UWTASP tele-antimicrobial stewardship program | echo

March 14, 2023

Agenda

- Statistics, Back to Basics
- Speaker: *Zahra Kassamali Escobar*

Agenda

- Why do I have to?
- The Gold standard: Randomized Controlled Trials
- Population selected
- Randomization and confounding variables
- Interpreting results, confidently
- Questions you should ask

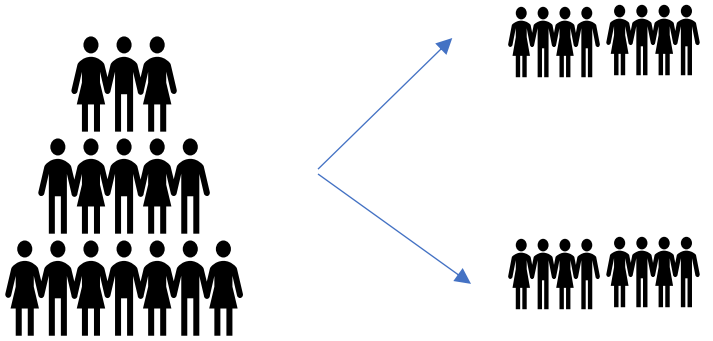
Why do I have to?

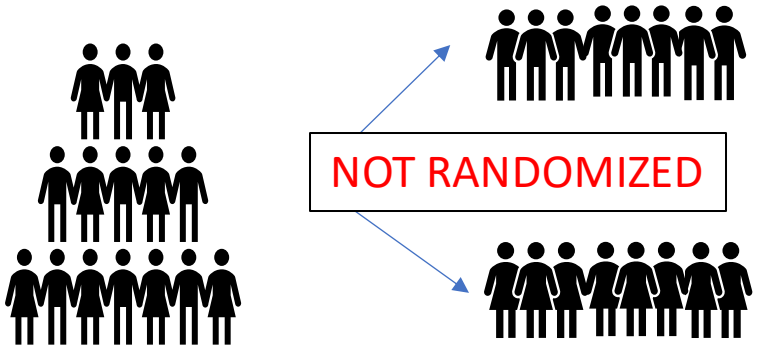
THINGS GOT REALLY INTERESTING WHEN THE STATISTICIAN STARTED DOING WARD ROUNDS.

- Statistics is the math we use to demonstrate relationships: causality, correlations, and lack of relationships
- Statistics may be math, but interpretation is subjective

The Gold Standard: Randomized Controlled Trials

- Removes bias
- Allocation into groups must be
  - concealed
  - random

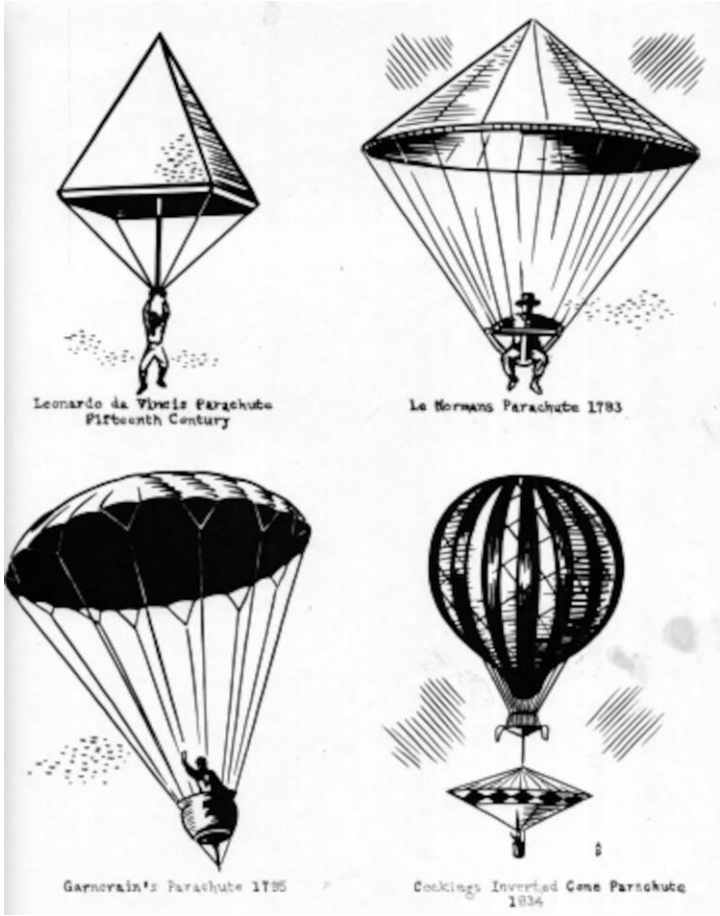




Parachute Use to Prevent Death

& major trauma related to gravitational challenge: systemic review of randomized controlled trials

- **Conclusions** As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials.



BMJ. 2003 Dec 20; 327(7429): 1459–1461. doi: 10.1136/bmj.327.7429.1459

Parachute Use to Prevent Death

& major trauma related to gravitational challenge: systemic review of randomized controlled trials

- **Conclusions** (cont)
  Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data.

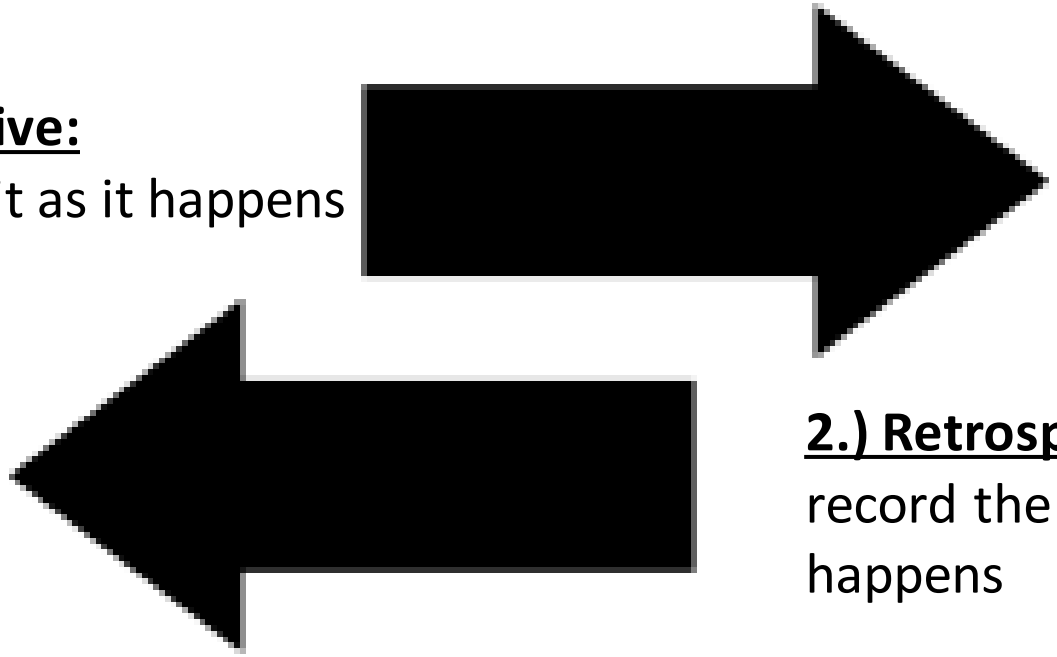
  We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

BMJ. 2003 Dec 20; 327(7429): 1459–1461. doi: 10.1136/bmj.327.7429.1459
Image from: https://www.merriam-webster.com/words-at-play/thems-fightin-words

What usually happens:
We observe the intervention but don't direct it

- Observational studies, 2 main types:

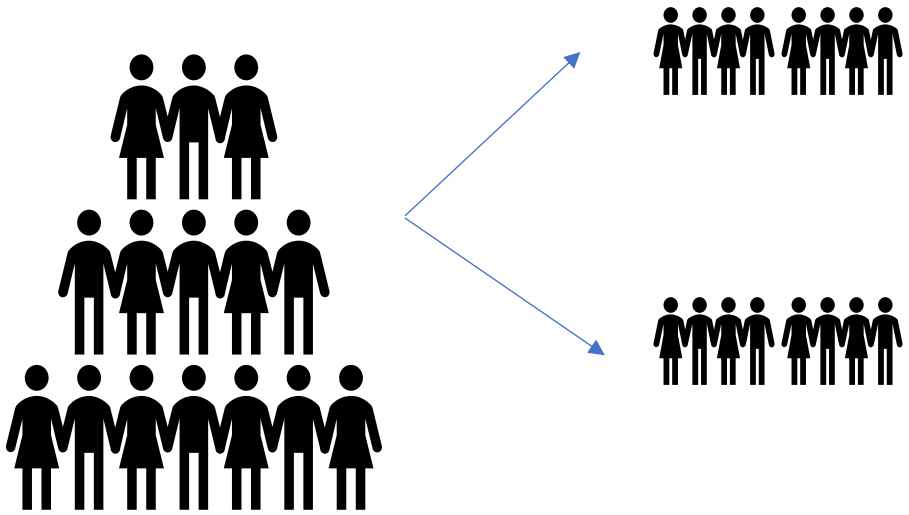
1.) Prospective:
record data it as it happens



2.) Retrospective:
record the data after it happens

The Problem with Observational Studies = BIAS

- Allocation into groups
  - Concealed
  - Random



How to Manage Bias?

Genetics

Quantity consumed

Food quality

Amount of Fat in their Diet → Weight of an Individual

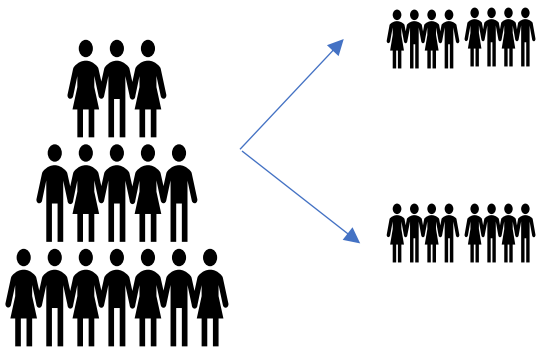
Income

Geography

Access to grocery stores

Education

How to Manage Bias?
1. Identify confounders



In a randomized trial, the confounders still exist but we assume they're evenly distributed if we did our randomization correctly

Amount of Fat in their Diet → Weight of an Individual

Genetics

Income

Geography

Access to grocery stores

Education

Food quality

Quantity consumed

How to Manage Bias?
2. Adjust for confounders

Words to look for in methods/analysis section:

- **Variables**
  (do they make clinical sense?)
- **Adjustment**
- **Model**

Adjust for confounders: 2 Examples

Words to look for in the methods/statistical analysis section:

- **Variables** (do they make clinical sense?)
- **Adjustment**
- **Model**

Statistical Analysis:

Variables *with a P-value of <0.10 in the* ***univariate*** *Cox* ***model*** *and those that differed across the three oral antimicrobial agent groups in theinitial comparison were included in the* ***multivariate*** *Cox proportional hazards regression analysis.*[1]

Variables included *in the overlap weights* ***model*** *were selected a priori using the literature and clinical judgment to identify risk factors associated with either recurrent bacteremia or mortality.*[2]

[1]Int J Antimicrob Agents. 2016 Nov;48(5):498-503. doi: 10.1016/j.ijantimicag.2016.07.013.
[2]JAMA Netw Open. 2020;3(10):e2020166. doi:10.1001/jamanetworkopen.2020.20166

Reading a paper with statistics in mind:

Original Investigation | Infectious Diseases

October 8, 2020

Oral β-Lactam Antibiotics vs Fluoroquinolones or Trimethoprim-Sulfamethoxazole for Definitive Treatment of Enterobacterales Bacteremia From a Urine Source

Jesse D. Sutton, PharmD, MS[1,2]; Vanessa W. Stevens, PhD[2,3]; Nai-Chung N. Chang, PhD[2,3]; Karim Khader, PhD[2,3]; Tristan T. Timbrook, PharmD, MBA[2,3,4]; Emily S. Spivak, MD, MHS[2,5]

» Author Affiliations | Article Information

JAMA Netw Open. 2020;3(10):e2020166. doi:10.1001/jamanetworkopen.2020.20166

1. Study Design & Included Population

Does the sample studied match your population of interest?

Abstract

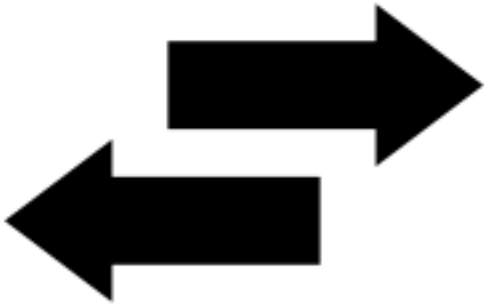
Importance Oral β-lactam antibiotics are traditionally not recommended to treat Enterobacterales bacteremia because of concerns over subtherapeutic serum concentrations, but there is a lack of outcomes data, specifically after initial treatment with parenteral antibiotics. Given the limited data and increasing limitations of fluoroquinolones or trimethoprim-sulfamethoxazole (TMP-SMX), oral β-lactam antibiotics may be a valuable additional treatment option.

Objective To compare definitive therapy with oral β-lactam antibiotics vs fluoroquinolones or TMP-SMX for Enterobacterales bacteremia from a suspected urine source.

Design, Setting, and Participants A retrospective cohort study was conducted from January 1, 2007, to September 30, 2015, at 114 Veterans Affairs hospitals among 4089 adults with *Escherichia coli*, *Klebsiella* spp, or *Proteus* spp bacteremia and matching urine culture results. Additional inclusion criteria were receipt of active parenter sion to an oral antibiotic. Exclusion criteria were previous Enterobacterales bacteremia, ur tis. Data were analyzed from April 15, 2019, to July 26, 2020.

Exposures Conversion of therapy to an oral β-lactam antibiotic vs fluoroquinolones or TM enteral antibiotics.

Main Outcomes and Measures The main outcome was a composite of either bacteremia. Propensity-based overlap weights were used to adjust for differe models were used to estimate adjusted relative risks (aRRs) and adjusted risk



2.) Retrospective:

record the data after it happens

2. Population
(Are they matched despite no randomization?

Table 1. Demographic, Clinical, and Treatment Characteristics

Characteristic	Patients, No. (%)	
	Fluoroquinolone or trimethoprim-sulfamethoxazole (n = 3134)	β-Lactam antibiotics (n = 955)
Age, median (IQR), y	69 (62-80)	73 (64-83)
Male	2847 (90.8)	884 (92.6)
Race/ethnicity		
White	1983 (63.3)	617 (64.6)
Black	714 (22.8)	202 (21.2)
Hispanic or Latino	185 (5.9)	53 (5.5)
Native American, Alaskan, Hawaiian, or Pacific Islander	41 (1.3)	13 (1.4)
Asian	20 (0.6)	3 (0.3)
Missing, unknown, or declined to answer	191 (6.1)	67 (7.0)
Preexisting conditions[a]		
Combined comorbidity score, median (IQR)	1 (0-2)	1 (0-3)
Chronic kidney disease	564 (18.0)	227 (23.8)
Chronic pulmonary disease	681 (21.7)	220 (23.0)
Heart failure	480 (15.3)	170 (17.8)
Diabetes with complication	402 (12.8)	130 (13.6)
Dementia	180 (5.7)	69 (7.2)
Immunosuppression	182 (5.8)	61 (6.4)
History of organ or stem cell transplant	72 (2.3)	22 (2.3)
Transplant antirejection medications within 90 d	64 (2.0)	20 (2.1)
High-dose corticosteroids within 30 d	39 (1.2)	17 (1.8)
Other immunosuppressive medication within 90 d	68 (2.2)	23 (2.4)
Leukopenia, leukocyte ≤1000 cells/μL	5 (0.2)	1 (0.1)
Metastatic cancer	144 (4.6)	47 (4.9)
Cirrhosis	88 (2.8)	20 (2.1)
HIV	40 (1.3)	10 (1.0)
Preexisting urologic conditions[a]		
History of urinary tract infection	886 (28.3)	401 (42.0)
Previous antibiotics active against gram-negative organisms within 30 d	398 (12.7)	222 (23.2)
Prostate hypertrophy	887 (28.3)	324 (33.9)
Urinary retention, obstruction, or other structural urologic abnormality	723 (23.1)	288 (30.2)
Urologic procedure within 90 d before oral step-down therapy	562 (17.9)	212 (22.2)
Prostate cancer	408 (13.0)	143 (15.0)
Spinal cord injury, paraplegia,	129 (4.1)	52 (5.4)

Table 1:

- Age
- Sex
- Pre-existing conditions
- Immunosuppression

3. Intervention

Comparable despite no randomization (i.e. time to antibiotic therapy, etc)

Table 1. Demographic, Clinical, and Treatment Characteristics (continued)

Characteristic	Patients, No. (%)	
	Fluoroquinolone or trimethoprim-sulfamethoxazole (n = 3134)	β-Lactam antibiotics (n = 955)
Acute characteristics[b]		
Time from hospitalization to bacteremia ≥48 h	159 (5.1)	28 (2.9)
Antibiotic initiation		
Intensive care unit	543 (17.3)	165 (17.3)
Vasopressors	122 (3.9)	30 (3.1)
Serum leukocyte ≥12 000 cells/μL	2145 (68.4)	615 (64.4)
Temperature ≥38.3 °C	1799 (57.4)	542 (56.8)
Treatment characteristics		
Time to in vitro active antibiotics, median (IQR), h	12 (6-20)	13 (7-21)
1st day of oral antibiotics alone, median (IQR), d	4 (4-5)	5 (4-5)
Oral antibiotic with in vitro activity	3077 (98.2)	937 (98.1)
Unknown	34 (1.1)	12 (1.3)
Antibiotic duration, median (IQR), d		
Total	14 (12-16)	14 (12-16)
Oral	10 (9-13)	10 (8-12)

Decision Point:

Outcomes:

Variable of interest

Rate in each treatment group

Comparative risk

Table 2. Outcomes

Outcome	Patients, No. (%)		aRD, % (95% CI)[a]	aRR (95% CI)[a]
	Fluoroquinolones or trimethoprim-sulfamethoxazole (n = 3134)	β-Lactam antibiotics (n = 955)		
30-d Mortality and recurrent bacteremia	94 (3.0)	42 (4.4)	0.99 (−0.42 to 2.40)	1.31 (0.87 to 1.95)
Mortality	82 (2.6)	29 (3.0)	0.06 (−1.13 to 1.26)	1.02 (0.67 to 1.56)
Recurrent bacteremia	12 (0.4)	14 (1.5)	1.03 (0.24 to 1.82)	3.43 (0.42 to 27.90)
90-d Mortality and recurrent bacteremia	238 (7.6)	96 (10.1)	1.81 (−0.24 to 3.87)	1.23 (0.96 to 1.56)
Mortality	208 (6.6)	75 (7.9)	0.68 (−1.16 to 2.52)	1.10 (0.85 to 1.42)
Recurrent bacteremia	34 (1.1)	25 (2.6)	1.38 (0.30 to 2.47)	2.15 (0.92 to 5.01)
Repeated hospitalization with UTI				
At 30 d	22 (0.7)	14 (1.5)	0.81 (−0.06 to 1.67)	2.08 (0.72 to 5.99)
At 90 d	46 (1.5)	29 (3.0)	1.46 (0.28 to 2.64)	1.94 (0.97 to 3.85)

Abbreviation: aRD, adjusted risk difference; aRR, adjusted relative risk; UTI, urinary tract infection.

[a] Risk difference and relative risk calculated with fluoroquinolones or trimethoprim-sulfamethoxazole as the reference group and β-lactam antibiotics as the intervention group.

Interpreting Outcomes:

Variable of interest

Rate in each treatment group

Comparative risk

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aRD: **Adjusted** risk difference = Risk with (β-lactam – Fluoroquinolone)

aRR: **Adjusted** relative risk = Risk with (β-lactam / Fluoroquinolone)

Interpreting Outcomes:

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aRD, % (95% CI)[a]
0.99 (−0.42 to 2.40)

aRD: **Adjusted** risk difference = Risk with (β-lactam - Fluoroquinolone)
Shows that <mortality and recurrent bacteremia> occurs about 1% more frequently with BL vs. FQ

aRR (95% CI)[a]
1.31 (0.87 to 1.95)

aRR: **Adjusted** relative risk = Risk with (β-lactam / Fluoroquinolone)
Shows that <mortality and recurrent bacteremia> occurs 31% more often with BL compared to mortality and recurrent bacteremia with FQs

<mortality and recurrent bacteremia> = <outcome of interest>
BL = Beta-lactam, FQ = fluoroquinolone

Interpreting Outcomes: Why Confidence intervals?

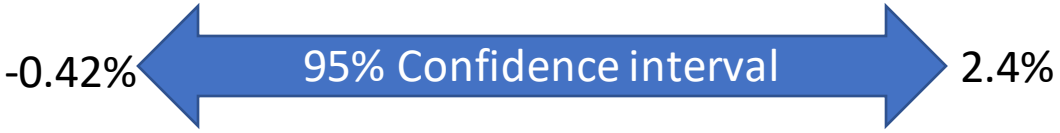
The confidence interval is the precision of your estimate

- A smaller interval is more precise and reliable
- A wider interval indicates more variation

Interpreting the Confidence Interval Absolute difference

aRD, % (95% CI)[a]
0.99 (−0.42 to 2.40)

aRD: **Adjusted** risk difference = Risk with (β-lactam - Fluoroquinolone)
Risk of mortality is 1% higher with βL vs. FQ and ranges from half a percent (0.42) less with BL to 2.4% more



Risk of mortality and recurrence might be 0.42% less with BL vs. FQ

Risk of mortality and recurrence might be 2.4% more with BL vs. FQ

Is this CI statistically significantly different?

Table 2. Outcomes

Outcome	Patients, No. (%)		aRD, % (95% CI)[a]	aRR (95% CI)[a]
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aRD = Adjusted risk difference

(β-lactam - Fluoroquinolone)

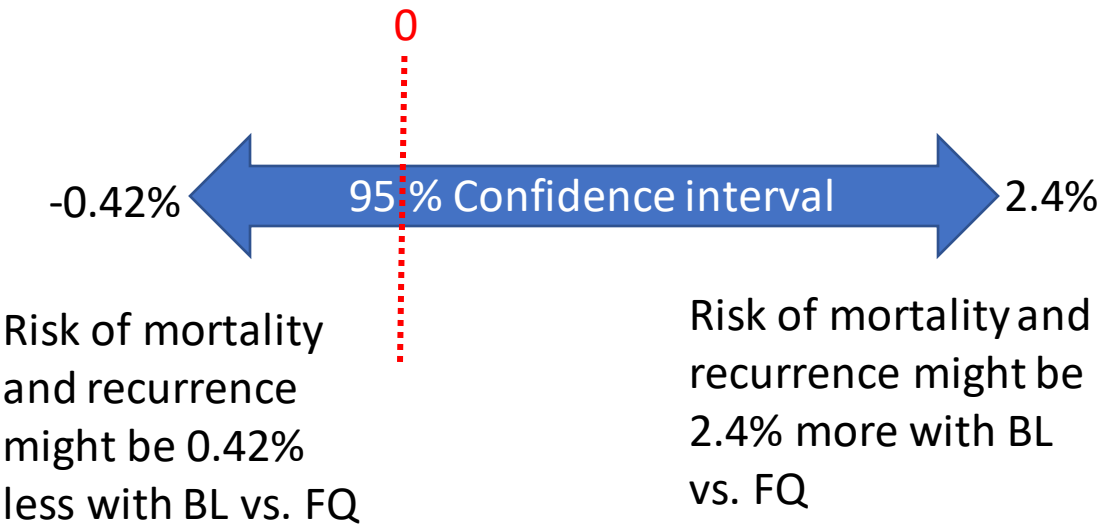
95% CI (-0.42 , 2.40)

Is this CI statistically significant?

No, because the confidence interval crosses zero

aRD = Adjusted risk difference
(β-lactam - Fluoroquinolone) = 0

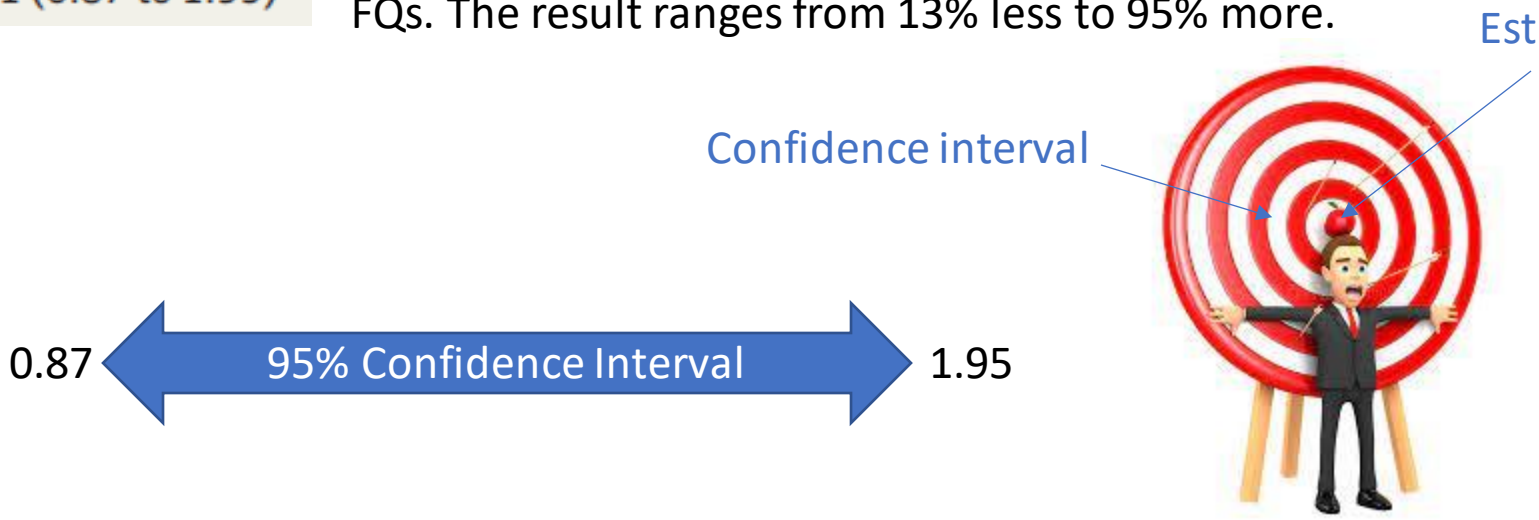
0.99, 95% CI (-0.42 to 2.40)



Interpreting the Confidence Interval: Relative difference

aRR (95% CI)[a]
1.31 (0.87 to 1.95)

aRR: **Adjusted relative risk** = Risk with (β-lactam / Fluoroquinolone)
Shows that mortality and recurrent bacteremia occurs 31% more often with BL compared to mortality and recurrent bacteremia with FQs. The result ranges from 13% less to 95% more.



Note the bigger numbers with relative risk and how they make you feel.
They can help put low frequency outcomes into context and/or add shock value

Is this CI statistically significantly different?

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aRR = Adjusted relative risk

(β-lactam / Fluoroquinolone)

95% CI (0.87 , 1.95)

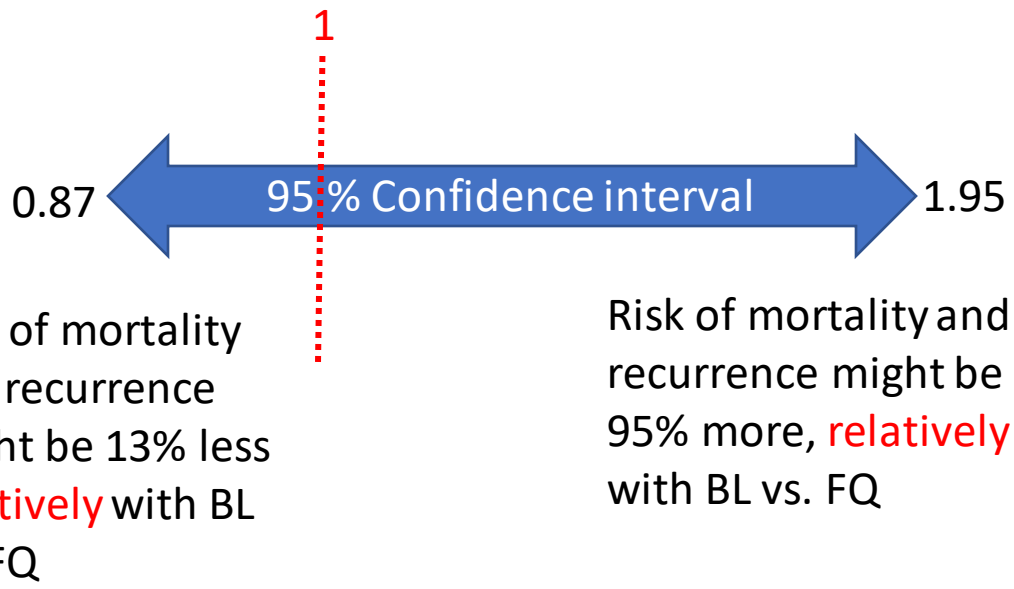
Is this statistically significantly different?

Is this CI statistically significant?

No, because the confidence interval crosses one

aRD = Adjusted relative risk
(β-lactam / Fluoroquinolone) = 1

1.31, 95% CI (0.87 to 1.95)



Note the bigger numbers with relative risk and how they make you feel.
They can help put low frequency outcomes into context and/or add shock value

Questions to ask

- What is the design of this study (randomized, observational, prospective, retrospective)?
- Does the sample studied match your population of interest?
- Are the groups evenly matched?
- Was the intervention applied evenly to each group?
- Did they account for confounding factors?
- Did they report absolute vs. relative differences?