

Practical strategies for addressing bias in observational research:

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

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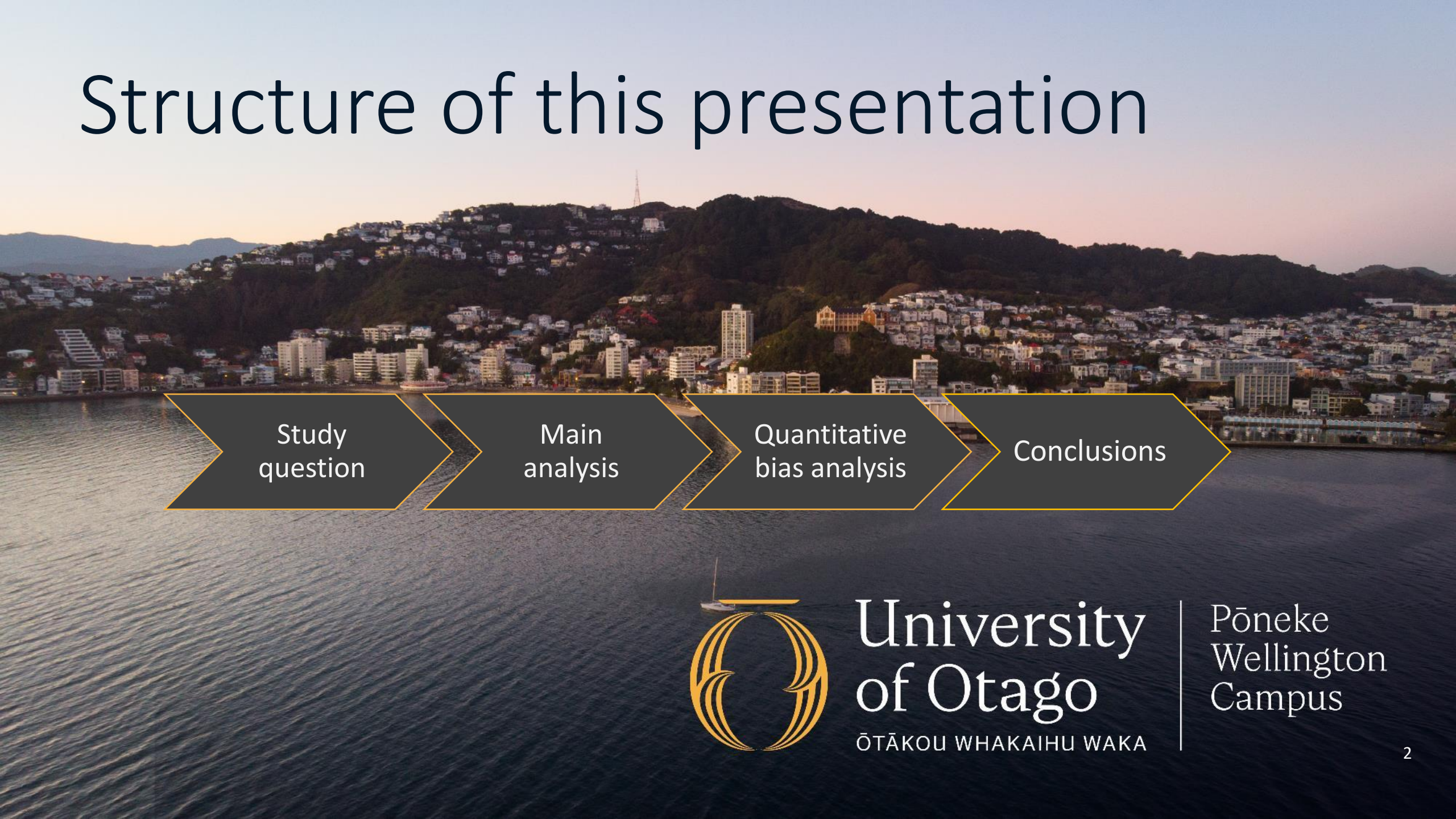
Thanks to: Professors Michael Baker and Tony Blakely

WCE

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Structure of this presentation



Study question

Main analysis

Quantitative bias analysis

Conclusions



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1. Study question

Meningococcal disease

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

Latest Video

NZ News

World

Sport

Business

Vote 2014

Vote Comp

Baby killed by deadly bug hours after GP visit

Meningococcal disease

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

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

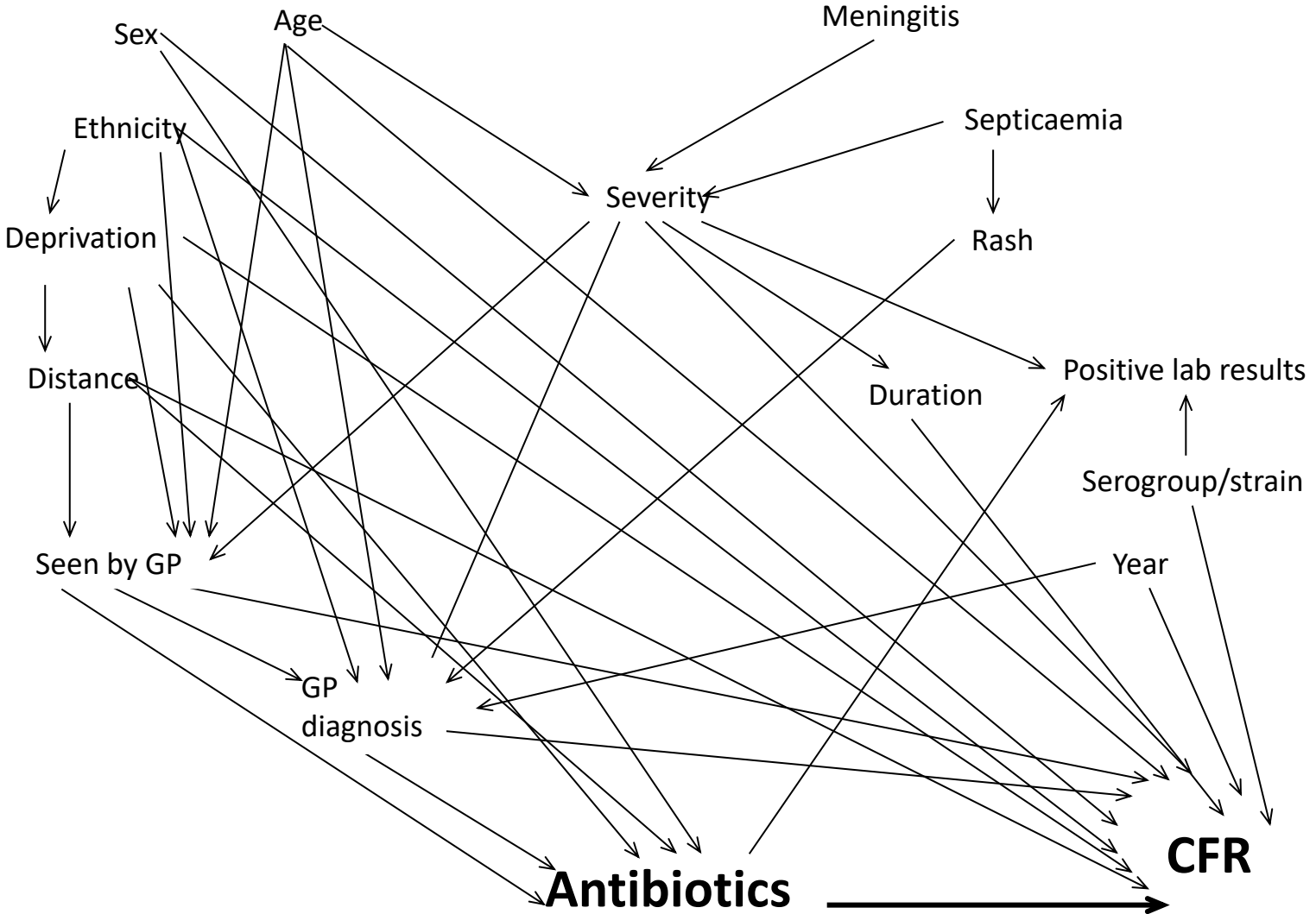
AND address or quantify likely sources of error:

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

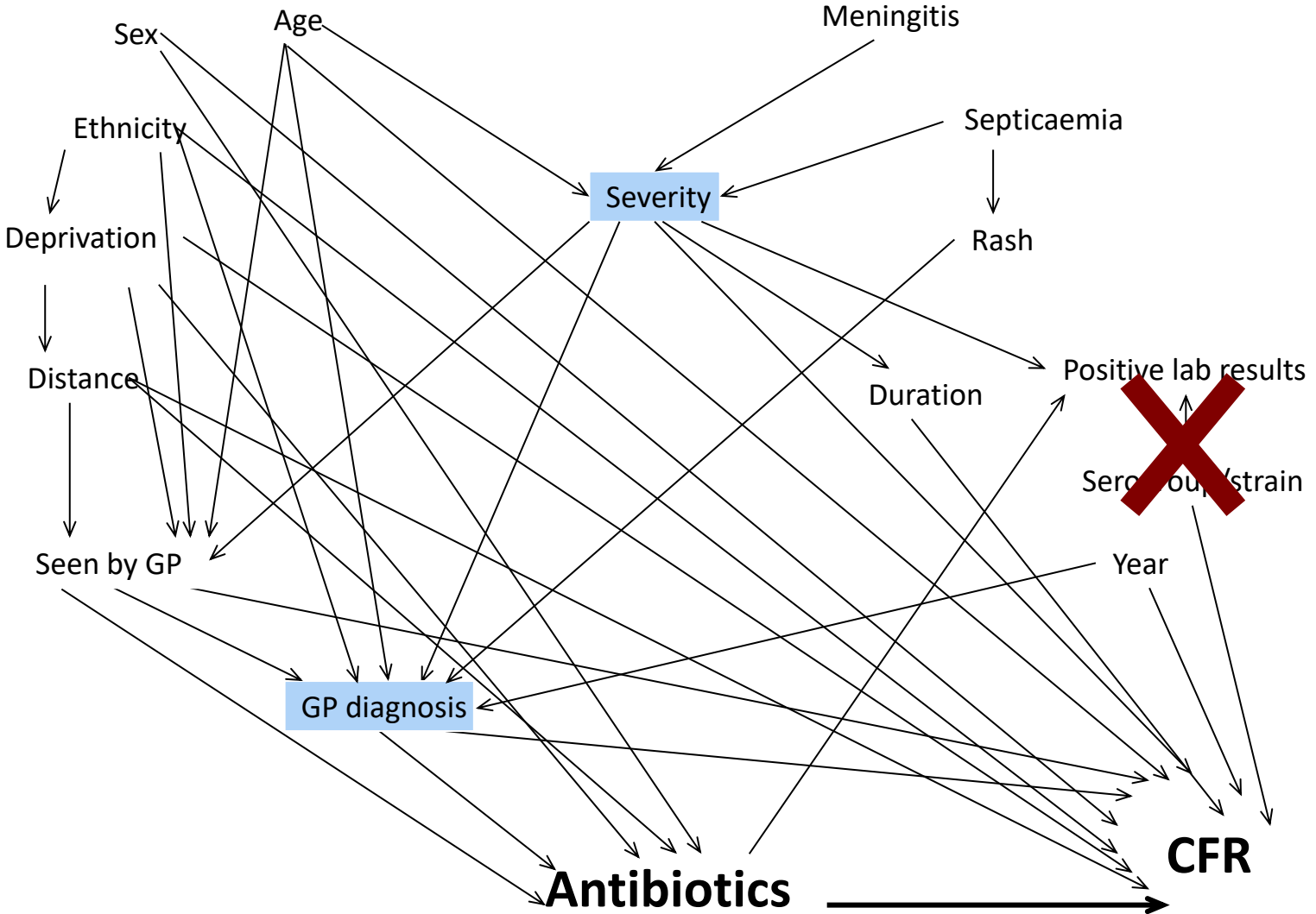
Main analysis

Regression model (glm) reporting adjusted risk ratios

Directed Acyclic Graphs (DAG) were helpful



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Selection bias

induced by complete case analysis

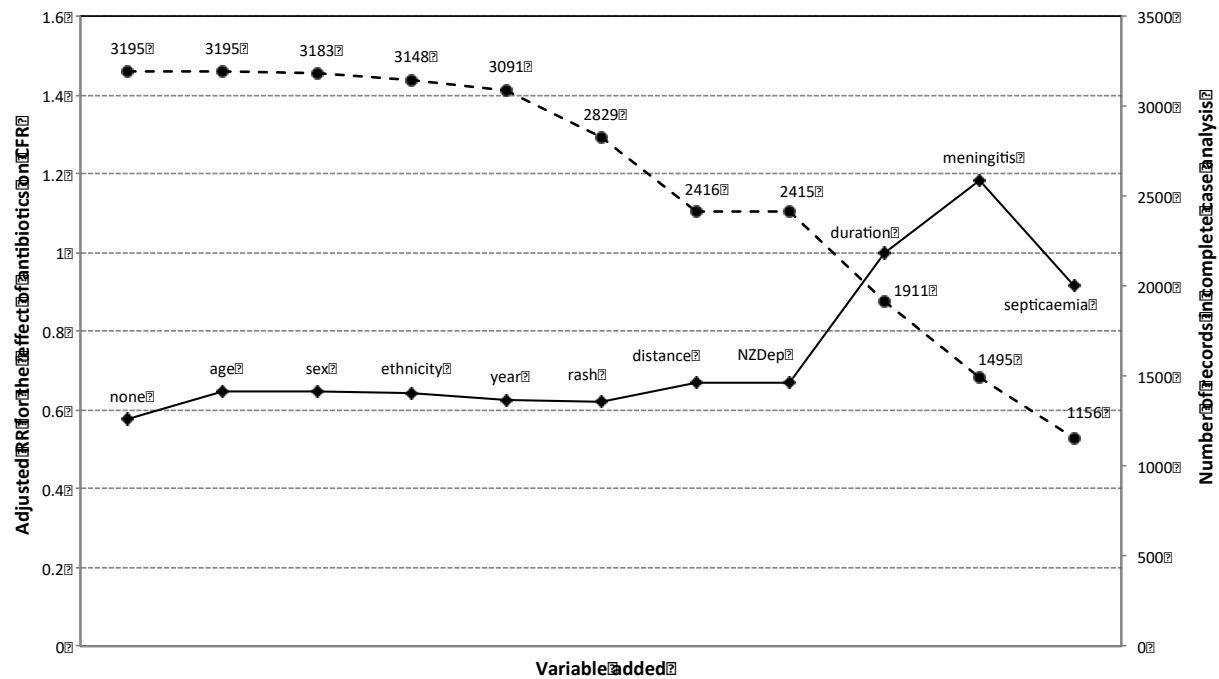
Concerns about:

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

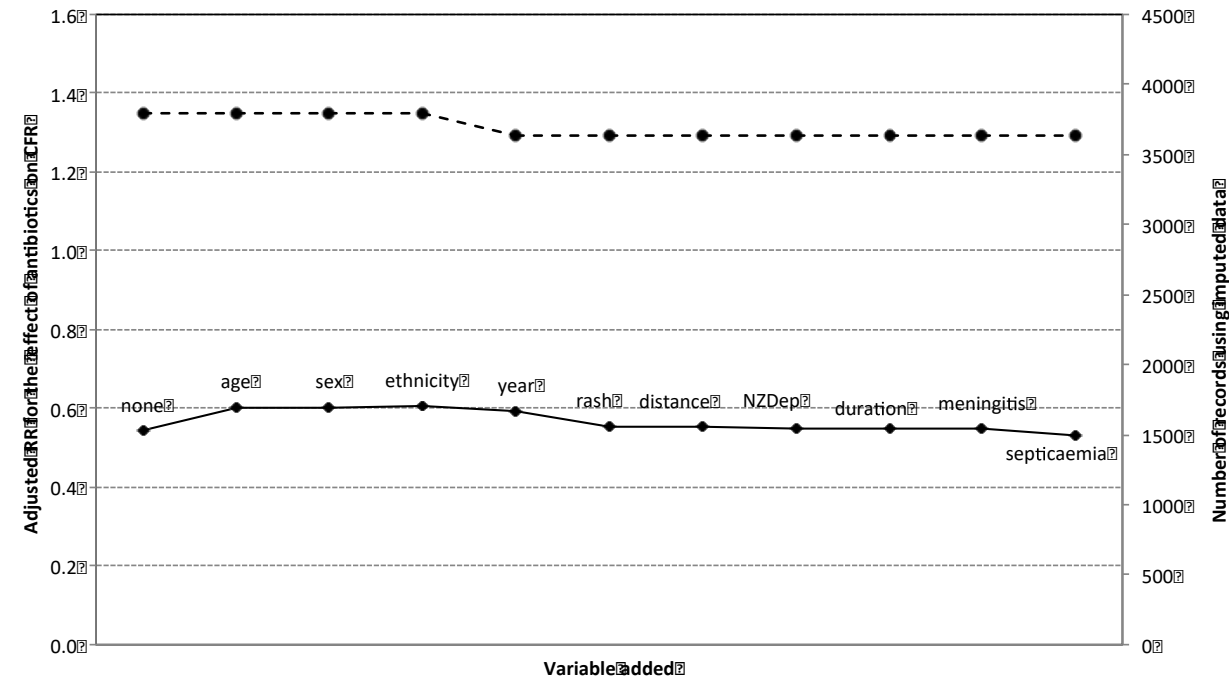
-> Multiple imputation using chained equations.

Multiple imputation reduced selection bias

Unimputed data



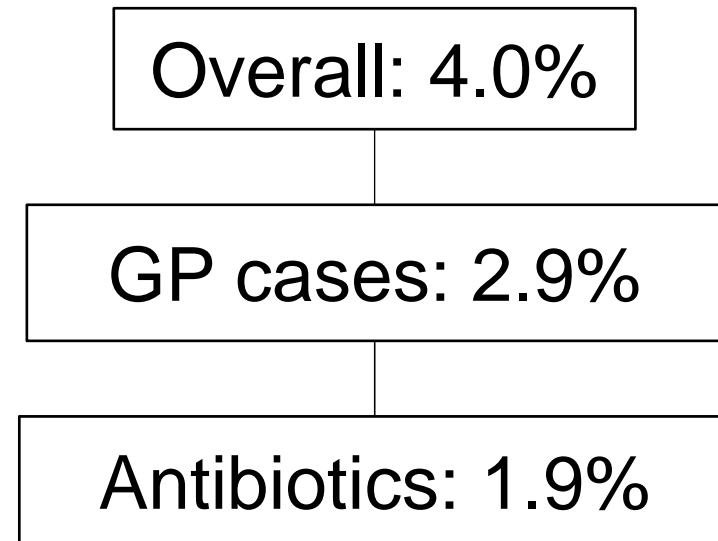
Imputed data



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 CONFOUNDER MISCLASSIFICATION

This spreadsheet can be used to conduct a probabilistic sensitivity analysis to correct for confounder misclassification and random error

Instructions
Enter the bias parameter distributions in the blue cells to the right and the observed data in the blue cells below.

Variable names	
Outcome	Death
Exposure	Antibiotics
Confounder	Rash

No. of simulations:

Run Simulation

Error checks
Illegal:

	Data (Enter Stratified Antibiotics-Death Data in Blue Cells)					
	Total		Rash +		Rash -	
	Antibiotics	Antibiot	Antibiotics	Antibiotics -	Antibiotics +	Antibiotics -
C10	25.4	84.6	23	73	2	11
Death	###	###	1181	1835	156	550
Total	1362	2470	1204	1908	158	561

Observed Crude and Adjusted Measures of Antibiotics-Death Relationship			
Crude Measure (95% CI)	Rash +	Rash -	
RR (Antibiotics-Death) 0.54 (0.35 - 0.84)	RR (Antibiotics-Death) 0.5	RR (Antibiotics-Death) 0.65	
OR (Antibiotics-Death) 0.54 (0.35 - 0.83)	OR (Antibiotics-Death) 0.43	OR (Antibiotics-Death) 0.64	

Standardized Morbidity Ratio		Mantel-Haenszel	
SMR _{RR} 0.52	RR _c 0.00	MH _{RR} 0.51	RR _c 0.00
SMR _{OR} 0.51	OR _c 0.00	MH _{OR} 0.50	OR _c 0.00

Single Simulated Corrected Estimate of Antibiotics-Death Relationship						
	Total		Rash +		Rash -	
	Antibiotics	Antibiot	Antibiotics	Antibiotics -	Antibiotics +	Antibiotics -
Death +	25	85	21.5	63.2	3.9	21.3
Death -	1337	2385	1114.4	1347.8	222.5	###
Total	1362	2470	1135.9	1411.1	226.4	###

Effect measures within strata of corrected confounder			
Crude Measure (95% CI)	C+	C-	
RR (ED) 0.42	RR (ED) 0.42	RR (ED) 0.86	
OR (ED) 0.41	OR (ED) 0.41	OR (ED) 0.85	

Standardized Morbidity Ratio		Mantel-Haenszel	
SMR _{RR} 0.43	RR _c 0.00	MH _{RR} 0.47	RR _c 0.00
SMR _{OR} 0.43	OR _c 0.00	MH _{OR} 0.46	OR _c 0.00

RR Simulation Results (N=5)	
Analysis Median [2.5 th - 97.5 th %]	
Conventional 0.54 (0.35 - 0.84)	
Systematic 0.47 (0.45 - 0.49)	
Total Error 0.48 (0.35 - 0.57)	

OR Simulation Results (N=5)	
Analysis Median [2.5 th - 97.5 th %]	
Conventional #REF!	
Systematic 0.46 (0.44 - 0.48)	
Total Error #REF!	

Rash + Conventional: 0.42 (0.27 - 0.67)	Rash - Conventional: 0.86 (0.19 - 3.82)
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Calculations	RR	OR	SE(LN(RR))	RR C+	RR C-	SE C+	SE C-
RR	0.47	OR(corrected)	0.46	0.42	0.86	0.24	0.76
SE(LN(RR))	0.22	SE(LN(OR))	###	0.334	2.532		
RR rand	0.517	Adj Var conditions?	###				
Negative cell	###	SE(LN(OR Corrected))	###				
		OR rand	###				

Correlation			
Se	Sp		
v	0.82	v	0.13
e1	0.39	e1	0.04
e0	0.56	e0	0.78
t	1.43	t	-1.9
f1	-0.45	f1	-3.1
f0	0.24	f0	1.27
p1	0.74	p1	0.04
p0	0.8	p0	0.27

Single Iteration											
Syst Error				+ Rand Error				Chosen Bias Parameters			
RR	OR	RR	OR	Se(D+)	Se(D-)	Sp(D+)	Sp(D-)	Sys RR	Rand RR	Sys RR	Rand RR
0.47	0.463	0.517	#REF!	97.2%	95.4%	45.9%	47.1%	0.42	0.39	0.86	2.53
0.43	0.477	0.35	#REF!	0.363	0.34	0.525	0.52	0.44	0.36	0.98	0.73
0.48	0.472	0.58	#REF!	0.37	0.35	0.523	0.52	0.44	0.43	0.89	1.22
0.47	0.463	0.51	#REF!	0.37	0.35	0.538	0.51	0.43	0.33	0.86	0.34
0.47	0.457	0.48	#REF!	0.371	0.34	0.486	0.46	0.41	0.52	0.95	0.62
0.45	0.44	0.37	#REF!	0.371	0.35	0.449	0.42	0.33	0.56	0.92	0.53

	RAND	PARAM	Chosen Param	Fixed for ND
Se(D+)	0.744	#REF!	#REF!	Se(D+) 0.97174
Se(D-)	0.804	#REF!	#REF!	Se(D-) 0.95412
Sp(D+)	0.04	#REF!	#REF!	Sp(D+) 0.45309
Sp(D-)	0.273	#REF!	#REF!	Sp(D-) 0.47076

- Beta distribution specifications**
Beta distribution? yes
- Calculator to estimate mean and SD**
Shape and position of distribution
Minimum: 0.27
Mode: 0.46
Maximum: 0.83
Mean = 0.49 (0.60)
SD = 0.03 (0.20)
- Estimate alpha and beta from mean and SD**
Alpha = 122 (3)
Beta = 127 (2)
- Bias parameters**
alpha: 1186.75, beta: 38.81
Se(D+): 1045.00, Se(D-): 56.31
Sp(D+): 141.54, Sp(D-): 126.53
- Correlation**
Corr Se: 0.75
Corr Sp: 0.75
- Misclassification** DIFF

E(x)	PARAMETERS
0.37	0.971741947
0.95	0.954120359
0.51	0.453093338
0.43	0.470755107

Alternative	Mean	SD
	0.20	0.05

Alpha	Beta
1216	128
126.6	51.2

Crude RR		Crude OR	
RR	0.544	OR	0.5
SE(LN(RR))	0.224	SE(LN(OR))	0.2

Chosen Values	
Se(D+)	37%
Se(D-)	35%
Sp(D+)	46%
Sp(D-)	47%

Negative cell check				
	C+	C-		
	0	0	0	0
	0	0	0	0
				Sum 0

No errors

Corrected Variance?

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		
<i>Selection bias</i>		
- Differential missingness	0.91 (0.37 - 2.25)	0.54 (0.35 - 0.84)
<i>Measured confounding</i>	0.54 (0.34 - 0.88)	
Quantitative bias analysis		
<i>Unmeasured confounding</i>		
- 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)
<i>Misclassification</i>		
- 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

