Emulating a target trial using observational data:

an application to estimating mortality of delays in concordant antibiotic treatment for bacteraemia accounting for time-varying confounding and immortal time biases

Cherry Lim DPhil

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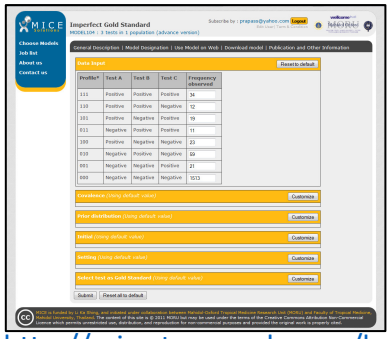
My background

MORU: Mahidol-Oxford tropical medicine Research Unit
AMR: antimicrobial resistance



http://mice.tropmedres.ac/home.aspx

Start of the AMR journey

Joined MORU, Bangkok, Thailand

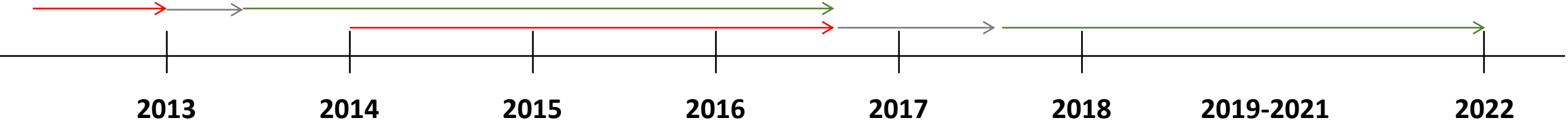
MSc with LSHTM

DPhil with Oxford

Post-doc

Master's fellowship

Training fellowship



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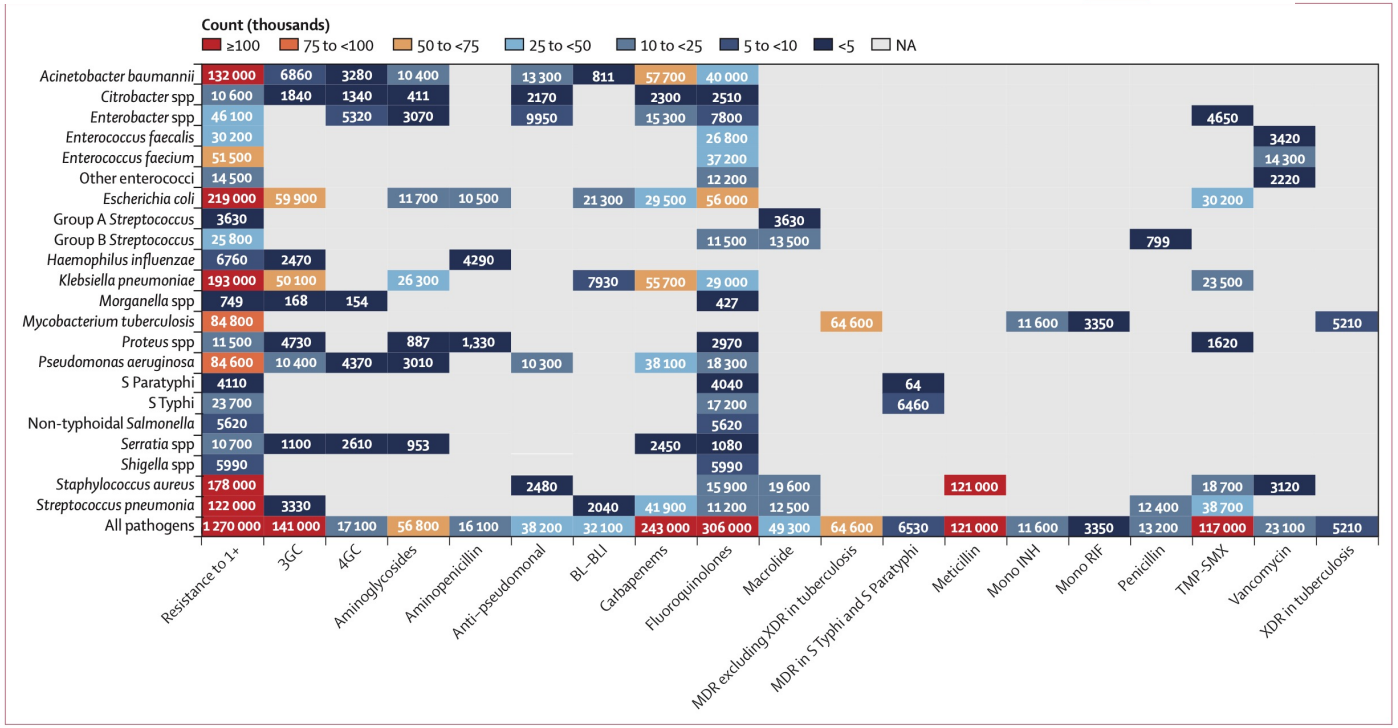
Outline

- Rational of the study
- Potential biases in observational data for answering our research question
- Emulating target trials using observational data

Global burden of AMR

Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

*Antimicrobial Resistance Collaborators**



Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022; **399**(10325): 629-55.

4.95 (95% UI 3.62-6.57) million deaths associated with bacterial AMR

1.27 (95% UI 0.91-1.71) million deaths attributable to bacterial AMR

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AMR burden in Thailand

eLIFE elifesciences.org

Epidemiology and burden of multidrug-resistant bacterial infection in a developing country

Cherry Lim[1†], Emi Takahashi[1†], Maliwan Hongsuwan[1], Vanaporn Wuthiekanun[1], Visanu Thamlikitkul[2], Soawapak Hinjoy[3], Nicholas PJ Day[1,4], Sharon J Peacock[1,5,6], Direk Limmathurotsakul[1,4,7*]

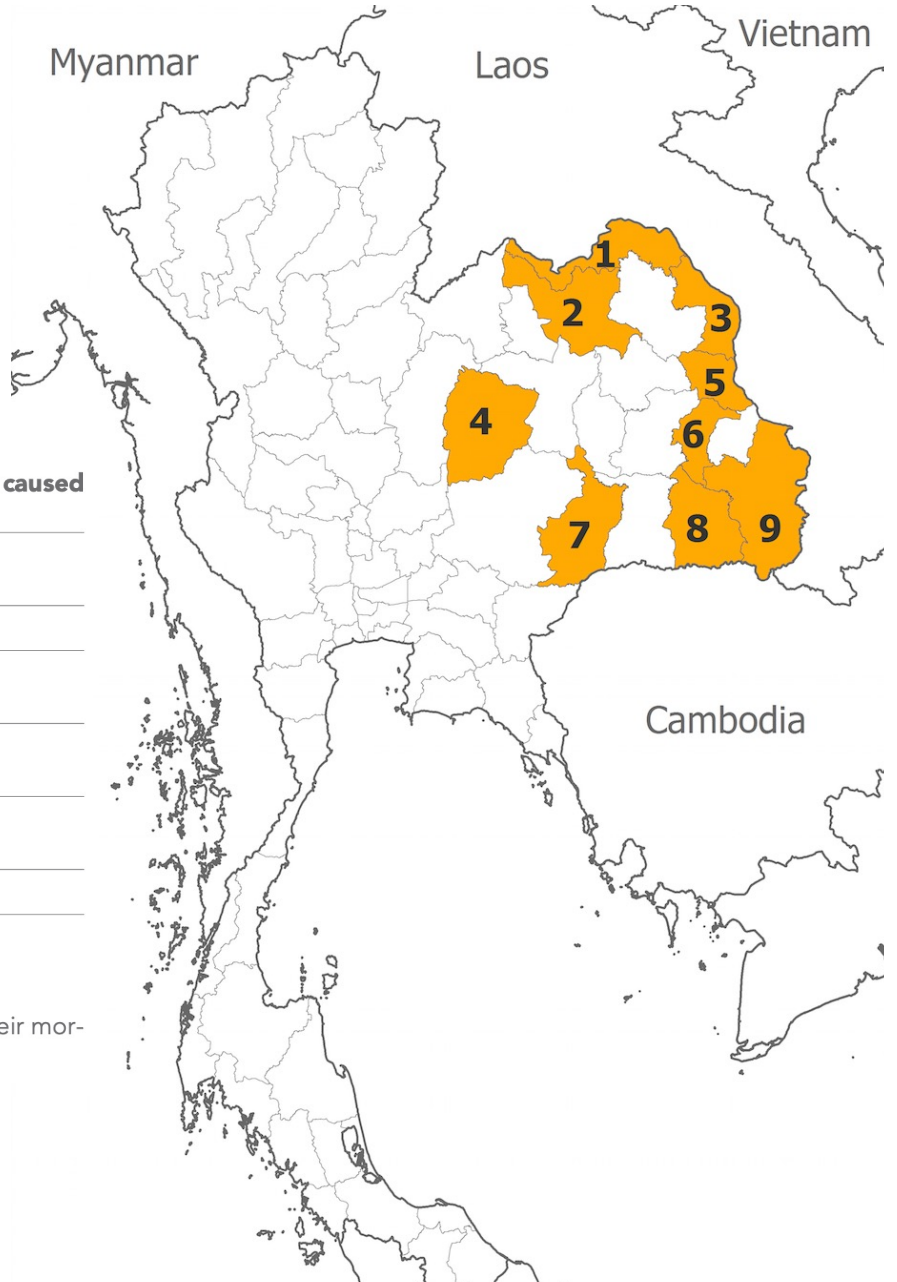
Table 8. Estimates of mortality attributable to multidrug-resistance (MDR) in hospital-acquired infection (HAI) in Thailand.

Pathogens	No of patients*	Estimated mortality (%)†	Estimated mortality if the infections were caused by non-MDR organisms (%)†, ‡	Estimated excess mortality caused by MDR (%)†, ‡
MDR *Staphylococcus aureus*	18,725	8262 (44%)	5463 (29%)	2799 (15%)
MDR *Escherichia coli*	11,116	2163 (19%)	1566 (14%)	597 (5%)
MDR *Klebsiella pneumoniae*	15,239	5267 (35%)	4979 (33%)	288 (2%)
MDR *Pseudomonas aeruginosa*	6118	3966 (65%)	3696 (60%)	270 (4%)
MDR *Acinetobacter* spp	36,553	25,551 (70%)	10,383 (28%)	15,168 (41%)
Total	87,751	45,209 (52%)	26,087 (30%)	19,122 (22%)

*Cumulative incidence of antimicrobial resistant HAI in Thailand 2010 estimated by ***Pumart et al. (2012)***.

†All parameters used to estimate the mortality and excess mortality are shown in ***Supplementary file 2***.

‡Excess mortality caused by MDR (mortality attributable to MDR) was defined as the difference in mortality of patients with MDR infection and their mortality if they were infected with non-MDR infections.



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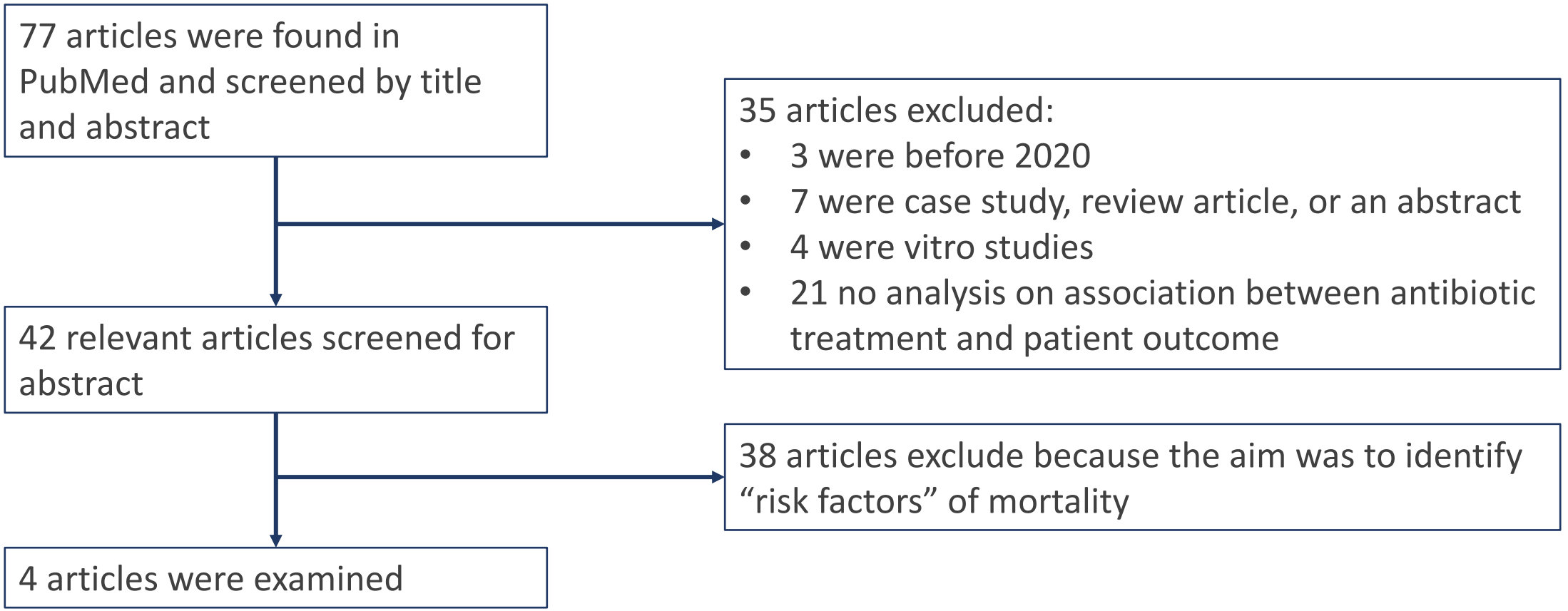
Publications on impact of discordant empirical antibiotics treatment

(((((Acinetobacter [TITLE]) AND ((("antibiotic" or "antibiotics" or "antimicrobial therapy" or "empiric therapy") and ("mortality" or "death" or "failure" or "survival") and ("bloodstream" or "bacteraemia" or "bacteremia" or “septicaemia” or "septicemia" or "sepsis") and ("inappropriate" or "appropriate" or "discordant" or "non concordant" or "concordant" or "delayed" or "covering" or "noncovering"))))))))



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Publications on impact of discordant empirical antibiotics treatment

Zilberberg *et al. Critical Care* (2016) 20:221
DOI 10.1186/s13054-016-1392-4

RESEARCH Open Access

Multidrug resistance, inappropriate empiric therapy, and hospital mortality in *Acinetobacter baumannii* pneumonia and sepsis

Marya D. Zilberberg[1*], Brian H. Nathanson[2], Kate Sulham[3], Weihong Fan[3] and Andrew F. Shorr[4]

"I(inappropriate)ET exposure was associated with higher hospital mortality (adjusted RRR 1.8, 95 % CI 1.4–2.3, $p < 0.001$)"

Shorr *et al. BMC Infectious Diseases* 2014, **14**:572
http://www.biomedcentral.com/1471-2334/14/572

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Predictors of hospital mortality among septic ICU patients with *Acinetobacter spp.* bacteremia: a cohort study

Andrew F Shorr[1], Marya D Zilberberg[2,3*], Scott T Micek[4] and Marin H Kollef[5,6]

"In multivariate analyses, non-IAAT emerged as an independent predictor of hospital death (risk ratio [RR] 1.42, 95% confidence interval [CI] 1.10-1.58)"

Impact of empirical antimicrobial therapy on the outcome of critically ill patients with *Acinetobacter* bacteremia

Hasan M. Al-Dorzi, Abdulaziz M. Asiri, Abdullah Shimemri, Hani M. Tamim[1], Sameera M. Al Johani[2], Tarek Al Dabbagh, Yaseen M. Arabi

Annals of Thoracic Medicine - Vol 10, Issue 4, October-December 2015

"Appropriate EAT was associated with lower ICU mortality risk (odds ratio: 0.15; 95% confidence interval: 0.03-0.96) on multivariate analysis."

Evaluation of the effect of appropriate antimicrobial therapy on mortality associated with *Acinetobacter nosocomialis* bacteraemia

S.-C. Kuo[1,2,3], Y.-T. Lee[1,2,4], S.-P. Yang[2,5], M.-C. Chiang[2,6], Y.-T. Lin[1,2], F.-C. Tseng[3], T.-L. Chen[1,2] and C.-P. Fung[1,2]

1) *Institute of Clinical Medicine, School of Medicine, National Yang-Ming University, Taipei,* 2) *Division of Infectious Diseases, Taipei Veterans General Hospital, Taipei,* 3) *National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Miaoli County,* 4) *Department of Medicine, Chutung Veterans Hospital, Hsinchu County,* 5) *School of Medicine, National Yang-Ming University, Taipei and* 6) *Institute of Public Health, School of Medicine, National Yang-Ming University, Taipei, Taiwan*

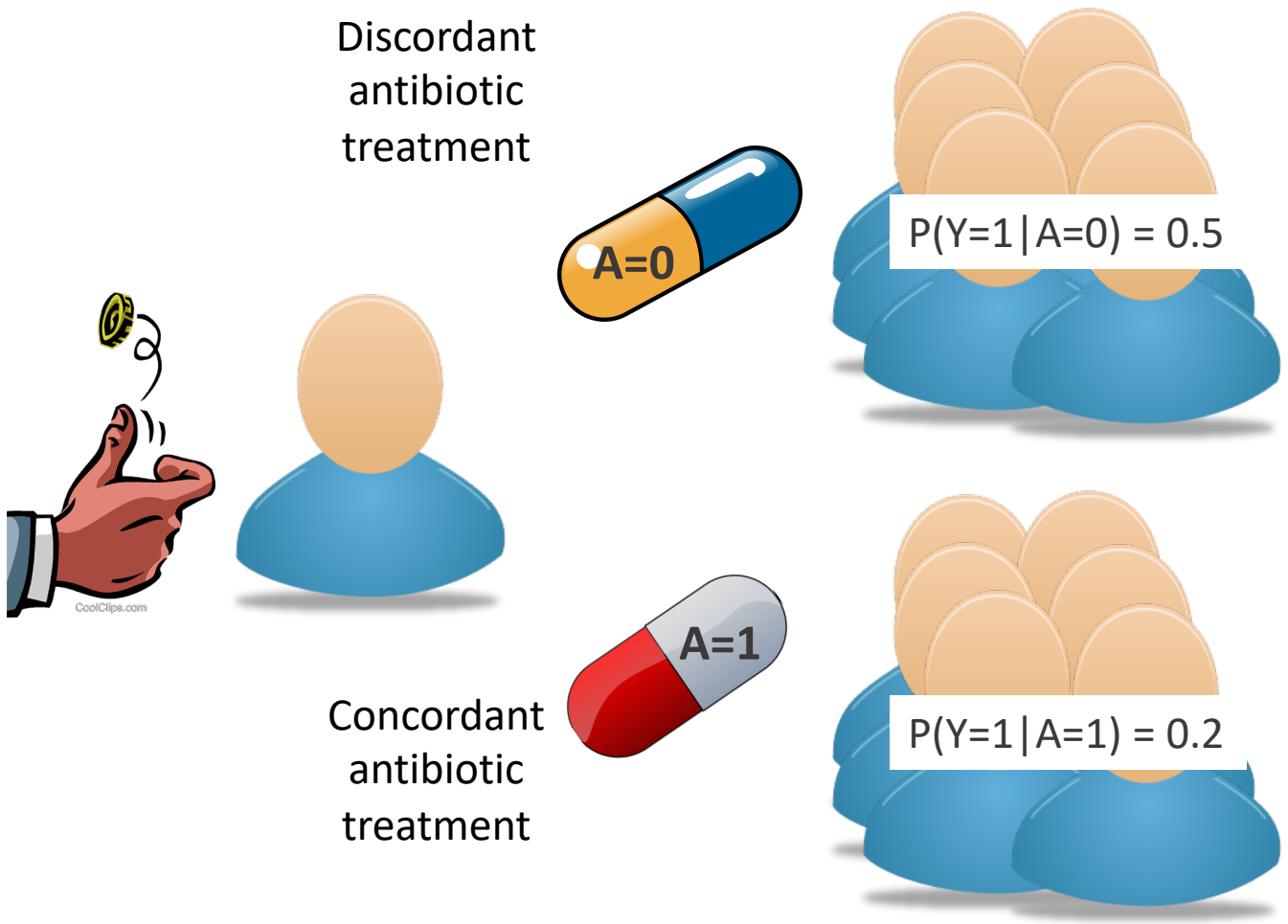
Clin Microbiol Infect 2013; **19:** 634–639
10.1111/j.1469-0691.2012.03967.x

"Appropriate antimicrobial therapy was not associated with reduced mortality regardless of disease severity."
Univariable analysis: 0.89 (0.39–2.02)

What is the causal effect of delaying concordant antibiotic treatment on patient survival in a low- and middle- income country setting?

- Important to support the design of empirical antibiotic treatment guideline

Randomised controlled trial



Under the ideal and perfect situation

Causal risk difference = 0.3

A key advantage of RCT

Exchangeability can be achieved

Unethical to intentionally delay appropriate treatment

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Observational data

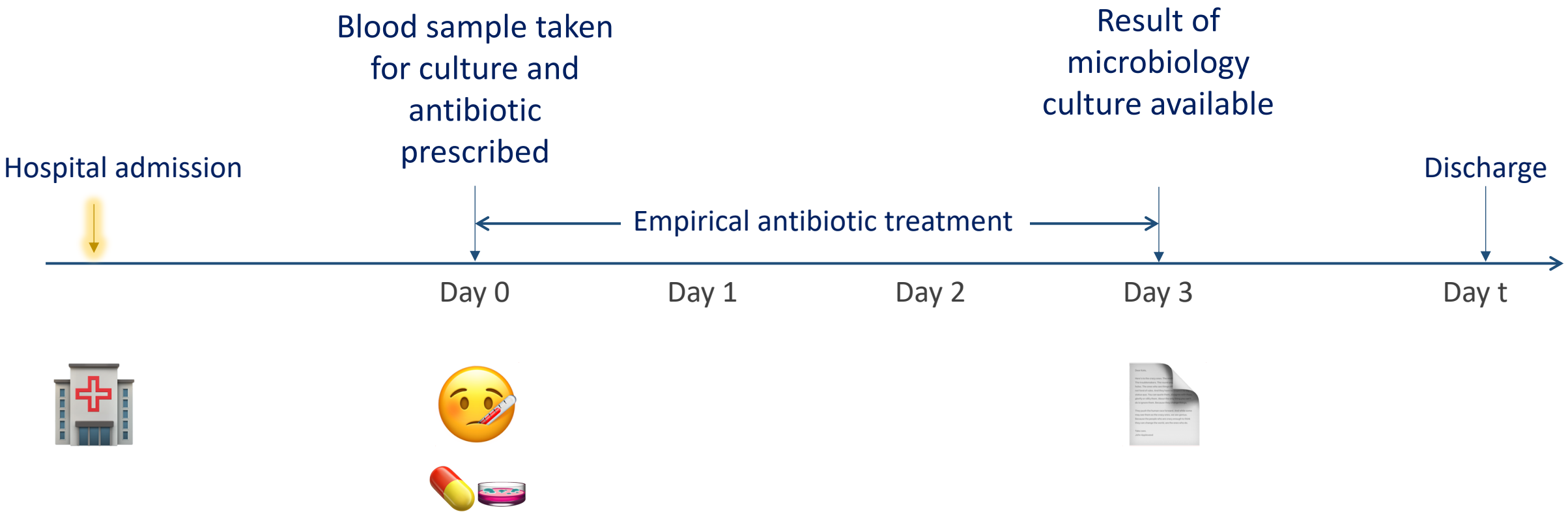
- Useful source of data when RCT is not feasible/ethical
- Large sample size is achievable
- Sample represents the “reality” better than that from RCT

Key considerations:

- “Association is not causation”
- How to adjust for different types of biases

Events during hospital stay for a case of hospital-acquired bacteraemia

A diagram to illustrate the key events of a patient with hospital-acquired bacteraemia



Immortal-time bias

Concordant antimicrobial therapy was defined as administration of ≥1 antimicrobial agent to which the causative pathogen was susceptible in vitro, within 48 hours after the onset of bacteraemia. Antimicrobial therapy that did not meet this definition was considered discordant.

Wolkewitz M., et al. J Clin Epidemiol. 2012;65:1171-80
Hernan M.A., et al. J Clin Epidemiol. 2016;79:70-5
Hernan M.A. BMJ. 2018;360:k182

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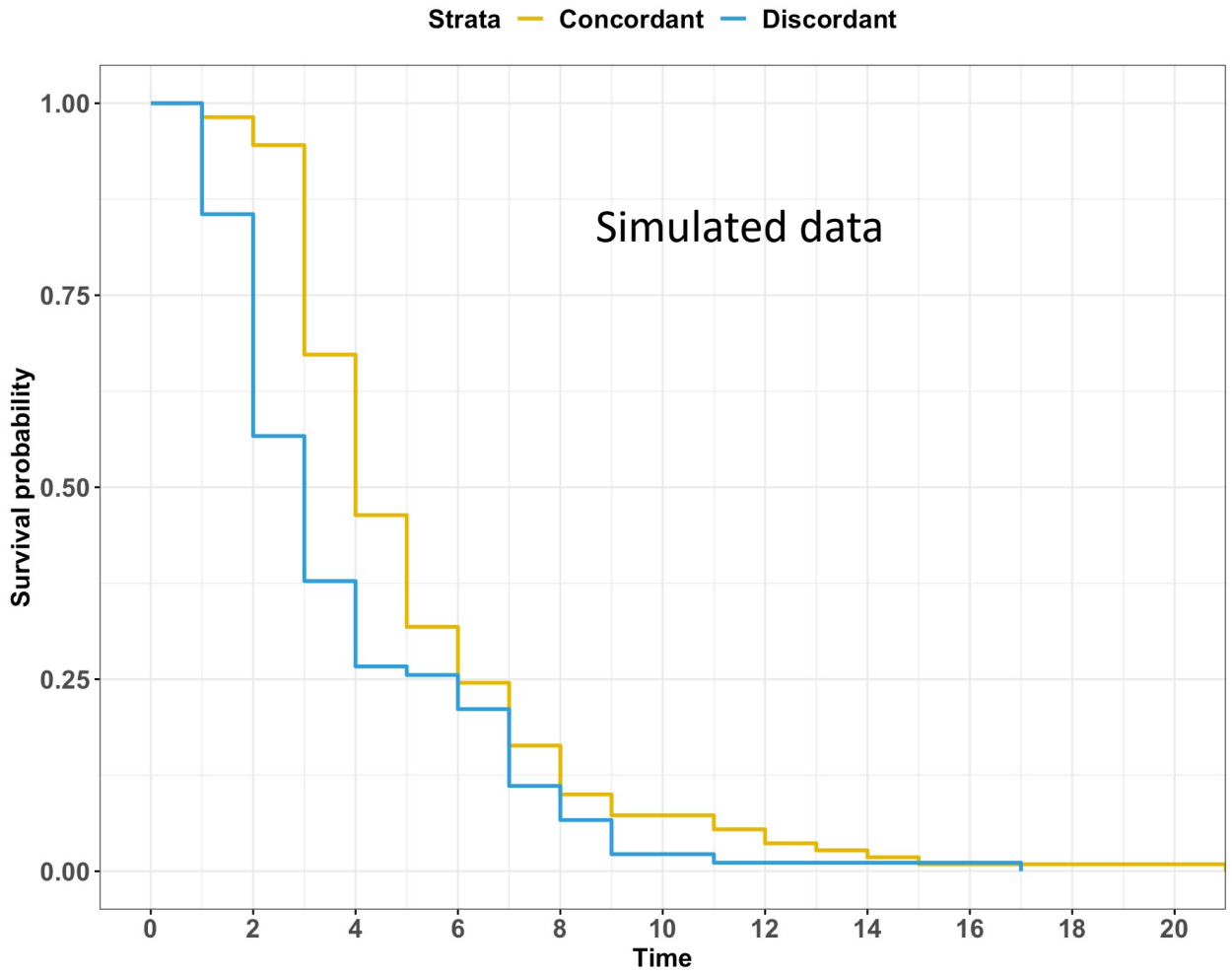

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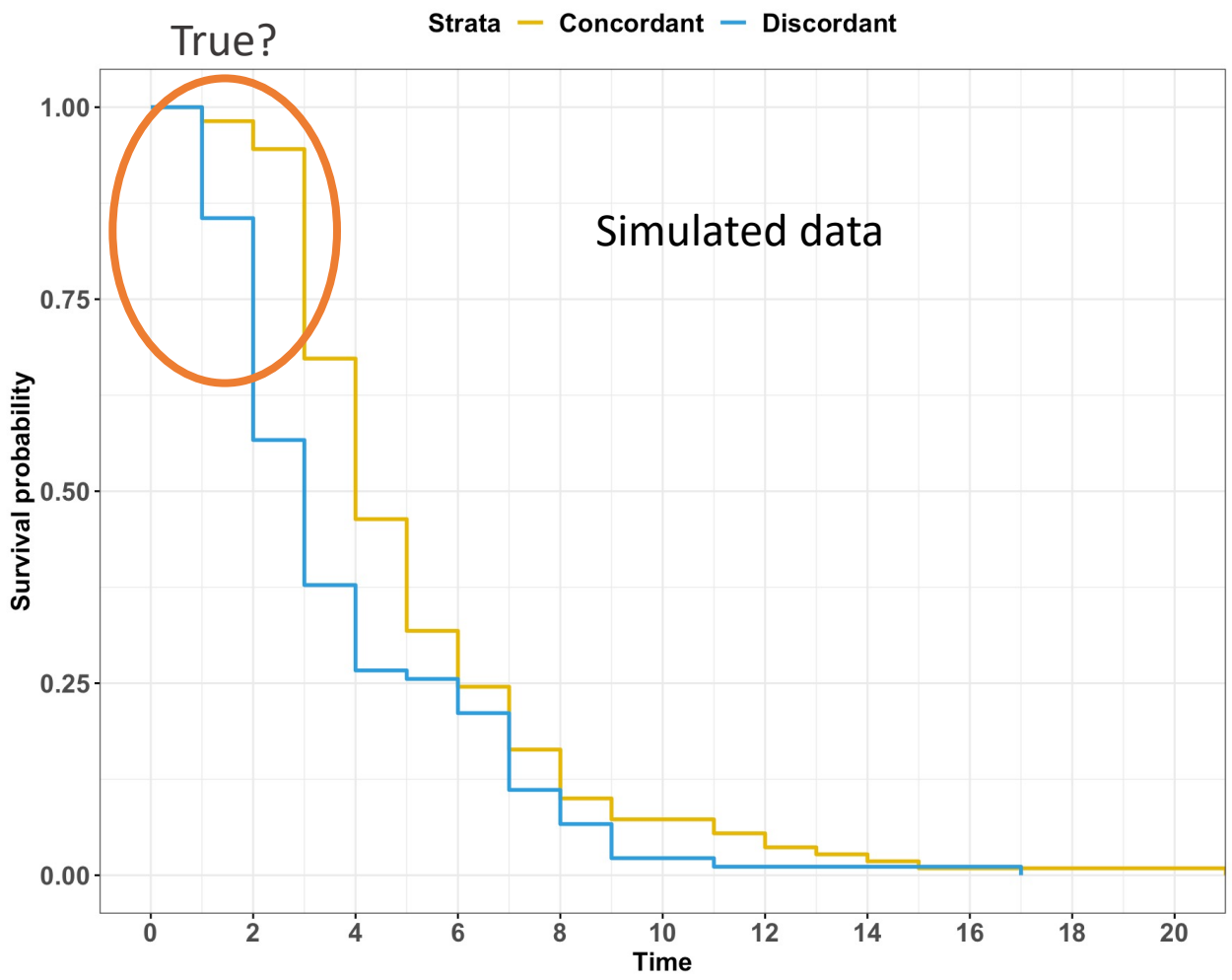

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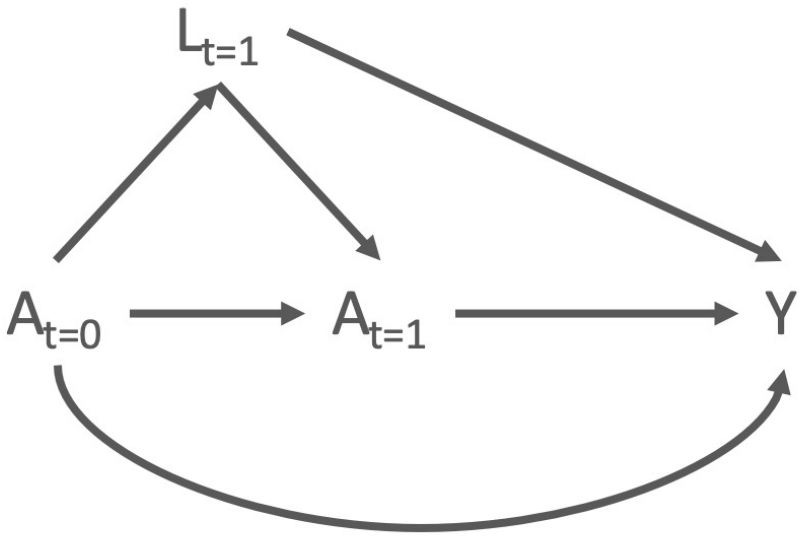
Time-varying exposure and time-varying confounder

- Time-varying exposure
- Time-varying confounder and the confounder is influenced by past treatment[1-3]



- $L_{t=1}$ is a confounder of $A_{t=1}$ -> Y and a mediator of $A_{t=0}$ -> Y
- Ignore $L_{t=1}$, then $\bar{A}$ -> Y is confounded
- Adjust for $L_{t=1}$, we can't estimate effect of $\bar{A}$ -> Y

A_t= empirical antibiotic treatment at time t
L_t= severity of infection at time t
Y= outcome

1. Daniel RM., et al. Stat in Med. 2012;32:1584-1618
2. Hernan MA., et al. Causal Conference. Chapman&Hall/CRC. 2017.
3. Fewell Z., et al. Stata J. 2004;4(4):402-20

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Counterfactual framework

- Contrasting counterfactual variables: $Y_{a=1}$ vs $Y_{a=0}$
- Emulate target trials using observational data[1,2]
- Estimate the causal effect using inverse-probability weighted estimation of marginal structural models

Measure of causal effect: $E[Y^{a=1}] - E[Y^{a=0}]$

1. Robins JM., et al. Epidemiology 2000;11(5):550-60
2. Hernan MA., Robins JM. Am J Epidemiol 2016;183(8)

Target trial- two treatment arms

Hernan MA., Robins JM. Am J Epidemiol 2016;183(8)

Protocol component	Description
Eligibility criteria	Patients who had been hospitalized for at least 2 calendar days on the date of collection of a blood sample from which *Acinetobacter* spp. was identified.
Treatment strategies	Days of delay in receiving concordant antibiotic treatment. The two treatment strategies were i) initiate an antibiotic regimen that is concordant to the *Acinetobacter* spp. isolated from blood sample without delay (i.e., on the same day as the blood sample is taken); ii) initiate a treatment that does not cover the *Acinetobacter* spp. isolated from blood sample at baseline.
Assignment procedures	Patients will be randomly assigned to one of two the antibiotic treatment strategies at baseline (on the day of blood sample collection).
Follow-up period	Starts at randomization and ends at day of discharge from the hospital, day of death within the hospital, or 30 days post randomization, whichever occurs first.
Outcome	Survival status within 30 days post randomization.
Causal contrasts of interest	Per-protocol effect; causal risk difference in 30-day mortality between the two arms.
Analysis plan	Per-protocol effect estimate requires adjustments for pre-defined confounders and immortal-time bias using marginal structural models with inverse-probability weights.

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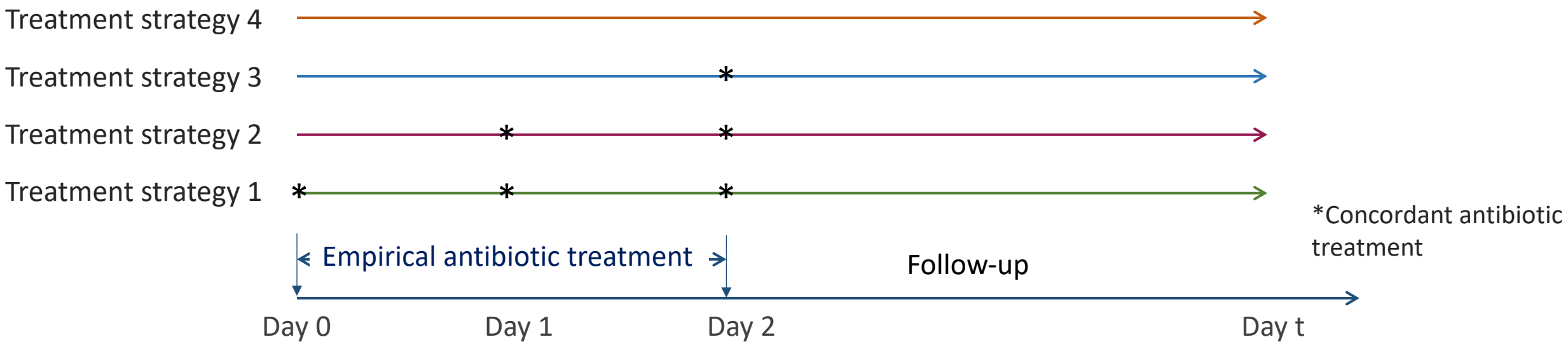
Target trial- four treatment arms

The four treatment strategies are:

- No delays in concordant antibiotic treatment
- 1 day of delay in concordant antibiotic treatment
- 2 day of delay in concordant antibiotic treatment
- ≥3 day of delay in concordant antibiotic treatment



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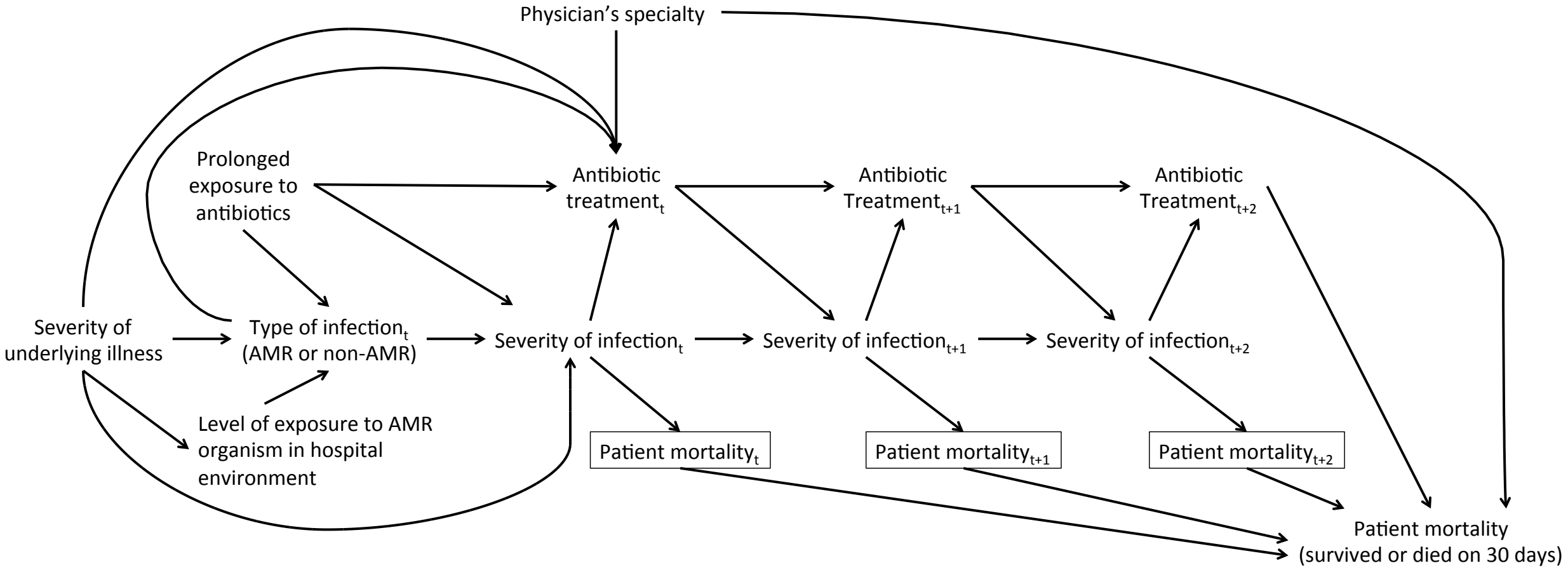
Directed acyclic graph

Directed acyclic graph



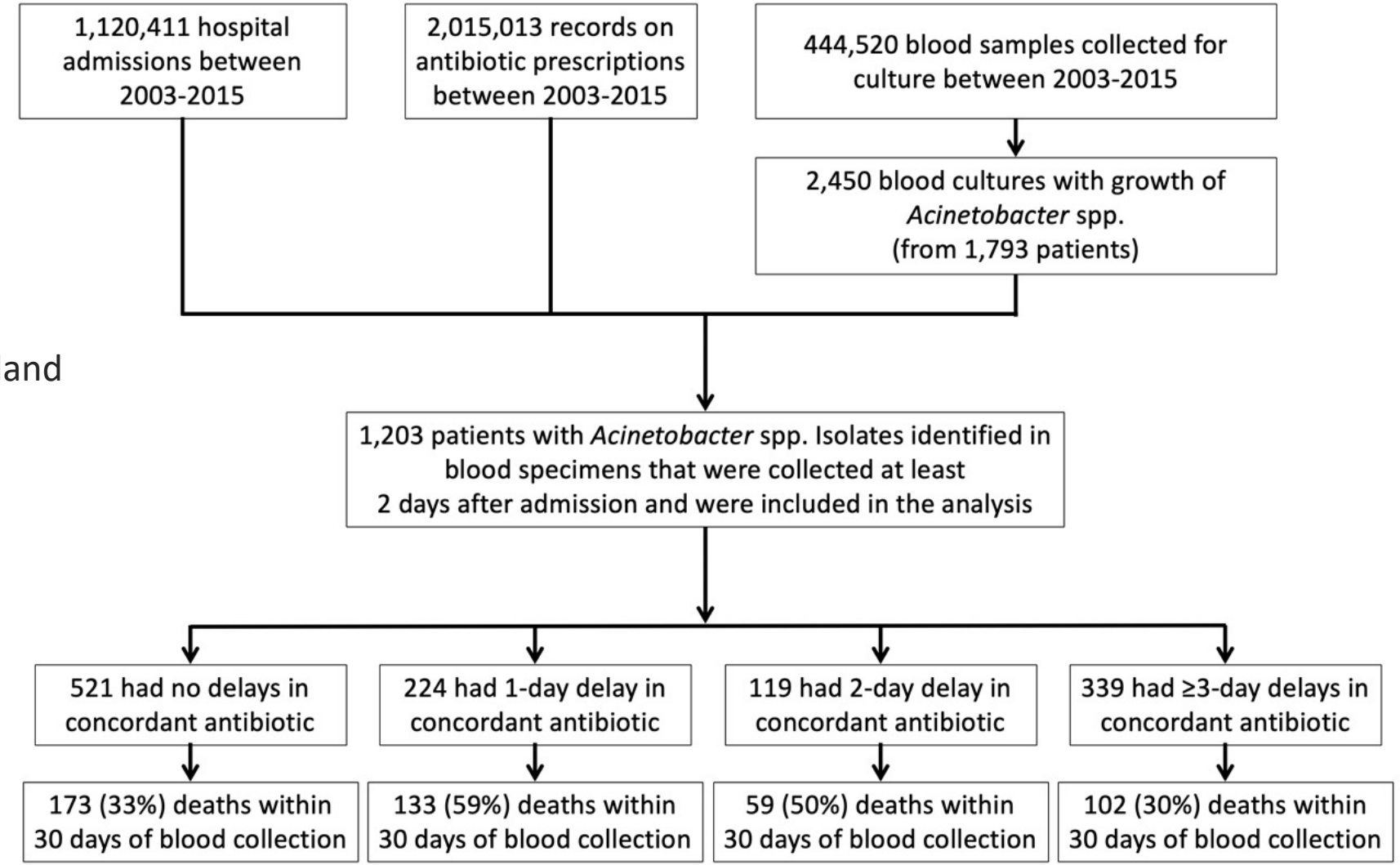
Arrows indicate the direction of a causal relationship; for instance, the relationship "severity of underlying illnesses may cause increases in the probability of antibiotic-resistant infection" is represented by an arrow from "Severity of underlying illness" to "Type of infection (AMR or non-AMR)".

Ethics committee approval

The study was approved by the Institutional Review Board of Sunpasitthiprasong Hospital (Ref. 005/2560).

Flow chart of patients

- Retrospective data
- 2003-2015
- Sunpasitthiprasong Hospital, Thailand



Crude mortality

Inverse-probability weights to adjust for time-varying confounder

- Assign a weight to each patients corresponding to the reciprocal of the product of the conditional probabilities of the observed antibiotic treatment at each time over the 3 days of empirical treatment, given the history of treatment and time-varying confounders at that time[1-3]
- The pseudo-population is then constructed by the weighted patients

$$IPW_i = \frac{1}{\prod_{t=0}^{T} P(A_t = a_{ti} \mid \overline{A}_{(t-1)} = \overline{a}_{(t-1)i}, \overline{L}_t = \overline{l}_{ti})}$$

Conditional probability mass function for subject i, given history of treatment A_{t-1} and confounder, L.

1. Robins JM., et al. Epidemiology 2000;11(5):550-60
2. Daniel RM., et al. Stat in Med. 2012;32:1584-1618
3. Hernan MA., et al. Causal Conference. Chapman&Hall/CRC. 2017

Inverse-probability weights to adjust for immortal-time bias

Departments of Epidemiology and Biostatistics, Harvard T H Chan School of Public Health, Harvard-MIT Division of Health Sciences of Technology, Boston, Massachusetts, MA 02115, USA

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miguel_hernan@post.harvard.edu

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2018;360:k182
http://dx.doi.org/10.1136/bmj.k182

Accepted: 5 December 2017

How to estimate the effect of treatment duration on survival outcomes using observational data

Miguel A Hernán

1. Assign each patient to every treatment strategy at time zero (cloning)
2. Assuming follow-up ends when patient stops being consistent with the assigned strategy (censoring)
3. Adjust for the selection bias due to step 2 by weighting the patients (inverse probability weighting)

Results a pseudo-population in which there is no immortal time bias

Patient characteristics

Baseline characteristics

	No delays in concordant antibiotic treatment (n=521)	One-day of delay in concordant antibiotic treatment (n=224)	Two-day of delay in concordant antibiotic treatment (n=119)	Three or more days of delay in concordant antibiotic treatment (n=339)
Age (years)	54 (26-69)	57 (12-70)	51 (14-69)	54 (6-70)
Female sex	212 (40.7%)	103 (46.0%)	56 (47.1%)	143 (42.2%)
Multi-drug resistance	364 (69.9%)	206 (92.0%)	103 (86.6%)	302 (89.1%)
Age-adjusted CCI score on admission	2 (0-4)	2 (0-5)	2 (0-4)	2 (0-4)

CCI: Charlson's comorbidities index

Patient characteristics

Surrogate for severity of infection

	No delays in concordant antibiotic treatment (n=521)	One-day of delay in concordant antibiotic treatment (n=224)	Two-day of delay in concordant antibiotic treatment (n=119)	Three or more days of delay in concordant antibiotic treatment (n=339)
Patients with vasopressor prescription on the day of blood sample collected for culture	211/521 (40.5%)	129/224 (57.6%)	50/119 (42.0%)	103/339 (30.4%)
Patients with vasopressor prescription on the second day of blood sample collected for culture	176/455 (38.7%)	22/54 (40.7%)	43/119 (36.1%)	117/339 (34.5%)
Patients with vasopressor prescription on the third day of blood sample collected for culture	133/390 (34.1%)	17/49 (34.7%)	15/39 (38.5%)	97/339 (28.6%)

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Patient characteristics

Transfer ICU

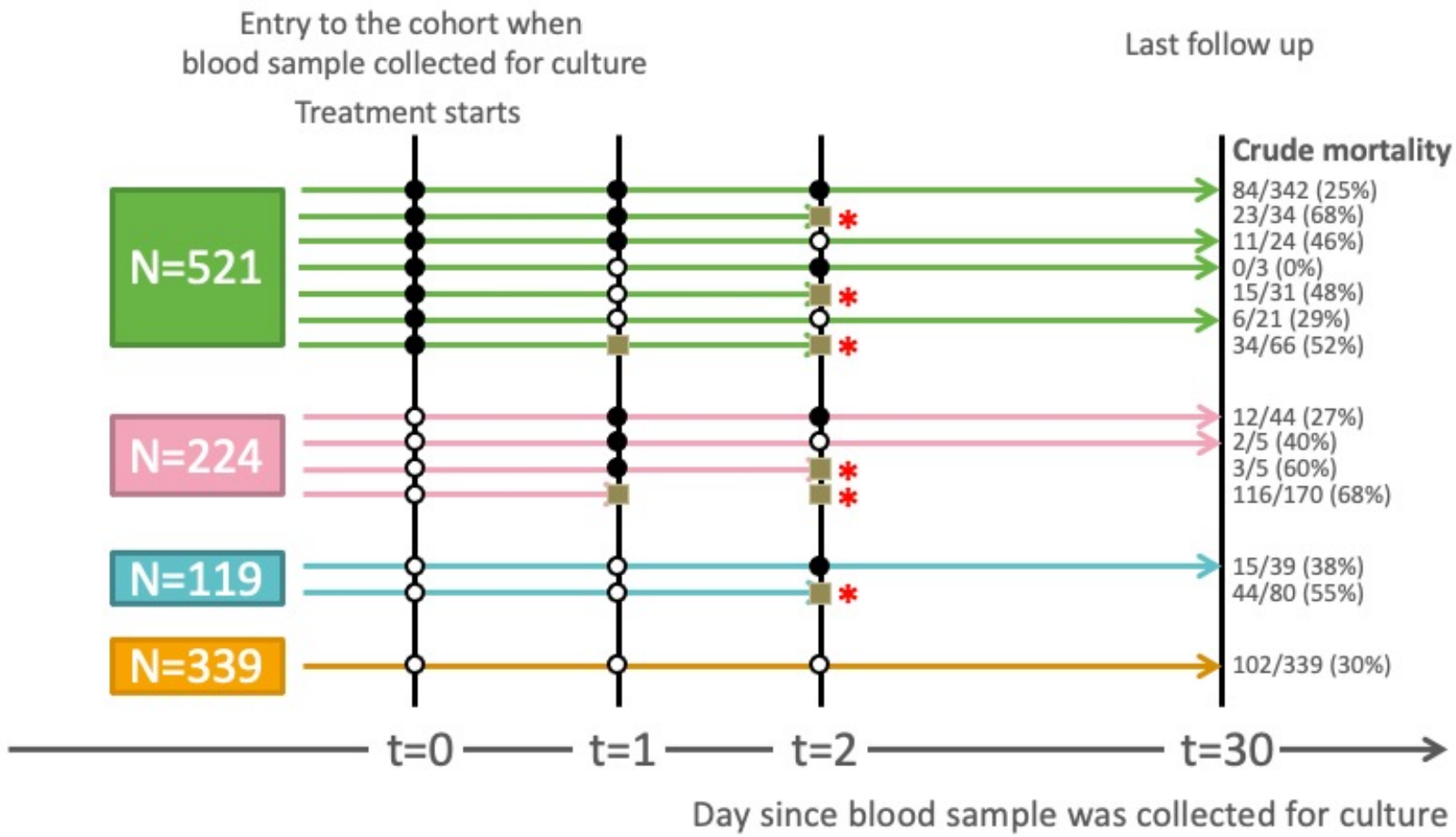
	No delays in concordant antibiotic treatment (n=521)	One-day of delay in concordant antibiotic treatment (n=224)	Two-day of delay in concordant antibiotic treatment (n=119)	Three or more days of delay in concordant antibiotic treatment (n=339)
Patients admitted to ICU on the day of hospitalisation	285 (54.7%)	159 (71.0%)	72 (60.5%)	162 (47.8%)
Patients in the ICU on the day of blood sample collected for culture	304 (58.3%)	156 (69.6%)	70 (58.8%)	191 (56.3%)

Patient characteristics

Other confounders and Patient outcomes

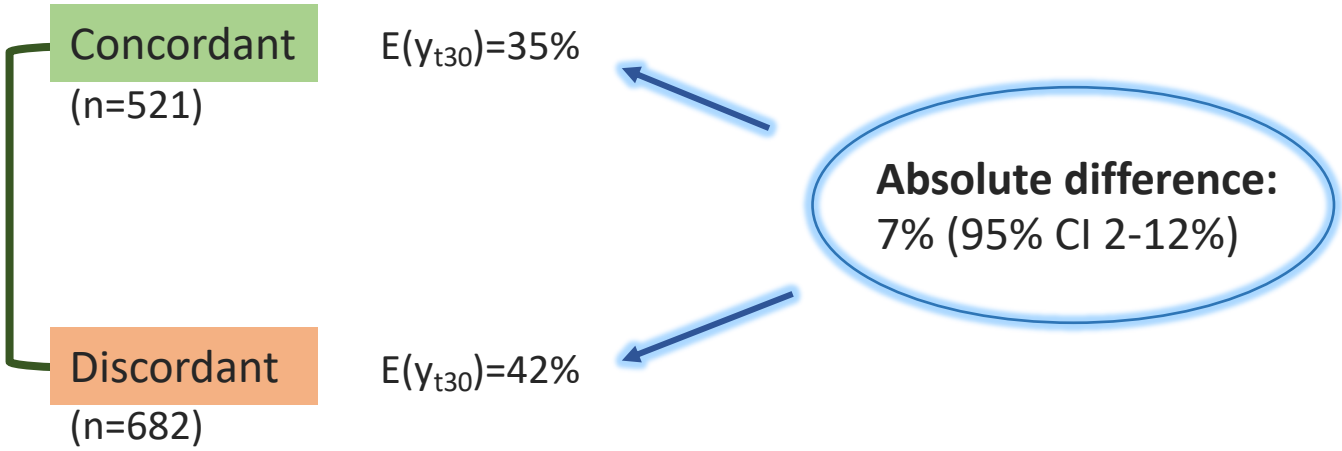
	No delays in concordant antibiotic treatment (n=521)	One-day of delay in concordant antibiotic treatment (n=224)	Two-day of delay in concordant antibiotic treatment (n=119)	Three or more days of delay in concordant antibiotic treatment (n=339)
Length of hospital stay since admission to blood sample collected for culture (days)	9 (6-19)	8 (6-15)	9 (6-15)	10 (6-17)
Days on antibiotic prior blood sample collection	8 (5-15)	5 (0-10)	7 (3-12)	7 (4-14)
30-day in-hospital mortality since blood collection	173 (33.2%)	133 (59.4%)	59 (49.6%)	102 (30.1%)

Discharge pattern



Results from emulating target trial 1

Expected mortality under each treatment regimens



For every 15 patients switching from discordant to concordant antibiotic treatment on t=0, we could have saved 1 life in this cohort of patients (if the estimated association is truly causal)

$E(y_{t30})$= Expected 30-day mortality

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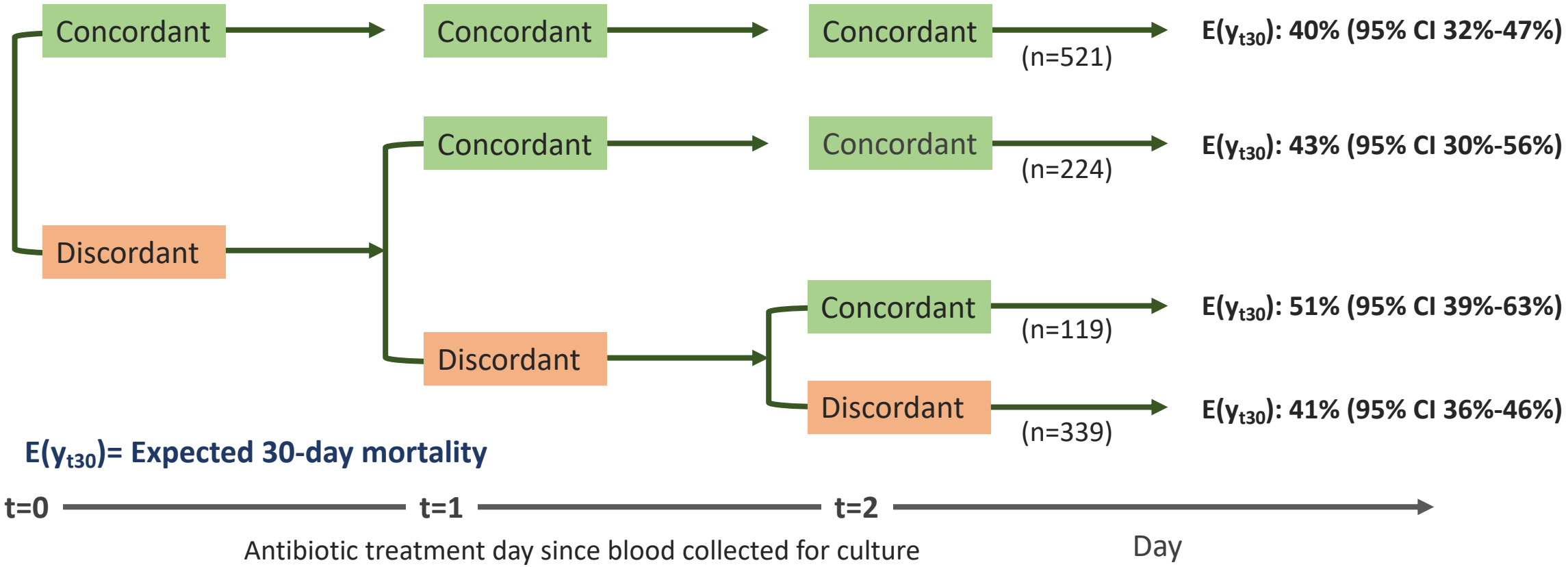
Results from emulating target trial 2

Expected mortality under each treatment regimens



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โรงพยาบาลสรรพสิทธิประสงค์

Nuffield Department of Medicine

University of Oxford

Limitations

- Transfer to ICU and prescription of vasopressor may only imperfectly represent severity of infection
- Results may not be generalisable to other settings
- Dose, frequency, and toxicity of the antibiotics were not taken into account
- Residual confounding is possible

Implications

- Highlight the needs to invest on effective control intervention to stop spread of resistant infection
- Evidence for the needs to develop rapid diagnostic tools to guide treatment
- Evidence to support the designing of empirical antibiotic treatment guideline

Future work

- Antibiotic overuse and spread of resistant infection
- Explore methods to transpose estimates to other target population (possible?)

Conclusion

- Accounting for confounding and immortal time biases is necessary when attempting to estimate causal effects of delayed concordant treatment.
- We need better and more detailed patient-level data.

Acknowledgement

Supervisors

- Ben Cooper
- Direk Limmathurotsakul
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- Guy Thwaites
- Mo Yin
- Prapit Teparrukkul
- Maliwan Hongsuwan
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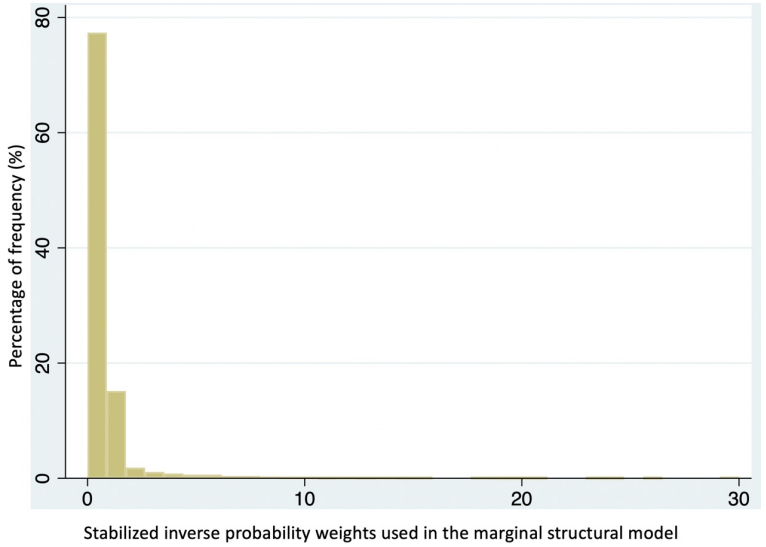
Advance Access publication:
May 27, 2021

Effect of Delays in Concordant Antibiotic Treatment on Mortality in Patients With Hospital-Acquired *Acinetobacter* Species Bacteremia: Emulating a Target Randomized Trial With a 13-Year Retrospective Cohort

Cherry Lim*, Yin Mo, Prapit Teparrukkul, Maliwan Hongsuwan, Nicholas P. J. Day, Direk Limmathurotsakul, and Ben S. Cooper*

Thank you

The mean and standard deviation of the IPWs were 0.889 and 2.369, respectively. The minimum and maximum IPWs were 0 and 30 respectively. The proportion of IPWs that had a value more than 5 was 0.032.



	No delays to concordant antibiotic treatment	1 day of delay to concordant antibiotic treatment	2 day of delay to concordant antibiotic treatment	At least 3 day of delay to concordant antibiotic treatment
Age (years)	55 (28-72)	57 (36-70)	48 (26-69)	54 (20-70)
Female gender	51%	49%	49%	38%
Multi-drug resistance	79%	85%	84%	74%
Age-adjusted CCI score on admission	2 (0-4)	3 (0-4)	2 (0-4)	2 (0-4)
Vasopressor prescribed on the day of blood specimen collected for culture	46%	51%	31%	32%
Admitted to ICU on the day of hospitalization	62%	66%	60%	45%
Admitted to ICU on the day of blood specimen collected for culture	67%	65%	58%	53%
Length of hospital stay since admission to blood specimen collected for culture date (days)	7 (5-15)	8 (5-16)	9 (5-17)	10 (6-17)
Days on antibiotic prior blood collection	7 (4-14)	6 (1-12)	8 (5-18)	8 (4-17)

Age, CCI score, length of hospital stay since admission to blood collection date, and days on antibiotic prior blood specimen collection are median (IQR), and other data are n (%). ICU=intensive care unit. CCI=Charlson Comorbidity Index Score; defined using ICD10 scores.[1] Multidrug resistance is defined as non-susceptible to ≥1 agent in ≥3 antimicrobial categories.[2]