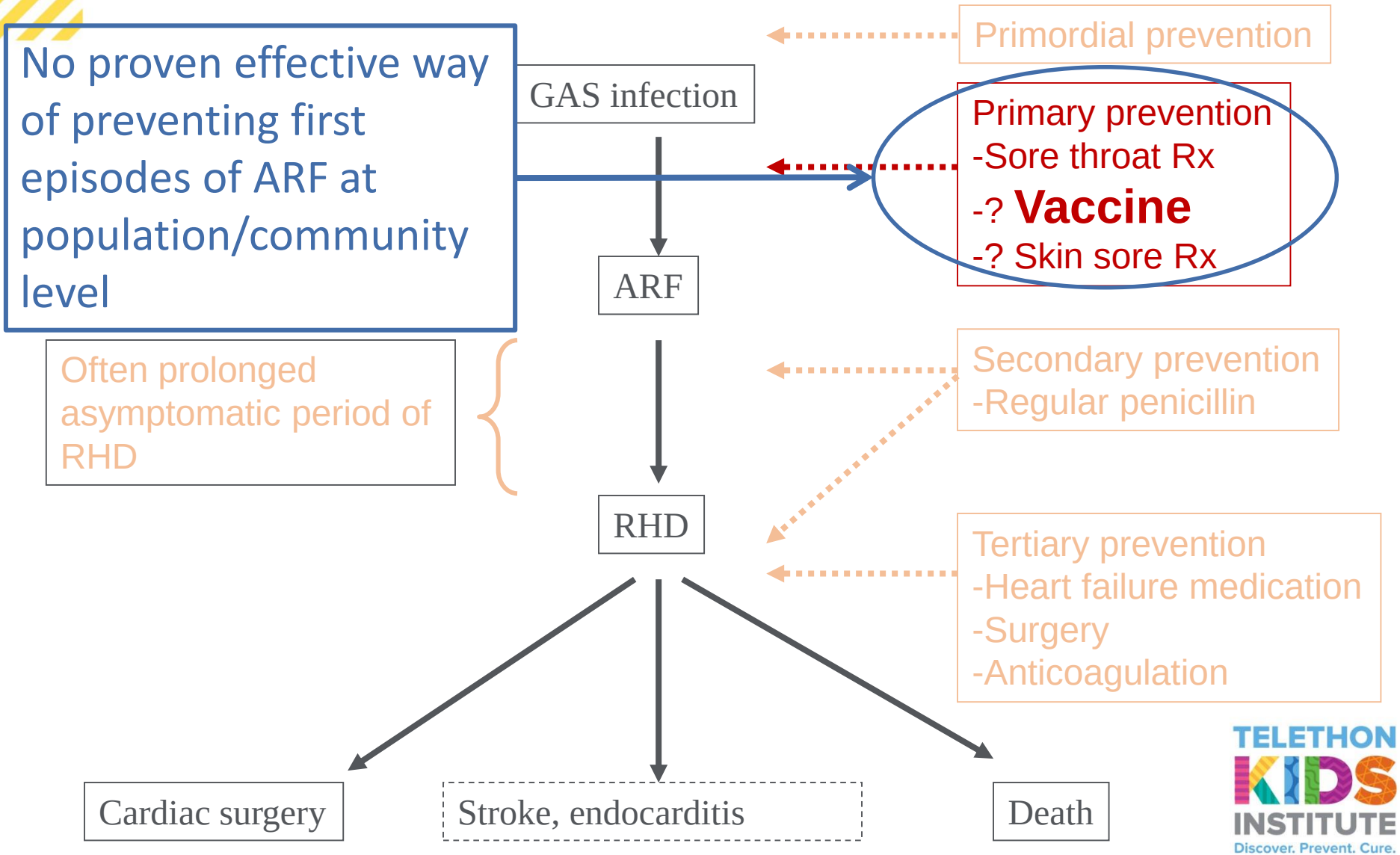


FIGURE 1. Average annual rates of ARF first admissions by household crowding quintile and ethnicity, New Zealand, 1996 to 2005.

Preventing RHD



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Antibiotics for the primary prevention of acute rheumatic fever: a meta-analysis

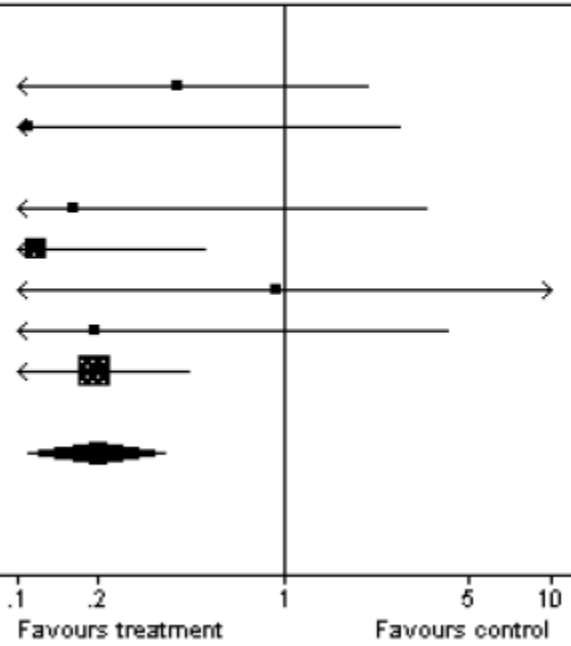
Katharine A Robertson[1,2], Jimmy A Volmink[1] and Bongani M Mayosi*[2]

BMC Cardiovascular Disorders 2005, **5**:11 doi:10.1186/1471-2261-5-11

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)
x 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]
x 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



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School-Based Prevention of Acute Rheumatic Fever

A Group Randomized Trial in New Zealand

Diana Lennon, FRACP, Joanna Stewart, MSc,† Elizabeth Farrell, MHSc,‡ Anne Palmer,§ and Henare Mason§*

Pediatr Infect Dis J 2009;28: 787–794

~20,000 children randomised, ~87,000 person-years

Analysis A
(1956/65 Jones Criteria):
24 cases v 29 cases: IRR: 0.79, 95%CI: 0.41–1.52, P= 0.47

Analysis B:
Included 8 additional cases (5 monoarthritis with NSAIDs, 3 with echo proven subclinical carditis) and excluded 2 cases (indolent carditis and HepB)
26 cases v 33 cases: IRR: 0.72, 95% CI: 0.40 –1.30, P=0.27

?underpowered (20-30% reduction but powered for 60%)

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Effectiveness of Population-based Primary Prevention of Acute Rheumatic Fever – Evaluation of a National Programme

6th June 2016

Dr. Susan Jack

Institute for Environmental Science & Research Ltd and Centre for International Health, University of Otago, New Zealand

Global Health Link Otago
Centre for International Health
University of Otago

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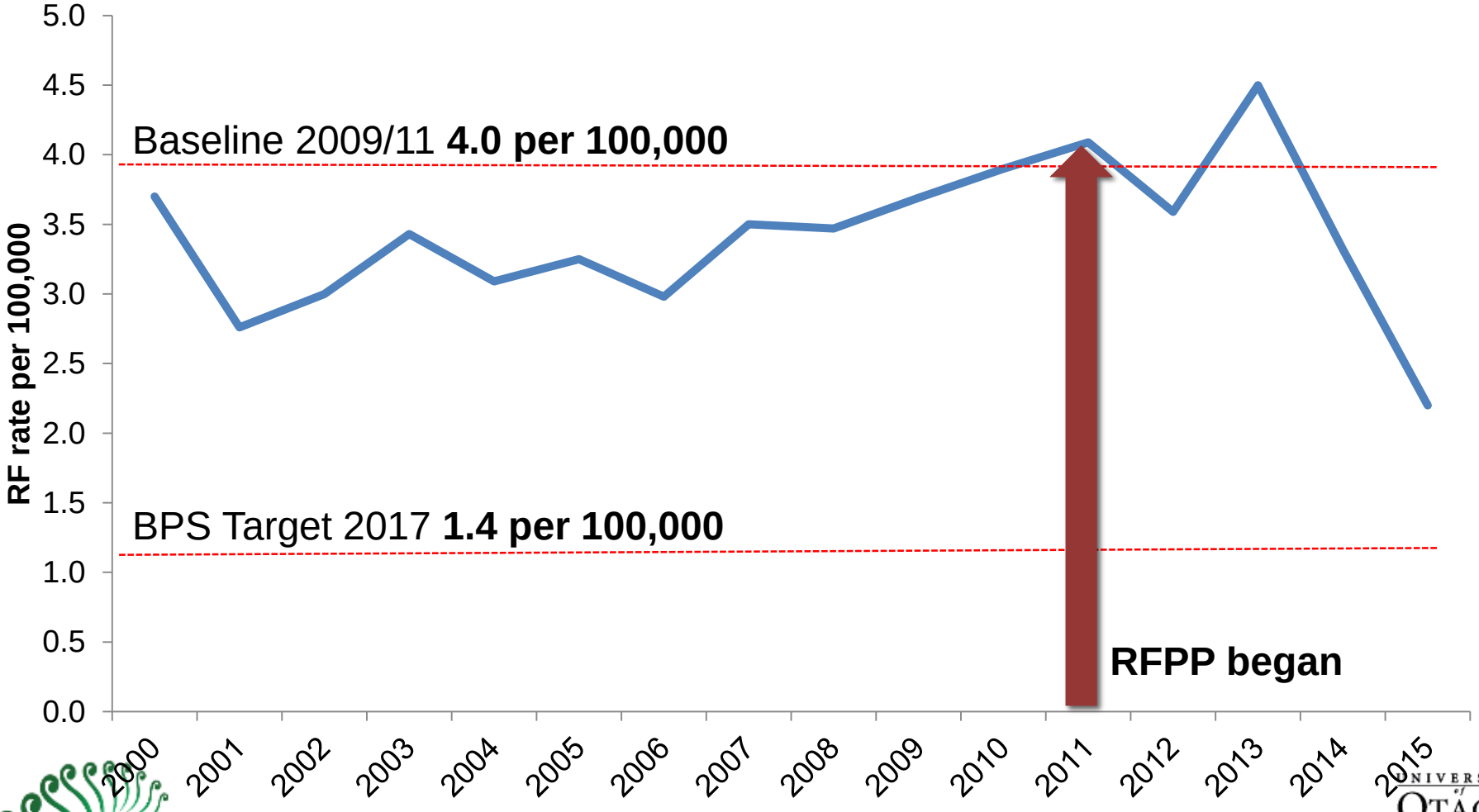
Total first episode RF hospitalization rates by year



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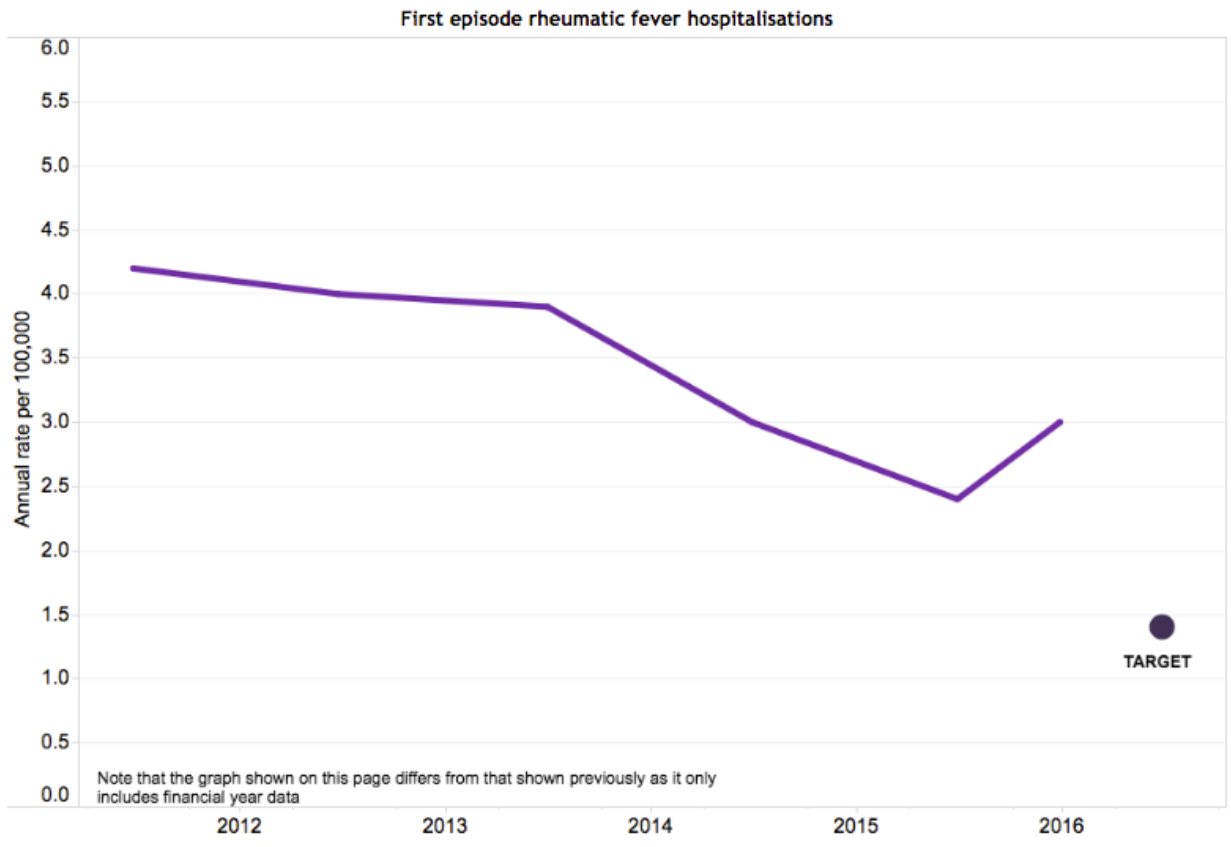
Effectiveness analysis findings 2012–2015

Scena	95% CI
Schools i RFPP DHB school-b servi	-8.1 to 43.7
Schools in high-risk D a school- servi	5.5 to 62.3
Schools in other DHB school-b servi	-61.3 to 36.9

RESULT 3: RHEUMATIC FEVER

The incidence rate for rheumatic fever initial hospitalisations for the 2016 calendar year is 3.0 cases per 100,000 people (137 hospitalisations). This represents a 23 percent statistically significant decrease in first episode rheumatic fever hospitalisations from the baseline (2009/10-2011/12) rate of 4.0 per 100,000.

Figure 2. First episode rheumatic fever hospitalisations, annual rate per 100,000, New Zealand 2002–2016



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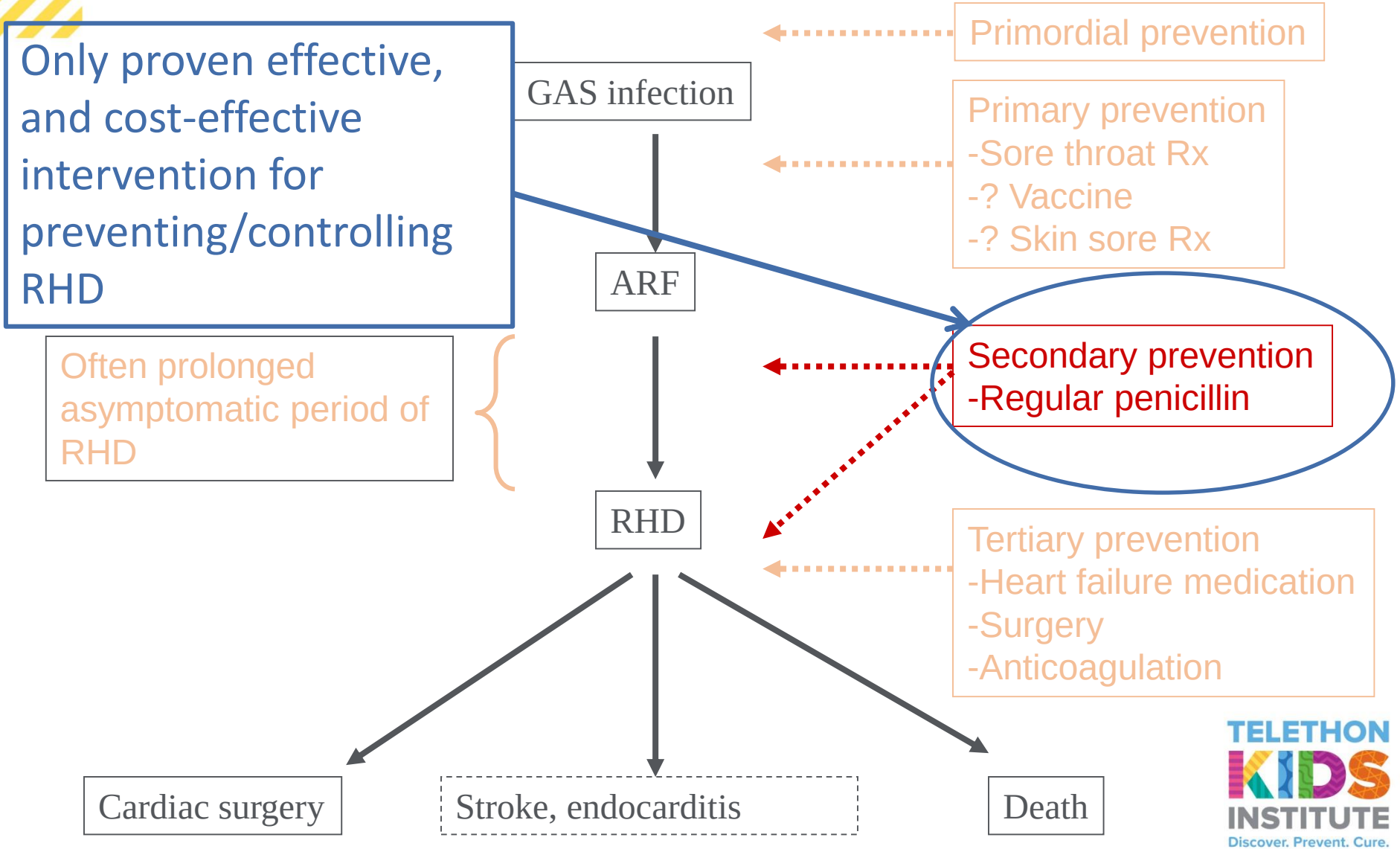
Preventing RHD



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Benzathine penicillin G

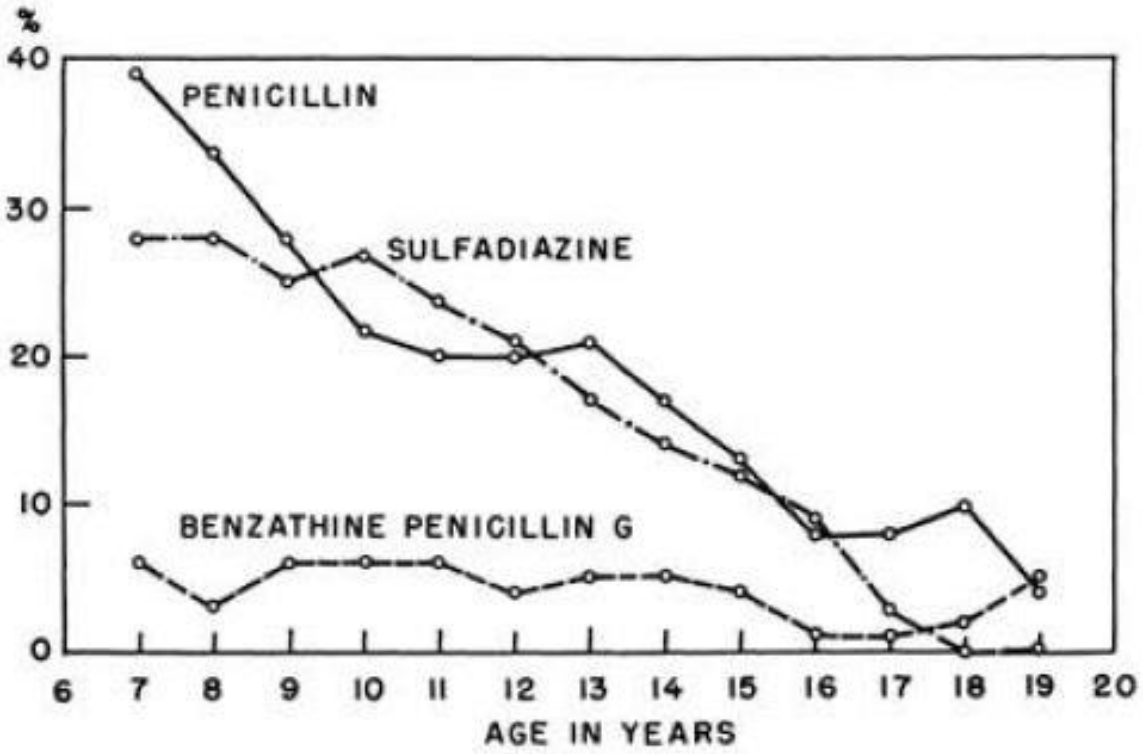

FIGURE 2. Rates of streptococcal infection per patient-year exclusive of carriers for each year of age by prophylaxis group.

Wood, H., A. Feinstein, A. Taranta, J. et al (1964). "Rheumatic fever in children and adolescents. III. comparative effectiveness of three prophylaxis regimes in preventing streptococcal infections and rheumatic recurrences." Annals of Internal Medicine 60(2): 31-46.

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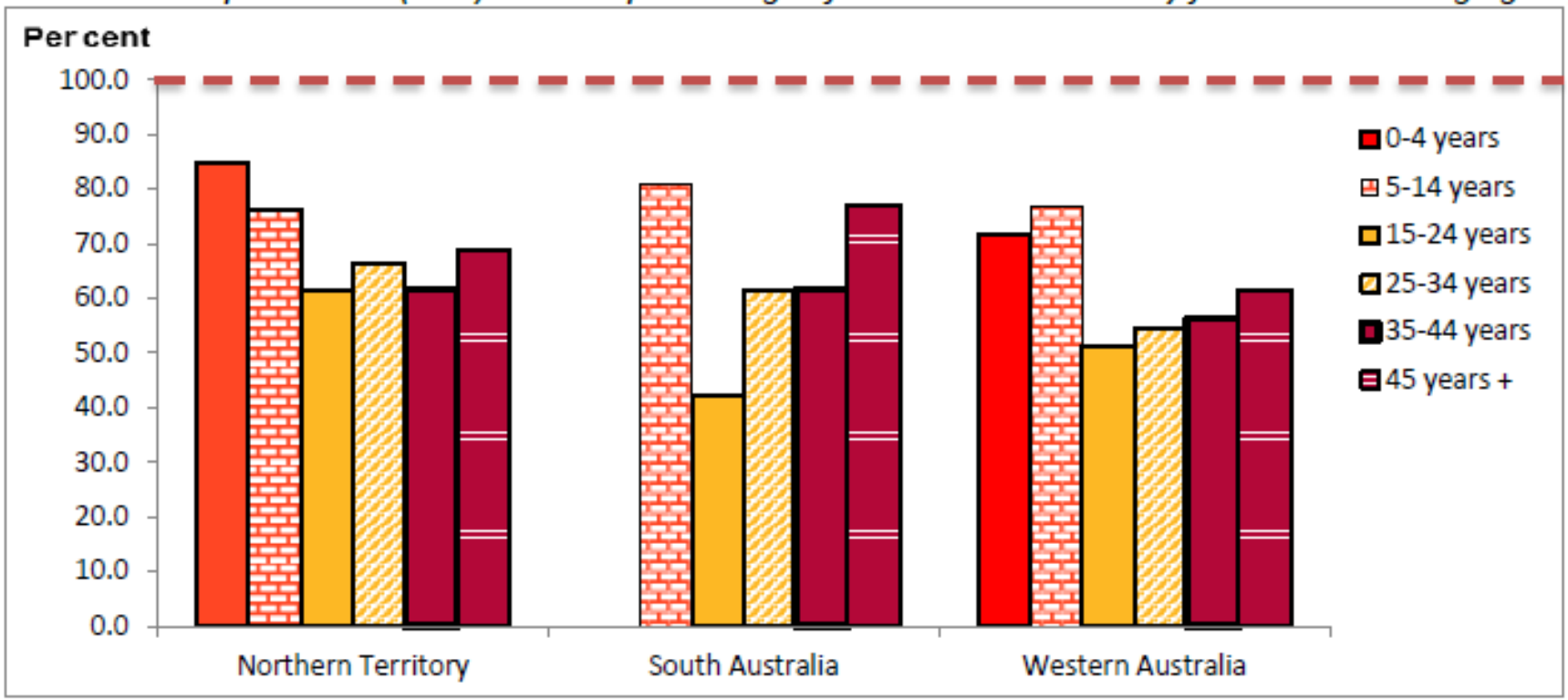
Figure 1 Benzathine penicillin G (BPG): median percentage of all scheduled doses by jurisdiction and age group



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Penicillin – existing supplies

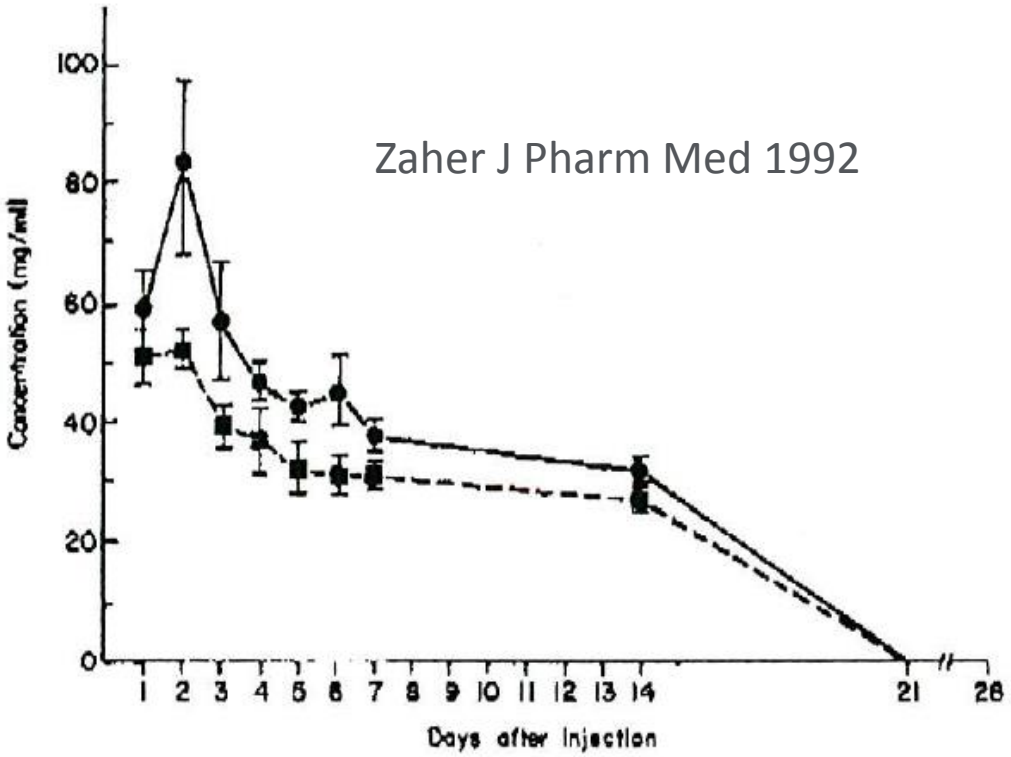

Fig. 1. Mean serum concentrations of penicillin 1–28 days after the intramuscular injection of 1.2 million units of benzathine penicillin G: (■) preparation No. 1, (●) preparation No. 2.

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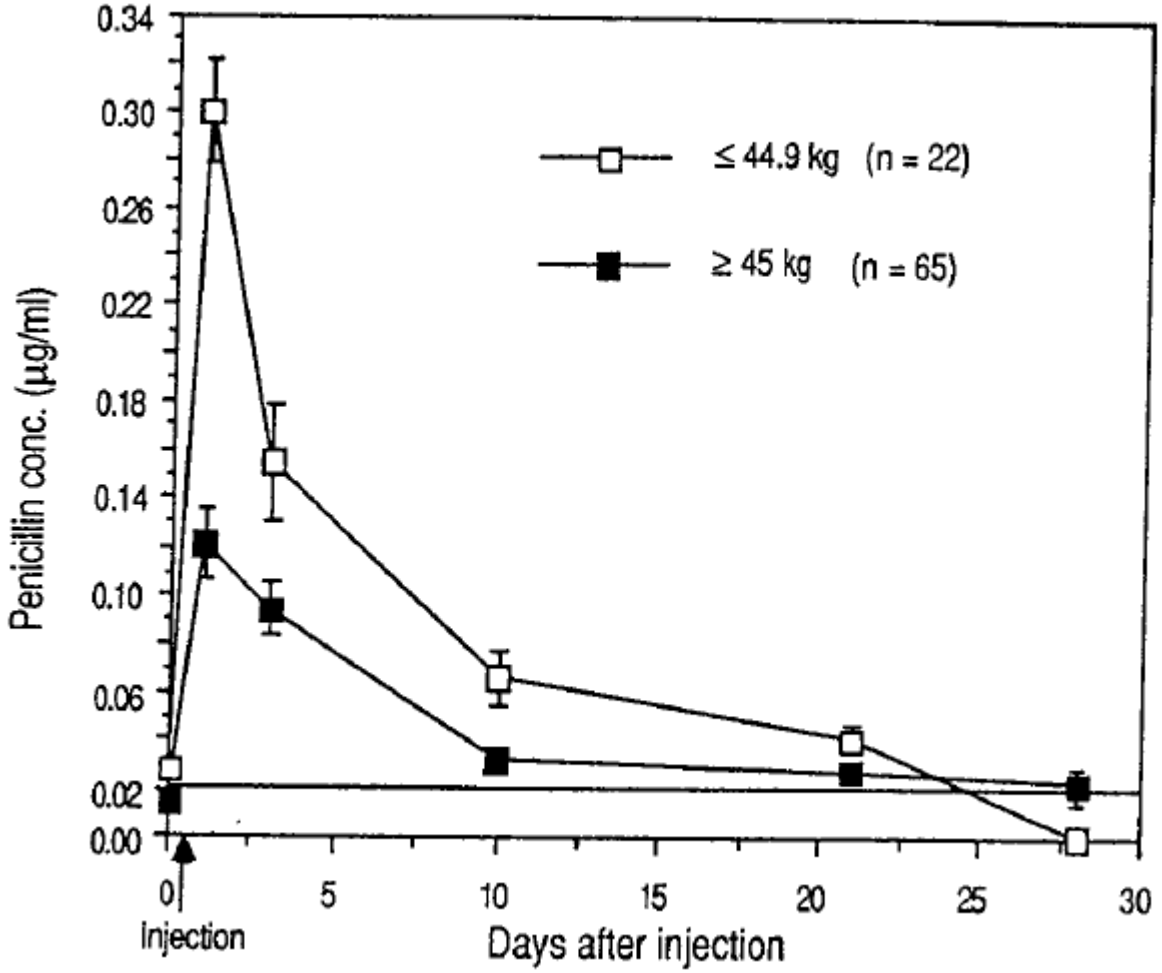
Penicillin – new formulation



Kaplan et al, J Pediatr 1989

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Reformulation of BPG

Goal: To develop a safe, effective reformulation of long-acting penicillin that encourages adherence to secondary prophylaxis

Effectiveness

BPG Pharmacokinetics

Development of an optimal dosing strategy to ensure full protection from recurrence of ARF

Safety

BPG Pharmacovigilance

Distinguish true anaphylaxis from syncopal episodes and other localised AE's to ensure prophylaxis programs are not disrupted

Adherence

Reformulation Preferences

Creation of a formulation based on patient and healthcare provider preferences, thus encouraging treatment adherence

BPG Quality, Safety, and Supply

Determine if current BPG supplies contain enough penicillin to protect patients against GAS colonisation. It will also help mitigate concerns about the safety of BPG, thus encouraging adherence

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canvas

Tools to Assess and Advance Group A Streptococcus Vaccines

Professor John Fraser

Dean of the Faculty of Medical and Health Sciences

University of Auckland, New Zealand

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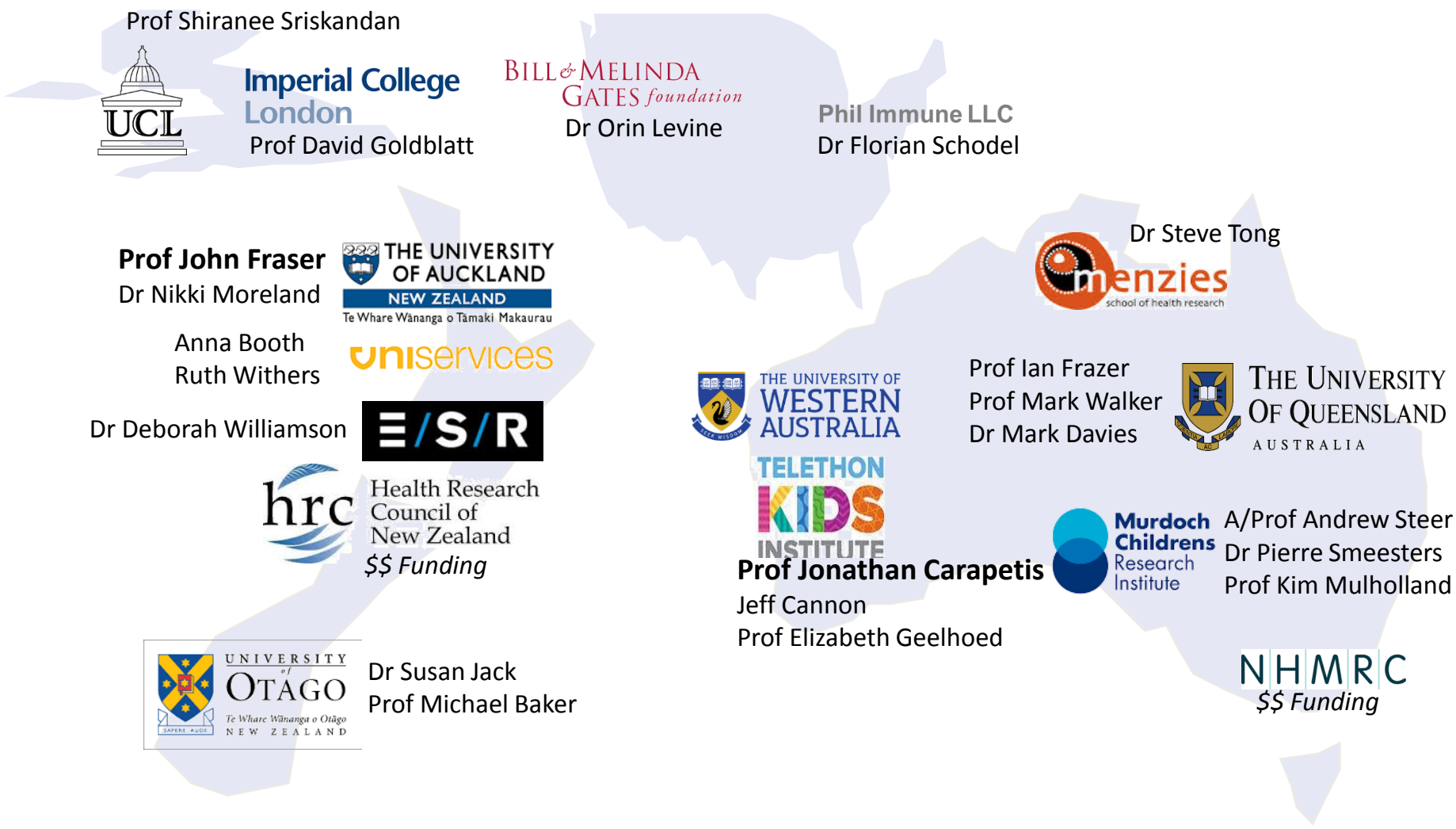
Te Whare Wānanga o Tāmaki Makaurau

CANVAS: international collaboration to accelerate development of a GAS vaccine



Preparing for a GAS vaccine: 3 key deliverables

1

GAS strain repository

- Comprehensive assessment of regional GAS strain epidemiology (*emm*-typing, whole genome sequencing)

2

GAS assay development

- Development of a robust assay to assess GAS vaccine efficacy

3

Economic evaluation

- Health economics analysis of GAS vaccine cost

Clinical development strategy for GAS vaccine candidate

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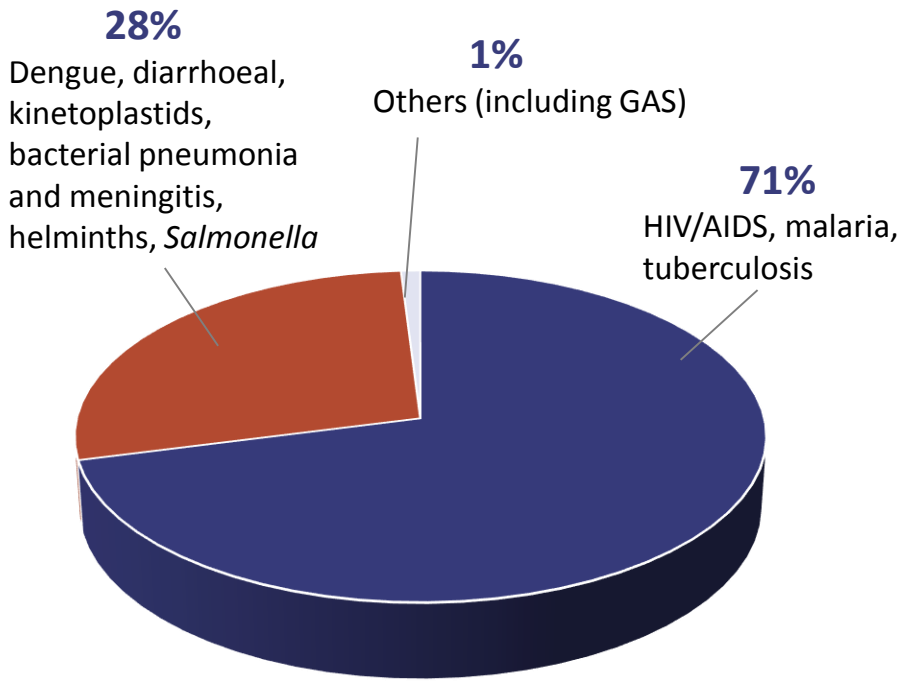
WHO is re-prioritising GAS vaccines

- PDVAC (WHO) has re-prioritised GAS vaccines
- CANVAS tools to assist GAS vaccine development will be publicly available

Investment in new vaccines for "neglected diseases"



<1% of $US1.3 billion invested in new vaccines against "neglected diseases" in 2012 was spent on GAS

PDVAC, Product Development for Vaccines Advisory Committee
MacLennan CA, Saul A. Proc Natl Acad Sci U S A. 2014;111:12307-12.

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END RHD CRE

Beginning of the endgame

CIA	Prof	Jonathan	Carapetis
CIB	Prof	Bart	Currie
CIC	Prof	Graeme	Maguire
CID	Prof	Dawn	Bessarab
CIE	Dr	Dan	McAullay
CIF	Ms	Heather	D'Antoine
CIG	Prof	Alex	Brown
CIH	A/Prof	Anna	Ralph
CII	A/Prof	Andrew	Steer
CIJ	Prof	Nicholas	de Klerk
AIA	A/Prof	Vicki	Krause
AIB	Prof	David	Atkinson
AIC	Dr	Gavin	Wheaton
AID	Dr	Thomas	Snelling
AIE	Dr	Stephanie	Trust
AIF	Ms	Claire	Boardman
AIG	Dr	Rosemary	Wyber
AIH	Dr	Samantha	Colquhoun
AII	Prof	Christopher	Reid

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END RHD Centre of Research Excellence

menzies school of health research

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Baker IDI HEART & DIABETES INSTITUTE

Murdoch Childrens Research Institute

SAHMRI South Australian Health & Medical Research Institute

END RHD CRE

Beginning of the endgame

We commit to identify a set of costed, step-wise interventions which are most likely to reduce the incidence of ARF and the prevalence of RHD for Indigenous Australians to the same level as non-Indigenous Australasians.

To eliminate RHD as a public health priority in Australia

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SAHMRI South Australian Health & Medical Research Institute


Burden of RHD
Measuring adherence
Penicillin
Evidence synthesis
Economic analysis
Endgame Strategy
Priority research
Impetigo/ Sore throat
END RHD CRE
Policy analysis
Developing an endgame for rheumatic heart disease in Australia
Prospectus 2015
Tertiary outcomes
SP Plus
Advocacy
The RHD Community
END RHD Coalition

1	Improving acceptability of products for secondary prophylaxis – including penicillin reformulation
2	New models for secondary prophylaxis delivery
3	‘SP plus’ intensive case management to improve primordial, primary and secondary prevention of ARF
4	State of the art secondary prophylaxis
5	Adherence measures and association between adherence and outcomes
6	Understanding contribution of GAS pharyngitis in the context of high impetigo prevalence
7	Modelling the effect of interventions
8	Understanding long term outcomes of tertiary prevention (with and without surgery)
9	Understanding optimal management of advanced RHD
10	Other - Community researchers / advocates living with RHD - ARF diagnostics - ARF immunomodulation - ARF/RHD geographic mapping

November 2016

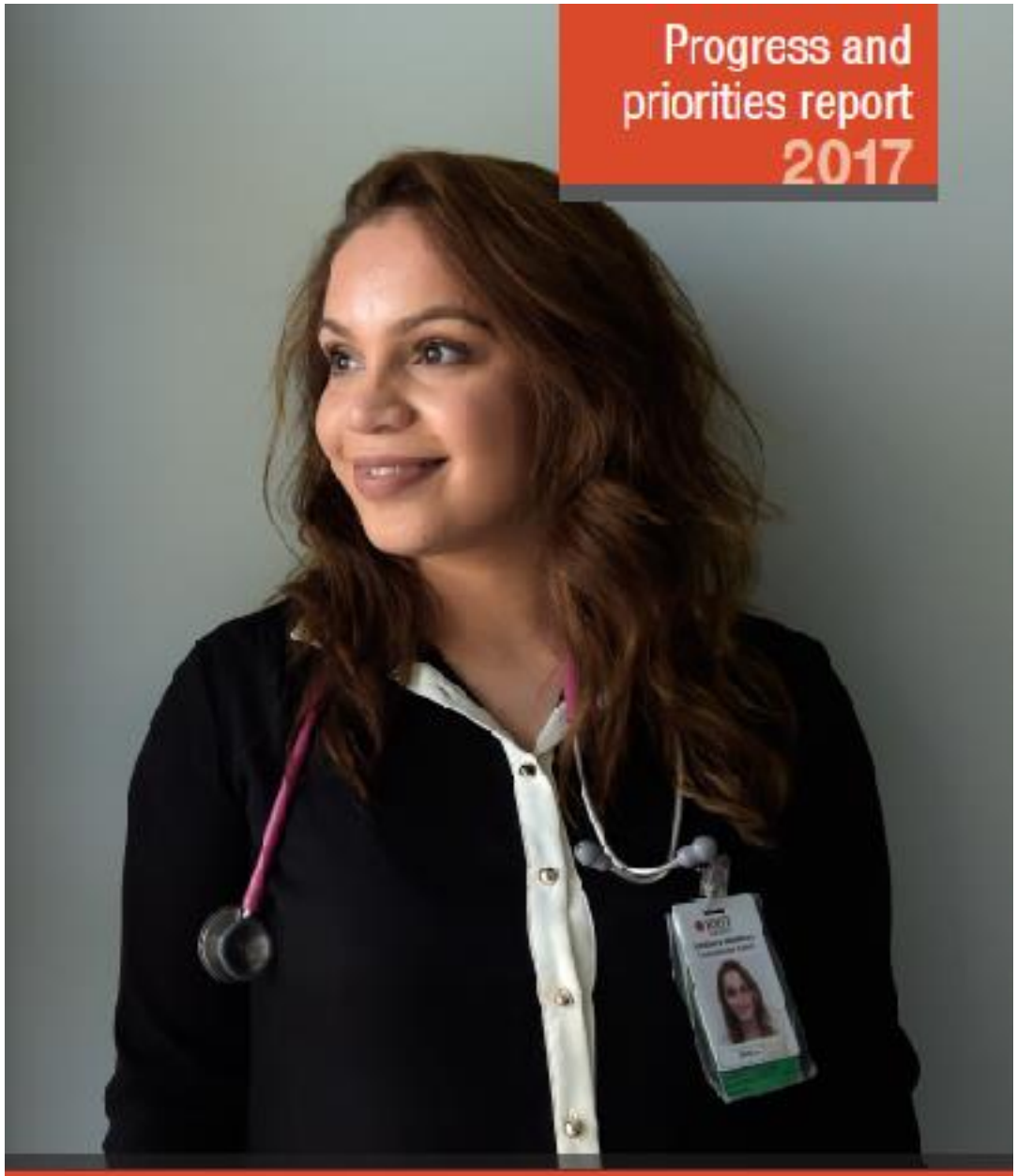
Launch of the AMA Indigenous Report Card and the END RHD Coalition

END RHD Coalition

Australian Government
Department of the Prime Minister and Cabinet

CLOSING THE GAP

PRIME MINISTER'S REPORT 2017

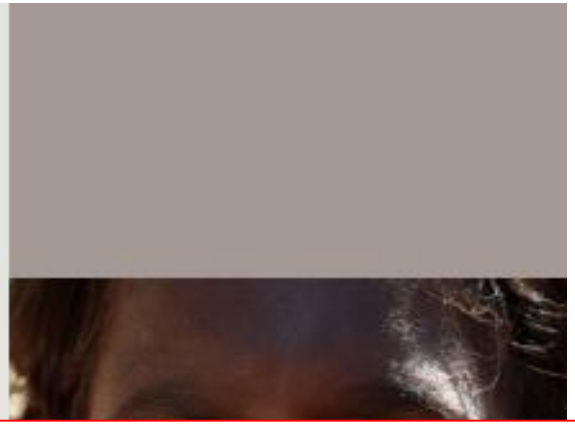


Progress and priorities report 2017

CLOSE THE GAP

Close the Gap Campaign Steering Committee

Previous *Progress and Priorities Reports* have advocated for new 'Closing the Gap' targets for incarceration, community violence and disability. To those recommendations, we add a call for a COAG target to eliminate the over-representation of Aboriginal and Torres Strait Islander children in out-of-home care by 2040. The *Family Matters Report* projects that if current trends in child removal aren't addressed "the population of Aboriginal and Torres Strait Islander children in care will almost triple in size by 2035."[51]

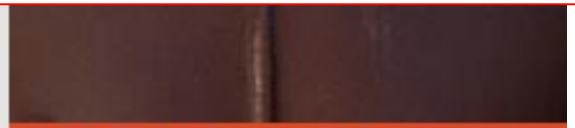


Why do Indigenous Australian's have amongst the highest rates of preventable and life-threatening rheumatic heart disease (RHD) in the world?

Addressing RHD delivers widespread benefits in health, education and employment.

Focussing on a sentinel condition like RHD not only saves lives and improves quality of life for Aboriginal and Torres Strait Islander children, it will help close the gap by addressing the wider health issues in Aboriginal and Torres Strait Islander communities; many of those conditions share the same root causes (overcrowding, poor housing conditions, inadequate nutrition and lack of access to healthcare). Healthy children can grow, learn and prosper.

Focussing on a sentinel condition like RHD not only saves lives and improves quality of life for Aboriginal and Torres Strait Islander children, it will help close the gap by addressing the wider health issues in Aboriginal and Torres Strait Islander communities; many of those conditions share the same root causes (overcrowding, poor housing conditions, inadequate nutrition and lack of access to healthcare). Healthy children can grow, learn and prosper.



RHD patient Trenton reveals his chest-scar, Edith Falls, Nitmiluk National Park, Northern Territory, Australia. Photo by Moonshine Agency from **www.TakeHeart.tv**

Closing the gap on Indigenous heart health

News / 2017.03.16

RHD develops from chronic damage done to heart valves due to attacks of acute rheumatic fever, with children and young adults most susceptible.

"The disease is completely preventable and can be eliminated by addressing environmental factors that raise the risk of infection. These include overcrowded housing, along with greater investment in resources to improve diagnosis, treatment and access to culturally appropriate health care services," Adj Professor Kelly said.

The Heart Foundation's Lighthouse Project, jointly delivered with the Australian Healthcare and Hospitals Association aims to deliver access to culturally appropriate health care services. The initiative's third phase was recently given the green light thanks to an $8 million federal government grant.

"Effectively addressing this issue will take a comprehensive national approach. We've seen such commitments made in other countries and similar action in Australia is an urgent necessity," Adj Professor Kelly said.

"The New Zealand government allocated $60 million over 6 years towards RHD control, with a population of only 4.5 million, and had an a significant decline in the disease."

The Heart Foundation's 2017-2018 Budget Submission calls for a 10 year, $100 million commitment from the Federal Government.

The Heart Foundation is a member of the Close the Gap Steering Committee and is committed to supporting all efforts to improve health outcomes for Aboriginal and Torres Strait Islander peoples.

A Call to Action to Prevent New Cases of RHD in Indigenous Australia by 2031

Recommendation 1: For Australian governments to commit to a target to prevent new cases of RHD reported among Indigenous people by 2031. As a milestone to achieving this target, Australian governments should also commit to a sub-target that no child in Australia dies of ARF and its complications by 2025.

Recommendation 2: To achieve the targets in Recommendation 1, Australian governments to work in partnership with Indigenous health bodies, experts, and key stakeholders to develop, fully fund, and implement a strategy to end RHD as a public health problem in Australia by 2031, comprising:

- an interim strategy (operational from 2016-2017 until 2021); and
- upon the 2020 receipt of the final report of the END RHD CRE, a comprehensive 10-year strategy (operational from 2021-2031).

The strategy should provide a firm foundation for an evidence-based, focussed, and cost-effective intergovernmental, multi-sectoral, and multidisciplinary national effort to prevent new cases of RHD reported among Indigenous people by 2031.

RHD Action

United to End Rheumatic Heart Disease

Medtronic WORLD HEART FEDERATION RhEACH

Preventable Condition Causes 275,000 Deaths Annually, Primarily Among Women, Children and Adolescents in Developing Countries

New York - September 29, 2015 - RHD Action, a new global movement to end rheumatic heart disease (RHD), launched today on the occasion of the United Nations General Assembly in New York. Global health experts, healthcare providers, people living with RHD and others called for new action against this easily preventable but neglected disease, which is a major cause of serious illness and death among women, children and adolescents in developing countries.

Caused by untreated strep throat infections that progress to permanent heart damage, RHD affects more than 32 million people globally, 80 percent of whom live in the developing world. Children and young adults bear the brunt of the disease, accounting for many of the 275,000 people who die from RHD every year. Pregnant women are at particularly high risk of death. Because RHD robs young people of their most productive years, it also causes an enormous economic burden, costing low- and middle-income countries an estimated $56 billion in lost productivity in 2013 alone. Greatly reducing the toll of RHD will be critical to achieving the newly established Sustainable Development Goals.

"Every death from RHD is a tragedy, because every one could have been prevented with penicillin, the oldest and still one of the cheapest antibiotics available," said Dr. Rosemary Wyber, Deputy Director of RhEACH, an RHD Action founding partner. "While the human and economic toll of the disease persists, RHD has lagged far behind many other illnesses when it comes to funding and attention. We call on world leaders gathered at the UN today to commit to eliminating RHD once and for all."

Treating strep throat with penicillin is highly effective in stopping the infection from progressing to RHD, and can cost as little as seven cents per at-risk child per year. But resources for RHD are minimal, accounting for only 0.1 percent of all research funding for neglected diseases. As a result, health systems are not equipped to prevent, treat or control this disease, health workers are often not trained to recognize and treat strep throat, and penicillin is often unavailable. Many people at risk are unaware of its causes and symptoms, so they do not seek medical attention for sore throats.

"Rheumatic heart disease is an injustice we know how to end" said former Australian Prime Minister Kevin Rudd, who was diagnosed with RHD as a child and had subsequent heart valve surgery. "It's time for governments to put this silent emergency at the top of the global health agenda. I'm very pleased that RHD Action will lead the global movement to consign RHD to the history books."

RHD Action-led by the World Heart Federation, RhEACH and Medtronic Philanthropy-calls for urgent action in three areas where concentrated efforts could lead to rapid progress in reducing the toll of the disease:

- Governments must integrate RHD prevention and control into existing health services, particularly for maternal, child health and primary care.

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RhEACH RHEUMATIC HEART DISEASE

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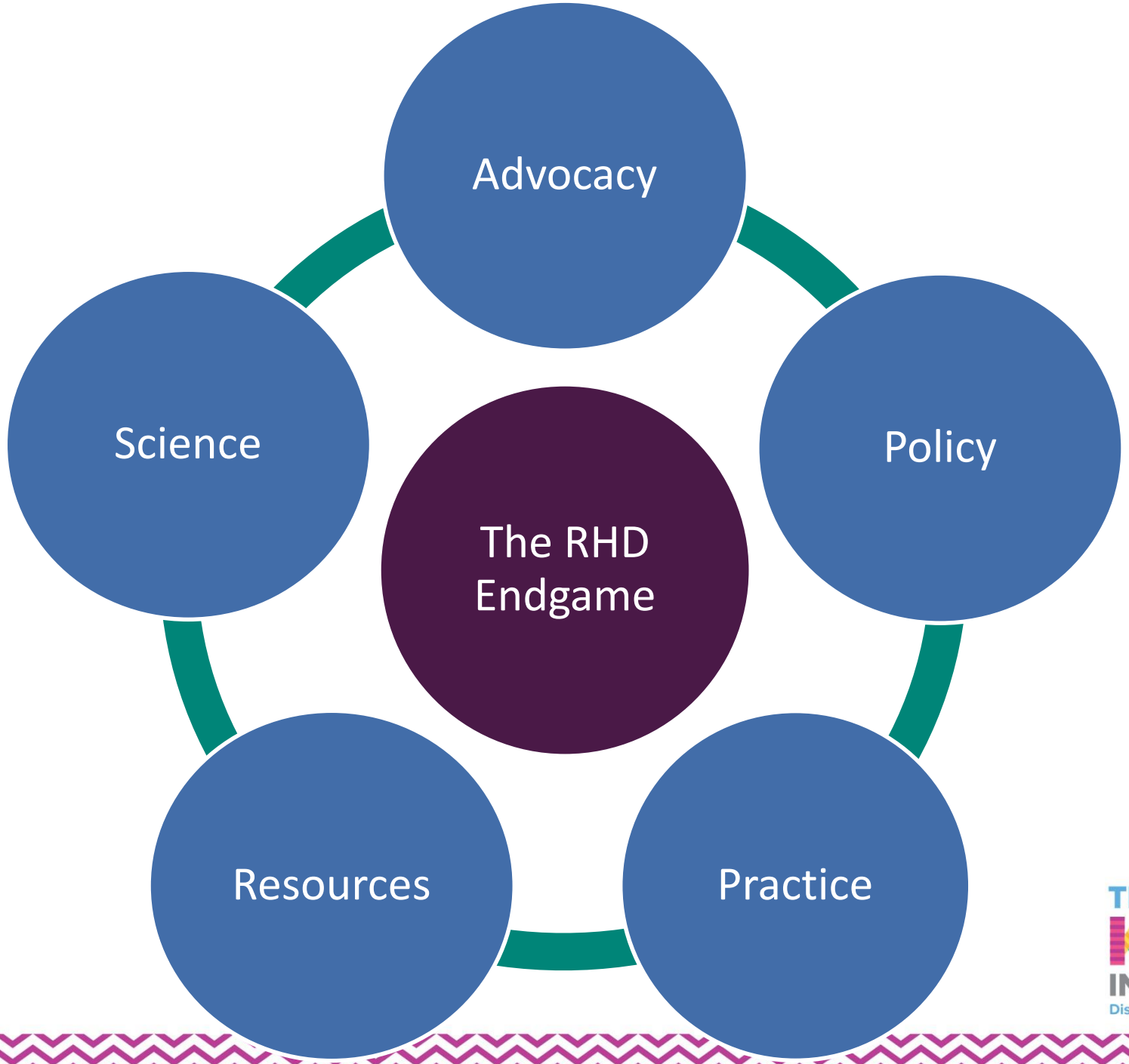
June 1, 2017: WHO Executive Board recommends a Resolution on 'Rheumatic Fever and Rheumatic Heart Disease' for adoption at the World Health Assembly in May 2018

"I want to highlight the importance of intersectoral work. I look at RHD - it is a CD, an NCD, it affects health systems and primary health care and prevention is done at maternal and child health care service. We can get most of the cases prevented… I just want to illustrate RHD as an item – it looks as if it is a standalone disease, but it actually requires so many departments and clusters in order to contribute to reducing the high disease burden affecting all regions. 33 million – it is a lot!

Margaret Chan, WHO DG, June 1, 2017



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