Otago Spotlight Series

Infectious Disease Research

Pre-hospital treatment of meningococcal disease

Amanda Kvalsvig

Department of Public Health
University of Otago
Wellington

PhD Supervisors

Michael Baker & Tony Blakely

Structure of this presentation

1. The study question
2. Methods
3. Results
4. Conclusions and next steps

Meningococcal disease

- Rapidly evolving, severe infection
- Hospital-based research suggests that early antibiotic treatment reduces case fatality risk

Meningococcal disease

- Rapidly evolving, severe infection
- Hospital-based research suggests that early antibiotic treatment reduces case fatality risk

Recommendation:

Give parenteral antibiotics in primary care, before hospital admission

The problem

1. Most studies suggesting a treatment benefit have **low study power**

   e.g. Cartwright, n=381: RR 0.6 (95% CI 0.2 – 1.5)

2. Two studies reported **increased odds of death** following antibiotics

Nørgård	adjusted OR 2.4 (1.0 – 5.6)
Harnden	adjusted OR 7.45 (1.47 – 37.67)

3. Systematic review (Hahné et al.):

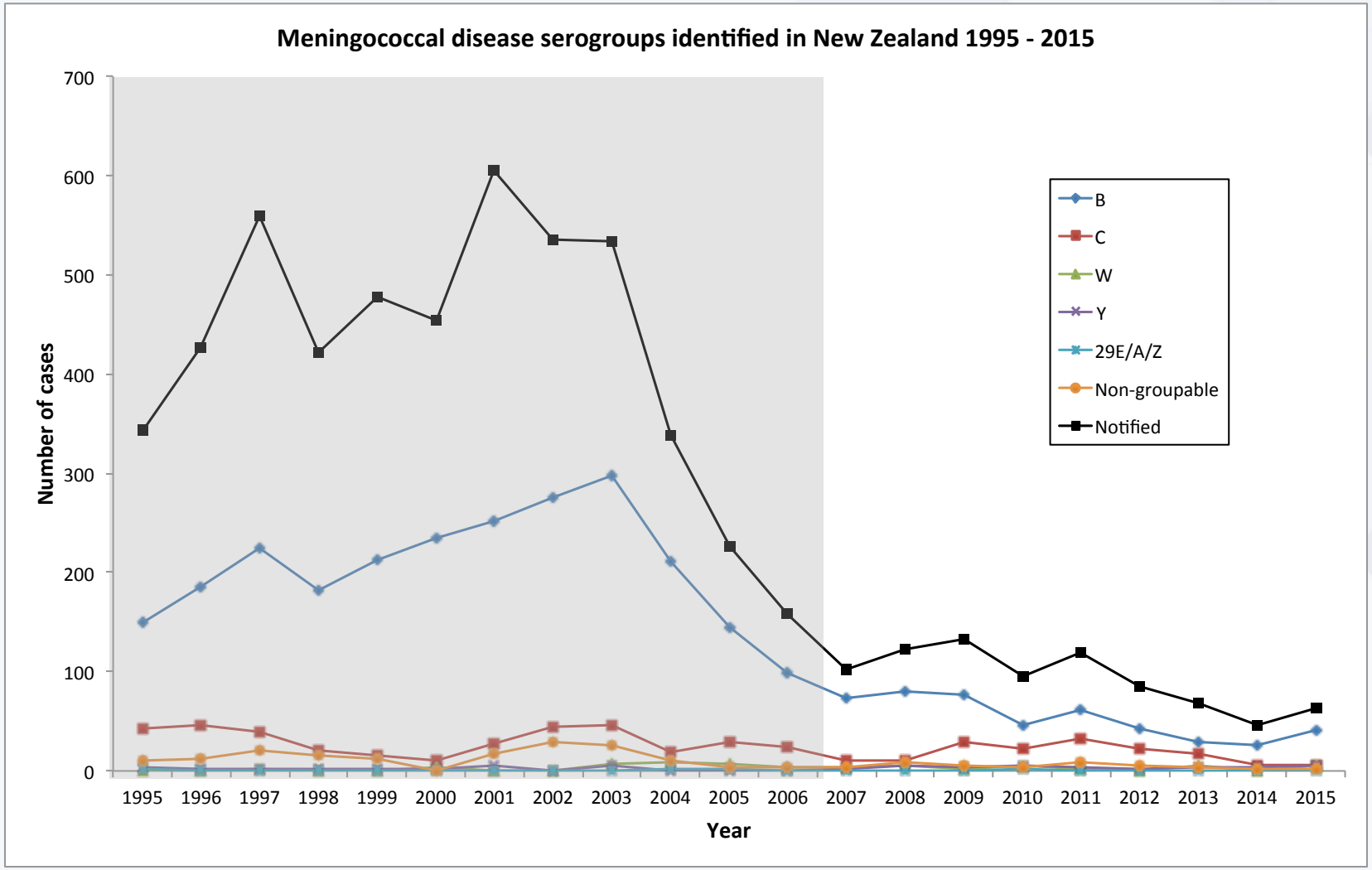
   "We cannot conclude from this review whether or not antibiotics given before admission have an effect on case fatality"

4. Cochrane reviews: **no randomised controlled trials** therefore did not comment

Meningococcal surveillance data

- **Notifiable** disease
- Surveillance database (**Episurv**): ESR collates data from
  - Notification (case report form)
  - Laboratories
- Information about whether the patient **saw a doctor** prior to admission (during study period this would have been a GP)
- **Pre-hospital antibiotic treatment recorded since 1995**

NZ meningococcal disease epidemic

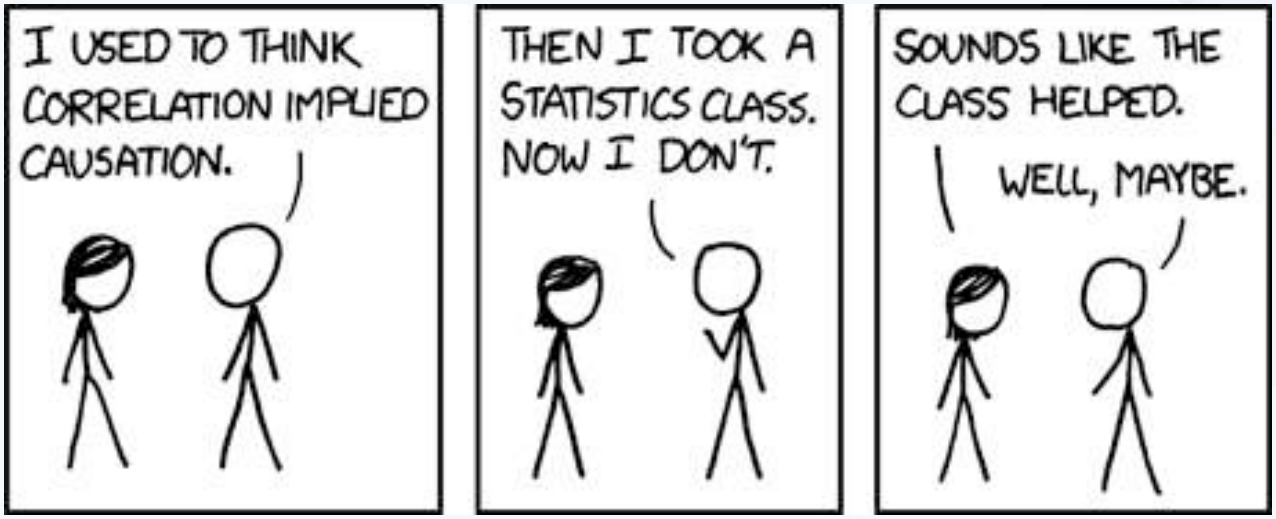


Study overview

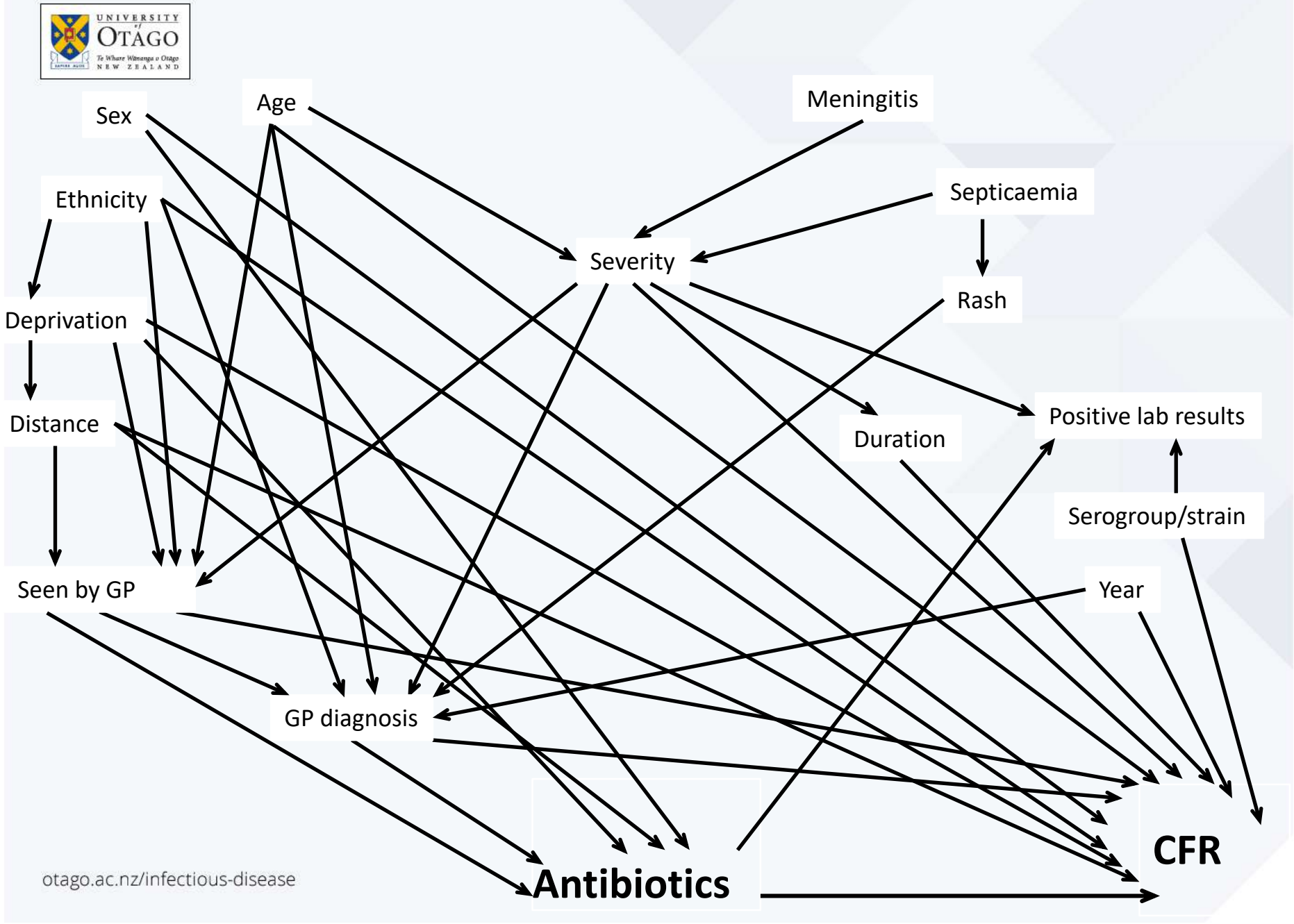
Estimate the effect of pre-hospital parenteral antibiotics on case fatality risk in meningococcal disease

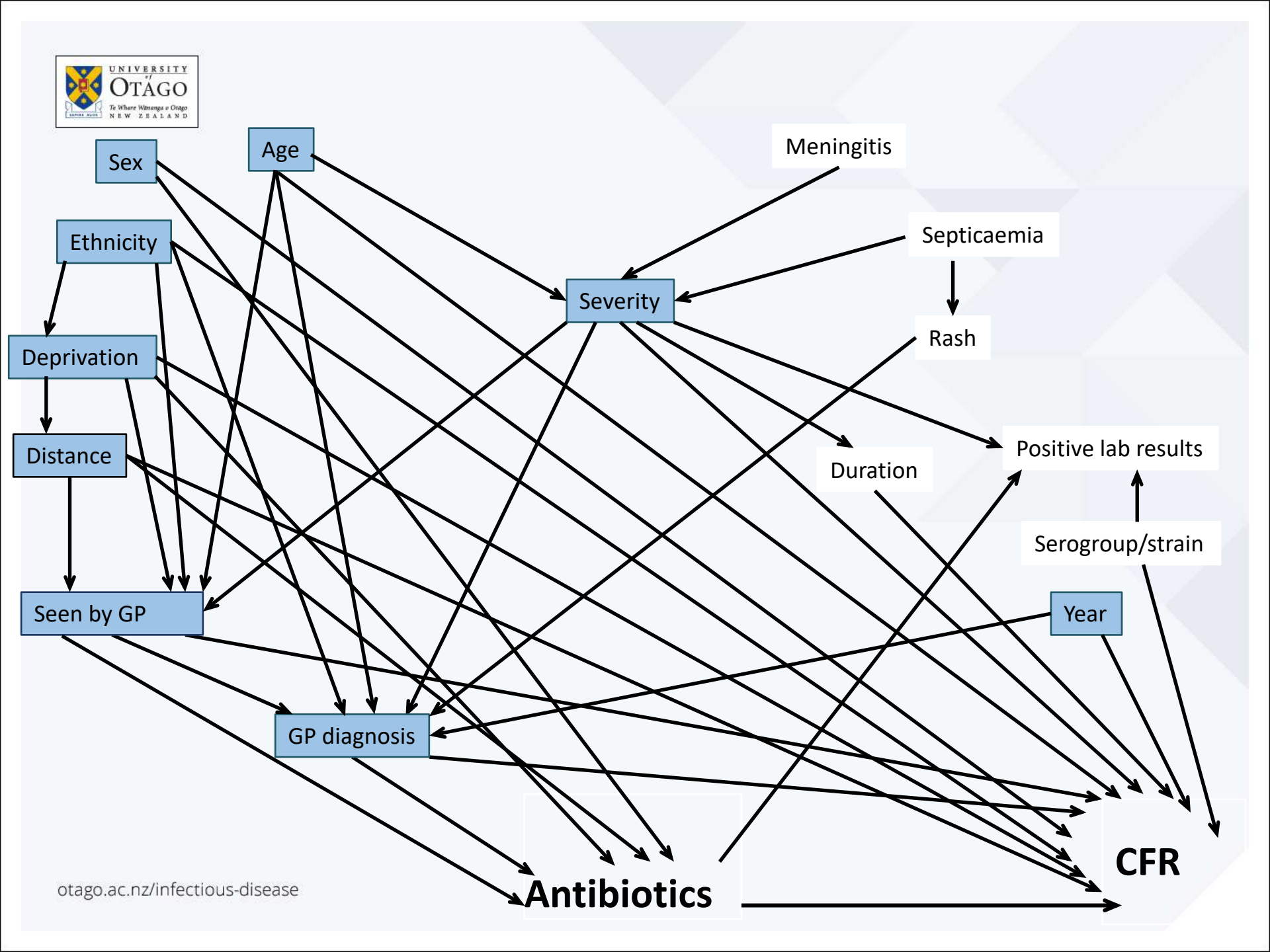
- **Data source:** NZ surveillance data 1995-2006
- **n =** 5340 (3427 general practitioner)
- **Exposure:** Pre-hospital parenteral antibiotics
- **Outcome:** Death vs survival

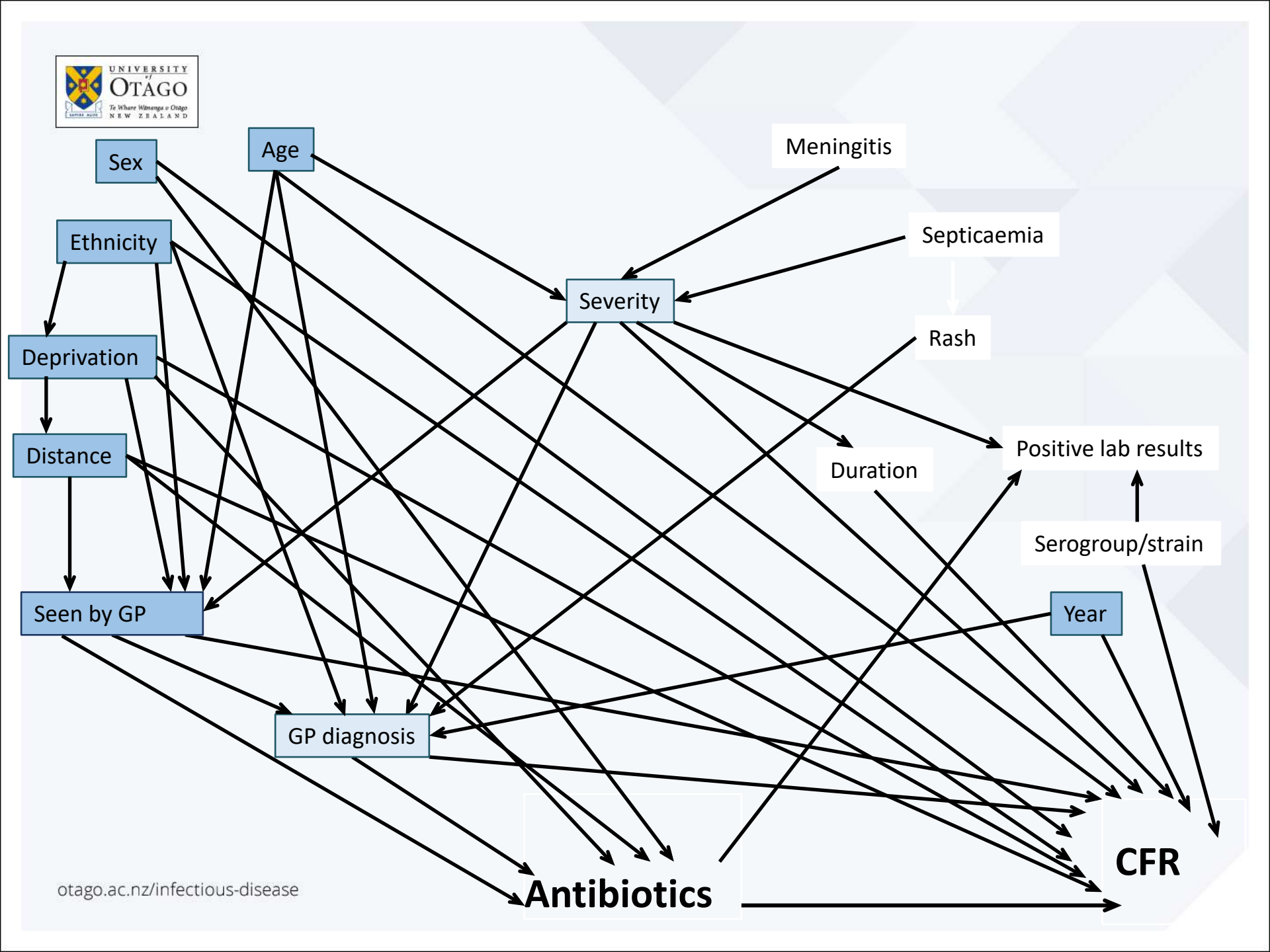
Bias in observational studies

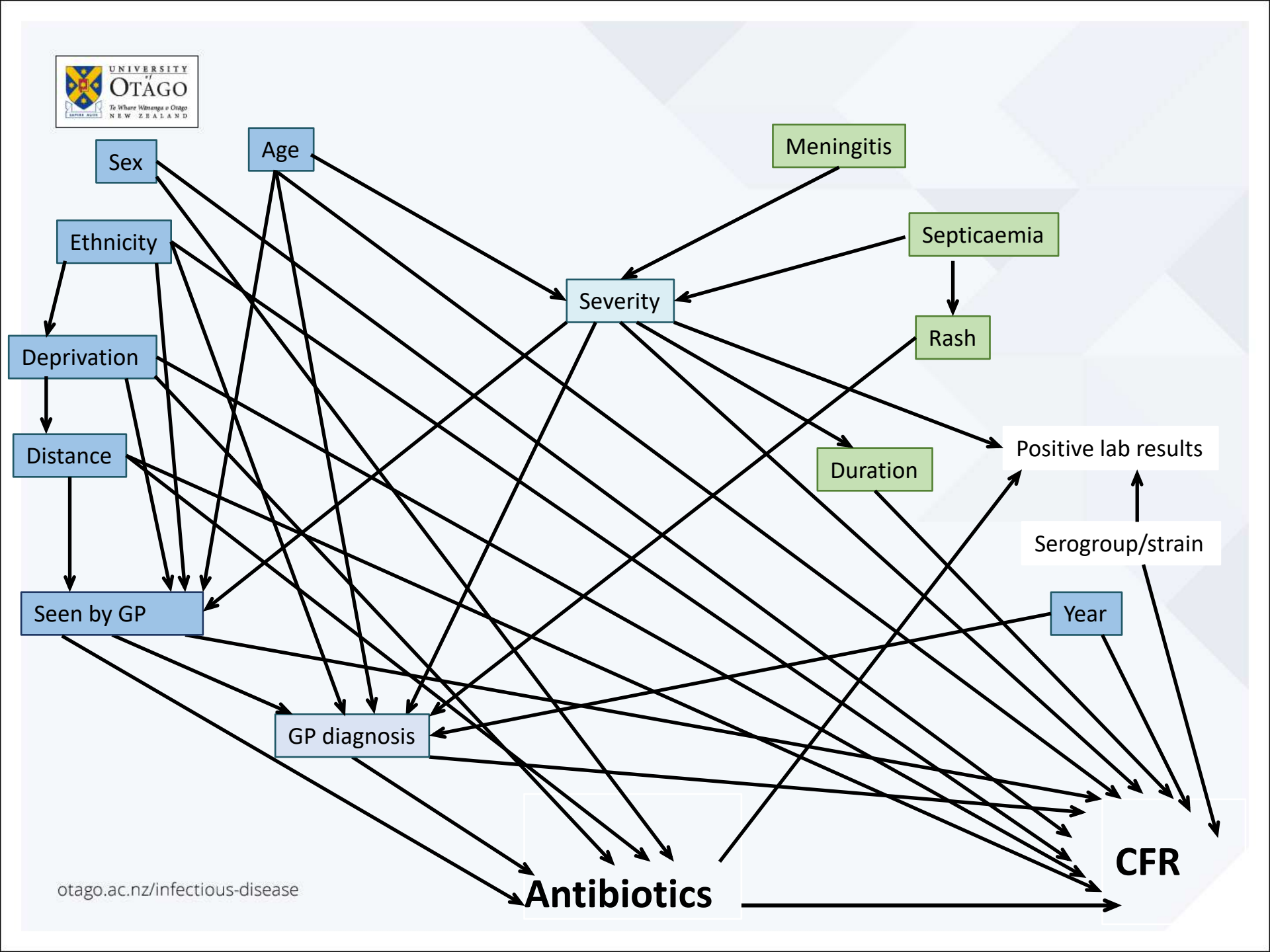


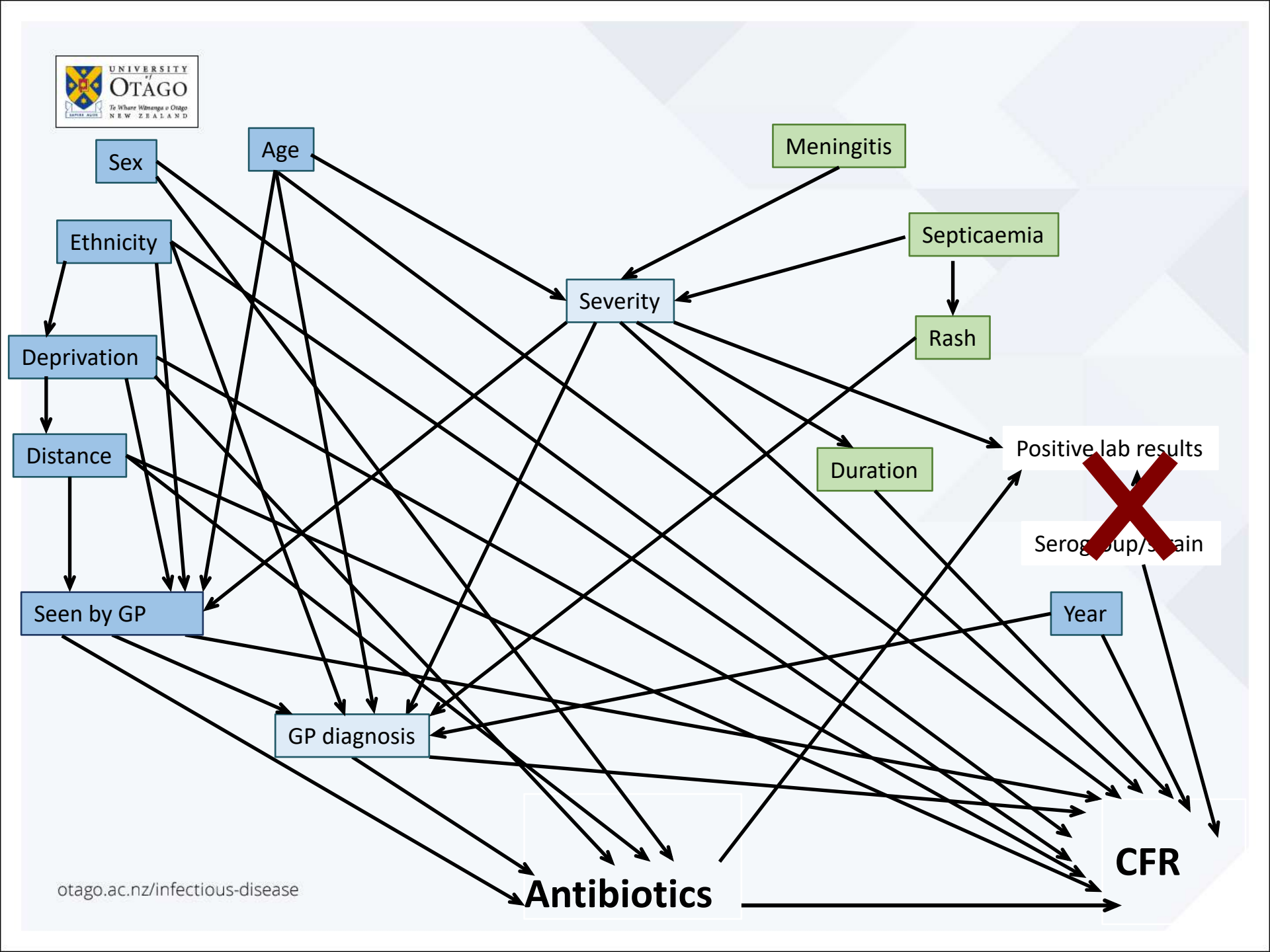
www.xkcd.com


Sex
Age
Meningitis
Ethnicity
Septicaemia
Severity
Rash
Deprivation
Distance
Positive lab results
Duration
Serogroup/strain
Seen by GP
Year
GP diagnosis
CFR
Antibiotics


Sex
Age
Meningitis
Ethnicity
Septicaemia
Severity
Rash
Deprivation
Distance
Positive lab results
Duration
Serogroup/strain
Seen by GP
Year
GP diagnosis
CFR
Antibiotics
otago.ac.nz/infectious-disease


Sex
Age
Meningitis
Ethnicity
Septicaemia
Severity
Deprivation
Rash
Distance
Positive lab results
Duration
Serogroup/strain
Seen by GP
Year
GP diagnosis
CFR
Antibiotics
otago.ac.nz/infectious-disease


Sex
Age
Meningitis
Ethnicity
Septicaemia
Severity
Rash
Deprivation
Distance
Positive lab results
Duration
Serogroup/strain
Seen by GP
Year
GP diagnosis
CFR
Antibiotics
otago.ac.nz/infectious-disease


Sex
Age
Meningitis
Ethnicity
Septicaemia
Severity
Rash
Deprivation
Distance
Positive lab results
Duration
Seen by GP
Year
GP diagnosis
CFR
Antibiotics
otago.ac.nz/infectious-disease

Missing data and complete case analysis

3427
cases saw a GP

Missing data and complete case analysis

3427
cases saw a GP

1156
Data complete for all covariates

Missing data and complete case analysis

Concerns about:

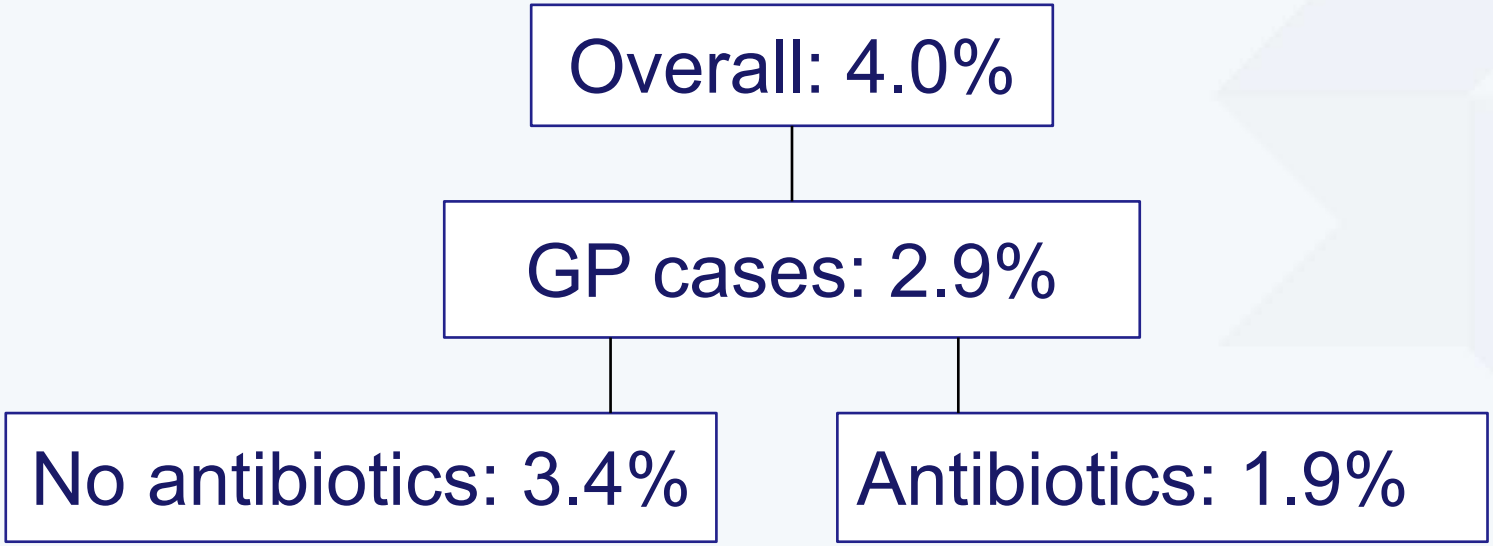
- Study power
- Selection bias

… led to decision to impute data

Multiple imputation using chained equations

Main analysis results

Case fatality risk



Adjusted RR of death following antibiotic treatment = 0.54 (95%CI 0.33 to 0.90).

Potential biases in this study

- **Selection bias** (from complete case analysis)
- **Misclassification** (e.g. treatment, petechial rash)
- **Unmeasured confounding** (severity, diagnosis)

Principles of quantitative bias analysis

- Identify potential biases of concern for the analysis
- Determine bias parameters using data internal or external to the study
- Adjust the estimate of effect to take the bias into account

Principles of quantitative bias analysis

- Identify potential biases of concern for the analysis
- Determine bias parameters using data internal or external to the study
- Adjust the estimate of effect to take the bias into account

- **Ask "What if" questions**
- **Follow the logic**

Misclassification of petechial rash

- Petechial rash at GP consult likely to be substantially mismeasured
- Woodward et al: sensitivity = 1.0 but specificity = 0.48
- Probabilistic bias analysis based on above parameters

Misclassification of petechial rash

- Petechial rash at GP consult likely to be substantially mismeasured
- Woodward et al: sensitivity = 1.0 but specificity = 0.48
- Probabilistic bias analysis based on above parameters

Effect of antibiotics on outcome

Observed risk ratio:	0.54	(0.35 – 0.84)
After adjustment:	0.47	(0.30 – 0.73)

Potential biases in this study

- **Selection bias** (from complete case analysis) ✓
- **Misclassification** (e.g. treatment, petechial rash) ✓
- **Unmeasured confounding** (severity, diagnosis) ✓

Public health conclusions

1. Pre-hospital antibiotics improve survival in meningococcal disease

2. No biases detected that would alter that conclusion

Methodological conclusions

1. New and emerging epidemiological methods provide us with a toolkit to identify and minimise bias.
2. The toolkit allows us to maximise the usefulness of the (imperfect) observational data that we have.
3. It's particularly valuable when a randomised controlled trial is not feasible.

Strengths of this study relative to previous research

Data infrastructure

- Large number of cases to analyse
- Information on exposure, outcome, confounders in surveillance data

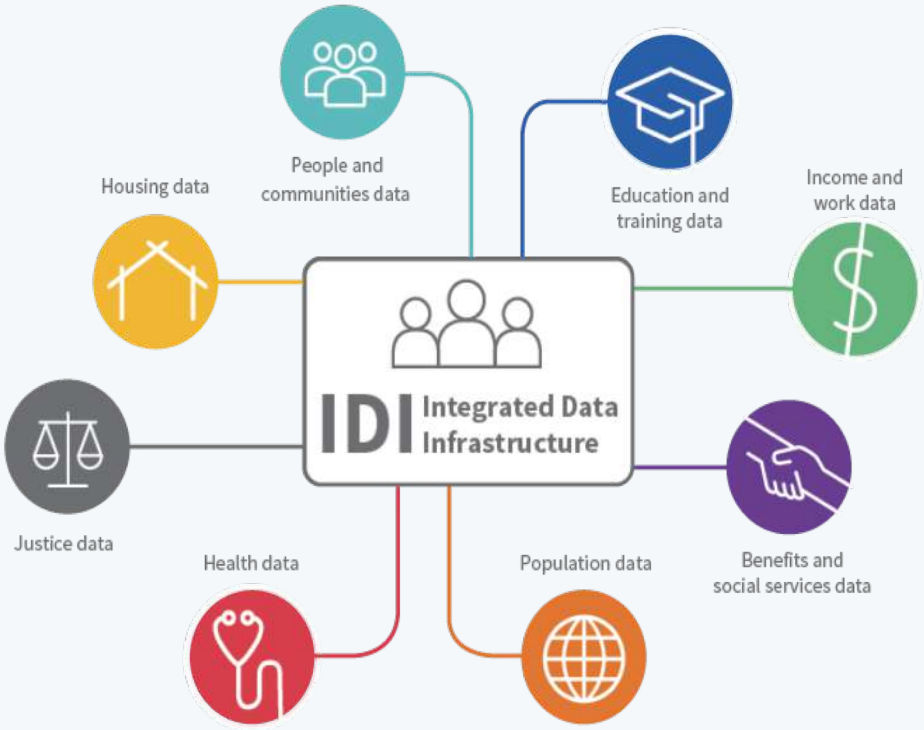
Analysis

- Use of causal modelling to determine the analysis model
- Estimate adjusted for proposed confounders
- Missing data addressed using multiple imputation
- Results tested using quantitative bias analysis methods

Challenges for translation

- Difficulty of early diagnosis of meningococcal disease: early symptoms and signs are nonspecific
- Proportion of cases treated was low and continues to decline
- Fewer cases are seeing a GP before admission
- Qualitative research: GPs reluctant to give parenteral antibiotics
- Some indications in the data of inequities in access to care

NZ Integrated Data Infrastructure

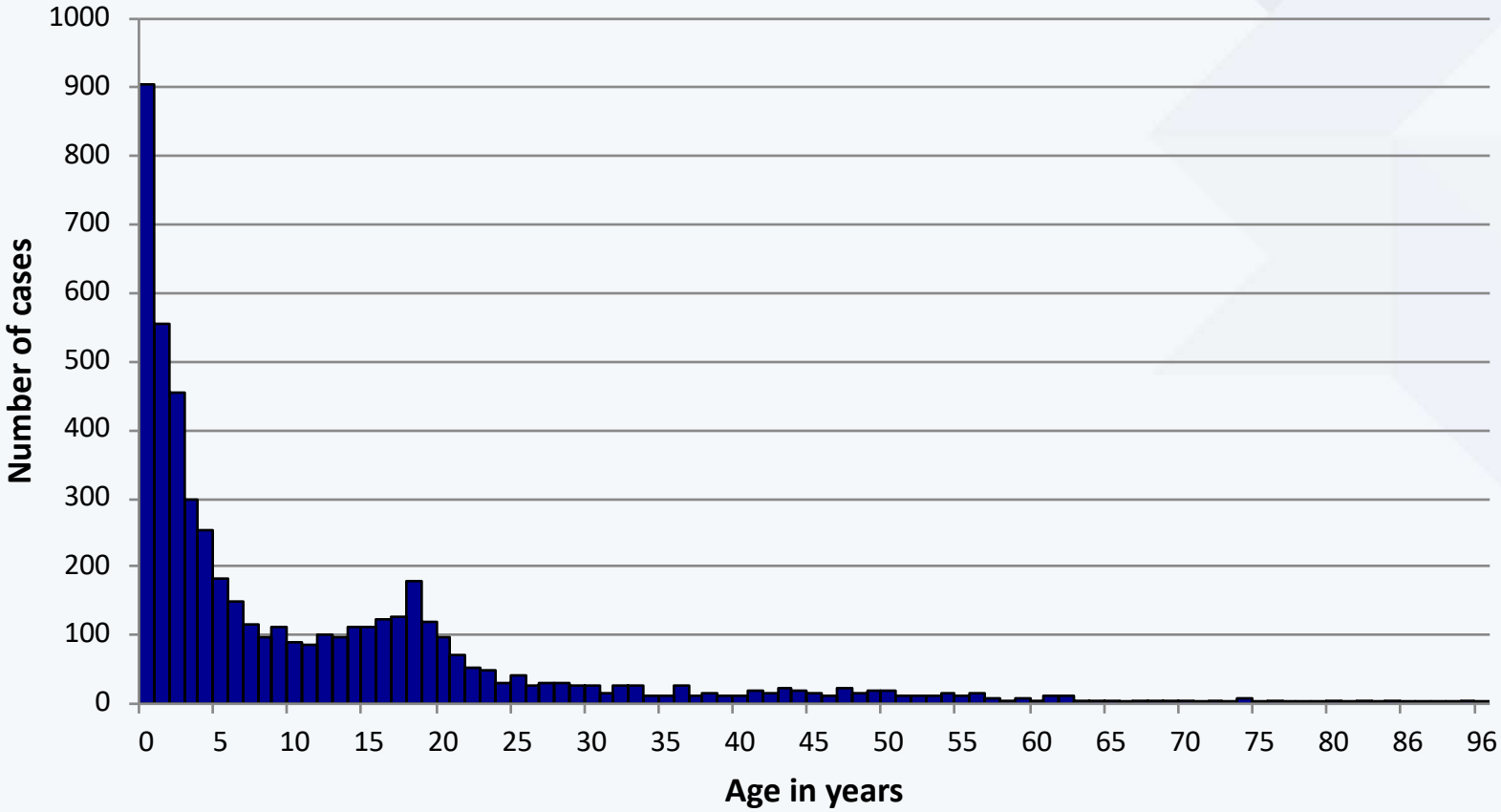


- Many potential applications for meningococcal disease epidemiology
- Causal epidemiological methods can help us to get the most out of our data

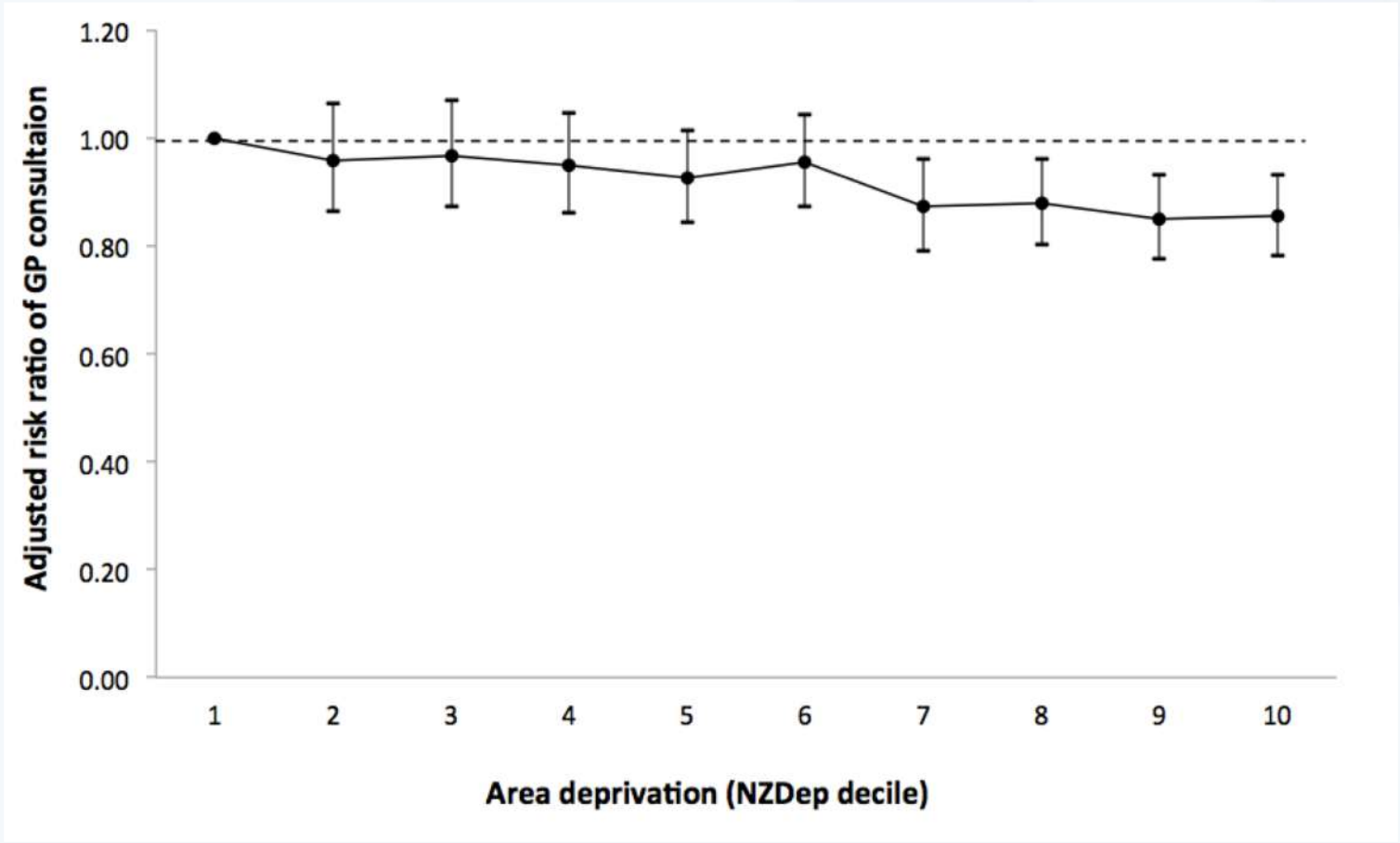
http://www.stats.govt.nz/


AVRORA

Age distribution 1995 - 2006

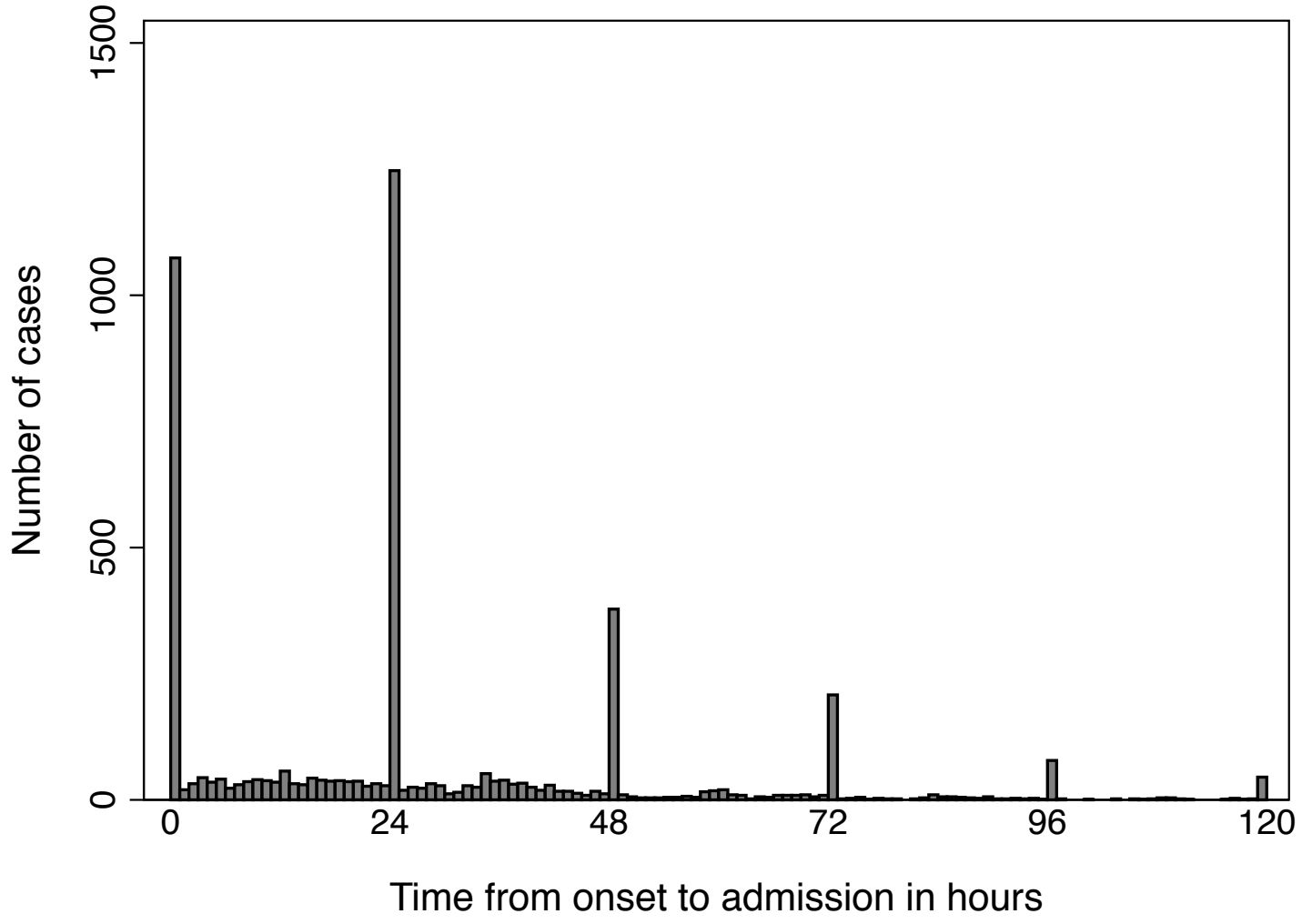


Area deprivation and GP consultation

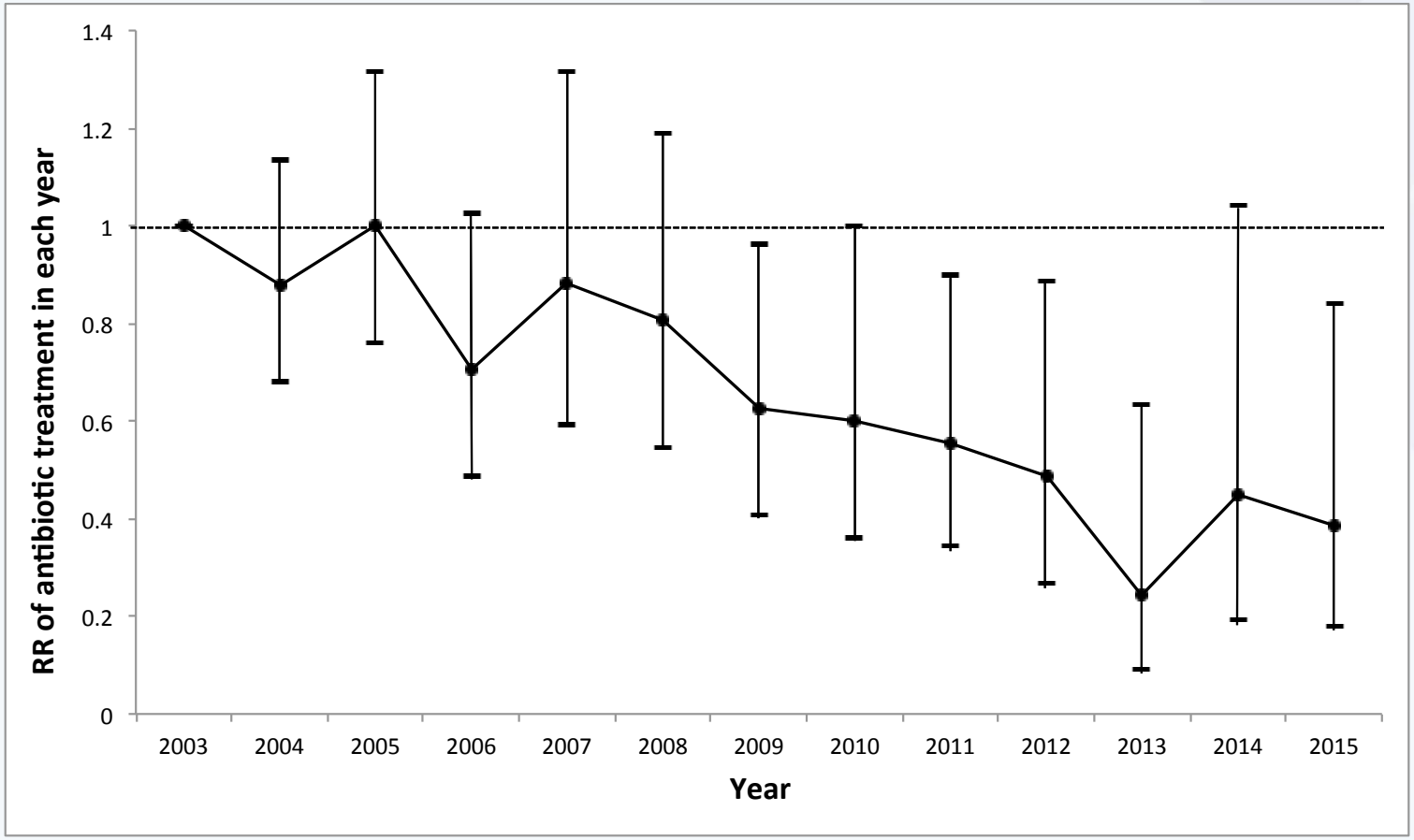


Risk ratio of seeing a GP by area deprivation, estimated using a generalised linear model and adjusted for age, sex and ethnicity. The reference category (RR=1.00) is the most advantaged decile (i.e. decile 1). The bars represent the 95% confidence interval around the RR.

Missing time measurements



Proportion of cases treated, 2003 - 2015



- RRs of the proportion of notified cases that were treated between 2003 and 2015, with 2003 as the reference year. The bars represent the 95% confidence interval around the RR.

Imputed, adjusted model (Stata)

GLM regression

Imputed dataset

Outcome

```
mi estimate, esampvaryok: glm died antibiotics
sex i.age i.eth2 NZDep10 rash septic meningitis
duration24 mi_distancekm year12 if seengp==1,
fam (poisson) link (log) vce(robust)
```

Confounders

GP only

Exposure

NZDep distribution 1995 - 2006