Interpreting randomized controlled trials

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Postma DF et al.

Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults

N Engl J Med 2015; 372:1312-1323

METHODS

In a **cluster-randomized, crossover trial** with strategies rotated in 4-month periods, we tested the noninferiority of the **beta-lactam** strategy to the **beta-lactam–macrolide** and **fluoroquinolone** strategies with respect to **90-day mortality**, in an intention-to-treat analysis, using a noninferiority margin of 3 percentage points and a two-sided 90% confidence interval.

Is the question of interest to my patients?

- Patients
- Intervention
- Comparison
- Outcome

Internal validity

- Randomization
- Allocation concealment
- Blinding
- Intention to treat analysis

Inclusion and exclusion criteria

- Inclusion:
  - Patients 18 years of age or older with clinically suspected CAP who required antibiotic treatment and hospitalization in a non-ICU ward.
- Exclusion:
  - cystic fibrosis

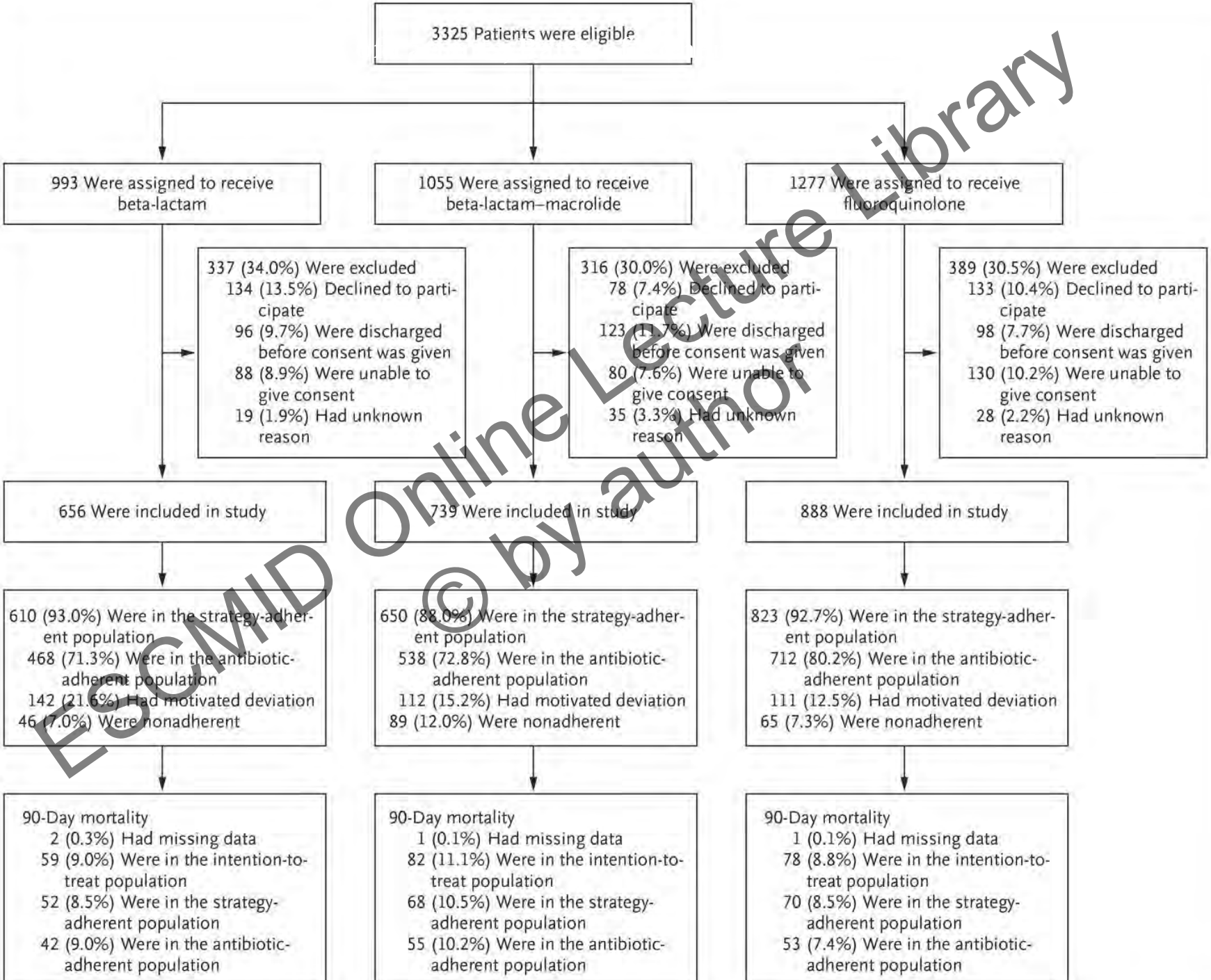


Table 2. Baseline Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Antibiotic Treatment Strategy		
	Beta-Lactam (N=656)	Beta-Lactam–Macrolide (N=739)	Fluoroquinolone (N=888)
Median age (interquartile range) — yr	70 (60–79)	70 (59–80)	71 (59–79)
Male sex — no. (%)	381 (58.1)	431 (58.3)	505 (56.9)
Median duration of symptoms (interquartile range) — days	3 (1–7)	3 (1–7)	3 (1–7)
Received antibiotics before admission — no./total no. (%)	219/637 (34.4)	227/721 (31.5)	303/873 (34.7)
Current smoker — no./total no. (%)	109/627 (17.4)	154/723 (21.3)	196/872 (22.5)
Past smoker — no./total no. (%)	379/627 (60.4)	398/723 (55.0)	490/872 (56.2)
Received influenza vaccination — no./total no. (%)	453/624 (72.6)	466/700 (66.6)	572/847 (67.5)
Received pneumococcal vaccination — no./total no. (%)			
PPSV23	16/594 (2.7)	18/671 (2.7)	13/822 (1.6)
PCV13	19/656 (2.9)	7/739 (0.9)	10/888 (1.1)
Dependency in ADL — no./total no. (%)†	199/637 (31.2)	200/714 (28.0)	257/870 (29.5)
Had one or more hospital stays in the previous year — no./total no. (%)	271/653 (41.5)	298/722 (41.3)	351/881 (39.8)
Had coexisting condition — no. (%)			
Cardiovascular disease	153 (23.3)	154 (20.8)	172 (19.4)
COPD or asthma	260 (39.6)	281 (38.0)	377 (42.5)
Other chronic pulmonary disease	64 (9.8)	97 (13.1)	61 (6.9)
Diabetes mellitus	118 (18.0)	101 (13.7)	161 (18.1)
Cancer‡	106 (16.2)	124 (16.8)	151 (17.0)
HIV/AIDS — no. (%)	3 (0.5)	6 (0.8)	6 (0.7)
Chronic renal failure or nephrotic syndrome	10 (1.5)	14 (1.9)	7 (0.8)
Receiving immunosuppressive therapy — no. (%)	59 (9.0)	57 (7.7)	93 (10.5)

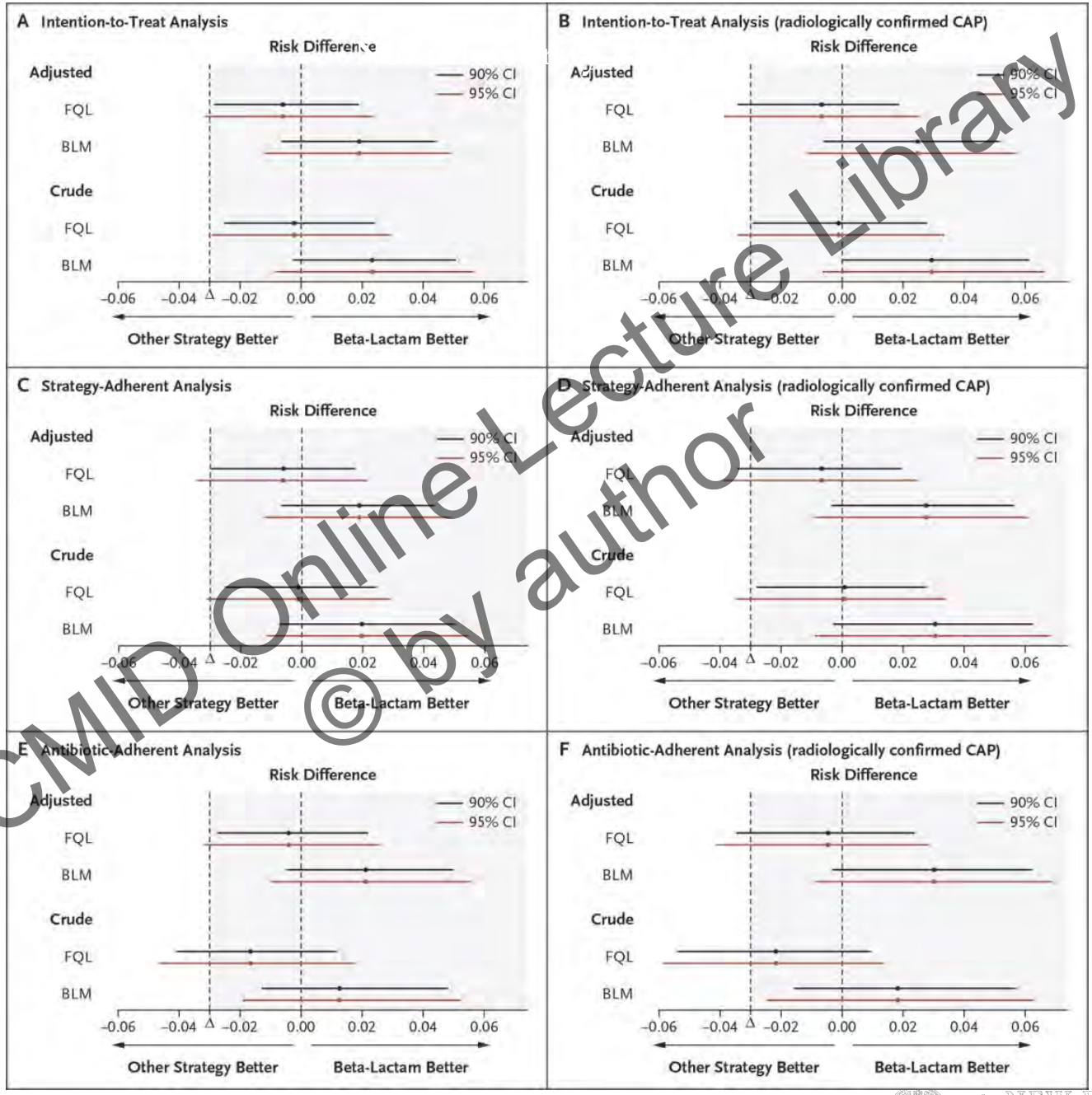
Avni T et al. Journal of the American Geriatrics Society 63:233–243, 2015

Table 3. Mean Participant Age in Randomized Controlled Trials (RCTs) and Observational

	RCT	Observational
Pneumonia Classification	Mean ± SD (n)	
CAP all trials[a]	54.0 ± 9.6 (23)	66.2 ± 8.1 (113)
CAP—ambulatory	45 ± 4.2 (2)	58.2 ± 17.5 (1)
CAP—ambulatory/hospitalized	45.6 ± 1.6 (3)	63.7 ± 7.04 (11)
CAP—hospitalized	55.0 ± 9.1 (16)	65.3 ± 8.2 (81)

Crude 90 day mortality rates:

- Beta-lactam : 9.0%
- Beta-lactam–macrolide: 11.1%
- Fluoroquinolone: 8.8%



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Secondary outcomes

- The median length of hospital stay was 6 days for all strategies, but the upper quartile was higher during the beta-lactam–macrolide strategy periods
- The median duration of intravenous treatment was 3 days during the fluoroquinolone strategy periods and 4 days during the other strategy periods
- The proportions of patients whose treatment started with oral antibiotics were 27% during the fluoroquinolone strategy periods, as compared with 13% and 10% during the beta-lactam and beta-lactam–macrolide strategy periods, respectively.

Paul M et al.

Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by meticillin resistant Staphylococcus aureus: randomised controlled trial.

BMJ 2015;350:h2219

Objective To show non-inferiority of trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of severe infections due to meticillin resistant *Staphylococcus aureus* (MRSA).

Design Parallel, open label, randomised controlled trial.

Setting Four acute care hospitals in Israel.

Participants Adults with severe infections caused by MRSA susceptible to trimethoprim-sulfamethoxazole and vancomycin. Patients with left sided endocarditis, meningitis, chronic haemodialysis, and prolonged neutropenia were excluded.

Primary outcome:

Treatment failure at seven days: a composite of:

- Death
- Persistence of fever or hypotension
- Non-improving Sequential Organ Failure Assessment (SOFA) score
- Persistent bacteraemia on day 7.

Is the question of interest to my patients?

- Patients
- Intervention
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Internal validity

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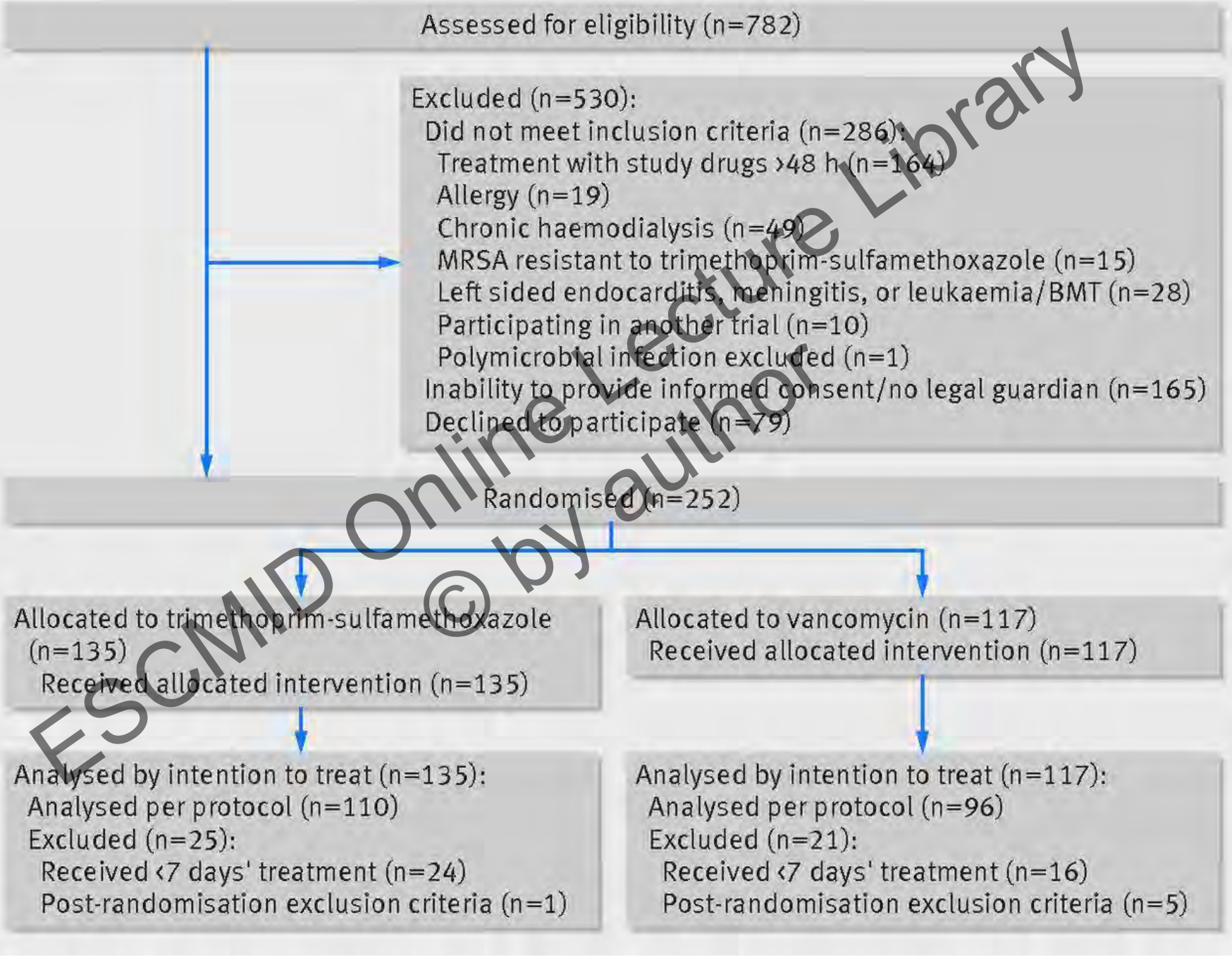

Results

- The failure rate with trimethoprim-sulfamethoxazole was 51/135 (38%) compared with 32/117 (27%) with vancomycin, and the 95% confidence interval for the difference fell outside the lower limit of the 15% predefined for non-inferiority (−1.2% to 21.5%).
- Restricting the analysis to patients in the vancomycin group whose isolates' minimum inhibitory concentrations were below 2 µg/mL resulted in a larger risk ratio in favour of vancomycin (1.64, 0.99 to 2.68).
- All cause 30 day mortality did not differ significantly between groups.
- Among patients with bacteraemia, mortality was nearly twice as high with trimethoprim-sulfamethoxazole—14/41 (34%) versus 9/50 (18%) with vancomycin (risk ratio 1.90, 0.92 to 3.93).

Paul M et al.

External validity of a randomised controlled trial on the treatment of severe infections caused by MRSA

BMJ Open 2015;**5**:e008838

Design

- **Objectives** To assess the external validity of a pragmatic, investigator-initiated RCT on treatment of severe infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), we compared patient characteristics and treatment effect estimates for **patients included in the RCT versus those excluded**.
- **Participants and outcomes** The RCT included hospitalised patients with documented or highly-probable invasive MRSA infections who were randomised to vancomycin versus trimethoprim-sulfamethoxazole (TMP-SMX) treatment, between 2007 and 2014. **A concomitant observational study prospectively included all consecutive patients, between 2008 and 2011, who were excluded from the RCT due to no consent, meningitis, left-sided endocarditis, severe neutropaenia, chronic renal dialysis or treatment with study medications for longer than 48 h.**

Results

- Excluded patients' functional and cognitive performance was significantly poorer than that of included patients.
- Sepsis was more severe among excluded patients.
- Clinical failure occurred in 83/252 (32.9%) versus 175/220 (79.5%) and deaths in 32 (12.7%) versus 64 (29.1%) for included versus excluded patients, $p<0.001$ for both comparisons.
- Comparing vancomycin to TMP-SMX, in the RCT mortality, was non-significantly lower with vancomycin (OR 0.76, 95% CIs 0.36 to 1.62), while in the observational analysis of excluded patients, mortality was significantly higher with vancomycin (OR 2.63, 1.04 to 6.65), $p=0.04$ for the difference.

Can I learn from this RCT?

- Is the question important to my patients?
  - Similar conditions/diseases?
  - Intervention of interest?
  - Control of interest?
  - The right outcome?
- Are my patients similar to the ones included in the study?
- Solid internal validity?
- Magnitude of results expressed as absolute measures?