

NZ evidence for the association between skin infection and rheumatic fever

**Michael Baker and
Co-investigators (including Nikki Moreland, Julie Bennett, Jane Zhang)
University of Otago, Wellington**

Auckland, September 2019

Outline

Background

- ARF & RHD epidemiology

Evidence for role of skin infections – **all results provisional until published**

- RF Risk Factors study
- GAS skin & throat infection progression study
- GAS skin & throat immune response study

Conclusions and Implication

- Conclusions
- Implications



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)**
 - **Acute post-streptococcal glomerulonephritis (APSGN)**



Methods for epidemiological analysis

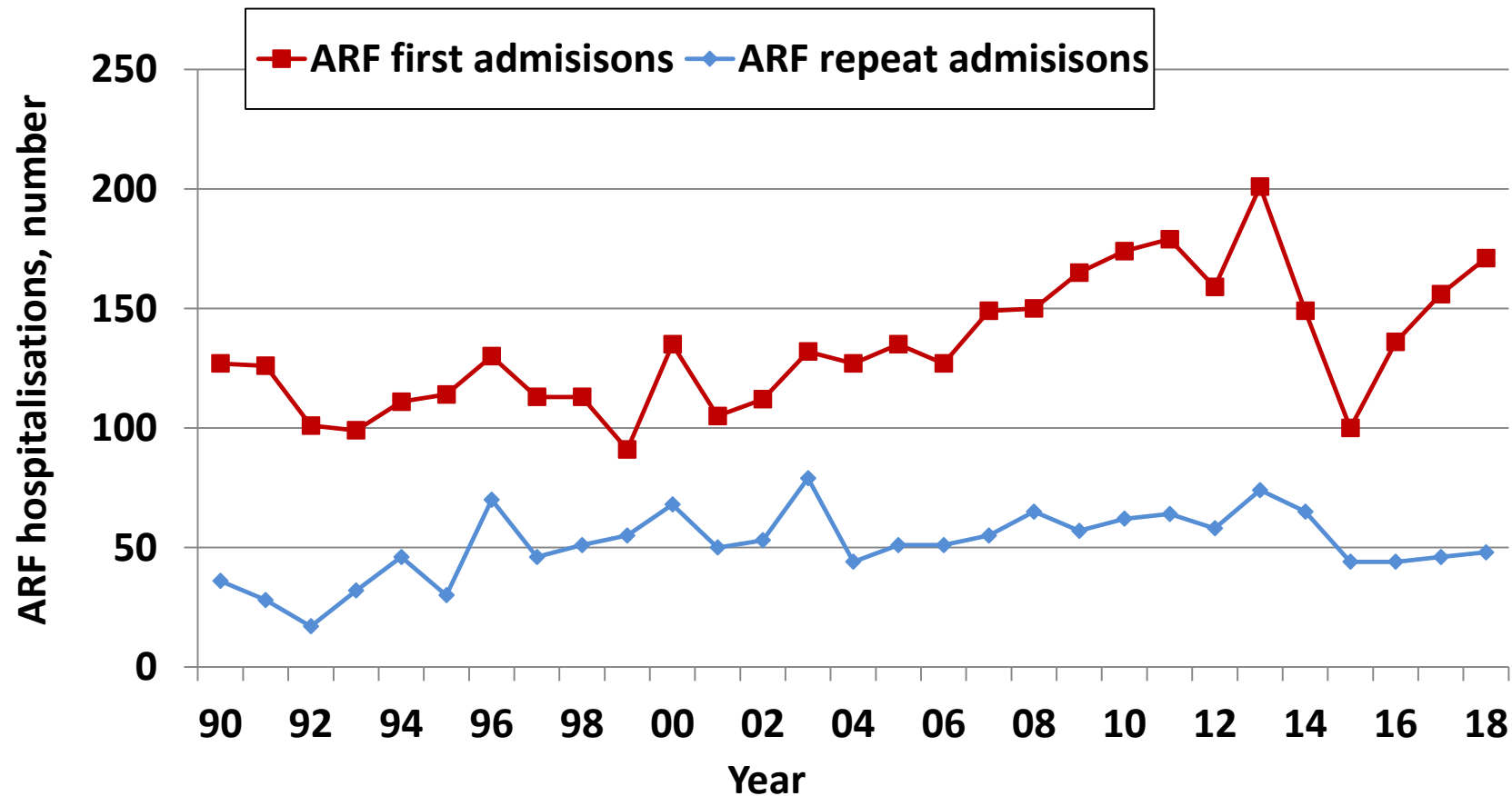
- **ARF** – First hospitalisation, principal diagnosis = ICD-10: I00-I02, no previous admission for ARF or RHD (=method used by MoH)
- **RHD** – First hospitalisation, principal diagnosis = ICD-10: I05-I09*, no previous admission for RHD.
- **RHD mortality** – Underlying cause of death = ICD-10: I05-I09*
- **Denominator populations** – From linear interpolation of census data

*Exclude: I07, I08.2, I08.8 and I08.9, '3969', '3970', plus for people ≥60 years exclude I05.8, I05.9, I08.0, I08.1 and I08.3, '3949', '3969'

ARF Cases by year, 1990-18

ARF first hospital admissions, range 91-201 pa

Average of 158 cases pa. 2010-18

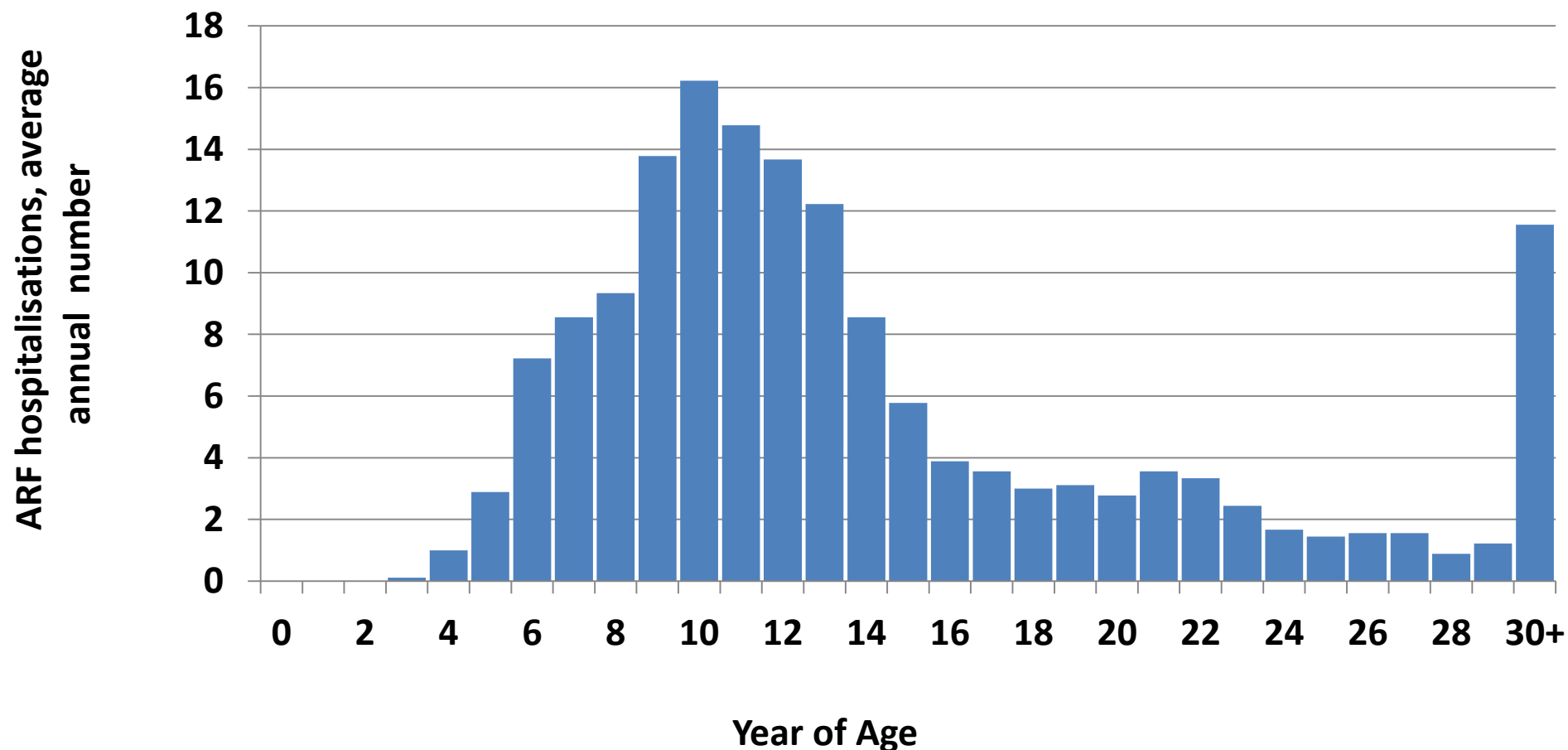


ARF cases by Age

ARF average of 158 cases pa. 2010-18

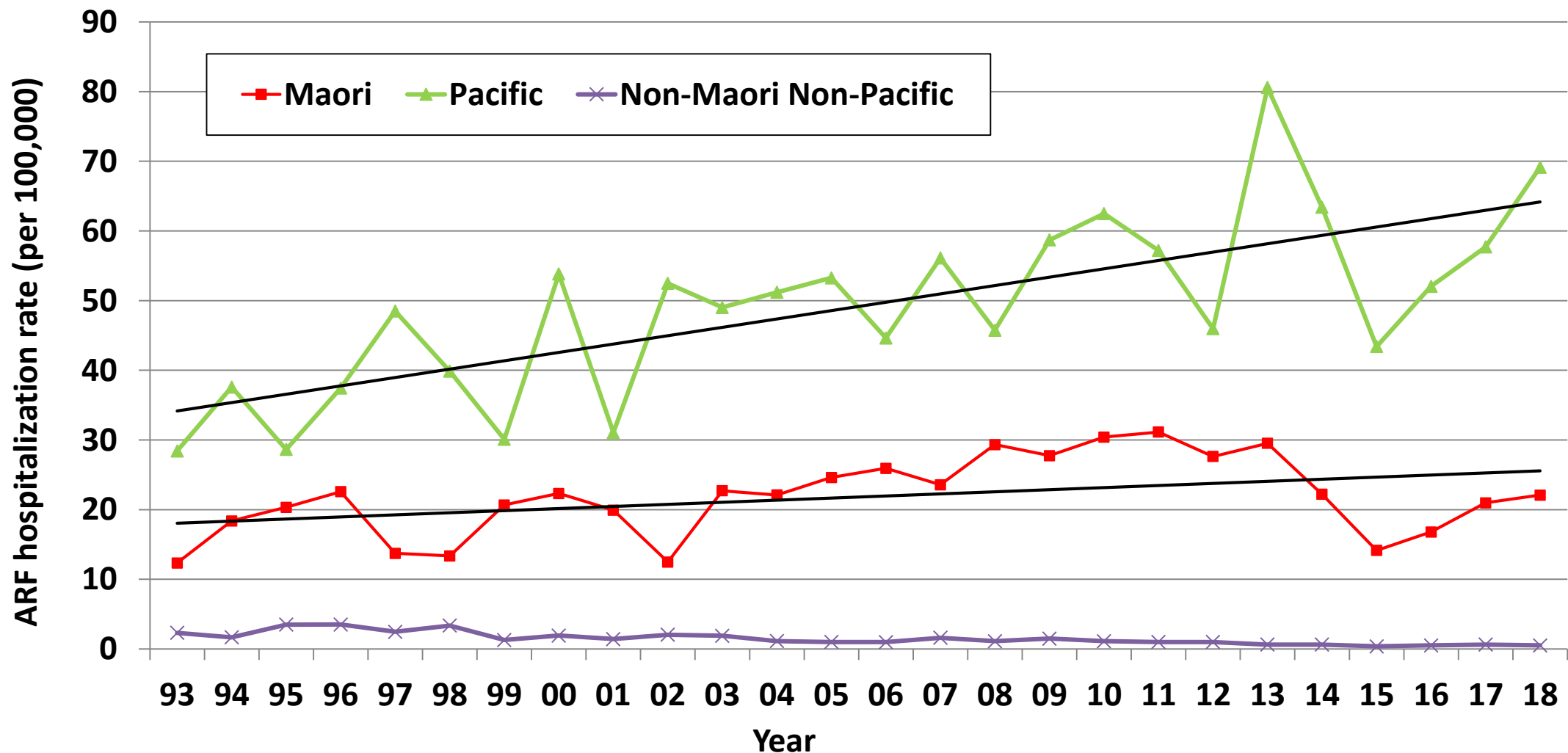
81.0% <20 years of age (10.9 per 100,000), Median age 12 years

Males 56.6% of cases



ARF incidence rate by ethnicity & year

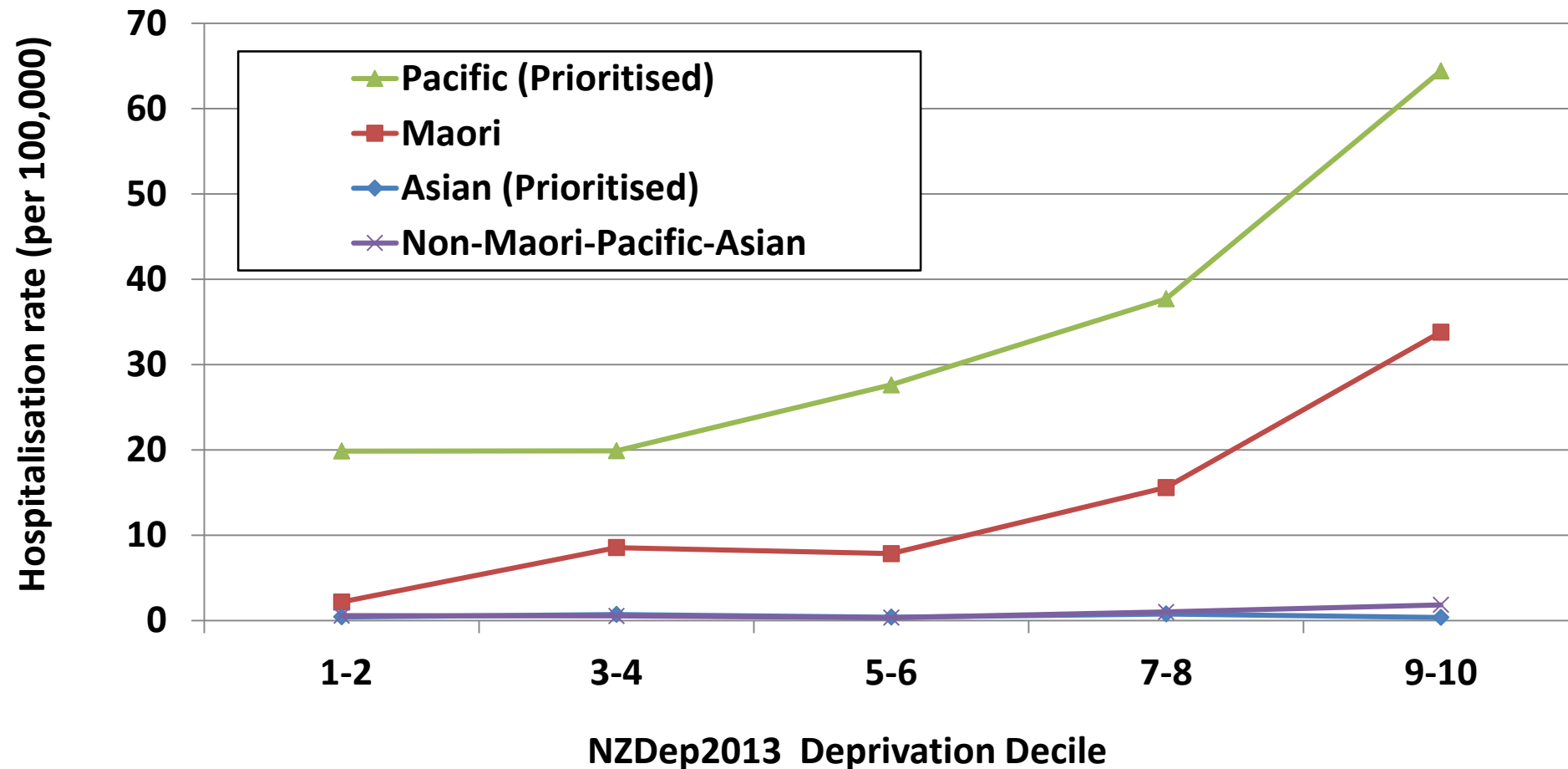
ARF incidence rate by major ethnic group & year, aged <20 years, 1993-2018



ARF incidence by ethnicity & deprivation

Incidence of ARF by ethnicity and deprivation (NZDep13)

Aged <20 years, Average annual rate, 2010-18

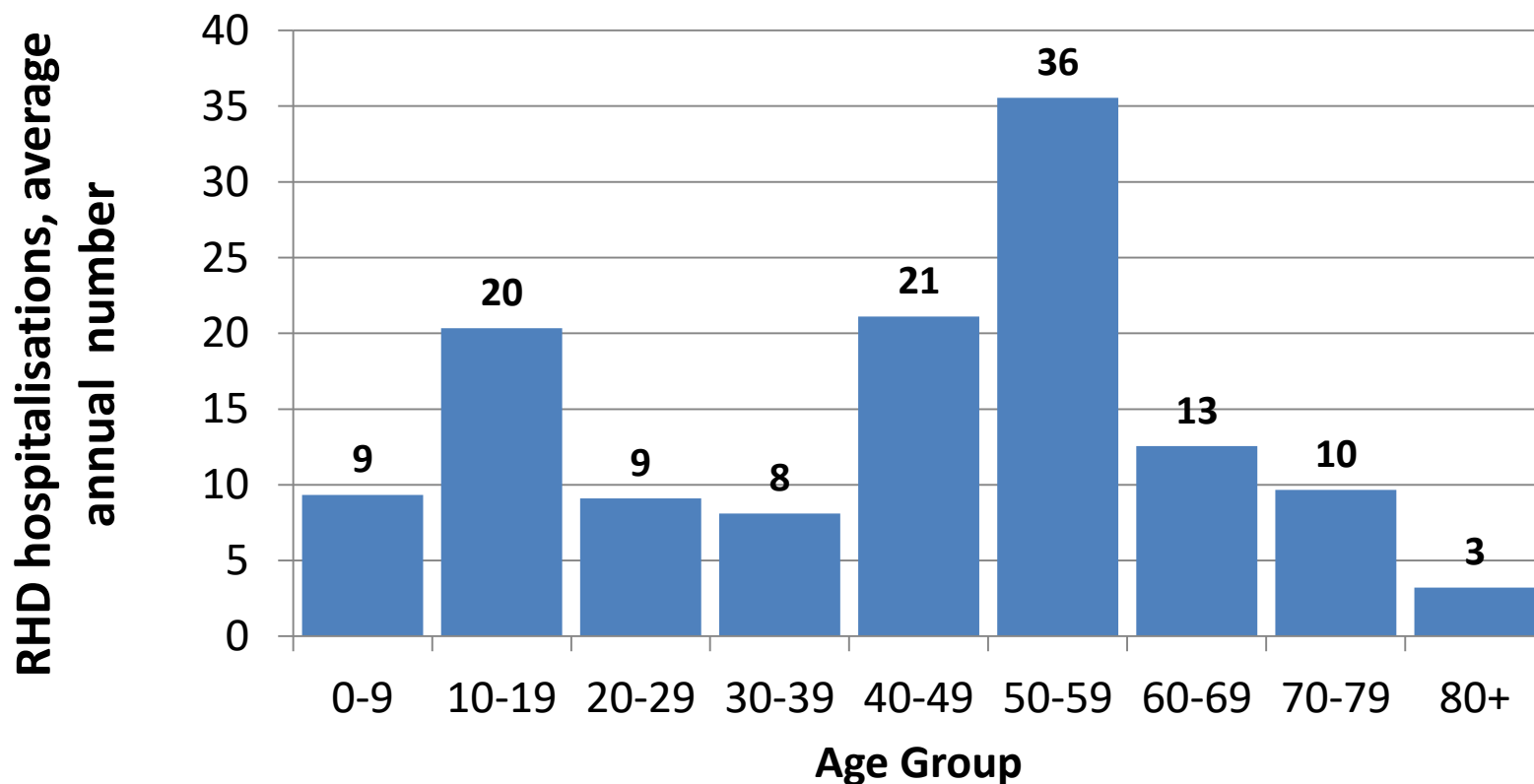


RHD hospitalisations by age group

RHD average of 129 first hospitalisations pa. 2010-18

Median age 48 years, ~ half <50 years

Males 48.4% of cases

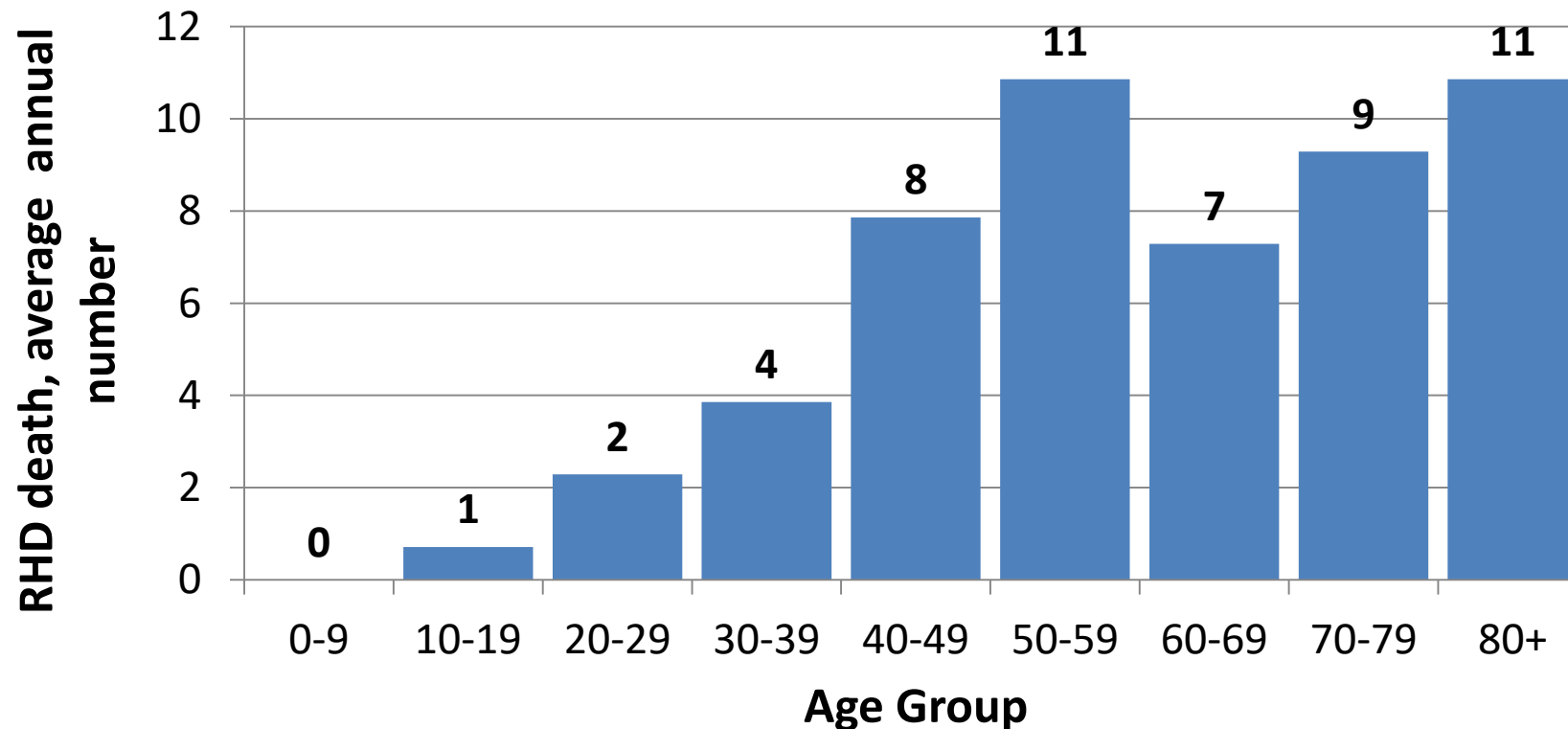


RHD Mortality by age group

Average 53 deaths pa, 2010-16

Median age 60 years, ~ half <60 years

Males 40.2% of cases





NZ RF Risk Factors Study

- **Investigators:** Michael Baker, Jason Gurney, Jane Oliver, Nikki Moreland, Deborah Williamson, Nevil Pierse, Nigel Wilson, Tony Merriman, Teuila Percival, Colleen Murray, Catherine Jackson, Richard Edwards, Lyndie Foster Page, Florina Chan Mow, Jane Zhang, Barry Gribben, Diana Lennon
- **Funding:** HRC partnership project grant (including MoH, Heart Foundation, Cure Kids)
- **Stage:** Writing-up

Goal of Risk Factors Study

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

Distal risks
factors /
Determinants



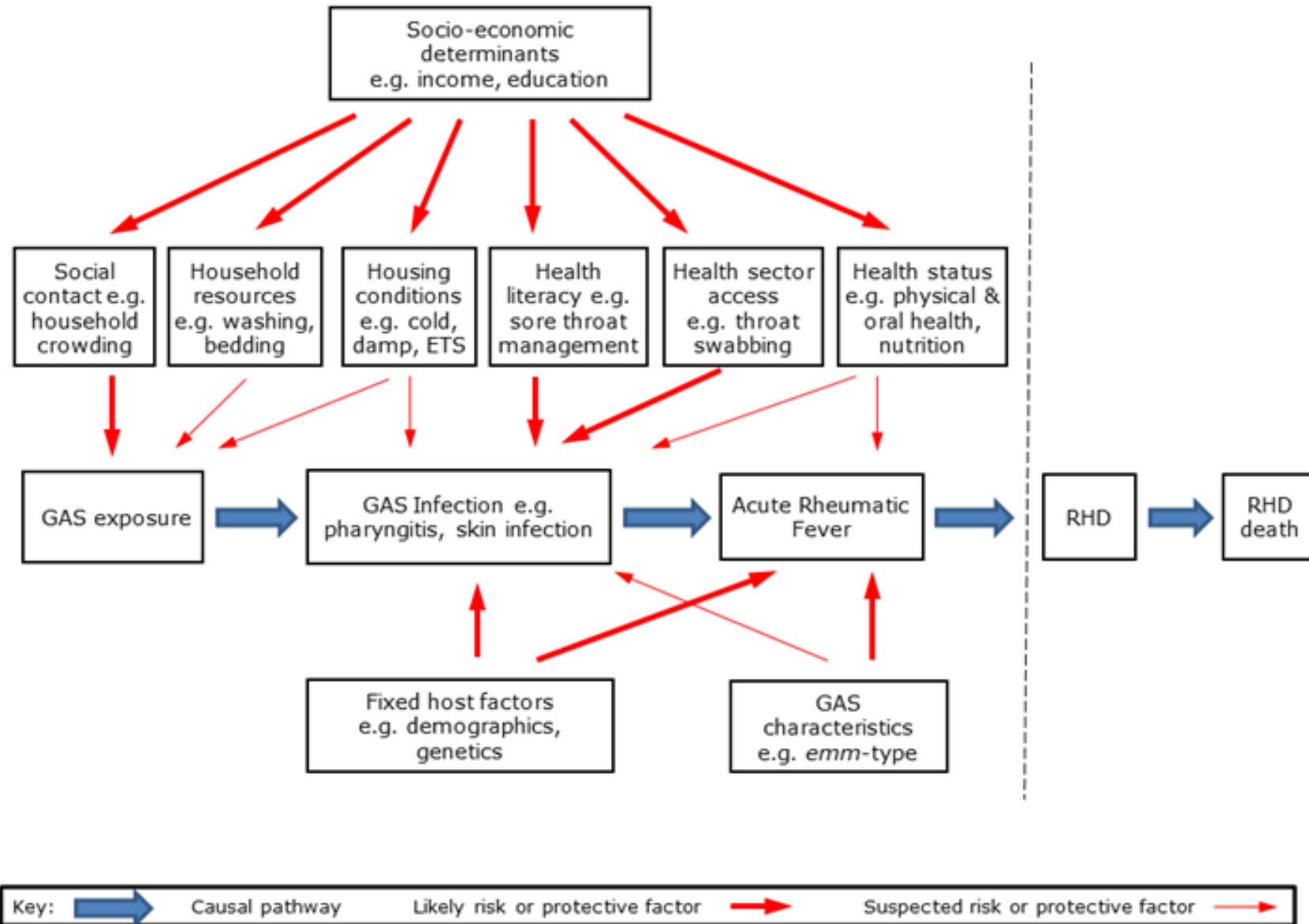
Proximal risk
factors



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
- Height, weight, BMI from clinical records (cases) or NZHS records (controls)

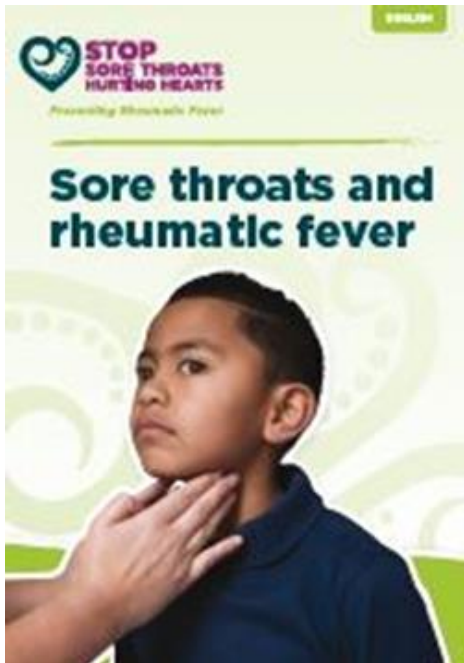
Results: Proximal exposures

**Sore throat 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	<0.0001

**Conditional = analysis of case with 3
matched controls**

**aOR = adjusted Odds Ratio,
adjusted for matching variables of
age, sex, ethnicity, deprivation, DHB**



Results: Proximal exposures

Skin infection in previous 4 weeks

Skin abscess



Skin abscess



Cellulitis



School sore



School sore



	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

Scabies

Burrows (arrows point to mites) Scabies on hand



Scabies between fingers

Scabies on hand



	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

Scabies infection without throat infection		UCL	LCL	p
Conditional aOR	7.22	0.50	105.1	0.148
Scabies infection with throat infection		UCL	LCL	p
Conditional aOR	8.41	0.55	129.6	0.127

Results: Household crowding

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

	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

ARF association with all measures of household crowding:

- Occupancy (people / house)
- Density (people / room)
- Crowding indices (CNOS)
- Self-assessed crowding

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	%
<i>Rental</i>	93	78.2	225	63.0
<i>Owned by occupant</i>	16	13.5	100	28
<i>Don't now</i>	10	8.4	32	9
Conditional aOR	3.65	1.81	7.02	0.002

Housing quality –
Association with “poor
or very poor” vs.
average or better
based on 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 & mould

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	3.57	2.15	5.93	<0.0001

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	62.0
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

Results: Nutrition - BMI

BMI

BMI	Case		Control	
	n	%	n	%
<18.5	12	10.1	94	26.3
18.5-24.9	34	28.6	150	42.0
25-29.9	31	26.1	54	15.1
30+	29	24.4	37	10.4
		UCL	LCL	p
aOR of BMI 30+	2.95	1.68	5.19	<0.0002

Results: Family History of RF

Relatives ever
diagnosed with
RF or RHD?

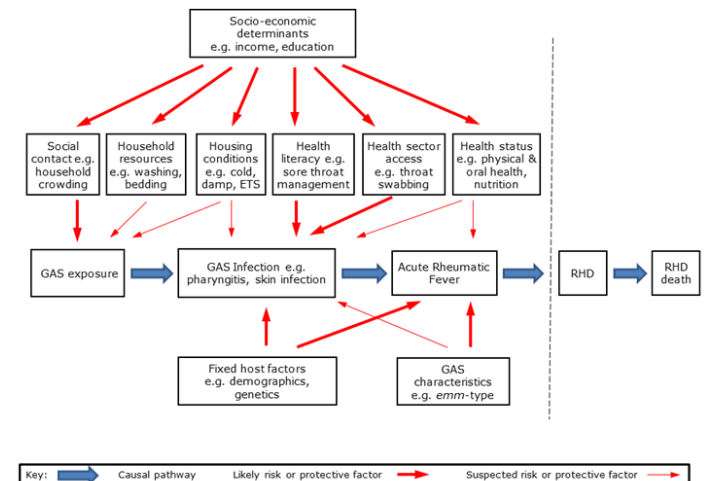
	Case		Control	
	n	%	n	%
1 or more	60	52.2	76	21.7
none	55	47.8	274	78.3
Don't Know	4	3.4	7	2.0
		UCL	LCL	p
Conditional aOR	4.22	2.57	6.94	<0.000

Results: 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

Summary of ARF risk factors

- Family history RF
- Repeated GAS exposures
 - History of multiple exposures by 5 years of age
 - ↑ Crowded housing
 - ↑ Household dampness & inadequate warm water for washing
- Role for SSB?
- Precipitating event is GAS pharyngitis & probably skin infection/scabies



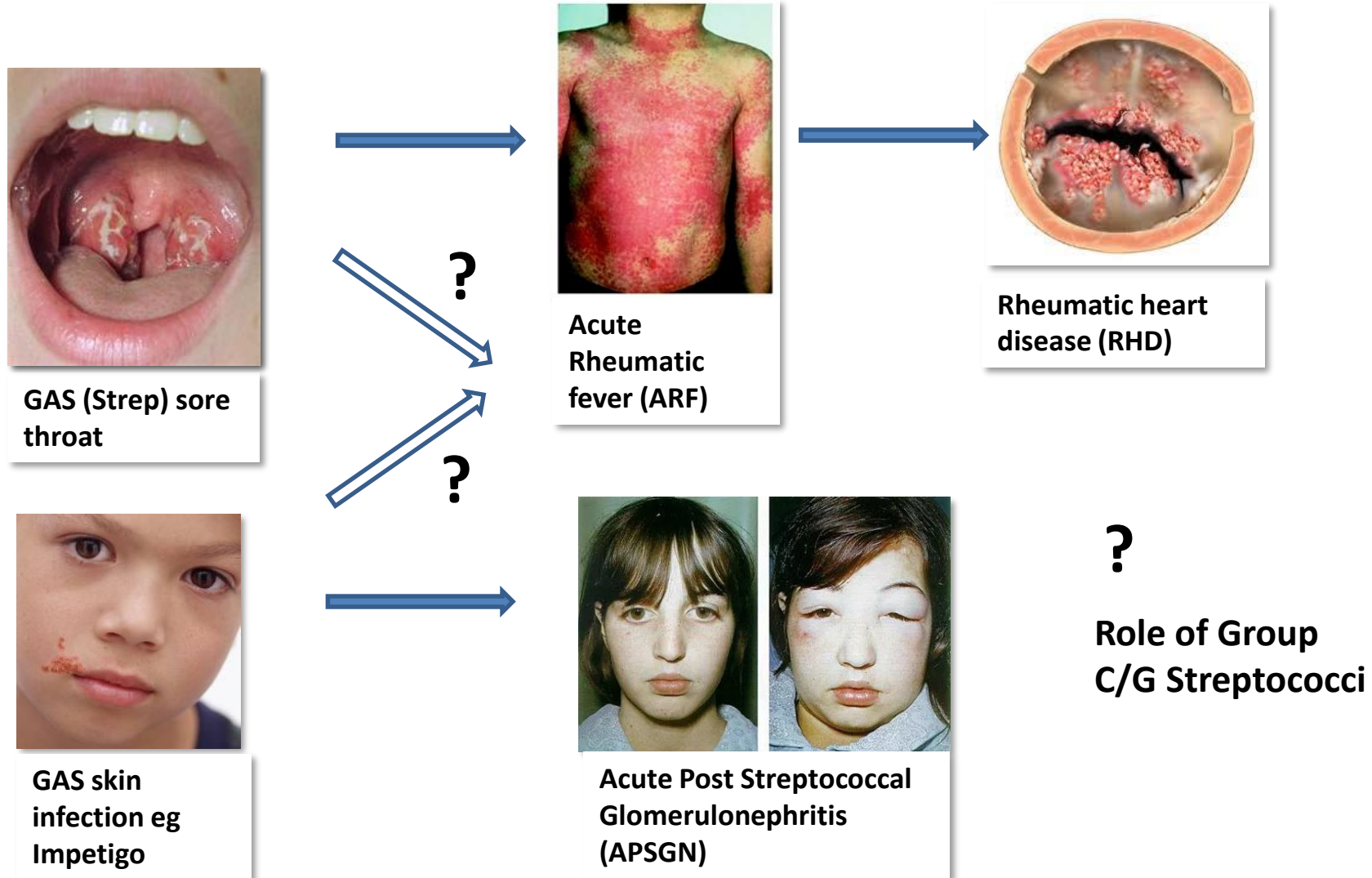


GAS skin & throat infection progression study

- **Investigators:** Michael Baker, Jane Oliver, Sally Thomas, Nikki Moreland, Deborah Williamson, Nevil Pierse, Susan Jack, Dianne Sika-Paotonu, Jane Zhang, Julie Bennett
- **Funding:** PhD scholarship (Lotteries Grant) Jane Oliver
- **Stage:** Writing-up

Role of skin infection

Conventional wisdom



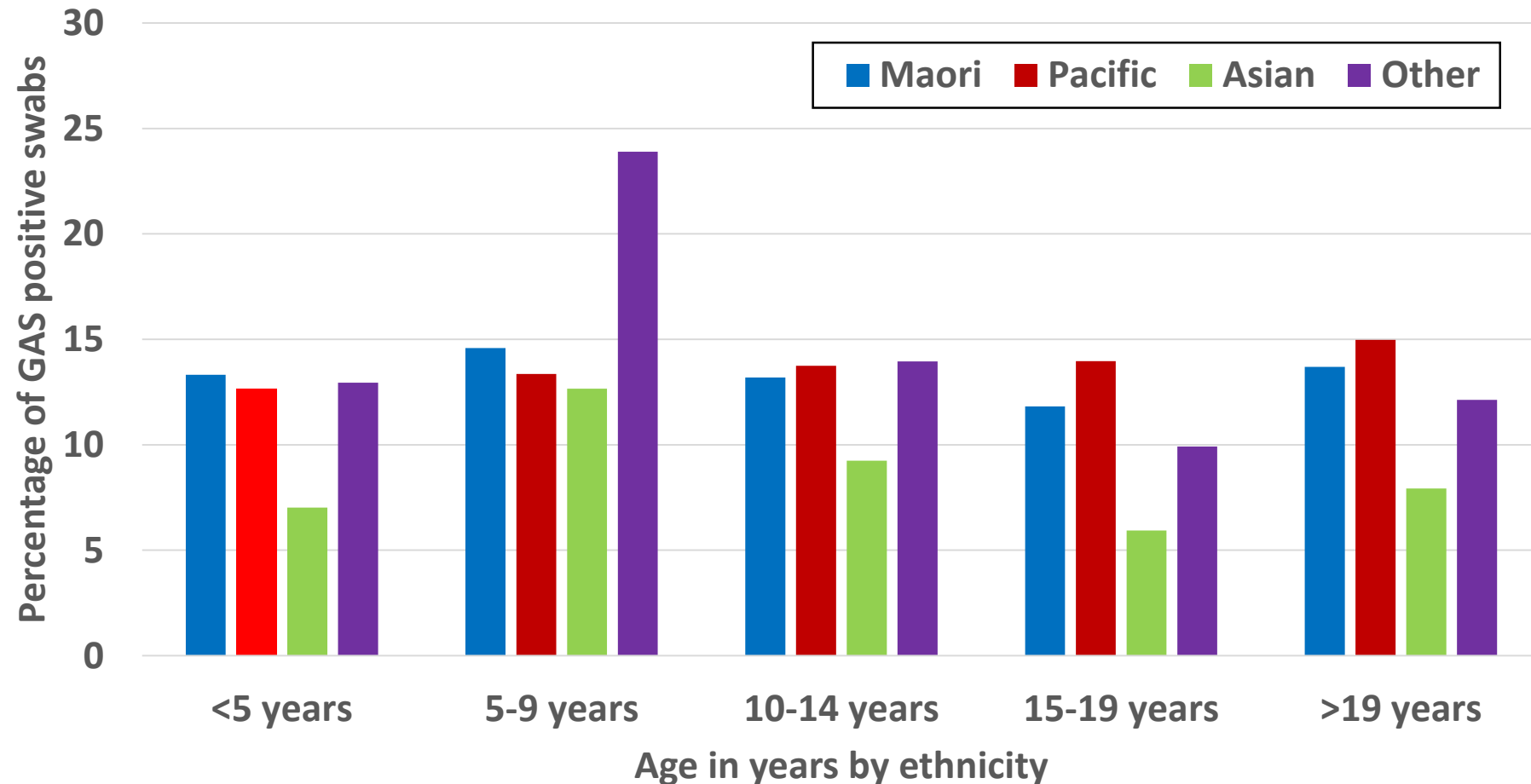
Methods

- **GAS exposure data sources**
 - Laboratory throat swab and skin swab test data from community labs (Labtests), Auckland Region (pop= 1.5 million), 2009-2017
 - Throat swabs n = 1,193,214
 - Skin swabs n = 407,744
- **Disease outcome & pharmaceutical data**
 - Hospitalisation first admissions
 - ARF (ICD.10 I00, I01, I02)
 - APSGN (ICD.10 N00, N05)
 - Pharmaceutical data for antibiotic dispensing
 - Linked to exposure using unique patient number (encrypted NHI)

GAS infection - Throat



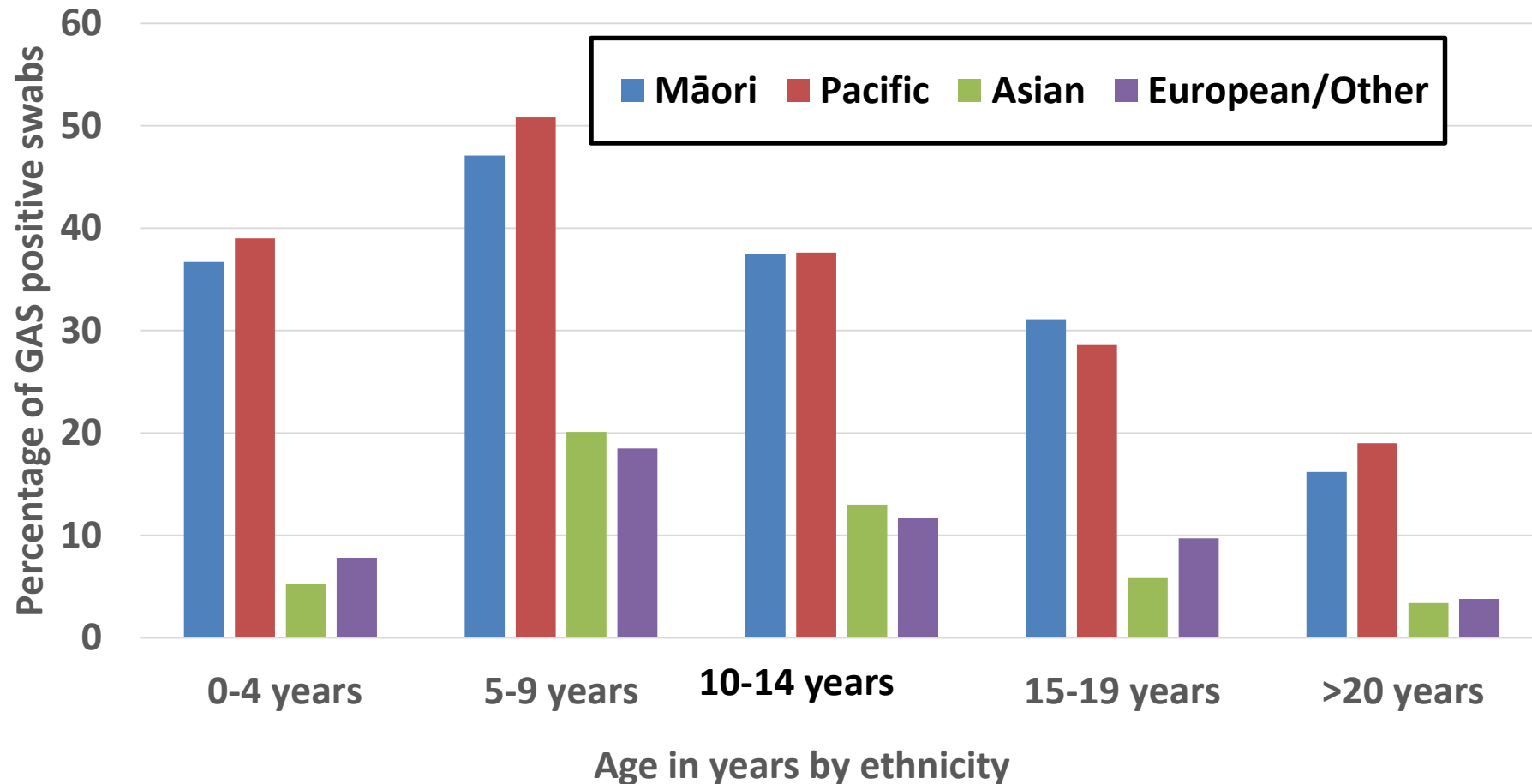
Similar proportion of GAS+ throat swabs for Māori and Pacific and European/Other, lower for Asian, Auckland 2010-17



GAS infection - Skin



Markedly higher proportion GAS+ skin swabs for Māori and Pacific compared with European/Other and Asian, Auckland 2010-17



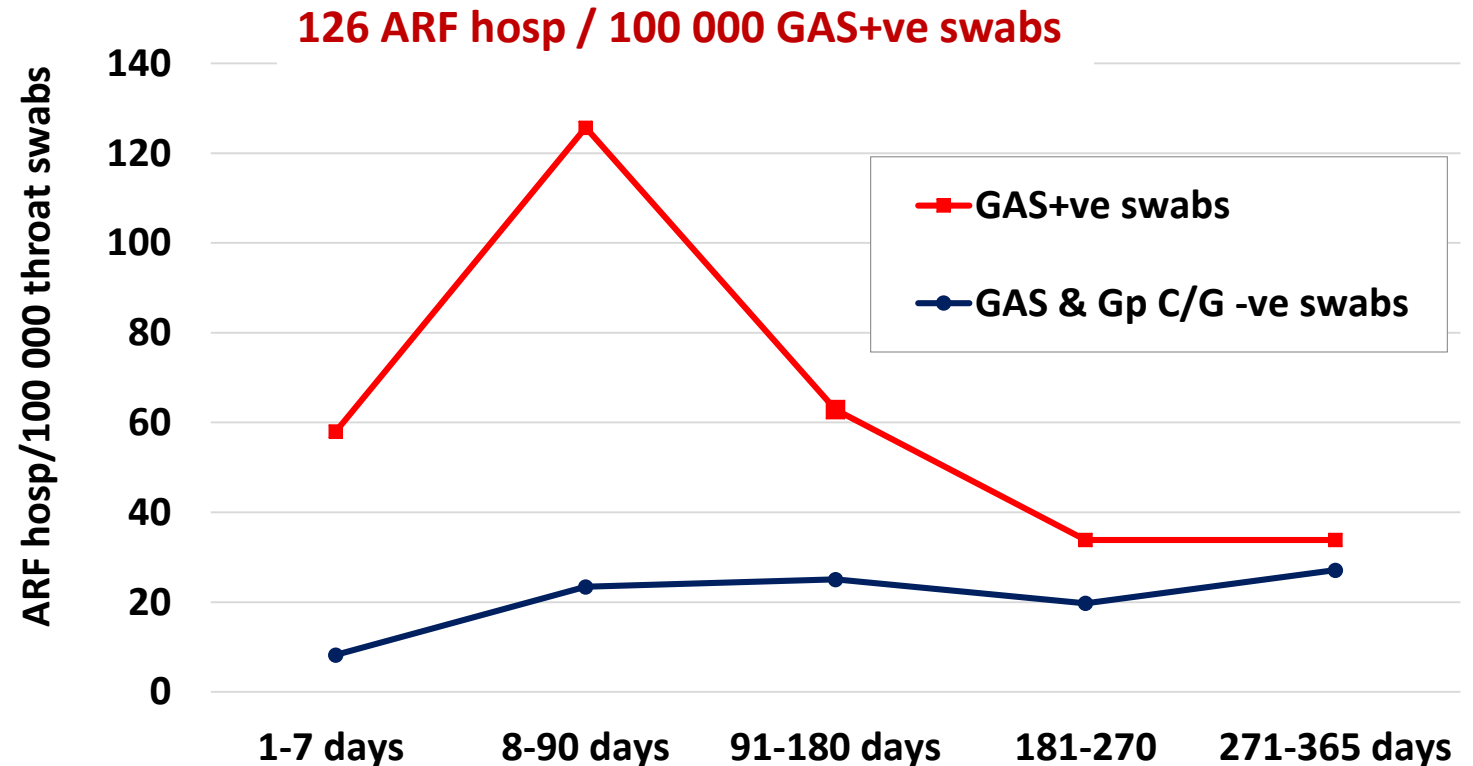
Progression GAS +ve throat swab to ARF



Children 10-19 years, ARF risk 8-90 days after GAS+ve throat swab compared with Strep-ve swab:

- Māori + Pacific: RR **5.37** (95% CI **3.69-7.82**)
- Māori 10-19yrs, 8-90 days: RR: **4.83** (95% CI **2.40-9.72**)
- Pacific 10-19yrs, 8-90 days: RR **5.57** (95% CI **3.57-8.71**)

ARF per 100,000
throat swabs by
days from
collection to ARF,
children **10-19**
years, Māori &
Pacific ethnicity,
Auckland 2010-17



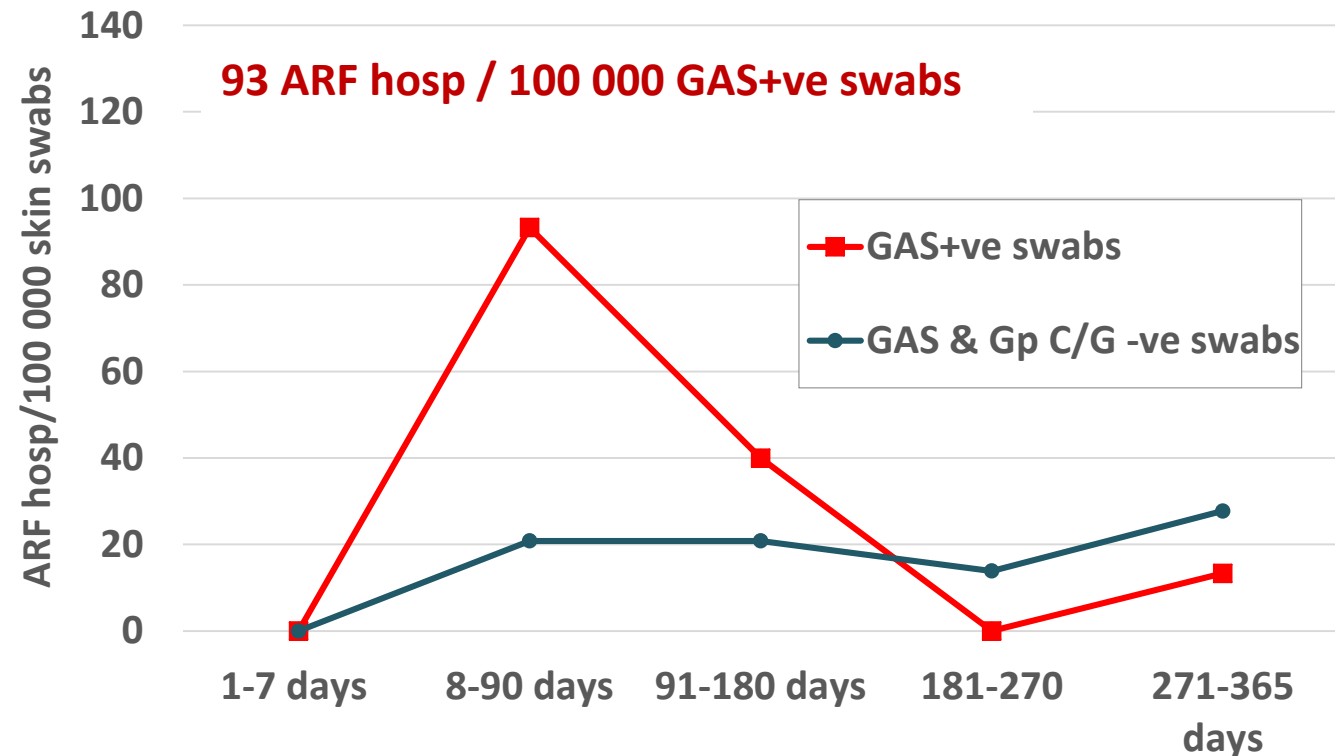
Progression GAS +ve skin swab to ARF



Children 10-19 years, ARF risk 8-90 days after GAS+ve skin swab compared with Strep-ve swabs:

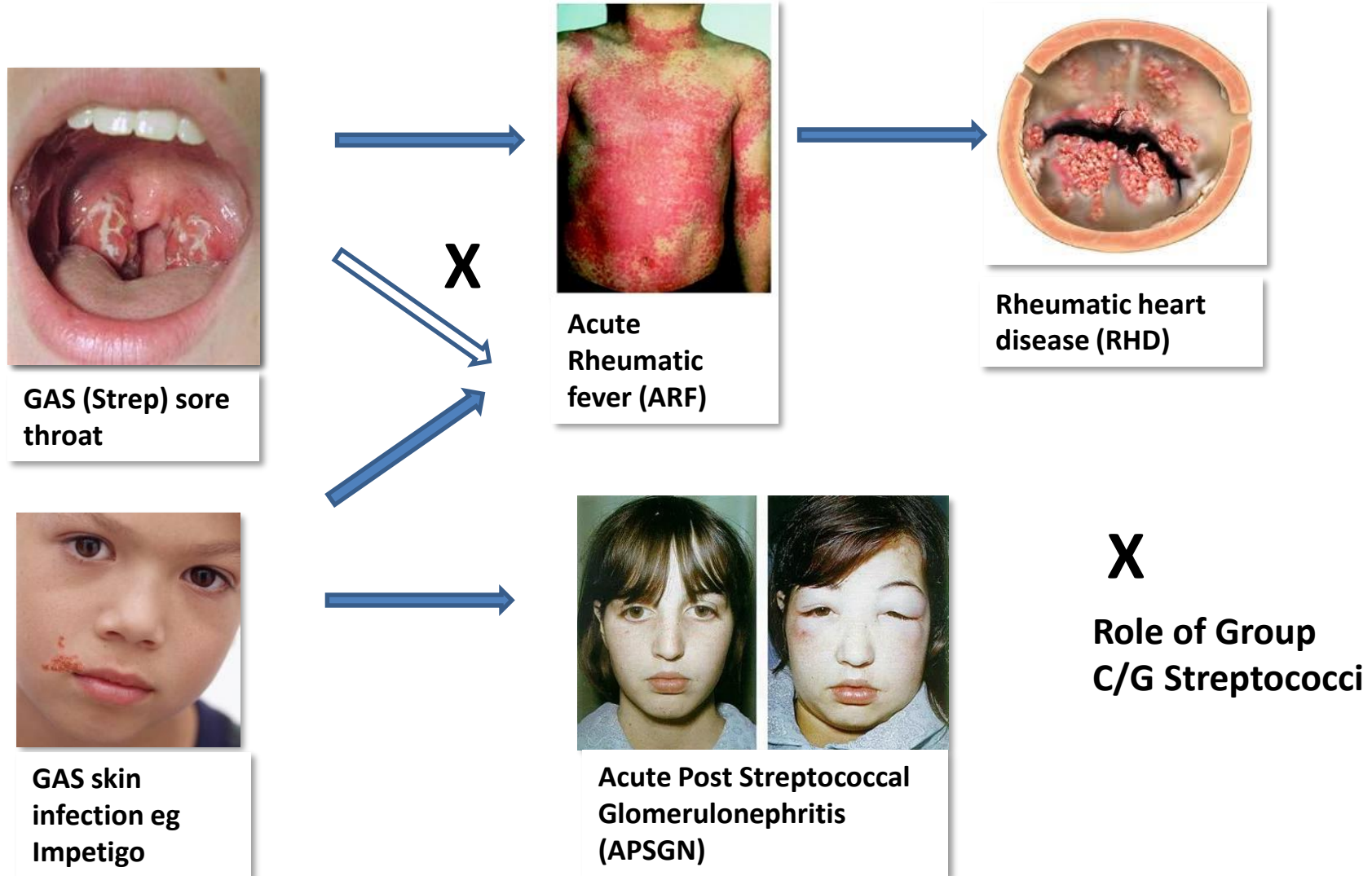
- Māori + Pacific: RR **4.48** (95% CI **1.16-17.32**)
- Māori 10-19yrs, 8-90 days: RR: not calculable - low numbers
- Pacific 10-19yrs, 8-90 days: RR: 3.89 (95% CI 0.97-15.54)

ARF per 100,000 skin swabs by days from collection to ARF, children **10-19 years**, **Māori & Pacific** ethnicity, Auckland 2010-16



Conclusions and Implications

Revised wisdom?



Summary of GAS skin & throat infection progression study

- GAS prevalence shows marked **ethnic differences** for **skin infections** (Māori & Pacific >> European/Other) but not throat
- GAS+ swabs associated with marked ↑ ARF risk in following 8-90 days for Māori and Pacific children. **Progression risk ~ 0.1% per GAS infection**

Throat: 126 ARF hosp / 100 000 GAS swabs

Skin: 93 ARF hosp / 100 000 GAS swabs

- Oral antibiotic dispensing **not** associated with reduced risk of ARF progression following GAS+ throat swab



Understanding GAS pharyngitis & skin infections as causes of ARF

- **Investigators:** Julie Bennett, Nicole Moreland, Jane Oliver, Julian Crane, Deborah A. Williamson, Dianne Sika-Paotonu, Matire Harwood, Arlo Upton, Susan Smith, Jonathan Carapetis, Michael Baker
- **Funding:** HRC project grant
- **Stage:** Data collection

GAS infection study methods

- **Prospective disease incidence study**, with case-control study
- Subjects: 1000 children, 5–14 years, Auckland
- **800 visited healthcare** → throat or skin swab for GAS
 - GAS throat swab positive pharyngitis (n = 200)
 - GAS carriage (n = 200)
 - GAS negative throat swab (n = 200)
 - GAS skin infections (n = 200)Testing: acute and convalescent ASO/ADB titres, viral PCR
- **200 asymptomatic**
Testing: single ASO/ADB titres, and a throat swab for microbial culture
- Caregivers interviewed using a questionnaire
- GAS isolates identified will be *emm* typed

GAS infection study **provisional incomplete** results

Children who had **throat GAS positive** cultures (N=327)

- **70% sero-conversion** (18% true - 2 fold increase, 52% probable - raised ULN)
- 30% carriers

Children who had a **skin GAS positive** culture (N=121)

- **71% sero-conversion** (11% true - 2 fold increase, 60% probable - raised ULN)
 - 12% of GAS positive skin children also had a GAS positive throat swab
 - All of those in the GAS positive skin swab group that had a positive GAS throat swab had sero-conversion

Conclusions

- GAS skin infections, in addition to throat infections, may initiate the immune response causing ARF, based on:
 - Similar immune response to throat infections
 - Similar risk of progression to ARF
 - Epidemiology, with high prevalence in Māori and Pacific children
- Self reported scabies infections also associated with ARF
- Also potential role for GAS skin infections in priming for ARF

Implications for reducing ARF/RHD

Improve
housing
environment



Distal risks
factors /
Determinants



Improve GAS
infection
treatment



Proximal risk
factors



Improve
management
of ARF cases



ARF/RHD



Interventions to reduce RF

1. Sustained improvement in the home environment of children

- **Reduce household crowding** - adequate supply of affordable, suitable housing eg construction of social housing & increased security of tenure
- **Reduce bed sharing by children** – a ‘bed for every child’
- **Sustained improvement in housing quality** - reduce damp & mould, insulation & heating, housing warrant of fitness, well homes programme
- **Address fuel poverty** – to reduce costs of home & water heating

Future Interventions to reduce RF

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

- **Intensive targeted approach** - based on family history of RF, ethnicity, ancestry, age
- **Injectable penicillin** - for sore throats in high risk groups
- **Focus on skin infection** – in high risk groups eg Māori & Pacific children <15 years
- **Focus on scabies** - Systematic approach to scabies treatment/elimination



Efficacy of mass drug administration with ivermectin for control of scabies and impetigo, with coadministration of azithromycin: a single-arm community intervention trial



Lucia Romaní, Michael Marks, Oliver Sokana, Titus Nasí, Bakaal Kamariki, Billie Cordell, Handan Wand, Margot J Whitfield, Daniel Engelman, Anthony W Solomon, John M Kaldor, Andrew C Steer

Summary

Lancet Infect Dis 2019;
19: S10-18
Published Online

Background In small community-based trials, mass drug administration of ivermectin has been shown to substantially decrease the prevalence of both scabies and secondary impetigo; however, their effect at large scale is untested. Additionally, combined mass administration of drugs for two or more neglected diseases has potential practical



Future Interventions to reduce RF

3. Integrated approach to Improve management of children with ARF

- Better diagnosis
- Improved tracking, and delivery of Benzathine Penicillin G (BPG)
- Establish national ARF/RHD register



Future Interventions to reduce RF

4. Integrated, community-focussed approach to designing & implementing future intervention

- Evidence-informed
- Co-designed
- Integrated delivery
- Evaluated
- Supported by sector

New Zealand Acute Rheumatic Fever and
Rheumatic Heart Disease Network



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
- **START Study (Aust. NHMRC)** – Improve ARF diagnostics
- **Strep A vaccine (International)** – Continue collaboration
- **Consider trial of intensive targeted intervention for high risk populations** – Screening questions, more intensive management (including skin infection, scabies)

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- Multiple collaborators



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- Laboratory staff in Lab tests (Auckland), Southern Community Laboratories (Wellington), DHBs, and ESR who have assisted with specimen collection, processing and testing;
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- Participating children and their families for assisting with interviews and testing.