UWTASP tele-antimicrobial stewardship program | echo

Reframing Outcomes: Number Needed to Treat (NNT) vs Number Needed to Harm (NNH)

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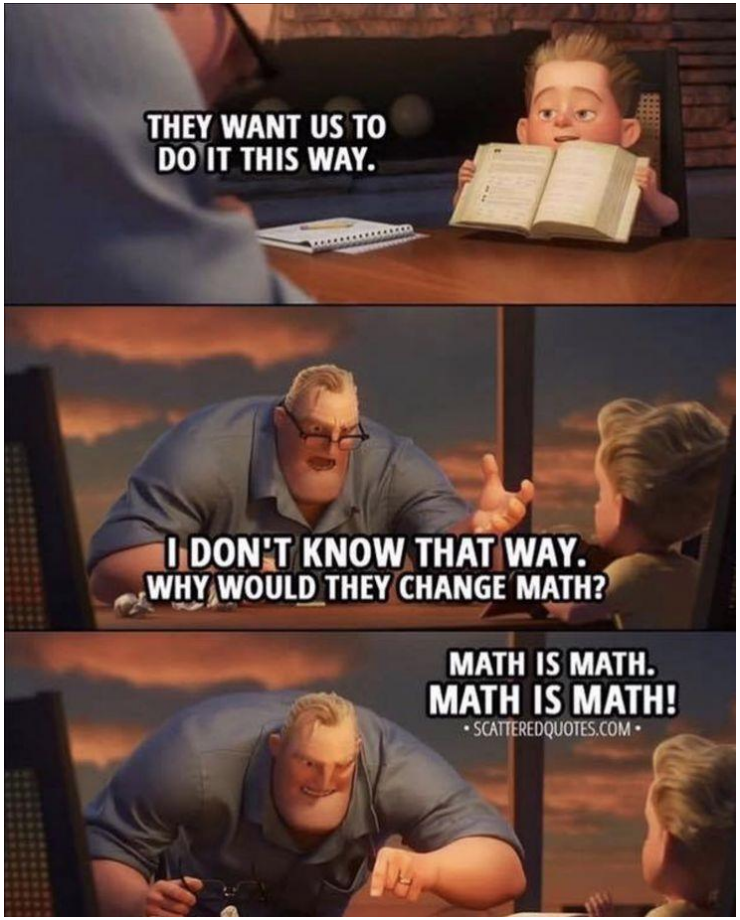
Project ECHO

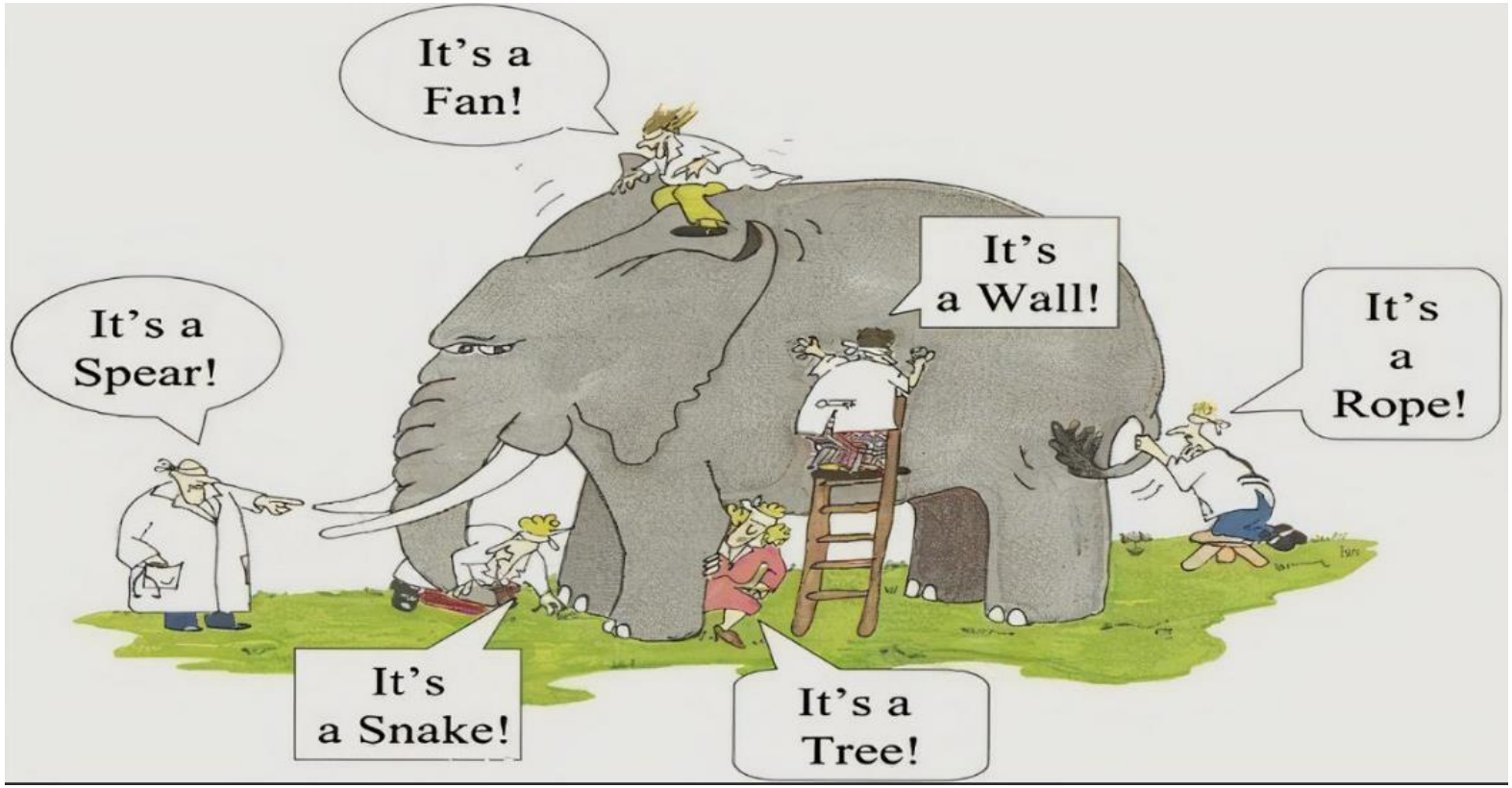
We need to talk about MATH!



- Statistics is the math we use to demonstrate relationships or establish the *lack of* relationships.

- Statistics is "sophisticated math" that requires interpretation

Observation alone can lead us astray……

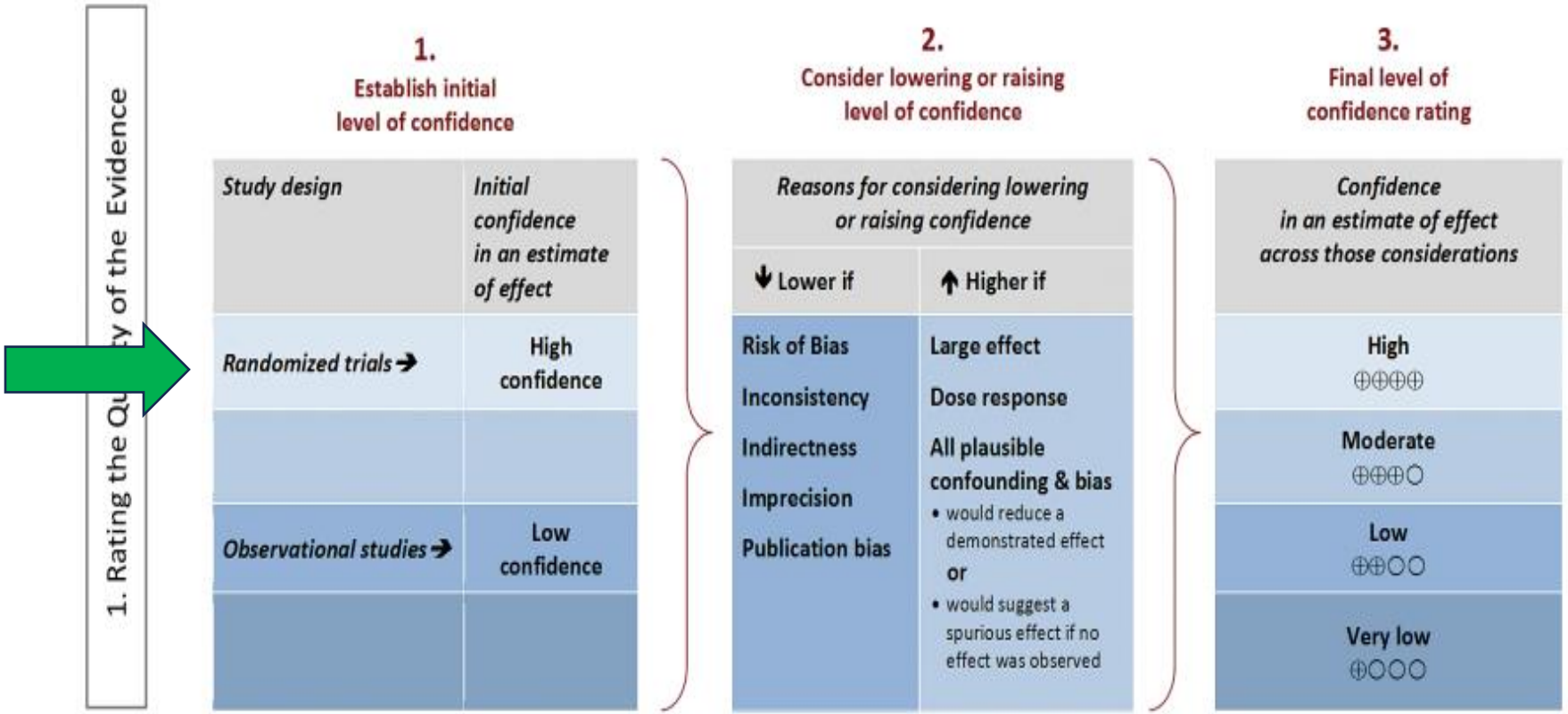


Though each was partly in the right, all were in the wrong.

https://www.sloww.co/blind-men-elephant/

Slide Courtesy of Zahra K. Escobar PharmD

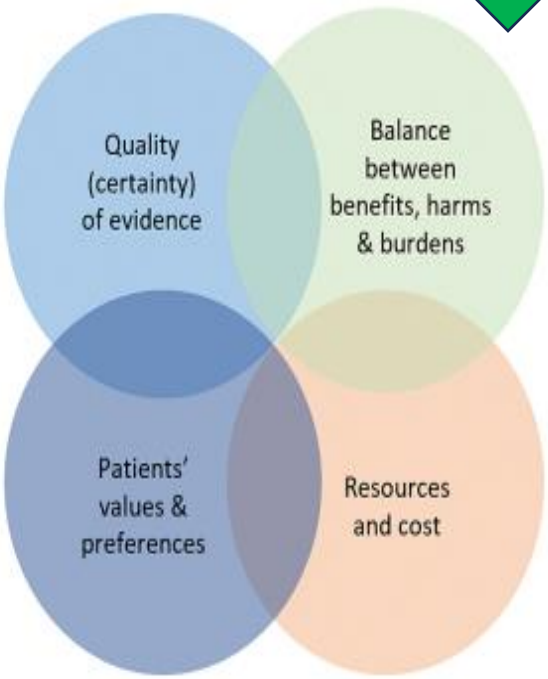
Quality of Evidence



Strength of Recommendation

NNT and NNH

2. Determinants of the Strength of Recommendation



3. Implication of the Strength of Recommendation

Strong

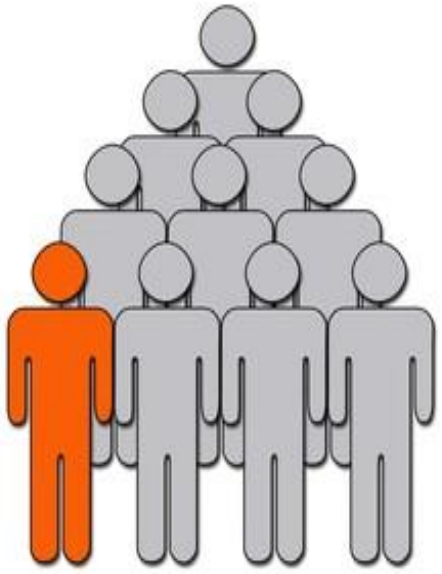
- Population: Most people in this situation would want the recommended course of action and only a small proportion would not
- Healthcare workers: Most people should receive the recommended course of action
- Policy makers: The recommendation can be adapted as a policy in most situations

Weak

- Population: The majority of people in this situation would want the recommended course of action, but many would not
- Healthcare workers: Be prepared to help people to make a decision that is consistent with their own values/decision aids and shared decision making
- Policy makers: There is a need for substantial debate and involvement of stakeholders

Number Need to Treat (NNT)

Intervention Group:
90% efficacy



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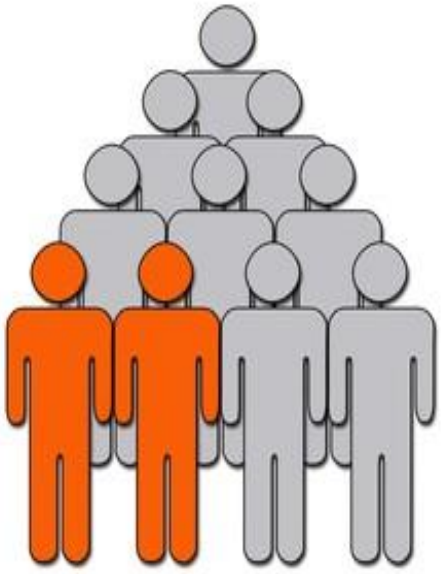
Control Group:
80% efficacy



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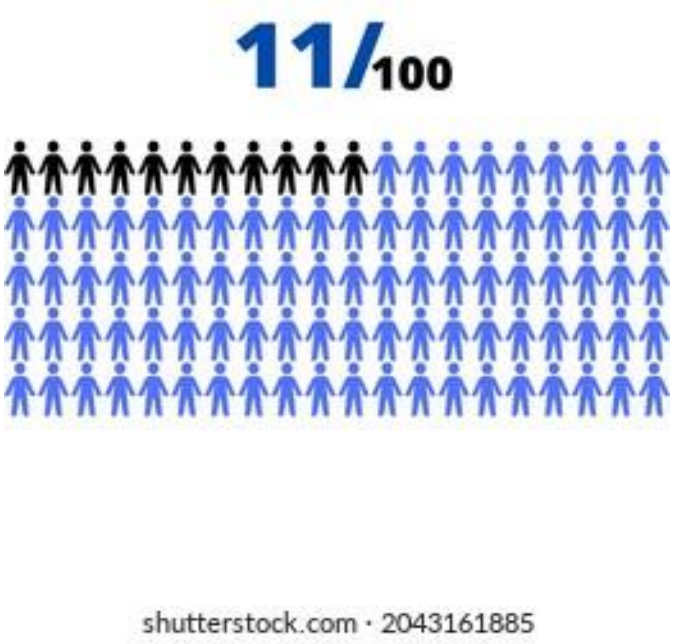
NNT = 1/ARR

- **Absolute Risk Reduction (ARR)**
  - Difference between the event rate in control group and intervention group
  - 90% - 80% = 10% = 0.1

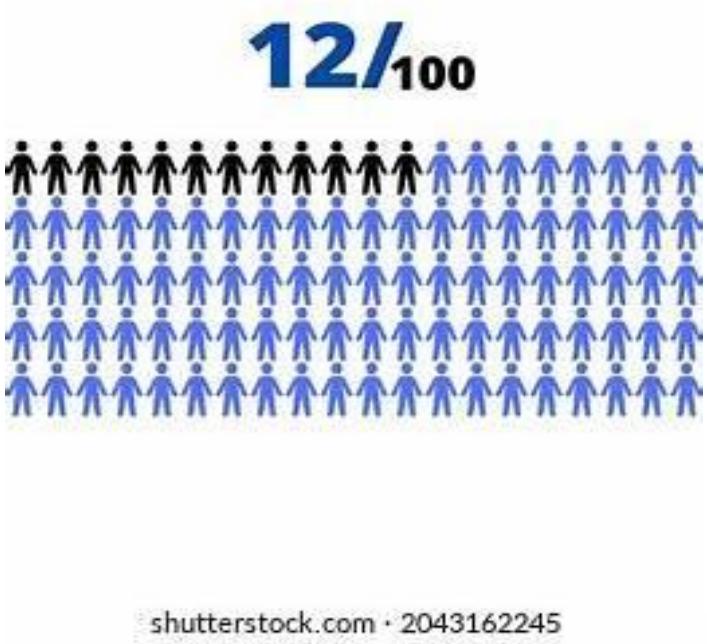
- **Number Needed to Treat (NNT)**
  - Inverse of the absolute risk reduction (ARR) expressed as a decimal.
  - NNT = 1/ARR
  - NNT = 1/0.1 = 10

Number Need to Harm (NNH)

Control Group:
11% ADR



Intervention Group:
12% ADR

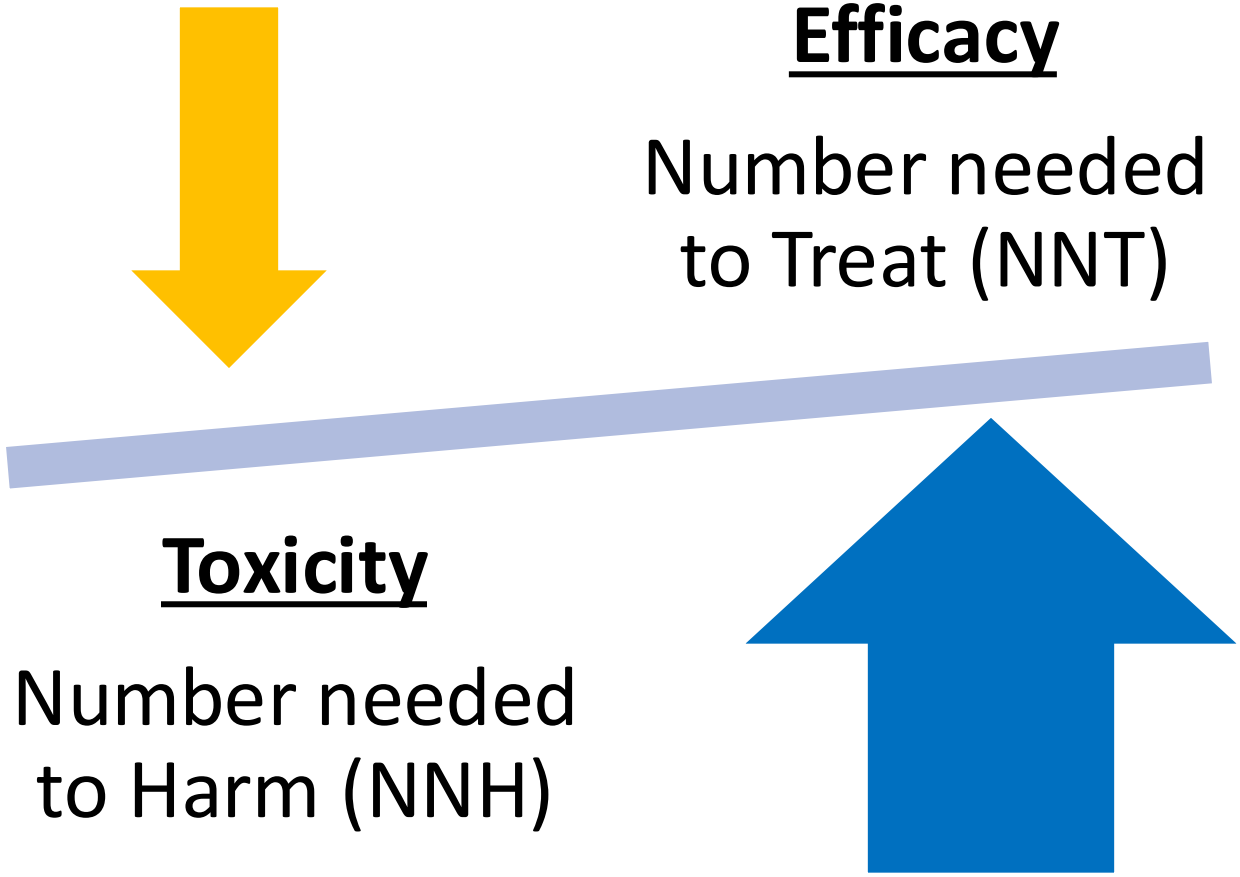


NNH = 1/ARI

- **Absolute Risk Increase (ARI)**
  - Difference between the event rate in control group and intervention group
  - 12% - 11% = 1% = 0.01

- **Number Needed to Harm (NNH)**
  - Inverse of the absolute risk increase (ARI) expressed as a decimal.
  - NNH = 1/ARI
  - NNH = 1/0.01 = 100

Balancing Efficacy and Toxicity



CAMERA-2 Trial

JAMA Network

QUESTION In adults with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, does the addition of 7 days of an antistaphylococcal β-lactam to standard antibiotic therapy (vancomycin or daptomycin) lead to improved clinical outcomes at 90 days?

CONCLUSION This randomized trial found that the addition of an antistaphylococcal β-lactam to standard antibiotic therapy did not significantly reduce the primary composite end point in patients with MRSA bacteremia.

POPULATION

231 Men
121 Women

Adults hospitalized with MRSA bacteremia

Mean age: **62** years

LOCATIONS

27
Hospitals in Australia, Singapore, New Zealand, and Israel

INTERVENTION

345 Patients analyzed

170
Combination therapy
IV vancomycin or daptomycin for 14-42 days plus IV β-lactam for 7 days

175
Standard therapy
IV vancomycin or daptomycin for 14-42 days

PRIMARY OUTCOME

Composite at 90 days of all-cause mortality, persistent bacteremia at day 5, microbiological relapse, and microbiological failure

FINDINGS

All-cause mortality, persistent bacteremia at day 5, microbiological relapse, and microbiological failure

Combination therapy
59 of 170 patients

Standard therapy
68 of 175 patients

The primary outcome was not significant:

Between-group difference: **−4.2%**
(95% CI, −14.3% to 6.0%)

Tong SYC, Lye DC, Yahav D, et al. Effect of vancomycin or daptomycin with vs without an antistaphylococcal ß-lactam on mortality, bacteremia, relapse, or treatment failure in patients with MRSA bacteremia: a randomized clinical trial [published February 11, 2020]. *JAMA*. doi:10.1001/jama.2020.0103

Let's look at AKI

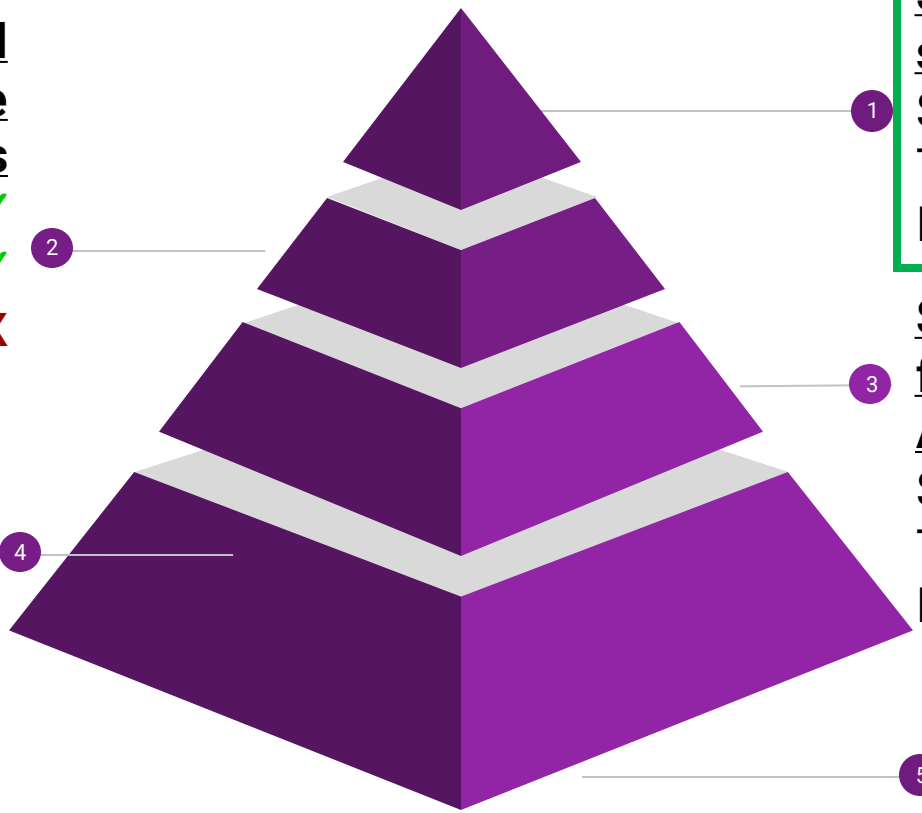
Secondary Outcomes[c]				
All-cause mortality[d]				
Day 14	13/170 (8)	13/174 (7)	0.2 (−5.4 to 5.8)	.95
Day 42	25/170 (15)	19/174 (11)	3.8 (−3.3 to 10.8)	.29
Day 90	35/170 (21)	28/174 (16)	4.5 (−3.7 to 12.7)	.28
Persistent bacteremia[e]				
Day 2	50/167 (30)	61/173 (35)	−5.3 (−15.3 to 4.6)	.29
Day 5	19/166 (11)	35/172 (20)	−8.9 (−16.6 to −1.2)	.02
Microbiological relapse[a]	14/169 (8)	18/175 (10)	−2.0 (−8.1 to 4.1)	.52
Microbiological treatment failure[a]	16/170 (9)	17/175 (10)	−0.3 (−6.5 to 5.9)	.92
Acute kidney injury[f]	34/145 (23)	9/145 (6)	17.2 (9.3 to 25.2)	<.001
Duration of intravenous antibiotics, mean (SD), d	29.3 (19.5)	28.1 (17.4)		.72

Absolute Risk Increase (ARI) = 23% - 6% = 17% = 0.17

Number Needed to Harm (NNH) = 1/0.17 = 6

If we give combination therapy to all patients with MRSA bacteremia, 1 out of 6 patients may develop harm (AKI)

DOOR Analysis – Desirability of Outcome Ranking



Survival with clinical success without AEs
Survival ✓
Treatment success ✓
No AKI ✓

Survival with clinical success and some AEs
Survival ✓
Treatment success ✓
AKI X

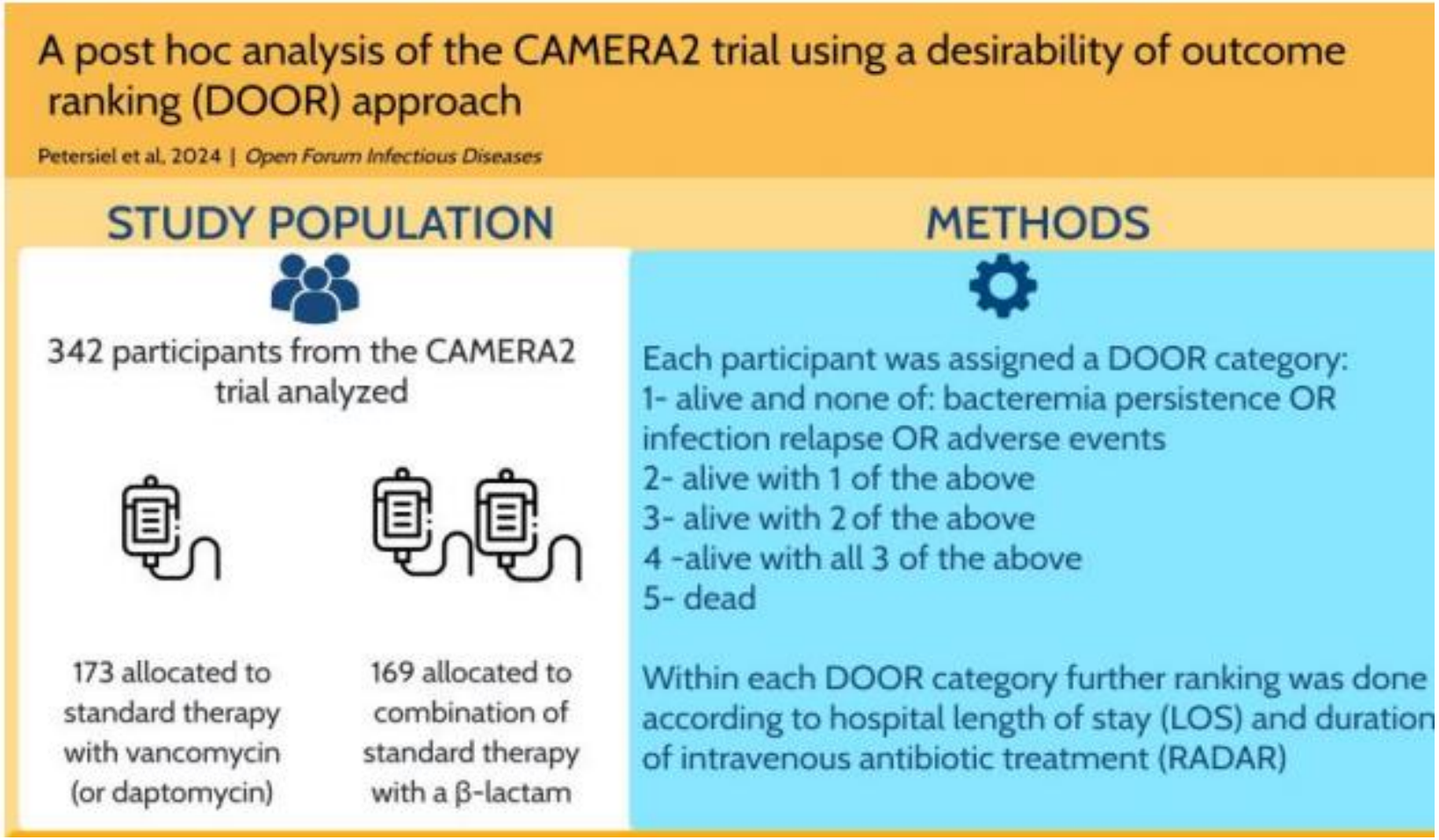
Survival with clinical failure but without AEs
Survival ✓
Treatment failure X
No AKI ✓

Survival with clinical failure and AEs
Survival ✓
Treatment failure X
AKI X

Death

Evans S, et al. Clinical Infectious Diseases. 2015; 61(5):800-806.
Slide Courtesy of Joanne Huang PharmD

CAMERA-2 and DOOR analysis



When considering both efficacy and safety, treatment of MRSA bacteremia with a combination of standard therapy and a β-lactam likely results in a worse clinical outcome than standard therapy

Open Forum Infectious Diseases https://doi.org/10.1093/ofid/ofae181

Table 2. Distribution of Participants Within Desirability of Outcome Ranking Categories for the CAMERA2 Trial by Treatment Group[a]

DOOR Category	Standard Therapy, No. (%) (n = 173)	Combination Therapy, No. (%) (n = 169)
1	99 (57.2)	82 (48.5)
2	35 (20.2)	42 (24.9)
3	11 (6.4)	8 (4.7)
4	0	2 (1.2)
5	28 (16.2)	35 (20.7)

Abbreviations: CAMERA2, Combination Antibiotics for MEthicillin Resistant *Staphylococcus aureus*; DOOR, desirability of outcome ranking.

[a]Data on 2 of the DOOR components were missing for 10 participants, who were excluded from the primary analysis: Data on 90-day mortality were missing for 6 participants (1.7%, 3 from each arm), and data on persistent bacteremia were missing for 4 participants (1.1%, 2 from each arm).

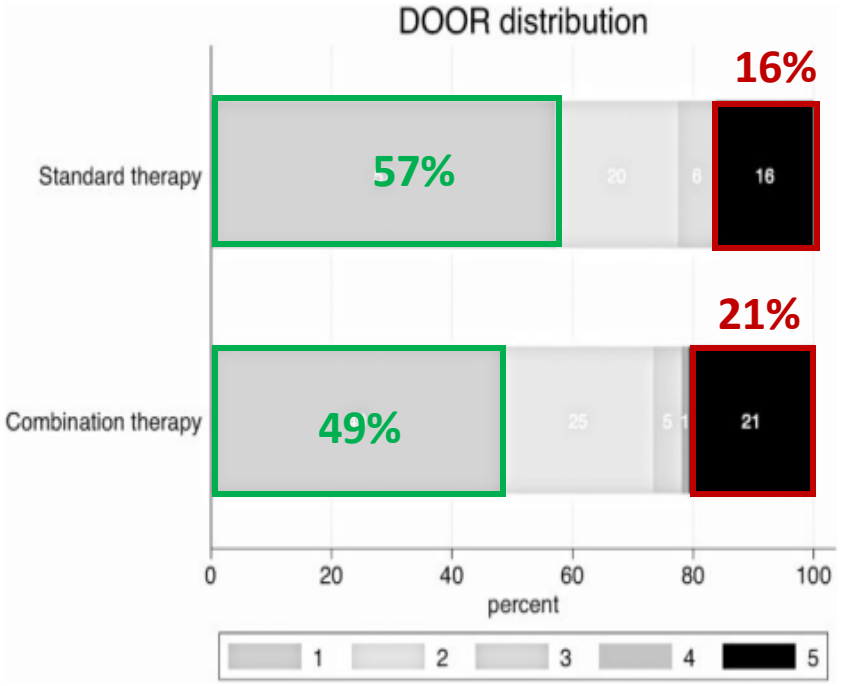


Figure 1. Desirability of outcome ranking (DOOR) distribution according to treatment groups: primary analysis. The DOOR is ranked from 1 (best) to 5 (worst). Percentages for each category are indicated within the bars.

Reframing Conclusions

- **JAMA (Original analysis):**
  - This randomized trial found that the addition of an anti-staphylococcal β-lactam to standard antibiotic therapy ***did not significantly reduce the primary composite endpoint*** (90-day mortality, persistent bacteremia at day 5, or microbiological relapse/failure) in patients with MRSA bacteremia

- **OFID (DOOR analysis):**
  - When ***considering both efficacy and safety***, treatment of MRSA bacteremia with a combination of standard therapy and a β-lactam ***likely results in a worse clinical outcome*** than standard therapy

Summary

- NNT – relative benefits of a given intervention. The **lower** the number, the **more effective** the treatment.

- NNH – relative harms of a given intervention. The **higher** the number, the **safer** the intervention.

- Desirability of outcome ranking – more pragmatic approach (balancing efficacy/toxicity)