MYTHS AND MISCONCEPTIONS IN THE MANAGEMENT OF SEPSIS

MERVYN SINGER

BLOOMSBURY INSTITUTE OF INTENSIVE CARE MEDICINE

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DISCUSSION POINTS ..

- Guidelines should be slavishly followed
- One size fits all
- Every hour of antibiotic delay kills
- How long should a course of antibiotics last?
- Sepsis mortality is improving
- Why do people die of sepsis?

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INDIVIDUALS VERSUS POPULATION

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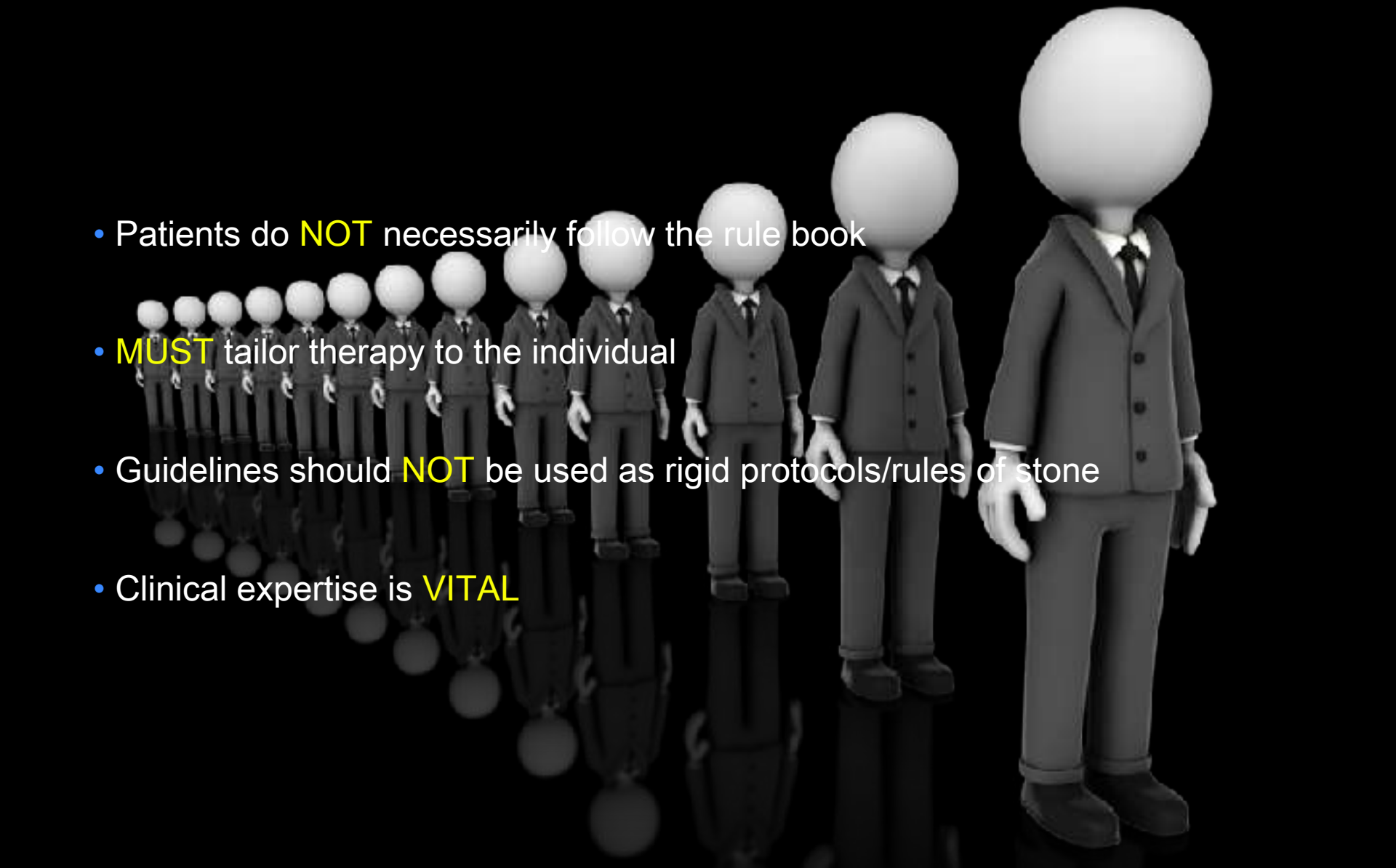

- Patients do NOT necessarily follow the rule book
- MUST tailor therapy to the individual
- Guidelines should NOT be used as rigid protocols/rules of stone
- Clinical expertise is VITAL

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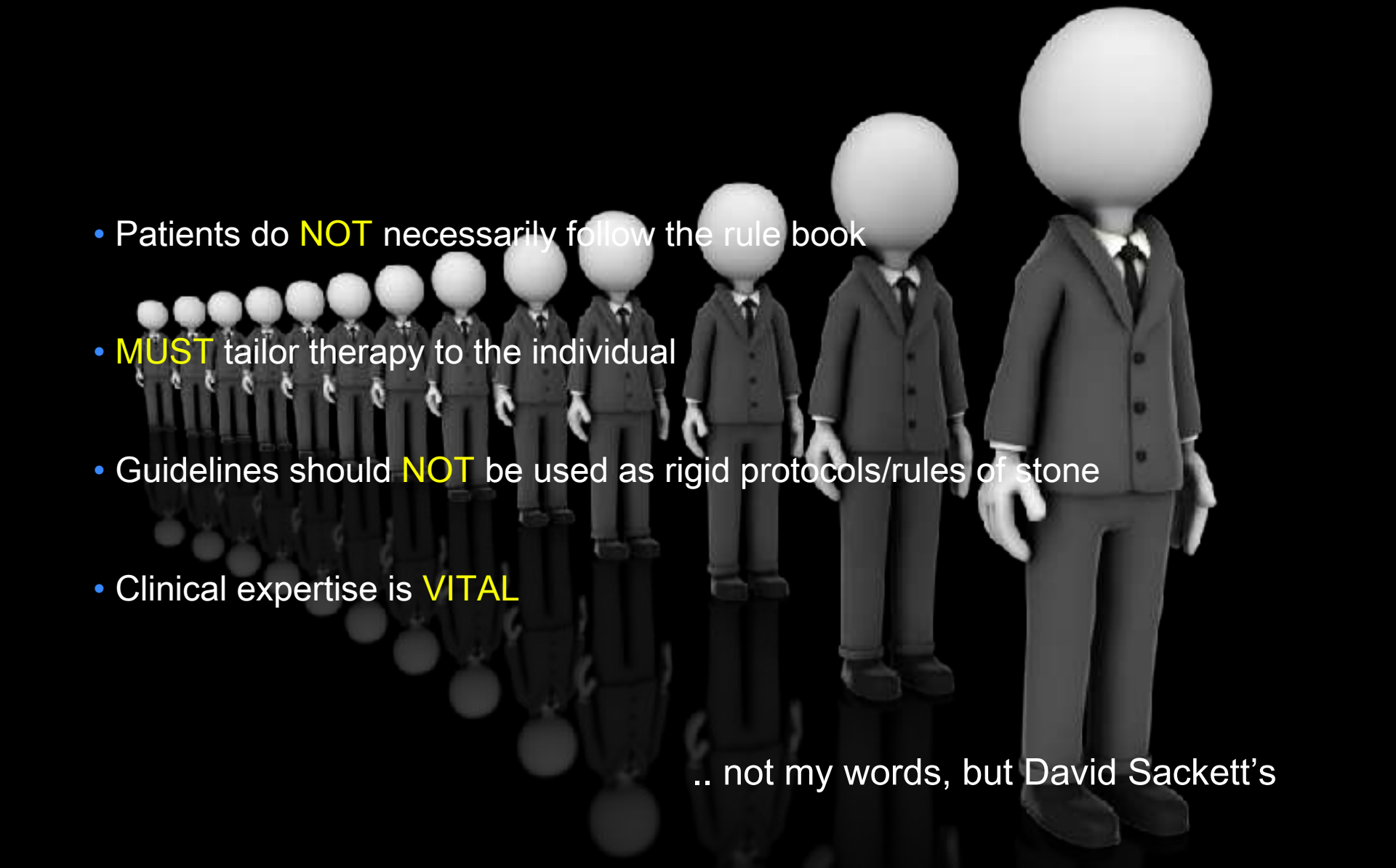

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- Clinical expertise is VITAL

.. not my words, but David Sackett's

Evidence based medicine: what it is and what it isn't

It's about integrating individual clinical expertise and the best external evidence

best available external evidence, and neither alone is enough. Without clinical expertise, practice risks becoming tyrannised by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient.

Professor

NHS Research and Development Centre for Evidence Based Medicine,
Oxford Radcliffe NHS Trust,
Oxford OX3 9DU

Evidence based medicine: what it is and what it isn't

It's about integrating individual clinical expertise and the best external evidence

Because it requires a bottom up approach that integrates the best external evidence with individual clinical expertise and patients' choice, it cannot result in slavish, cookbook approaches to individual patient care. External clinical evidence can inform, but can never replace, individual clinical expertise, and it is this expertise that decides whether the external evidence applies to the individual patient at all and, if so, how it should be integrated into a clinical decision. Similarly, any external guideline must be integrated with individual clinical expertise in deciding whether and how it matches the patient's clinical state, predicament, and preferences, and thus whether it should be applied. Clinicians who fear top down cookbooks will find the advocates of evidence based medicine joining them at the barricades.

Professor

QUALITY - OR LACK - OF EVIDENC

2016 Descriptor	
Strength	Strong
	Weak
Quality	High
	Moderate
	Low
	Very Low
Ungraded strong recommendation	Best Practice Statement

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- Overall evidence base for sepsis is - sadly - rather weak
- Only a few awarded ‘high’ quality (but generally ‘do nots’ rather than ‘do’s’)

DOGMA SHOULDN'T RULE ...

- Need decent evidence to confirm need to change
- For example, Rivers showed EGDT was beneficial in 2001 .. but why?

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EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

VARIABLE	STANDARD THERAPY (N=133)	EARLY GOAL-DIRECTED THERAPY (N=130)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
In-hospital mortality†				
All patients	59 (46.5)	38 (30.5)	0.58 (0.38–0.87)	0.009

with severe sepsis and septic shock. (N Engl J Med 2001;345:1368-77.)

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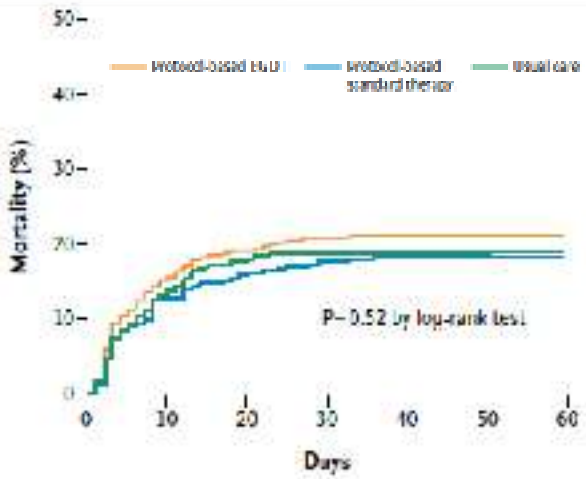
ORIGINAL ARTICLE

A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*



No. at Risk							
Protocol-based EGDT	439	373	350	348	347	347	347
Protocol-based standard therapy	446	389	371	368	366	366	365
Usual care	456	396	376	371	371	371	370

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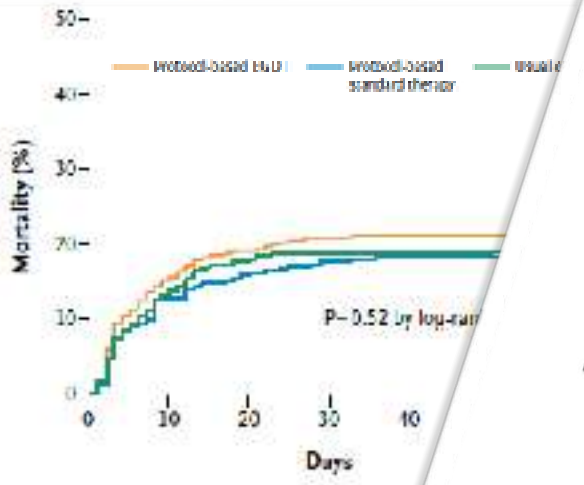

Goal-Directed Resuscitation for Patients with Early Septic Shock

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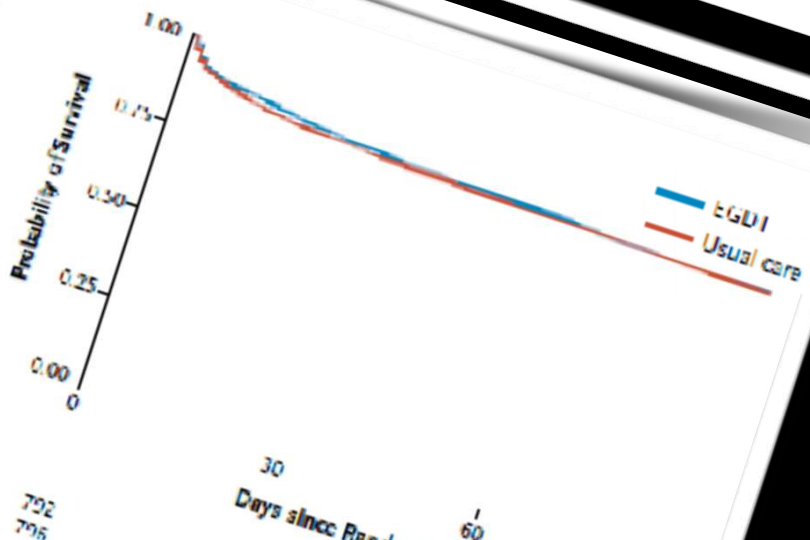

N Engl J Med 2014;371:1496-506

ORIGINAL

A Randomi… sed Care

for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*

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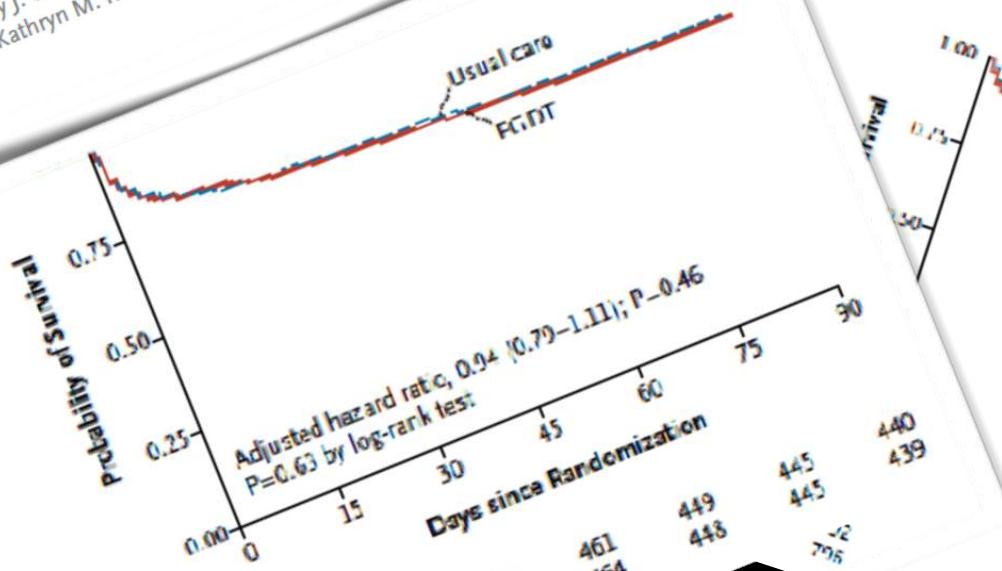

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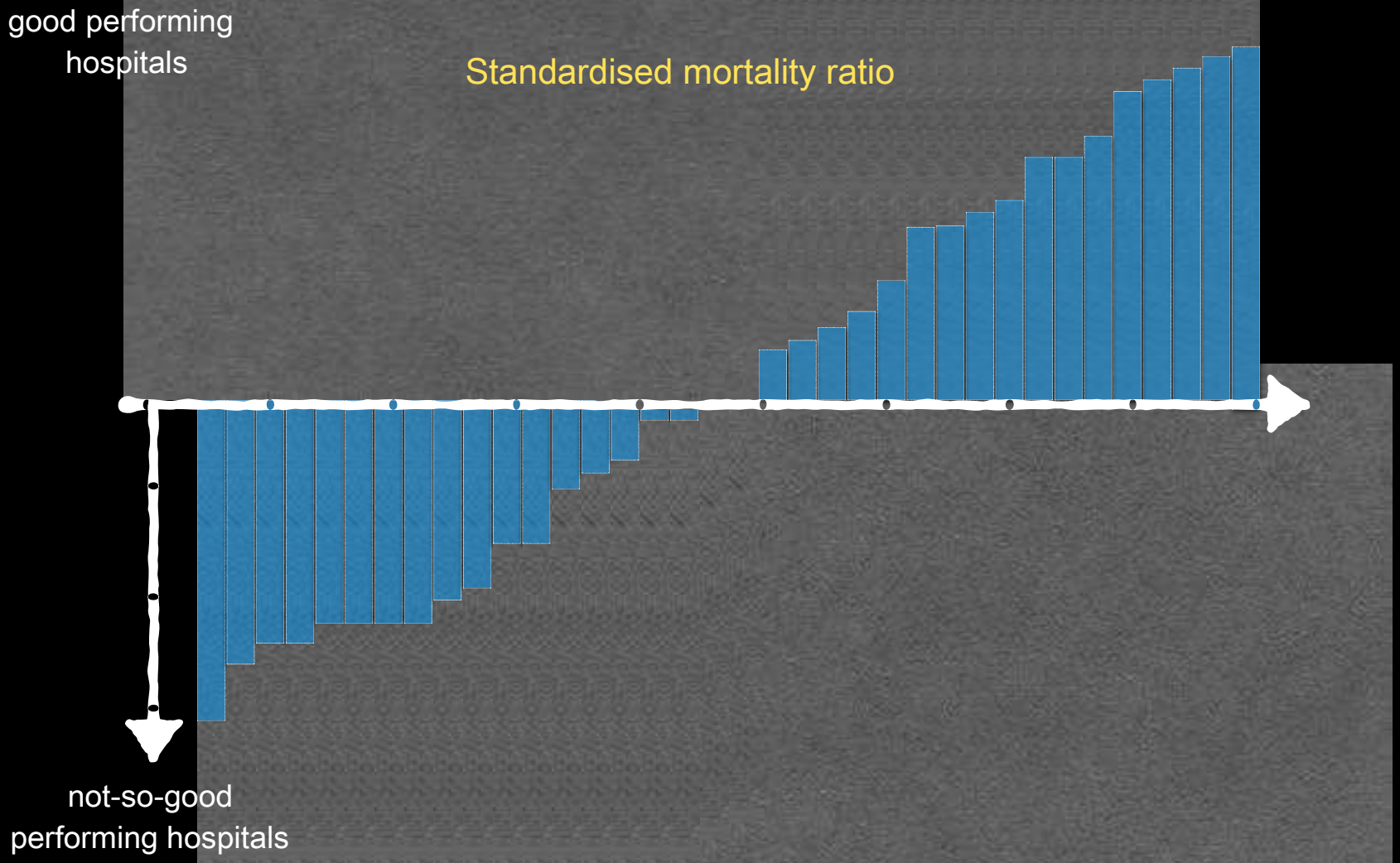
TAKE-HOME MESSAGE

- Identify patient early
- Treat promptly and appropriately
- .. but the specific Rivers' protocol doesn't seem to offer any overall added benefit

LOWEST COMMON DENOMINATOR?



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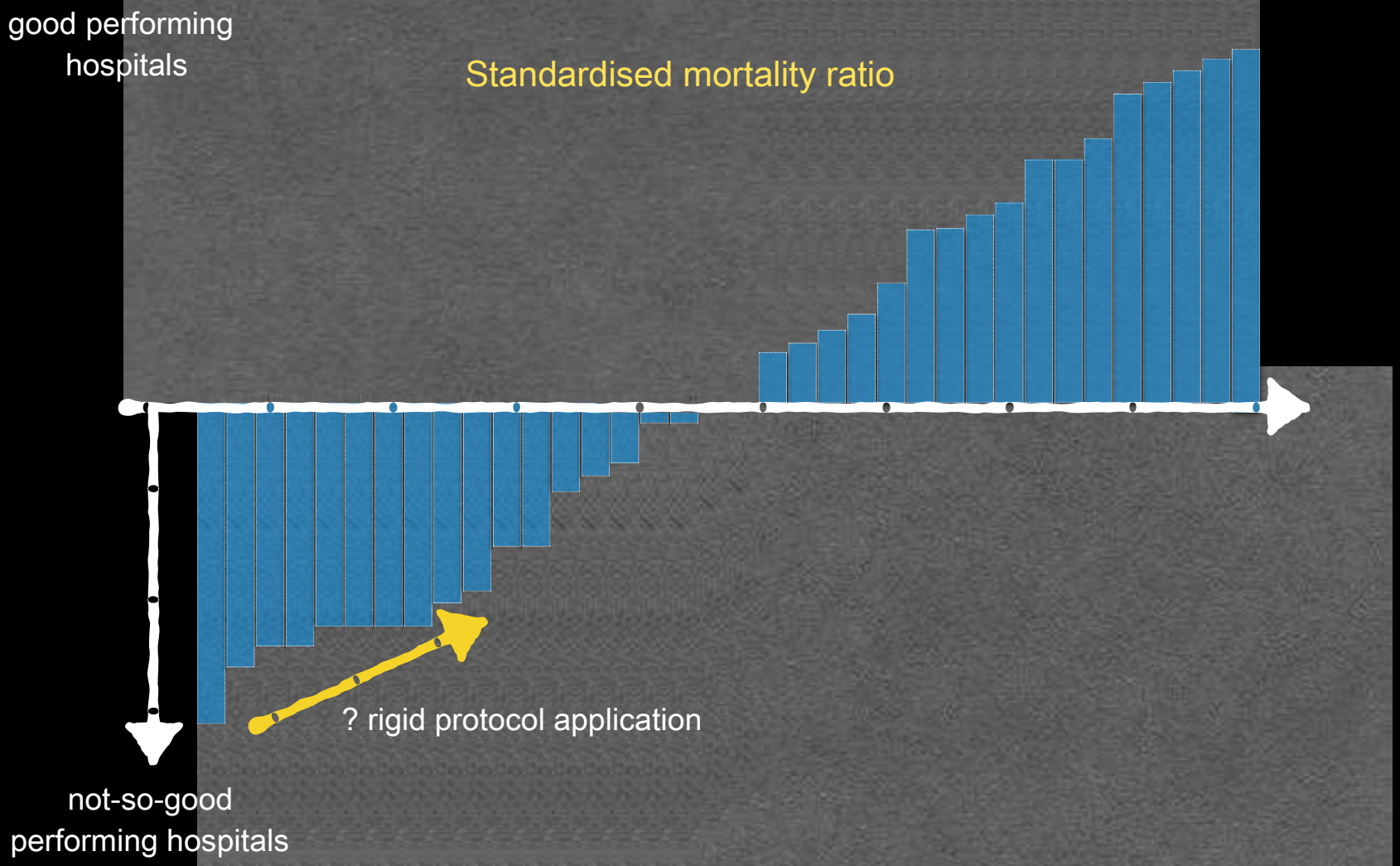

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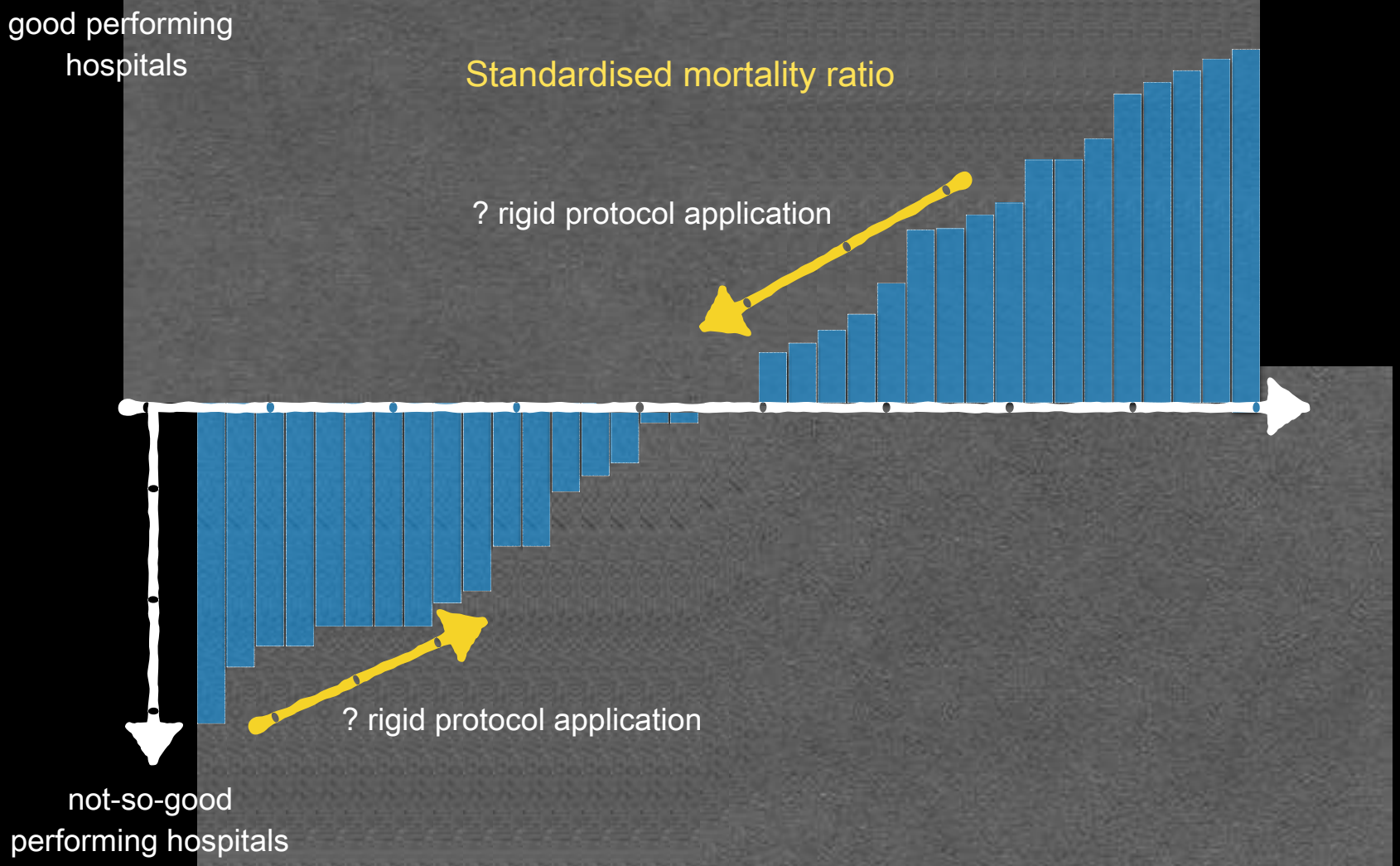

LOWEST COMMON DENOMINATOR?

good performing hospitals

Standardised mortality ratio

? rigid protocol application

? rigid protocol application

not-so-good performing hospitals

BUT....

Guidelines are often taken too literally by:

- clinical zealots
- institutions
- governments

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Guidelines are often taken too literally by:

- clinical zealots
- institutions
- governments

.. with financial penalties or ‘name-and-shame’ for non-compliance

TAKE-HOME MESSAGE

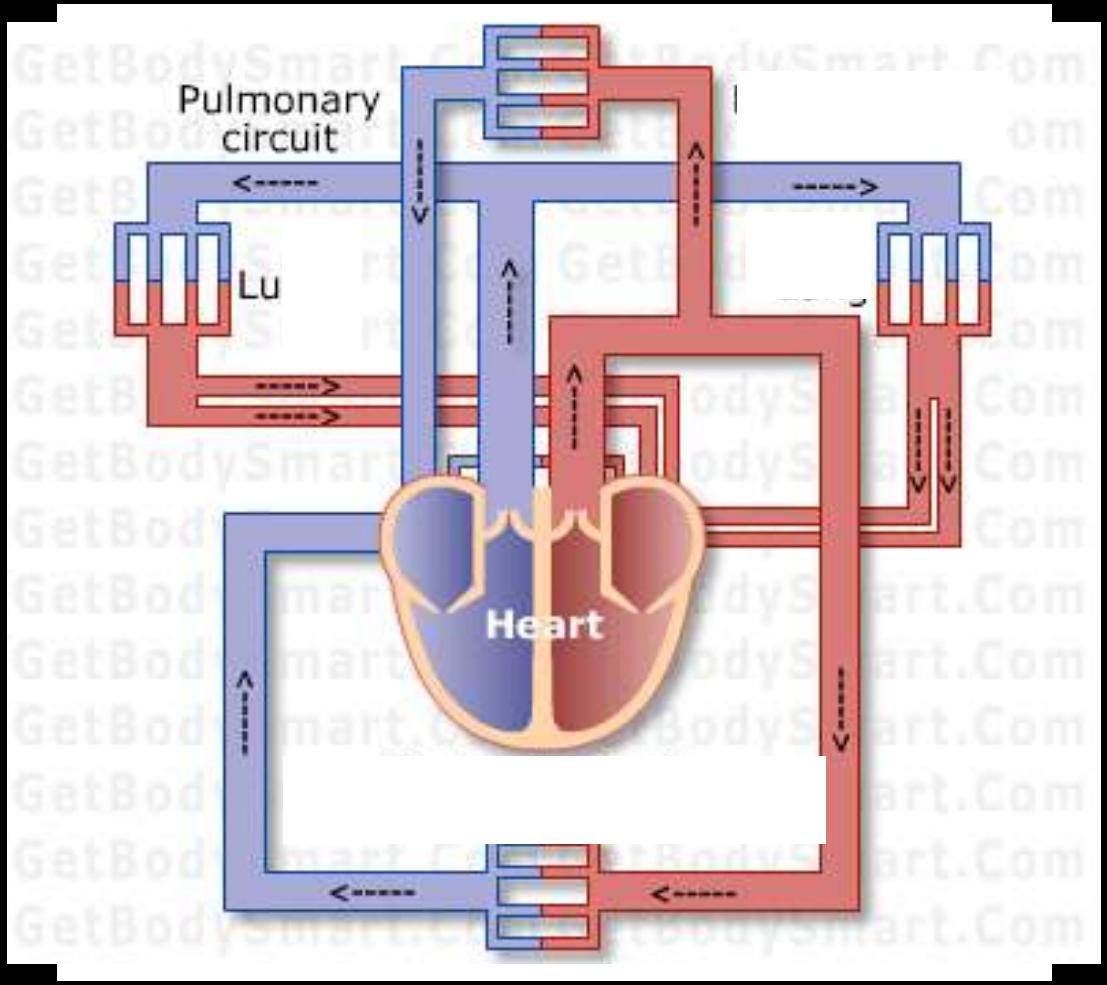
- Use guidelines/protocols as an aide memoire
- .. but not rules of stone
- Don’t be afraid to deviate .. but be able to justify why

DISCUSSION POINTS ..

- Guidelines should be slavishly followed
- One size fits all
- Every hour of antibiotic delay kills
- How long should a course of antibiotics last?
- Sepsis mortality is improving
- Why do people die of sepsis?

THE INTERVENTION .. OR TARGETED ENDPOIN

.. MUST BE RATIONAL FOR EVERYONE



ORIGINAL ARTICLE

High versus Low Blood-Pressure Target in Patients with Septic Shock

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D., Bruno Megarbane, M.D., Ph.D., Nadia Anguel, M.D., Jean-Paul Mira, M.D., Ph.D., Pierre-François Dequin, M.D., Ph.D., Soizic Gergaud, M.D., Nicolas Weiss, M.D., Ph.D., François Legay, M.D., Yves Le Tulzo, M.D., Ph.D., Marie Conrad, M.D., René Robert, M.D., Ph.D., Frédéric Gonzalez, M.D., Christophe Guitton, M.D., Ph.D., Fabienne Tamion, M.D., Ph.D., Jean-Marie Tonnelier, M.D., Pierre Guezennec, M.D., Thierry Van Der Linden, M.D., Antoine Vieillard-Baron, M.D., Ph.D., Eric Mariotte, M.D., Gaël Pradel, M.D., Olivier Lesieur, M.D., Jean-Damien Ricard, M.D., Ph.D., Fabien Hervé, M.D., Damien Du Cheyron, M.D., Ph.D., Claude Guerin, M.D., Ph.D., Alain Mercat, M.D., Ph.D., Jean-Louis Teboul, M.D., Ph.D., and Peter Radermacher, M.D., Ph.D. for the SEPSISPAM Investigators*

N Engl J Med 2014;370:1583-93.

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BACKGROUND

The Surviving Sepsis Campaign recommends targeting a mean arterial pressure of at least 65 mm Hg during initial resuscitation of patients with septic shock. However, whether this blood-pressure target is more or less effective than a higher target is unknown.

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In a multicenter, open-label trial, we randomly assigned 776 patients with septic shock to undergo resuscitation with a mean arterial pressure target of either 80 to 85 mm Hg (high-target group) or 65 to 70 mm Hg (low-target group). The primary end point was mortality at day 28.

ORIGINAL ARTICLE

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SO WHY TARGET A POPULATION,

AND NOT AN INDIVIDUAL!!!!!

High versus Low Blood-Pressure Target in Patients with Septic Shock

Variable	Low-Target Group (N=388)	High-Target Group (N=388)	P Value
Secondary outcomes — no./total no. (%)			
Death at day 90†	164 (42.3)	170 (43.8)	0.74
Survival at day 28 without organ support‡	241 (62.1)	235 (60.6)	0.66
Doubling of plasma creatinine	161 (41.5)	150 (38.7)	0.42
No chronic hypertension	71/215 (33.0)	85/221 (38.5)	0.32
Chronic hypertension	90/173 (52.0)	65/167 (38.9)	0.02
Renal-replacement therapy from day 1 to day 7	139 (35.8)	130 (33.5)	0.50
No chronic hypertension	66/215 (30.7)	77/221 (34.8)	0.36
Chronic hypertension	73/173 (42.2)	53/167 (31.7)	0.046
Serious adverse events — no. (%)			
Any	69 (17.8)	74 (19.1)	0.64
Acute myocardial infarction§	2 (0.5)	7 (1.8)	0.18
Atrial fibrillation	11 (2.8)	26 (6.7)	0.02

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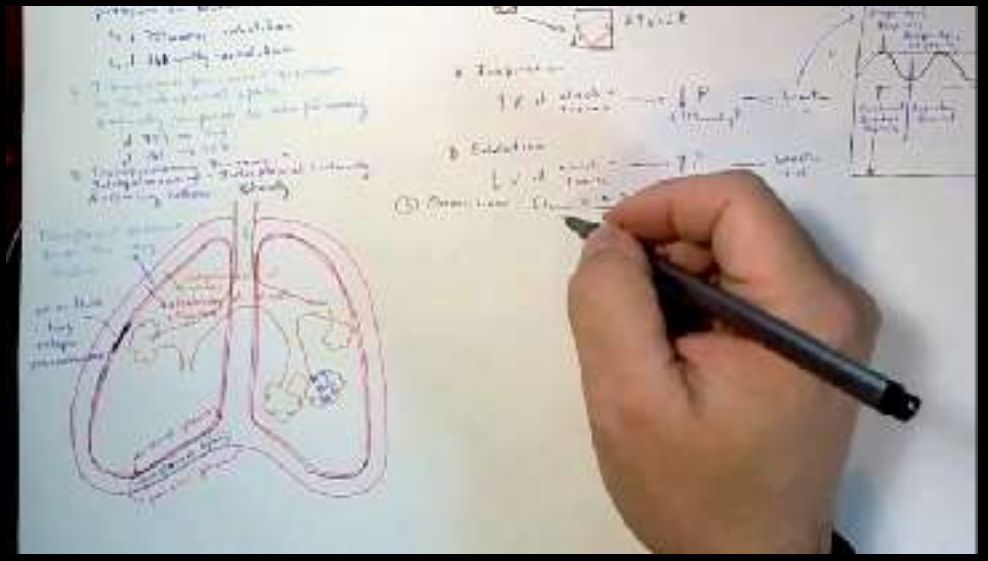

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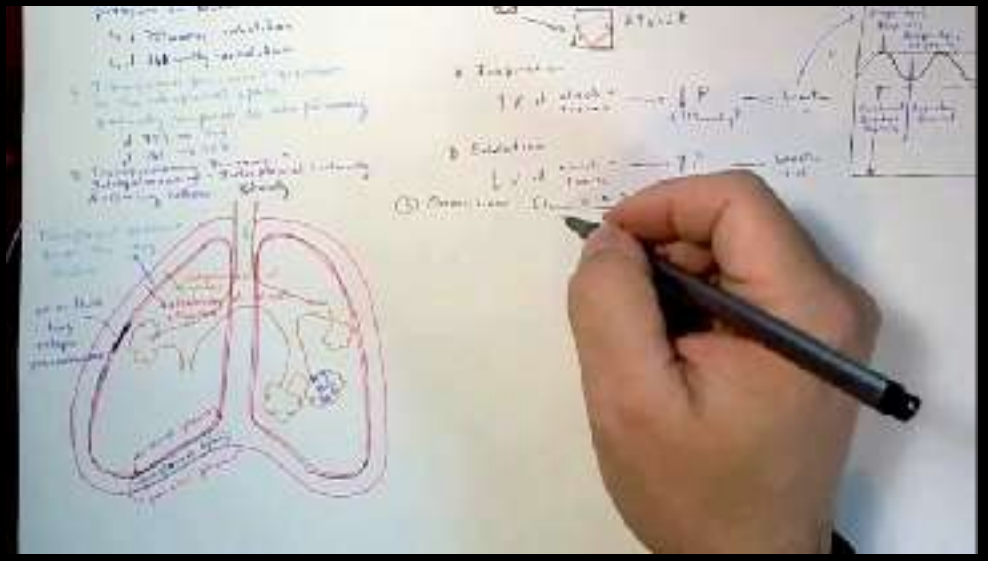

- Titrate to the individual e.g. what BP suits them? MAP 55-60 or 75-80?

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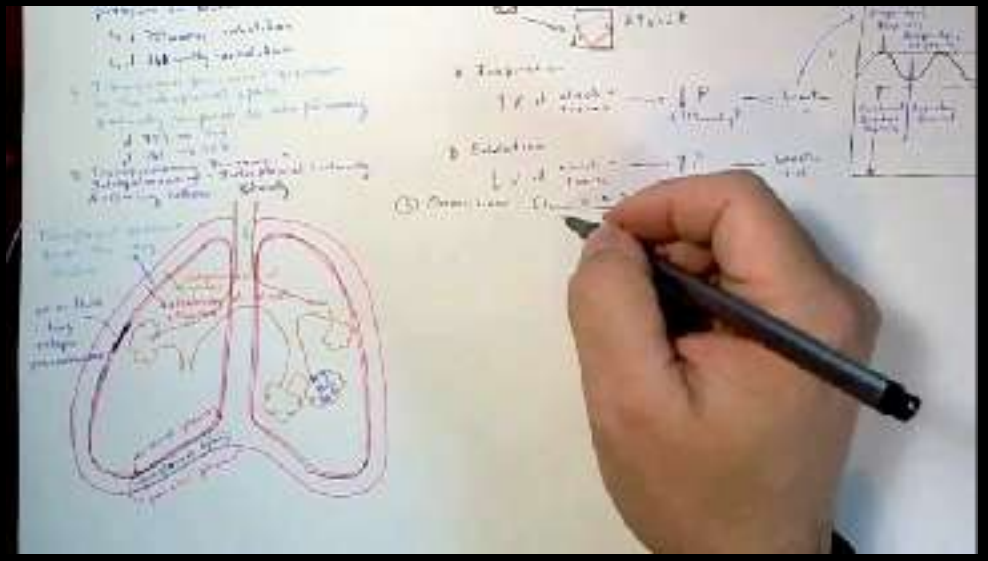

- Titrate to the individual e.g. what BP suits them? MAP 55-60 or 75-80?
- Titrate to a goal
  - if a patient needs fluid (if hypovolaemia -> hypoperfusion), give fluid
  - if not hypovolaemic and hypoperfused, don’t give fluid

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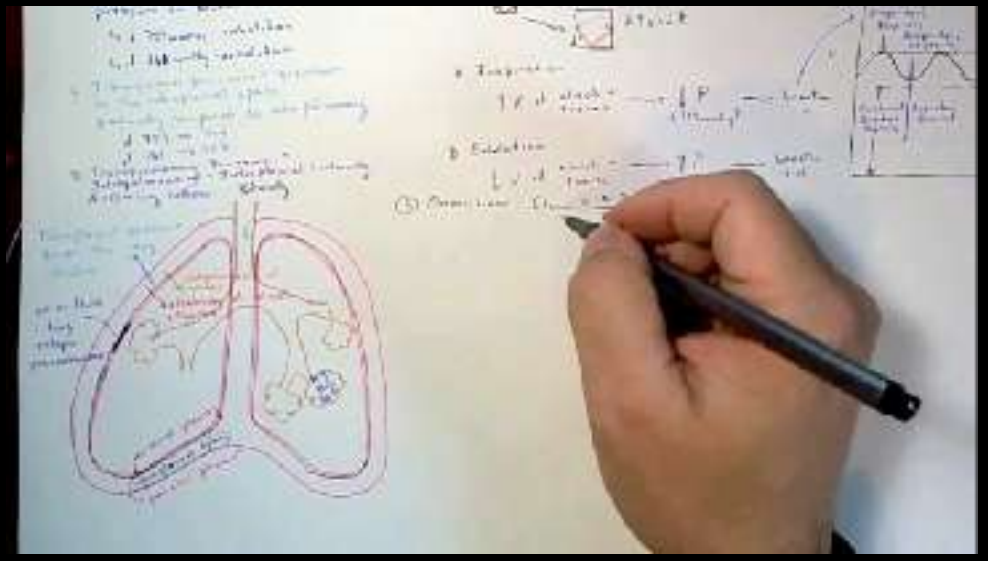

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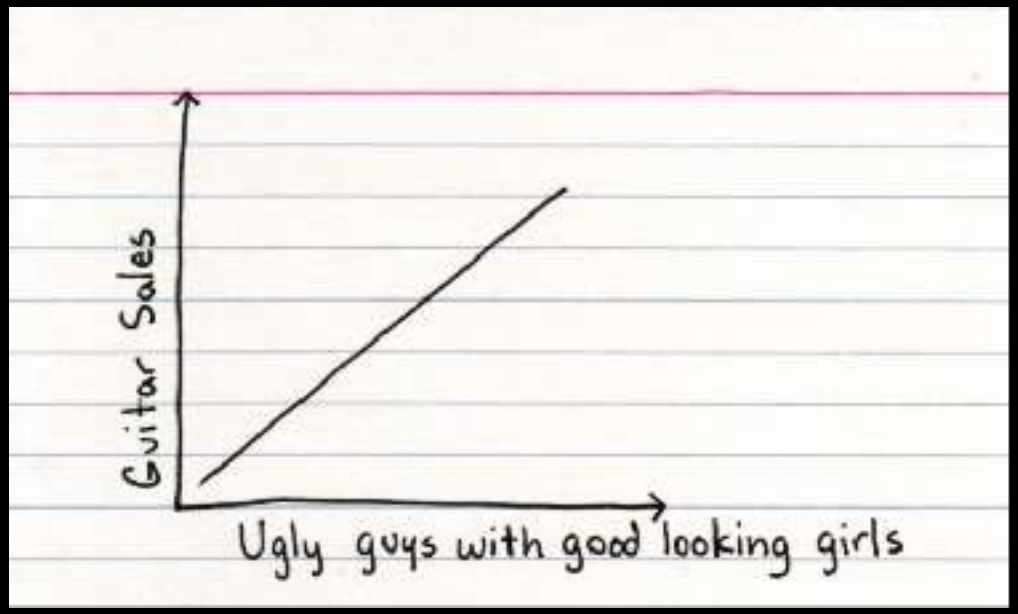
  - if a patient needs fluid (if hypovolaemia -> hypoperfusion), give fluid
  - if not hypovolaemic and hypoperfused, don't give fluid
- Avoid excess - too much fluid, too much oxygen, too much catecholamine …

DISCUSSION POINTS ..

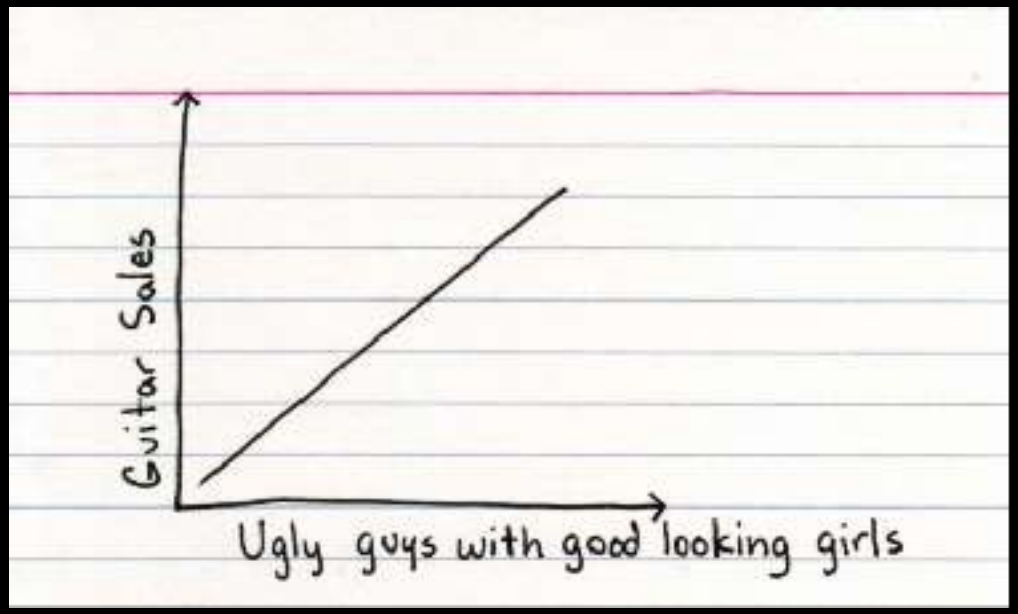
- Guidelines should be slavishly followed
- One size fits all
- Every hour of antibiotic delay kills
- How long should a course of antibiotics last?
- Sepsis mortality is improving
- Why do people die of sepsis?

INTERESTING FACTS - 1



INTERESTING FACTS - 1

- Multiple papers - including EVERY prospective study I'm aware of - do NOT show a correlation between a short-term delay in administering antibiotics and mortality



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- .. and use complex adjustments to find a mortality difference
- .. and often incorporate very delayed treatment (>6h) into the analysis

INTERESTING FACTS - 2

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- .. and often lack biological plausibility
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Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*

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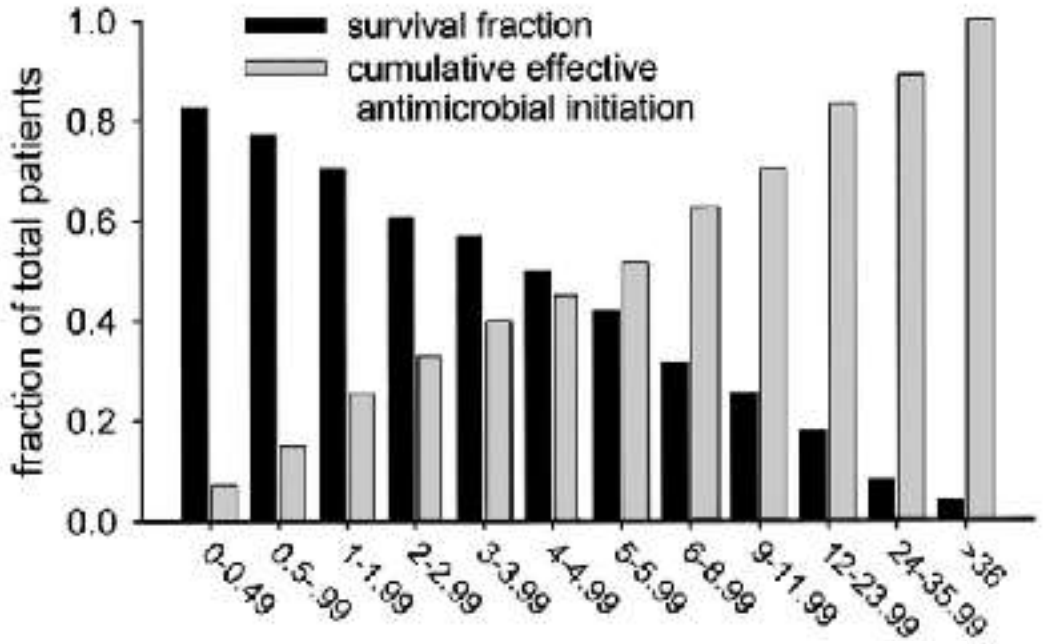
Crit Care Med 2006; 34:1589–1596

Survival



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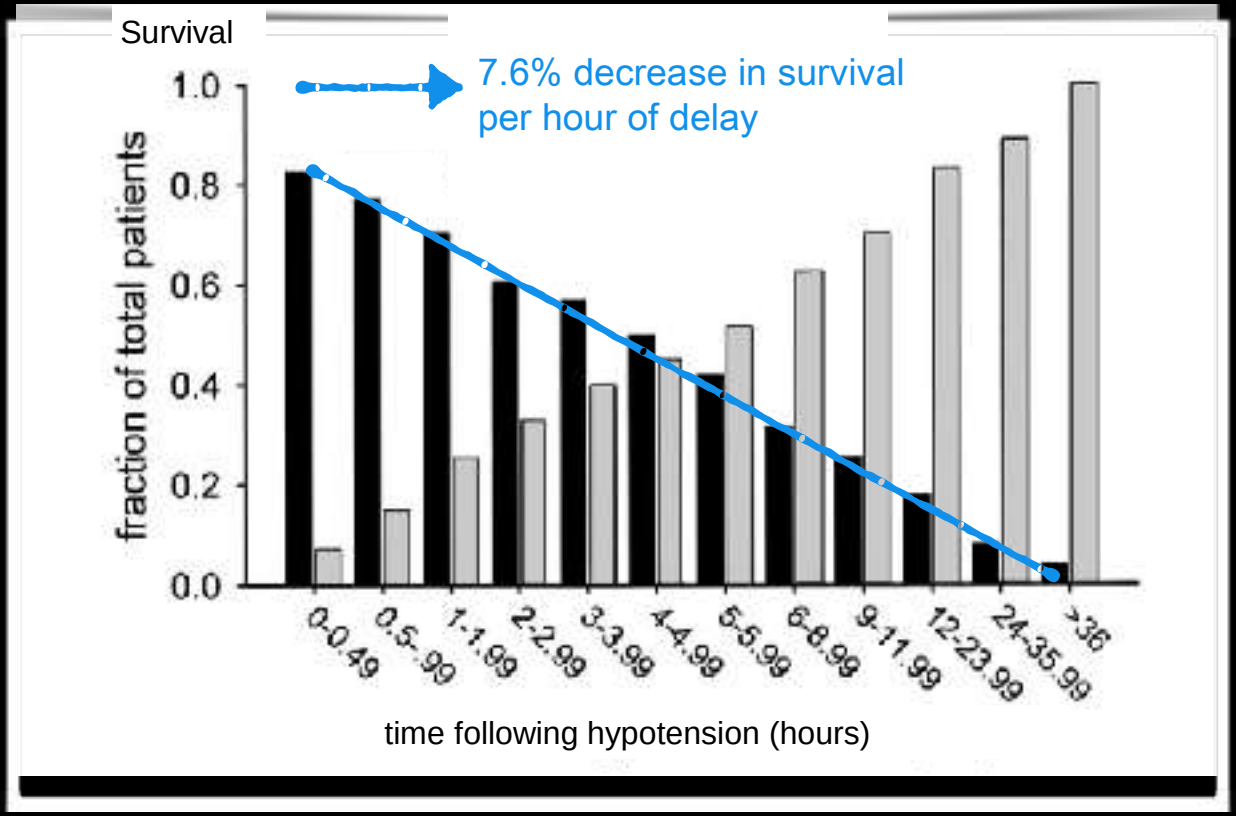

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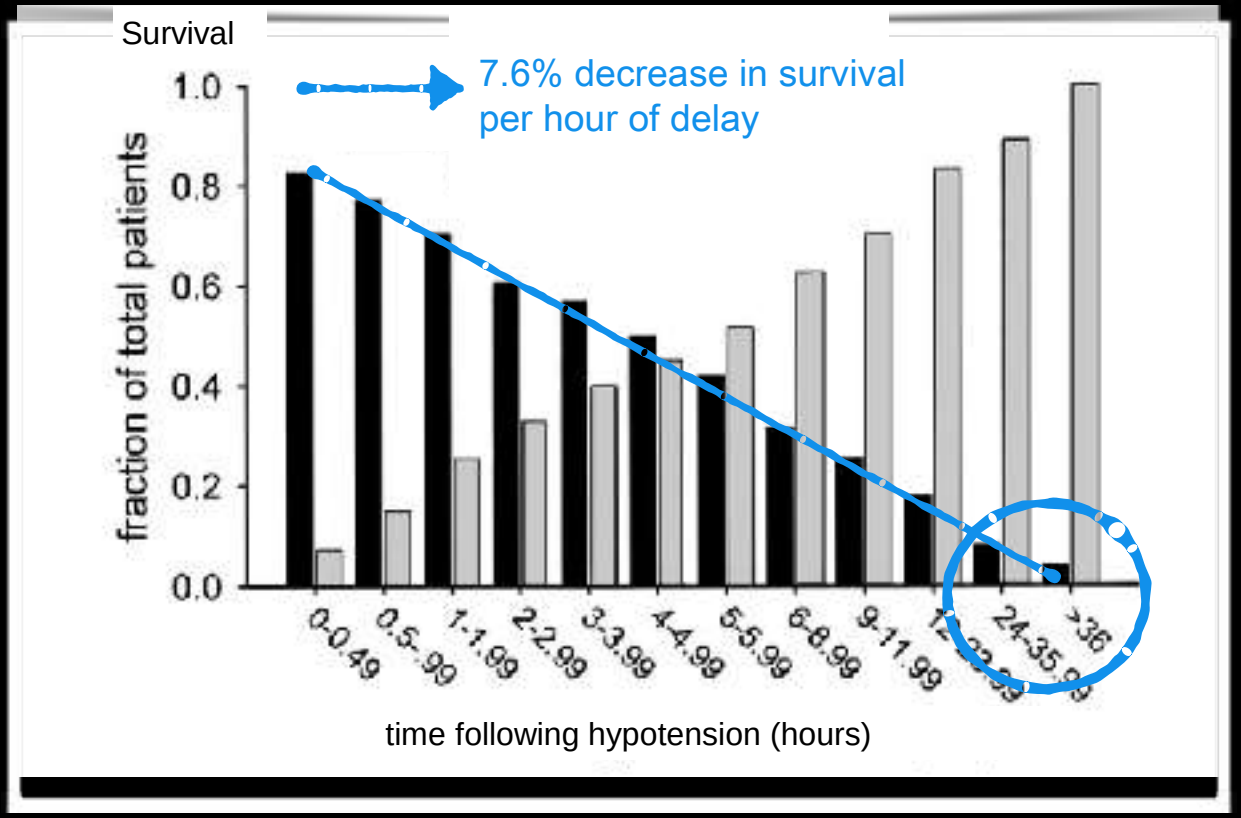

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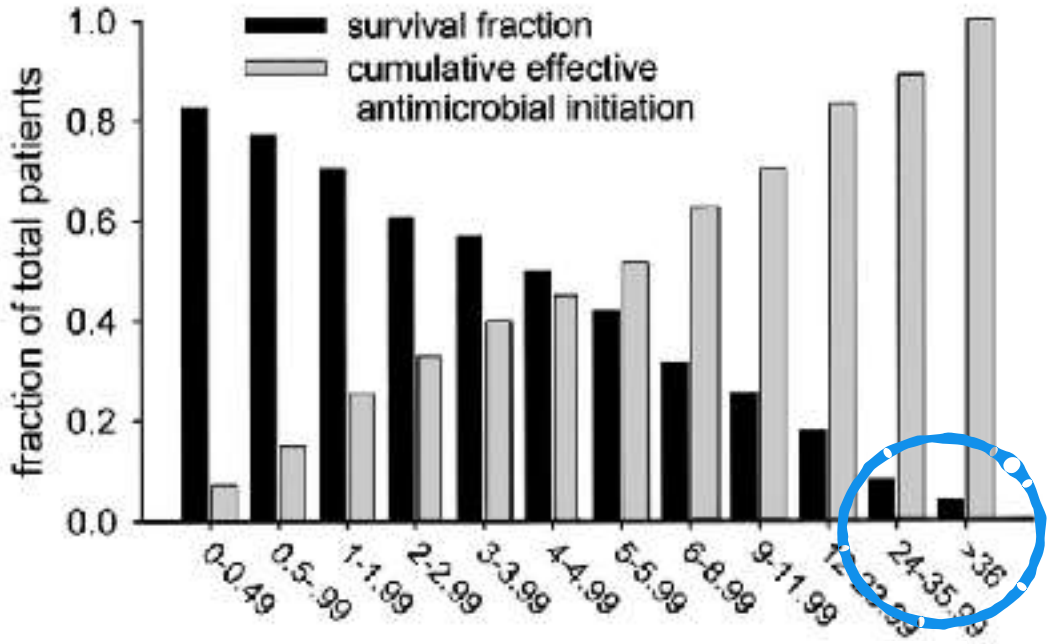

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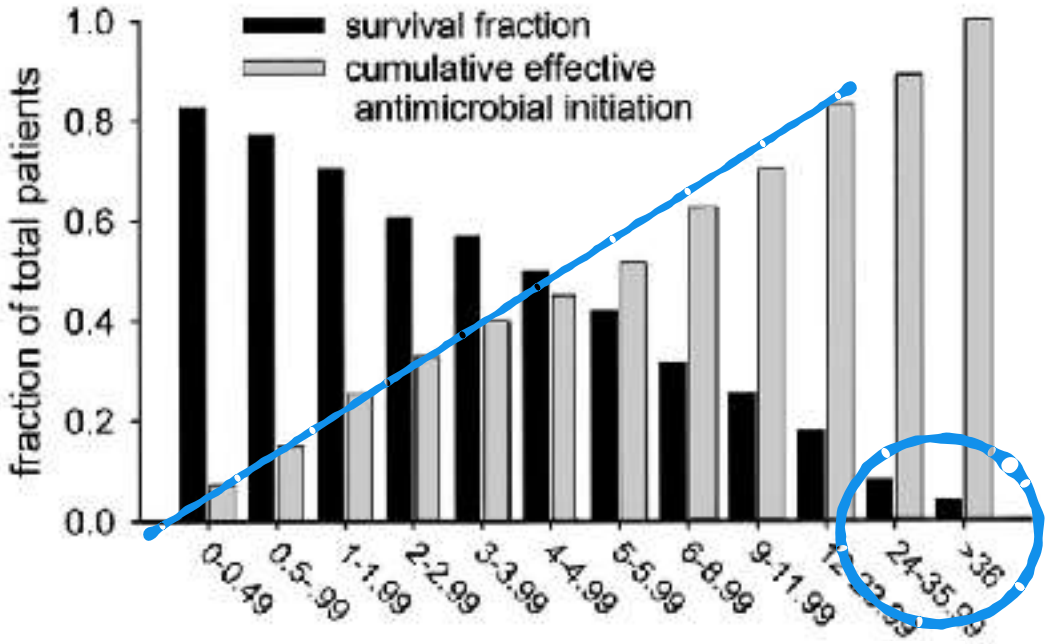

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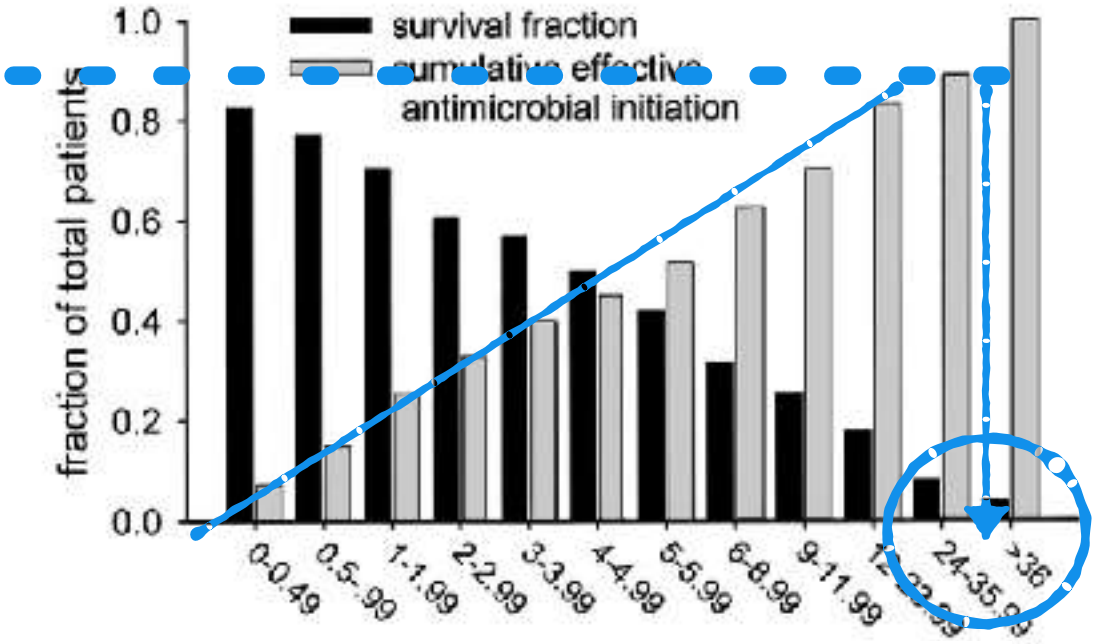

time following hypotension (hours)

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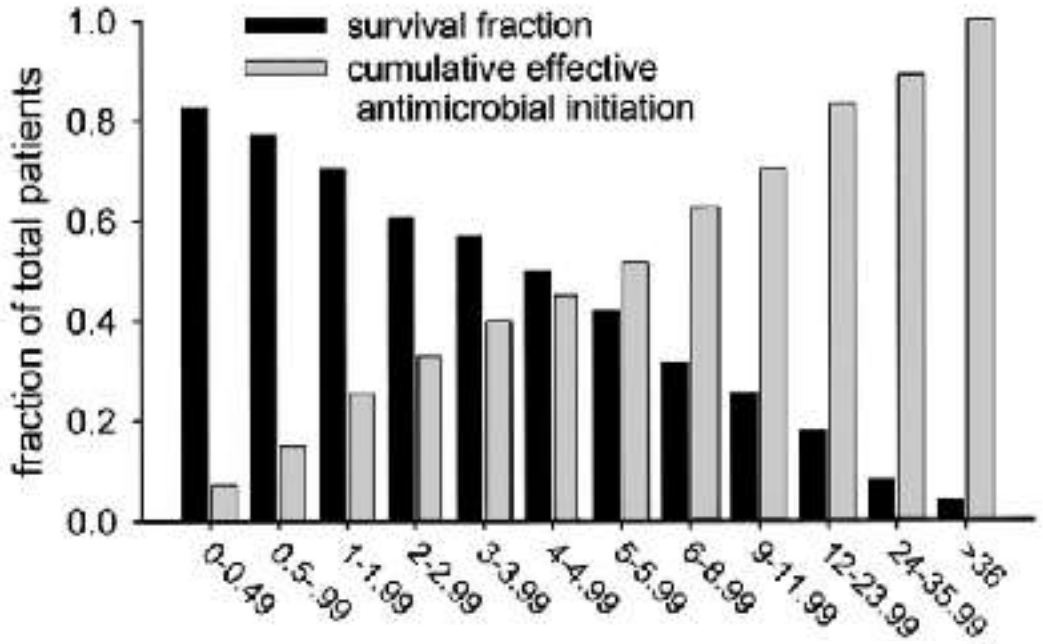

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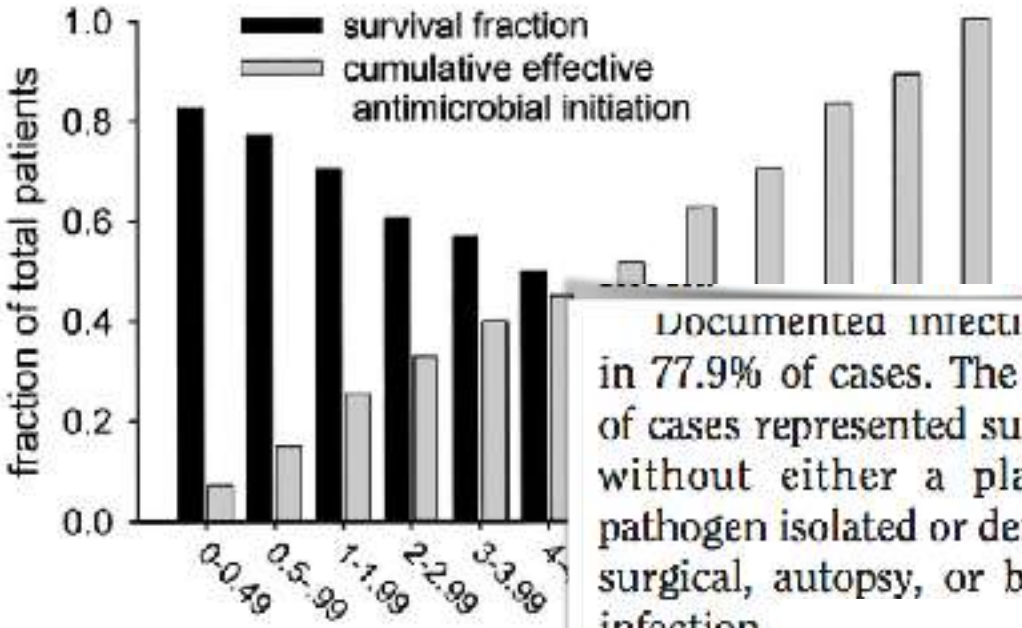

Documented infections were present in 77.9% of cases. The remaining 22.1% of cases represented suspected infections without either a plausible bacterial pathogen isolated or definitive radiologic, surgical, autopsy, or biopsy evidence of infection.

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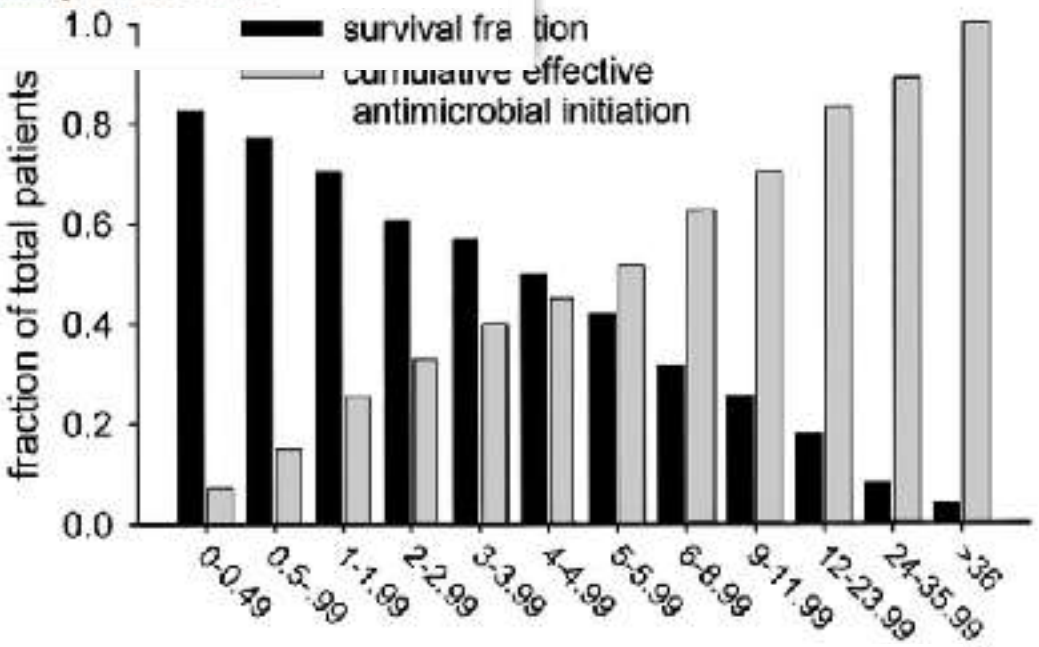

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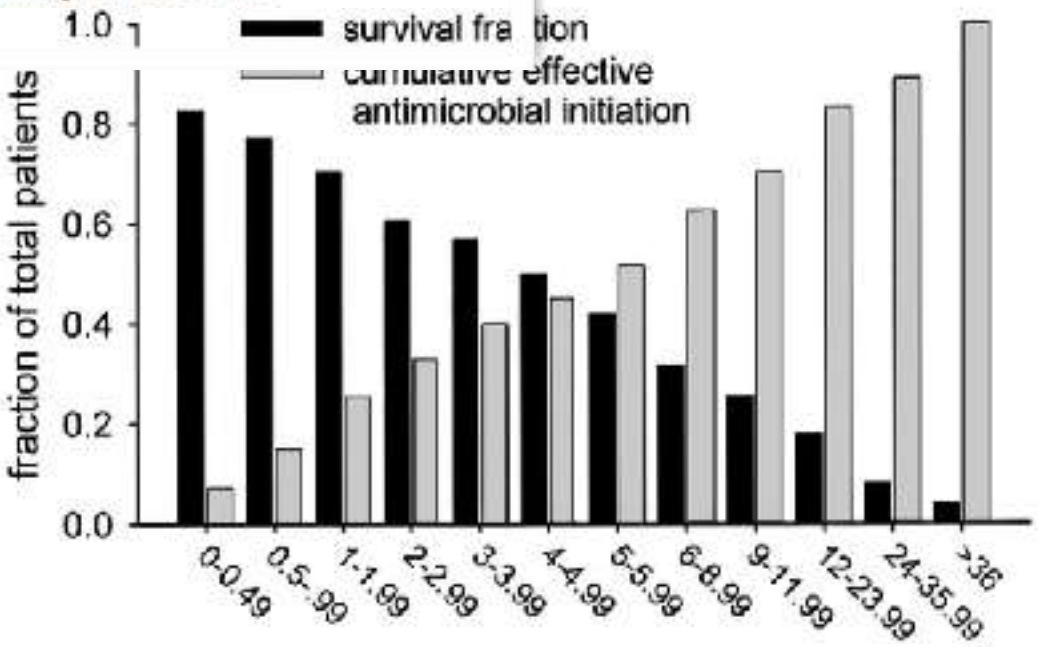

n=2154

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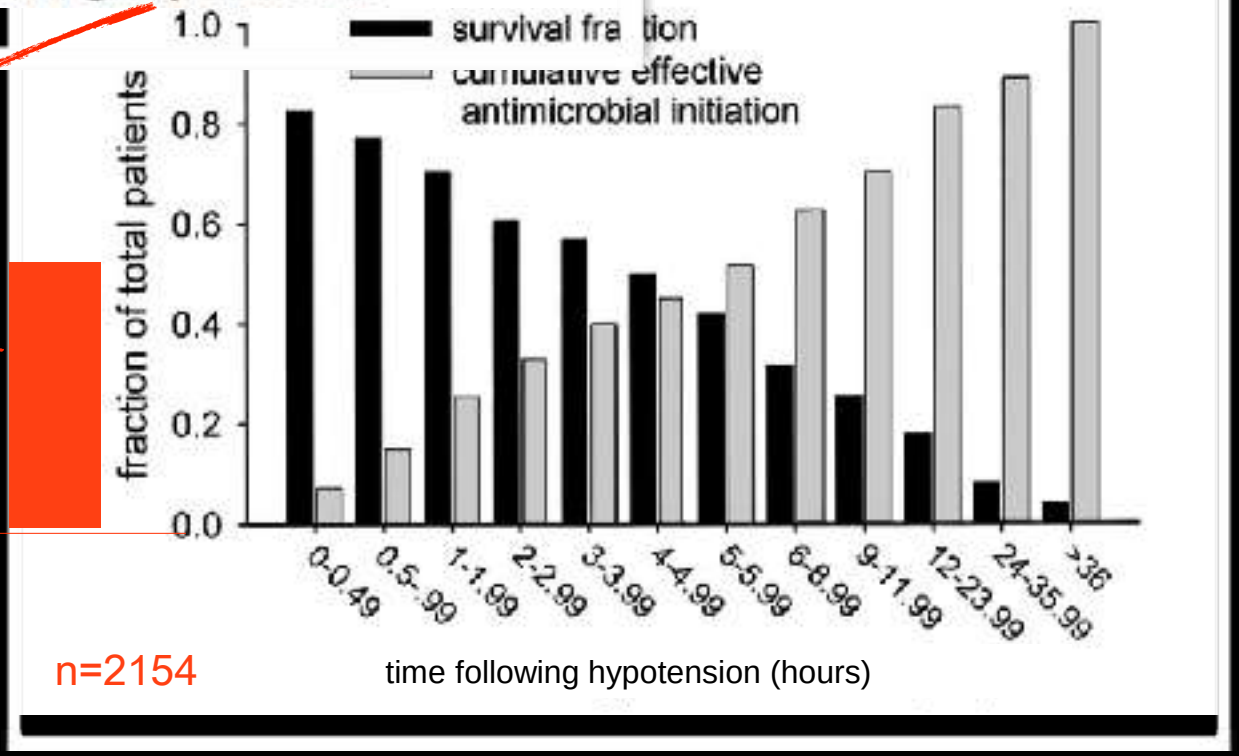

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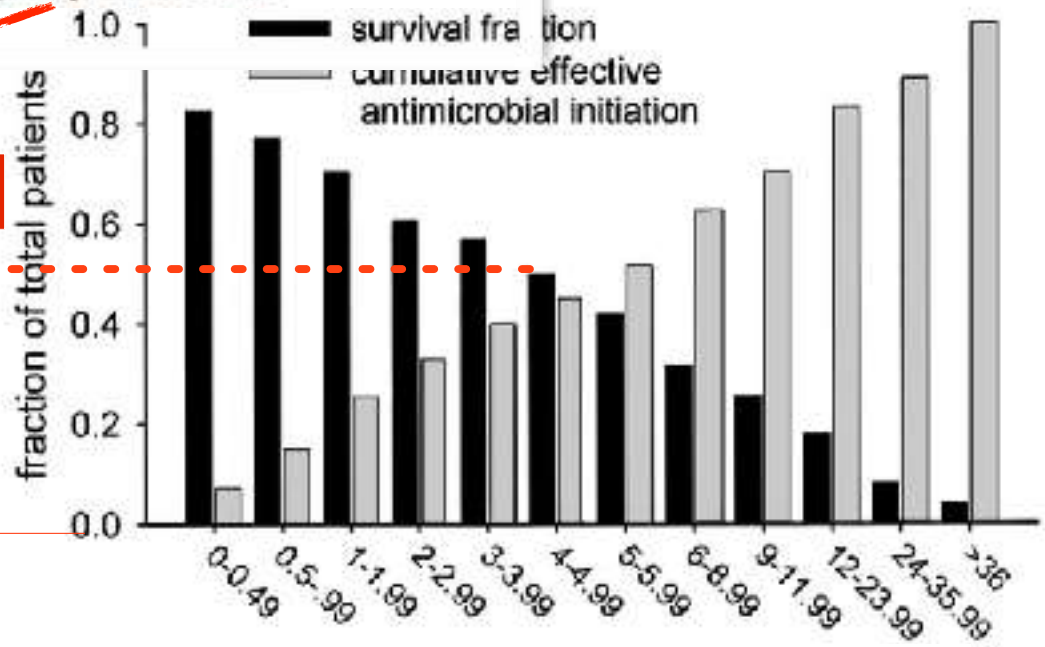
Survival

n=558



n=2154

time following hypotension (hours)

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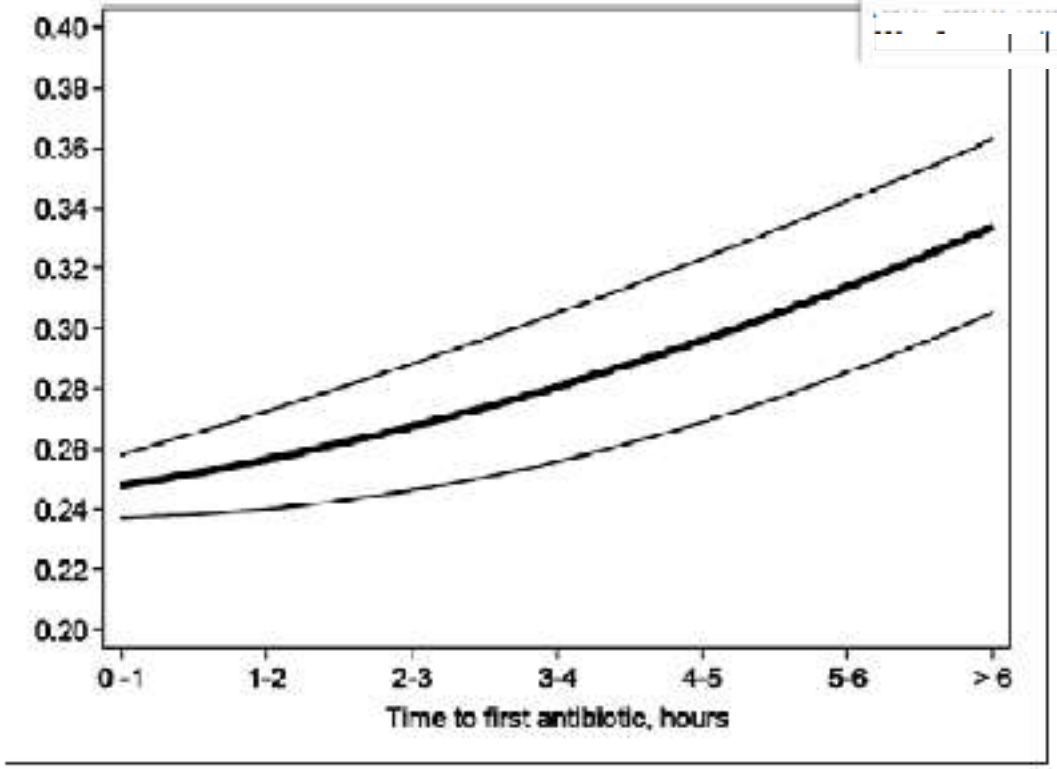

Figure 2. Predicted hospital mortality and the associated 95% CIs for time to first antibiotic administration. The results are adjusted by the sepsis severity score (SSS), ICU admission source (emergency department [ED],

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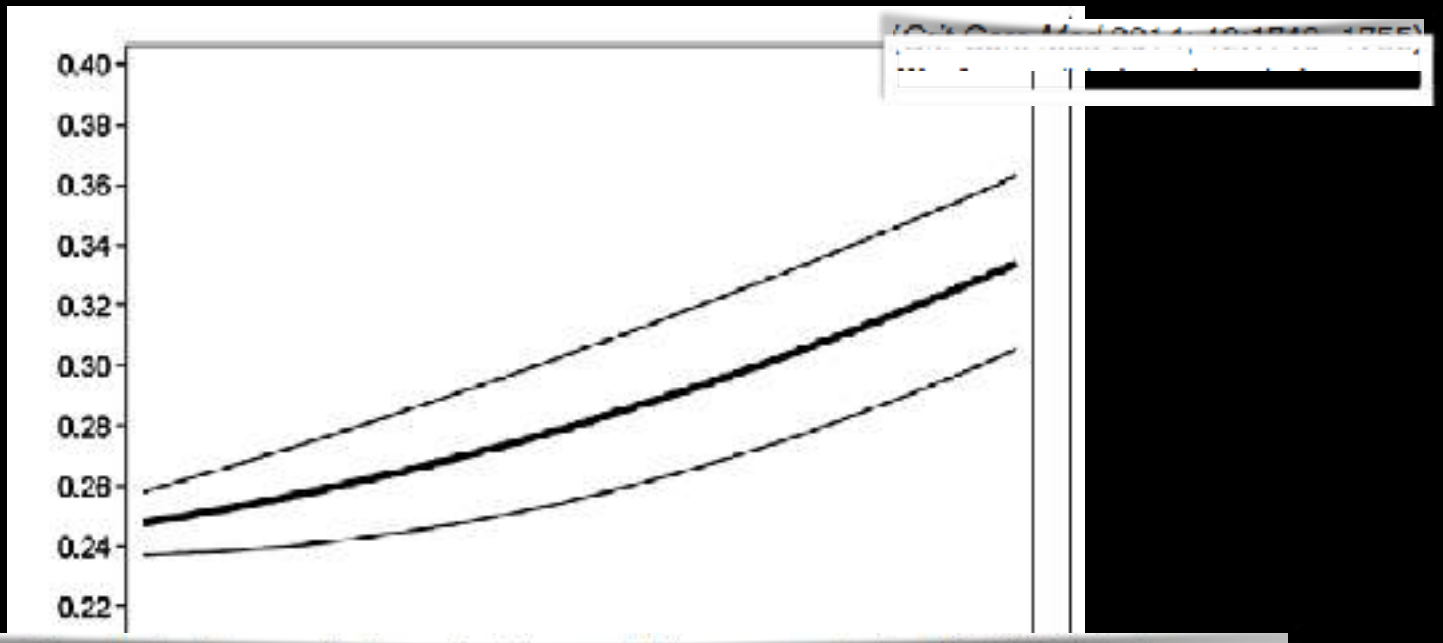

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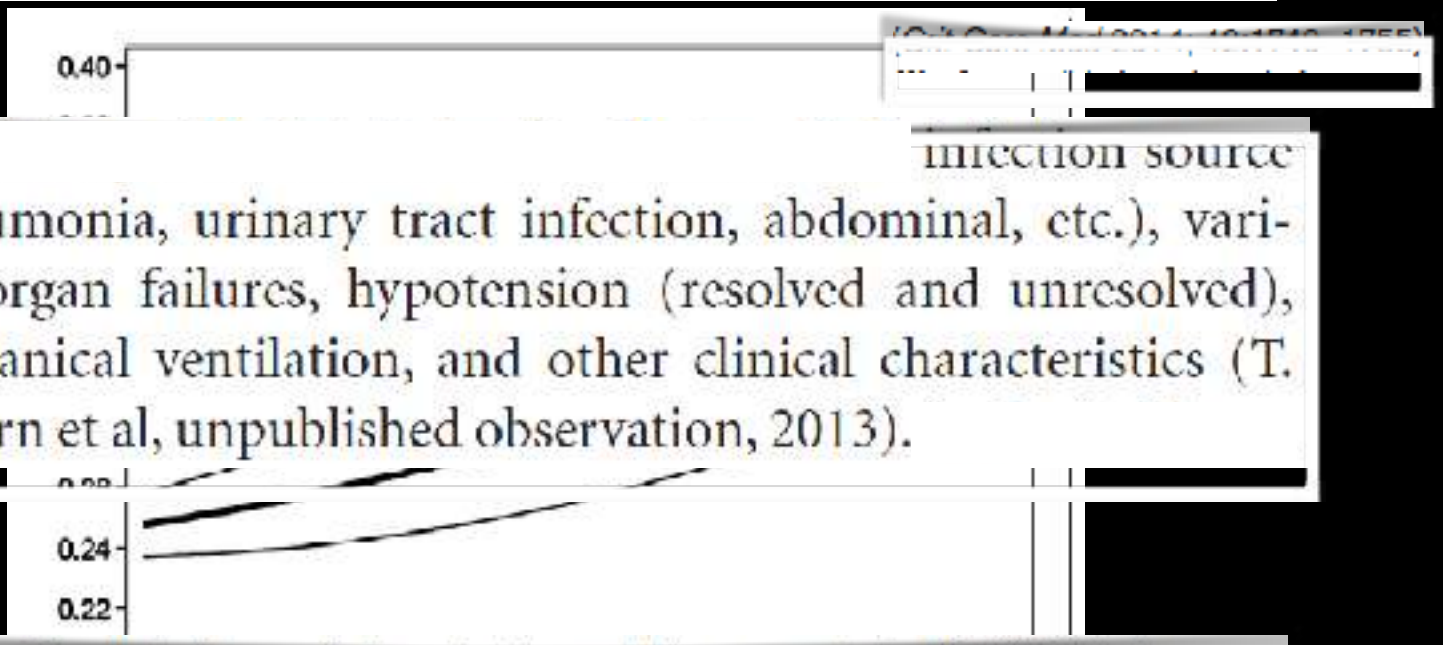

infection source (pneumonia, urinary tract infection, abdominal, etc.), various organ failures, hypotension (resolved and unresolved), mechanical ventilation, and other clinical characteristics (T. Osborn et al, unpublished observation, 2013).

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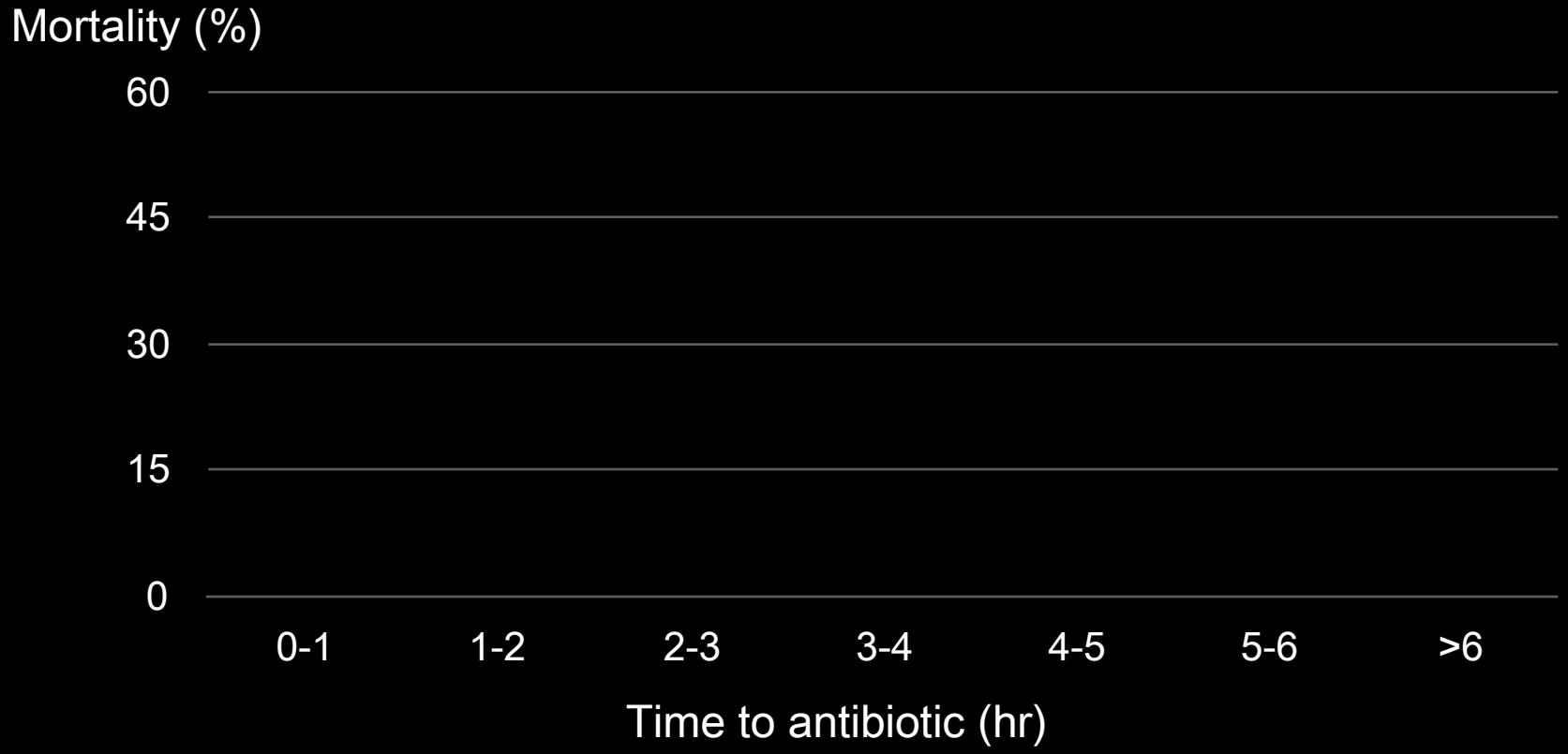
ED
Ward
ICU



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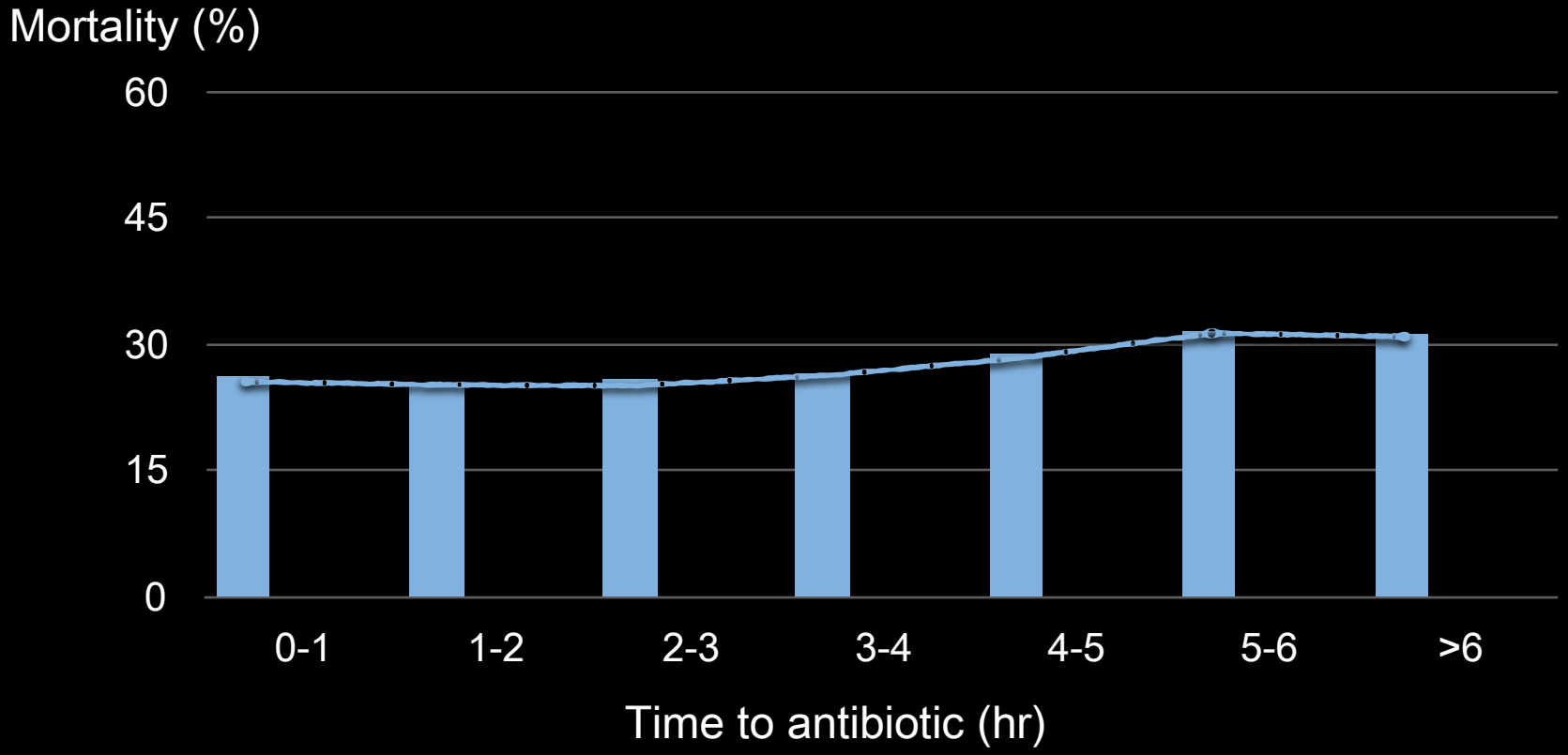

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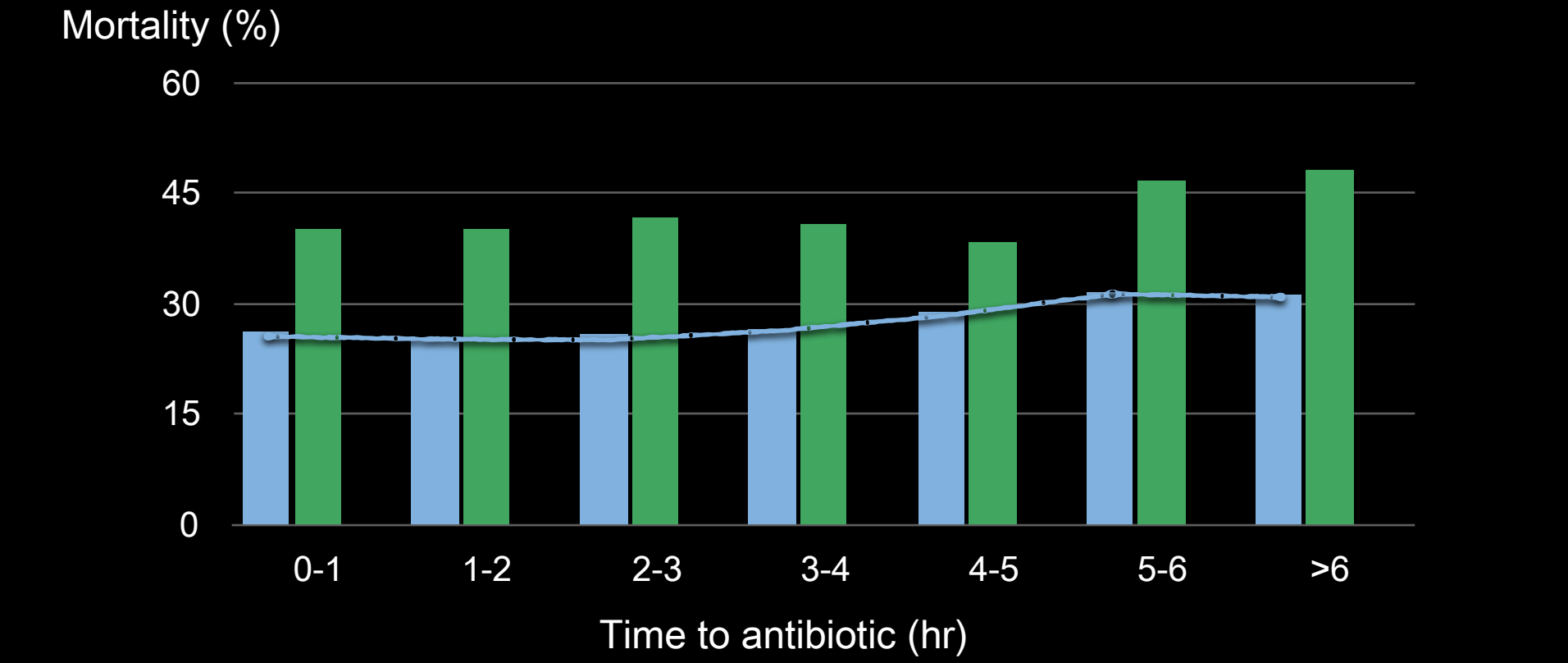

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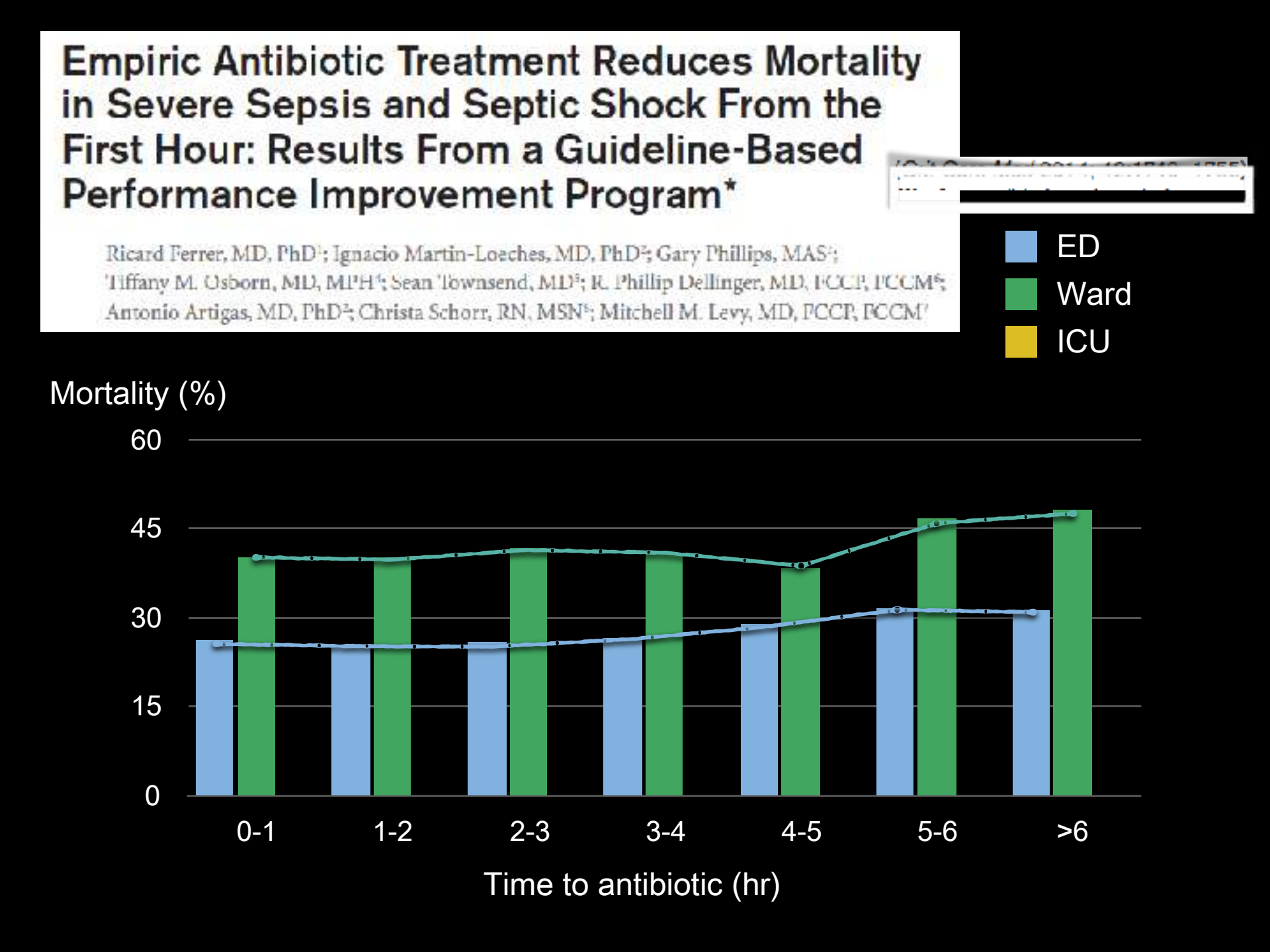

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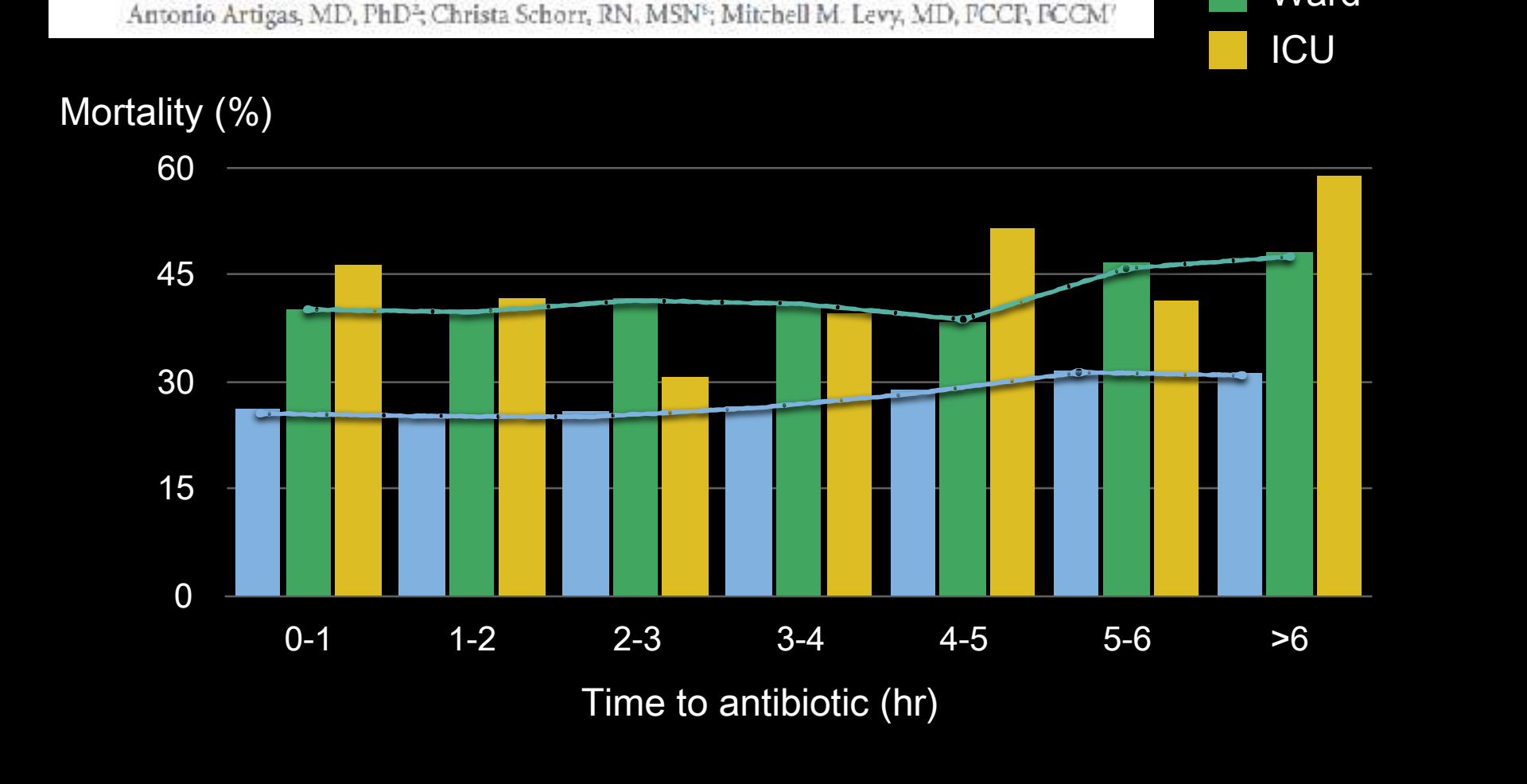

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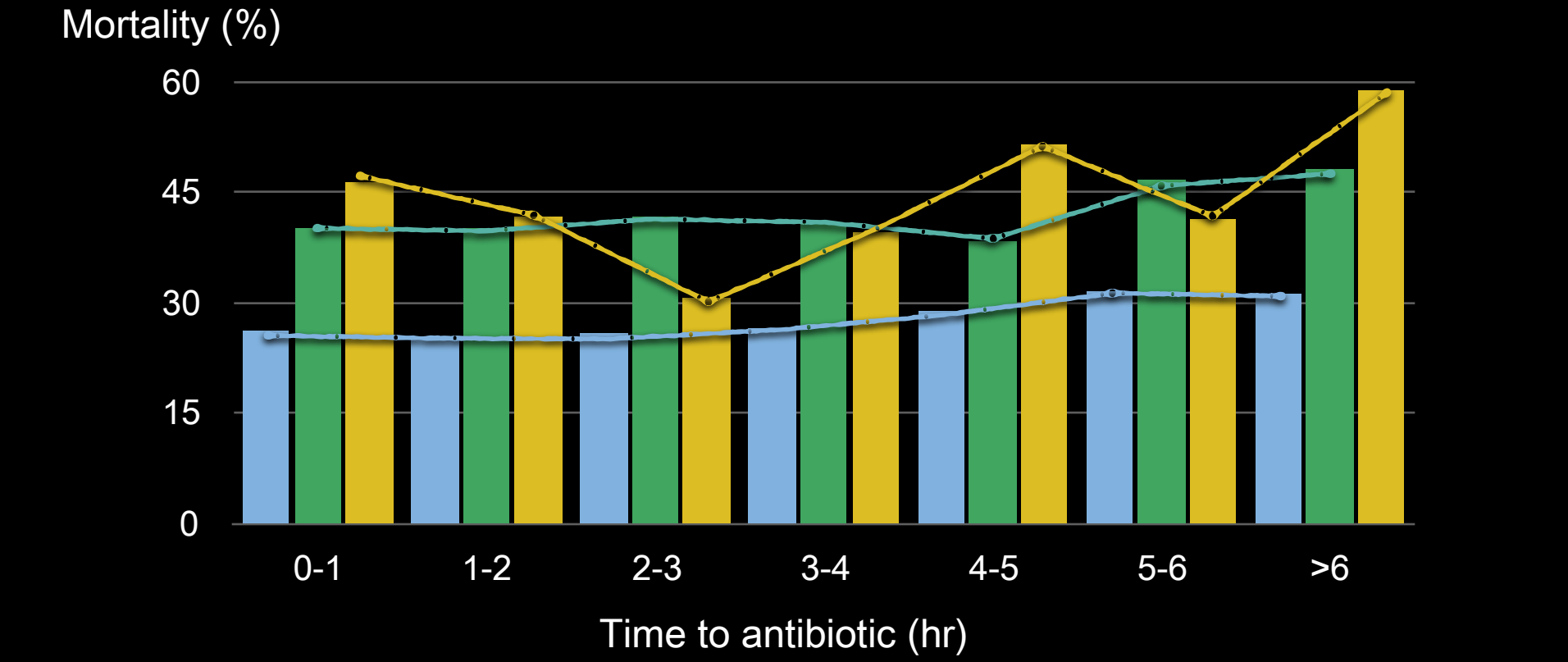

Quality Improvement Initiative for Severe Sepsis and Septic Shock Reduces 90-Day Mortality: A 7.5-Year Observational Study*

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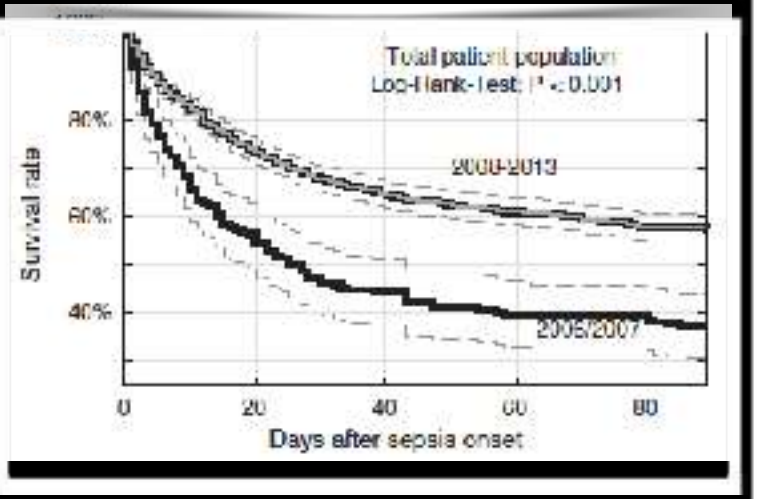

	Full Model	
	Hazard Ratio (95% CI)	p
Blood cultures before antibiotic therapy		
No	Reference	
Yes	0.698 (0.57–0.82)	< 0.001
Calculated antibiotic therapy		
Not adequate	Reference	
Adequate	0.646 (0.52–0.80)	< 0.001
Time to antibiotic therapy, hr		
≤ 1	Reference	
1–6	1.125 (0.92–1.37)	0.242
> 6	1.215 (0.96–1.54)	0.104

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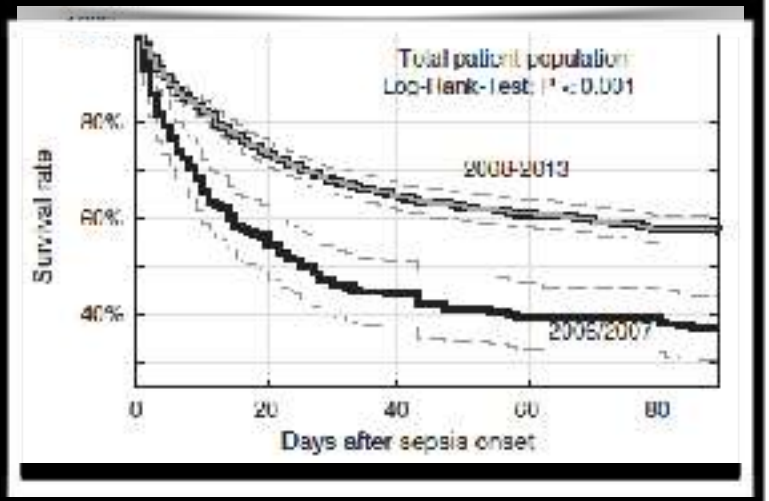

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Calculated antibiotic therapy		
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- 1373 ICU patients between 2006-13 coded as septic/septic shock

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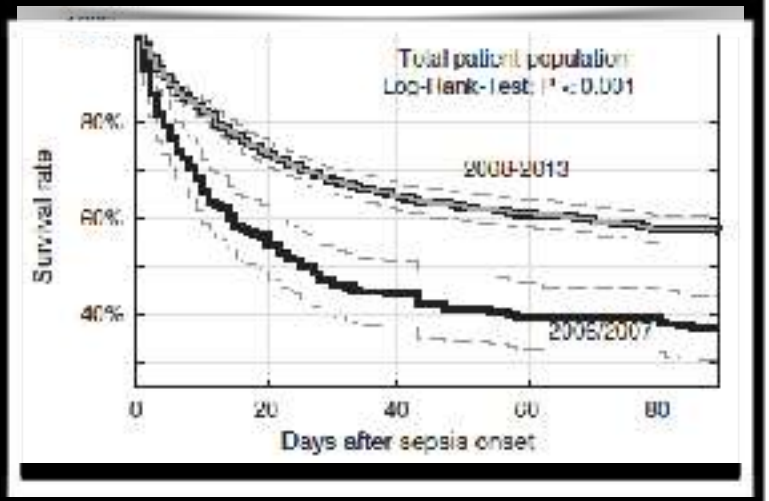

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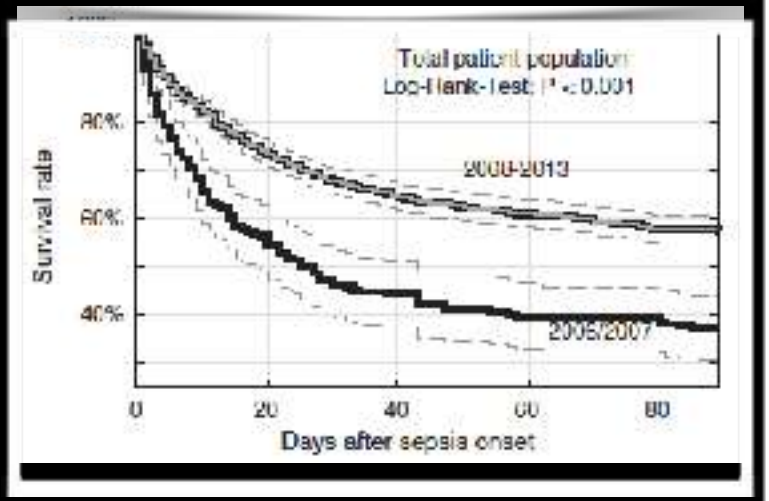

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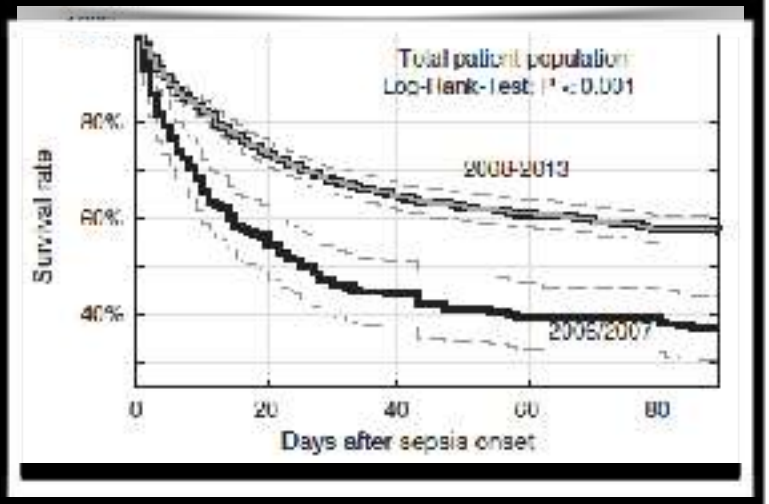
> 6	1.215 (0.96–1.54)	0.104

- 1373 ICU patients between 2006-13 coded as septic/septic shock

Quality Improvement Initiative for Severe Sepsis and Septic Shock Reduces 90-Day Mortality: A 7.5-Year Observational Study*

Christian S. Scheer, MD[1]; Christian Fuchs, MD[1]; Sven-Olaf Kuhn, MD[1]; Marcus Vollmer, MSM[1]; Sebastian Rehberg, MD, PhD[1]; Sigrun Friesecke, MD[2]; Peter Abel, MD[3]; Veronika Balau, MD[4]; Christoph Bandt, PhD[5]; Konrad Meissner, MD, PhD[1]; Klaus Hahnenkamp, MD, PhD[1]; Matthias Gründling, MD[1]



	Full Model	
	Hazard Ratio (95% CI)	p
Blood cultures before antibiotic therapy		
No	Reference	
Yes	0.688 (0.57–0.82)	< 0.001
Calculated antibiotic therapy		
Not adequate	Reference	
Adequate	0.646 (0.52–0.80)	< 0.001
Time to antibiotic therapy, hr		
≤ 1	Reference	
1–6	1.125 (0.92–1.37)	0.242
> 6	1.215 (0.96–1.54)	0.104

- 1373 ICU patients between 2006-13 coded as septic/septic shock

Mandated Emergency Care for Sepsis

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BACKGROUND

In 2013, New York began requiring hospitals to follow protocols for the early identification and treatment of sepsis. However, there is controversy about whether more rapid treatment of sepsis improves outcomes in patients.

METHODS

We studied data from patients with sepsis and septic shock that were reported to the New York State Department of Health from April 1, 2014, to June 30, 2016. Patients had a sepsis protocol initiated within 6 hours after arrival in the emergency department and had all items in a 3-hour bundle of care for patients with sepsis (i.e., blood cultures, broad-spectrum antibiotic agents, and lactate measurement) completed within 12 hours. Multilevel models were used to assess the associations between the time until completion of the 3-hour bundle and risk-adjusted mortality. We also examined the times to the administration of antibiotics and to the completion of an initial bolus of intravenous fluid.

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[redacted]

Among patients who had the 3-hour bundle completed within 12 hours, a longer time to the completion of the bundle was associated with higher risk-adjusted in-hospital mortality (odds ratio, 1.04 per hour; 95% confidence interval [CI], 1.02 to 1.05; P<0.001), as was a longer time to the administration of antibiotics (odds ratio, 1.04 per hour; 95% CI, 1.03 to 1.06; P<0.001) but not a longer time to the completion of a bolus of intravenous fluids (odds ratio, 1.01 per hour; 95% CI, 0.99 to 1.02; P=0.21).

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Characteristic	All Patients (N = 49,331)	3-Hr Bundle Completed in 3 Hr		P Value*
		Yes (N = 40,696)	No (N = 8635)	
Positive blood cultures — no. (%)	14,574 (29.5)	12,322 (30.3)	2252 (26.1)	<0.001
Septic shock — no. (%)	22,336 (45.3)	18,393 (45.2)	3943 (45.7)	0.43
Teaching facility — no. (%)	40,257 (81.6)	7,739 (19.0)	7300 (84.5)	<0.001
In-hospital death — no. (%)	11,251 (22.8)	9,213 (22.6)	2038 (23.6)	0.05

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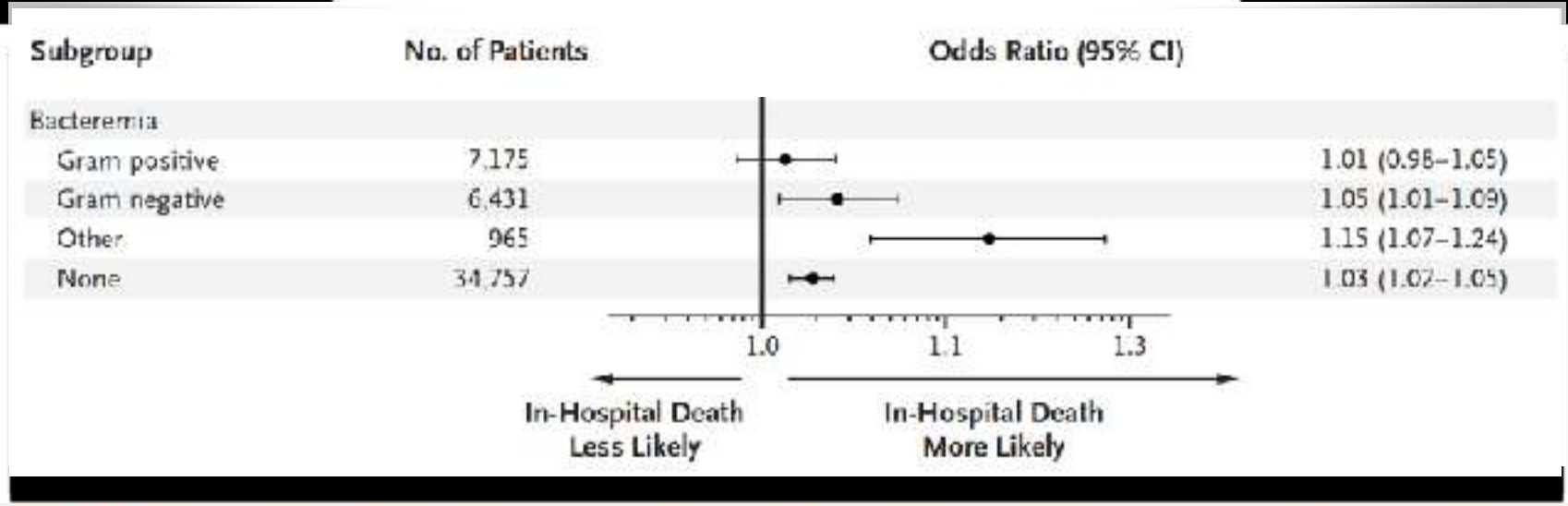

Figure 2. Risk-Adjusted Odds Ratios of In-Hospital Death in the Primary Model and Prespecified Subgroups.

Shown are odds ratios, with 95% confidence intervals, for in-hospital death for each hour that it took to complete the 3-hour bundle.

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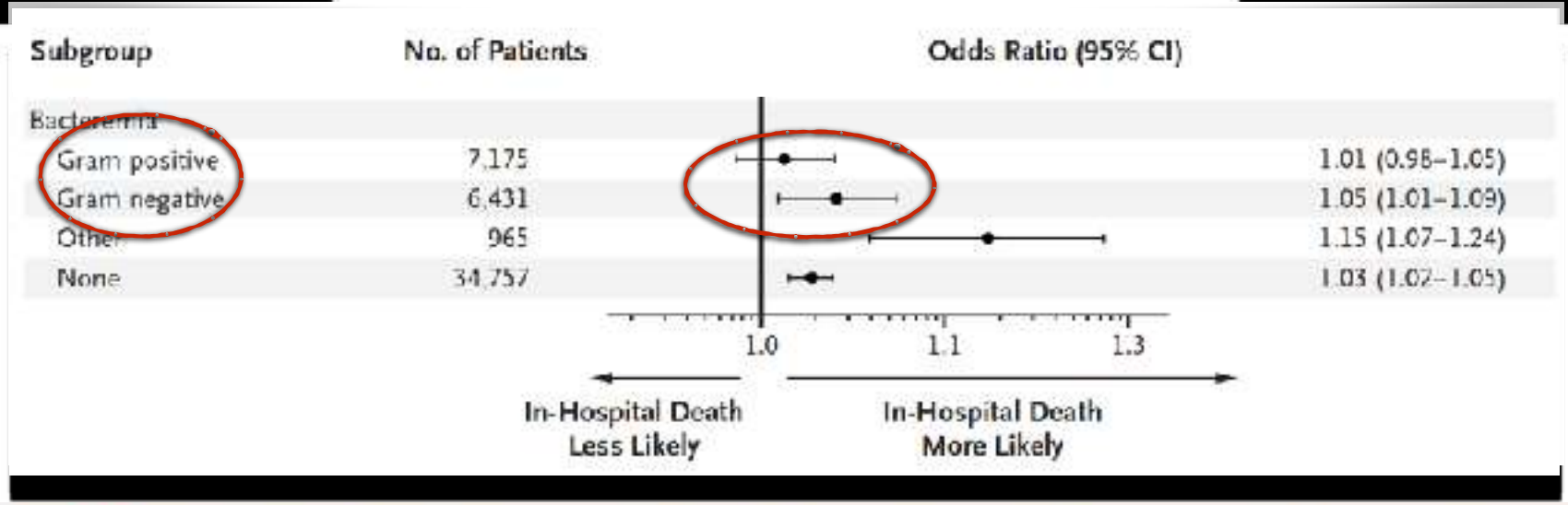

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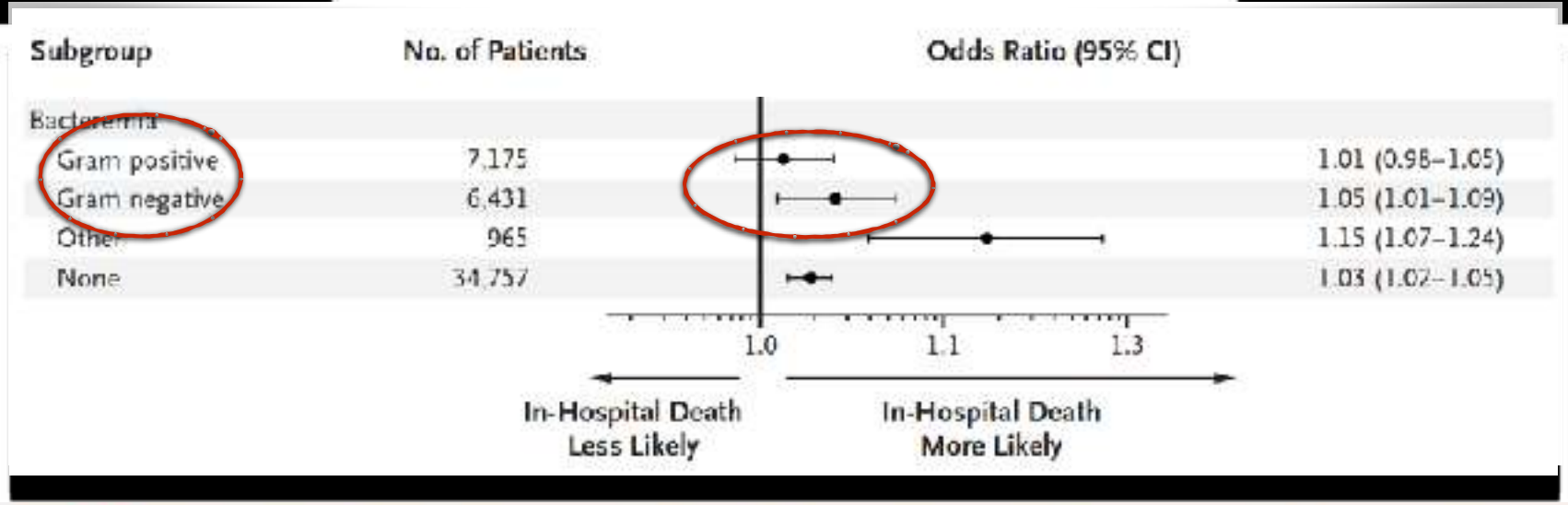

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… and no data on antibiotic sensitivities, adequacy of dosing, source control, etc..

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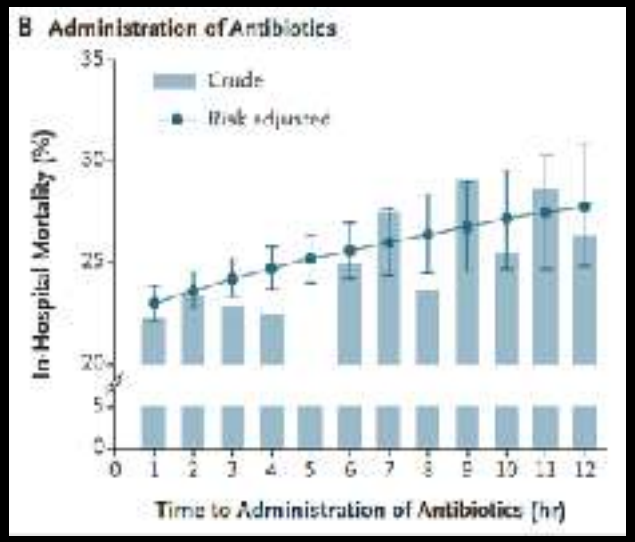

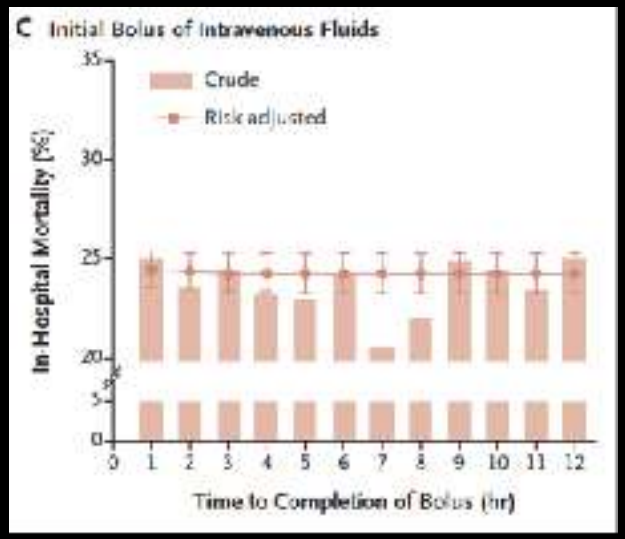

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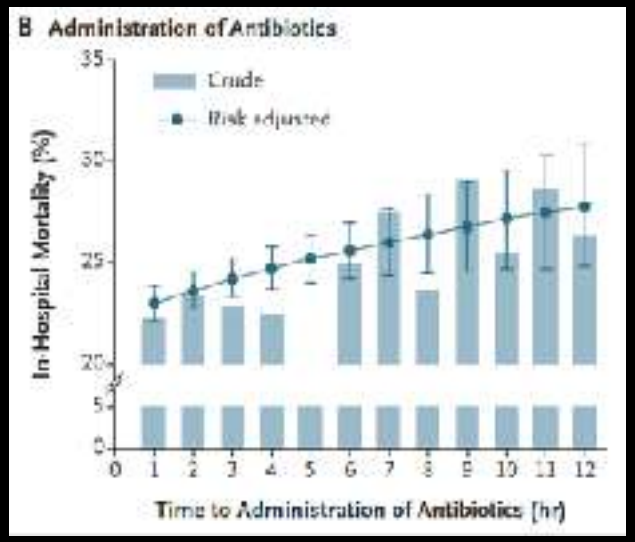
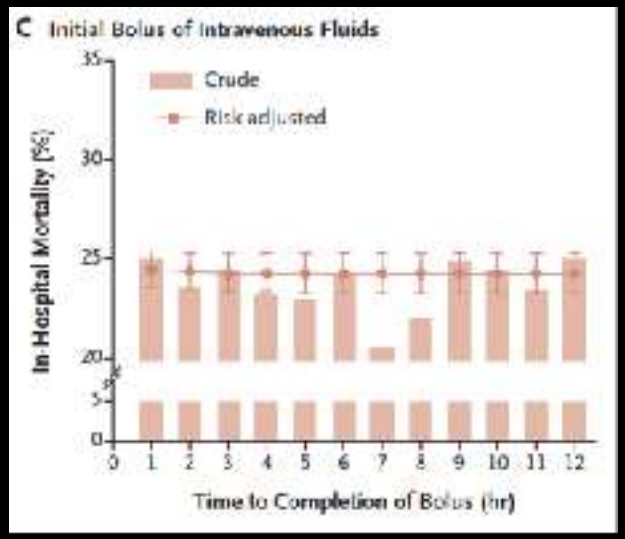
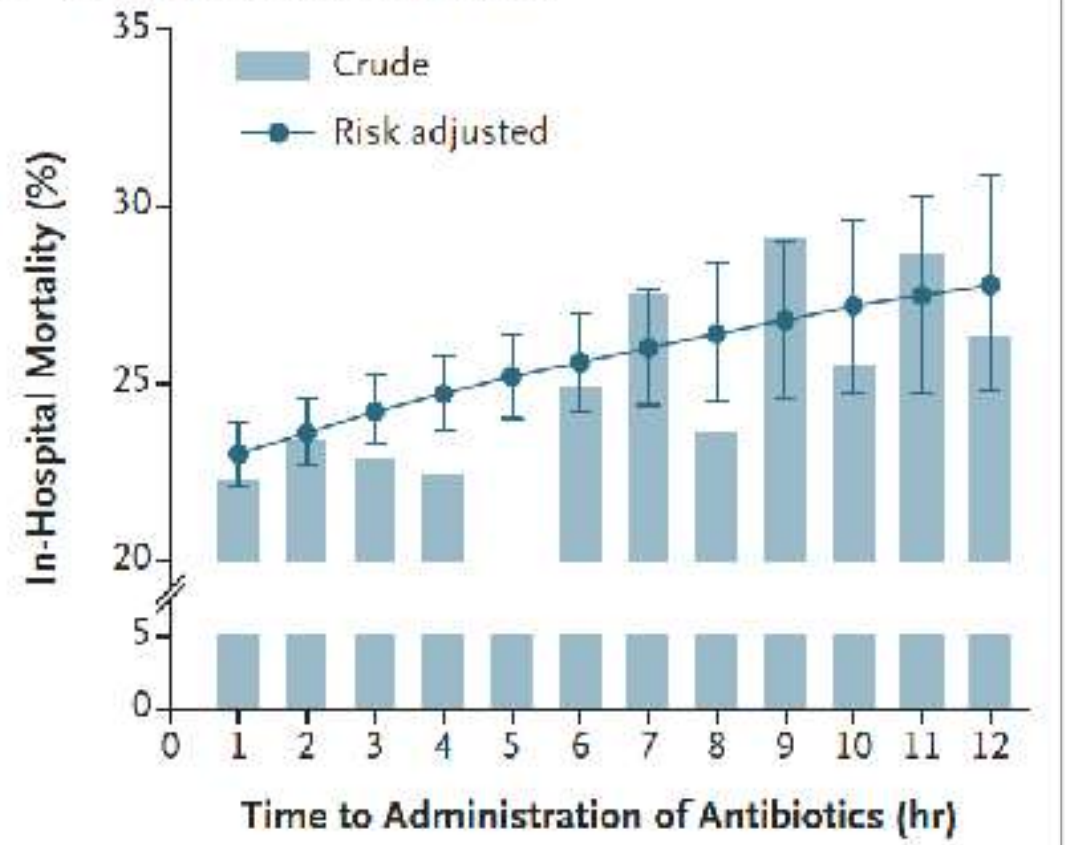




.. yet 45% of patients (early and late treated) had ‘septic shock’!!

Mandated Emergency Care for Sepsis



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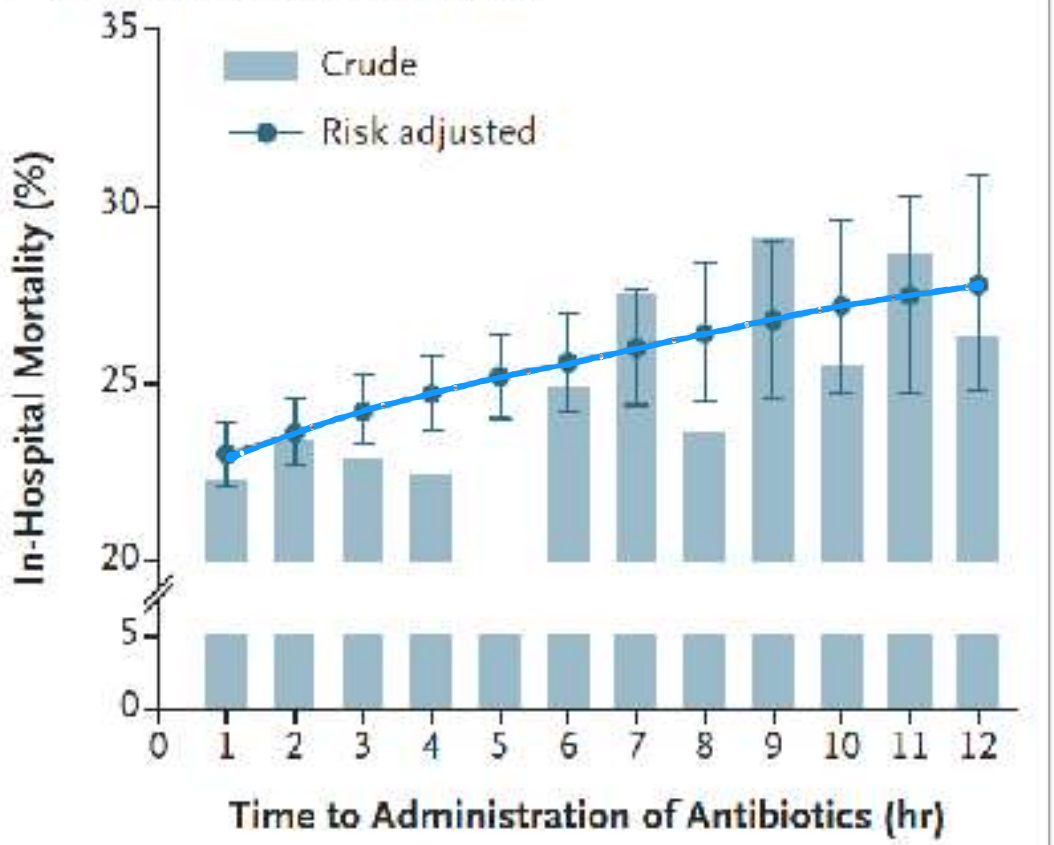

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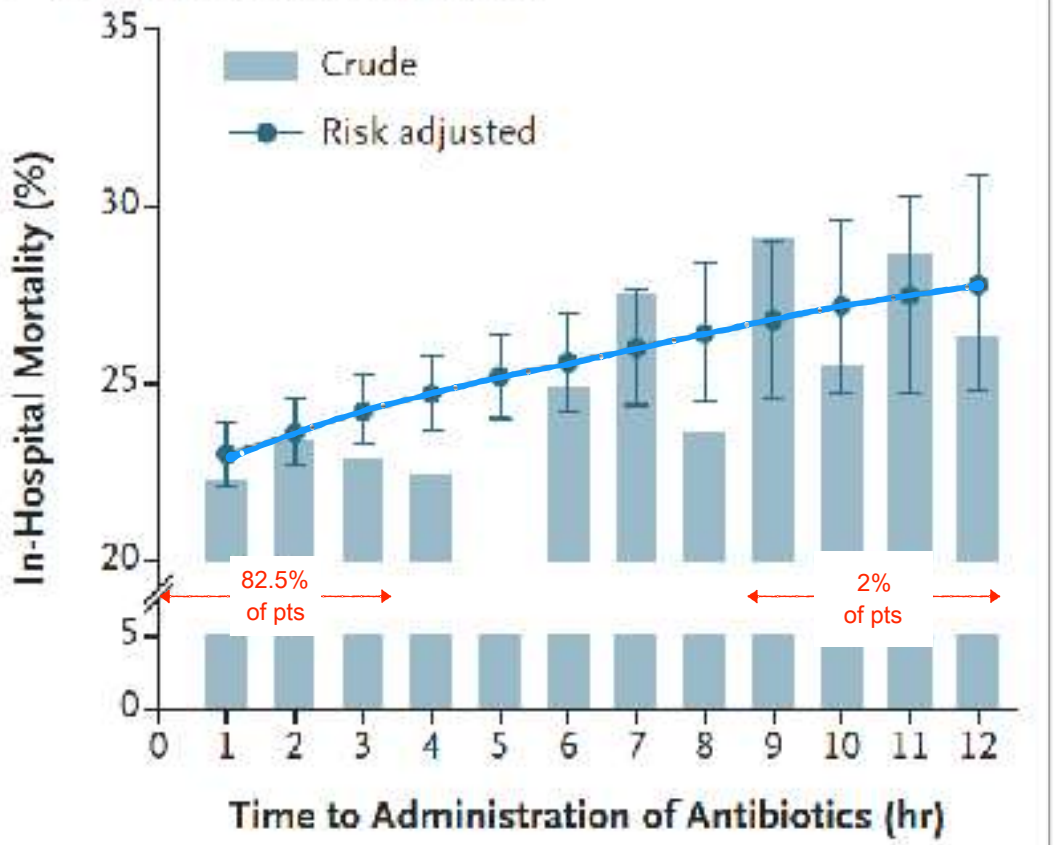

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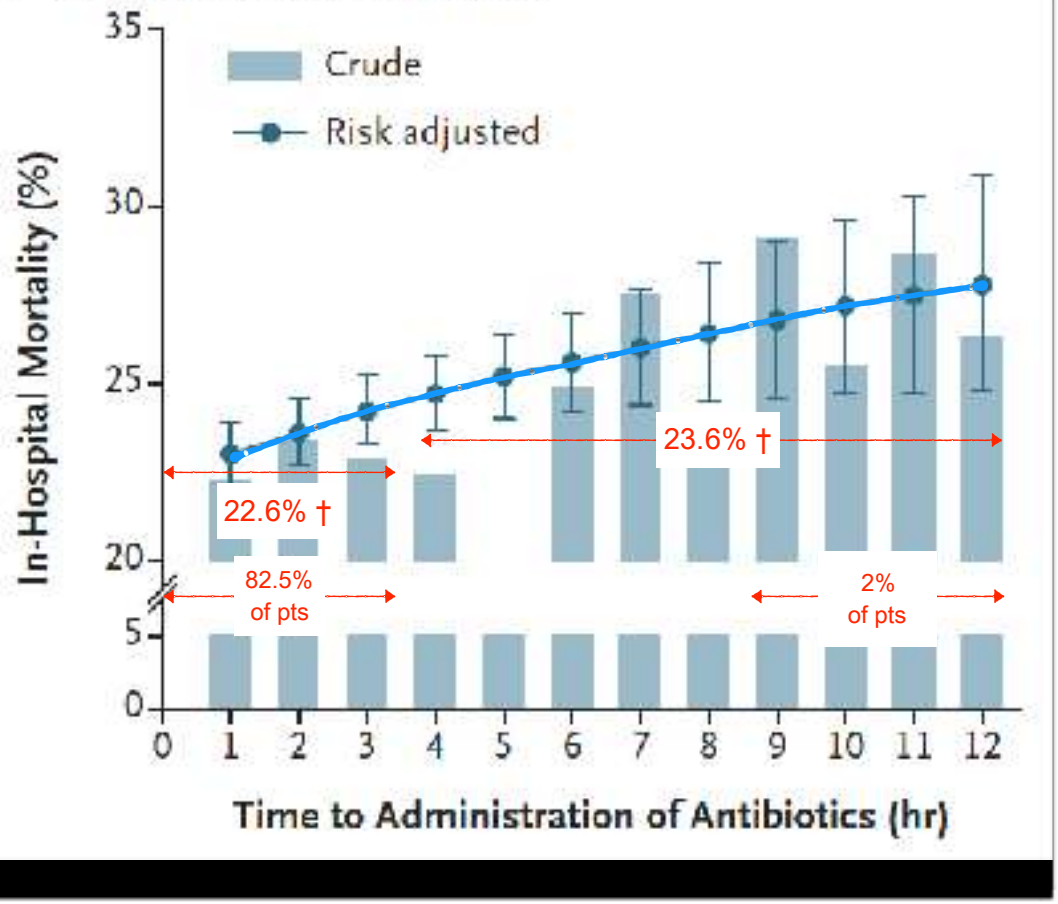

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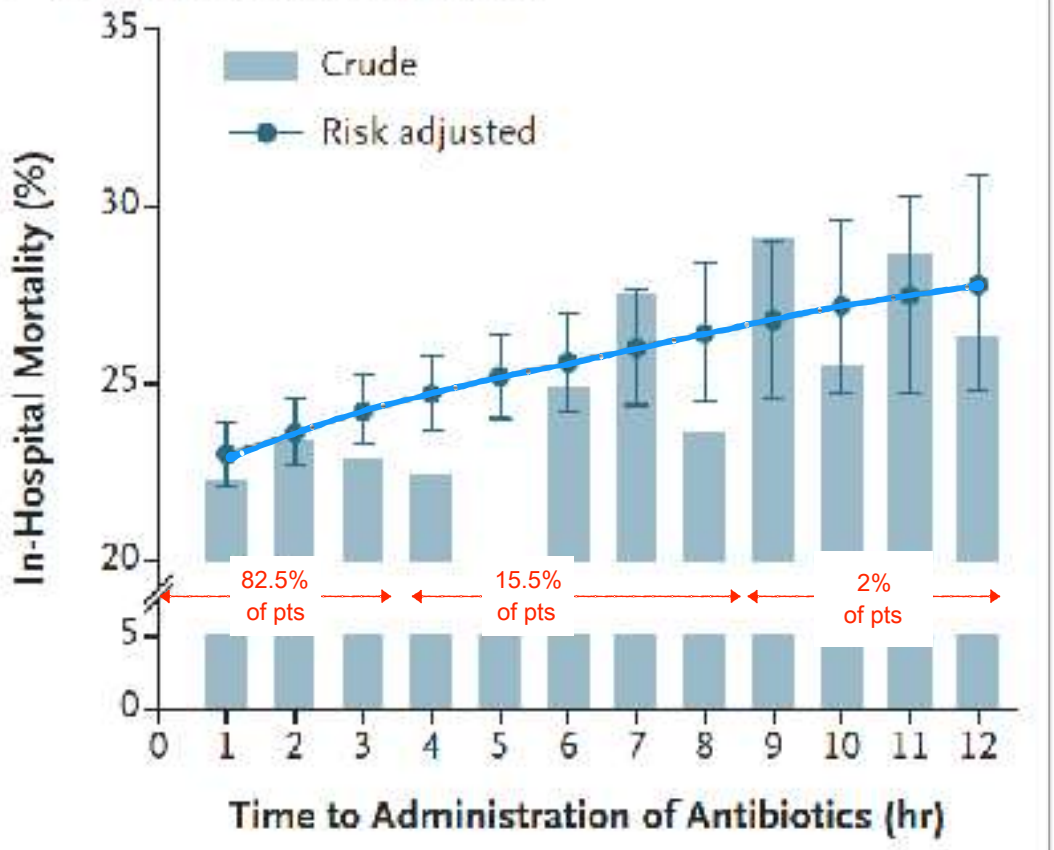

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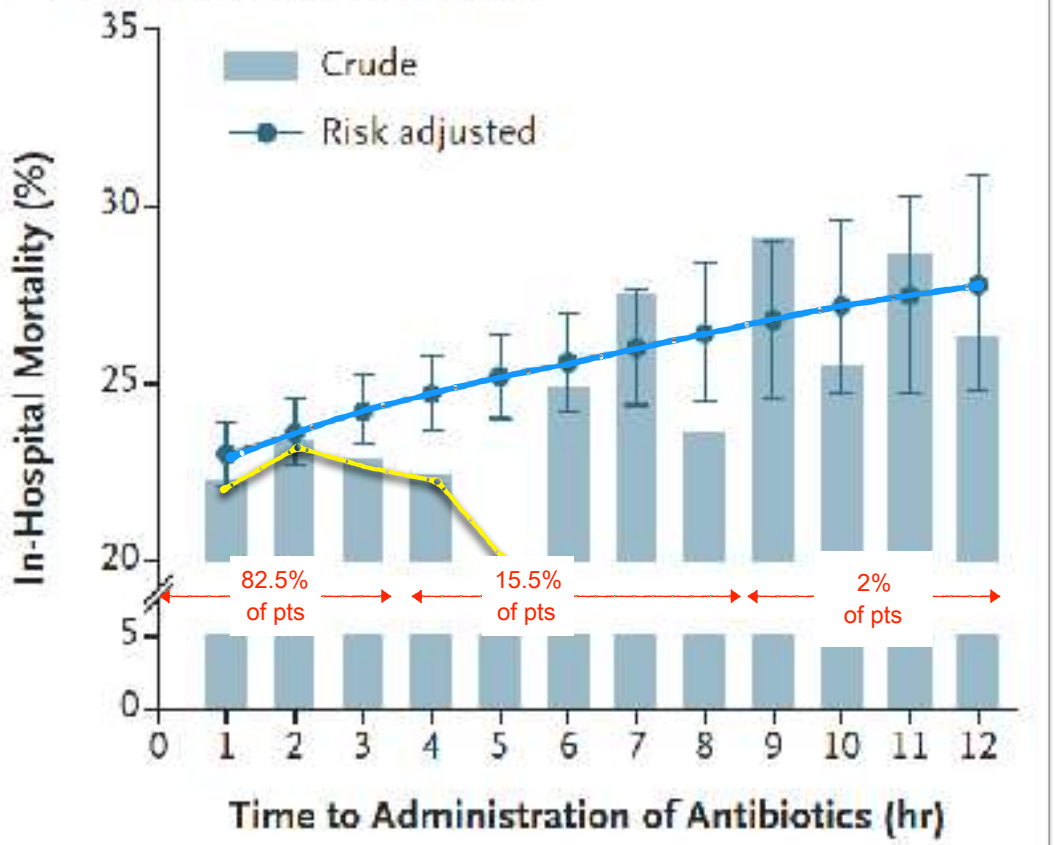

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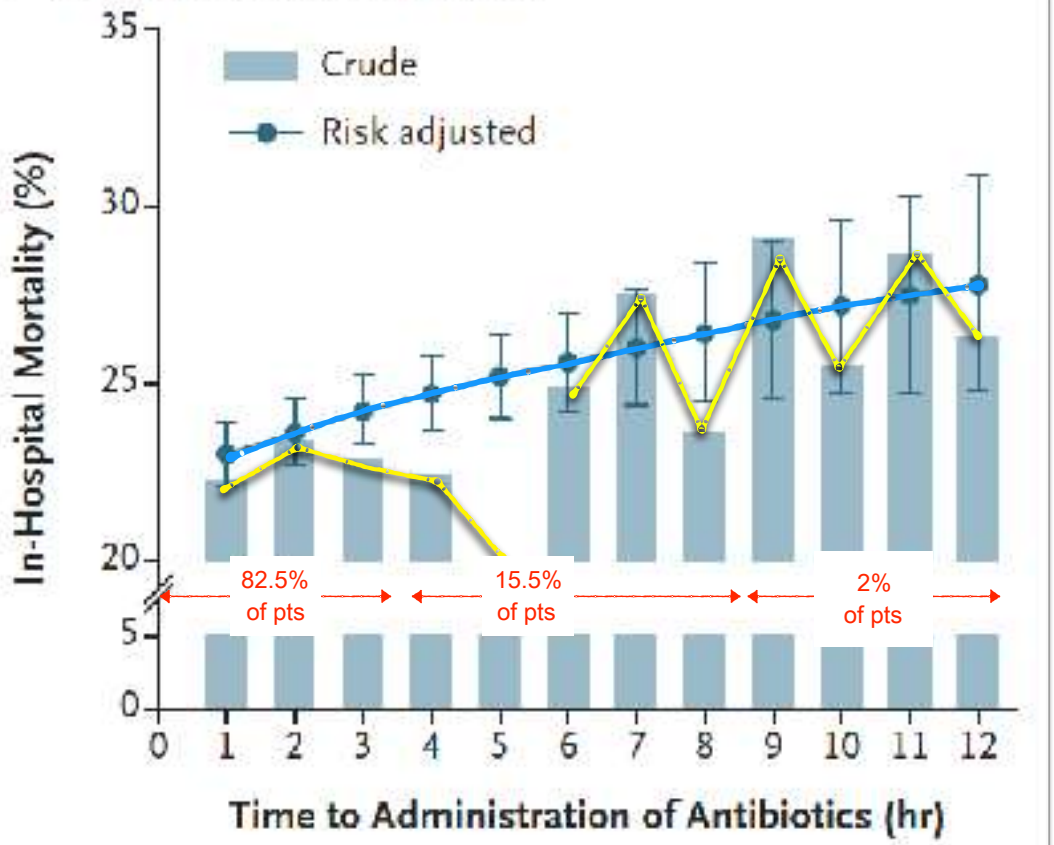

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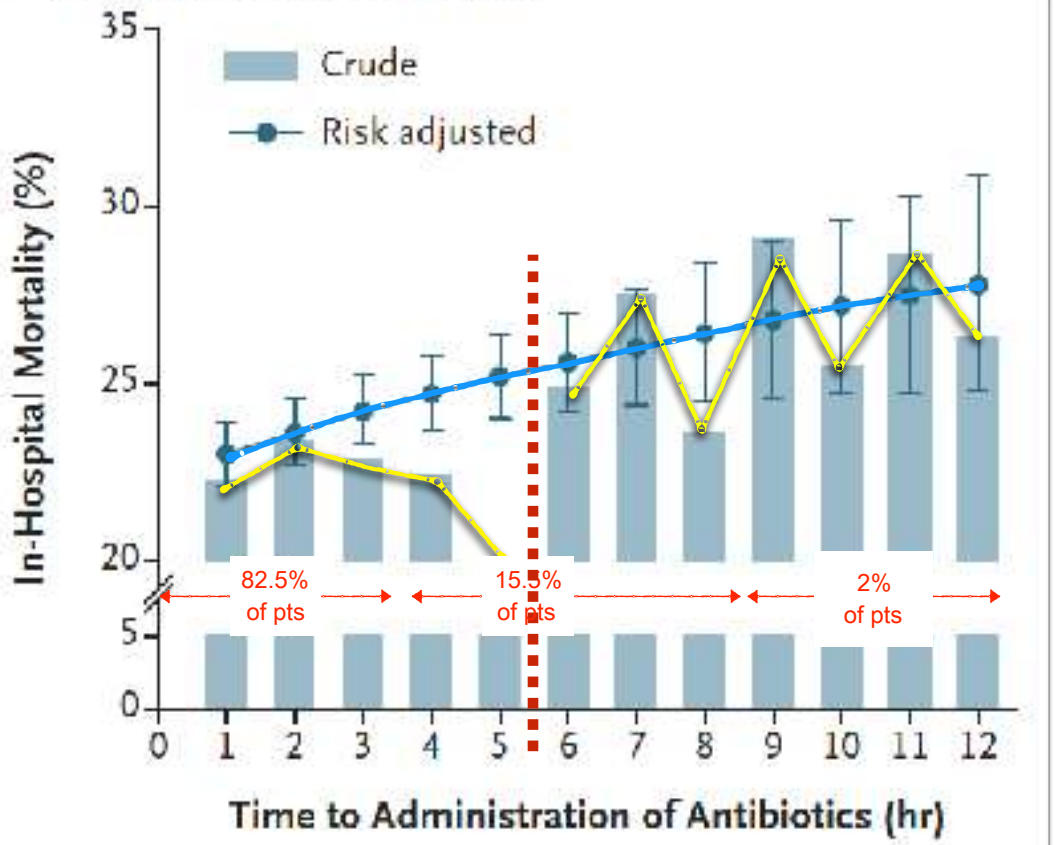

PROSPECTIVE STUDIES SHOW NO DIFFERENC

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- Often designed to specifically look at impact of antibiotics on outcomes
- None show an ‘each-hour-delay-kills’ signal

  - Puskarich, CCM 2011 septic shock (ED)
  - Hranjec, Lancet Infect Dis 2012 sepsis/septic shock (ICU)
  - Kaasch, Infection 2013 S aureus bacteraemia (Ward/ICU)
  - Bloos, Crit Care 2014 sepsis/septic shock (ICU)
  - De Groot, Crit Care 2015 ED sepsis/septic shock (ED)
  - Fitzpatrick, Clin Microbiol Infect 2016 Gm -tive bacteraemia (Ward)
  - Alan, Lancet Respir Dis 2018 sepsis (pre-hospital ED)

The association between time to antibiotics and relevant clinical outcomes in emergency department patients with various stages of sepsis: a prospective multi-center study

Ras de Groot[1*], Annemieke Arvers[2], Daan H Gerling[1], Douwe Rijpsma[2], Paul van Amstel[3], Dirk Linzel[3], Piet J Kostense[4], Marianne Jonker[1] and Evert de Jonge[1]

- prospective observational study in 3 Dutch EDs
- hospitalized ED patients requiring iv antibiotics
- stratified by illness severity (low, intermediate, high)
- time to antibiotics <1 hour vs 1-3 hours v >3 hours
- 1168 patients enrolled - overall mortality 10%
- 85% received antibiotics within 3 hours, 95% within 6 hours

Critical Care (2015) 19:194

The association between time to antibiotics and relevant clinical outcomes in emergency department patients with various stages of sepsis: a prospective multi-center study

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- No association between time to a/b and surviving days outside hospital or mortality
- In low illness severity group, delayed (>3h) antibiotics associated with more surviving days outside hospital (HR 1.46 (95%CI 1.05-202)

Critical Care (2015) 19:194

Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial

Nadia Alam, Erick Oskam, Patricia M Stassen, Pieternel van Exter, Peter M van de Ven, Harm R Haak, Frits Holleman, Arthur van Zanten, Hien van Leeuwen-Nguyen, Victor Bon, Bart A M Duineveld, Rishi S Nannan Panday, Mark H H Kramer, Prabath W B Nanayakkara, on behalf of the PHANTASi Trial investigators and the ORCA (Onderzoeks Consortium Acute Geneeskunde) Research Consortium the Netherlands*

[redacted]

6: 40–50

[redacted]

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- 2672 patients randomised to receive pre-hospital antibiotics (ceftriaxone 2g) from paramedics on suspicion of sepsis OR start antibiotics in ED
- Mean 96 minute difference in time to administration of antibiotics

6: 40–50

Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial

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[redacted]

	group (n=1137)	group (n=1535)	(95% CI)	difference (%, 95% CI)	
28 day mortality	93 (8%)*	120 (8%)	0·95 (0·74 to 1·24)	−0·37 (−2·5 to 1·7)	0·78
90 day mortality	134 (12%)*	178 (12%)	0·98 (0·80 to 1·21)	−0·20 (−2·7 to 2·3)	0·87
Median TTA in the ED (min)	70 (36–128)	..	..	..	..
TTA in the ED (min)					
0–60	410 (42%)	..	..	..	..
61–120	254 (26%)	..	..	..	..
121–180	125 (13%)	..	..	..	..
181–240	78 (8%)	..	..	..	..
>240	56 (6%)	..	..	..	..
Missing	50 (5%)	..	..	..	..
No antibiotics in the ED	164 (14%)	..	..	..	..
Intensive care unit admission	98 (9%)	155 (10%)	1·17 (0·92 to 1·49)	1·5 (−0·73 to 3·7)	0·19
28 day re-admission	119 (10%)	102 (7%)	..	..	0·0004
Median length of stay (days)					
Intensive care unit	3 (2–8)	4 (2–10)	..	..	0·28
Hospital	5 (3–9)	6 (4–10)	..	..	0·12

[redacted]

6: 40–50

[redacted]

Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial

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28 day mortality	93 (8%)*	120 (8%)	0·95 (0·74 to 1·24)	−0·37 (−2·5 to 1·7)	0·78
90 day mortality	134 (12%)*	175 (12%)	0·93 (0·80 to 1·21)	−0·20 (−2·7 to 2·3)	0·87
Median TTA in the ED (min)	78 (36–128)	..	..	..	..
TTA in the ED (min)					
0–60	410 (42%)	..	..	..	..
61–120	254 (26%)	..	..	..	..
121–180	125 (13%)	..	..	..	..
181–240	78 (8%)	..	..	..	..
>240	56 (6%)	..	..	..	..
Missing	59 (5%)	..	..	..	..
No antibiotics in the ED	164 (14%)	..	..	..	..
Intensive care unit admission	98 (9%)	151 (10%)	1·17 (0·92 to 1·49)	1·5 (−0·73 to 3·7)	0·19
28 day readmission†	119 (10%)	102 (7%)	..	..	0·0004
Median length of stay (days)					
Intensive care unit	3 (2–8)	4 (2–10)	..	..	0·28
Hospital	6 (3–9)	6 (4–10)	..	..	0·12

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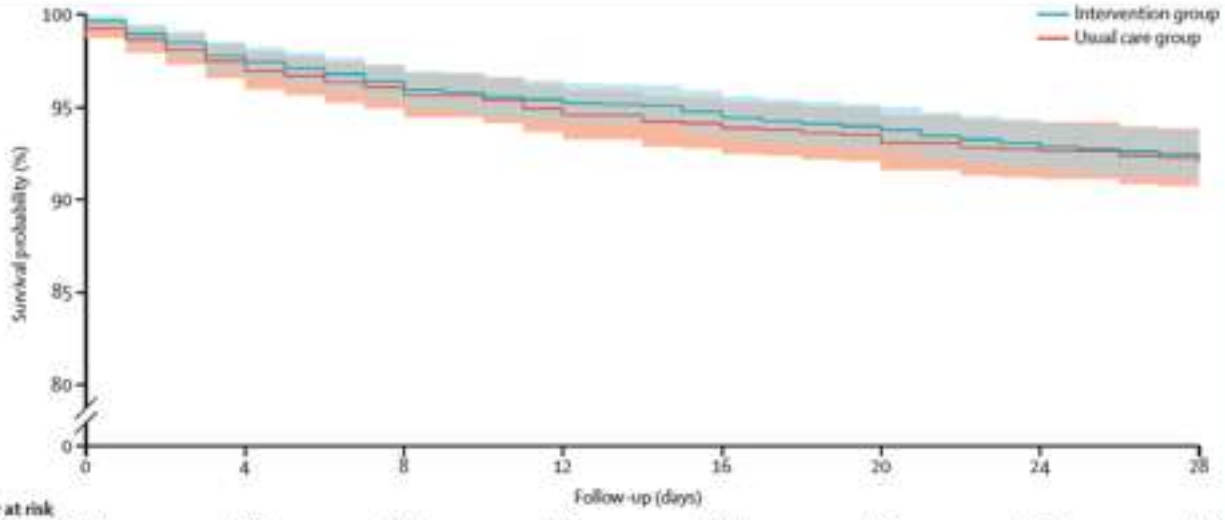
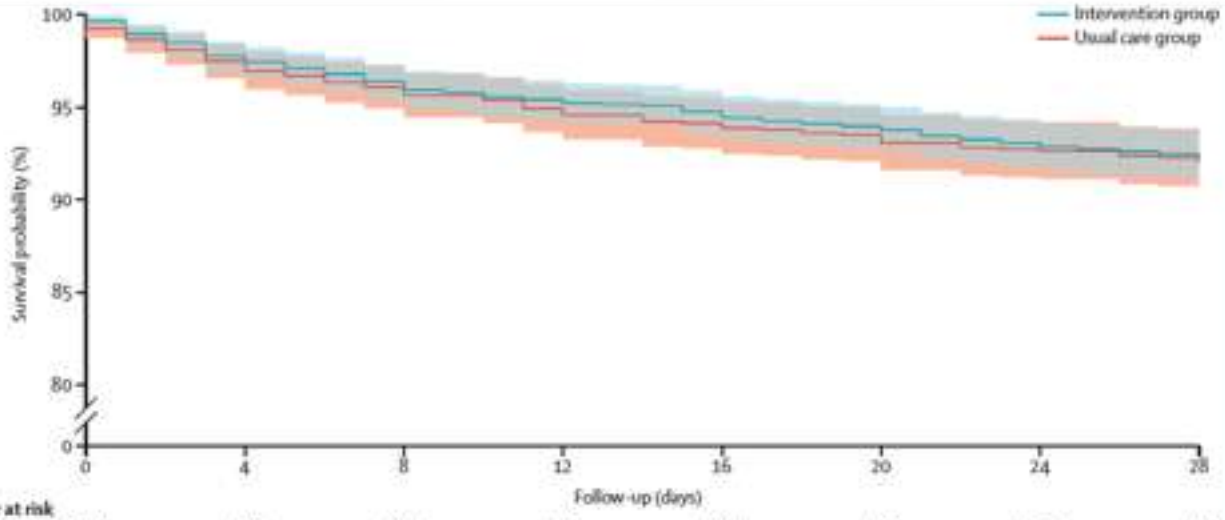
6: 40–50



Number at risk								
Intervention group	1136	1107	1091	1078	1069	1062	1053	1048
Usual care group	1535	1500	1479	1464	1454	1442	1428	1419

B

	Usual care group (n=1137)	Intervention group (n=1535)	Relative risk (95% CI)	p value
Age (years)				
<65	12/276 (4%)	6/336 (2%)	0·41 (0·16–1·08)	0·10
≥65	81/860 (9%)	114/1199 (10%)	1·01 (0·77–1·32)	1·00
qSOFA (prehospital)				
<2	59/872 (7%)	71/1132 (6%)	0·93 (0·66–1·29)	0·72
2	25/180 (14%)	45/318 (14%)	1·02 (0·65–1·60)	1·00
NEWS (prehospital)				
<5	7/146 (5%)	7/192 (4%)	0·76 (0·27–2·12)	0·80
≥5	53/622 (9%)	71/827 (9%)	1·01 (0·72–1·42)	1·00
SBP (prehospital)				
<100	15/112 (13%)	25/181 (14%)	1·03 (0·57–1·87)	1·00
>100	75/1001 (7%)	95/1337 (7%)	0·95 (0·71–1·27)	0·78
Severity of sepsis				
Sepsis	8/424 (2%)	12/579 (2%)	1·10 (0·45–2·66)	1·00
Severe sepsis	74/656 (11%)	88/868 (10%)	0·90 (0·67–1·20)	0·53
Septic shock	10/37 (27%)	19/66 (29%)	1·07 (0·56–2·04)	0·85
Overall	**93/1136 (8%)**	**120/1535 (8%)**	**0·95 (0·74–1·24)**	**0·78**



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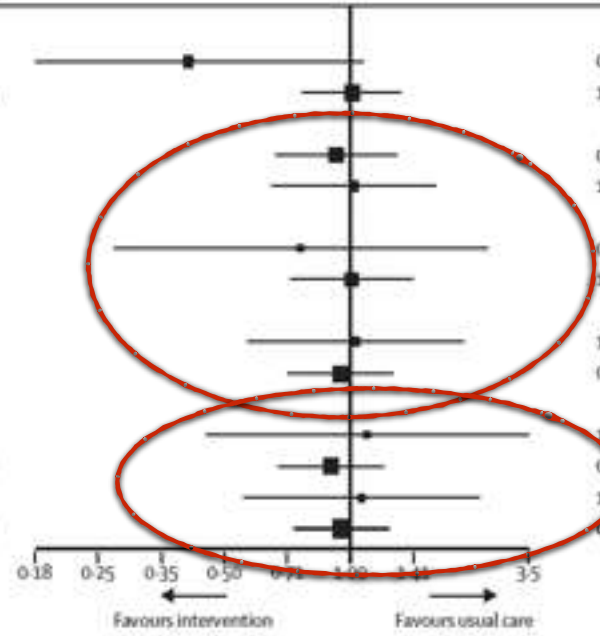


Antibiotics for Sepsis: Does Each Hour Really Count, or Is It Incestuous Amplification?

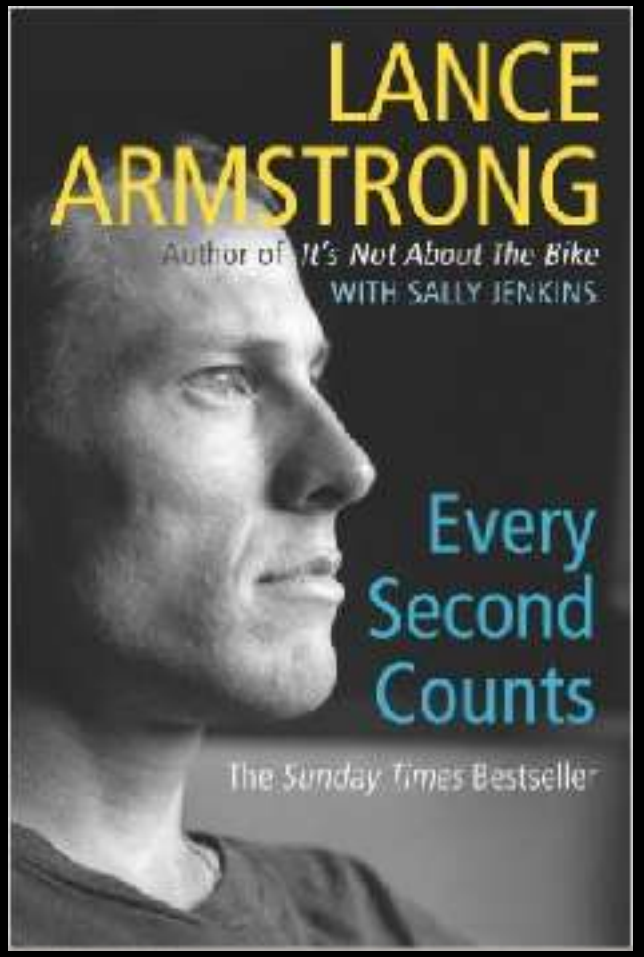
Mervyn Singer

Incestuous amplification—the (extreme) reinforcement of ideas and/or beliefs that occurs when like-minded people communicate with each other (1).

TAKE-HOME MESSAGE

TAKE-HOME MESSAGE

- Every second doesn't count .. but reasonable/rational to treat sepsis and septic shock promptly
- Rather than simply throwing antibiotics at the patient, apply some thought, seek advice, and think source control

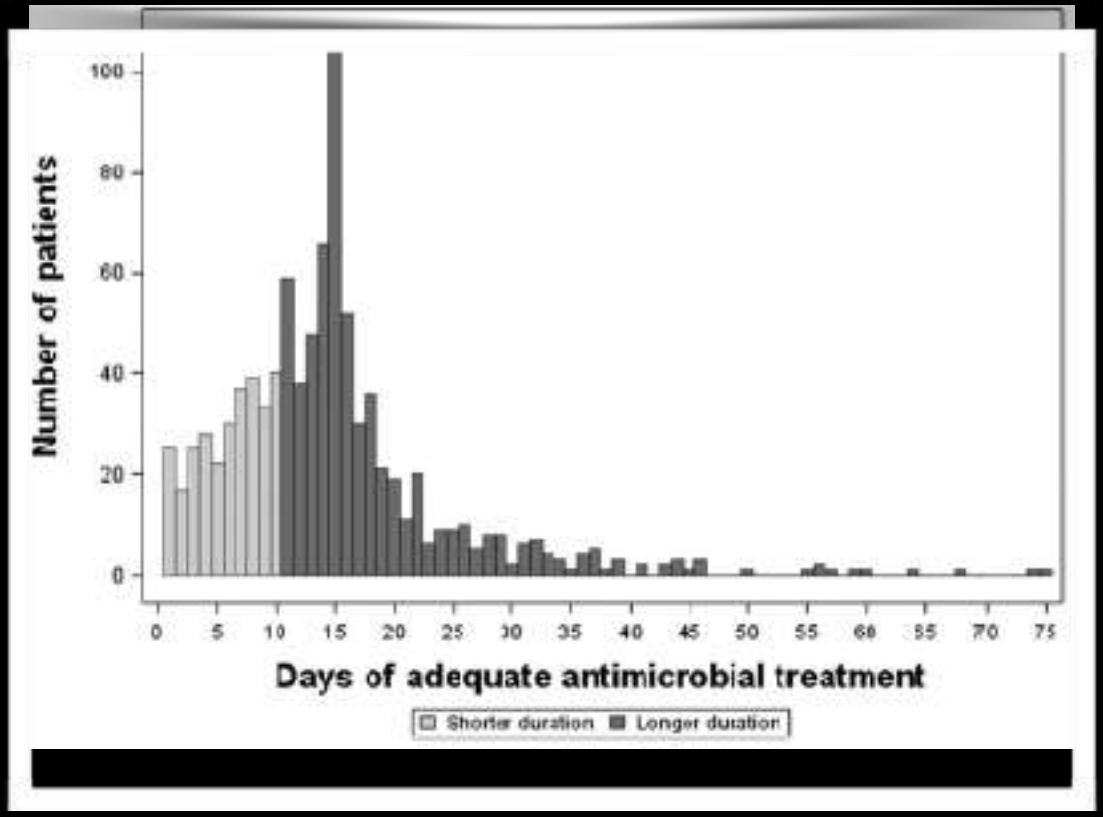


DISCUSSION POINTS ..

- Guidelines should be slavishly followed
- One size fits all
- Every hour of antibiotic delay kills
- How long should a course of antibiotics last?
- Sepsis mortality is improving
- Why do people die of sepsis?

Duration of Antimicrobial Treatment for Bacteremia in Canadian Critically Ill Patients*

Nick Daneman, MD[1]; Asger H. Kishu, MBBS[2]; Wei Xiong, MSc[2]; Sean M. Bagshaw, MD[3]; Peter Dodek, MD[4]; Richard Hall, MD[5]; Anand Kumar, MD[6]; Francois Lamontagne, MD[7]; Francois Lauzier, MD[8]; John Marshall, MD[9]; Claudio M. Martin, MD[10]; Lauralyn McIntyre, MD[11]; John Muscedere, MD[12]; Steve Reynolds, MD[13]; Henry T. Stelfox, MD[14]; Deborah J. Cook, MD[15]; Robert A. Fowler, MD[16]; on behalf of the Canadian Critical Care Trials Group



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Crit Care Med 2016;44:256–264

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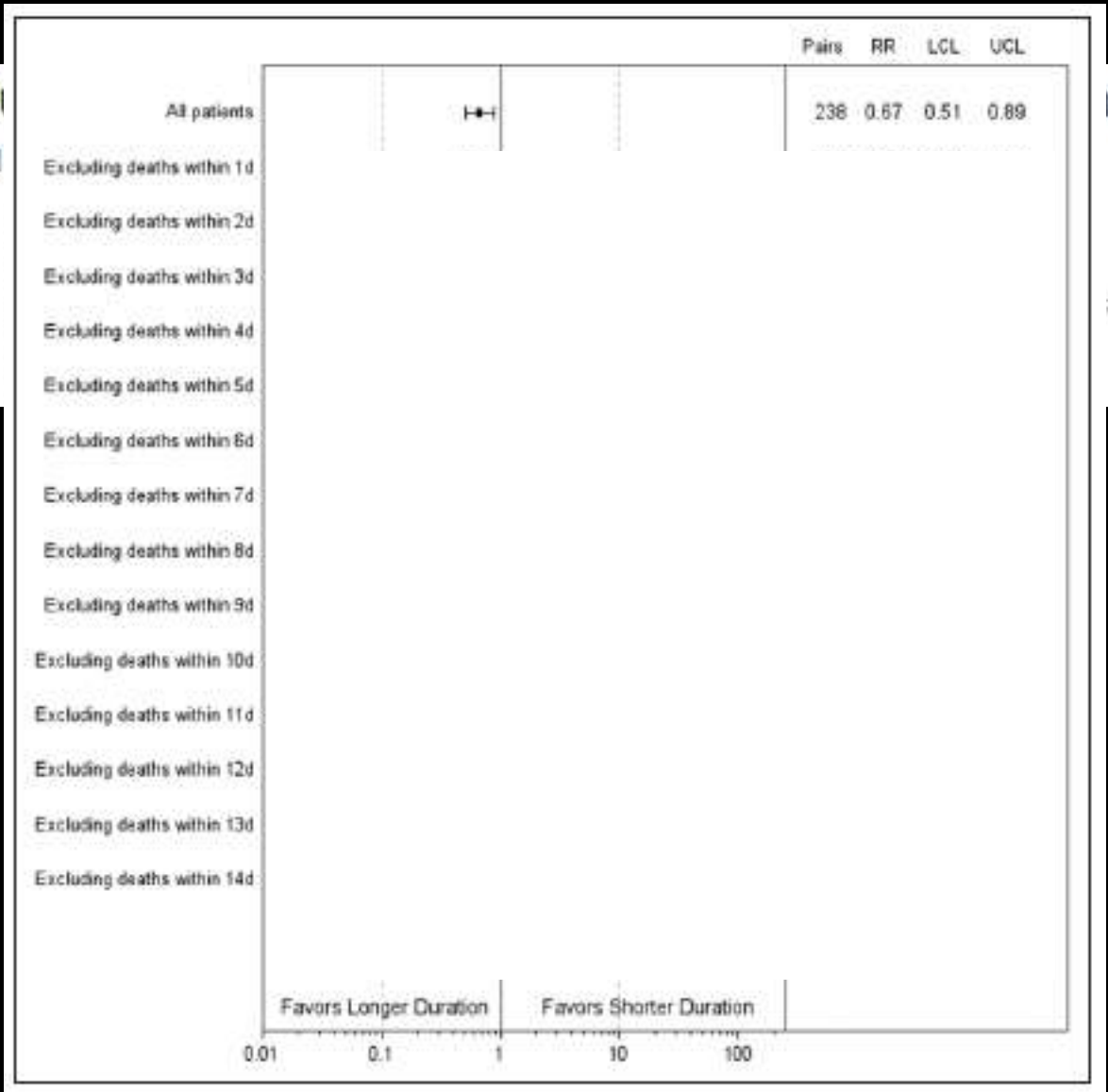
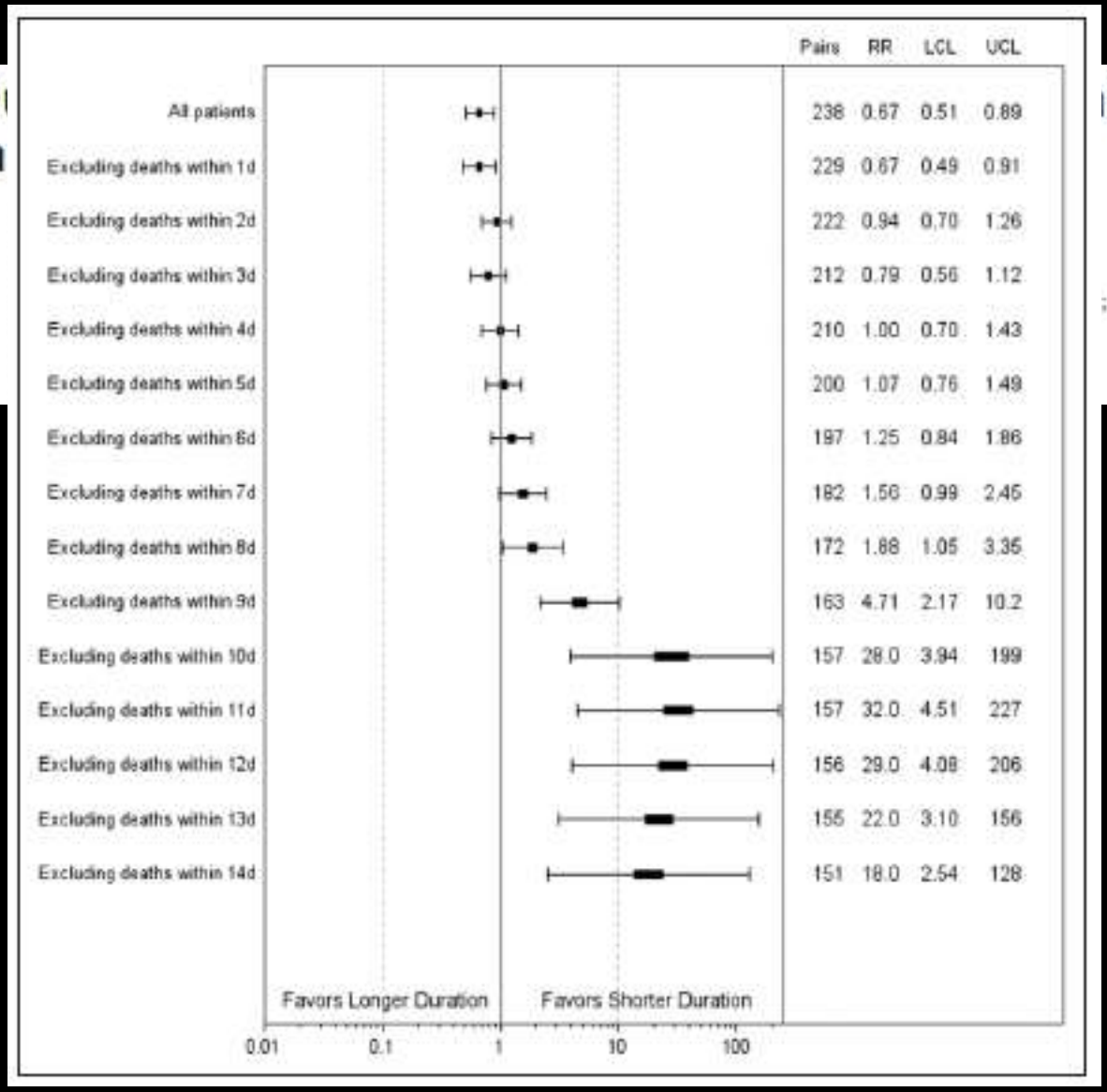


Figure 2. Impact of excluding early deaths on the association of treatment duration and survival among propensity-matched patients receiving shorter versus longer duration antimicrobial treatment.



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a study sufficiently powered to exclude clinically important outcome differences, there could be large-scale reductions in antimicrobial use and complications for critically ill patients.

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Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults

A Randomized Trial

Jean Chastre, MD
Michel Wolff, MD
Jean-Yves Fagon, MD
Sylvie Chevret, MD
Franck Thomas, MD
Delphine Wermert, MD
Eva Clementi, MD
Jesus Gonzalez, MD
Dominique Jusserand, MD
Pierre Asfar, MD

Context The optimal duration of antimicrobial treatment for ventilator-associated pneumonia (VAP) is unknown. Shortening the length of treatment may help to contain the emergence of multiresistant bacteria in the intensive care unit (ICU).

Objective To determine whether 8 days is as effective as 15 days of antibiotic treatment of patients with microbiologically proven VAP.

Design, Setting, and Participants Prospective, randomized, double-blind (until day 8) clinical trial conducted in 51 French ICUs. A total of 401 patients diagnosed as having developed VAP by quantitative culture results of bronchoscopic specimens and who had received initial appropriate empirical antimicrobial therapy were enrolled between May 1999 and June 2002.

Intervention A total of 197 patients were randomly assigned to receive 8 days and 204 to receive 15 days of therapy with an antibiotic regimen selected by the treating physician.

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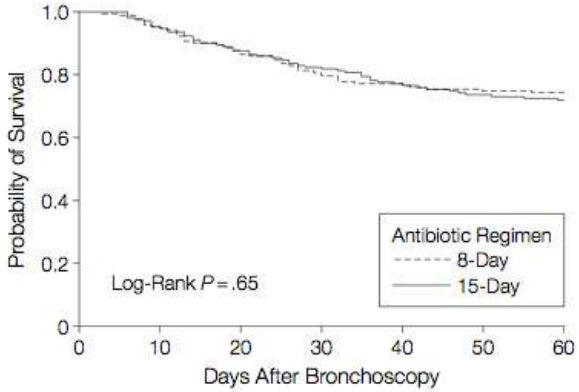
Figure 2. Kaplan-Meier Estimates of the Probability of Survival



No. at Risk							
8-Day Antibiotic Regimen	197	187	172	158	151	148	147
15-Day Antibiotic Regimen	204	194	179	167	157	151	147

Probability of survival is for the 60 days after ventilator-assisted pneumonia onset as a function of the duration of antibiotic administration.

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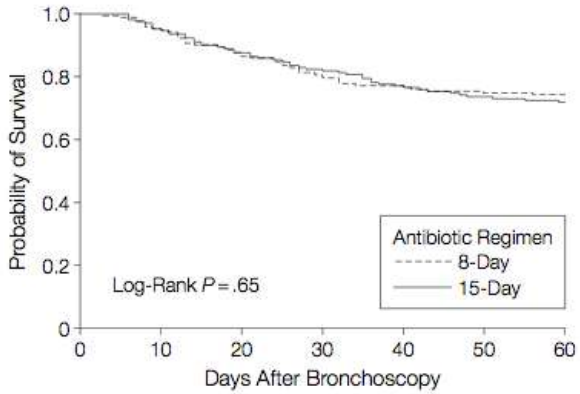

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Notably, among patients who developed recurrent pulmonary infections, multiresistant pathogens emerged significantly less frequently in those who had received 8 days of antibiotics (42.1% vs 62.3% of recurrent infections; $P = .04$).

Early Antibiotic Discontinuation in Patients With Clinically Suspected Ventilator-Associated Pneumonia and Negative Quantitative Bronchoscopy Cultures*

Kirthana Raman, PharmD[1–3]; Michael D. Nailor, PharmD, BCPS (AQ-ID)[1,4]; David P. Nicolau, PharmD, FCCP, FIDSA[4,5]; Jaber Aslanzadeh PhD, D(ABMM)[4]; Michelle Nadeau, PharmD[2]; Joseph L. Kuti, PharmD[4]

	Early Discontinuation ($n = 40$)	Late Discontinuation ($n = 49$)	p
Duration of antibiotics	4 (3, 4)	9 (6, 14)	<0.001

Conclusions: In this severely ill population with clinically suspected ventilator-associated pneumonia and negative quantitative bronchoalveolar lavage cultures, early discontinuation of antibiotics did not affect mortality and was associated with a lower frequency of MDR superinfections.

(Crit Care Med 2015; 43:1659–1666)

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J Antimicrob Chemother 2015; 70: 273–278

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- Less ICU-acquired MRSA, MDR Gram -tives, VRE and fluconazole-resistant candidaemia c/f similar audit in 2000

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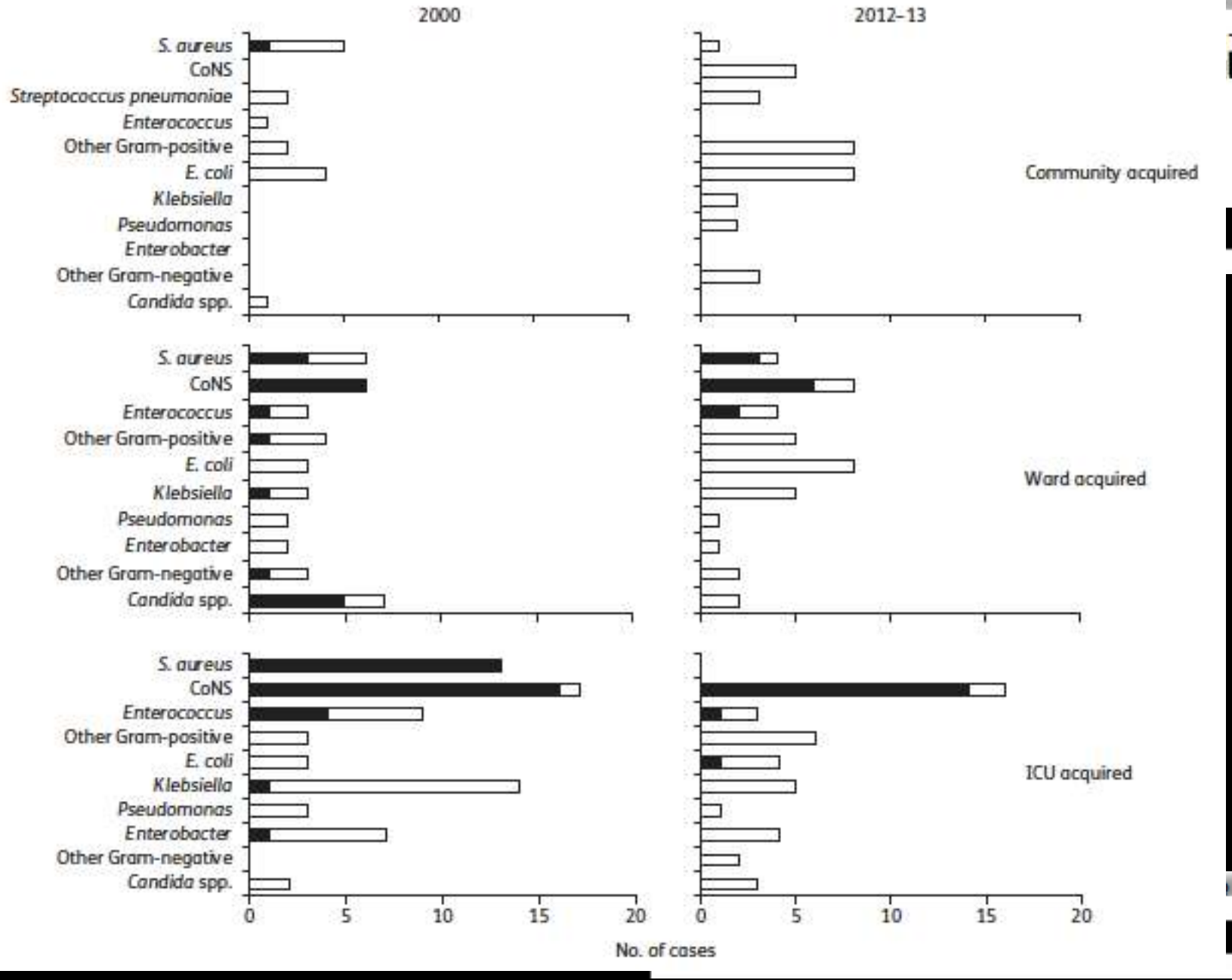
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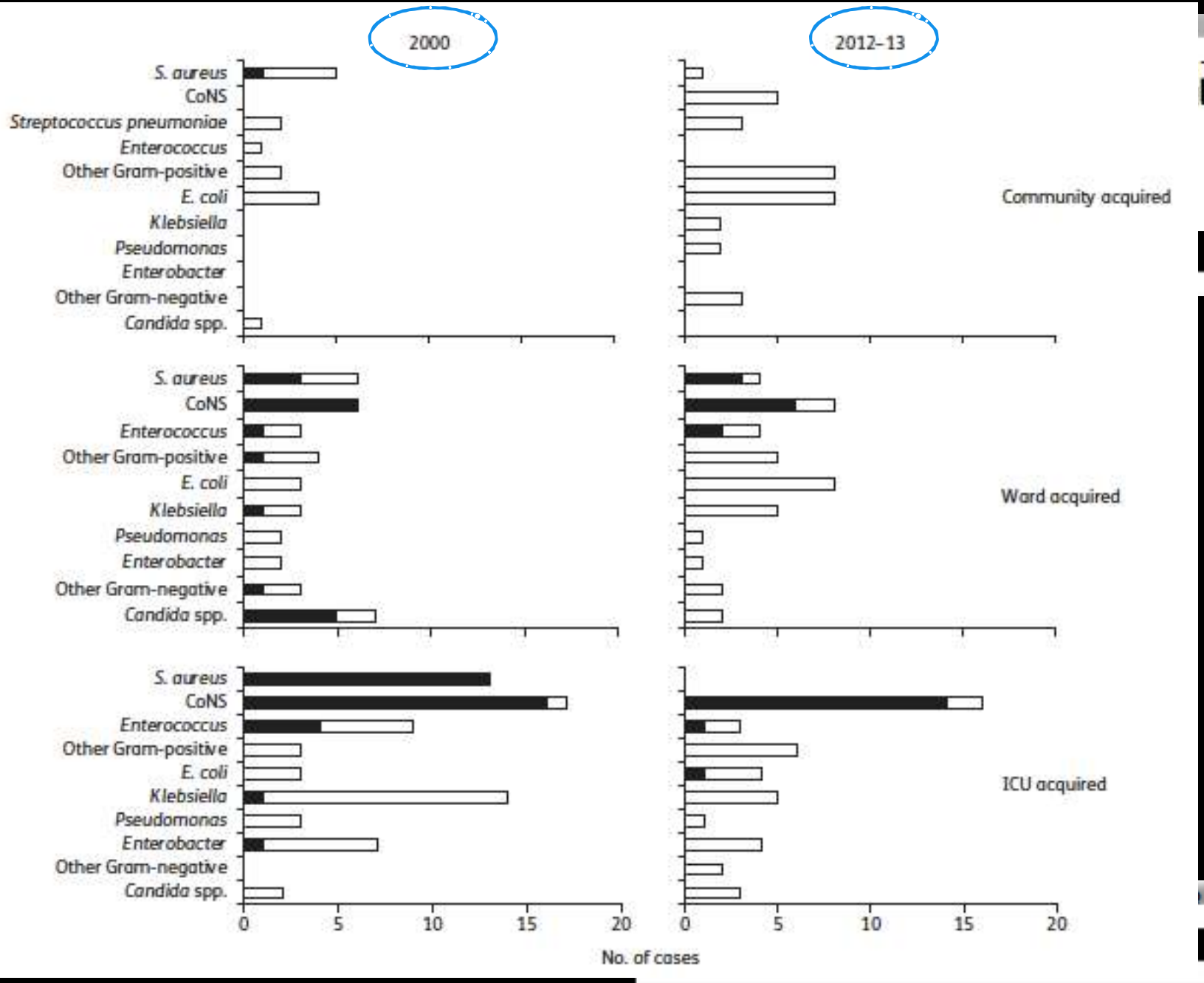
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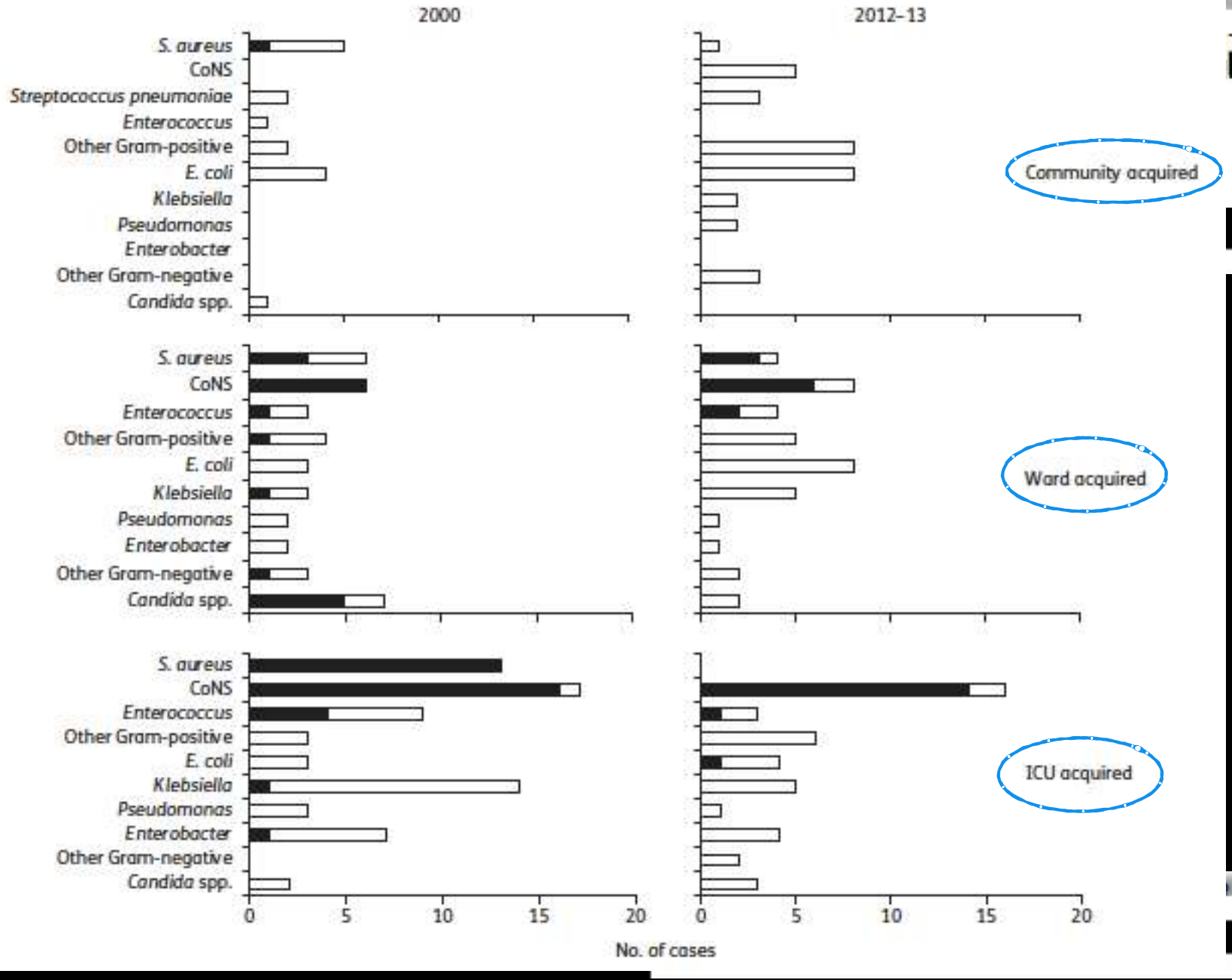
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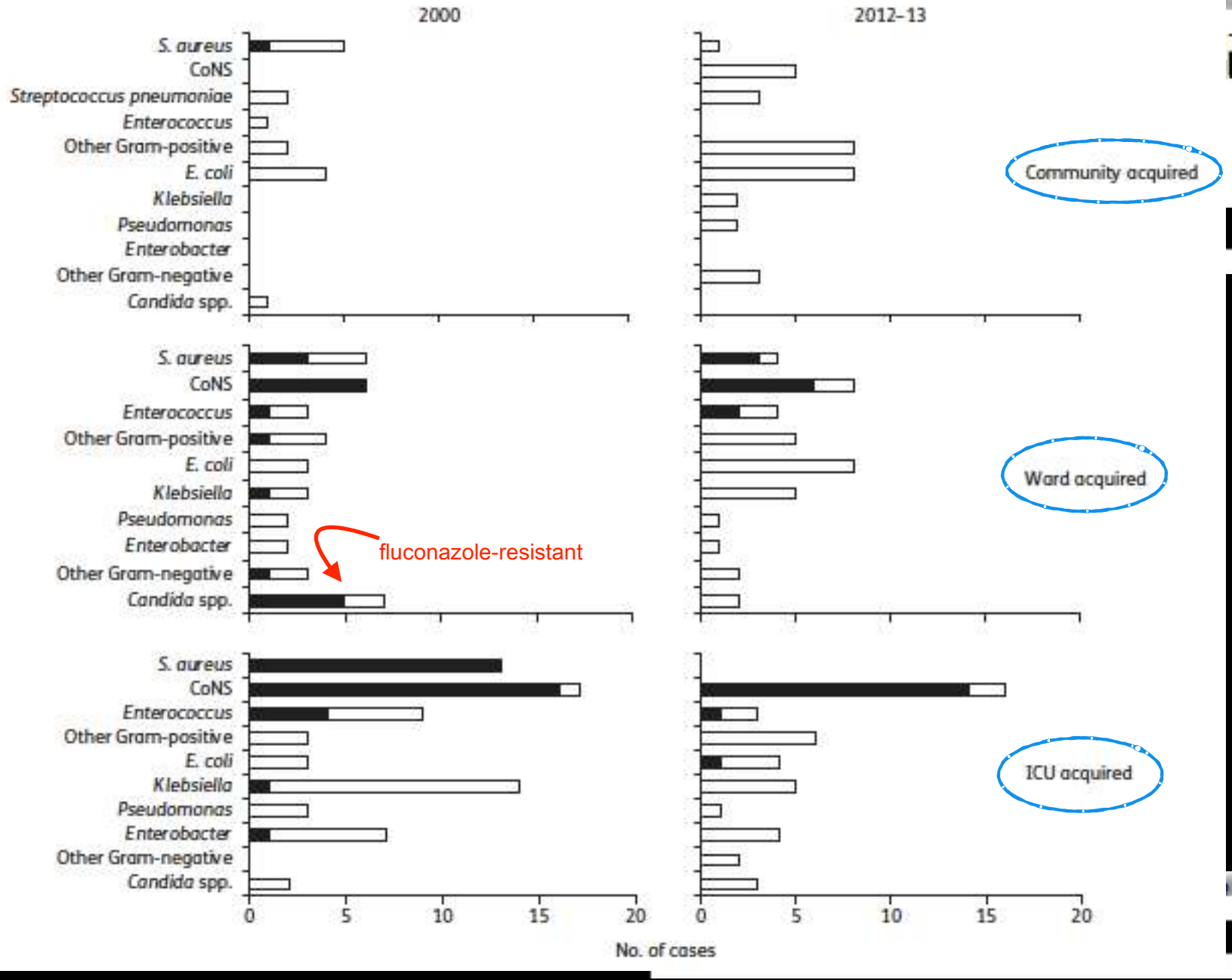
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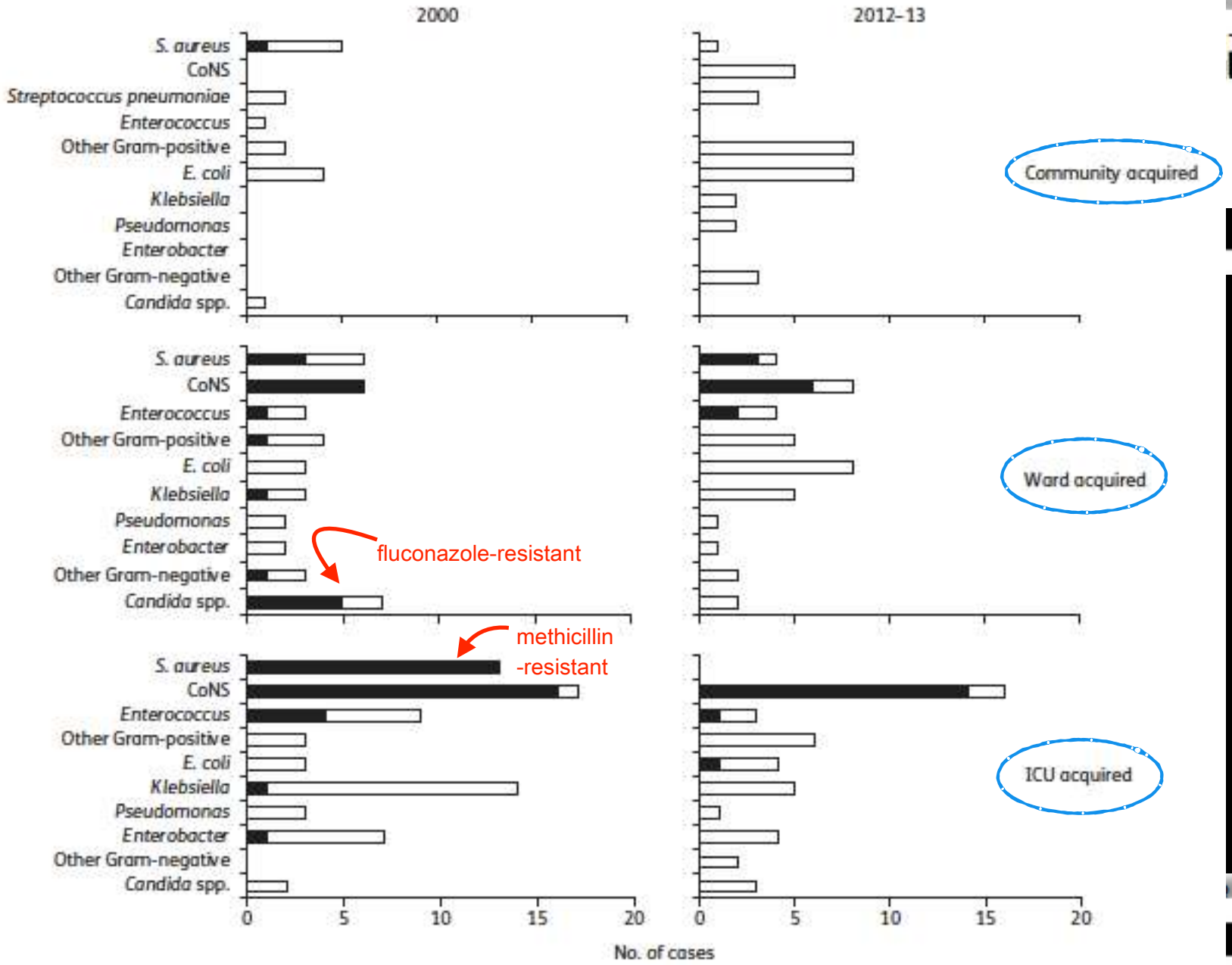
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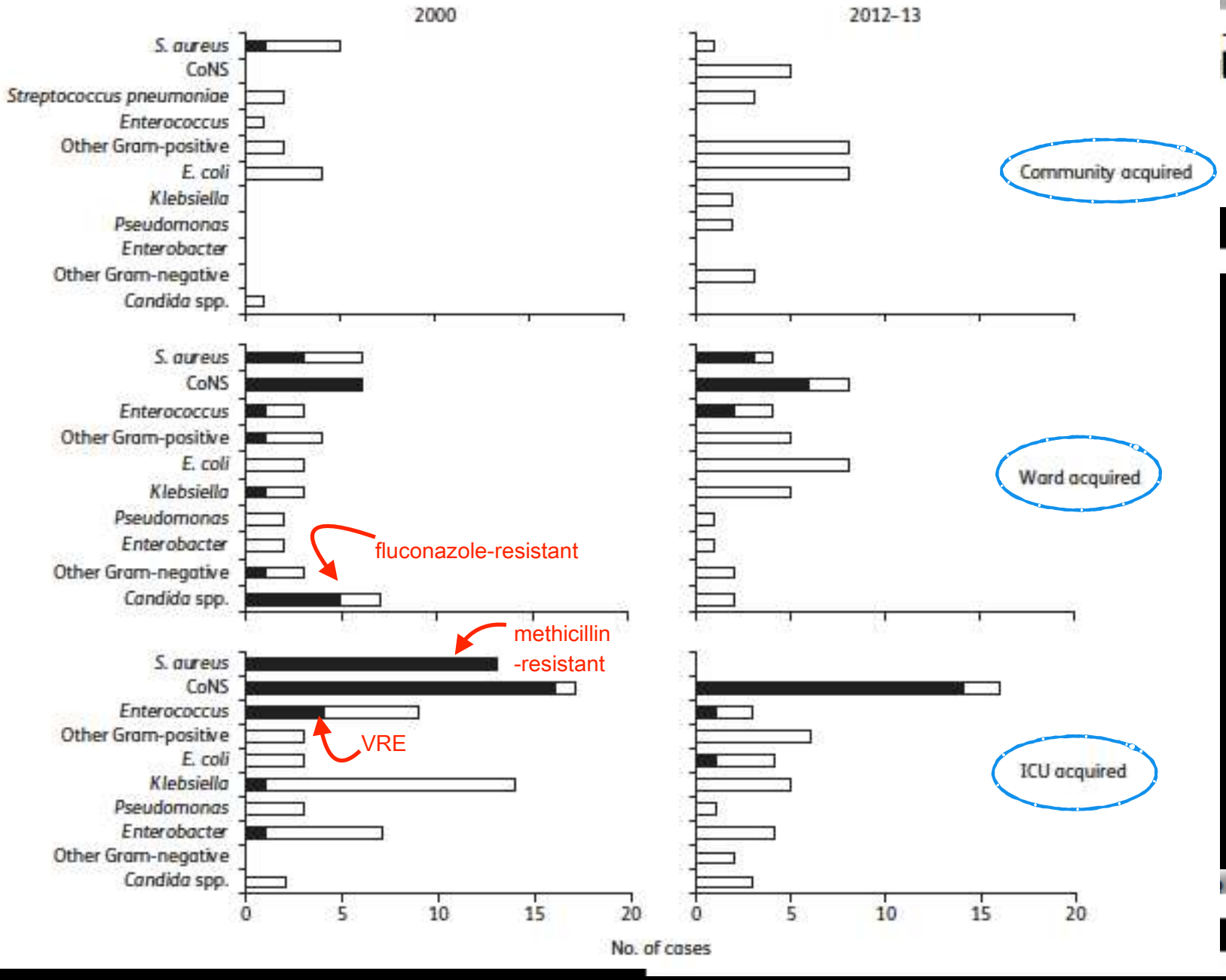
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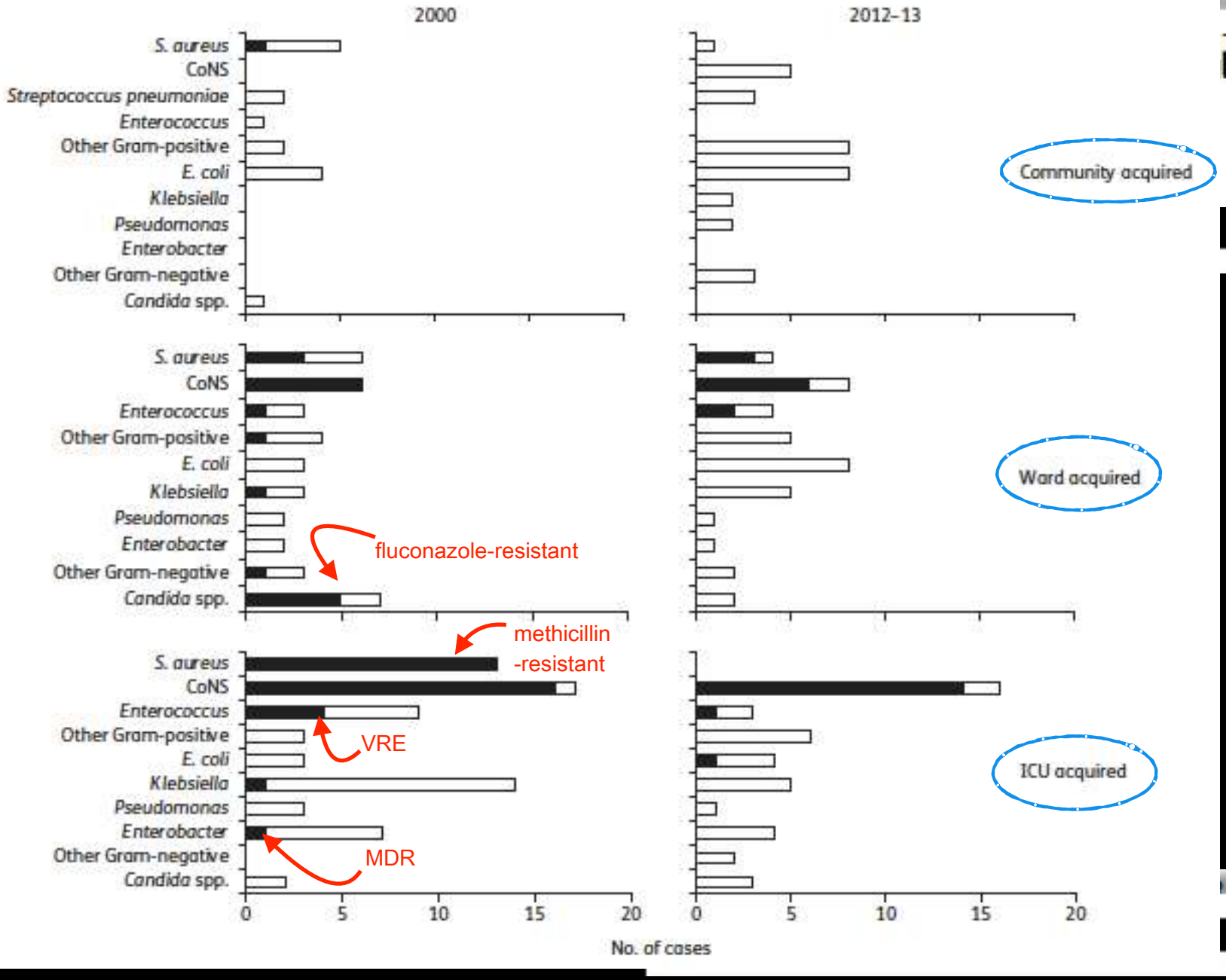
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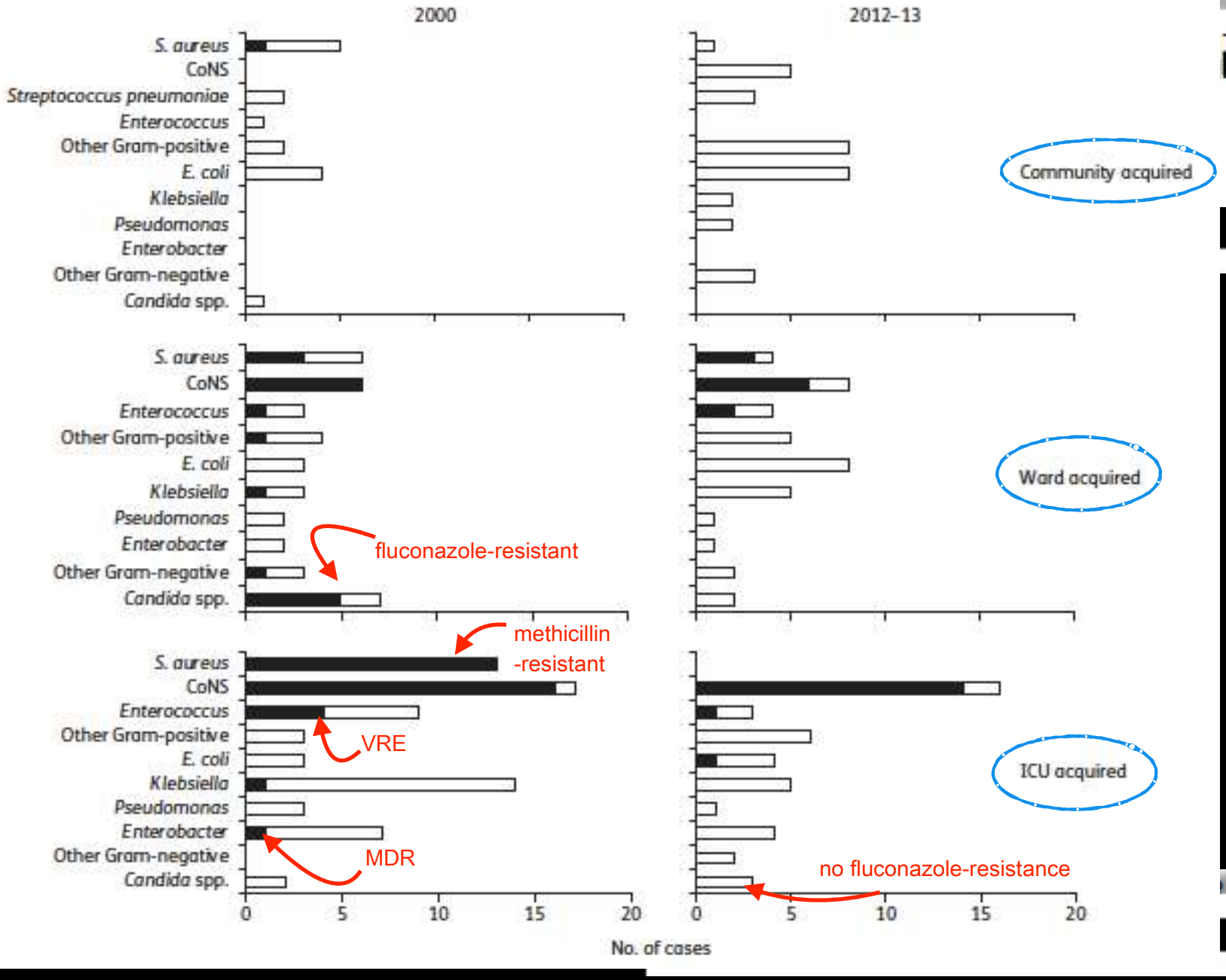
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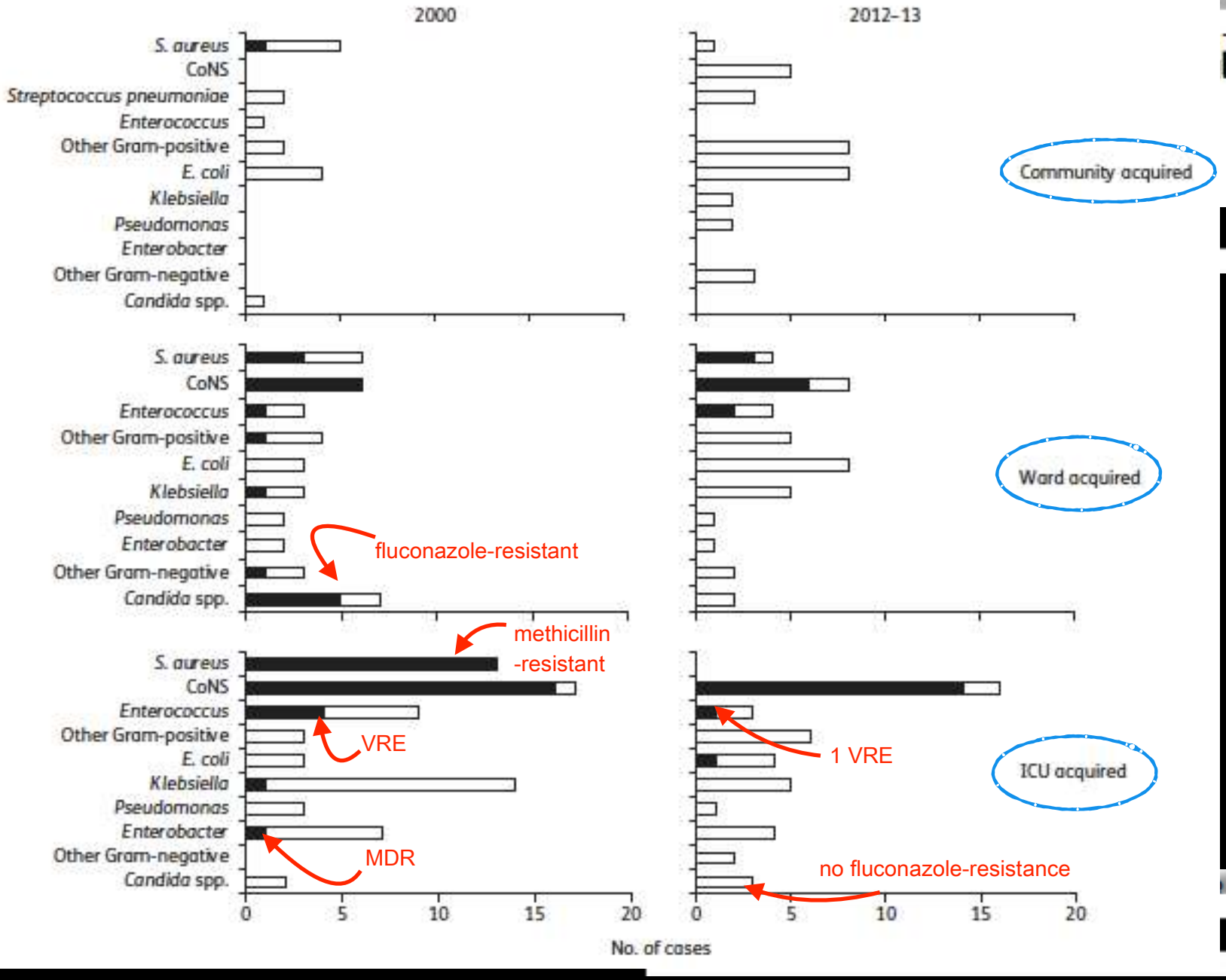
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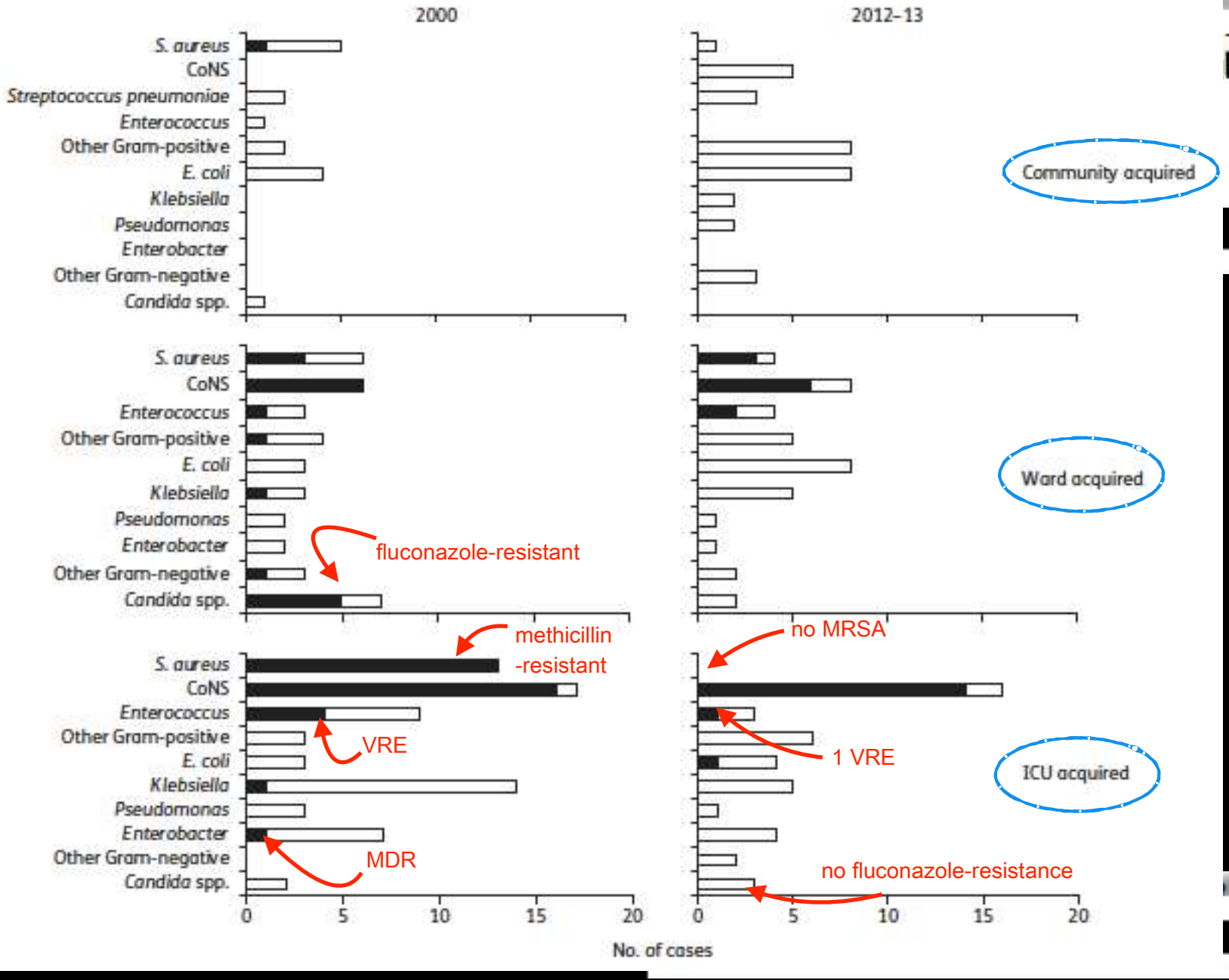
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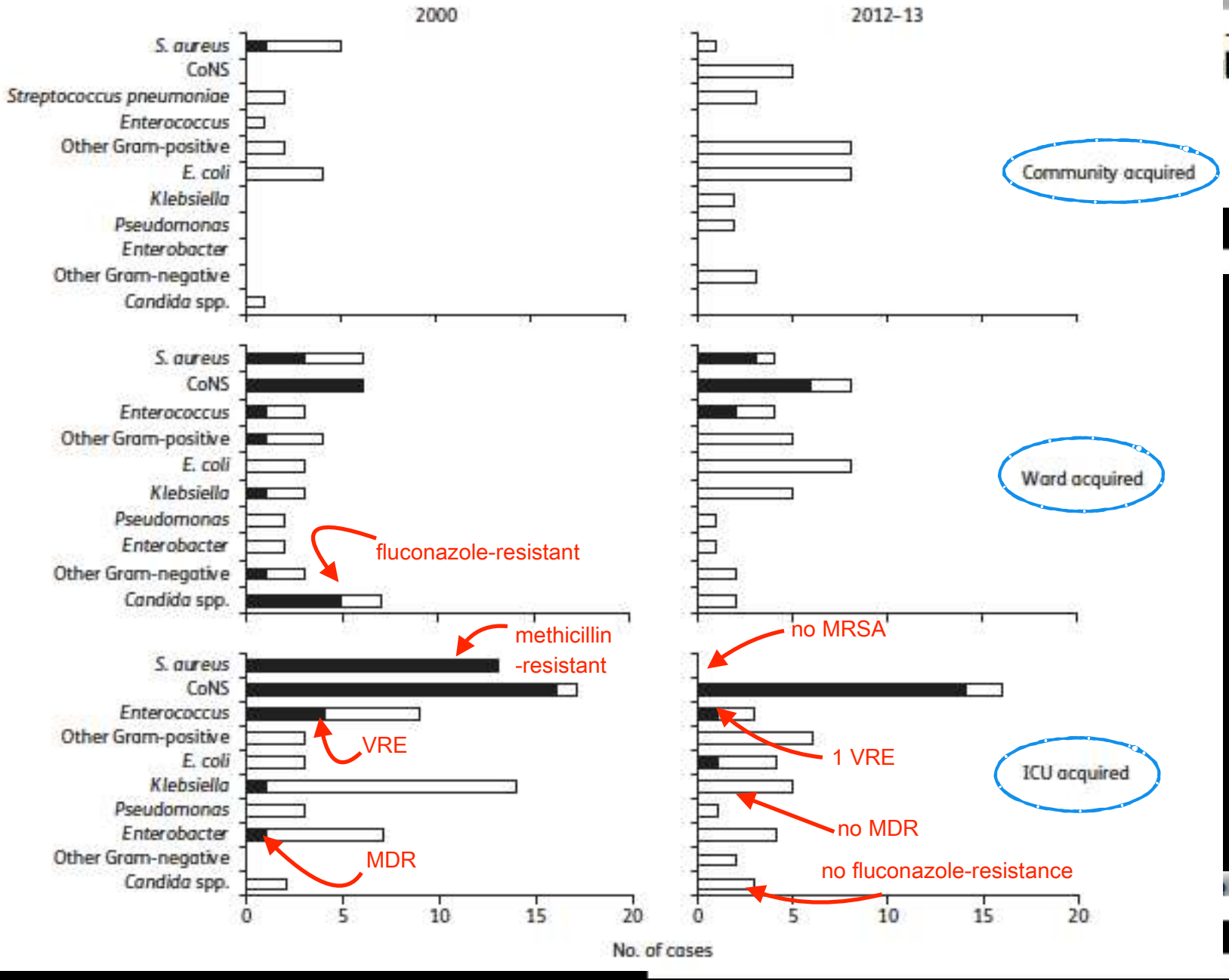
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Other Gram-positive
E. coli
Klebsiella
Pseudomonas
Enterobacter
Other Gram-negative
Candida spp.
Community acquired
Ward acquired
fluconazole-resistant
methicillin
-resistant
no MRSA
VRE
1 VRE
ICU acquired
MDR
no MDR
no fluconazole-resistance
0
5
10
15
20
No. of cases

for Intraabdominal Infection

R.G. Sawyer, J.A. Claridge, A.B. Nathens, O.D. Rotstein, T.M. Duane, H.L. Evans, C.H. Cook, P.J. O'Neill, J.E. Mazuski, R. Askari, M.A. Wilson, L.M. Napolitano, N. Namias, P.R. Miller, E.P. Dellinger, C.M. Watson, R. Coimbra, D.L. Dent, S.F. Lowry,* C.S. Cocanour, M.A. West, K.L. Banton, W.G. Cheadle, P.A. Lipsett, C.A. Guidry, and K. Popovsky

METHODS

We randomly assigned 518 patients with complicated intraabdominal infection and adequate source control to receive antibiotics until 2 days after the resolution of fever, leukocytosis, and ileus, with a maximum of 10 days of therapy (control group), or to receive a fixed course of antibiotics (experimental group) for 4±1 calendar days. The primary outcome was a composite of surgical-site infection, recurrent intraabdominal infection, or death within 30 days after the index source-control procedure, according to treatment group.

N Engl J Med 2015;372:1996-2005.

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RESULTS

antibiotic therapy was 4.0 days (interquartile range, 4.0 to 5.0) in the experimental group, as compared with 8.0 days (interquartile range, 5.0 to 10.0) in the control group

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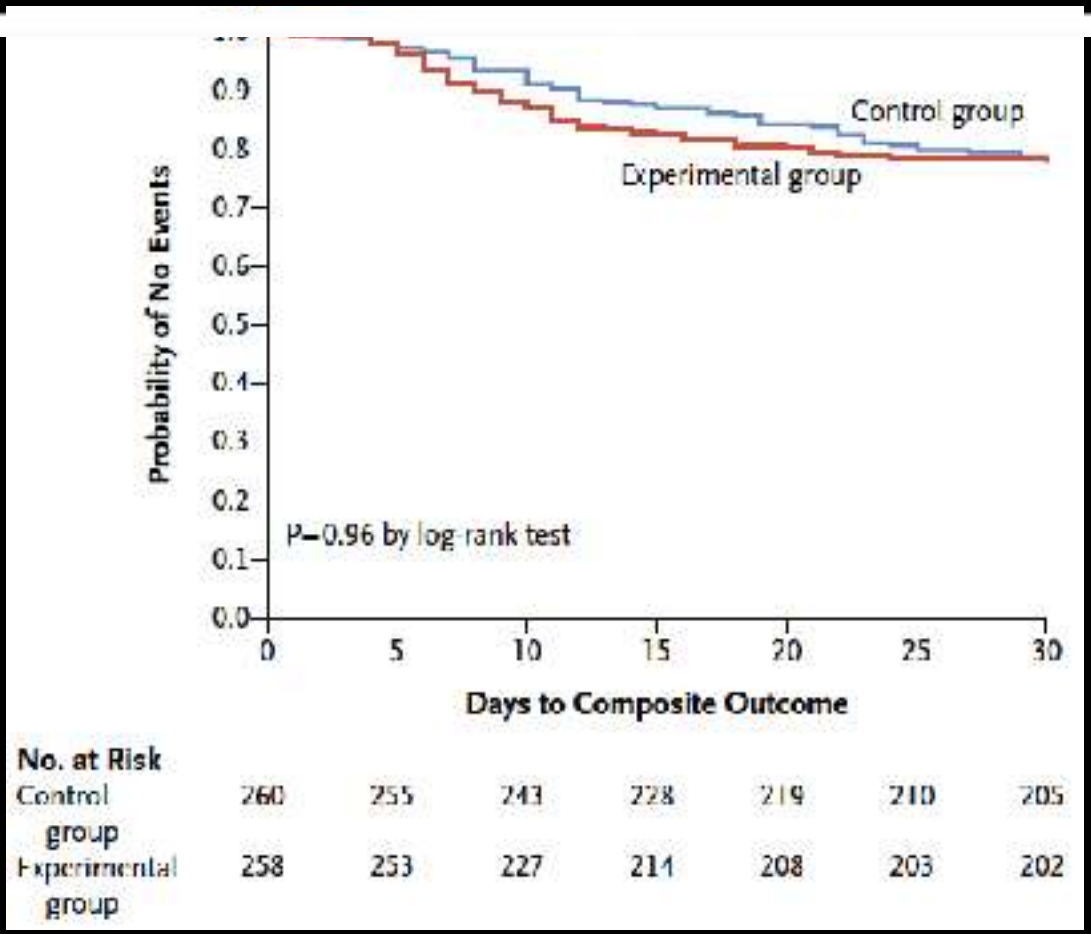


4 vs 8 days

N Engl J Med 2015;37 2:1996-2005.

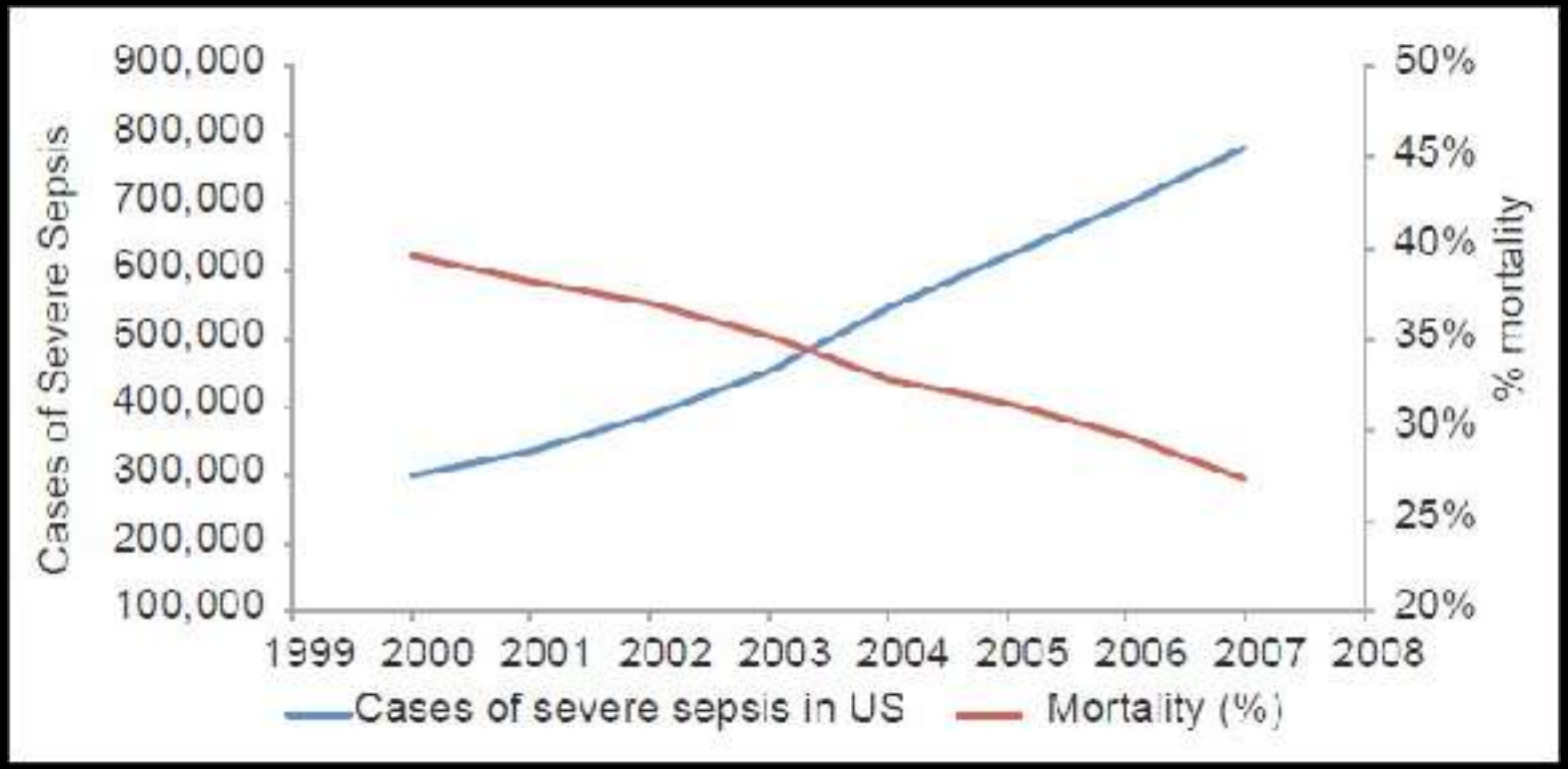
DISCUSSION POINTS ..

- Guidelines should be slavishly followed
- One size fits all
- Every hour of antibiotic delay kills
- How long should a course of antibiotics last?
- Sepsis mortality is improving
- Why do people die of sepsis?


PLANET HYPE

Nationwide Trends of Severe Sepsis in the 21st Century (2000-2007)

Cagan Kumar, MD; Nilay Kumar, MD, MPH; Amit Taneja, MD; Thomas Kaleekal, MD; Sergey Tarima, PhD; Emily McGinley, MPH; Edgar Jimenez, MD; Anand Mohan, MD; Rumi Ahmed Khan, MD; Jeff Whittle, MD; Elizabeth Jacobs, MD, FCCP; and Rahul Nanchal, MD, FCCP; from the Milwaukee Initiative in Critical Care Outcomes Research (MICCOR) Group of Investigators



CHEST 2011; 140(5):1223–1231

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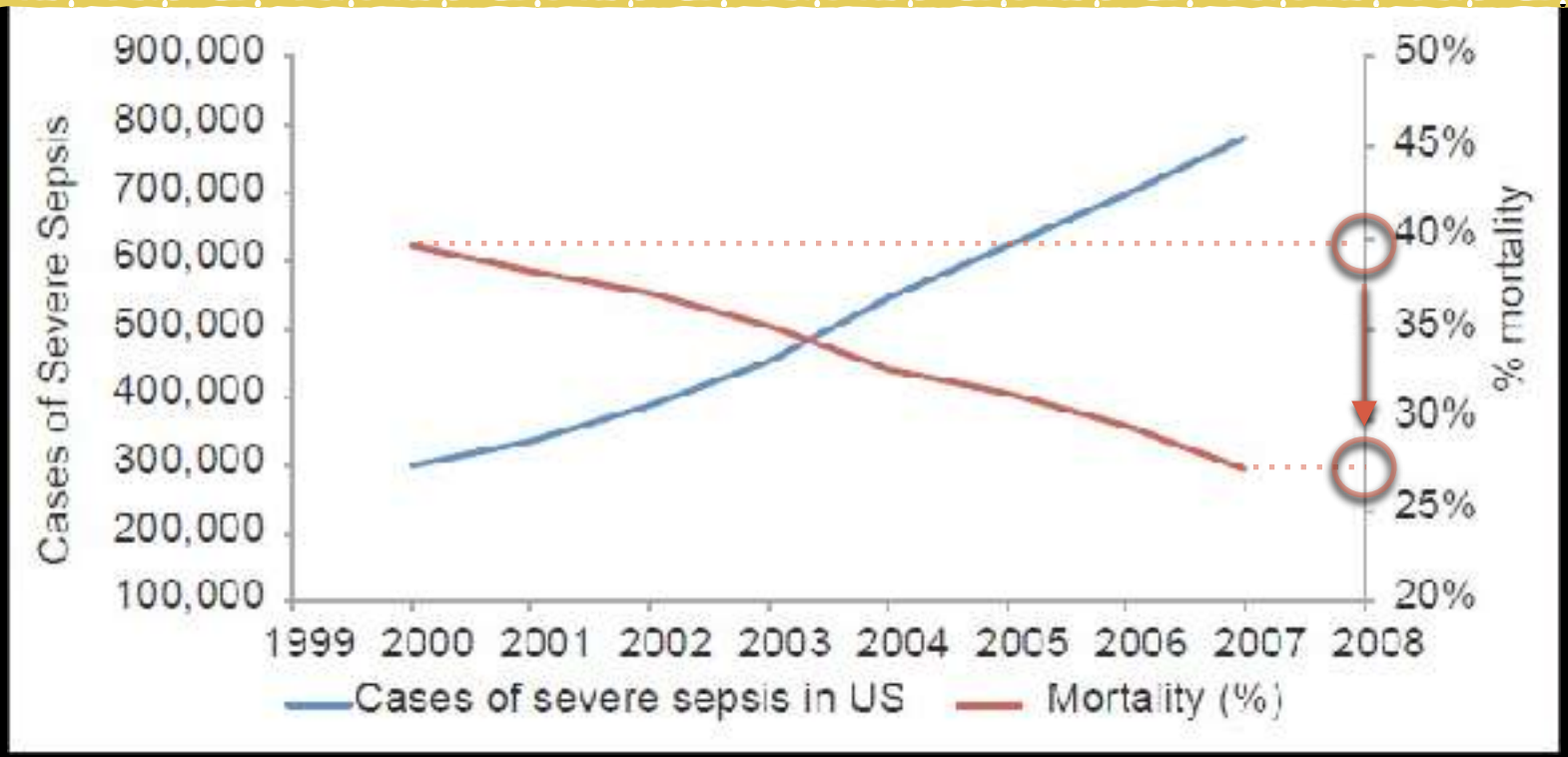
Conclusions: **An increasing number of admissions for severe sepsis combined with declining mortality rates contribute to more individuals surviving to hospital discharge.**



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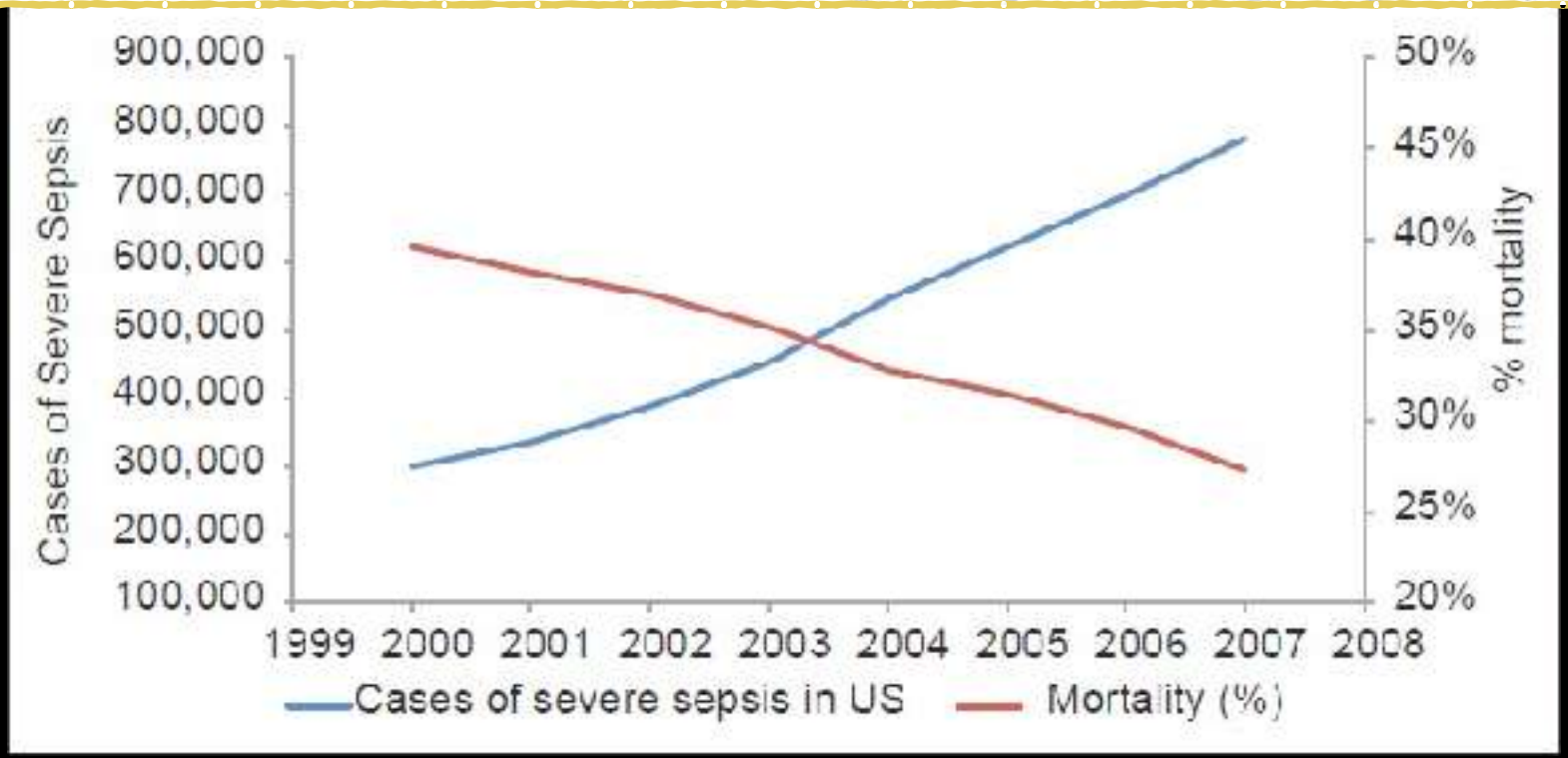

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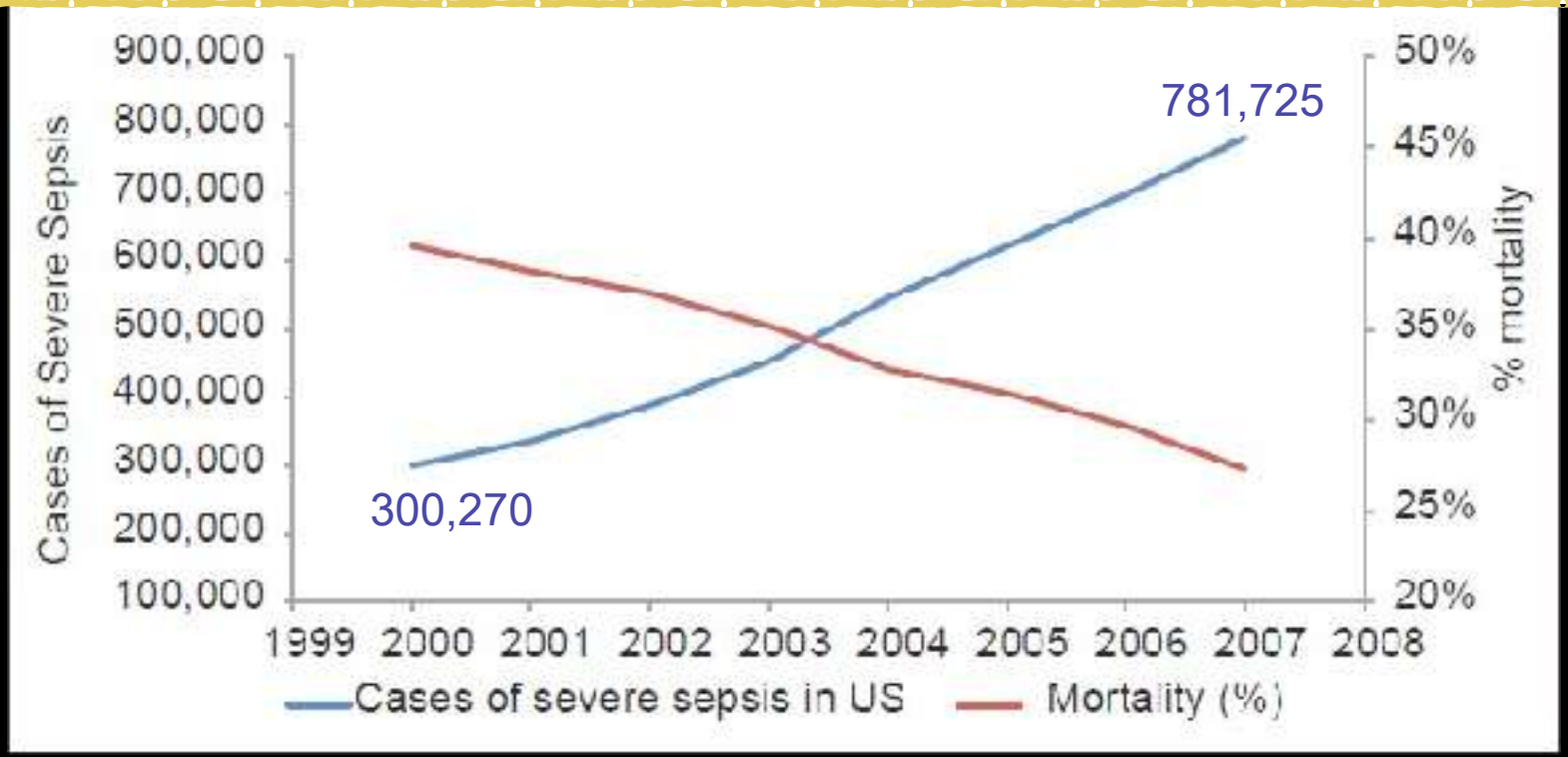

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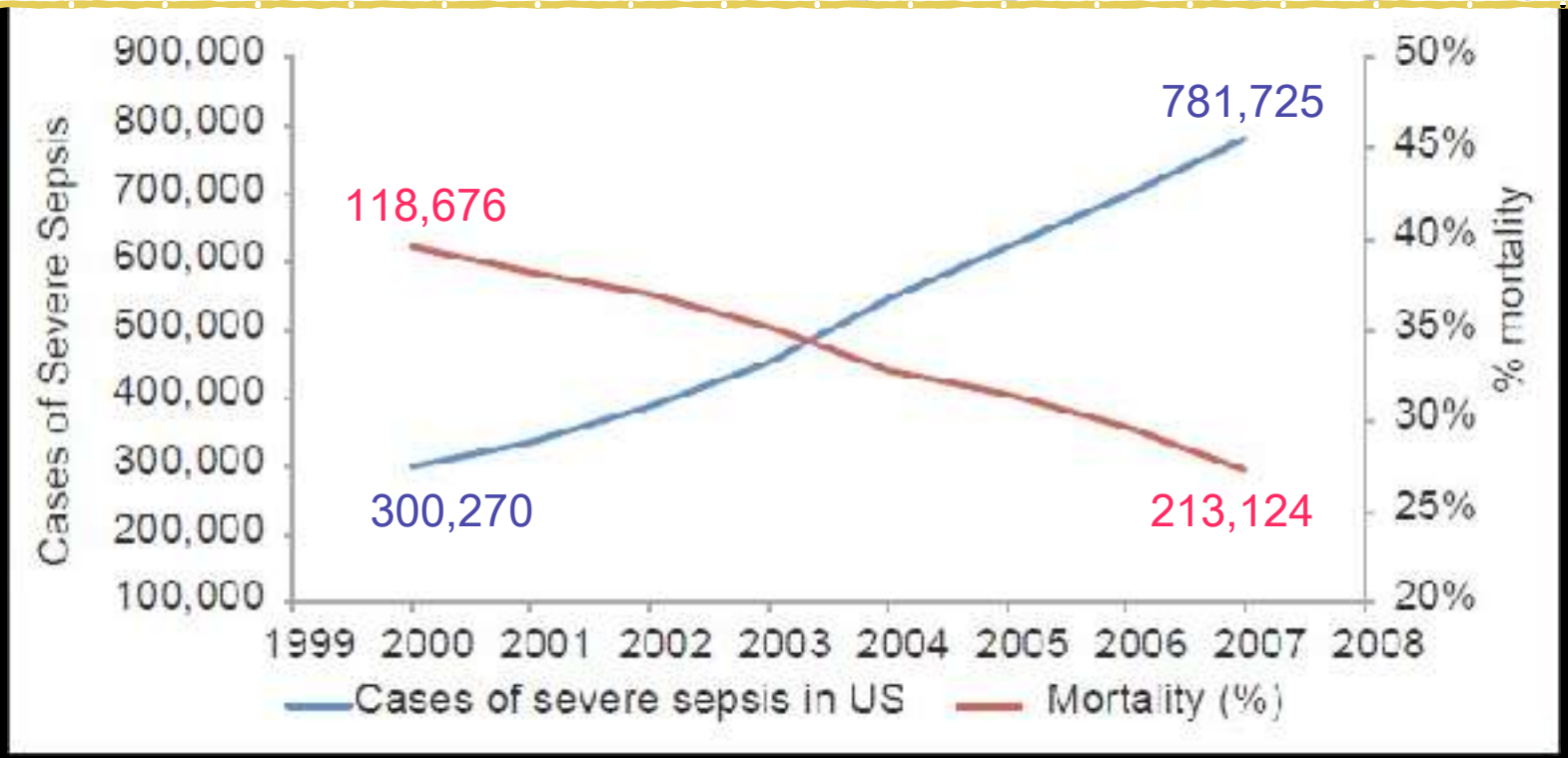

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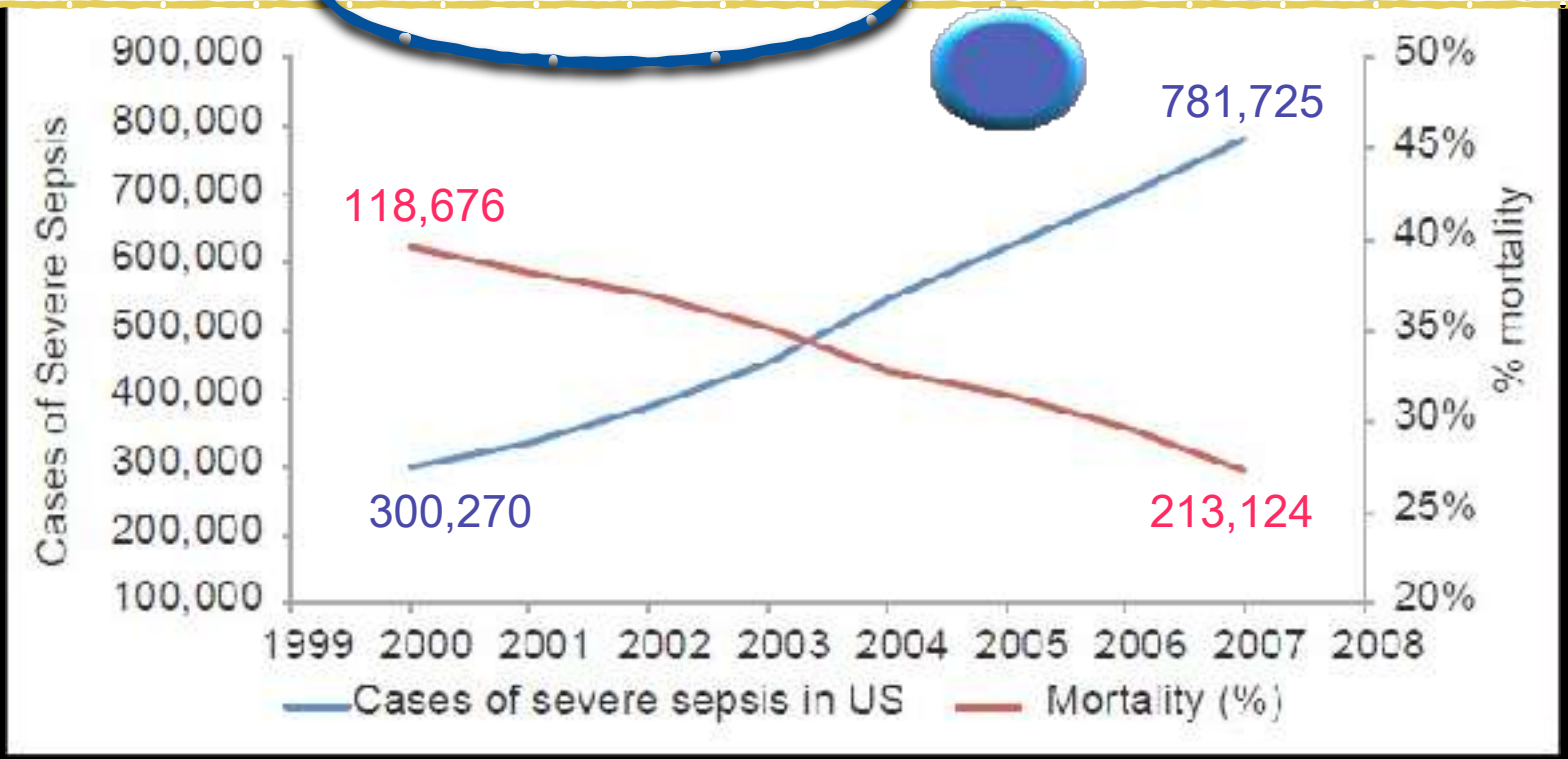

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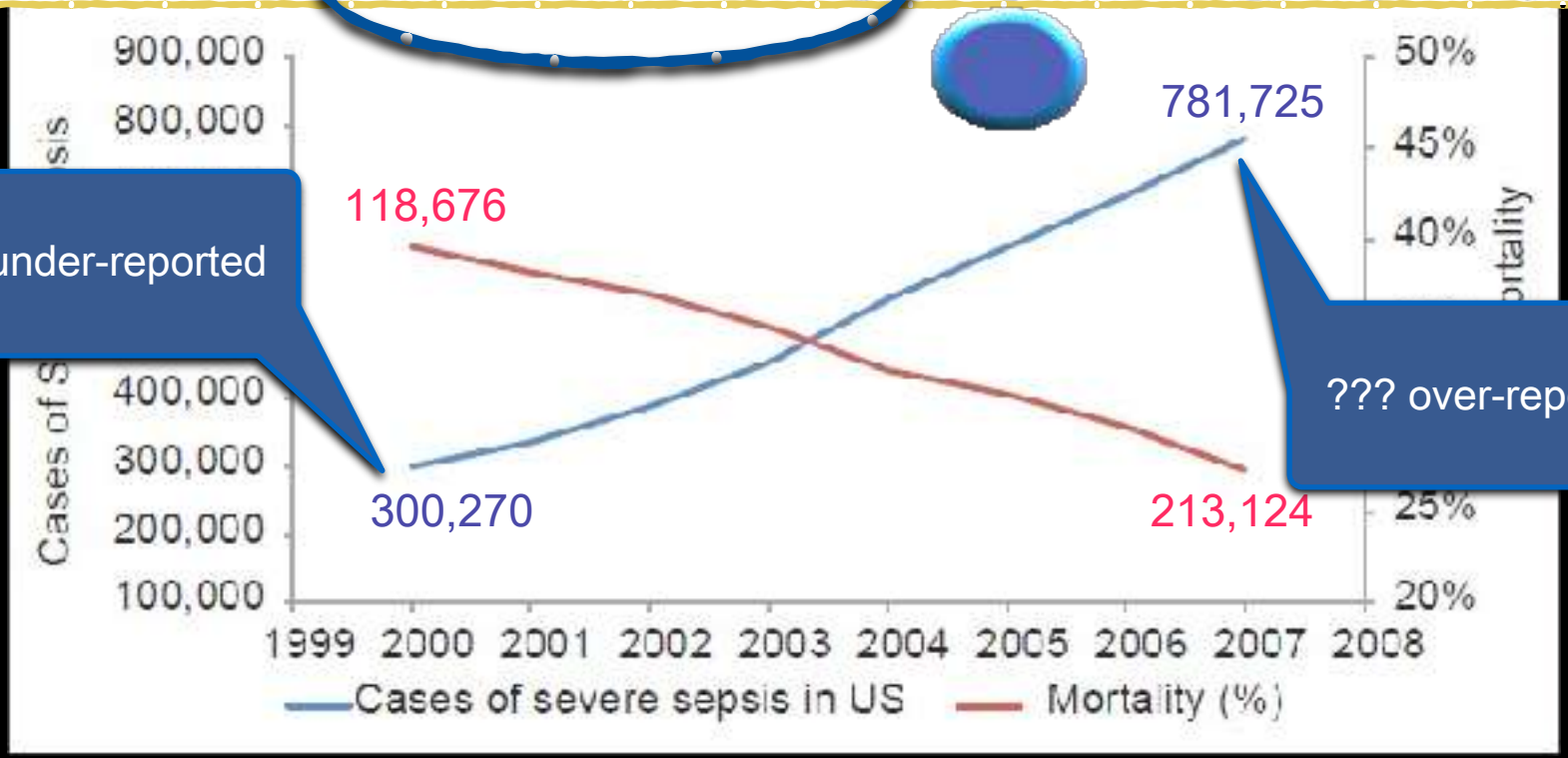

??? under-reported

??? over-reported

CHEST 2011; 140(5):1223–1231

Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009-2014

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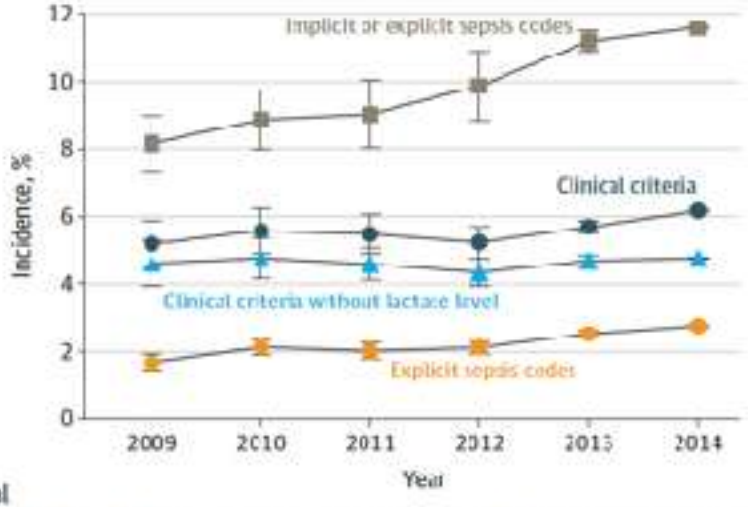
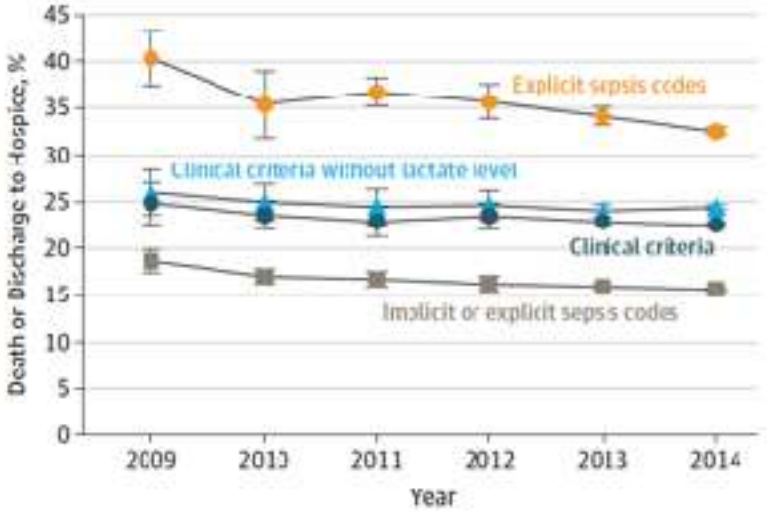
A Adjusted sepsis incidence



Annual total hospitalizations, No.	696807	737695	747236	780153	2485637	2354056

C Adjusted in-hospital sepsis mortality or discharge to hospice



JAMA. 2017;318(13):1241-1249.

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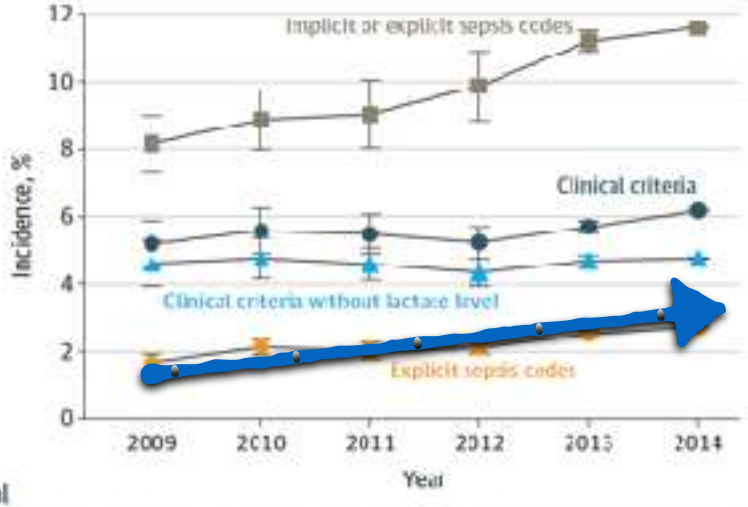

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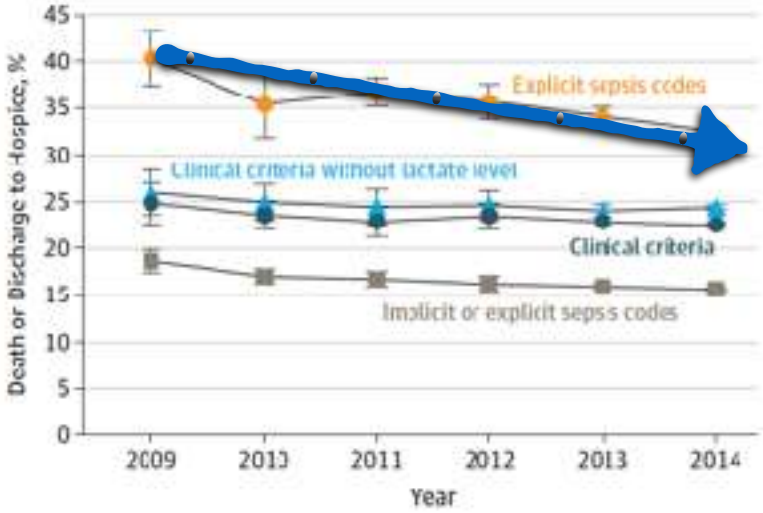

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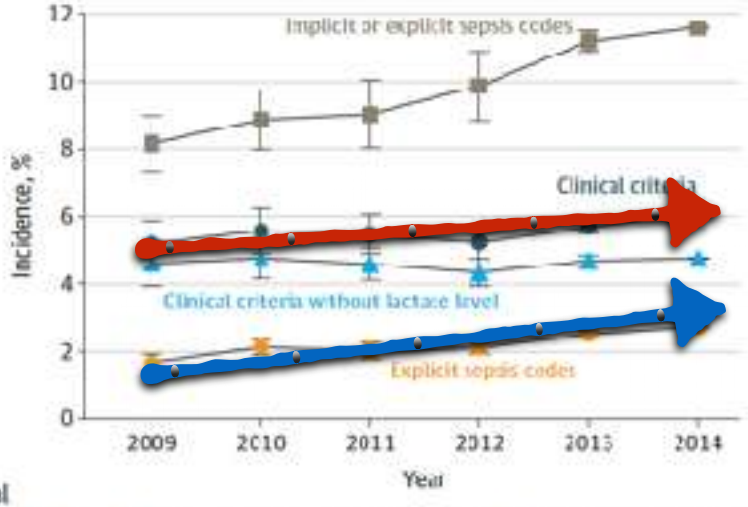

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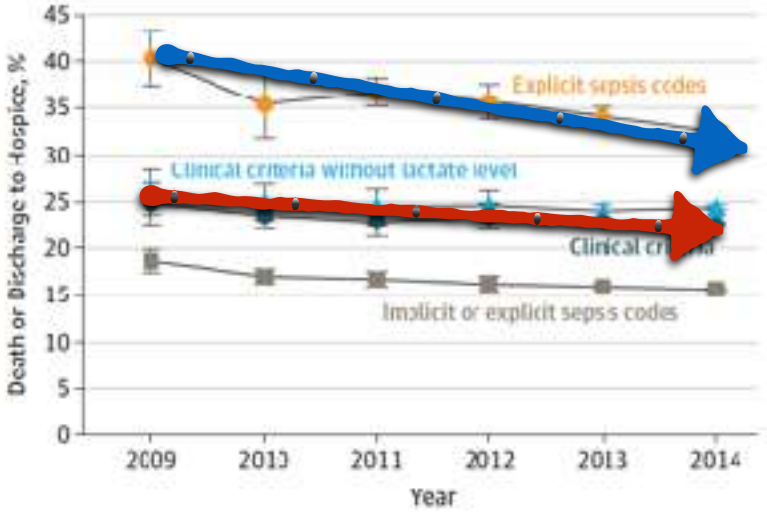

JAMA. 2017;318(13):1241-1249.

Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012

Kirsi-Maija Kaukonen, MD, PhD, EDIC; Michael Bailey, PhD; Satoshi Suzuki, MD; David Pilcher, FCICM; Rinaldo Bellomo, MD, PhD

A Mortality

Year of ICU Admission	No. of Events	
	Sepsis	No Sepsis
2000	949	4807
2001	1271	5855
2002	1455	6484
2003	1573	6996
2004	1841	7383
2005	1833	7825
2006	1961	7765
2007	2090	7844
2008	2106	7541
2009	2264	7943
2010	2386	8302
2011	2418	8535
2012	2300	8010

JAMA. 2014;311(13):1308-1316.

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patients with severe sepsis or septic shock and other patients in the database for the decline in mortality over time (odds ratio [OR], 0.94 [95% CI, 0.94-0.95] vs 0.94 [95% CI, 0.94-0.94]; $P = .37$).

DISCUSSION POINTS ..

- Guidelines should be slavishly followed
- One size fits all
- Every hour of antibiotic delay kills
- How long should a course of antibiotics last?
- Sepsis mortality is improving
- Why do people die of sepsis?

THE UK SEPSIS TRUST

INFO FOR PUBLIC ~ INFO FOR PROFESSIONALS ~

SEPSIS KILLS

44,000

PEOPLE EVERY YEAR IN THE UK

Click to tweet this now

EVERY

3.5

SECONDS SOMEONE DIES FROM SEPSIS

Click to tweet this now

SEPSIS IS THE

BIGGES

DIRECT CAUSE OF DEATH IN UK PREGNANCIES

Click to tweet this #sepsisfact no

Fact sou

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MAINTAINING A SENSE OF PROPORTION...

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  .. with 32,300 in-hospital deaths = 2.5% mortality rate

MAINTAINING A SENSE OF PROPORTION…

- 34 million antibiotic prescriptions by English GPs in 2015-6
- 1.3 million hospital patient episodes with a sepsis/infection code in England p.a.
- BUT … only 11,000 cases of sepsis had an ICU admission

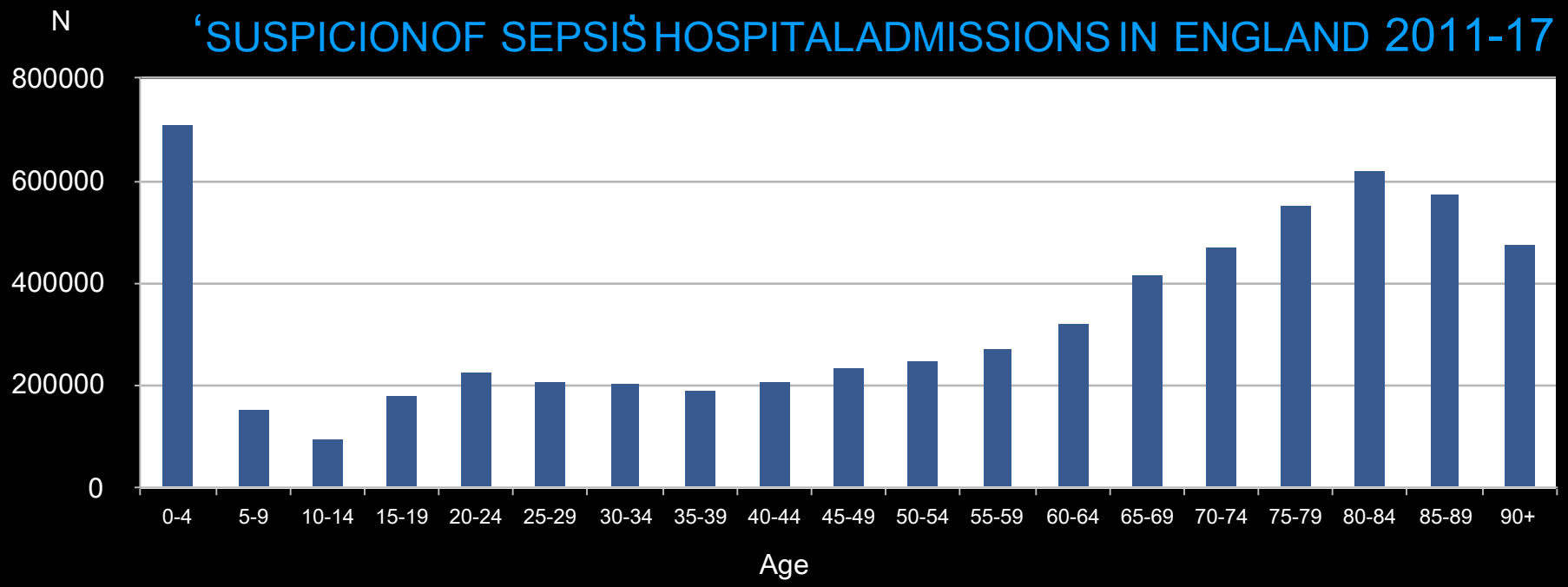

DO ALL SEPTIC PATIENTS WARRANT
LIFE-PROLONGING TREATMENT??

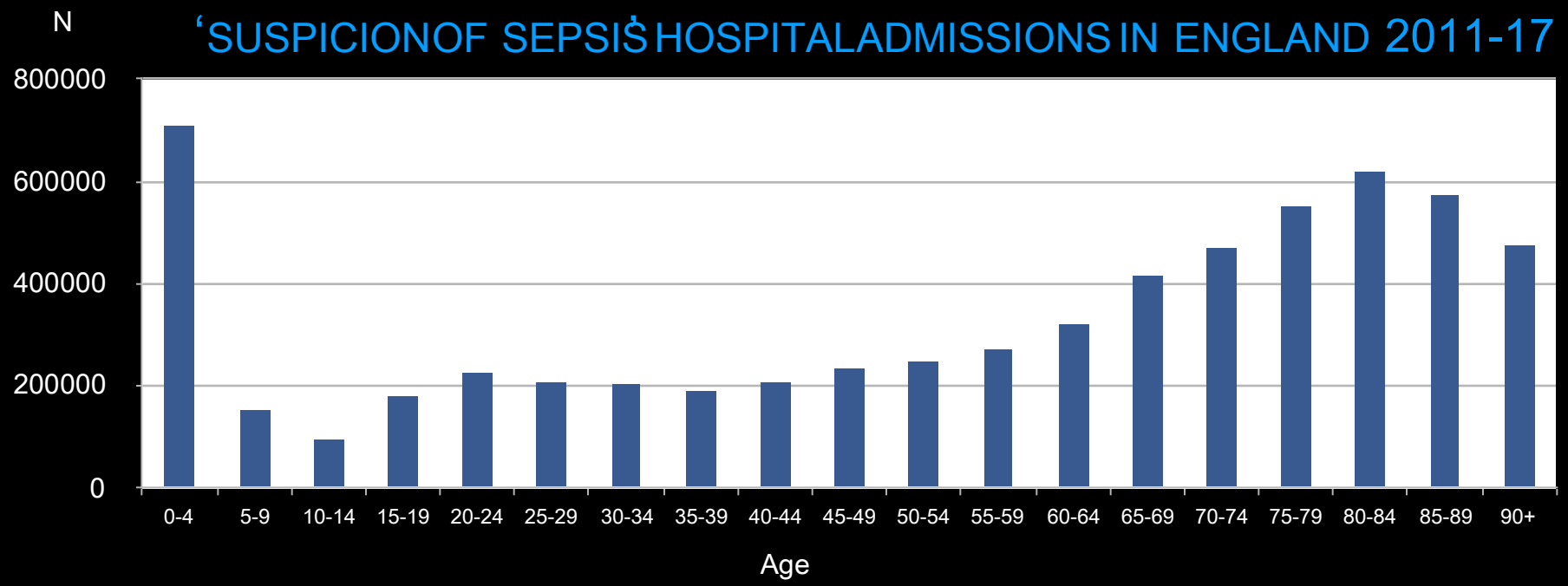
DO ALL SEPTIC PATIENTS WARRANT LIFE-PROLONGING TREATMENT???

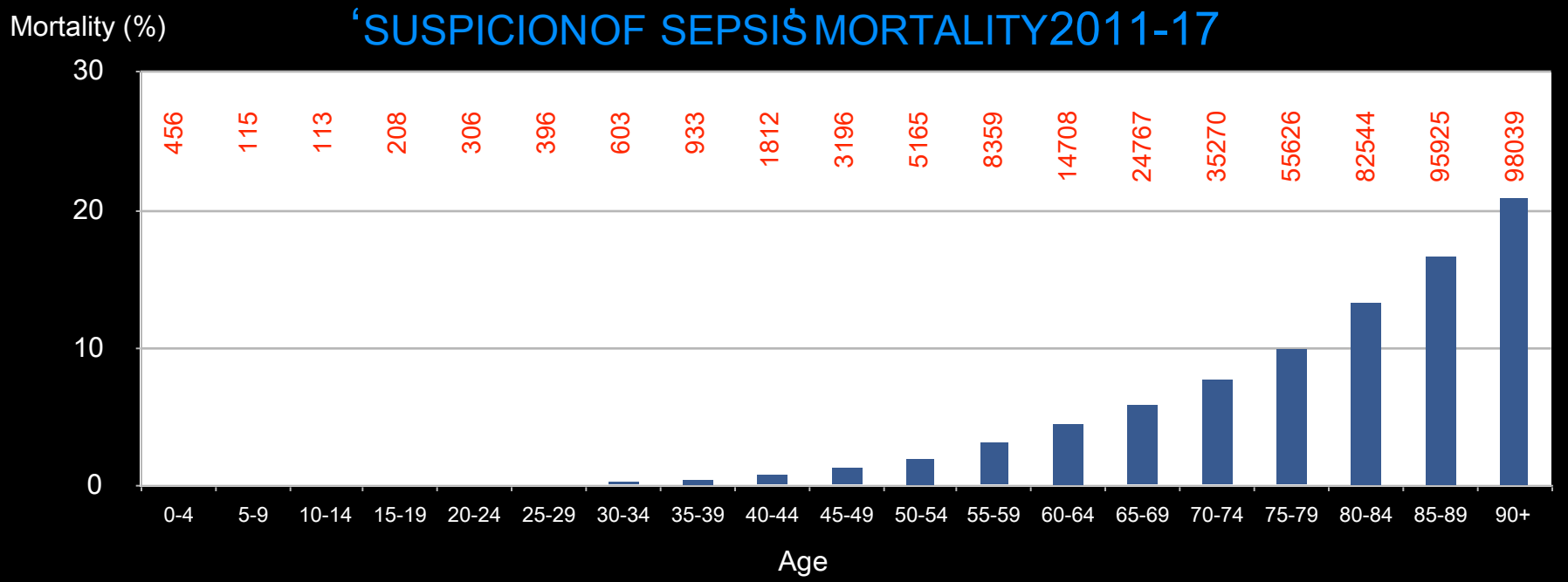
"Pneumonia is the old man's friend" - Sir William Osler

Patients may be allowed to die from sepsis due to the severity of their underlying comorbidity - terminal cancer, severe stroke, end-stage chronic organ failure, severe dementia …

‘SUSPICION OF SEPSIS’ HOSPITAL ADMISSIONS IN ENGLAND 2011-17




N
'SUSPICIONOF SEPSIS' HOSPITALADMISSIONS IN ENGLAND 2011-17
800000
600000
400000
200000
0
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
90+
Age


Mortality (%)
'SUSPICIONOF SEPSIS' MORTALITY2011-17
30
20
10
0
456
115
113
208
306
396
603
933
1812
3196
5165
8359
14708
24767
35270
55626
82544
95925
98039
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
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60-64
65-69
70-74
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90+
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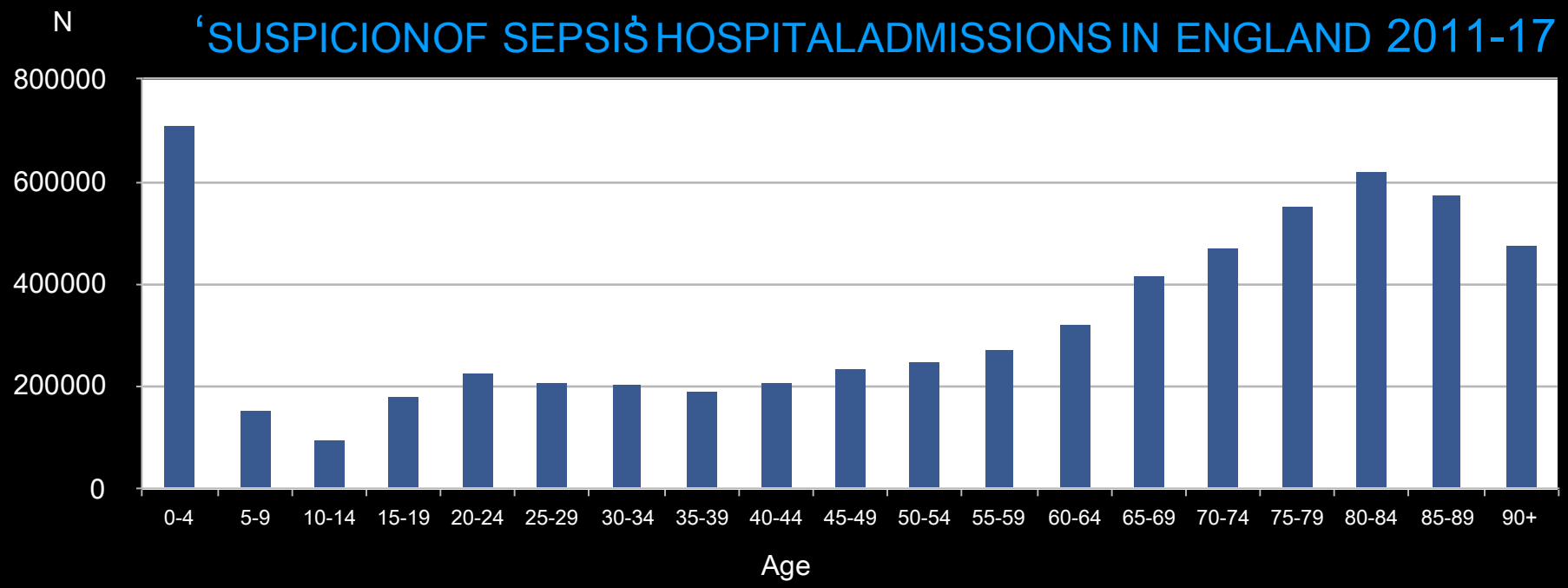
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15-19
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35-39
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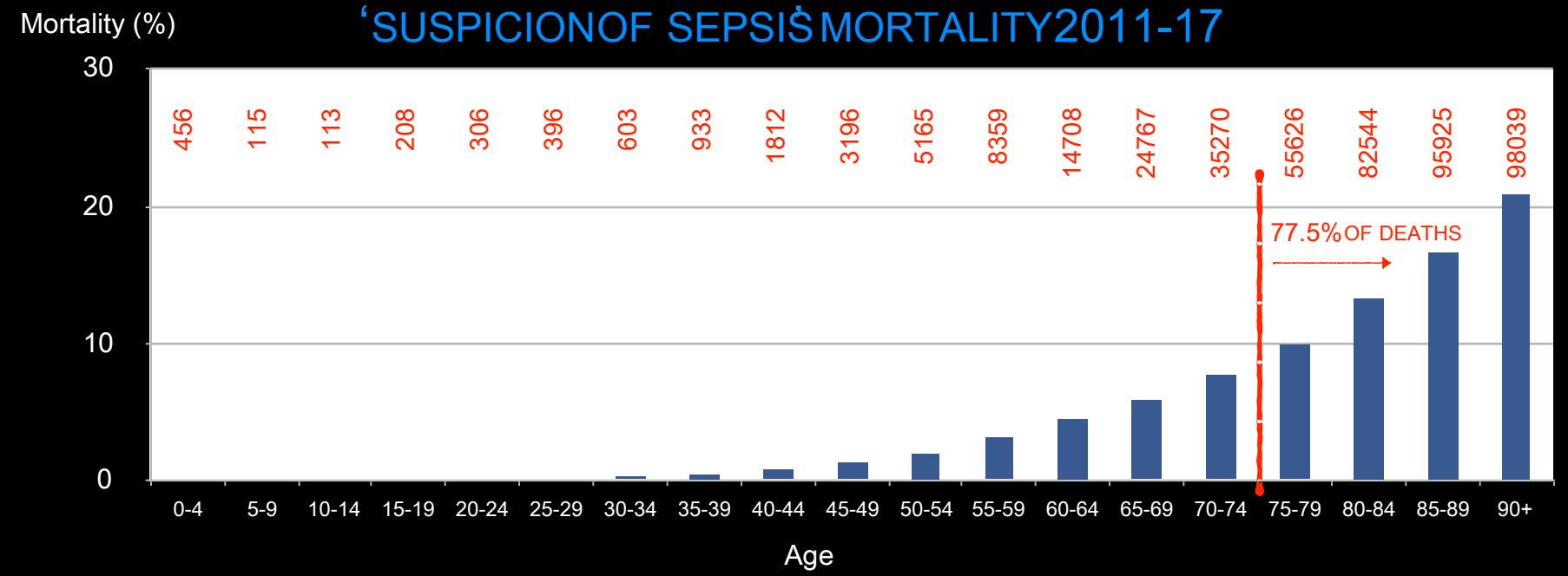
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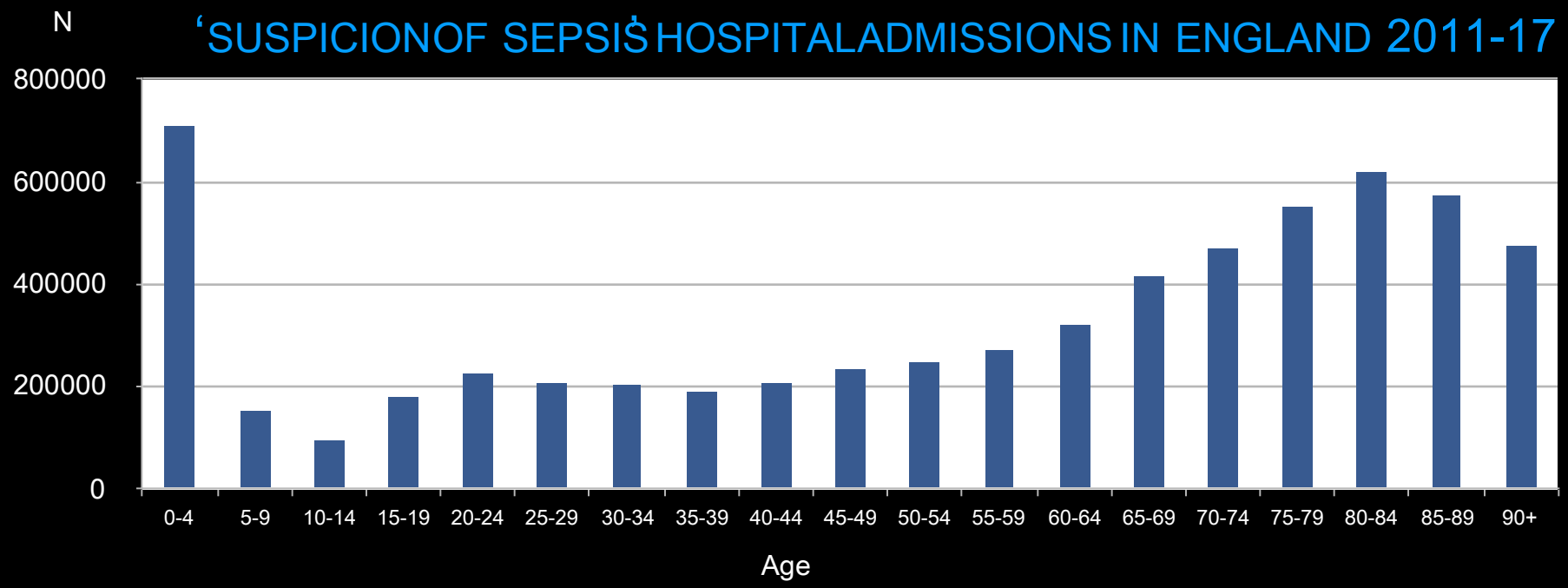
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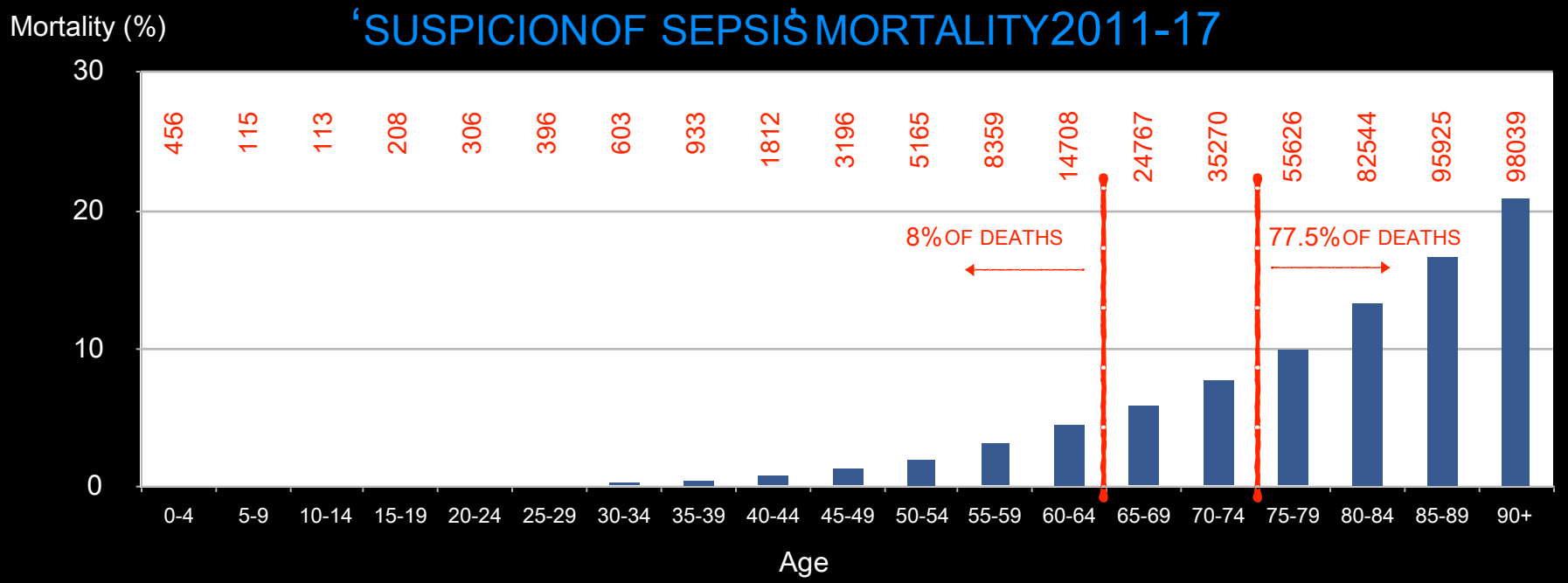
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5165
8359
14708
24767
35270
55626
82544
95925
98039
8% OF DEATHS
77.5% OF DEATHS
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
90+
Age

Mandated Emergency Care for Sepsis

Christopher W. Seymour, M.D., Foster Gesten, M.D., Hallie C. Prescott, M.D., Marcus E. Friedrich, M.D., Theodore J. Iwashyna, M.D., Ph.D., Gary S. Phillips, M.A.S., Stanley Lemeshow, Ph.D., Tiffany Osborn, M.D., M.P.H., Kathleen M. Terry, Ph.D., and Mitchell M. Levy, M.D.

Race — no. (%)†	
White	33,075 (67.0)
Black	8,269 (16.8)
Asian	2,167 (4.4)
Other	5,820 (11.8)
Hispanic ethnic group — no. (%)†	4,851 (9.8)
Coexisting condition — no. (%)	
Chronic respiratory failure	5,738 (11.6)
Congestive heart failure	10,092 (20.5)
End-stage renal disease	5,207 (10.6)
Admission source — no. (%)	
Home	33,464 (67.8)
Skilled nursing facility	13,233 (26.8)
Other‡	2,634 (5.3)
Chronic respiratory failure	5,738 (11.6)
Congestive heart failure	10,092 (20.5)
End-stage renal disease	5,207 (10.6)

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Black	8,269 (16.8)
Asian	2,167 (4.4)
Other	5,820 (11.8)
Hispanic ethnic group — no. (%)†	4,85[illegible] (9.[illegible])
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Dementia?

Stroke?

Other severe disability?

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- Sepsis only constitutes a small proportion of infection … but should be identified and acted upon promptly .. but with some thought applied

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