Defining Exposures and Outcomes: Inpatient Considerations

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Disclosures

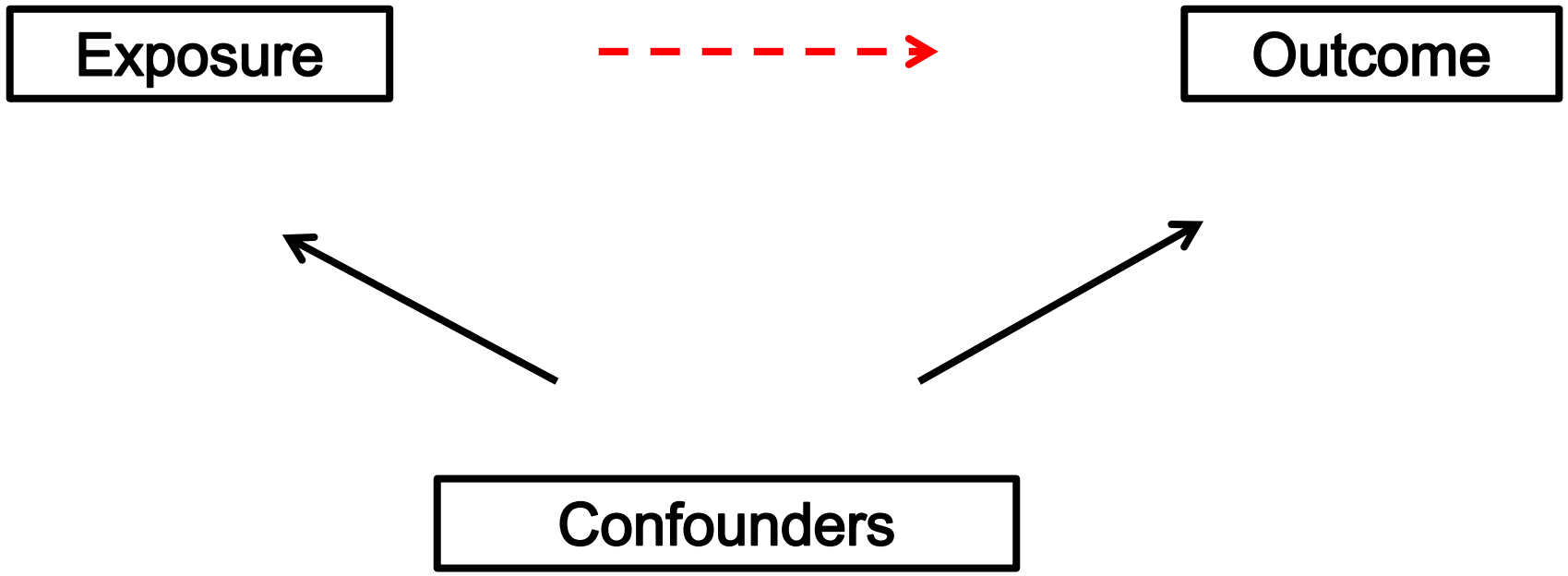
- I am not an epidemiologist.

Something the patient was exposed to
[antibiotic, microorganism]

Individual attribute
[Immunocompromised]

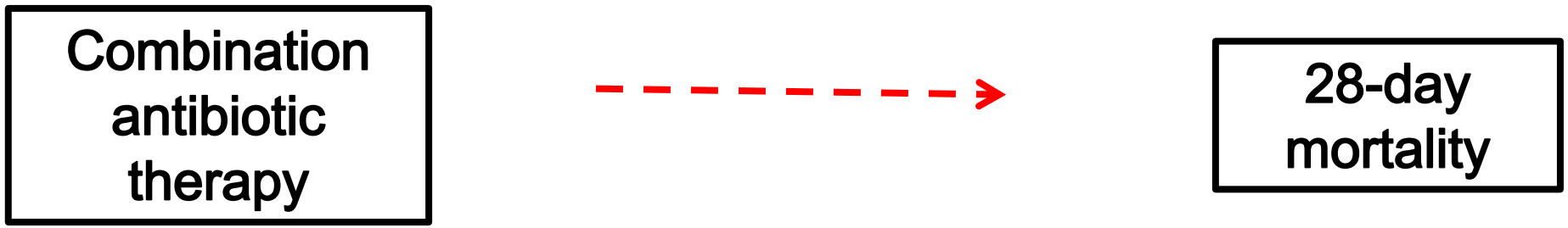
Intervention
[Antibiotic time-out tool]

An event under consideration
[Length of hospital stay, mortality]

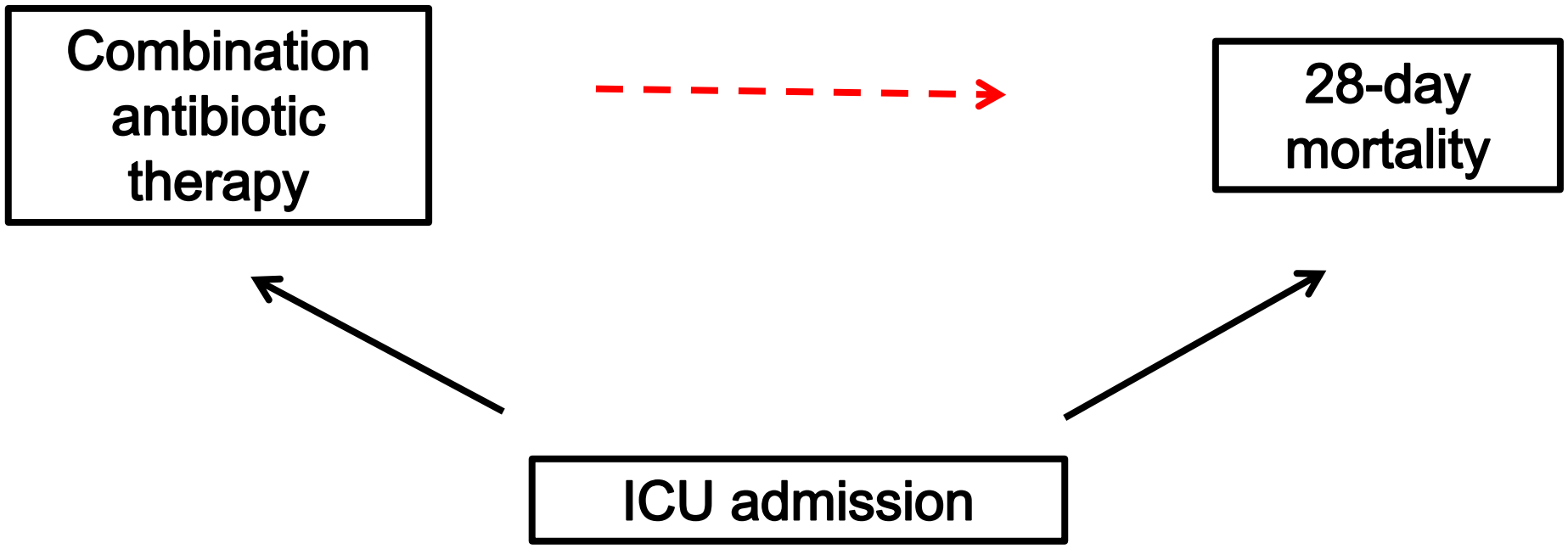

Exposure
Outcome
Confounders

Confounders

- Variables associated with the exposure of interest and a potential cause of the outcome of interest
  - Should not be an intermediate step in the causal pathway
- Can lead to bias that distorts the magnitude of the relationship between the exposure and outcome



Study question: Do patients with gram-negative bacteremia who receive combination antibiotic therapy (β-lactam and aminoglycoside) have an improved odds of 28-day survival?



Study question: Do patients with gram-negative bacteremia who receive combination antibiotic therapy (β-lactam and aminoglycoside) have an improved odds of 28-day survival?

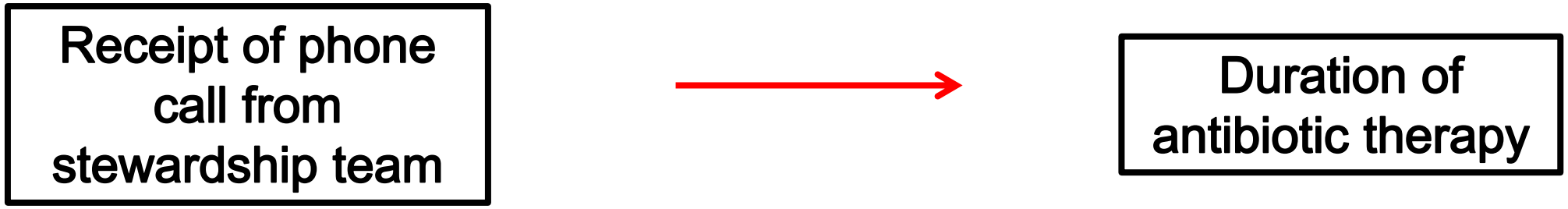
You Need a Project for Your PGY-2 Resident…

- The optimal duration of antibiotic therapy for gram-negative bacteremia remains unclear
- The IDSA guidelines suggest a duration between 7-14 days
- Some observational studies such 7 days and 14 days of therapy have equivalent outcomes
- Prolonged antibiotic exposure has been associated with adverse drug events, emergence of antibiotic resistance, *Clostridium difficile* infections, etc.

What is the Best Approach to Evaluate this Question?

- Quasi-experimental study
  - Will phone calls from the stewardship team at the time blood cultures result reduce the duration of antibiotic therapy for gram-negative bacteremia?

- Cohort study
  - Does decreasing the duration of antibiotic therapy for gram-negative bacteremia increase 28-day mortality?



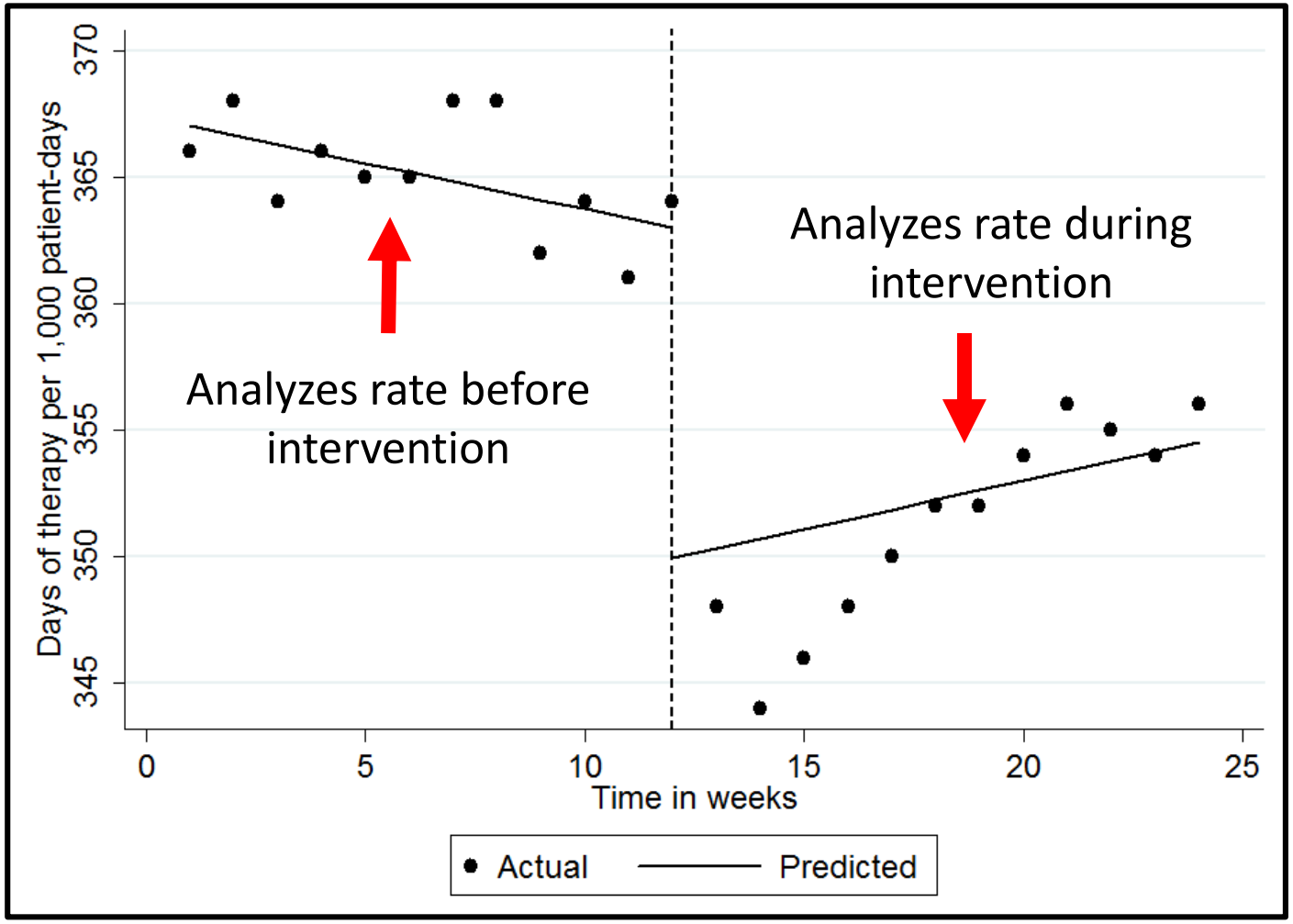
Hypothesis: A phone call from the stewardship team to prescribers discussing duration of therapy every time a gram-negative organism is isolated from the bloodstream will reduce the duration of antibiotic therapy prescribed.

When Should I Consider a Quasi-Experimental Study?

- Population characteristics should generally be consistent over time
- Intervention should be uniformly applied
- Need a defined implementation start date
- Normalize count data
  - e.g., days of antibiotic therapy per 1,000 patient-days, *C. difficile* infection rates per 100 hospital admissions, etc.
- Select outcome measurable across units of time using a consistent approach
- Control group optional
  - e.g., duration of antibiotic use for another syndrome, duration of antibiotic use in a non-intervention unit, duration of antibiotic use for gram-positive agents, etc.

Shardell M, et al. Clin Infec Dis 2007; 45:901-7.

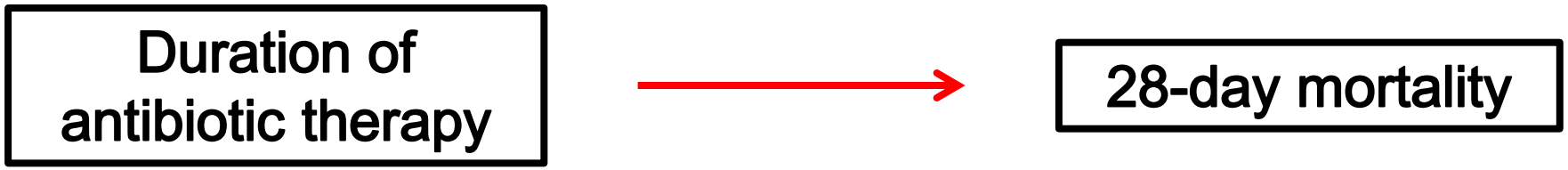
Interrupted-Time Series Analysis



Accounts for pre-existing trends

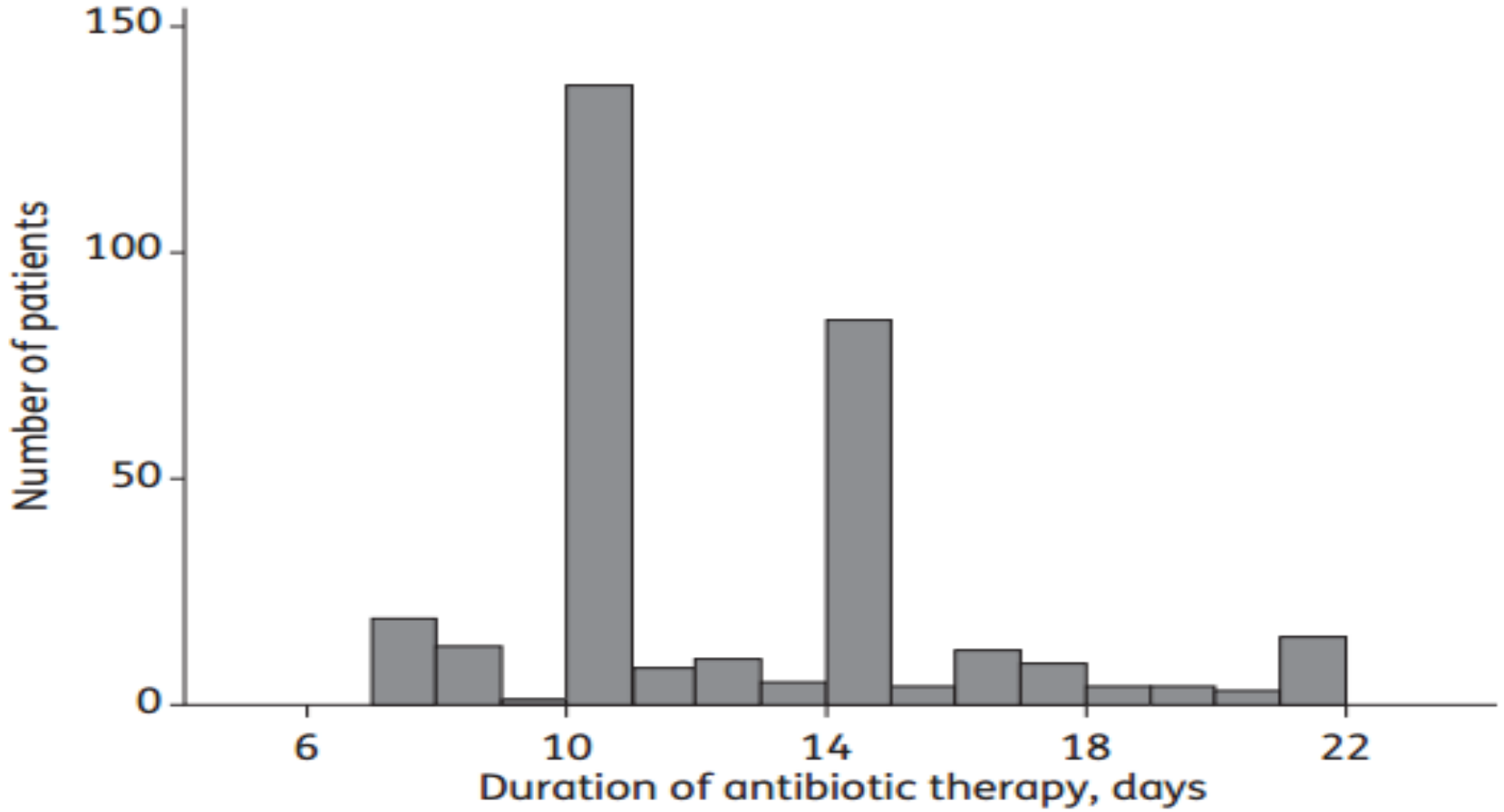
Drawbacks:

- Requires prolonged periods of time for evaluation
- Changes in other interventions or outcome definitions over time can introduce bias



Hypothesis: Reducing the median duration of antibiotic therapy for gram-negative bacteremia will not increase 28-day mortality.

Continuous Versus Categorical Exposure?



Learning When to Be Discrete: Continuous vs. Categorical Variables

Continuous

- For every additional year of age, patients have twice the odds of developing colon cancer.

Categorical

- Patients ≥50 years of age have twice the odds of developing colon cancer compared to younger patients.


Short-course antibiotic therapy (10 days)
Outcome

What Outcomes Appeal to Clinicians?

- Most clinicians want to see improvements in patient-centered outcomes
- They want to know that the status quo is harming patients, necessitating a change in practice
- Or, a change in treatment practices will not worsen clinical outcomes
- Ideally, a stewardship intervention will result in both of these

Short-course Empiric Antibiotic Therapy for Patients with Pulmonary Infiltrates in the Intensive Care Unit

A Proposed Solution for Indiscriminate Antibiotic Prescription

NINA SINGH, PAUL ROGERS, CHARLES W. ATWOOD, MARILYN M. WAGENER, and VICTOR L. YU

- Components of Clinical Pulmonary Infection Score (CPIS)
  - Temperature
  - Peripheral white blood cell count
  - Tracheal sections
  - Oxygenation
  - Progression of pulmonary infiltrate
  - Culture of tracheal aspirate

- A score >6 is suggestive of pneumonia

Singh N, et al. Am J Respir Crit Care Med 2000;162:505-11.

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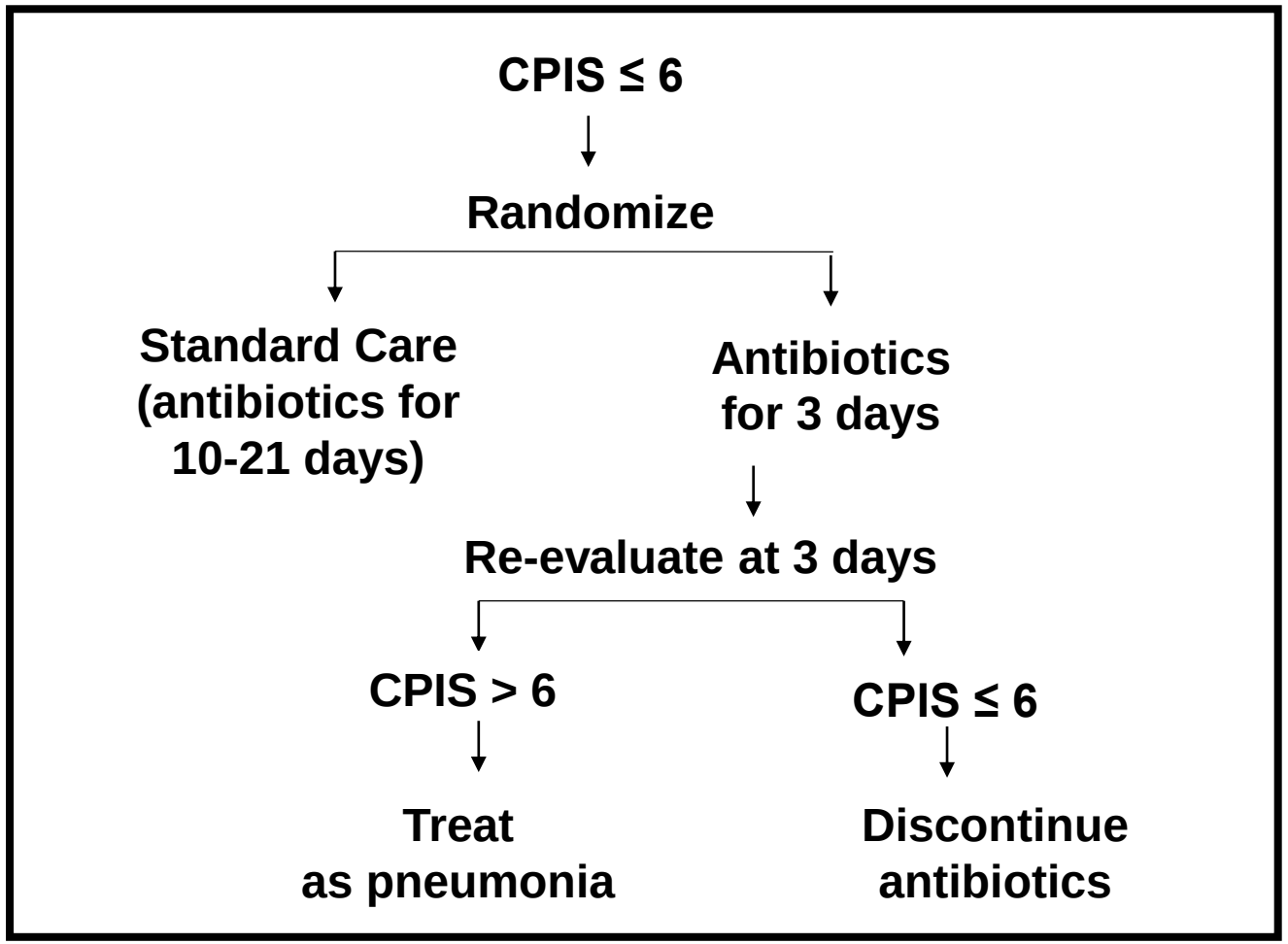
Median antibiotic duration: 10 days



Median antibiotic duration: 3 days

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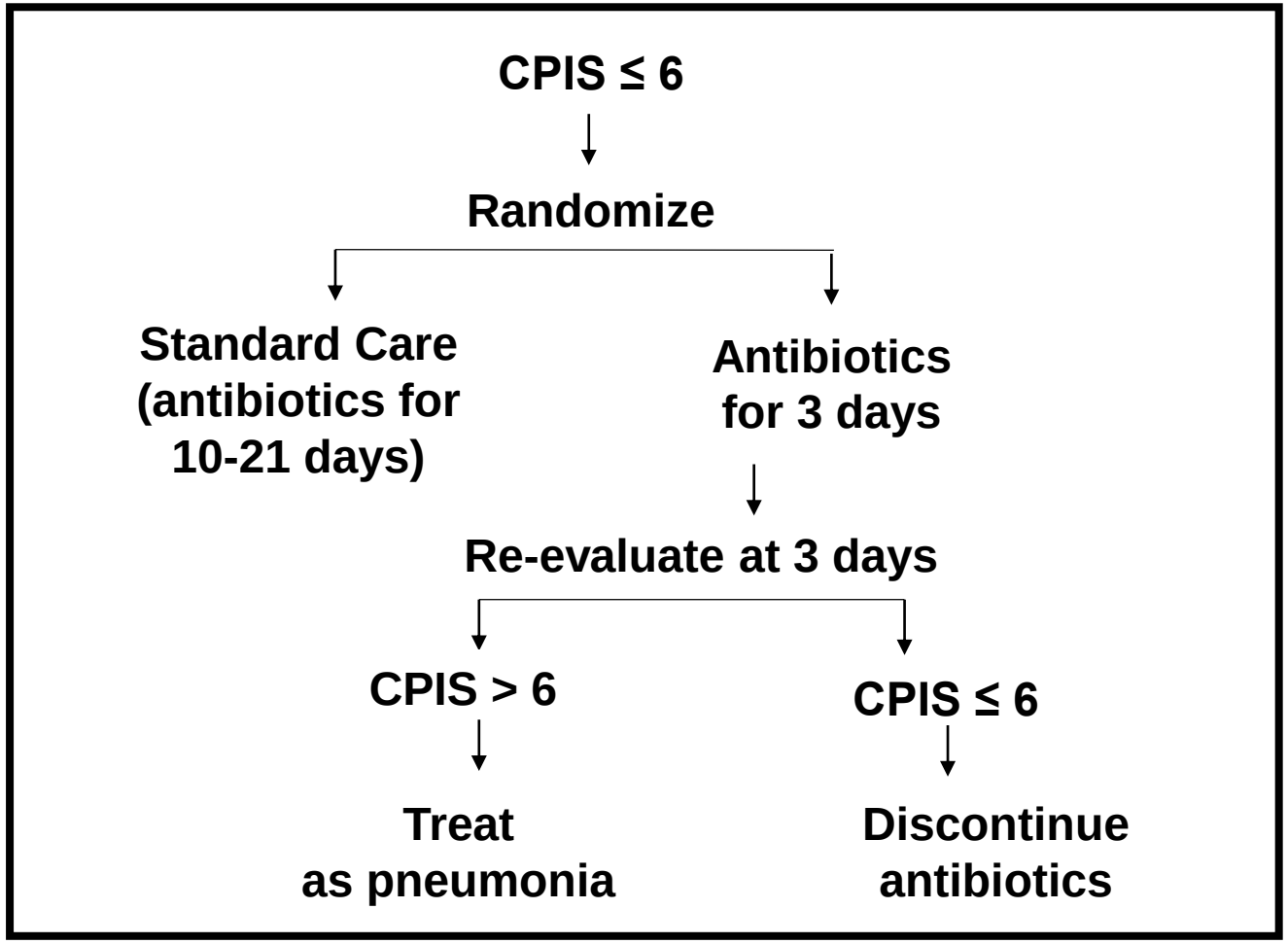
ICU length of stay: 15 days



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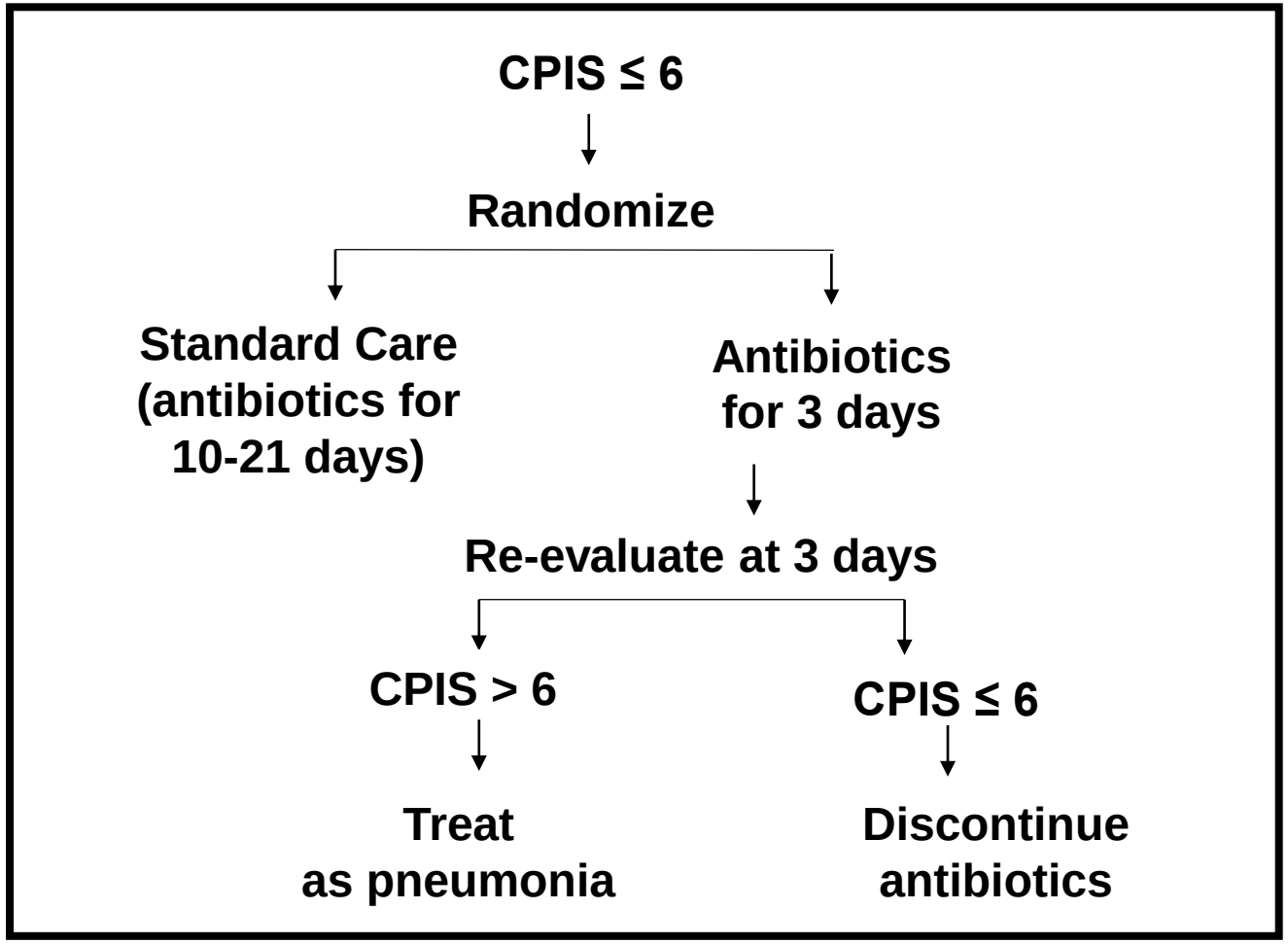
35% developed antibiotic resistance



15% developed antibiotic resistance

Singh N et al. Am J Respir Crit Care Med 2000;162:505-11.

Why Was this Study Successful?

- It focused on a single diagnosis
- The goal of the intervention focused on improving patient outcomes and not decreasing antibiotic use
- If focused on a diagnosis with good evidence to support the treatment recommendations
- It involved multiple opportunities for interventions along the way that could be scalable to the comfort level of the treating clinician
- The treating clinician ultimately made all treatment decisions
- It showed that the stewardship outcome was safe
  - No increased mortality or increased ICU length of stay in the intervention group
- The “harm” caused by the status quo impacted the patients in the study
  - Decreased subsequent antibiotic resistant organisms in the intervention group

Process Measures

- Antibiotic usage
- Antibiotic costs

Clinical Measures

- *C. difficile* infections
- Central-line complications
- End-organ toxicity
- Mortality
- Length of hospital stay
- Infection recurrence
- Antibiotic resistance

Balancing Measures

- Hospital readmissions
- Delays in patient discharges

Selecting Meaningful Outcomes

Harm with the Status Quo

- **Antibiotic resistance**
  - Issues with antibiograms
  - Time consuming to evaluate patient-level resistance
- ***Clostridium difficile***
  - Lapses in infection control
  - Relatively rare outcome
  - May occur months after intervention
  - Higher associations with certain agents
  - Confounding due to overtesting
- **PICC complications**
  - Infectious, thrombotic, mechanical
- **End-organ toxicity**
  - Except for acute kidney injury, relatively rare outcome

No Harm with the Intervention

- **Mortality**
  - Relatively rare outcome – especially attributable mortality
- **Length of stay**
  - Most useful for studies where promoting IV to oral switch or decreased antibiotic duration
- **Infection recurrence**
- **Hospital readmission**

MAJOR ARTICLE

Impact of an Antimicrobial Stewardship Intervention on Shortening the Duration of Therapy for Community-Acquired Pneumonia

- **Goal**
  - Reduce duration of therapy from baseline median of 10 days to 5 days of antibiotics for CAP
- **Approach**
  - Assess knowledge and behavior with a survey of medicine housestaff
  - Revision of treatment guidelines with involvement of medicine housestaff and simplification of recommendations
  - Educational lectures reviewing evidence for CAP recommendations
  - Direct, real-time discussion of management with housestaff
  - Feedback results to housestaff

Avdic E, et al Clin Infect Dis 2012;54:1581.

Results

	Baseline n=56	Intervention n=63	P-value
Median duration of therapy	10 days	7 days	<0.001
30-day readmissions	15%	8%	0.22
C. difficile infections	5%	2%	0.28

Patient characteristics similar between the two periods

Avdic E, et al Clin Infect Dis 2012;54:1581.

Sustained Impact of an Antibiotic Stewardship Intervention for Community-Acquired Pneumonia

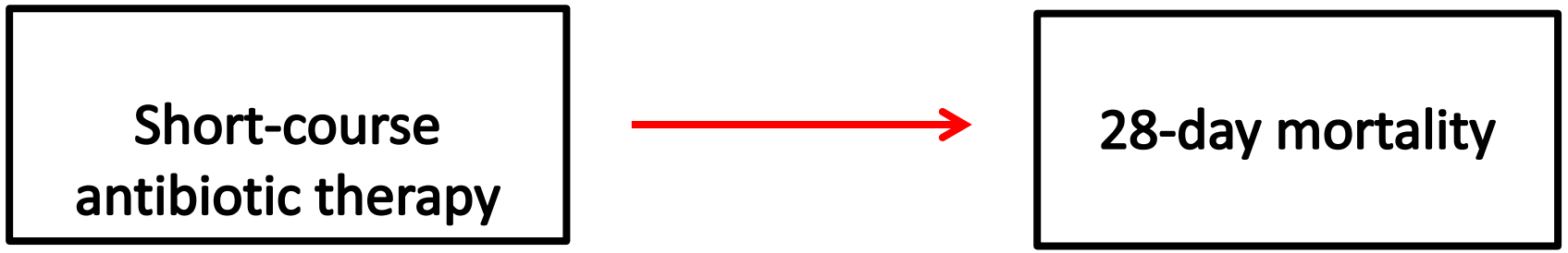
INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY

	Baseline n=56	**Intervention n=63**	**3 years later n=72**
Median duration of therapy	10 days	7 days	7 days
30-day readmissions	15%	8%	8%
C. difficile infections	5%	2%	1%

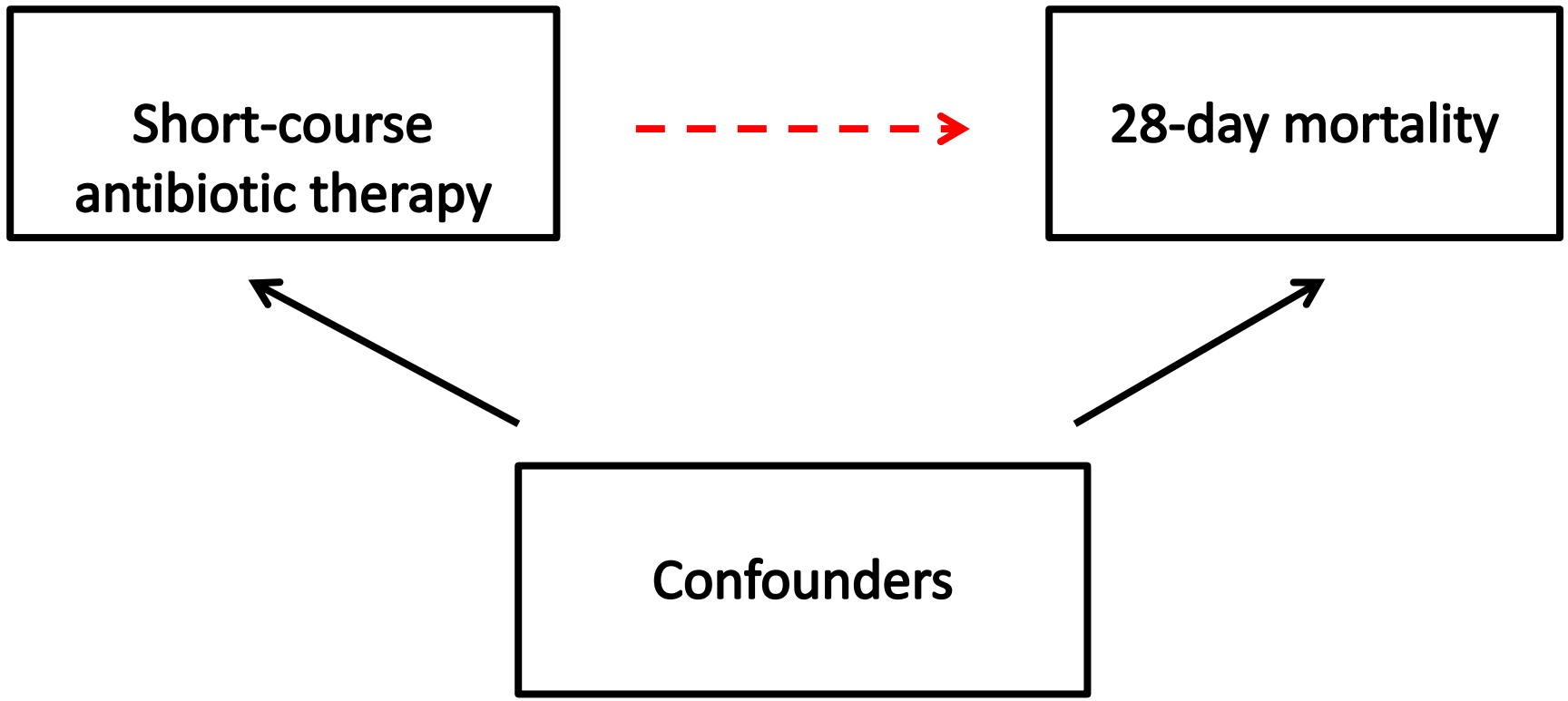
Patients characteristics similar between the three periods

Li DX, et al. Infec Cont Hosp Epidemiol 2016;8:1-4.

Back to Our Study…



Hypothesis: A short-course of antibiotic therapy for gram-negative bacteremia will not increase 28-day mortality.


Short-course antibiotic therapy
28-day mortality
Confounders

Two Patients with *E. coli* Bacteremia….

10 days of antibiotics

Age = 75 years
Renal transplant
Intra-abdominal source
Intensive care unit
Pitt bacteremia score = 6

14 days of antibiotics

Age = 37 years
Otherwise healthy
Urinary source
General ward
Pitt bacteremia score = 1

Assessing Covariate Balance

	Short-Course n=183	Prolonged-Course n=501	P-value
Age (median, IQR)	57 (43-68)	59 (48-68)	0.43
Male (n, %)	90 (49%)	341 (68%)	<0.01
Race/Ethnicity (n, %)			
Hispanic	10 (5%)	20 (4%)	0.40
White	70 (38%)	271 (54%)	<0.01
Black	93 (51%)	190 (38%)	<0.01
Asian	9 (5%)	15 (3%)	0.24

Assessing Covariate Balance

	Short-Course n=183	Prolonged-Course n=501	P-value
ICU on day 1 (n, %)	53 (29%)	215 (43%)	<0.01
Pitt bacteremia score on day 1 (median, IQR)	2 (1-3)	2 (2-4)	0.02
Source of bacteremia (n, %)			
Pneumonia	11 (6%)	50 (10%)	0.12
Skin and soft tissue	7 (4%)	40 (8%)	0.06
Urinary tract	97 (53%)	115 (23%)	<0.01
Biliary	16 (9%)	70 (14%)	0.06
Intra-abdominal	22 (12%)	130 (26%)	<0.01
Catheter-associated	27 (15%)	100 (20%)	0.14
Osteoarticular	2 (1%)	10 (2%)	0.53

Assessing Covariate Balance

	Short-Course n=183	Prolonged-Course n=501	P-value
End-Stage Liver Disease	21 (12%)	62 (12%)	0.79
End-Stage Renal Disease	34 (19%)	51 (10%)	<0.01
Diabetes	25 (6%)	57 (10%)	0.43
Human Immunodeficiency Virus	21 (11%)	15 (3%)	<0.01
Chemotherapy within 6 months	38 (21%)	240 (48%)	<0.01
Immunomodulatory therapy ≤ 30 d	21 (5%)	35 (7%)	0.37
Solid organ transplant	26 (14%)	99 (20%)	<0.01
Bone marrow transplant ≤ 12 mo	13 (3%)	25 (5%)	0.35
ANC 0-200 cells/ml	4 (1%)	40 (8%)	<0.01

Addressing Confounding by Indication

- Impact of an intervention best assessed by randomizing treatment assignments to ensure patients are similar in the short-course and prolonged-course groups

- Randomization is not possible in observational studies so adjustment for other differences is necessary to obtain valid estimates of the associations between the exposure and outcome

- Consider multivariable regression analysis or propensity score methods
  - Regression analysis determines how the estimate of the outcome changes when a variable changes, while the other variables are held constant

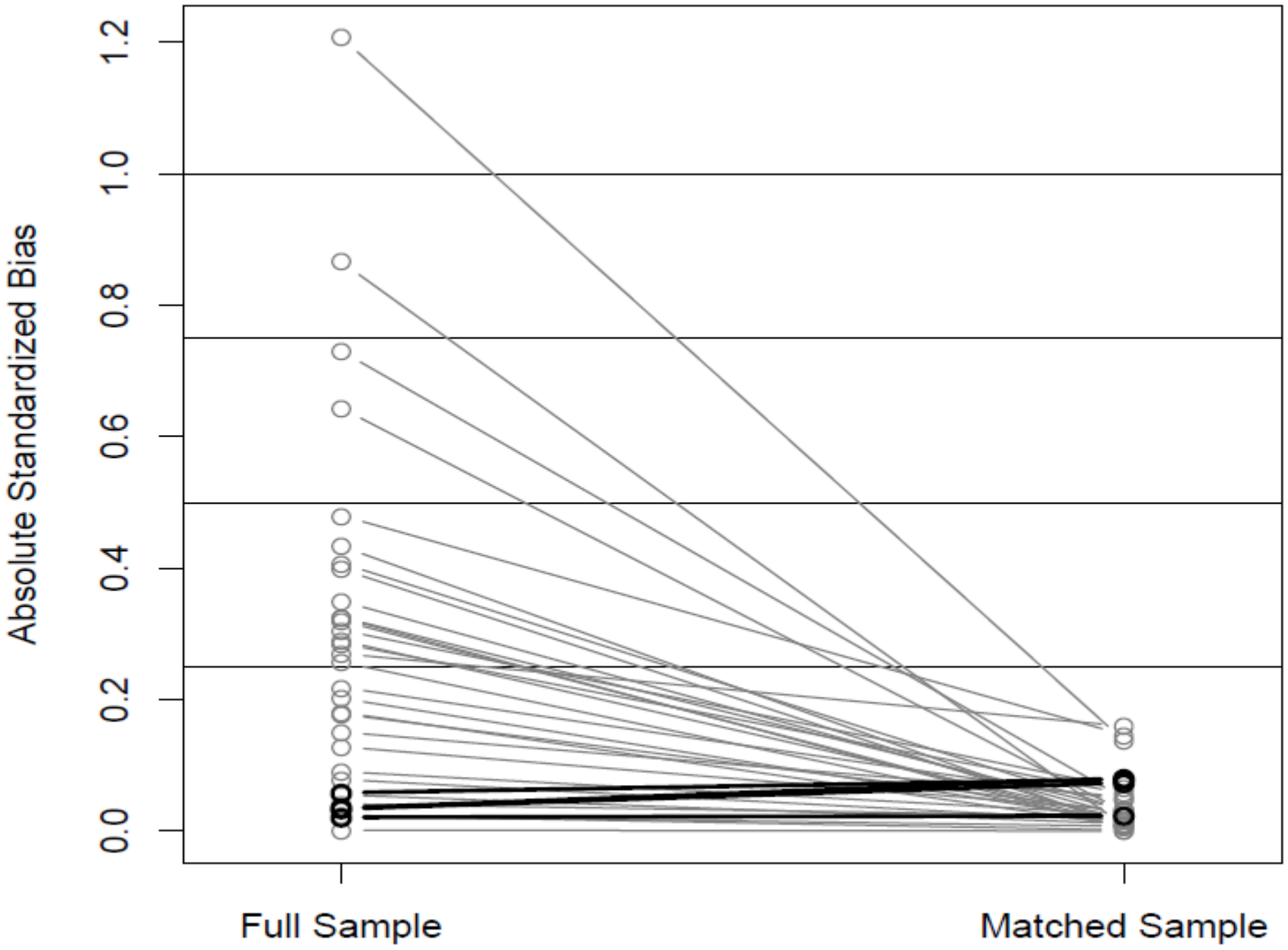
Using Propensity Score Methods to Account for Differences in the Exposed and Unexposed

- Goal is to develop short-course and prolonged-course groups that are similar in all characteristics expect the duration of therapy prescribed
- The propensity score is the probability a patient would receive short-course therapy, based on characteristics of the patient, organism, and treating clinician
- Generally estimated using multivariable logistic regression, in which patient characteristics are the predictors to determine the odds of being assigned to the short-course group
- These probabilities are estimated (ranging from 0 to 1) for each patient in the study population
- These probabilities- the propensity scores- are then used to adjust for differences between the short-course and prolonged-course groups
  - A standardized bias >0.10 represent imbalance between the distribution of covariates

Propensity-Score Matching

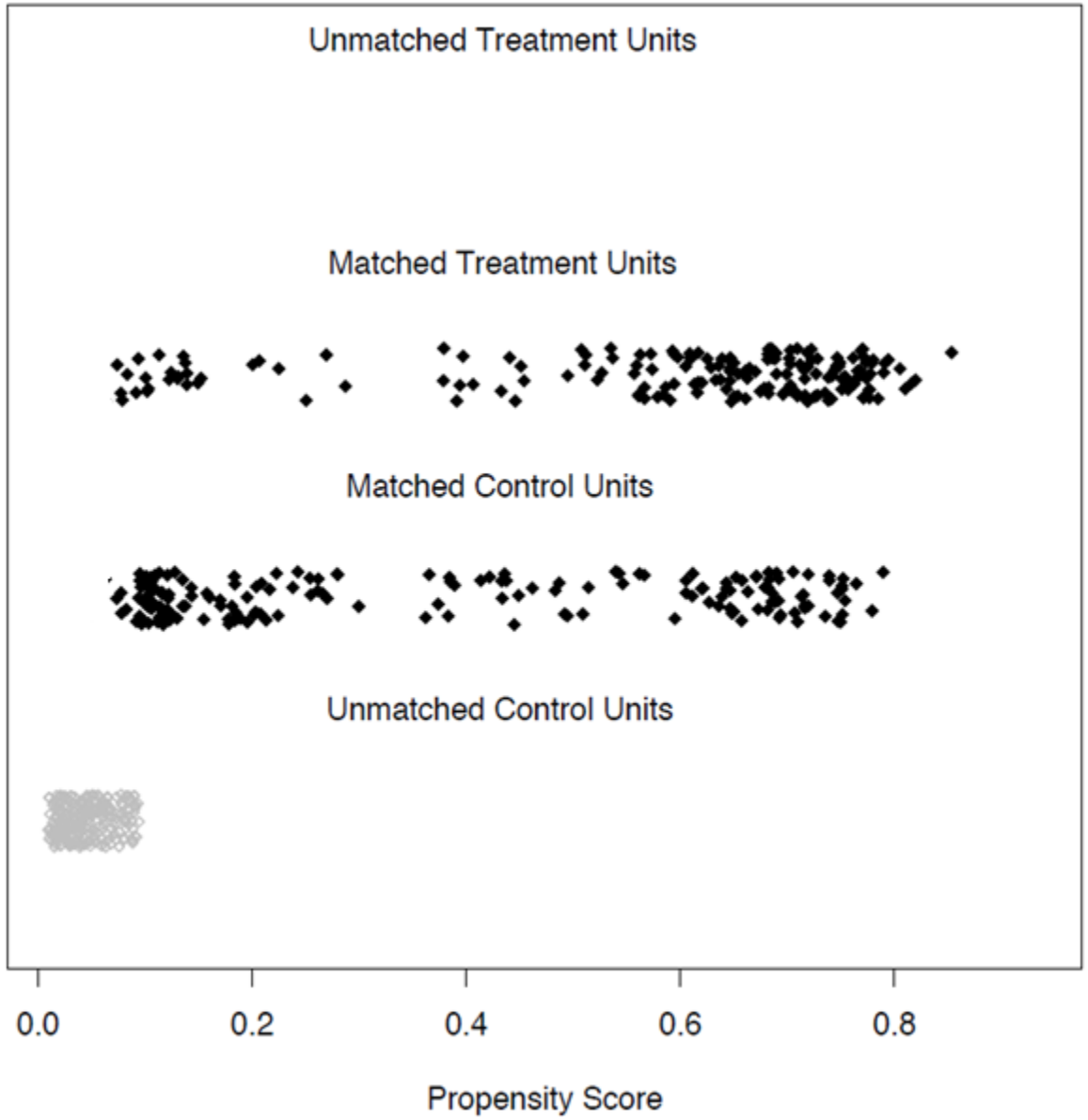
- Matching patients who received short-course therapy and those that did not based on similar or identical propensity scores
  - Most commonly 1:1 nearest neighbor matching (can do 2:1, 3:1,..)
  - Can do some exact matching
  - Can do matching with replacement or without replacement: if enough good matches, match without replacement
  - Can impose a “caliper” to limit matches to be within some range of propensity score values (commonly 0.25 propensity score standard deviations)

- Generally reduces your sample size as patients without a match are excluded
  - Need a reasonably large cohort of patients



Residual confounding likely will always still persist!

Jitter Plot


Unmatched Treatment Units
Matched Treatment Units
Matched Control Units
Unmatched Control Units
0.0
0.2
0.4
0.6
0.8
Propensity Score

Propensity-Score Stratification

- Separating study participants into distinct strata with similar propensity score values
  - Generally 5 strata used

- The association between short-course therapy and 28-day mortality is estimated within each stratum or pooled across strata to provide an estimate of this relationship

- A challenge with this approach may be having enough short-course and prolonged-course people within each strata

Propensity Score Weighting

- Propensity scores are used to calculate weights for each individual who are “down-weighted” or “up-weighted” to create a contrived population of short-course people who look similar to the prolonged-course group
  - When someone prescribed short-course therapy looks like the patients who received prolonged-course therapy, we clone that patient in the data (upweighting)
  - Someone who is already over-represented in the short-course group gets reduced in influence (downweighting)
  - A new “pseudo-population” of short-course people who look much more like the prolonged-course group is developed
- Does not sacrifice people who cannot be matched; everyone in cohort is included

Steps in Propensity Score Matching

1- Identify your cohort of patients with gram-negative bacteremia

2- Define your exposure and outcome

3- Select covariates on which to match (i.e., what variables might influence the decision to prescribe short-course therapy?)

4- Estimate the propensity score generally using logistic regression (the outcome is the odds of receiving short-course therapy and the exposures are the variables identified in #3)

5- Run the diagnostics to find the best matches for patients

6- Check for appropriate balance (covariate distribution) between the two propensity-score matched groups

7- Determine the odds ratio for 28-day mortality on the propensity-score matched sample (less prone to cheating)

Assessing Covariate Balance AFTER Matching

	Short-Course n=170	Prolonged-Course n=170	Standardized Bias
Age (median, IQR)	59 (45-69)	59 (48-68)	0.07
Male (n, %)	100 (60%)	113 (68%)	0.16
Race/Ethnicity (n, %)			
Hispanic	8 (5%)	7 (4%)	0.06
White	74 (44%)	90 (54%)	0.20
Black	76 (46%)	63 (38%)	0.16
Asian	6 (4%)	5 (3%)	0.03

Assessing Covariate Balance AFTER Matching

	Short-Course n=170	Prolonged-Course n=170	Standardized Bias
ICU on day 1 (n, %)	60 (36%)	72 (43%)	0.15
Pitt bacteremia score on day 1	2 (1-3)	2 (1-4)	0.05
Source of bacteremia (n, %)			
Pneumonia	16 (10%)	16 (10%)	<0.01
Skin and soft tissue	10 (6%)	13 (8%)	0.07
Urinary tract	52 (31%)	39 (23%)	0.16
Biliary	22 (13%)	23 (14%)	0.02
Intra-abdominal	29 (17%)	43 (26%)	0.19
Catheter-associated	38 (23%)	33 (20%)	0.08
Osteoarticular	3 (2%)	3 (2%)	<0.01

Assessing Covariate Balance AFTER Matching

	Short-Course n=170	Prolonged-Course n=170	Standardized Bias
End-Stage Liver Disease	13 (8%)	18 (11%)	0.11
End-Stage Renal Disease	15 (9%)	15 (9%)	0.001
Diabetes	16 (10%)	16 (10%)	0.001
Human Immunodeficiency Virus	8 (5%)	5 (3%)	0.09
Chemotherapy within 6 months	34 (20%)	48 (29%)	0.20
Immunomodulatory therapy ≤ 30 d	10 (6%)	12 (7%)	0.05
Solid organ transplant	23 (14%)	23 (14%)	0.001
Bone marrow transplant ≤ 12 mo	6 (4%)	8 (5%)	0.06
ANC 0-200 cells/ml	2 (1%)	3 (2%)	0.05

Outcomes

	Short-Course n=170	**Prolonged-Course n=170**	**P-value**
28-day all-cause mortality	10%	10%	0.97
C. difficile infections	2%	2%	0.87
Subsequent MDRGN infections	4%	7%	0.09

Summary

- Always define your question, primary exposure, primary outcome, and potential confounders up front
  - Consider focusing on an infectious diseases syndrome
  - Ask clinicians what outcomes data are important to them
  - Feed back data to providers
  - Publish your findings to guide others and to give the intervention credibility

- Know when to ask for help