Otago Spotlight Series

Infectious Disease Research

Rheumatic Fever: How can we end this terrible disease of poverty?

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Outline

- **ARF/RHD**
  - Background
  - Epidemiology
- **Studies of mechanisms & risk factors**
  - RF Risk Factors study
  - GAS skin & throat infection linkage study
- **Studies of interventions**
  - Probiotic intervention trial
  - RFPP Evaluation
  - RF progression study
  - Healthy housing referral services
- **Implications for the future**
  - Future interventions & research

Rheumatic heart disease

Impetigo

Strep throat

Streptococcus pyogenes
= Group A Streptococcus (GAS)
Gram positive cocci
completely sensitive to penicillin
~10% are asymptomatic carriers

Rheumatic fever

Scarlet fever

Streptococcal toxic shock

Cellulitis and necrotizing fasciitis

GAS disease

Diseases following GAS:

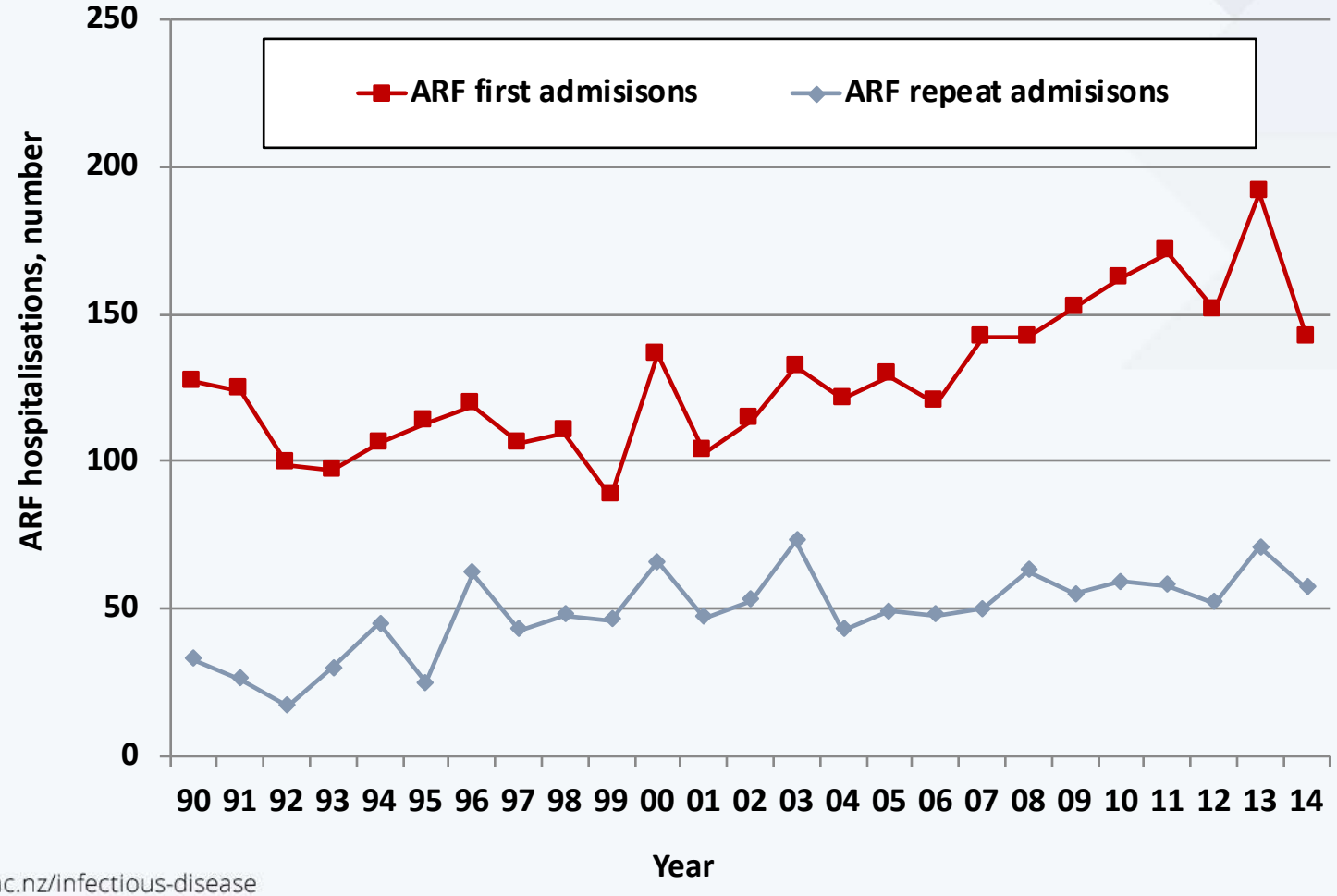
- **Superficial infection**
  - Pharyngitis
  - Impetigo, Pyoderma
- **Invasive diseases**
  - Septicaemia
  - Pneumonia, osteomyelitis…
  - Necrotising fasciitis
- **Toxin mediated diseases**
  - Scarlet fever
  - Streptococcal toxic shock syndrome
- **Post-streptococcal autoimmune sequelae**
  - **Acute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

Key features of ARF

- May develop 2-4 weeks after a sore throat (pharyngitis) or possibly skin infection
- May be asymptomatic or difficult to diagnose
- Painful swelling of joint(s)
- Fever, tiredness, stomach ache (mesenteric adenitis)
- Sometimes a rash or lumps under the skin (immune depositions)
- Fidgety, unusual movements (chorea)
- Evidence of heart murmurs signals RHD

Epidemiology

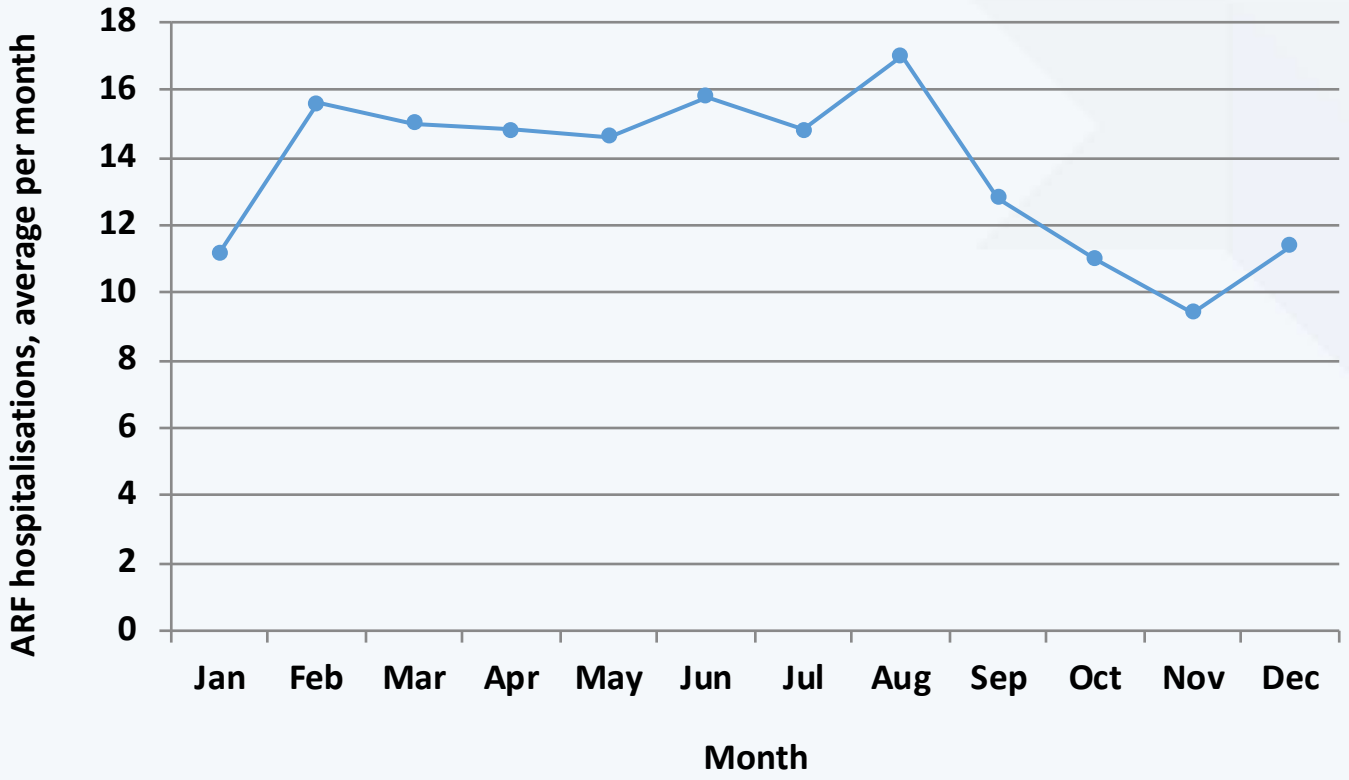
Incidence of ARF – Rate = 3.4/100,000 in 2014



Epidemiology

Incidence by month – monthly average 2010-14

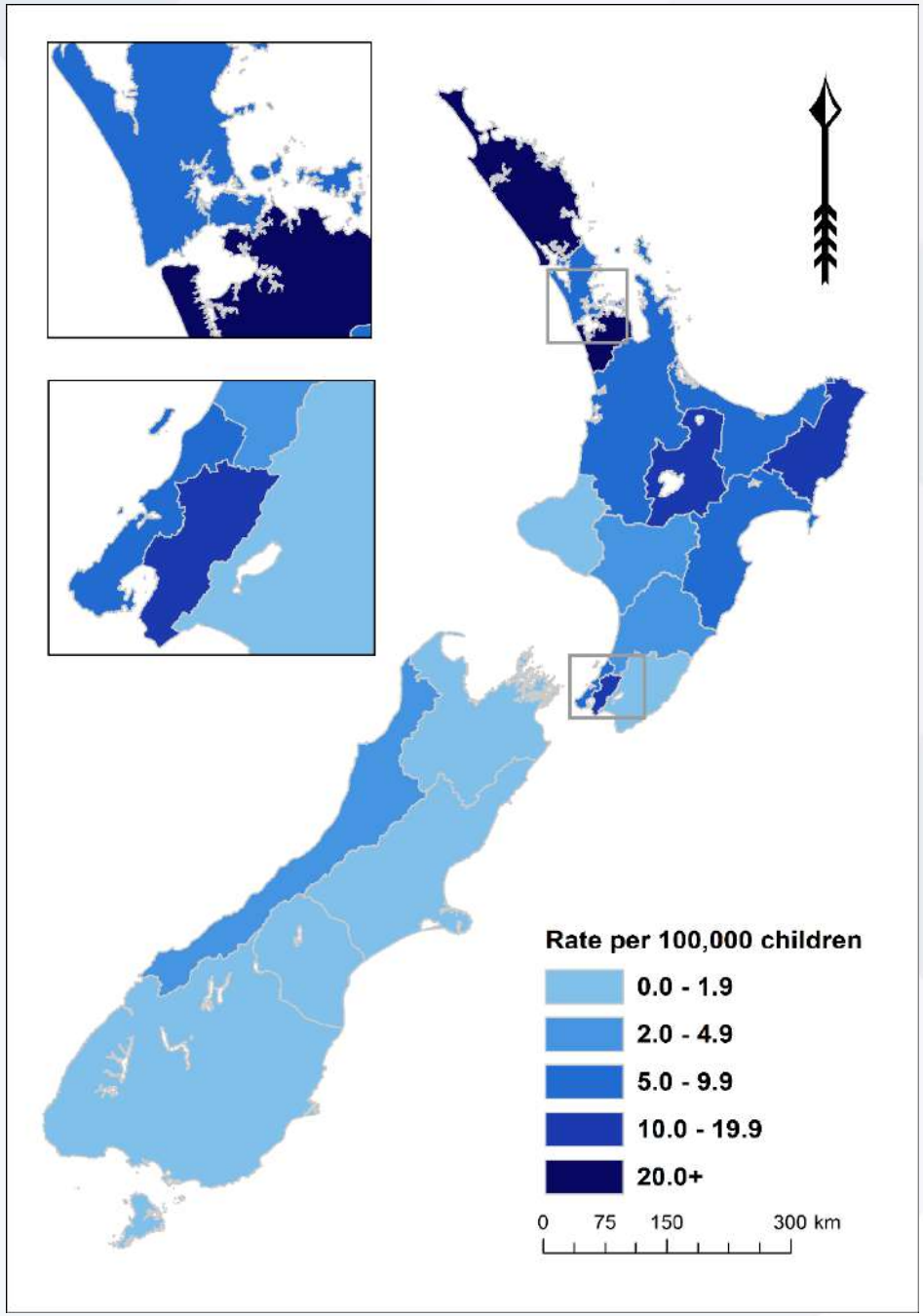
Modest Autumn–Winter peak



Epidemiology

ARF concentrated in North Island (97.5% of cases in those <20 years, 2010-14)

11 (out of 20) District Health Boards with rates of 5.0 per 100,000 or higher accounted for 94% cases



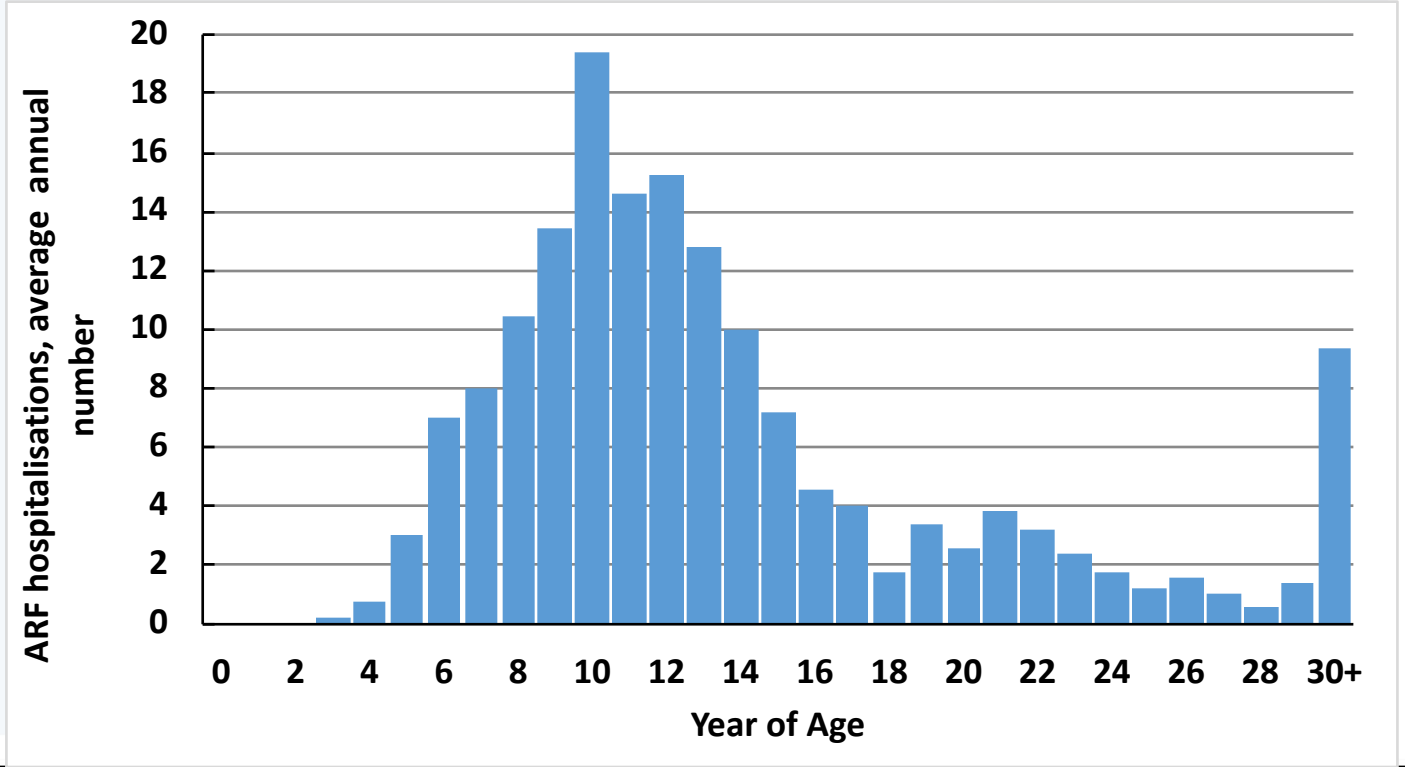
Epidemiology

ARF incidence by age – average by single year, 2010-14

82.4% <20 years of age (12.0 per 100,000)

Median age 12 years

Males 56.0% of cases



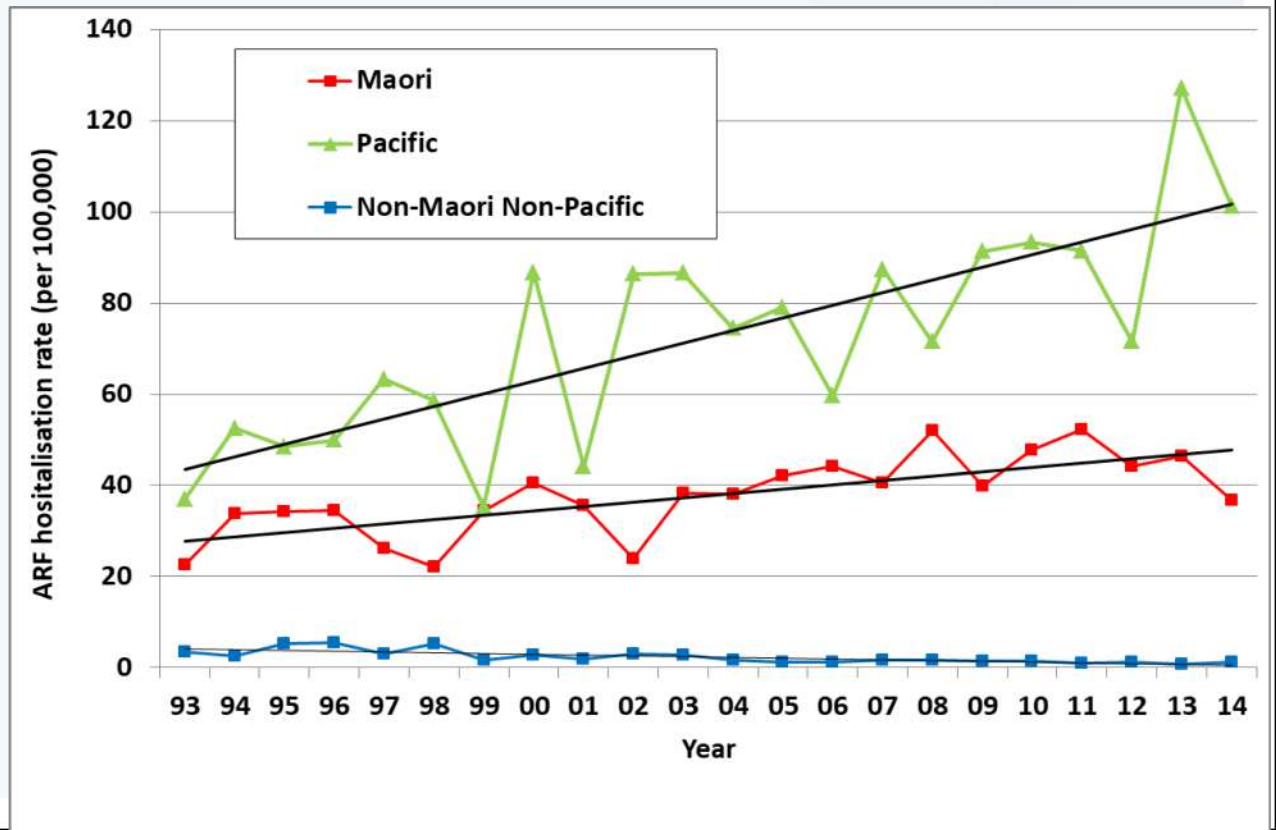
Epidemiology

Incidence by ethnicity aged <20 years, 2010-14

Māori 54.0%, RR 29.7 (vs. European/Other)

Pacific, 38.0%, RR 63.9 (vs. European/Other)

European/Others 7.0%

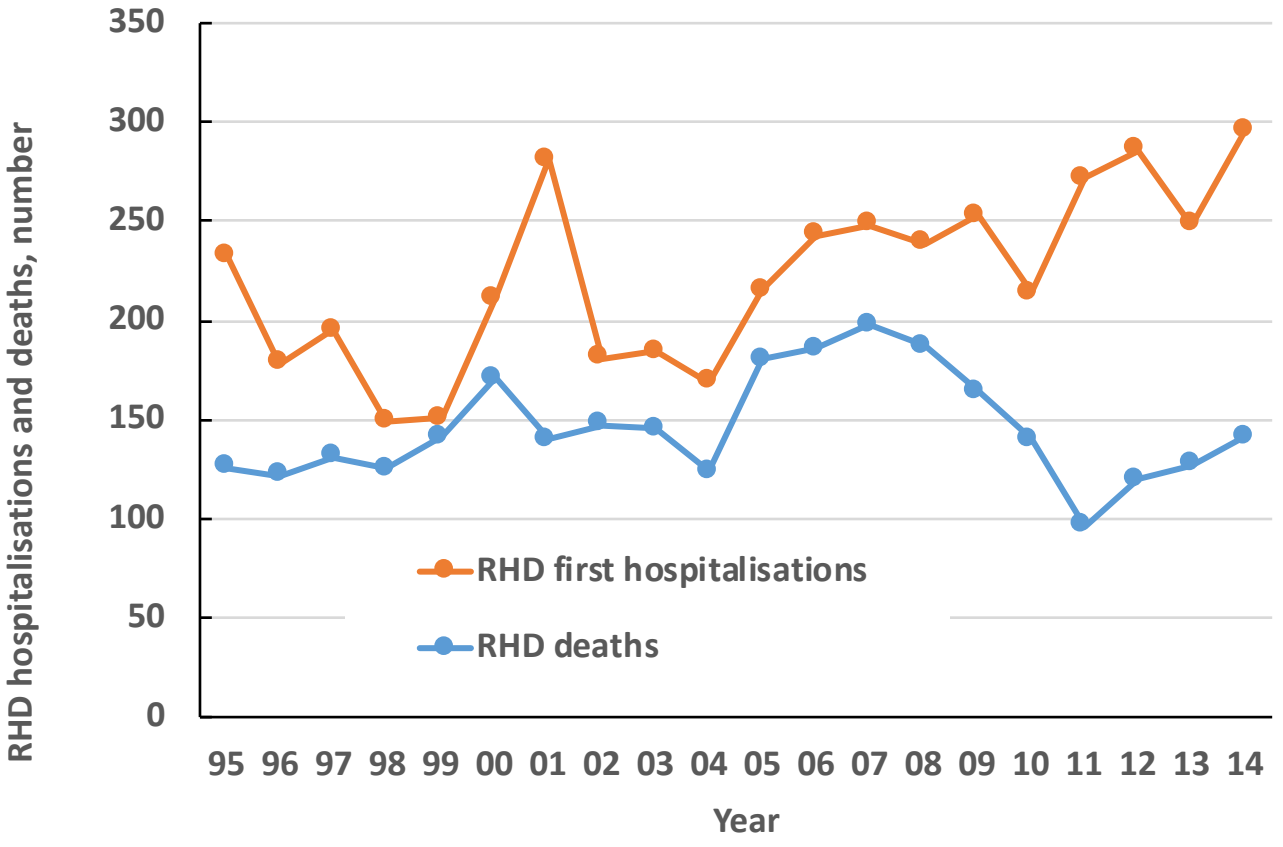


Epidemiology

RHD 2010-2014

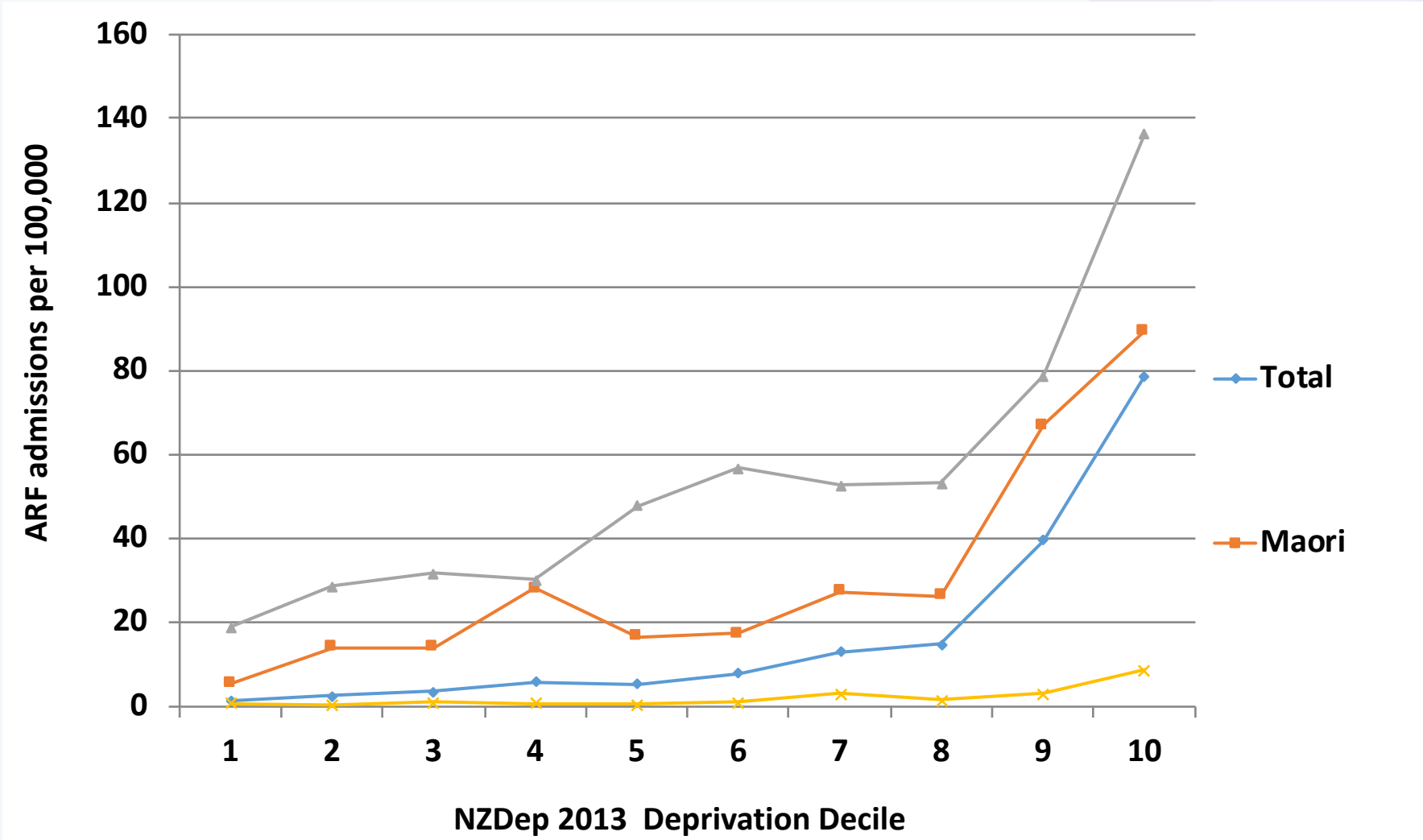
263 first hospitalisations per year

125 RHD deaths per year



Epidemiology

Incidence of ARF by ethnicity and deprivation (NZDep13)



NZ RF Risk Factors Study

Rheumatic Fever
RISK FACTORS STUDY

- **Investigators:** Michael Baker, Jason Gurney, Jane Oliver, Nikki Moreland, Deborah Williamson, Nevil Pierse, Nigel Wilson, Tony R Merriman, Teuila Percival, Colleen Murray, Catherine Jackson, Richard Edwards, Lyndie Foster Page, Florina Chan Mow, Jane Zhang, Barry Gribben, Diana Lennon
- **Funding**: HRC
- **Stage**: Data analysis

Goal of Risk Factors Study

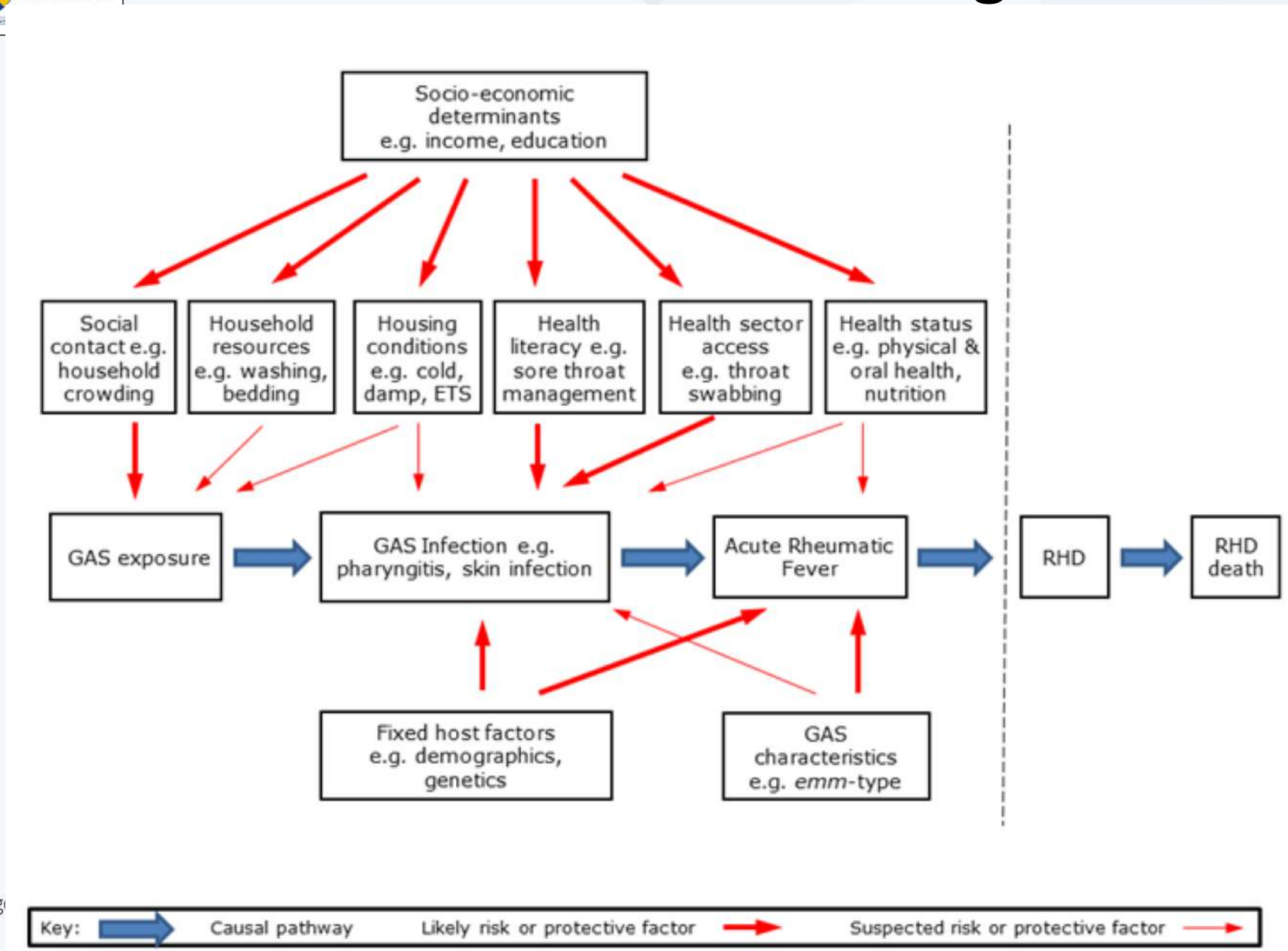
To identify modifiable risk factors for ARF to inform prevention policy & interventions

Distal risks factors / Determinants

Proximal risk factors

ARF/RHD

Risk Factors under investigation



Methods

Case-control study

- 119 ARF cases (definite & probable) after excluding 19 cases that didn't meet case definition

Compared with:

- 357 closely matched controls (time, age, ethnicity, deprivation, DHB, gender) ie 3 per case

Methods

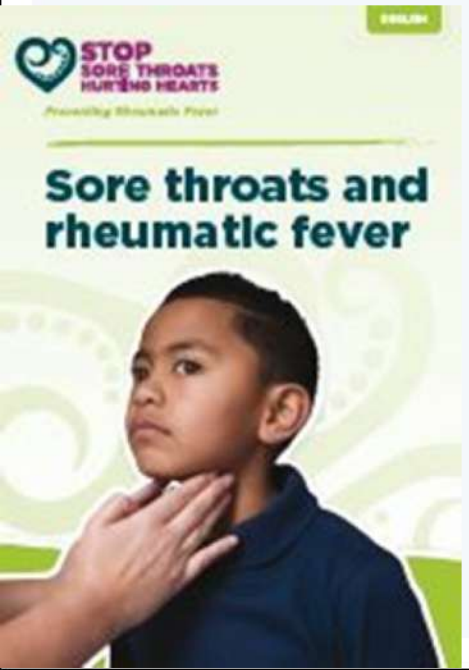
Data collection

- Questionnaire completed in a face-to-face interview by Māori and Pacific interviewers
- A subset of cases and controls also provided blood for additional testing, including ferritin, vitamin D, immunological markers, genetics; hair nicotine
- Linked data on dental health, previous hospitalisations, housing, schools attended

Results: Proximal exposures

Throat infection in previous 4 weeks

	Case		Control	
	n	%	n	%
Yes	59	49.5	101	28.3
No	55	46.2	253	70.9
Don't Know	5	4.2	3	0.8
		UCL	LCL	p
Conditional aOR	**2.52**	1.60	3.99	<0.003



Results: Proximal exposures

Skin infection in previous 4 weeks

	Case		Control	
	n	%	n	%
Yes	25	21.0	36	10.1
No	93	78.2	321	89.9
Don't Know	1	0.8	0	0.0
		UCL	LCL	p
Conditional aOR	**2.30**	1.30	4.07	0.004

Skin infection without throat infection		UCL	LCL	p
Conditional aOR	1.25	0.50	3.09	0.631
Skin infection with throat infection		**UCL**	**LCL**	**p**
Conditional aOR	**13.13**	2.88	59.96	0.009

Results: Proximal exposures

Scabies in previous 4 weeks

	Case		Control	
	n	%	n	%
Yes	7	5.8	5	1.4
No	112	94.1	349	97.8
Don't Know	0	0	3	0.8
		UCL	LCL	p
Conditional aOR	**5.44**	1.62	18.24	0.006

Results: Household crowding

Bedroom deficit of one or more (Canadian National Occupancy Standard)

	Case		Control	
	n	%	n	%
0 bedroom deficit	86	72.4	320	89.7
1 Bedroom deficit	22	18.5	22	6.2
2 Bedroom deficit	7	5.9	13	3.6
3 or more Bedroom deficit	4	3.4	2	0.6
Conditional aOR	**3.78**	2.13	6.72	<0.0001

Results: Bed sharing

Usually share a bed in the last 4 weeks?

	Case		Control	
	n	%	n	%
Yes	64	53.8	137	38.4
No	55	46.2	218	61.1
Don't Know			2	0.6
Conditional aOR	**2.31**	1.44	3.69	0.001

Does anyone sleep in case/control's bed when they aren't using it (**'hot bedding'**)?

	Case		Control	
	n	%	n	%
Yes	21	17.6	17	4.8
No	98	82.4	338	94.7
Don't Know				
Conditional aOR	**4.40**	2.15	9.03	<0.0001

Results: Housing tenure & quality

Housing tenure – proportion living in rental housing

	Case		Control	
	n	%	n	%
Rental	93	78.2	225	63.0
Owned by occupant	16	13.5	100	28
Don't now	10	8.4	32	9
Conditional aOR	**3.65**	1.81	7.02	0.002

Housing quality – Self rating on 5-point scale

	Case		Control	
	n	%	n	%
Poor, Very poor	31	26.0	24	6.7
Average or better	88	73.9	332	93
Don't Know			1	0.3
Conditional aOR	**5.17**	2.70	9.90	<0.0001

Results: Household damp

Household damp & mould based on 3 questions:

- **Mould on the walls or ceilings** in bedrooms or living rooms in the last 12 months
- **Damp walls or ceilings** in bedrooms or living rooms the last 12 months?
- **Damp or musty smell** in bedrooms or living rooms over the last 12 months?

	Case		Control	
	n	%	n	%
Yes	75	63.0	135	37.8
No	44	37.0	221	61.9
Don't Know				
Conditional aOR	**3.47**	2.10	5.74	<0.0000

Results: Household cold

Household cold based on sum of 4 questions:

- In winter, is your home **colder than you would like**?
- In winter, do you put up with **feeling cold inside to save on heating costs**?
- Did case/control need to **share a sleeping room just to stay warm** in the last 4 weeks?
- Has your house been so cold that you **shivered** in the last 4 weeks?

	Case		Control	
	n	%	n	%
Yes	90	75.6	221	62
No	29	24.4	134	37.5
Don't Know			2	0.6
Conditional aOR	**2.16**	1.3	3.57	0.003

Results: Household washing resources

Composite measure based on 2 questions:

- Does case/control sometimes have a **cold or lukewarm bath/shower** because there is not enough hot water? (shown here)
- Does case/control sometimes have to **put off having a bath/shower** because there is not enough hot water?

	Case		Control	
	n	%	n	%
Yes	30	25.2	40	11.2
No	89	74.8	315	88.2
Don't Know			2	0.6
Conditional aOR	**3.11**	1.66	5.81	<0.00001

Results: Nutrition

Sugar sweetened drinks -How many sugar-sweetened drinks (including fruit juice), but not including diet drinks, does case/control normally drink per day?

	Case		Control	
	n	%	n	%
1 or more	70	58.7	131	36.9
None	49	41.2	220	61.6
Don't Know				
Conditional aOR	**2.43**	1.55	3.81	<0.0000

Vegetables - On average, how many servings of vegetables eaten per day?

	Case		Control	
	n	%	n	%
1 or less	64	53.8	143	40.1
2 or more	55	46.2	214	60
Don't Know				
Conditional aOR	**1.96**	1.25	3.08	0.003

Results: Family History of RF

Relatives ever diagnosed with RF or RHD?

	Case		Control	
	n	%	n	%
1 or more	60	52.2	76	21.7
none	55	47.8	274	78.3
Don't Know	4	3.4	7	2.0
		UCL	LCL	p
Conditional aOR	**4.22**	2.57	6.94	<0.000

Results: Health service access

Barriers to primary care access:

- Unable to be seen within 24 hrs
- Didn't visit because of cost
- Didn't visit because of transport
- Didn't visit because of childcare
- Didn't fill prescription because of cost

	Case		Control	
	n	%	n	%
2-5 barriers	27	22.6	51	14.3
0 or 1 barrier	92	77.3	306	85.8
		UCL	LCL	p
Conditional aOR	**1.73**	1.00	2.98	0.050

Results: Health service access

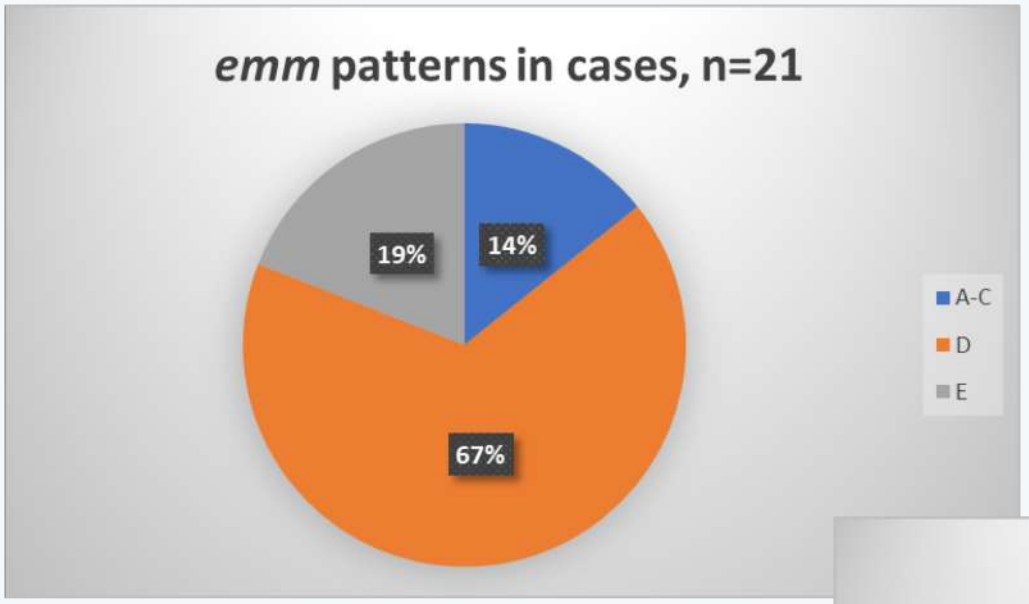
Current school has a throat swabbing programme for rheumatic fever?

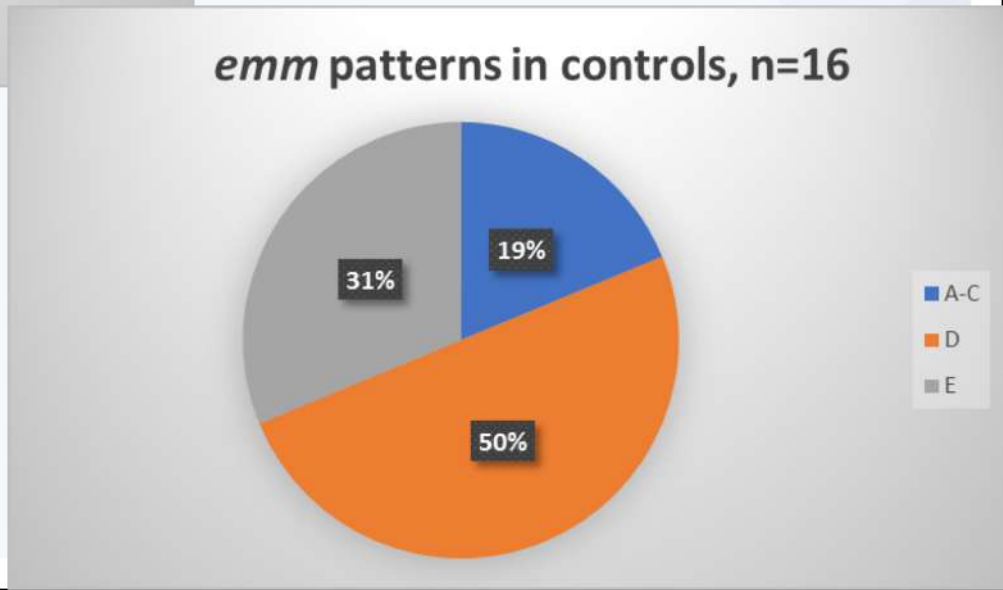
	Case		Control	
	n	%	n	%
Yes	59	49.6	138	38.7
No	37	31.1	144	40.3
Don't Know/ missing	23	18.5	75	21
		UCL	LCL	p
Conditional aOR	**2.36**	1.30	4.28	2.36

Results: Multivariate

Variable	Units	OR	LCL	UCL	Pr(>|z|)
Family History RF	y/n	**6.02**	2.95	12.27	<0.001
Mould Score	0to9	**1.14**	1.001	1.23	0.0475
Limited hot water	0to3	**1.63**	1.02	2.64	0.04
Household Crowding	People/ room	**3.79**	1.82	7.92	0.0004
Sugar Sweetened Beverages	0to9	**1.47**	1.18	1.83	0.0005

Organism factors



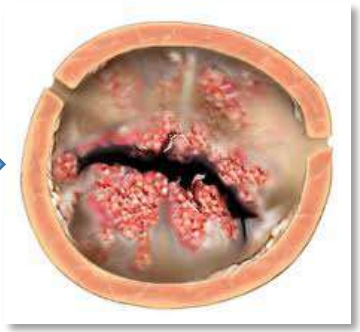


Role of skin infection

Conventional wisdom

GAS (Strep) sore throat

Acute Rheumatic fever (ARF)



Rheumatic heart disease (RHD)

?

?

GAS skin infection eg Impetigo

Acute Post Streptococcal Glomerulonephritis (APSGN)

?

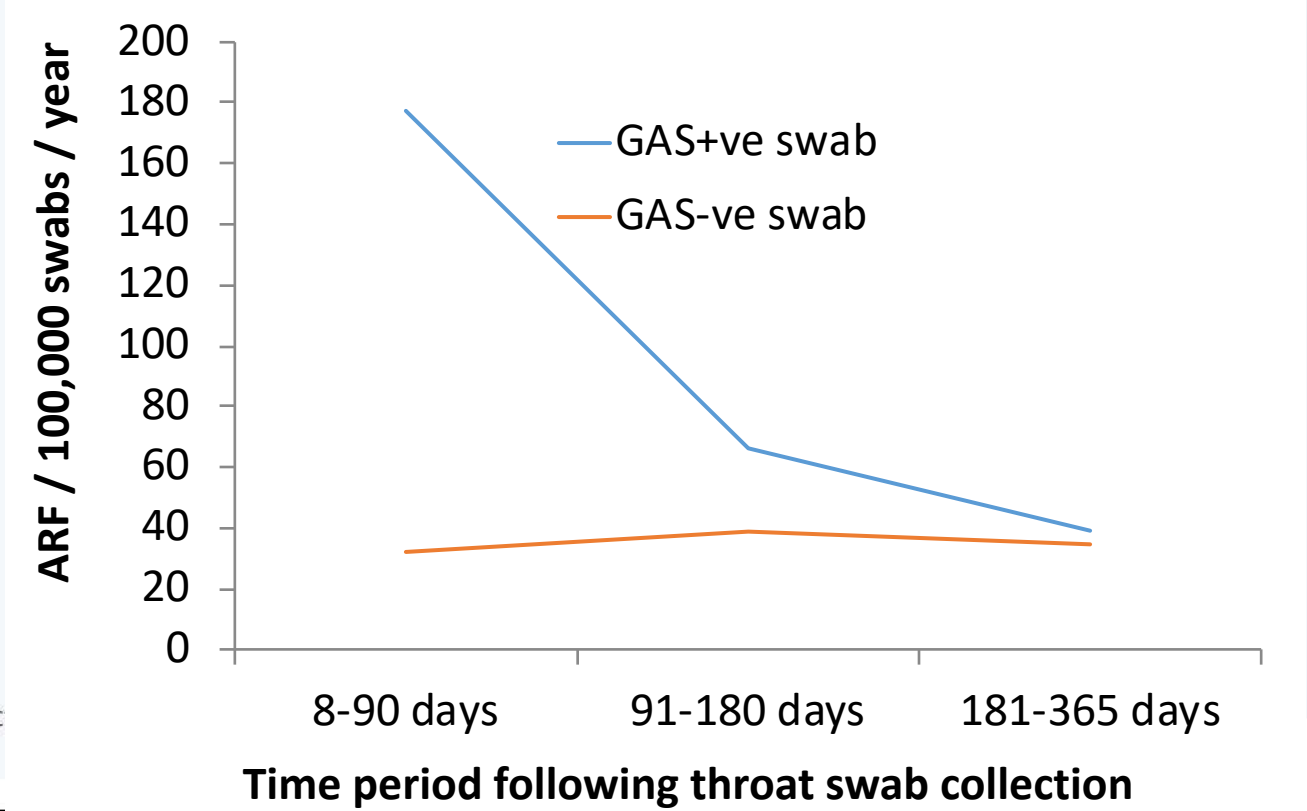
Role of Group C/G Streptococci

Methods

- **GAS exposure data sources**
  - Laboratory throat swab and skin swab test data, community labs (Labtests), Auckland Region (pop= 1.5 million), 2009-2016
  - Hospitalisations for specific clinical conditions (eg Strep pharyngitis, skin infections) NZ (pop=4.5 million), 2001-15
- **Disease outcome data sources**
  - Hospitalisation data on first admissions for ARF (ICD.10 I00, I01, I02) APSGN (ICD.10 N00, N05)
  - Linked to exposure using unique patient number (encrypted NHI)

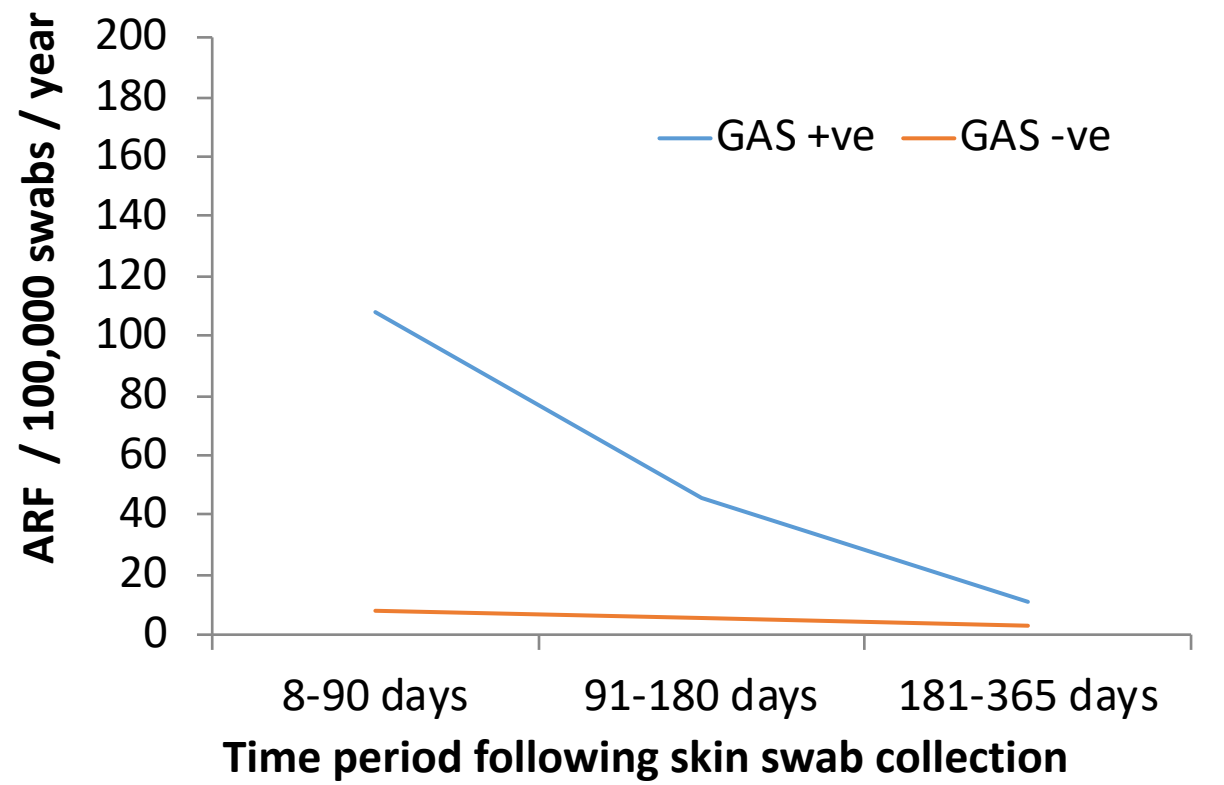
ARF following GAS +ve throat swab

- ARF cases (N=155) in 365 days following GAS+ve throat swabs (N=163,534) vs. risk ARF (N=378) following GAS & Group C/G -ve throat swabs (N=1,029,680)
- All ages, 8-90 days, RR=**5.53** (95%CI **3.96-7.72**)
  - Total 5-19 years, 8-90 days, RR=**8.57** (95%CI **4.27-17.23**)
  - Māori 5-19 years, 8-90 days, RR=**7.32** (95%CI **2.14-24.99**)
  - Pacific 5-19 years, 8-90 days, RR=**7.28** (95%CI **3.09-17.16**)



ARF following GAS +ve skin swab

- ARF cases (N= 23) in 365 days following GAS +ve skin swab (N=53 544) vs. risk ARF (N= 18) following GAS & Group C/G -ve skin swabs (N= 354 200)
- All ages, 8-90 days, RR= **14.33** (95% CI **5.45-37.71**)
  - Total 5-19y olds, 8-90 days: RR **5.95** (95% CI **2.06-17.08**)
  - Māori 5-19y olds, 8-90 days: RR 7.34 (95% CI 0.35-152.82)
  - Pacific 5-19y olds, 8-90 days: RR 2.33 (95% CI 0.76-7.12)



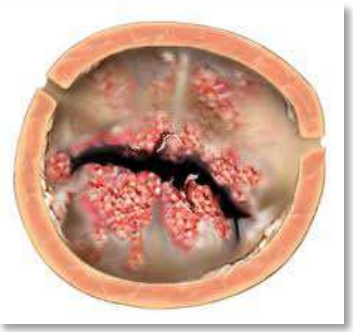
Conclusions and Implications

Revised wisdom?

GAS (Strep) sore throat

X

Acute Rheumatic fever (ARF)



Rheumatic heart disease (RHD)

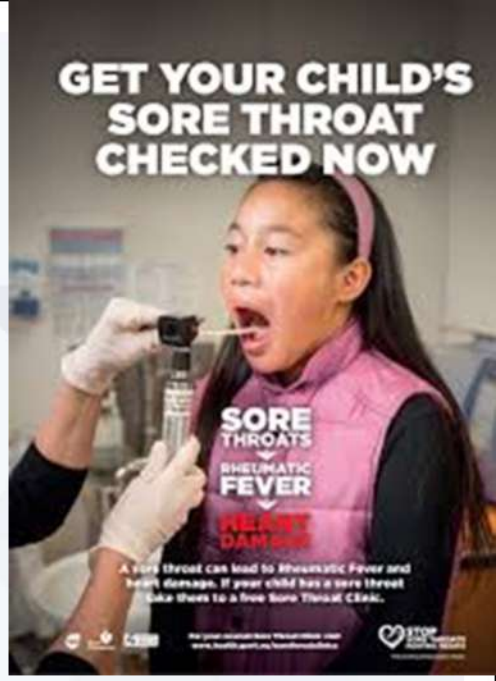
GAS skin infection eg Impetigo

Acute Post Streptococcal Glomerulonephritis (APSGN)

X

Role of Group C/G Streptococci

Evaluating RF Interventions



Interventions

- RFPP evaluation
- BLIS (probiotic) trial
- Secondary prophylaxis and disease progression
- Healthy housing referral (well homes)

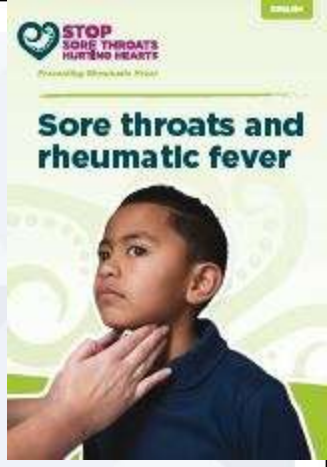
Evaluation of RFPP

Evaluation of Rheumatic Fever Prevention Programme (RFPP) – sore throat management component

- **Investigators**: Evaluation team: Susan Jack, Michael Baker, Debbie Williamson, Yvonne Galloway, Nevil Pierse, Richard Milne, Graham Mackereth, Jane Zhang, Jane Oliver. Advisors: Jonathan Carapetis, Andrew Steer, Paul Scuffham, Catherine Jackson, Matire Harwood, Dianne Sika-Paotonu, Murray Tilyard
- **Funding:** NZ Ministry of Health
- **Stage**: Report and published paper

Source: Jack et al. Primary Prevention of Rheumatic Fever in the 21st Century: Evaluation of a National Programme. Int J Epi 2018.

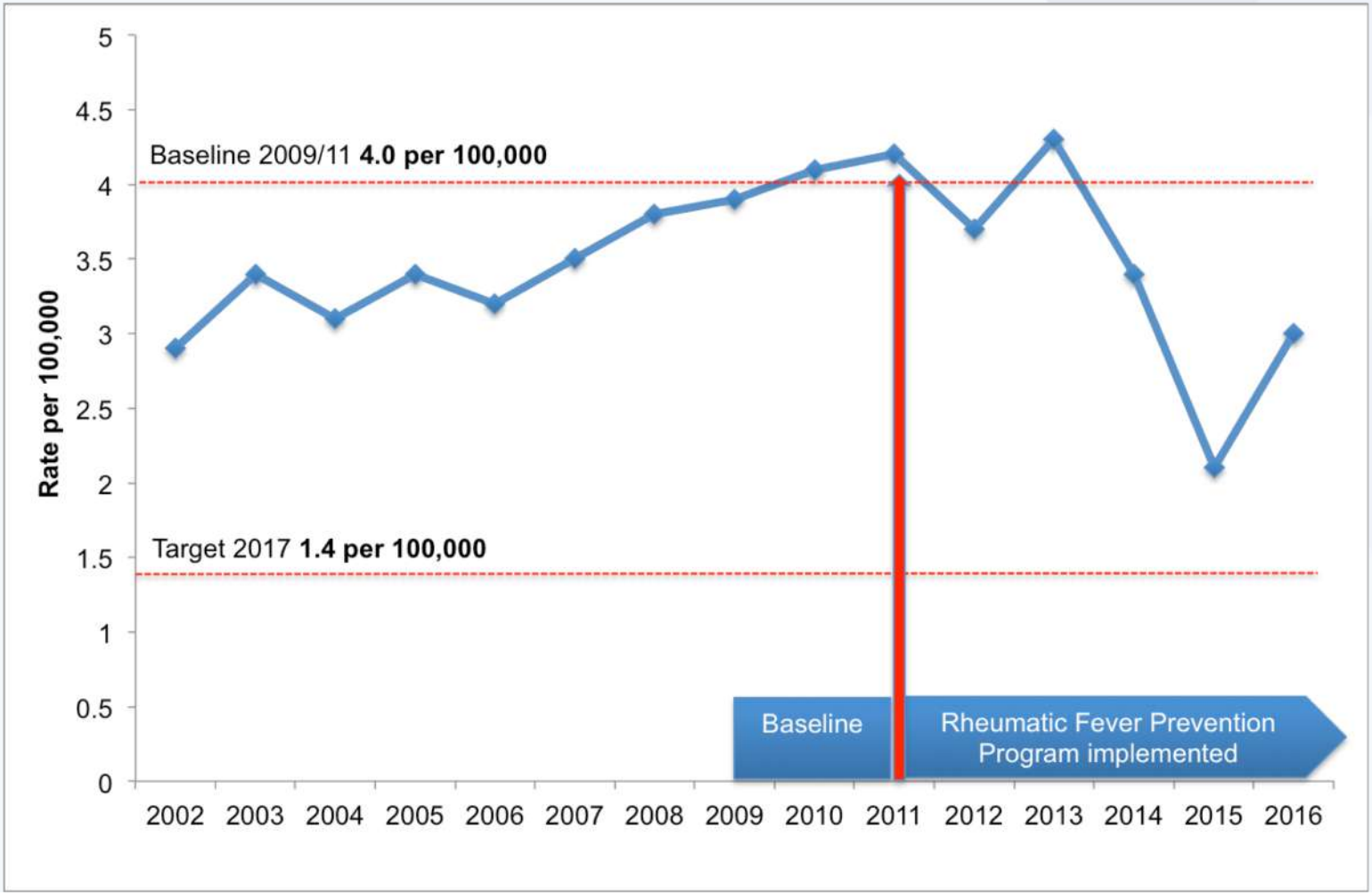
Evaluation of RFPP



- The main activity of the RFPP is sore throat treatment
- School-based throat swabbing programme in 230 schools across 10 North Island DHBs
- Primary care programme with 108 free drop-in sore throat clinics
- Aims to improve management of sore throats in high-risk children across the country.
- Increases health literacy amongst professionals and the public

Evaluation of RFPP

Total first episode RF hospitalization rates by year



Source: Jack et al. Primary Prevention of Rheumatic Fever in the 21st Century: Evaluation of a National Programme. Int J Epi 2018.

Evaluation of RFPP

Effectiveness analysis findings 2012–2016

Scenario	Number of cases exposed/person-days exposed	Number of cases not-exposed/person-days not-exposed	ARF decline (%)	95% CI
Schools in all 10 RFPP DHB regions with a school-based service	123/ 68,465,350	54/ 23,093,207	23.2	-5.8 to 44.2
Schools in Counties Manukau with a school-based service	52/ 32,165,368	30/ 9,945,963	46.4	16.0 to 65.8
Schools in the nine other DHB regions with a school-based service	71/ 36,299,982	24/ 13,147,244	-7.1	-70.2 to 32.5

Source: Jack et al. Primary Prevention of Rheumatic Fever in the 21st Century: Evaluation of a National Programme. Int J Epi 2018, accepted.

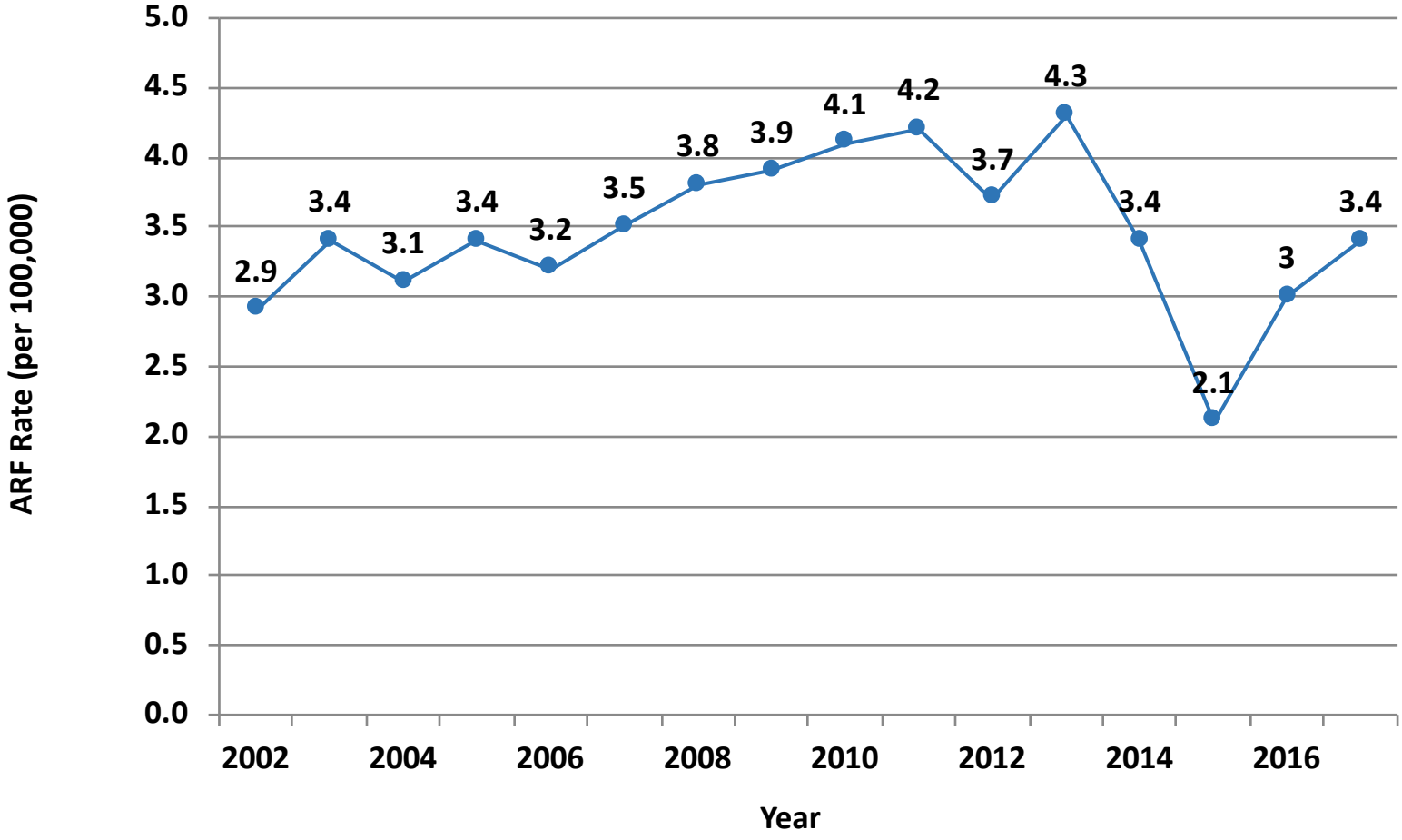
Evaluation of RFPP

- The RFPP school-based sore throat component is expensive, however it may be justified for areas with:
  - concentrated populations of high risk children
  - a well-run high-coverage programme
  - possibly also with management of skin infections

- Other approaches are needed where high risk populations are dispersed or for lower risk populations

Source: Jack et al. Primary Prevention of Rheumatic Fever in the 21st Century: Evaluation of a National Programme. Int J Epi 2018.

Evaluation of RFPP



Source: NZ Ministry of Health. National incidence of ARF, based on first hospitalisations for ARF

Trial of probiotics to prevent ARF

- Preventing GAS pharyngitis with BLIS-producing oral probiotic
- Bacteriocin-Like Inhibitory Substances (BLIS) naturally produced by *Streptococcus salivarius* commensal of the human tongue
- John Tagg observed that children colonised with BLIS-producing *S. salivarius* less likely to acquire *S. pyogenes*

Trial of probiotics to prevent ARF

Oral BLIS Trial

- **Investigators:** Julian Crane, Michael Baker, Debbie Williamson, Nevil Pierse, Kristin Wickens, Tosh Stanley, Ramona Tiatia
- **Method**: Pragmatic trial with 1314 children participating in school based sore throat management programme quasi-randomized to receive either K12 (2.5 x 109 cfu's per lozenge) or placebo lozenges and continued observed daily treatment (in the school week, during school time) for one school year.

Trial of probiotics to prevent ARF

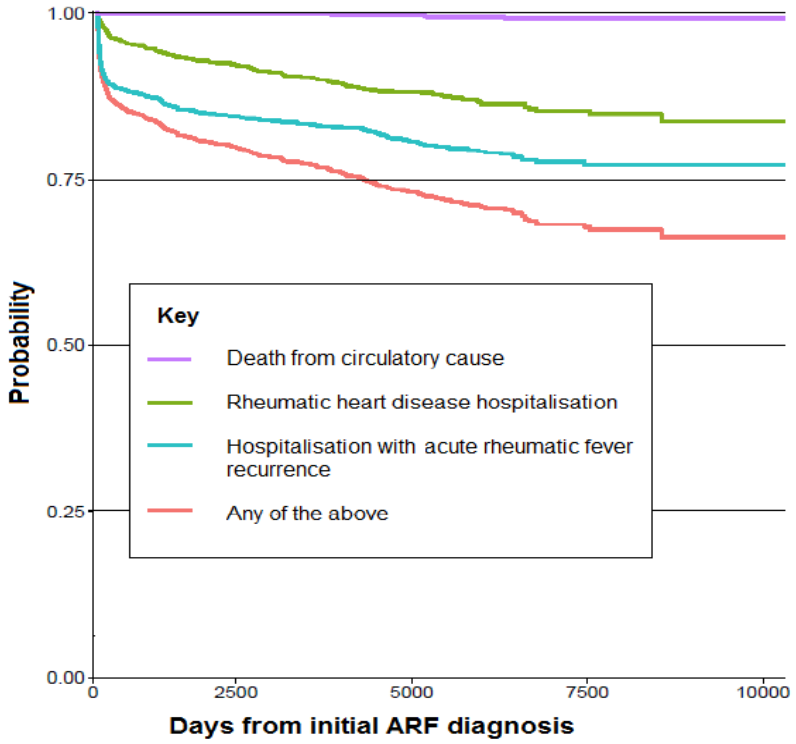
Oral BLIS Trial

- Non-significant 11.2% reduction in positive swabs amongst children receiving K12. greater for older children, aged 7-9 years, 15.6%, and for children 10 years and older, 30.2%.
- Conclusion: S. salivarius (K12) had modest non-significant effects on culture-positive sore throats when given at school, during the school day. routine use of this probiotic in the prevention of pharyngitis associated with GAS detection is not supported.

Source: Doyle, et al. The Effect of the Oral Probiotic Streptococcus salivarius: (K12) on Group A Streptococcus Pharyngitis: A Pragmatic Trial In Schools. Pediatric Infect Dis J 2018; 37: 619–23

ARF Progression

- 2,182 initial ARF hospitalisations 1989-2012 identified using ICD coding in the National Minimum Dataset (NMDS)
- Retrospective analysis identified cases first hospitalised with RHD (NMDS) between 2010-2015 when aged <40 years



ARF Progression

- **Progression risk**
  - 14.9% experienced ARF recurrence, 11.2% developed RHD, 8 cases died of cardiovascular causes
  - Most (75.6%) of 2,182 cases survived & not hospitalised with recurrence/ RHD
- **Progression risk by population group**
  - Female higher risk disease progression, OR: 1.27 (1.05-1.54), shorter time (HR: 1.20 (1.02-1.42).
  - Māori higher risk disease progression (ORs: 1.56, 1.12-2.22), shorter time (HRs 1.65, 1.21-2.25)
  - Pacific higher risk progression (OR 1.67, 1.18-2.39) and shorter time (HR 1.75, 1.28-2.41) compared with European/Others

Source: Oliver et al. Progression of acute rheumatic fever to recurrence, rheumatic heart disease and death in New Zealand children and youth: A cohort study. Submitted

ARF Progression

- The majority (65.1%) of new RHD cases aged <40 years, admitted 2010-15, had never been previously hospitalised with ARF in NZ

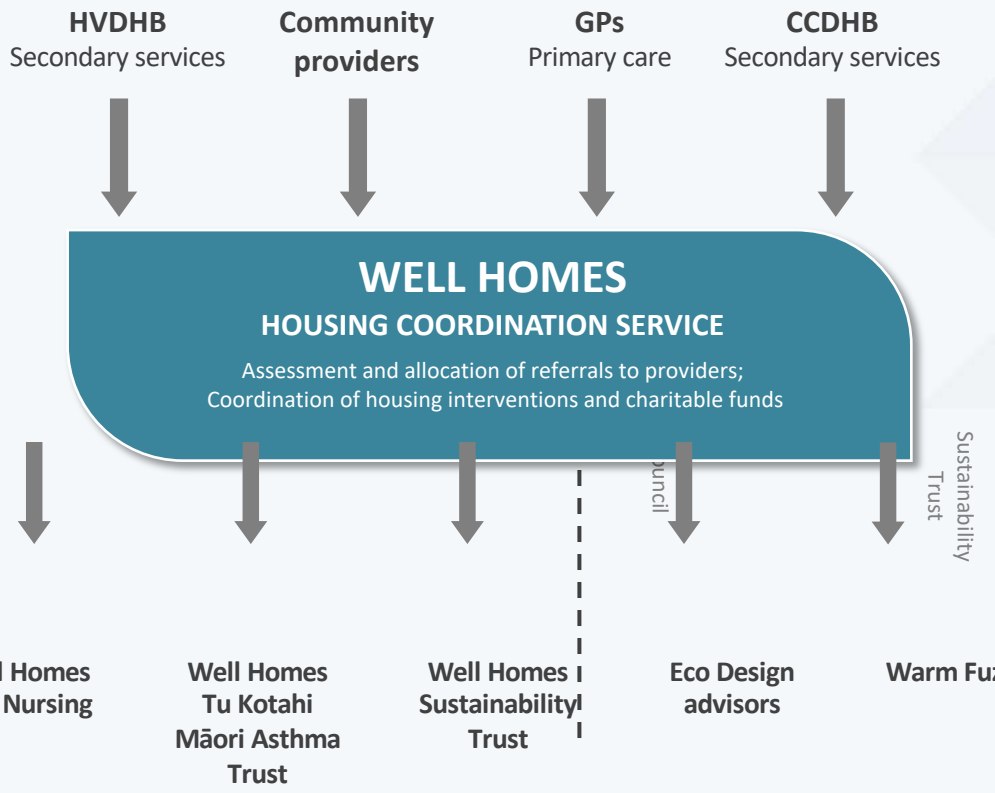
Healthy Housing Referral evaluation

SHELTER (Safe Housing Ensuring Long Term Effective Recovery)

- Aims to quantify effects of multifaceted housing intervention
- Well Homes is a housing coordination service supported by Regional Public Health Service, Tu Kotahi Maori Asthma Trust, and Sustainability Trust.
- Whānau referred to Well Homes visited by a housing assessor, who identifies potential housing issues, provides education on healthy housing, referral for assistance

Well Homes

REFERRAL SOURCES



Well Homes is a **free** service that may be able to help your whānau with:


BEDS & BEDDING


CARPET


CURTAINS


HEATING


INSULATION


MINOR REPAIRS


MOULD CLEANING KITS

MSD/WORK & INCOME ASSISTANCE


OTHER - I.E. HEALTH OR SOCIAL REFERRALS


SOCIAL HOUSING RELOCATION


VENTILATION

Please phone us on 0800 675 675

Healthy Housing Referral evaluation

SHELTER Study

- Evaluation uses hospitalisation data to measure the effects of receiving the Well Homes intervention on health of children previously hospitalised due to health conditions related to housing
- Investigators: Nevil Pierse, Michael Baker et al
- Funding: HRC Programme Grant (Housing and Health/He Kainga Oranga)

Interventions to reduce RF

1. Sustained improvement in the home environment of children

- **Reduce bed sharing by children** – a 'bed for every child'.
- **Reduce household crowding** - adequate supply of affordable, suitable housing eg construction of social housing and increase security of tenure
- **Sustained improvement in housing quality** - reduce damp and mould, insulation and heating, housing warrant of fitness
- **Address fuel poverty** – to improve energy efficiency, reduce costs of home and water heating
- **Reduce exposure to tobacco smoke** in homes and cars, and reducing respiratory infections more generally

Future Interventions to reduce RF

2. Revise the population approach to GAS infection management - Could include:

- More intensive, targeted approach based on family history of rheumatic fever, ethnicity, ancestry, age
- Treatment of both sore throats and skin infections
- Use of injectable penicillin and potentially prophylactic treatment
- Scabies treatment

Future Interventions to reduce RF

3. **Improve the diet of children** – The RF Risk Factors study provides further evidence to support reducing consumption of sugar sweetened beverages

4. **Improve management of children with ARF** – Better diagnosis, tracking, and delivery of Benzathine Penicillin G (BPG) or alternatives

5. **Vaccination** – Support international collaboration to develop and trial Strep A vaccine

Future research & evaluation

- **GAS infection study in Auckland (HRC)** – Focus on role of skin infection & effectiveness of oral antibiotics
- **RF Endgame project (HRC)** – considering effectiveness & economics of full range of interventions
- **Continue evaluation of healthy housing referral programmes** (HRC) – Well Homes programme
- **Consider trial of intensive targeted intervention for high risk populations** – Screening questions, more intensive management

Rheumatic fever - a disease of poverty and of politics

Jacinda Ardern – PM and Minister of Child Poverty reduction

Dame Tariana Turia – Former leader of Maori Party and advocate for RF prevention