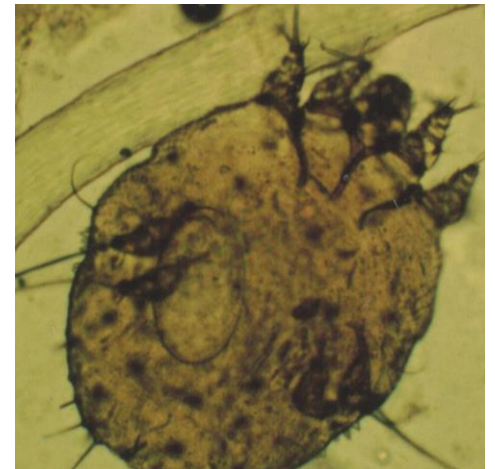


Why is scabies a likely cause of acute rheumatic fever?

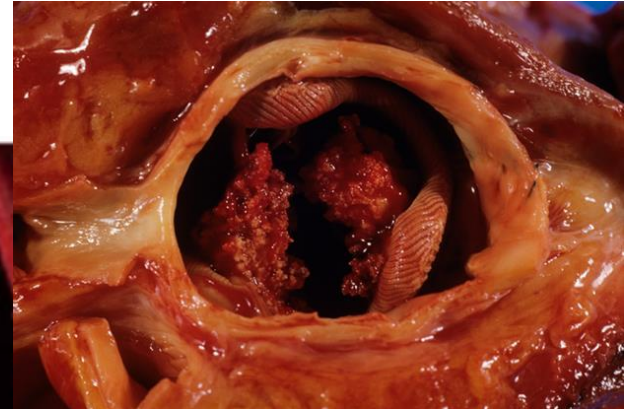
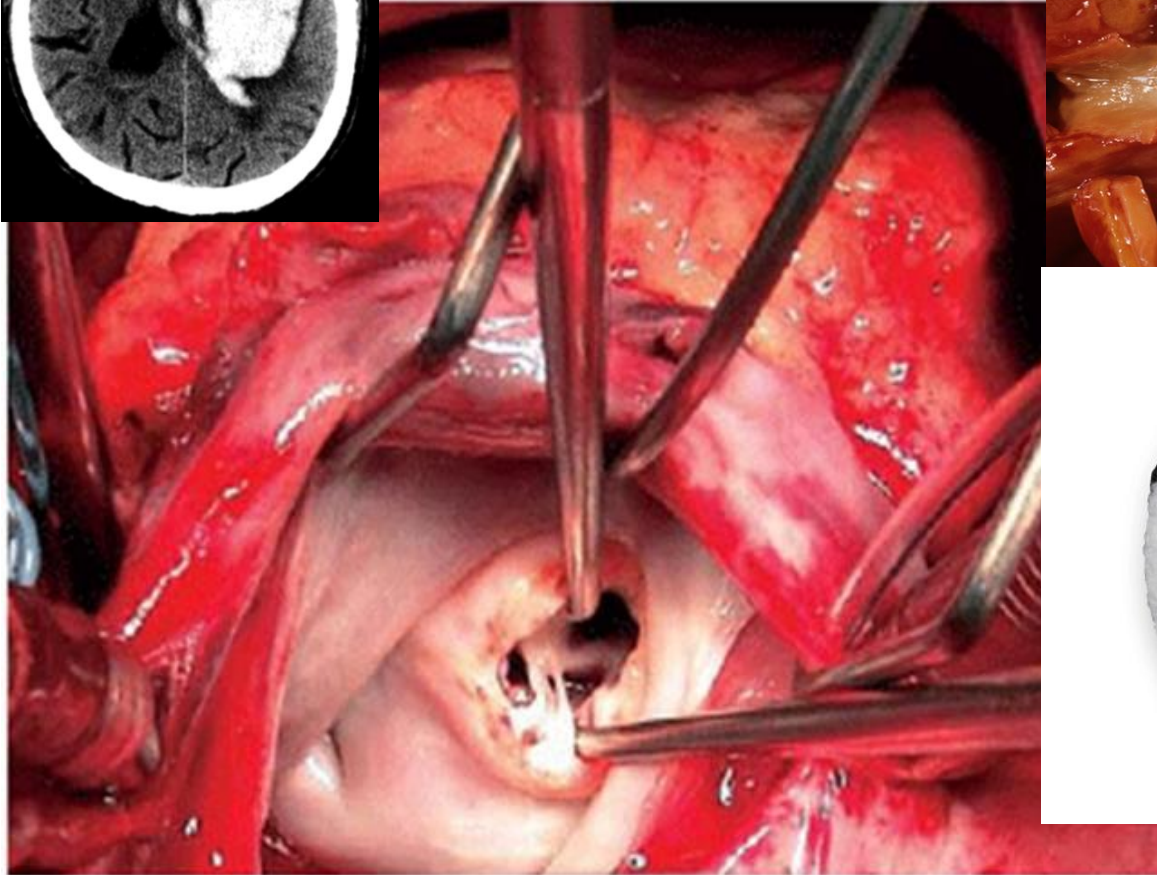
Simon Thornley



Summary

- Introduction – why is ARF important?
- What is the cause of ARF?
- How did I get interested in scabies?
- Could scabies be a cause?
- Geographic relationship
- Results?

Sequela of ARF



A costly disease...

- *The average annual DRG-based cost of hospitalisations for ARF/RHD across all age groups (2000-2009) was **\$12 million**, with heart surgery accounting for 71% of the cost.*

Milne, Richard J., et al. "Mortality and hospitalisation costs of rheumatic fever and rheumatic heart disease in New Zealand." *Journal of Paediatrics and Child Health* 48.8 (2012): 692-697.

The problem...

Middlemore Hospital overflowing with patients

SAMANTHA SMITH

Last updated 10:49, March 22 2016



Jarred Williamson

Middlemore Hospital is treating more than 2000 patients each week - unheard of for this time of year.

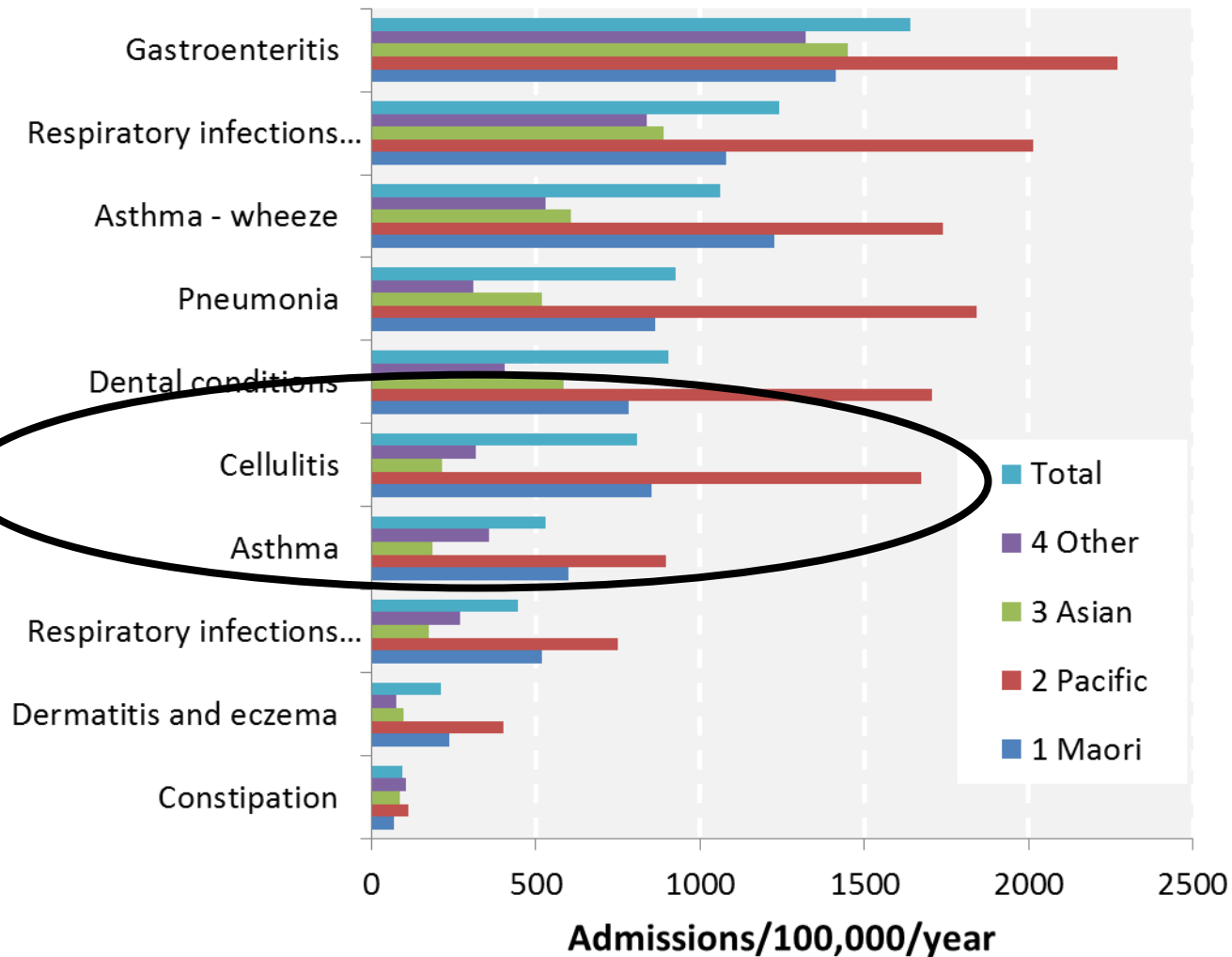
Middlemore Hospital is already bursting at the seams and it's not even winter.

Last week the hospital was at 106 per cent capacity while today it was at 108 per cent.

Emergency Care had 320 patients through in one day last week and staff are expecting that to climb to 350 with an average of 104 patients admitted.

Simon...
*sort it
out...!!!*

Preventable hospital visits (0 to 4 years)



Skin infection characteristics

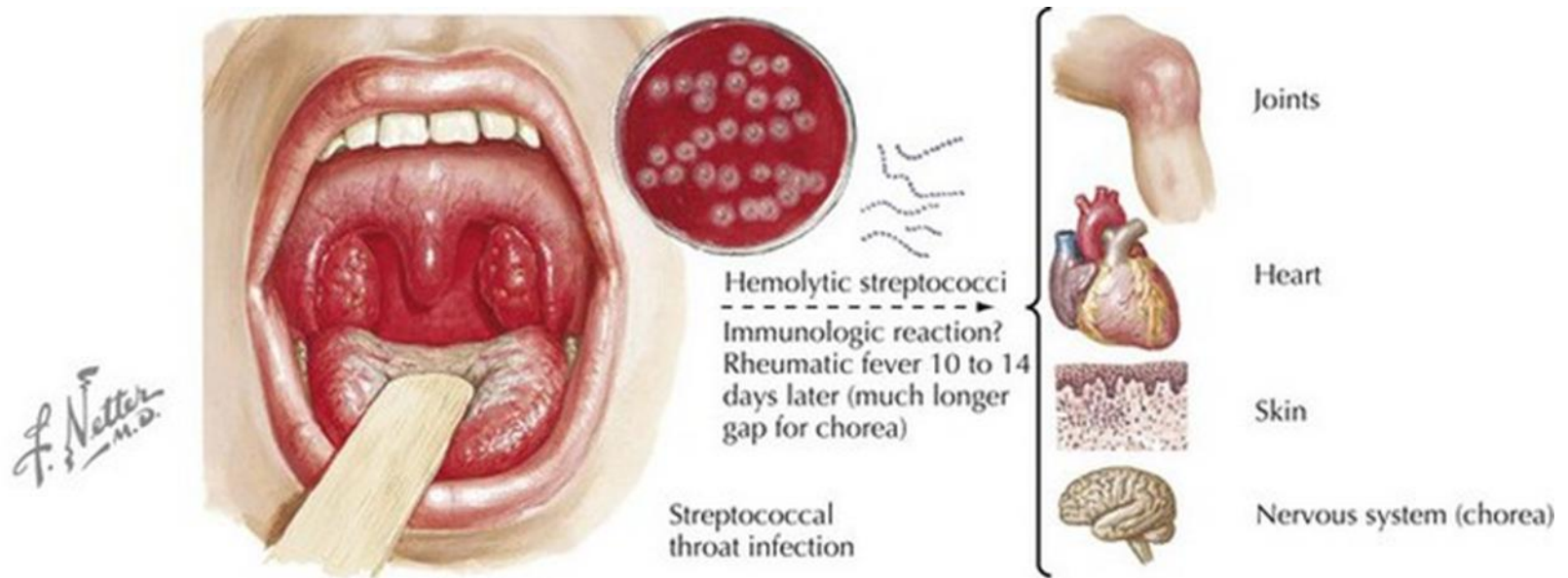
- 1/3 diabetes
- By ethnicity
 - 37% Pacific (pop: 23%)
 - 25% Māori (pop: 16%)
 - 31% European or Other (38%)

Scabies treatment in South Ak

- 8,000 treatments/year
 - **3%** Māori and Pacific
 - **0.3%** European and Other
- Mainly pre-schoolers
- Majority of treatment permethrin
 - little ivermectin use
- 60% in decile 9 and 10 areas (Māngere & Otara)
- 15% repeat script in a year

Is scabies the cause of ARF?

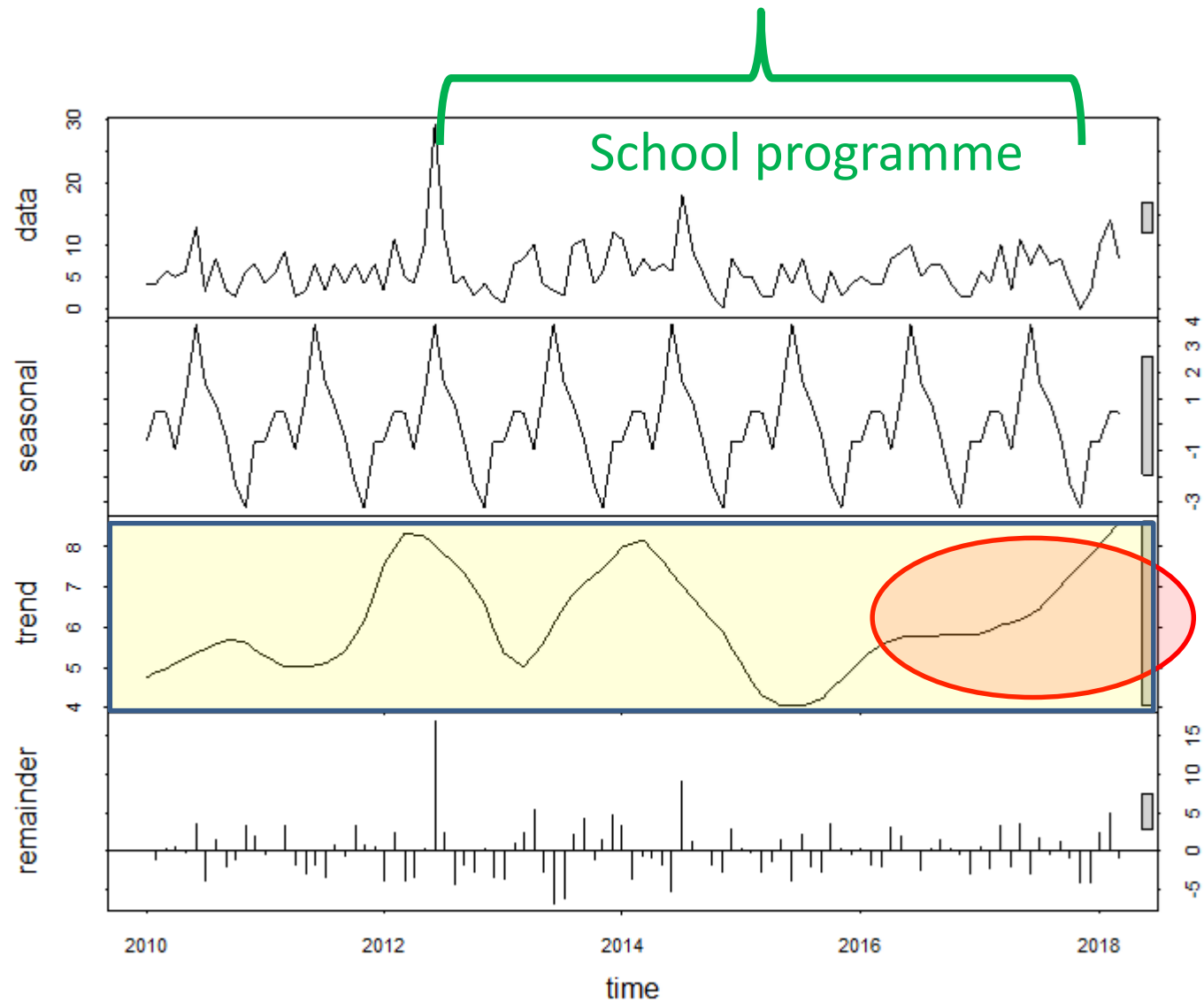
- Traditional theory – all about strep. throat.



What do we know about ARF?

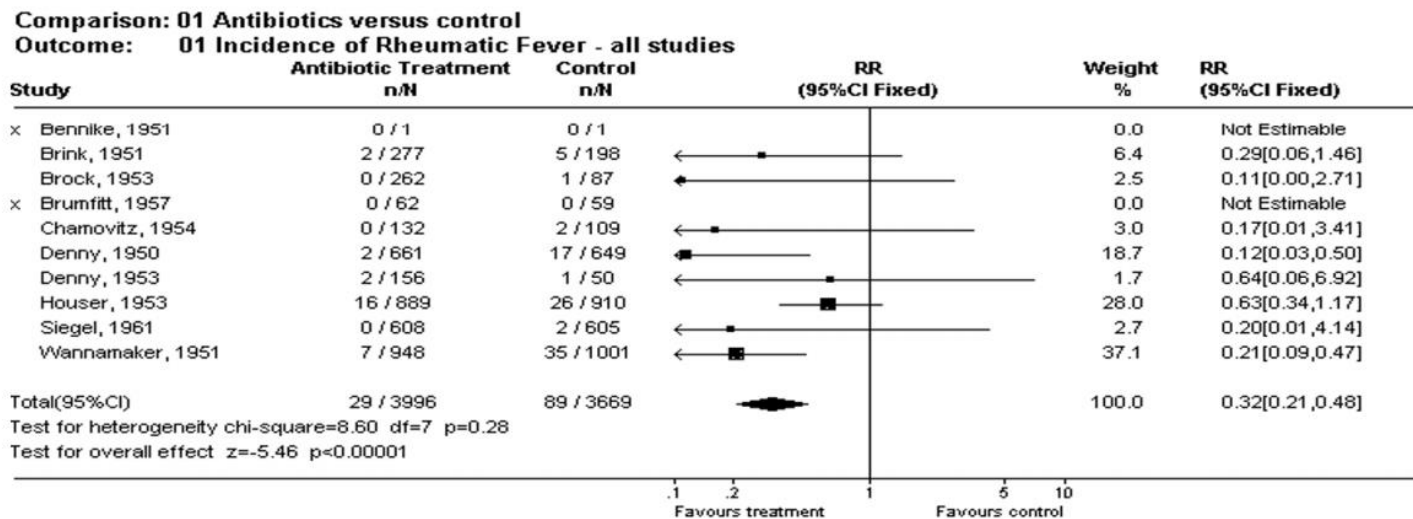
- Almost exclusively disease of Māori and Pacific children.
- Linked to streptococcal sore throat infection
- Clustered in families, associated with overcrowding & poverty
- Many cases also have bacterial skin infection
- Diagnostic criteria based on evidence of strep infection and clinical features.

STL... Trends in Auckland...



All about penicillin?

- Generally, based on the idea that treating with penicillin reduced the incidence of rheumatic fever



Notice, incidence of rheumatic fever an order of magnitude higher than present day.
 No positive trials since 60s. Almost all trials conducted in military barracks.

How effective is throat swabbing?

- Cluster RCT school based GAS throat infection programme
 - 24 (55/100,000) cases occurred in clinic schools and 29 (67/100,000) in non-clinic schools, a 21% reduction when adjusted for demography and study design ($P= 0.47$)
 - 14/22 cases had sore throats, 10 had throat swabs and 5 were positive
 - Cases in treatment group classified as “*swab or penicillin failure*”

Lennon, Diana, et al. "School-based prevention of acute rheumatic fever: a group randomized trial in New Zealand." *The Pediatric infectious disease journal* 28.9 (2009): 787-794.

Chinks in GAS throat → ARF theory

- Many cases of ARF do not have sore throat
- Sore throat not part of diagnostic criteria
- Some populations have low rates of GAS in throat, but highest rates of ARF in world.
- School programme, based on treating sore throats, resulted in no difference and many “treatment failures” and “swabbing failures”
- No apparent relationship between GAS and ARF epidemiology

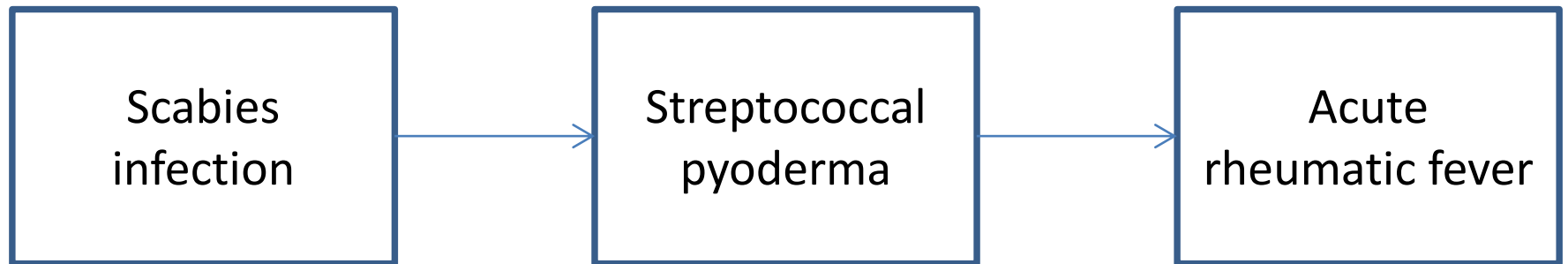
Is scabies the cause of ARF?

- Traditional theory – all about strep. throat.
- Cohort study shows very strong (crude HR = 27; adj. HR = 9) association between diagnosis in hospital
- Prof. Michael Baker shows strong association between self-reported scabies and ARF (photos)
 - However, only 5% of cases have scabies.

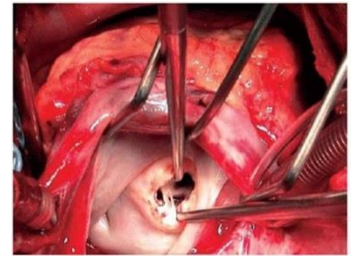
Scabies

- Known cause of post-streptococcal GN, cellulitis (strep) and abscess (staph).
- Highest prevalence region in world is Pacific
- Known to be difficult to diagnose, even for dermatologists.
- Almost exclusively treated with permethrin in NZ

Hypothesis



Cohort study



3 to 12 years;
 $n = 213,957$

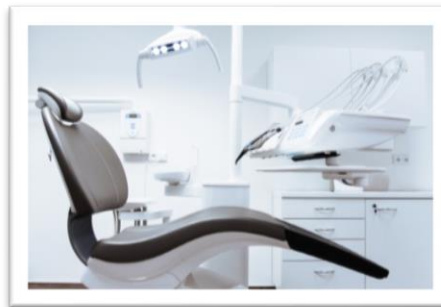
Mean 5.1 years follow-up

Rheumatic
fever in
hospital; $n =$
440

Scabies in
hospital

First dental exam

Scabies in
hospital



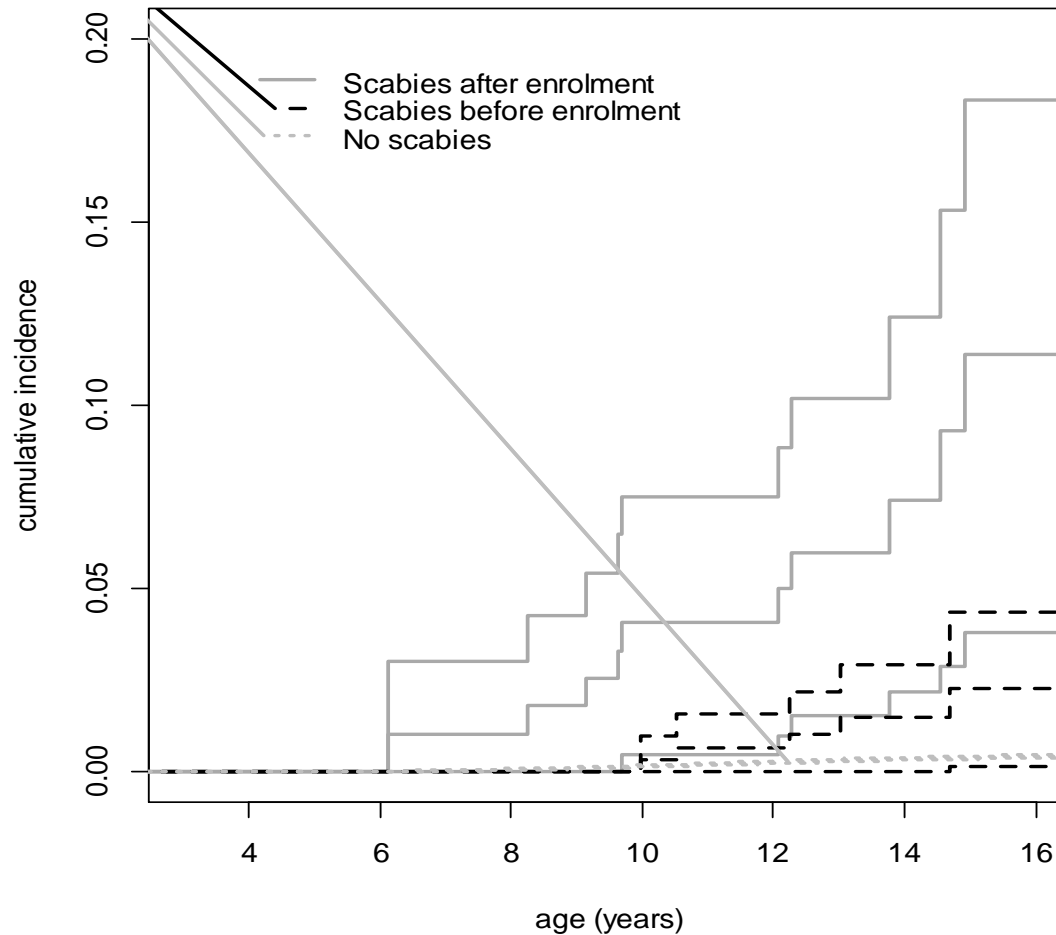
$n = 624$

Confounders

Age, gender, ethnicity,
SES, rotten teeth

$n = 214$

KM Plot



Scabies after
enrolment
Cum. Inc. =
12%!

No scabies,
cum. incidence
very low

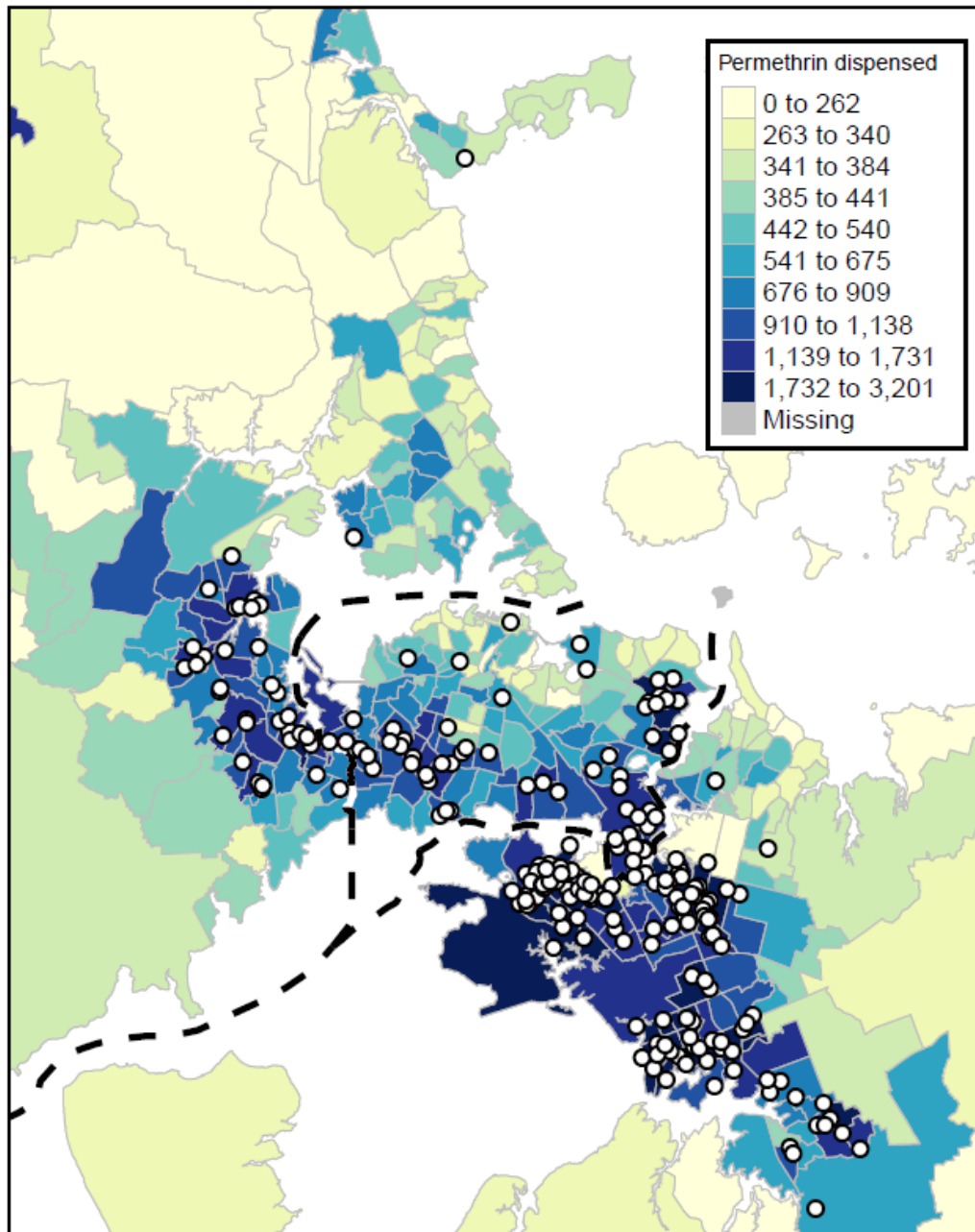
Cox regression

Risk factors	Crude HR (95% CI)	Adjusted† HR (95% CI)
Ethnicity (ref: NZ European and Other)		
Pacific	34.9 (23.3 to 52.2)	20.0 (13.1 to 30.6)
Māori	21.1 (13.9 to 32.1)	14.4 (9.35 to 22.1)
Deprived (deciles 9 and 10 vs. other)	7.08 (5.77 to 8.69)	2.23 (1.80 to 2.77)
Scabies (ref: No scabies diagnosis)		
Diagnosis before enrolment only	11.3 (6.33 to 20.2)	1.64 (0.68 to 3.97)
Diagnosis after enrolment	26.0 (14.2 to 47.4)	8.98 (4.79 to 16.8)
Total caries (per 4 affected teeth)‡	1.76 (1.59 to 1.94)	1.26 (1.12 to 1.42)

**800%
increase
in risk**

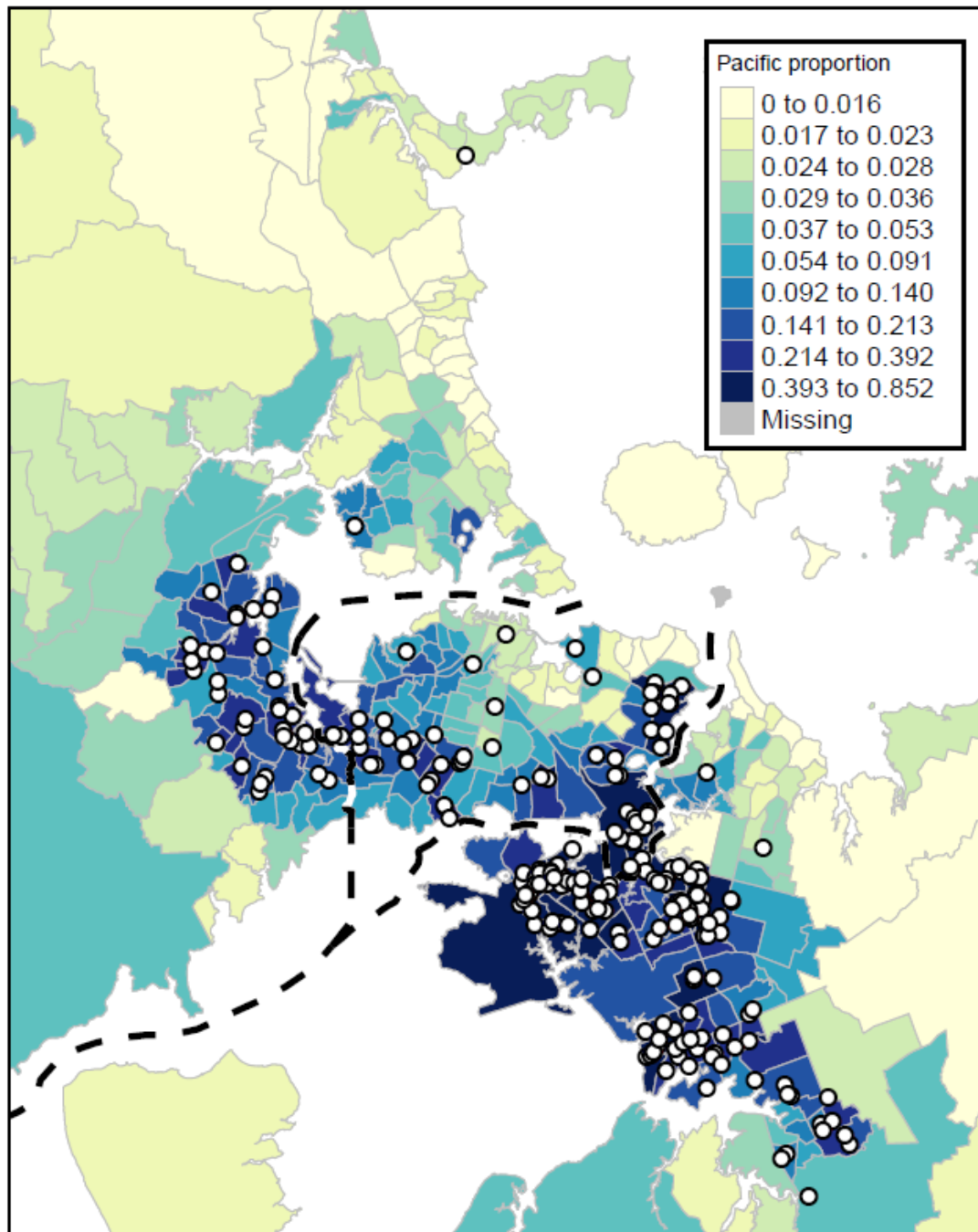
Geographic association?

- What is geographic association between prescribing for permethrin and ARF?
- **Population** - Auckland
- **Exposure** – dispensing of permethrin by CAU (rate/100,000/year; Pharms)
- **Outcome** – incidence of ARF (rate/100,000/year; Episurv)
- **Confounders** – Māori/Pacific/SES



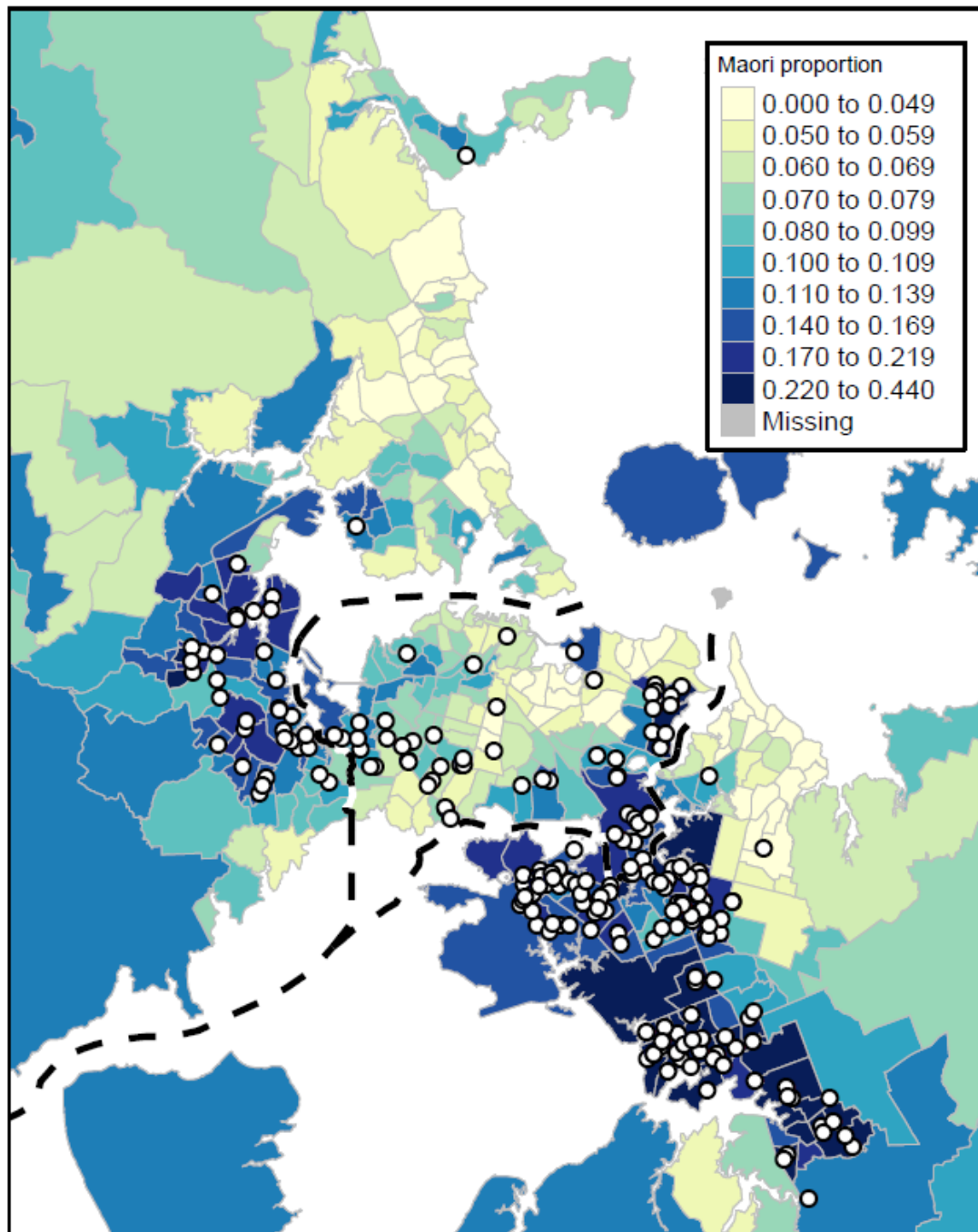
Permethrin
& ARF

Convinced?



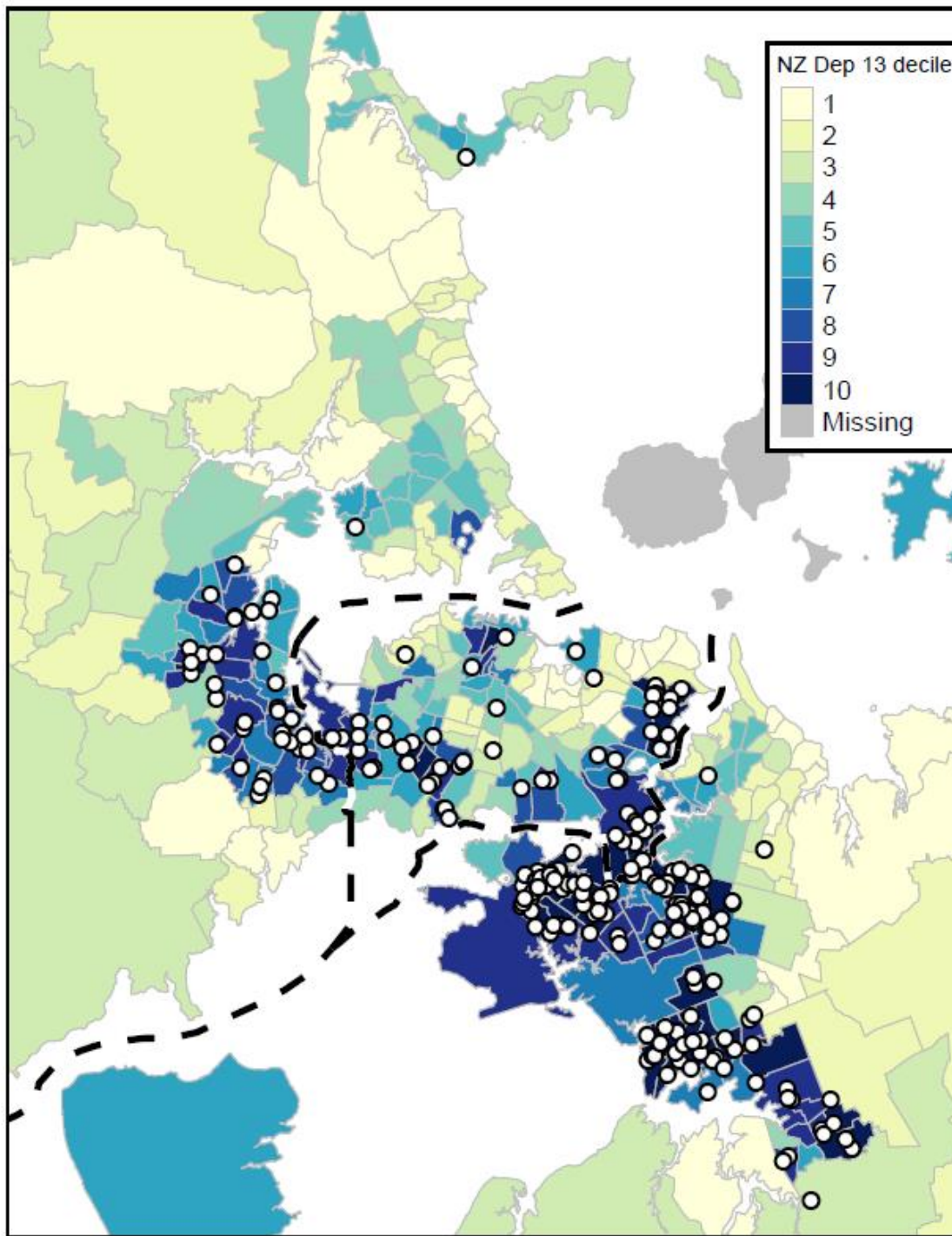
Pacific &
ARF

Convinced?



Māori &
ARF

Convinced?



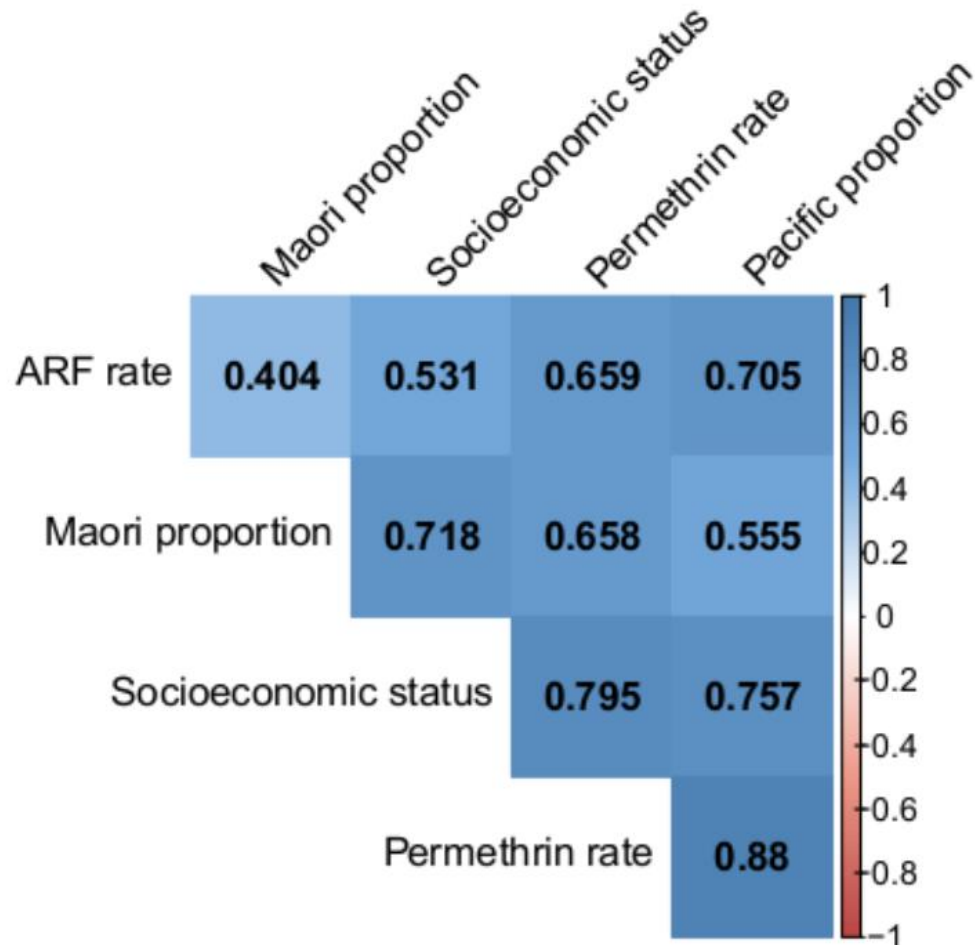
Poverty &
ARF

Convinced?

https://sithor.shinyapps.io/Regression_example_permethrin_rheumatic_fever/

How to make sense of this?
Regression to the rescue!

Collinearity is high!

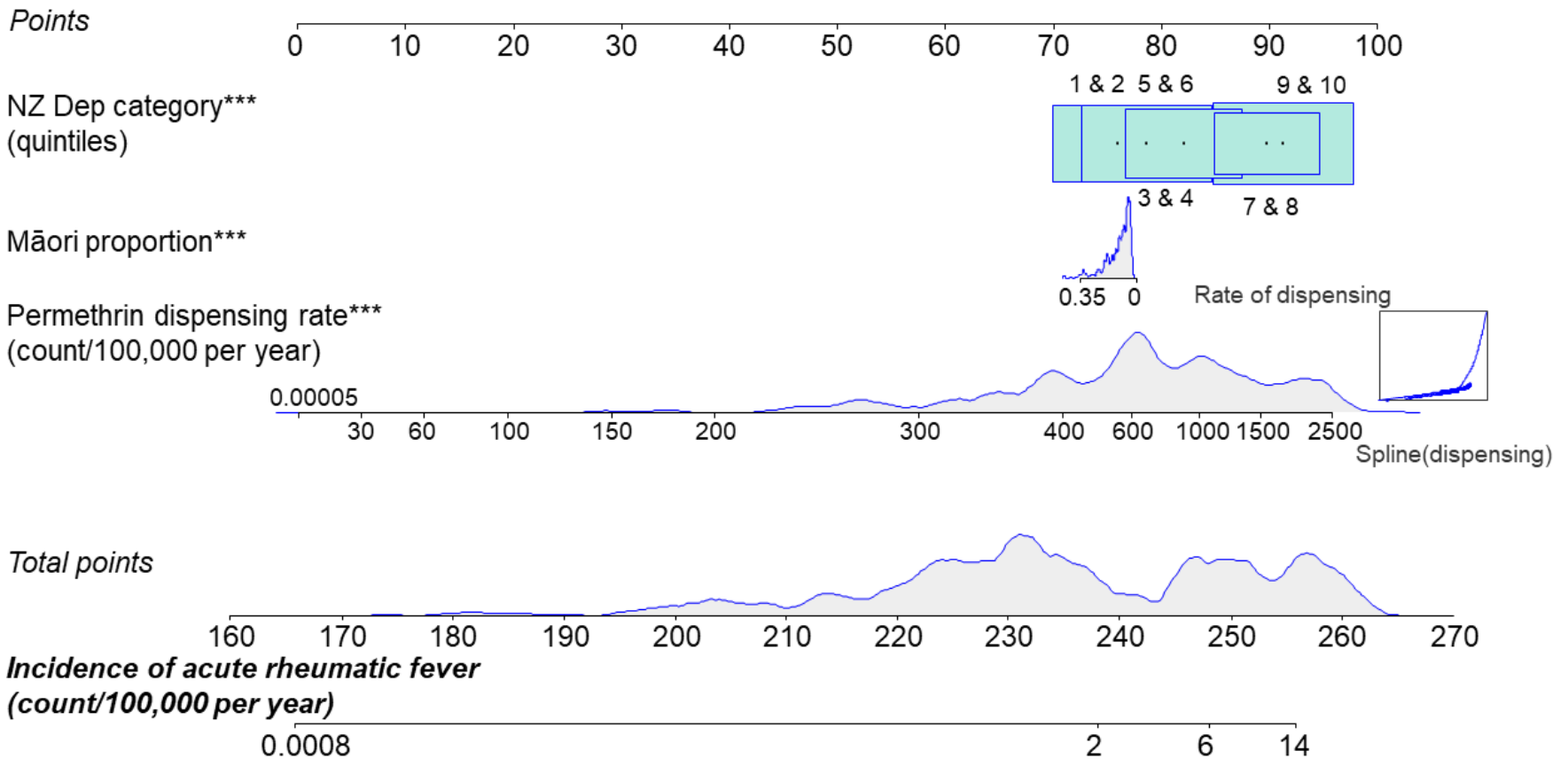


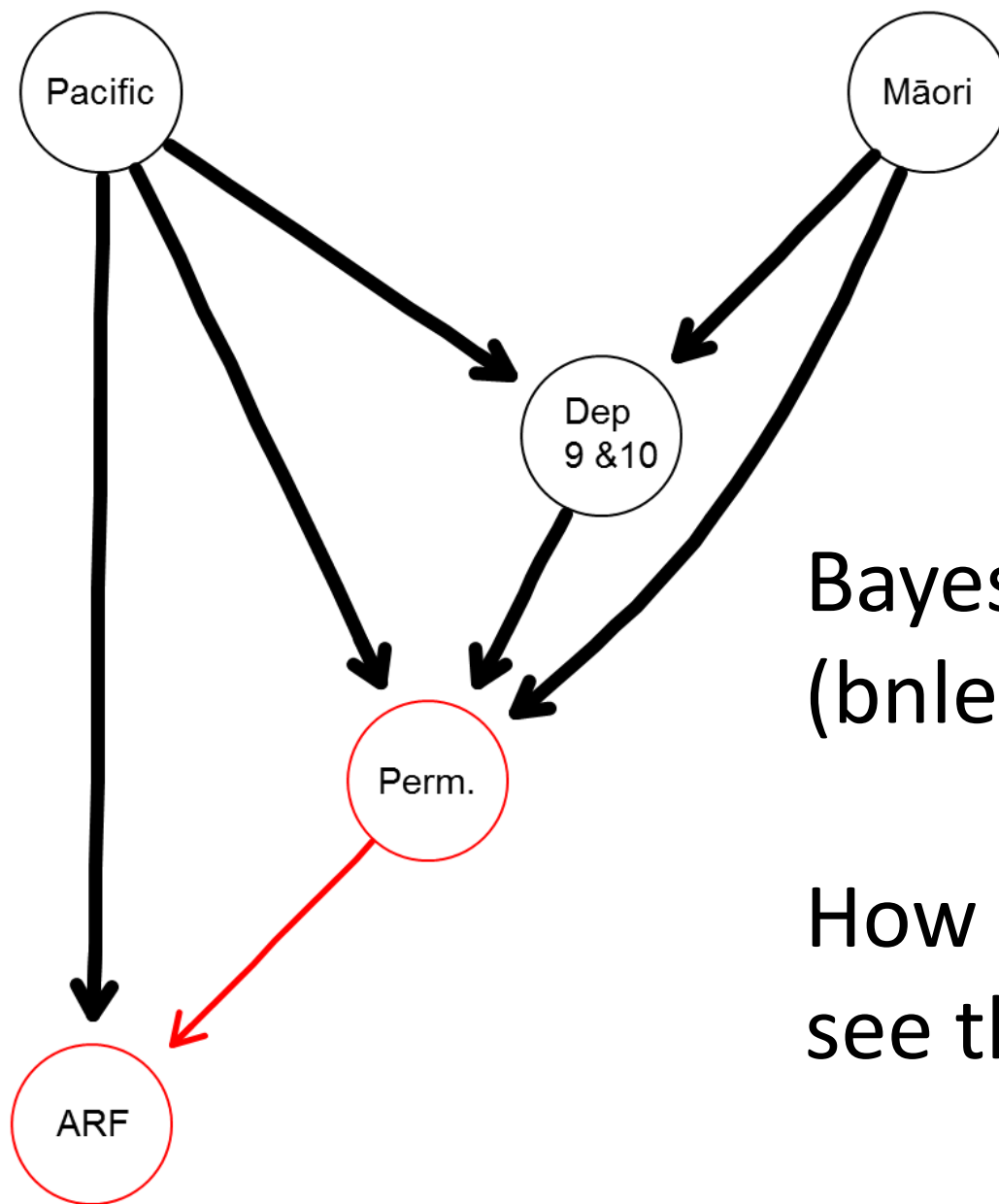
Traditional analysis... q-Poisson

Risk factor	Low risk*	High risk*	Crude inc. rate ratio	Adj. inc. rate ratio†
Proportion of Māori residents	0.052	0.182	3.88 (3.37 to 4.47)	0.808 (0.630 to 1.04)
Proportion of Pacific residents	0.022	0.271	2.79 (2.52 to 3.09)	Omitted due to collinearity
SES (NZ Dep13)	3 and 4	1 and 2 (least dep.)	2.70 (0.669 to 10.9)	1.33 (0.343 to 5.15)
	5 and 6		5.32 (1.42 to 20.0)	1.92 (0.496 to 7.43)
	7 and 8		21.4 (6.59 to 69.3)	4.45 (1.10 to 18.1)
	9 and 10		47.4 (14.2 to 158)	5.24 (1.28 to 21.5)
Annual inc. permethrin (per 100,000 people per year)	323	1294	43.2 (12.7 to 147)	16.5 (3.82 to 71.6)

*Comparisons are taken at the 16th and 84th centiles of the distribution for continuous variables

Multi-variable regression regplot (R Marshall)





Bayesian networks
(bnlearn R library)

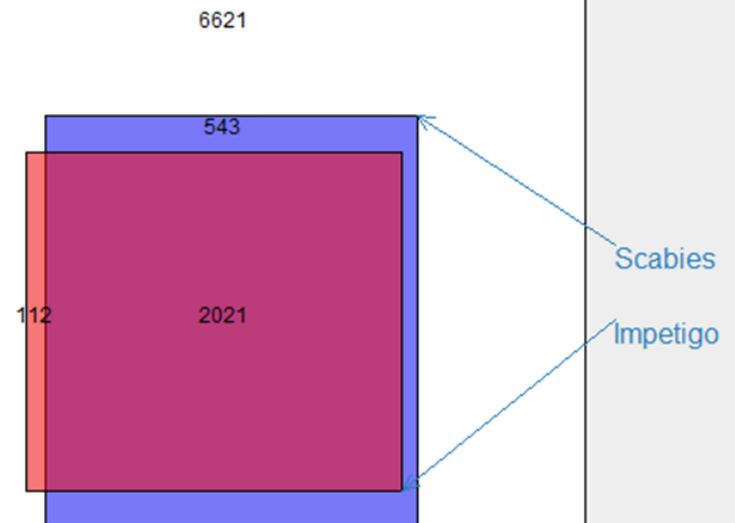
How does a computer
see the relationship?

Scabies & Impetigo

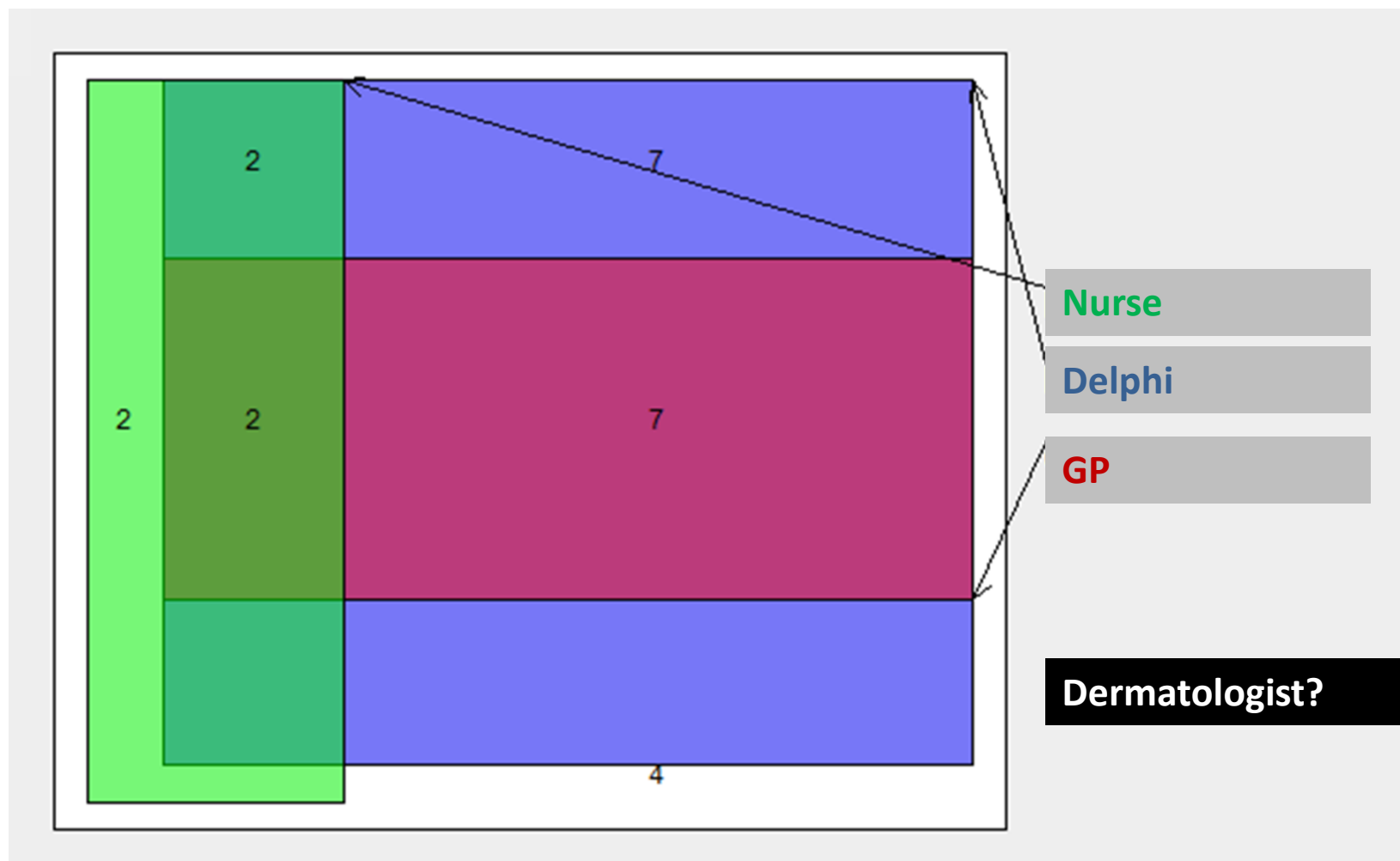


- Accepted treatment these days... topical and systemic antibiotics
- What about scabies?

Romani L, Koroivueta J, Steer AC, et al.
Scabies and impetigo prevalence and risk
factors in Fiji: a national survey.
PLoS Negl Trop Dis. 2015; 9:e0003452



Scabies diagnosis ECEC study



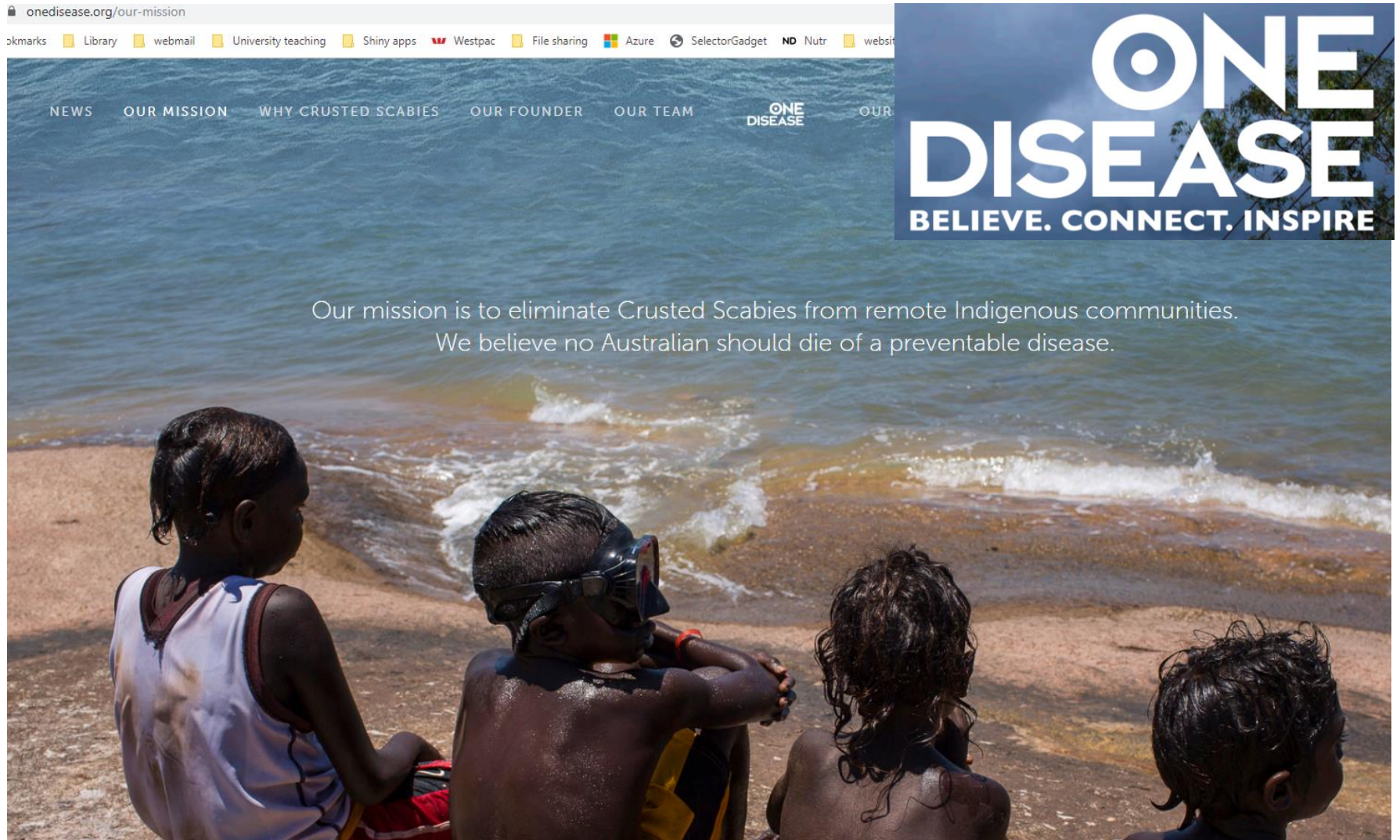
Some musings on results

- Adjusting for ethnicity and SES reduces association between permethrin and ARF, since all these variables are closely related.
- Since ethnicity and SES are strong risk factors for ARF, if scabies were truly causal, it would be expected that they are closely related to permethrin, and permethrin related to ARF.
- Permethrin use, if effective, should protect from ARF if scabies a true cause???

More musings...

- Adjustment for related risk factors “shares” or “dilutes” risk from causal factor.
- Traditional regression does not consider likely causal relationships between predictor variables.
- Bayesian networks more plausible causal representation.

Recent trip to Darwin



Is there a causal relationship?

- Bradford-Hill criteria

- Strong association (X – strongest association I've seen)
- Dose-response (X – after, vs. before)
- Biological plausibility (X – path to Group A strep, complement)
- Coherence (X – Pacific has high prev. scabies)
- Consistency (X – West Indies, Ethiopia, East Timor)
- Temporality (X – cohort study)
- Analogy (X – post-streptococcal GN linked to scabies)
- Experiment (Missing, but experimental evidence shows reducing scabies reduces bacterial skin infection, a likely precursor of ARF.)

When considering a new treatment...

- Introducing a new treatment is usually a consideration of the costs and benefits...
 - Particularly benefits to cases (true +) & harms to non-cases (false +)
- The downsides of overtreating scabies is small
 - Best evidence is for “overtreating” approach
- The potential upsides of effectively treating scabies are high
 - Bacterial skin infection, PSGN, probably ARF.

Vets and farmers are ahead of us...



Should scabies be notifiable?

- Currently Schedule 1, Part 2 Health Act 1956
- does the disease present a material public health risk in New Zealand?
- would surveillance and analysis be enhanced?

Summary

- Fresh new approach to ARF prevention
- \$70 million school prevention programme has been disappointing
- If true, permethrin ineffective... ivermectin? Pharmac criteria?
- Causation is often a neglected issue in epidemiology, but really is the *raison d'être* of the epidemiologist. BN networks helpful
- Scabies is notifiable in NT, Australia, and UK, not in NZ. Need to make scabies or at least crusted scabies notifiable!