External validity of RCTs in infectious diseases

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External validity:

Are the trial results applicable to other patients?

Mainly:

Are the trial results applicable to my patients?

Aspects of external validity

- Intervention: for example:
  - Is the intervention relevant at my location? (e.g. different resistance patterns).
  - Can I employ it the way it was used in the RCT? (e.g. a complex intervention)
- Control: is my daily practice similar to the control?
- Outcome: is the outcome relevant to my patients?
- **Population**
  - **Are the results applicable to patients that are similar/identical with the trial patients?**
  - **Can we learn from the results about other groups of patients?**

A bad example: neuraminidase inhibitors for influenza

- RCTs of neuraminidase inhibitors included >24,000 participants.
- Almost 100% young and without underlying diseases.
- Very modest effect (if at all)
- Can we learn from these studies on people with congestive heart failure or COPD or cancer who were afflicted by influenza?

Participation of Elderly Adults in Randomized Controlled Trials Addressing Antibiotic Treatment of Pneumonia: Avni T et al. J Am Geriatr Soc. 2015 Feb;63(2):233-43

- Systematic review and meta-analysis
- Objective: To examine how relevant current evidence on antibiotic treatment of pneumonia is for elderly adults.
- Randomized controlled trials (RCTs; N = 43) comparing different antibiotics and prospective observational studies on pneumonia (N = 182) published 2005-2015.
- No exclusion criteria that were based on age.

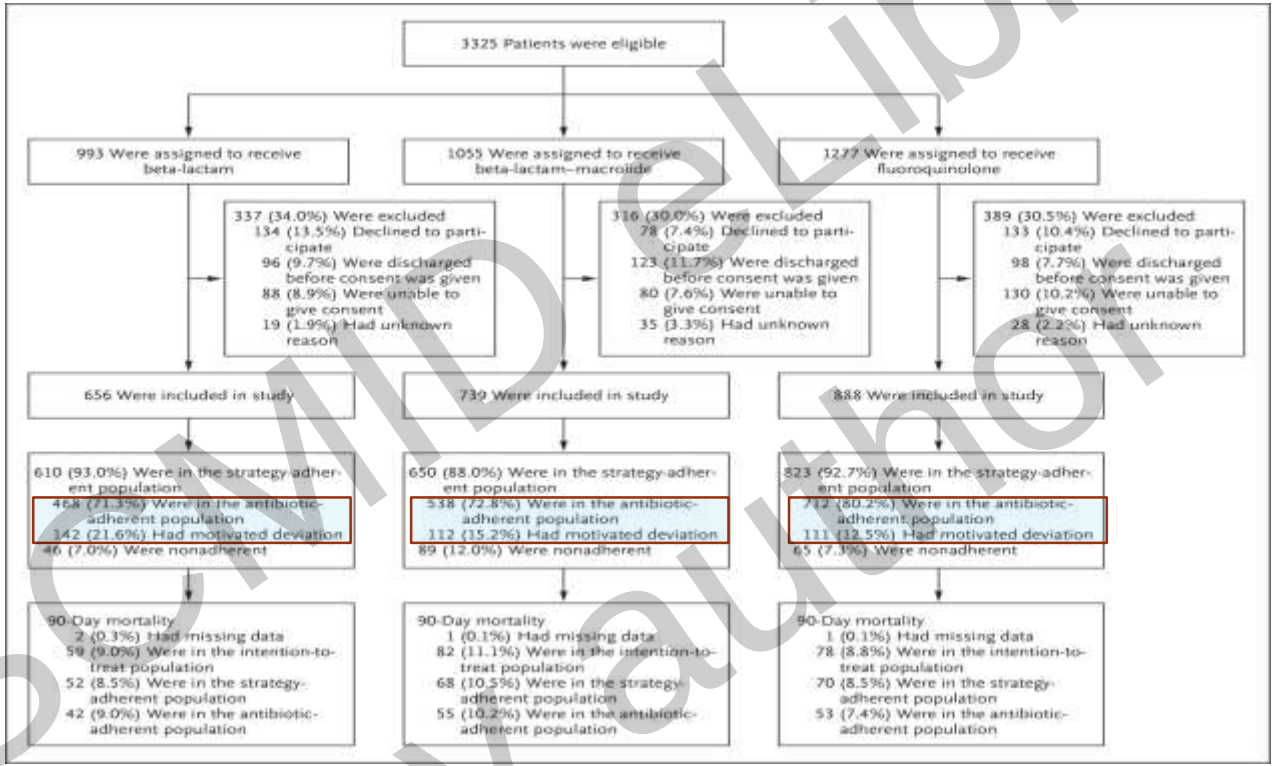
Participation of old people in RCTs on treatment of pneumonia: mean age

Pneumonia Classification	RCT	Observational
	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)
CAP—hospitalized, HCAP included	68.0 ± 3.5 (2)	65.3 ± 7.5 (20)
Hospitalized, all	56.4 ± 9.5 (18)	66.2 ± 8.14 (101)

Avni T et al. J Am Geriatr Soc. 2015 Feb;63(2):233-43

Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults: Postma DF et al.. N Engl J Med 2015; 372:1312-1323

- Cluster-randomized, crossover trial with strategies rotated in 4-month periods
- Intervention: Beta-lactam alone vs beta-lactam–macrolide vs fluoroquinolone strategies
- Inclusion: Suspected CAP who required antibiotic treatment and hospitalization in a non-ICU ward
- Exclusion: cystic fibrosis
- "Obtaining informed consent before intervention was deemed unnecessary, because patients did not undergo randomization individually, and all the antibiotics we studied are used in current practice."
- "Written informed consent obtained within 72 hours after admission was required for data collection".
- Outcome: 90-day mortality
- **The median age of the patients was 70 years.**
- Crude 90-day mortality was 9.0%.
- Conclusions: Noninferiority of the beta-lactam strategy



Postma DF et al. N Engl J Med 2015;372:1312-1323.

Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by meticillin resistant Staphylococcus aureus: randomised controlled trial: Paul M. et al. 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).
- Participants:
  - Included: Adults with severe infections caused by MRSA susceptible to trimethoprim-sulfamethoxazole and vancomycin.
  - Excluded: Patients with left sided endocarditis, meningitis, chronic haemodialysis, and prolonged neutropenia were excluded.
  - Informed consent (by the patient or legal guardian) was obtained.
- Main outcomes:
  - Primary efficacy outcome: treatment failure assessed at day 7: death, persistence of bacteremia, haemodynamic instability or fever, stable or worsening Sequential Organ Failure Assessment score.
  - Primary safety outcome: all cause mortality at day 30.

Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by meticillin resistant Staphylococcus aureus: randomised controlled trial: Paul M. et al. BMJ 2015;350:h2219

- 252 patients were included
- Treatment failure:
  - Trimethoprim-sulfamethoxazole: 51/135, 38%
  - Vancomycin: 32/117, 27%
- 30 day mortality: 32/252 (13%), with no significant difference between arms.
- Mortality in patients with bacteraemia:
  - Trimethoprim-sulfamethoxazole:14/41 (34%)
  - Vancomycin: 9/50 (18%).
- Conclusions: High dose trimethoprim-sulfamethoxazole did not achieve non-inferiority to vancomycin in the treatment of severe MRSA infections.

External validity of a randomised controlled trial on the treatment of severe infections caused by MRSA: BMJ Open. 2015 Sep 11;5(9):e008838.s

- We compared patient characteristics and treatment effect estimates for patients included in the RCT versus those excluded
- 220 patients excluded from the RCT due to;
  - no consent
  - meningitis
  - left-sided endocarditis
  - severe neutropaenia
  - chronic renal dialysis
  - treatment with study medications for longer than 48 h
- Compared with 252 included patients.

Reasons for exclusion

Table 1 Reason for exclusion of patients from the RCT (and inclusion in the observational study)

Reason for exclusion	N (%) (Total N=220)
Treatment with study drugs >48 h prior to identification	73 (33.2%)
Refusal to sign an informed consent	44 (20%)
Inability to provide informed consent and no legal guardian	40 (18.2%)
Chronic dialysis	29 (13.2%)
Resistance to one of the study antibiotics	14 (6.4%)
Left-side endocarditis	8 (3.6%)
Acute leucaemia with neutropaenia	7 (3.2%)
Hypersensitivity to one of the antibiotics in the trial	2 (0.9%)
Meningitis	2 (0.9%)
Participation in other trial	1 (0.5%)

RCT, randomised controlled trial.

Baseline characteristics:

	RCT included N=252	Excluded N=220	p Value
Age, years (mean±SD)	65.8±17	67.9±17.2	0.192
Female sex	86 (34.1%)	90 (40.9%)	0.129
Admission from home	194 (77%)	145 (65.9%)	0.008
Functional capacity—bedridden	53 (21%)	115 (52.3%)	<0.001
Dementia	12 (4.8%)	41 (18.6%)	<0.001
Congestive heart failure	50 (19.8%)	40 (18.2%)	0.647
Ischaemic heart disease	80 (31.7%)	63 (28.6%)	0.463
Cerebrovascular accident in the past	44 (17.5%)	57 (25.9%)	0.026
Chronic lung disease	35 (13.9%)	27 (12.3%)	0.604
Diabetes mellitus	102 (40.5%)	88 (40%)	0.916
Chronic renal failure	6 (2.4%)	39 (17.7%)	<0.001
Manifest malignancy	49 (19.4%)	58 (26.4%)	0.073
McCabe score—no fatal disease	196 (77.8%)	166 (75.5%)	0.551
Charlson score (median, percentile)	2 (1–4)	3 (2–4)	0.008

Baseline characteristics (cont.):

	RCT included N=252	Excluded N=220	p Value
Predisposition			
Hospital-acquired infection†	173 (68.7%)	138 (62.7%)	0.176
Nasogastric tube prior to infection	26 (10.3%)	80 (36.4%)	<0.001
Urine catheter prior to infection	80 (31.7%)	138 (62.7%)	<0.001
Central venous catheter prior to infection	32 (12.7%)	104 (47.2%)	<0.001
Foreign body prior to infection‡	84 (33.3%)	26 (11.8%)	<0.001
Surgery 30 days prior to infection	121 (48%)	77 (35%)	0.004
Mechanical ventilation at onset	27 (10.7%)	98 (44.5%)	<0.001

Baseline characteristics (cont.):

	RCT	Obs.	
Infection characteristics and presentation			
Bacteraemia	91 (36.1%)	91 (41.4%)	0.242
Any microbiologically (MRSA)-documented infection	245 (97.2%)	167 (75.9%)	<0.001
Source of infection			<0.001
Central venous catheter-related	16 (6.3%)	53 (24.1%)	
Other endovascular	9 (3.6%)	9 (4.1%)	
Pneumonia	27 (10.7%)	30 (13.6%)	
Skin, soft tissue, bone or joint	168 (66.7%)	54 (24.5%)	
Other documented source	17 (6.7%)	4 (1.8%)	
Primary, unknown source	15 (6%)	70 (31.8%)	

Management:

	RCT	Obs.	
Vancomycin levels measured¶	97/117 (82.9%)	95/167 (56.9%)	<0.001
Mean vancomycin trough levels (median, IQR)¶	14.9 (10.4–21), N=97	14 (11–22.8), N=95	0.778
Vancomycin trough levels >10 mg/dL attained	80/97 (82.5%)	79/95 (83.2%)	0.9
Total treatment duration, days (median, IQR)**	15 (11–28)	11 (5–18)	<0.001
Treatment duration in 30-day survivors, days (median, IQR)**	17 (12–30), N=220	12 (7–22) N=156	<0.001

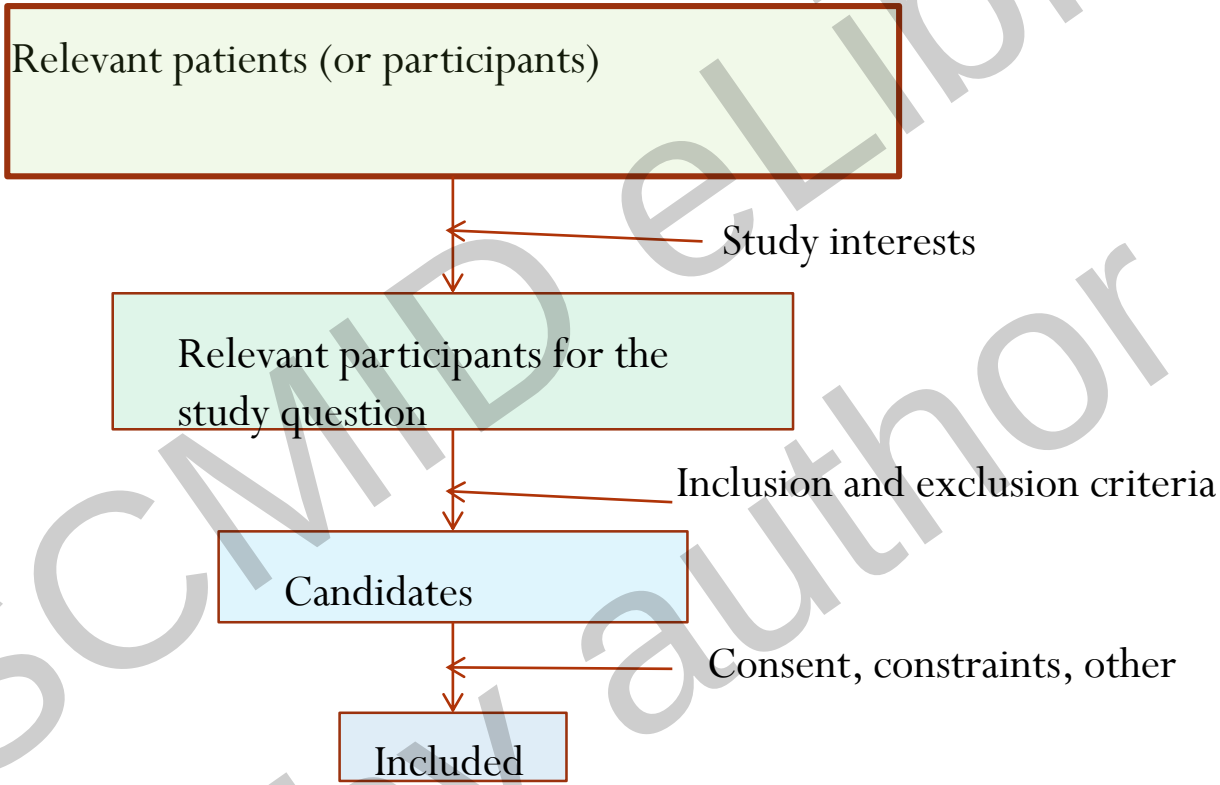
Treatment effects

Table 4 Treatment effects

	RCT included N=252		Excluded N=220		p Value*
	Vancomycin	TMP-SMX	Vancomycin	TMP-SMX	
Clinical failure	32/117 (27.4%)	51/135 (37.8%)	137/167 (82%)	31/39 (79.5%)	
	OR 0.62 (0.36–1.06)		OR 1.18 (0.49–2.82)		0.216
30-day all-cause mortality	13/117 (11.1%)	19/135 (14.1%)	54/167 (32.3%)	6/39 (15.4%)	
	0.76 (0.36–1.62)		2.63 (1.04–6.65)		0.04

*p Values comparing the ORs of vancomycin versus TMP-SMX among included and excluded patients.
RCT, randomised controlled trial; TMP-SMX, trimethoprim-sulfamethoxazole.

To sum up:



Conclusions (1): Learning from the population included in the RCT

- Define your population of interest.
- Was the relevant population addressed by the RCT?
- Who were actually included in the RCT and how much do they resemble my population of interest?
- Can I learn by extrapolation about other groups of patients?

Conclusions (2): How to improve external validity (population)

- A better link: industry ⇔ practitioners ⇔ patients, public ⇔ academy researchers ⇔ maybe even regulator to address problems of interest and populations of interest.
- Solve the problem of informed consent in RCTs of infections.
- Thorough description of the included **and excluded** participants.

Thanks