Practical strategies for addressing bias in observational research:

A worked example using meningococcal disease surveillance data in Aotearoa New Zealand

A/Prof Amanda Kvalsvig

University of Otago | Ōtākou Whakaihu Waka, Aotearoa New Zealand

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Structure of this presentation

University of Otago
ŌTĀKOU WHAKAIHU WAKA
Pōneke Wellington Campus

1. Study question

Meningococcal disease

- Rapidly evolving, severe infection
- In hospital, early antibiotic treatment reduces case fatality risk

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Recommendation:
Give parenteral antibiotics in primary care, before hospital admission

The problem: Recommendation not supported by evidence

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

Study overview

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

Setting	Aotearoa New Zealand, MenB epidemic
Data source:	Surveillance data 1995-2006
n =	5340 (3427 general practitioner)
Exposure:	Pre-hospital parenteral antibiotics
Outcome:	Death vs survival

Study overview

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

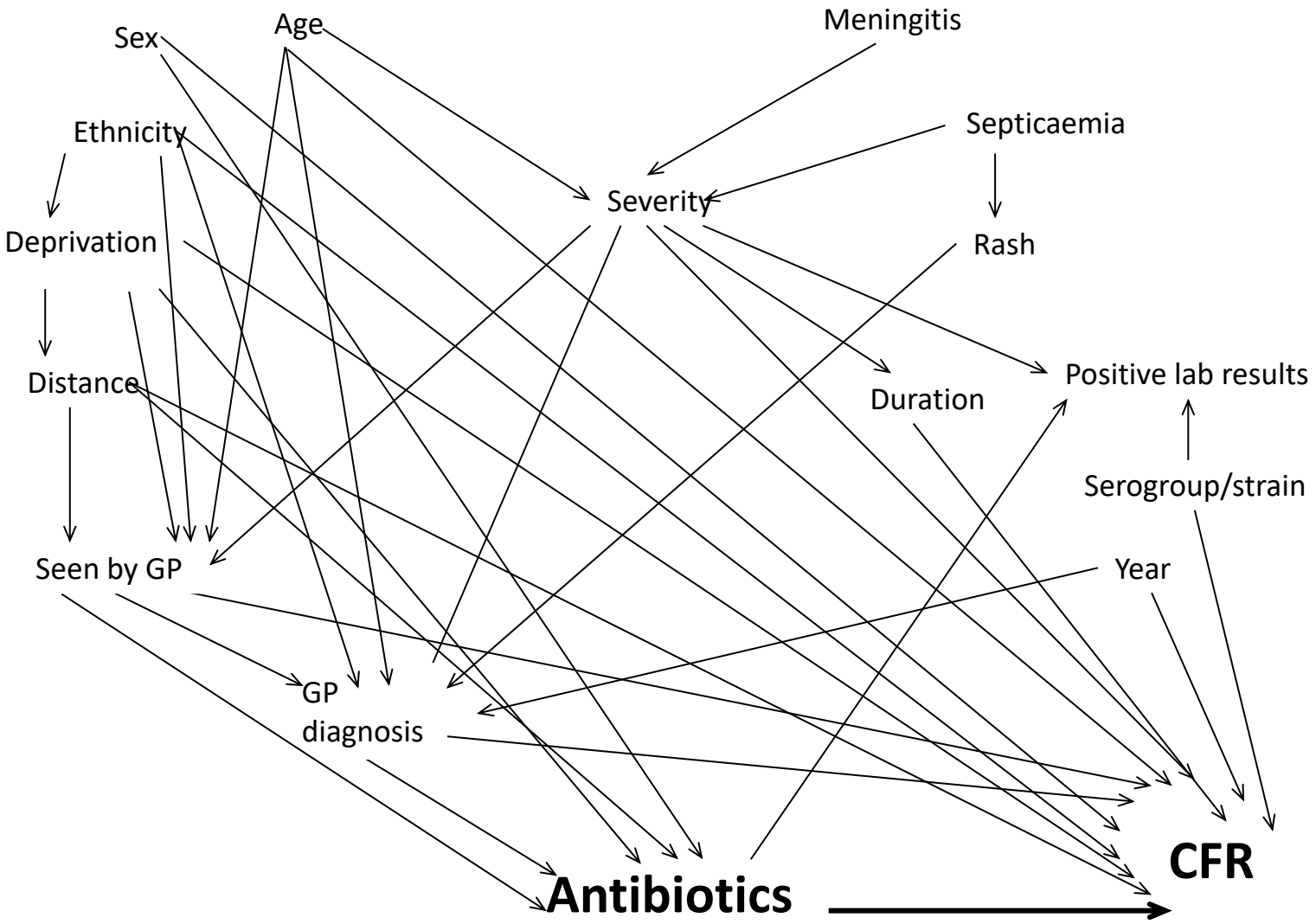
AND address or quantify likely sources of error:

- Random error
- Systematic error
  - *Selection bias*
  - *Measurement error (misclassification)*
  - *Unmeasured confounding*

Main analysis

Regression model (glm) reporting adjusted risk ratios

Directed Acyclic Graphs (DAG) were helpful



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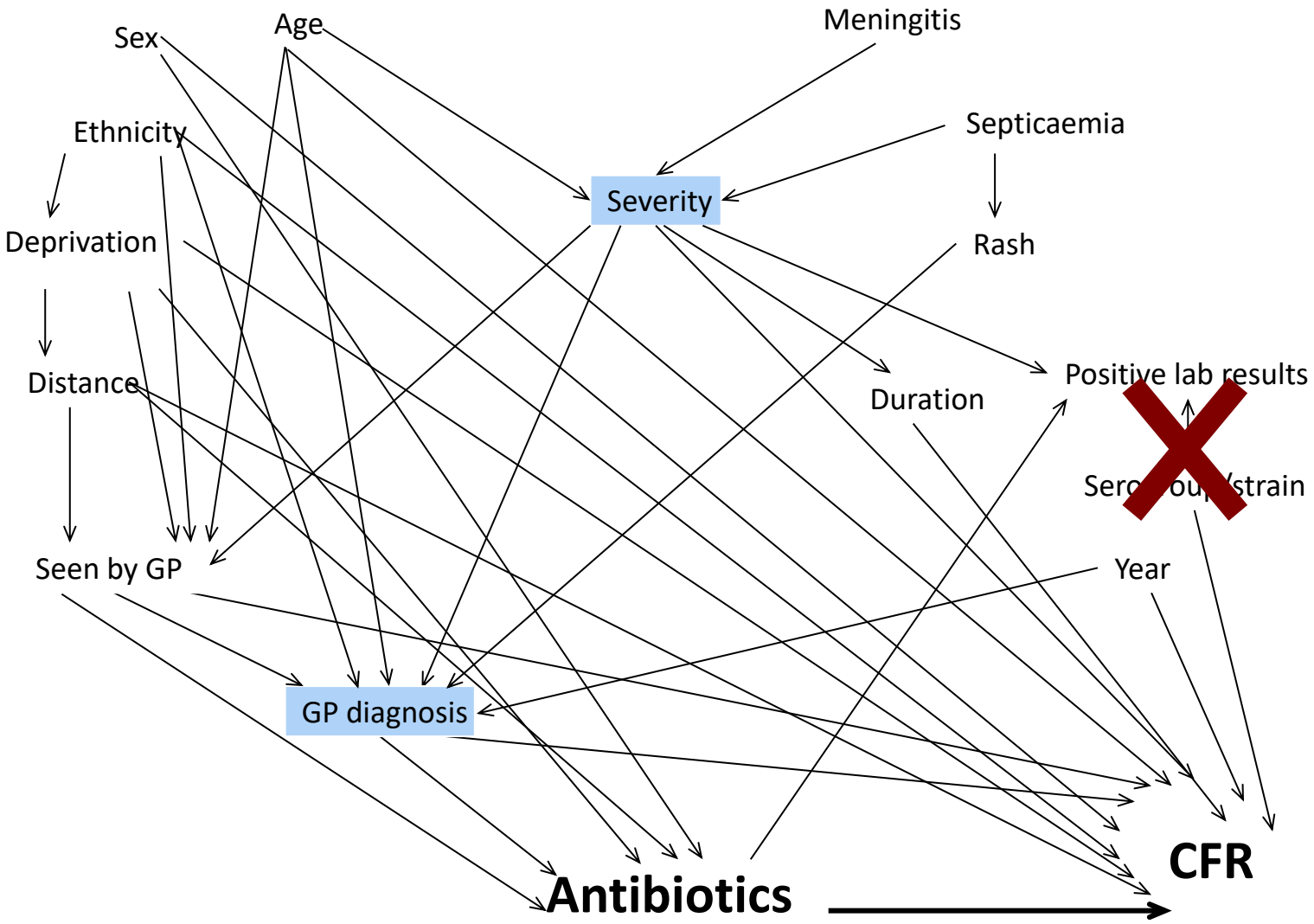


Selection bias

induced by complete case analysis

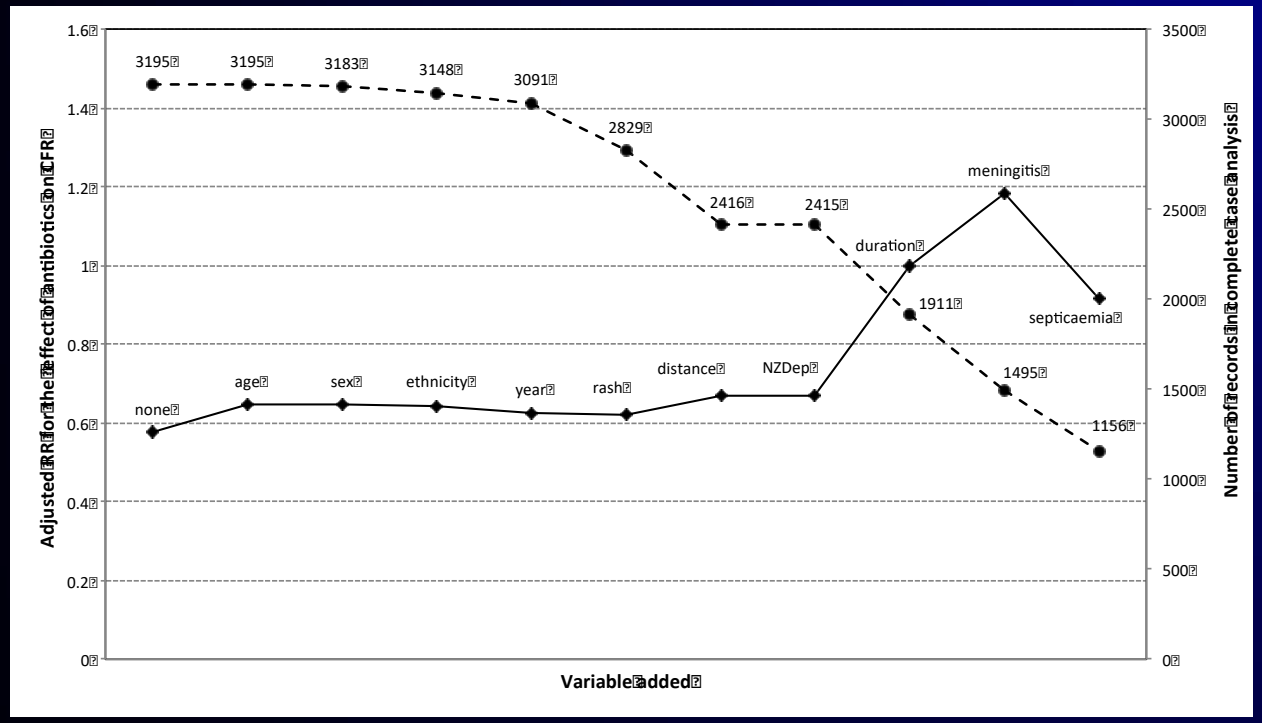
Concerns about:

- Study power
- Selection bias - differential missingness on one covariate.

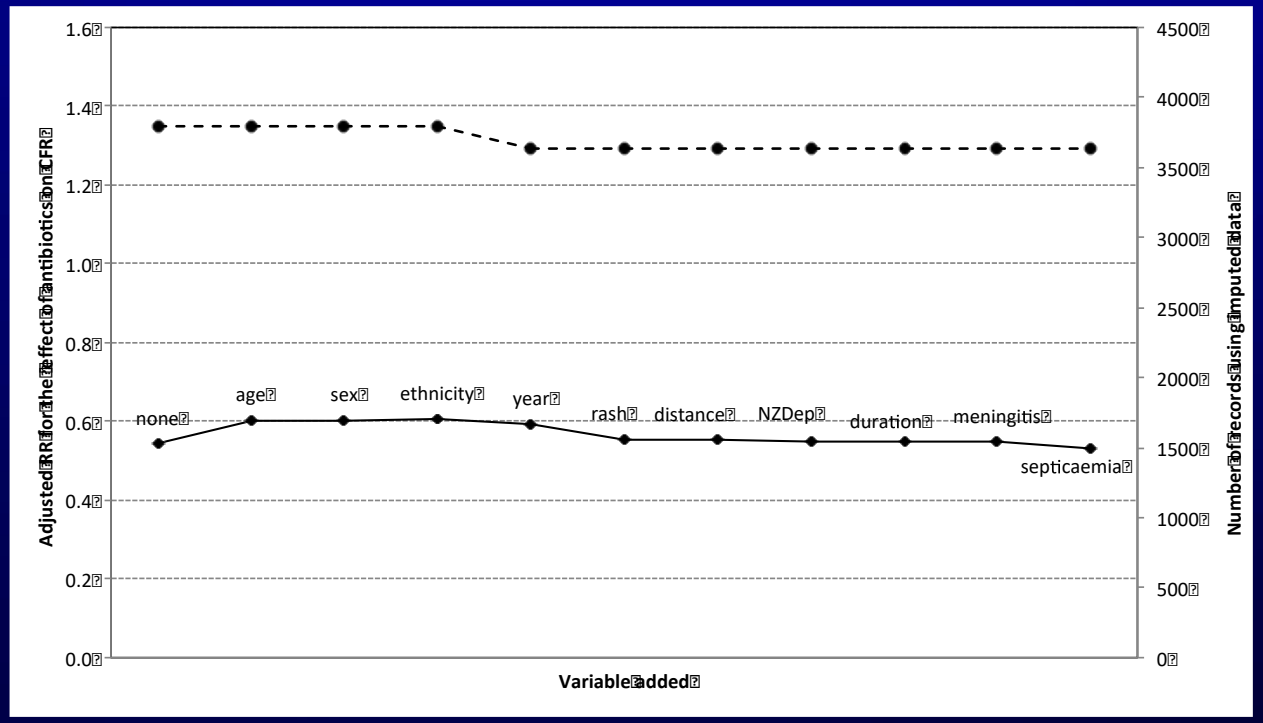
-> Multiple imputation using chained equations.

Multiple imputation reduced selection bias

Unimputed data



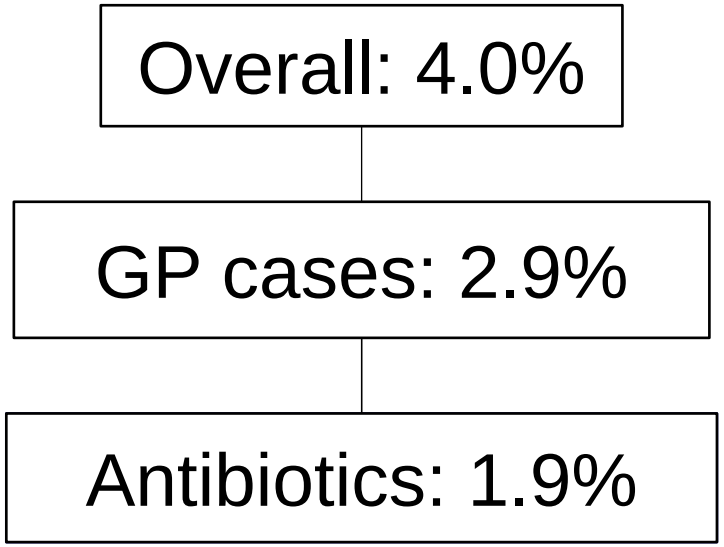
Imputed data



Changes in the estimated OR of antibiotic effect as covariates are added to the model, ordered from least missing to most missing. The dotted line and right axis show the number of records included in each analysis.

Main analysis results

Meningococcal disease case fatality risk



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

3. Quantitative bias analysis

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.

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

Key biases for this research question

Selection bias

- complete case analysis

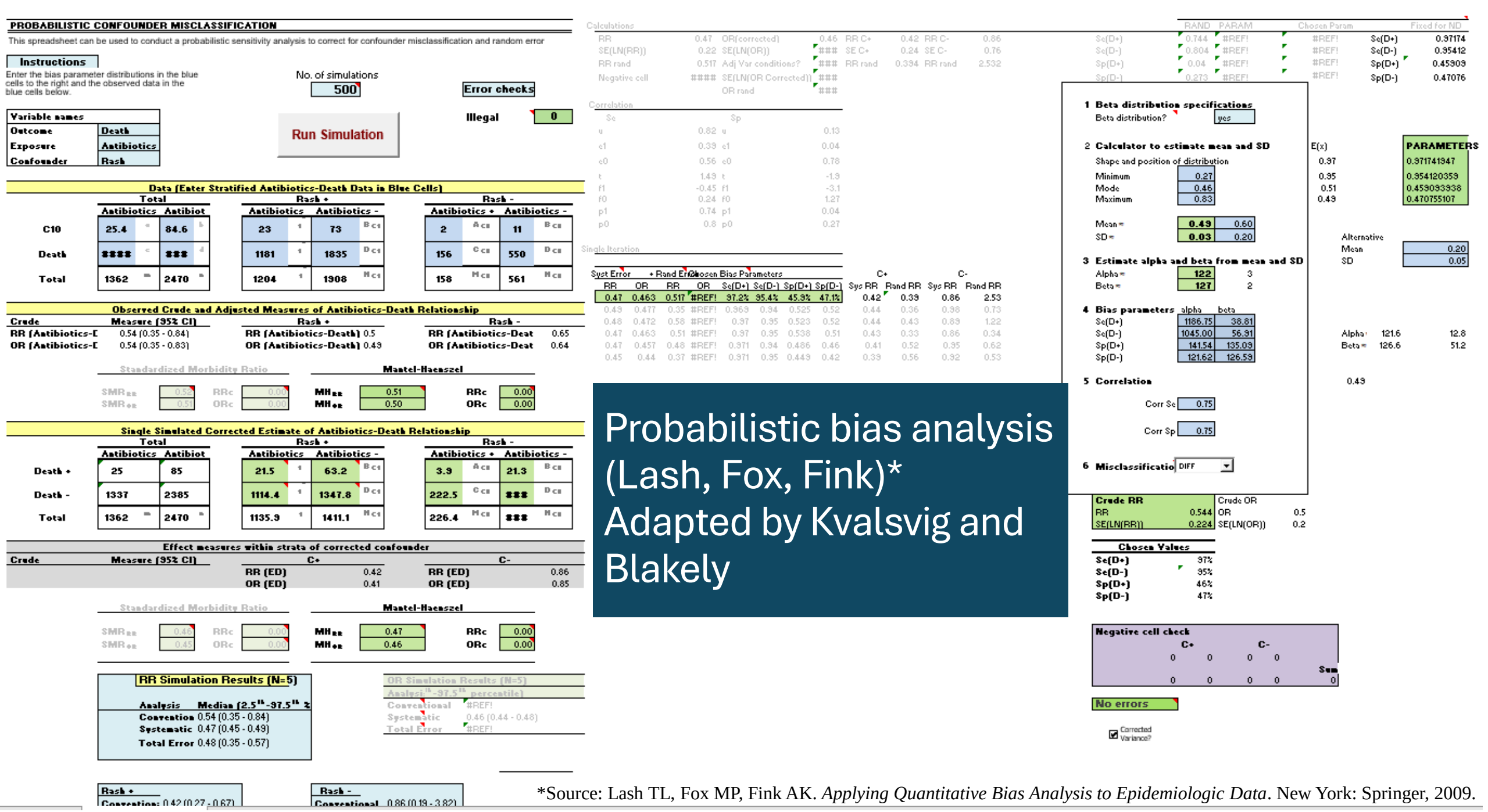
Misclassification bias

- treatment, petechial rash

Unmeasured confounding

- severity, diagnosis

- **Ask “What if?” questions**
- **Follow the logic**



Probabilistic bias analysis (Lash, Fox, Fink)*
Adapted by Kvalsvig and Blakely

*Source: Lash TL, Fox MP, Fink AK. *Applying Quantitative Bias Analysis to Epidemiologic Data*. New York: Springer, 2009.

Applying QBA to previously published studies

Quantitative critique

- Previous studies with similar designs would have had many of the same biases but did not address them
- Some specific biases in published studies could be (partially) quantified - explaining the opposite direction of effect

What difference did quantitative bias analysis make?

	RR (95% CI) before adjustment for bias	RR (95% CI) after adjustment for bias
Main analysis		
Selection bias		
- Differential missingness	0.91 (0.37 - 2.25)	**0.54 (0.35 - 0.84)**
Measured confounding	0.54 (0.34 - 0.88)	
Quantitative bias analysis		
Unmeasured confounding		
- GP diagnosis	0.54 (0.35 - 0.84)	0.59 (0.37 - 0.94)
- Severity (part measured)	0.54 (0.35 - 0.84)	0.51 (0.32 - 0.84)
Misclassification		
- Exposure (Rx)	0.54 (0.35 - 0.84)	0.41 (0.25 - 0.72)
- Confounder (petechial rash)	0.54 (0.35 - 0.84)	0.47 (0.30 - 0.73)

What difference did quantitative bias analysis make?

Strengthened causal inference

- Cohesive results showing strong internal consistency
- Estimates shifted in the direction predicted by theory
- Bias parameters had to be implausibly large to generate a meaningful change in the estimates.

Strong support for advice to Government

- Evidence-informed policy for meningococcal disease management.

4. Conclusions

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.

Thank you