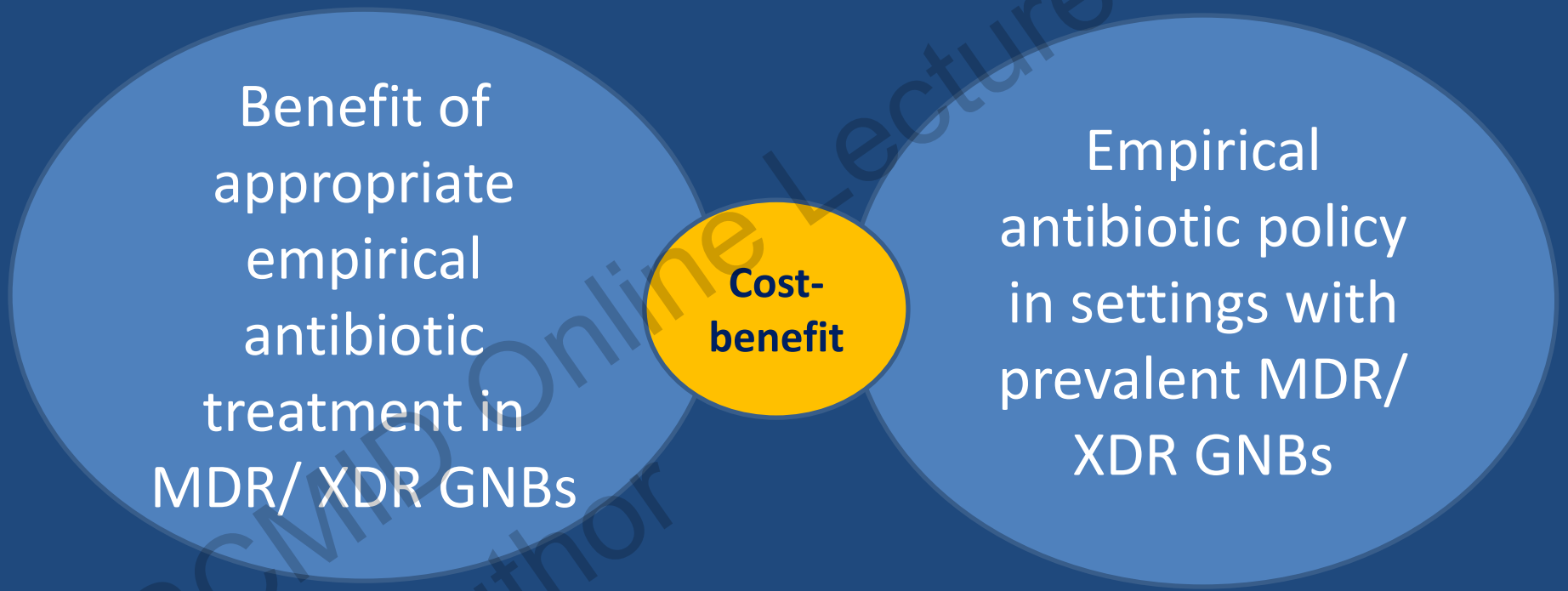
Empirical therapy for MDR and XDR Gram-negatives

Case-based decisions in the era of XDR Gram-negatives: towards individualised therapy?

Mical Paul
Infectious Diseases
Rambam Health Care Campus

Topics



Benefit of appropriate empirical antibiotic treatment in MDR/XDR GNB

- Special patient population: survival more strongly affected by underlying conditions
- Fitness cost of resistance in GNB?
- Methodological: patients with MDR/XDR GNB are sicker on average than patients with susceptible bacteria and appropriate empirical treatment is more difficult to achieve

Overall benefit of antibiotic treatment

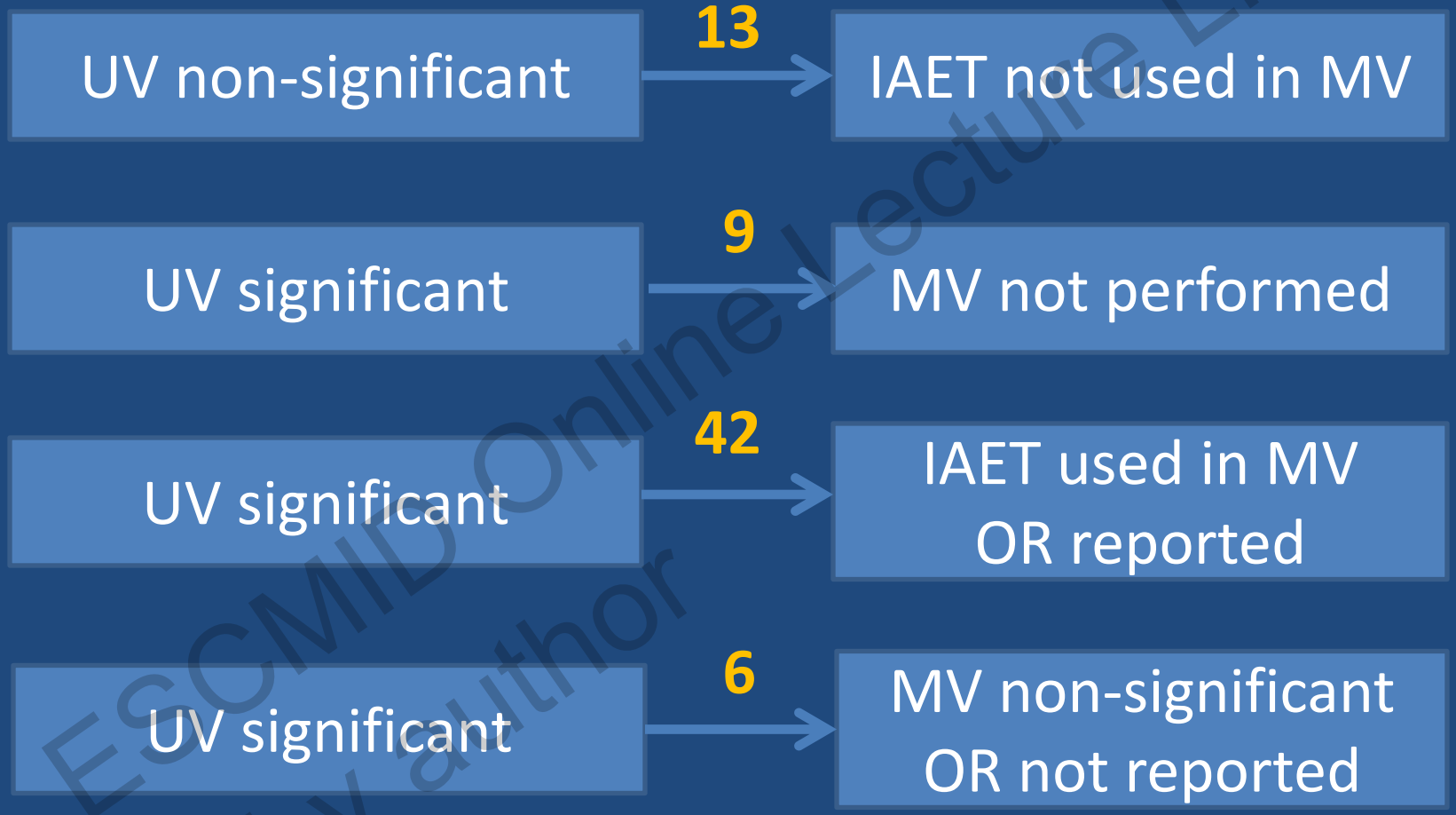
- Systematic review and meta-analysis
- Prospective observational studies published between 1975-2008 assessing at least 50 patients
  - Including adults with sepsis, by definition microbiologically documented
  - Assessing the association between inappropriate empirical antibiotic treatment (IEAT), defined at least by in-vitro coverage, and mortality
- Primary outcome: all cause mortality; preferably at a fixed point in time; preferably at 30 days

Paul et al. Antimicrob Agents Chemother 2010; 54(11): 4851-63

IAET and mortality: unadjusted

Analysis	N studies	OR (95% CI)	P for difference	Heterogeneity I-square
All studies	69	2.1 (1.83-2.41)		69%
Setting			0.71	
Hospital	40	2.06 (1.74-2.43)		72%
ICU	26	2.18 (1.7-2.79)		62%
Place of acquisition			0.15	
Community	7	3.66 (1.97-6.79)		64%
Hospital	22	2.26 (1.77-2.88)		56%
Year study start			0.65	
<1990	15	2.01 (1.52-2.66)		82%
1990-1999	31	2.04 (1.66-2.5)		57%
2000-2006	17	2.4 (1.75-3.28)		70%

IAET and mortality: adjusted



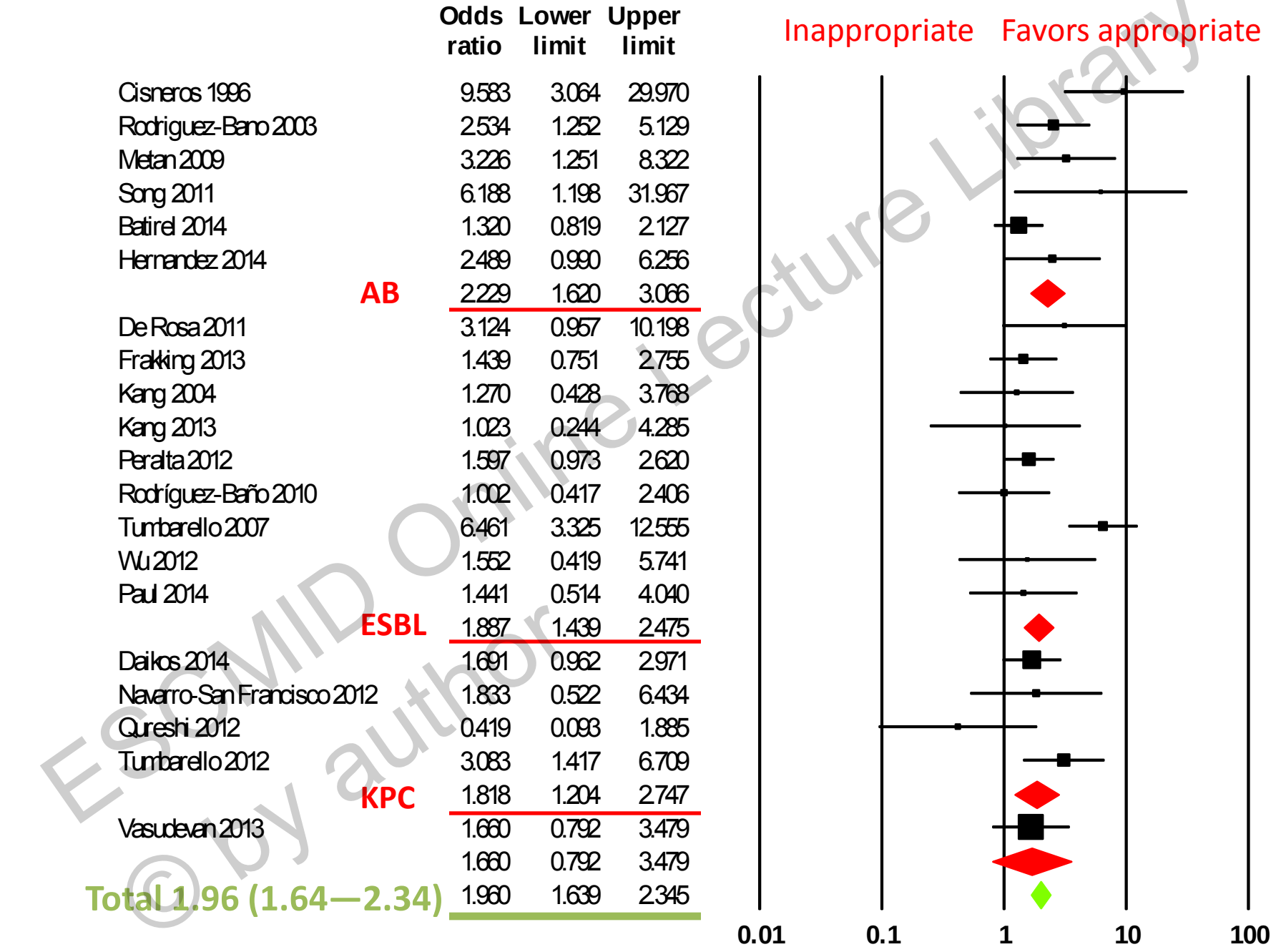
48/70 studies included in MV meta-analysis

IAET and mortality: adjusted

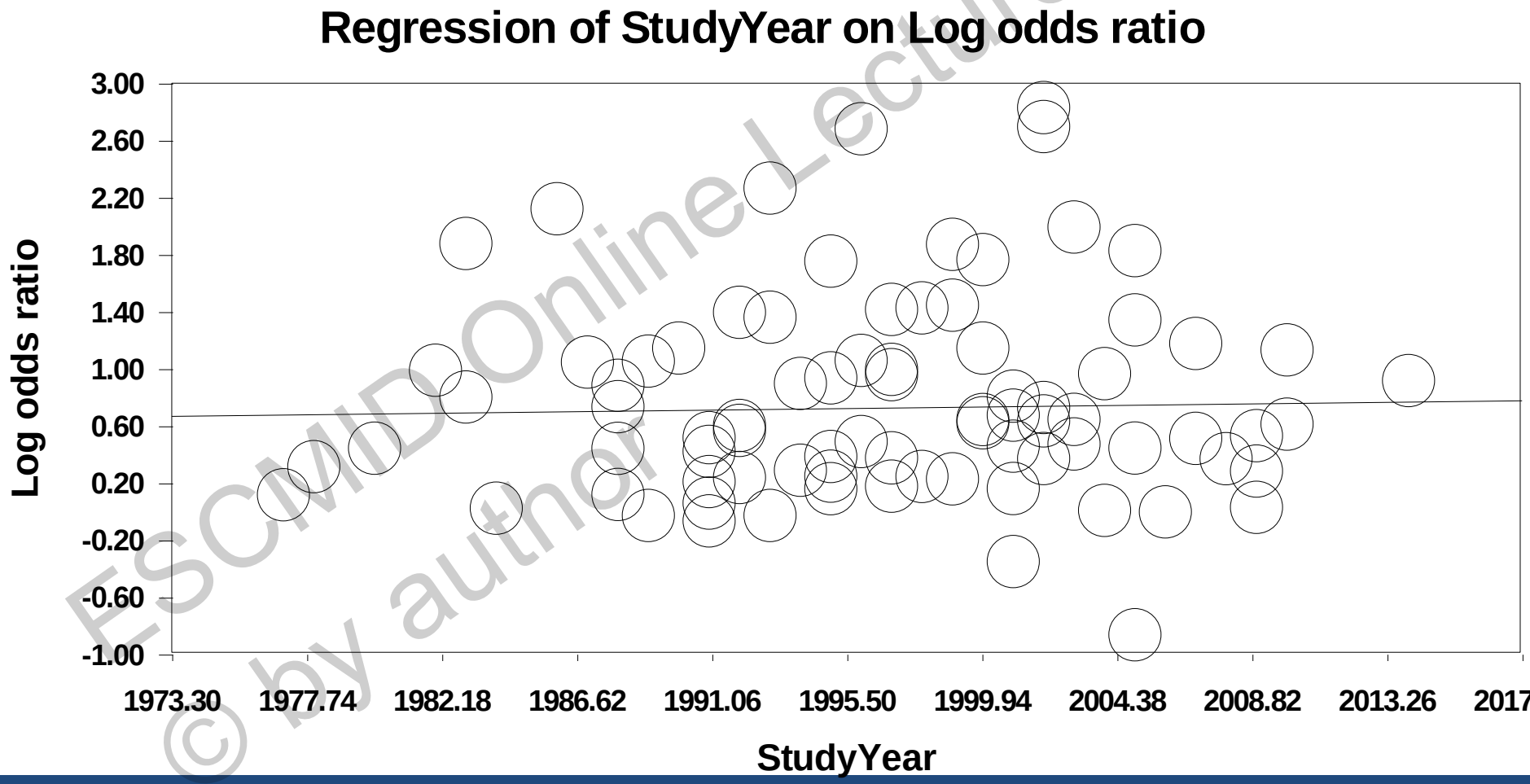
Analysis	N studies	OR (95% CI)	P for difference	I-square
All studies	48	2.06 (1.69-2.49)		80%
Studies with adequate adjustment	**26**	**1.60 (1.37-1.86)**		**46%**
Setting			0.23	
Hospital	30	1.78 (1.52-2.09)		57%
ICU	18	2.4 (1.51-3.81)		86%
Place of acquisition			0.67	
Community	4	2.38 (1.67-3.41)		7%
Hospital	17	2.18 (1.59-3.0)		70%
Year study start			0.15	
<1990	7	1.66 (1.33-2.07)		54%
1990-1999	26	1.97 (1.42-2.72)		80%
2000-2006	14	2.64 (1.74-4.0)		84%

Update: MDR Gram-negatives

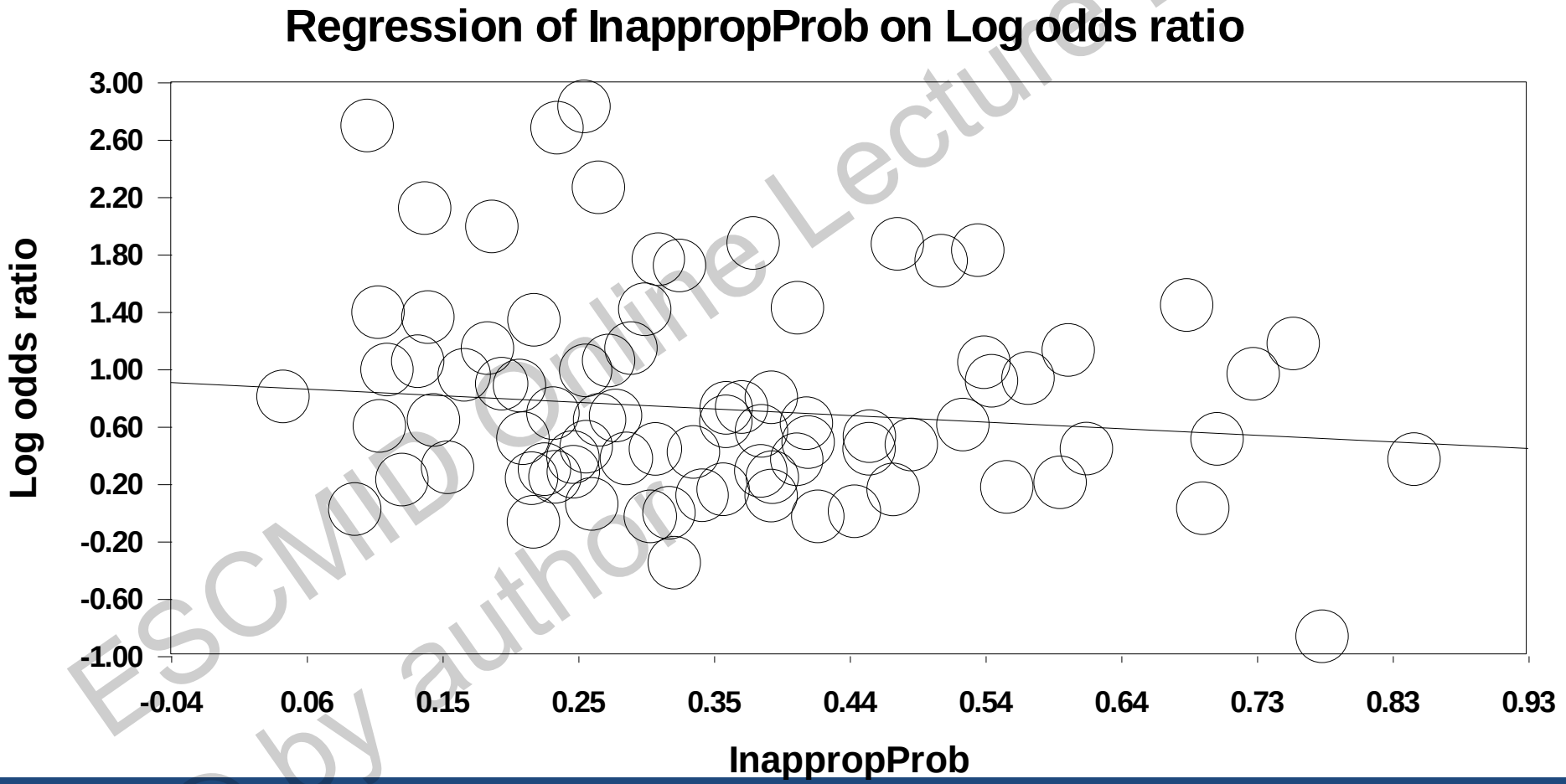
- Search string: *(appropriate OR inappropriate OR adequate OR inadequate) AND empirical OR empiric) AND antibiotic AND (mdro OR mdr OR multidrug resistant OR carbapenem-resistant OR esbl)*
- Prospective or retrospective studies, with no minimum sample size limit
- Published until 30 April 2014
- All cause mortality



Unadjusted ORs for IEAT and all-cause mortality: by year

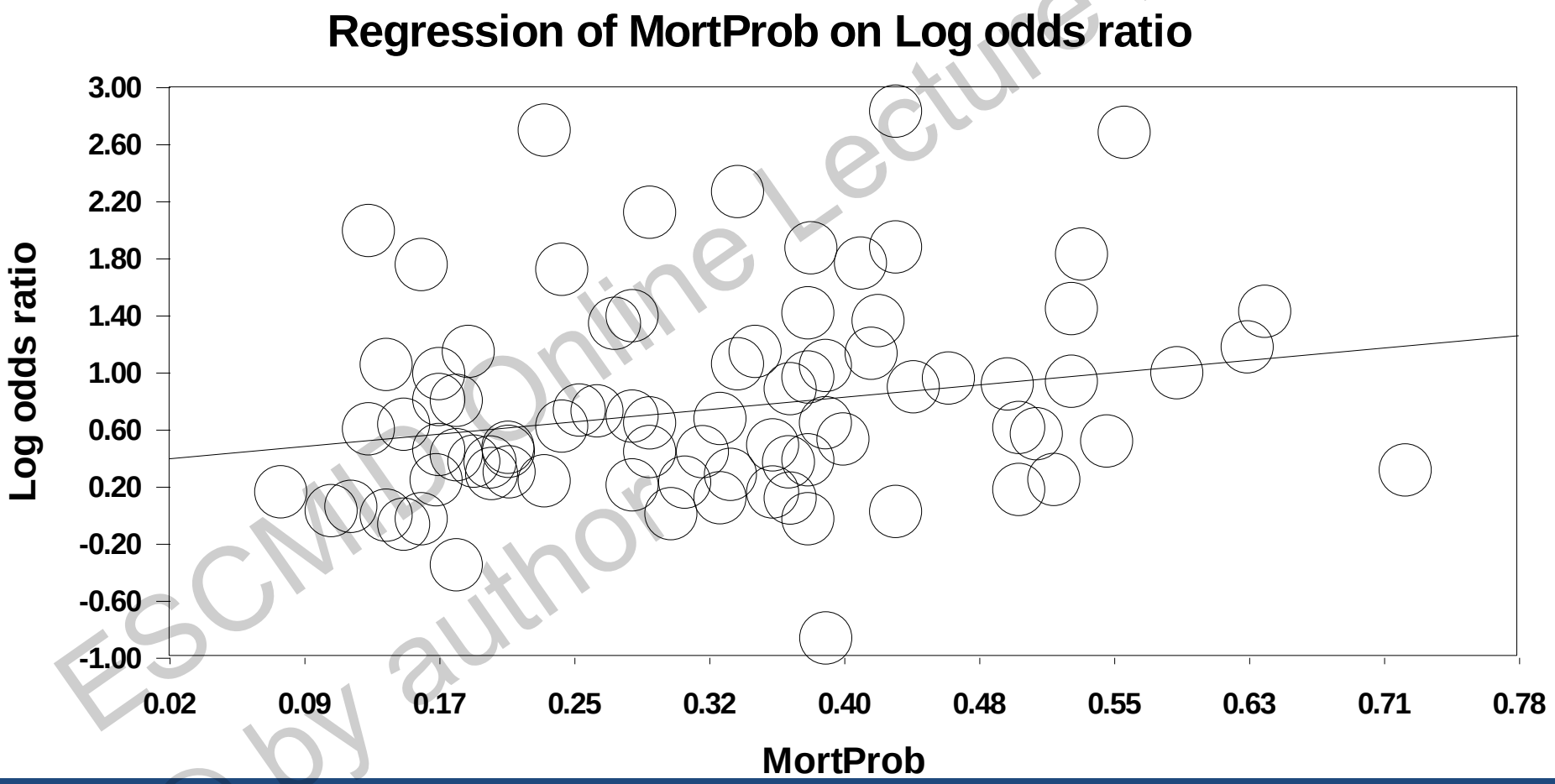


Un adjusted ORs for IEAT and all-cause mortality: by IEAT rate



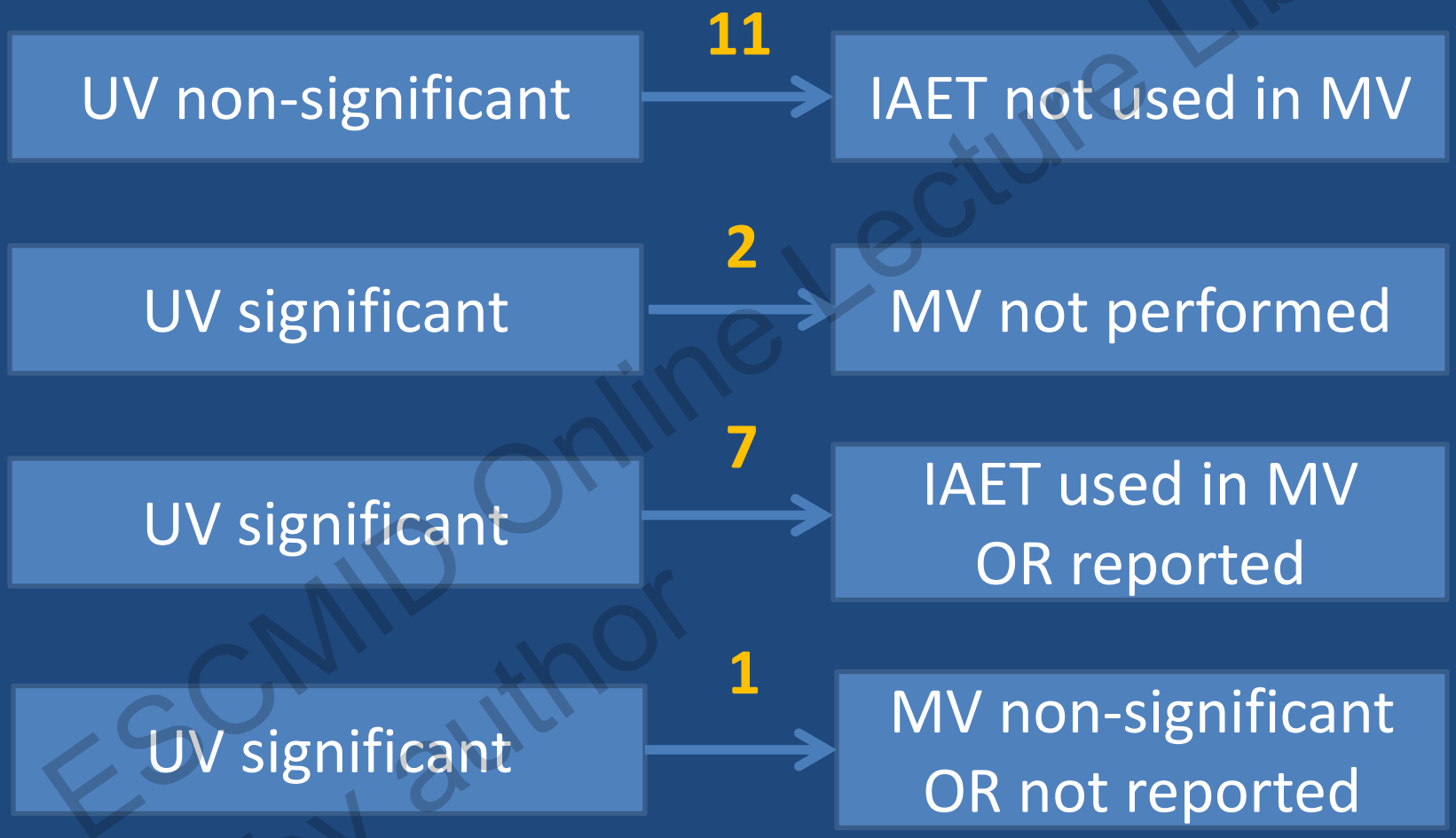
P for meta-regression slope = 0.21

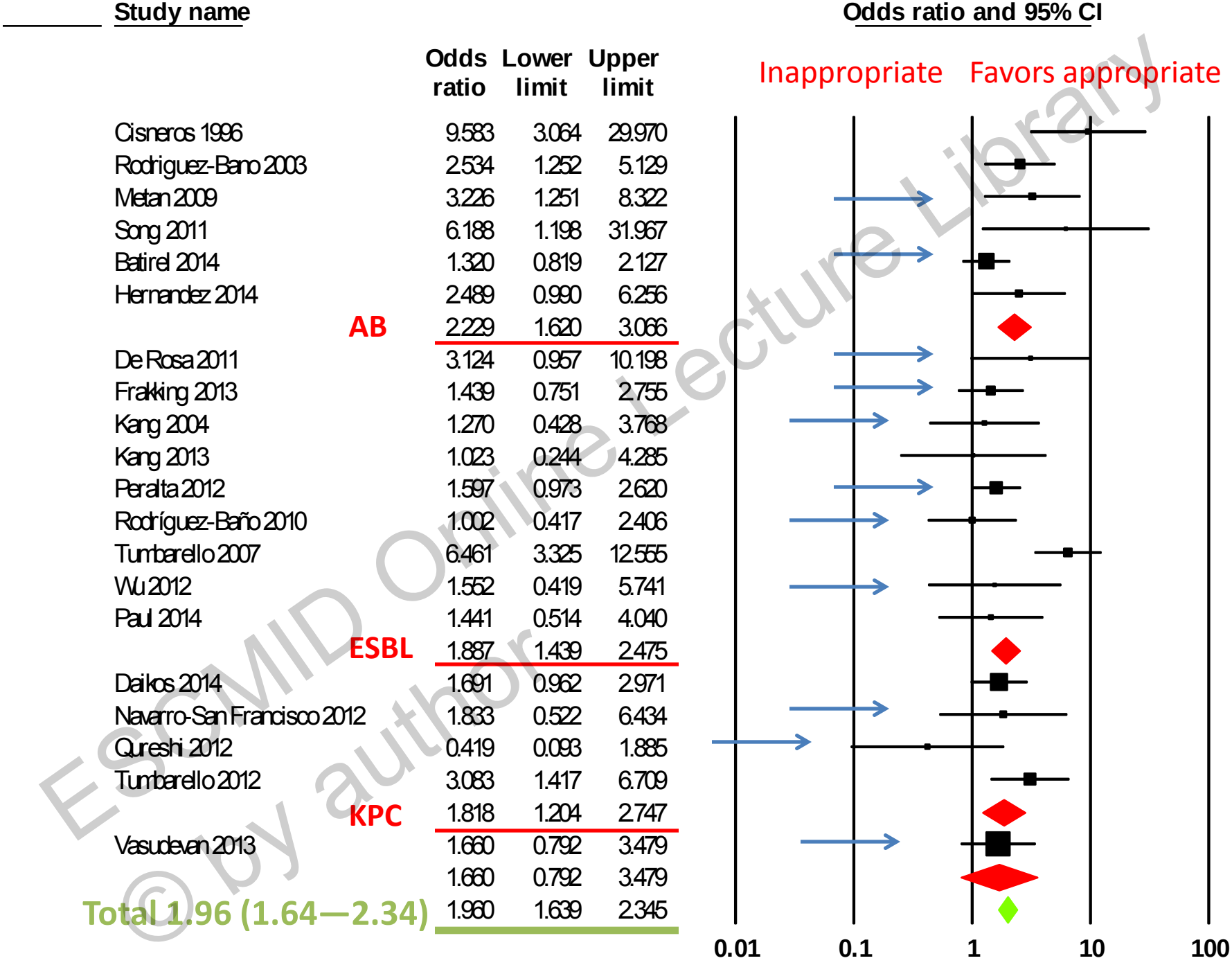
Un adjusted ORs for IEAT and all-cause mortality: by mortality



P for meta-regression slope = 0.02

IAET and mortality: adjusted MDR





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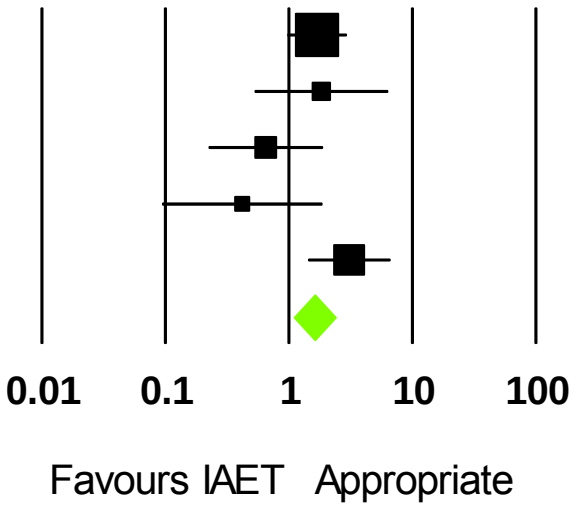
Focus on CRE/KPC

Univariate analysis. I^2=53%

Study name	Odds ratio	Lower limit	Upper limit
Daikos 2014	1.691	0.962	2.971
Navarro-San Francisco 2012	1.833	0.522	6.434
Paul 2014	0.650	0.221	1.908
Qureshi 2012	0.419	0.093	1.885
Tumbarello 2012	3.083	1.417	6.709
	1.594	1.085	2.343



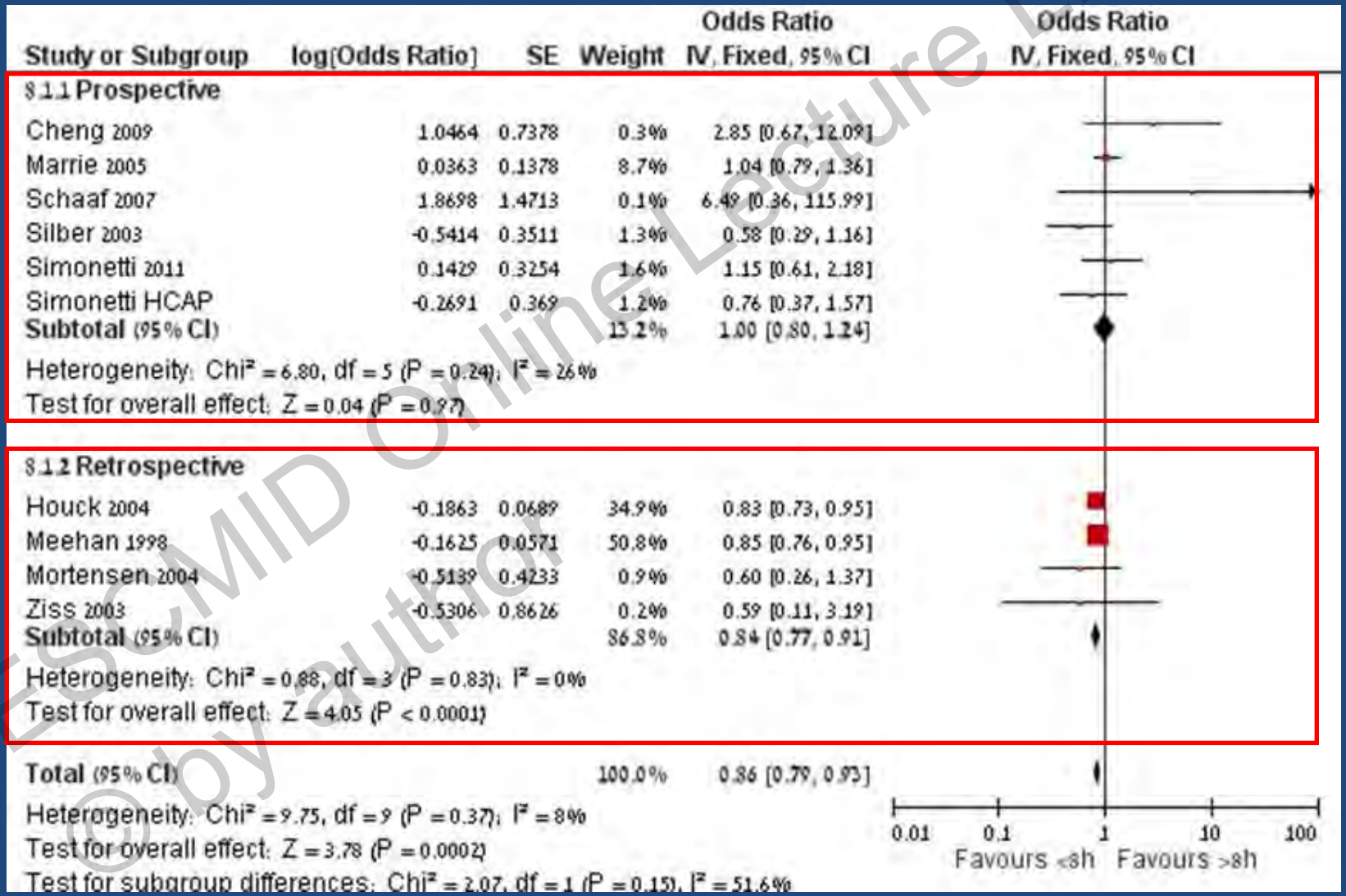
Benefit of appropriate empirical antibiotic treatment in MDR/XDR

- Benefit in MDR/ XDR assumed similar to that known overall
- Known benefit is limited to severe infections, i.e. bacteremia (all but 2 studies)
- A conservative overall estimate is an adjusted odds ratio of 1.60 (1.37-1.86) for IAET and all-cause mortality

Empirical antibiotic policy in settings with prevalent MDR/ XDR GNBs

- Appropriate empirical antibiotic treatment carries benefit in severe infections caused by MDR/XDR
- Attempting to cover XDR/ MDR empirically entails treatment of many patients with broad-spectrum/ last resort antibiotics

CAP: treatment within 8hr and mortality adjusted ORs



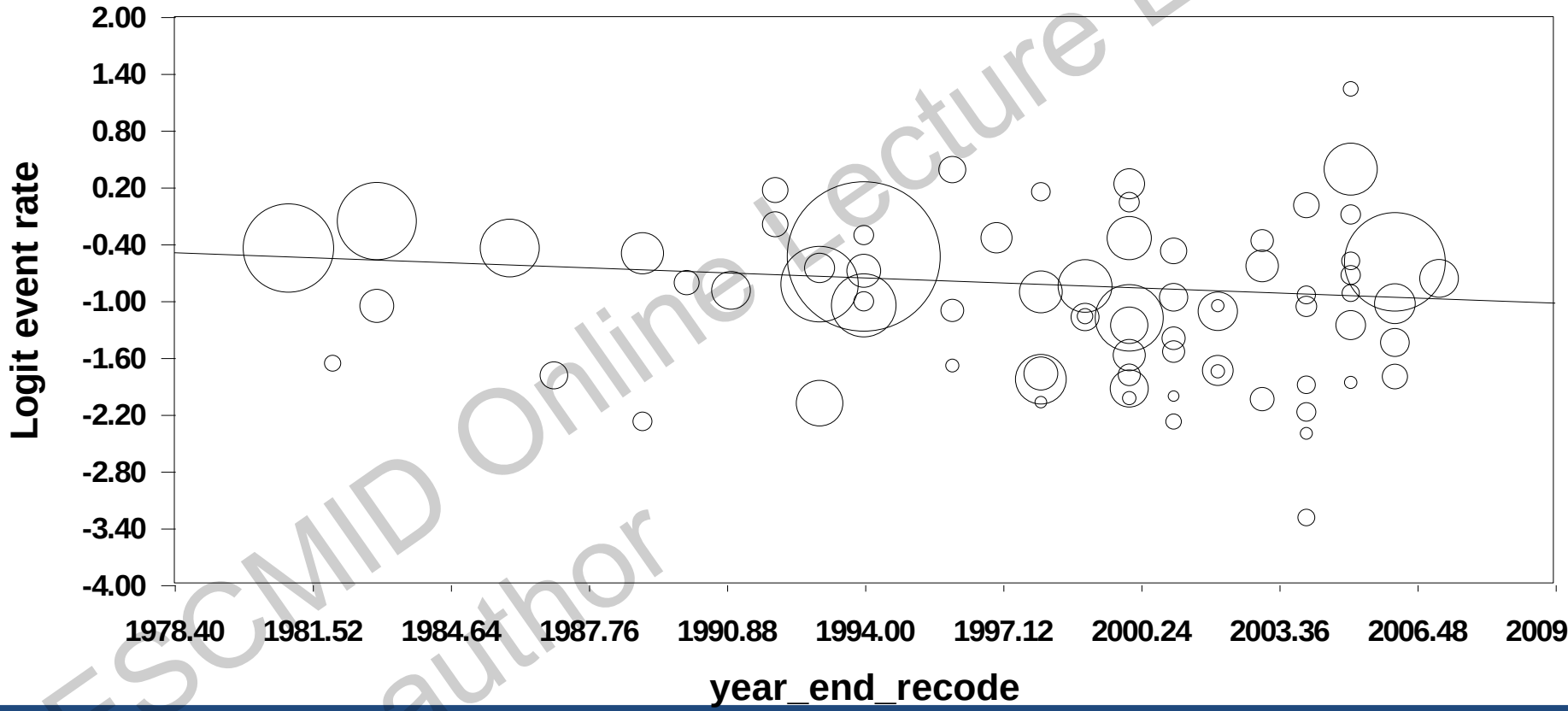
Empirical antibiotic policy in settings with prevalent MDR/ XDR GNBs

- Appropriate empirical antibiotic treatment carries benefit in severe infections caused by MDR/XDR
- Attempting to cover XDR/ MDR empirically entails treatment of many patients with broad-spectrum/ last resort antibiotics
- We do not have good predictive tools at bedside to say who is the patient with severe CRE infection who will gain from empirical treatment

CR clinical infections: predictive models

	Cases	Controls	Diagnostic performance	Validation	PPV/ NPV
Martin 2013	CRE bacteremia	ESBL+ bacteremia	Yes	No	21%/ 97%
Marchaim ECCMID 2014	XDR-GNB bacteremia	MDR-GNB bacteremia	Yes	No	65%/ 74%
Huang 2012	CR-AB	CS-AB	No	No	
Schechner 2013	CRE carriers with clinical infection	CRE carriers w/o infection	No	No	
Borer 2012	CRE carriers with clinical infection	CRE carriers w/o infection	No	No	
Mouloudi 2010	KPC bacteremia	CS KP bacteremia	No	No	
Kim 2014	CRGNB HAP	CSGNB HAP	No	No	
Dizbay 2014	CR KP infections	CS PK infections	No	No	
Kim 2014	HSCT with CR-AB bacteremia	HSCT without infection	No	No	

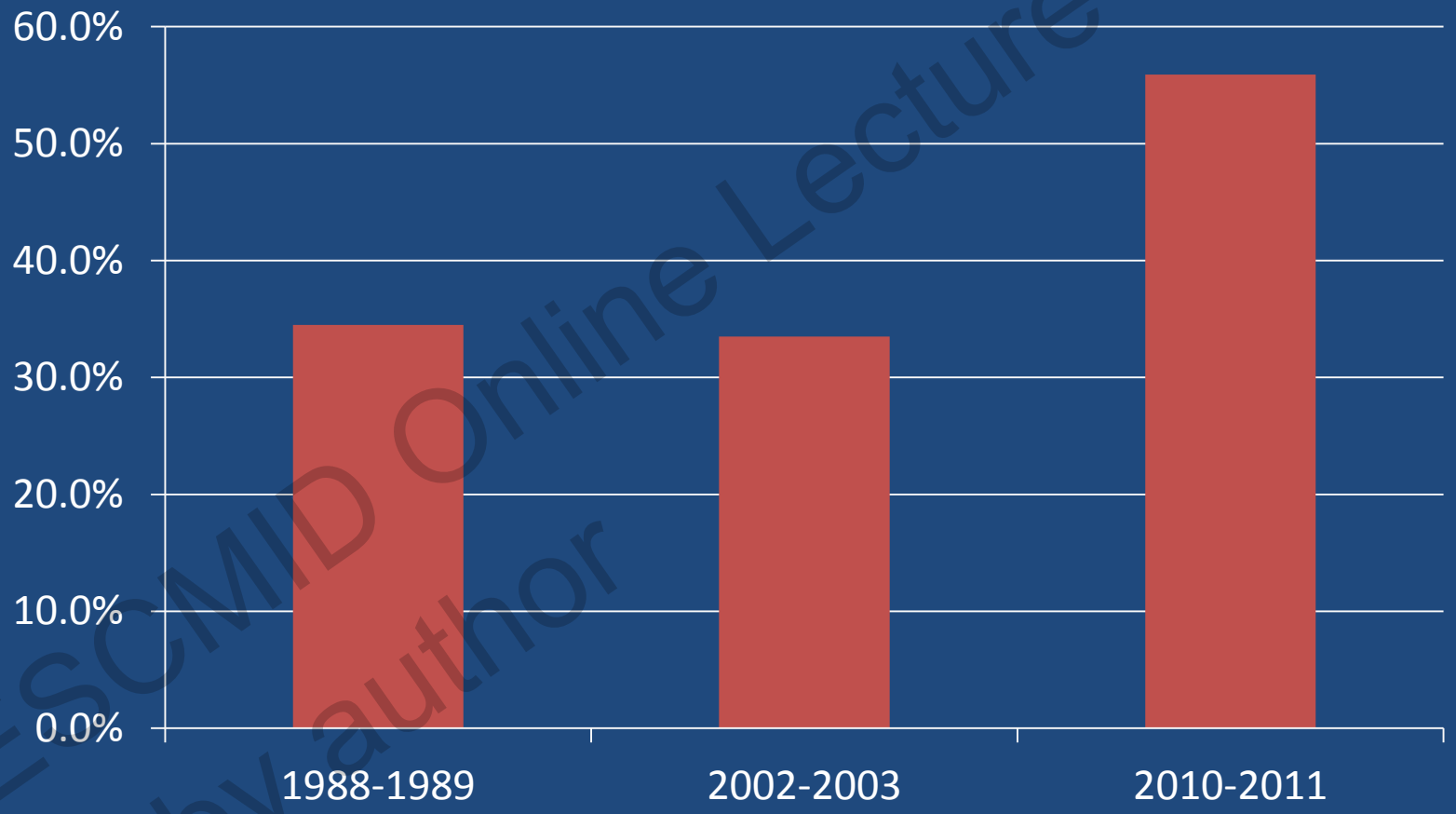
Rates of IAET by year



87 studies, 92 cohorts, 27,628 patients, 1977-2007
Pooled rate of IAET 26.3% (95% CI 23.7-29%). P for slope 0.24

Kariv et al. Clin Microbiol Infect. 2013 Jul;19(7):629-33

Rate of IAET by time
Bloodstream infections, single center



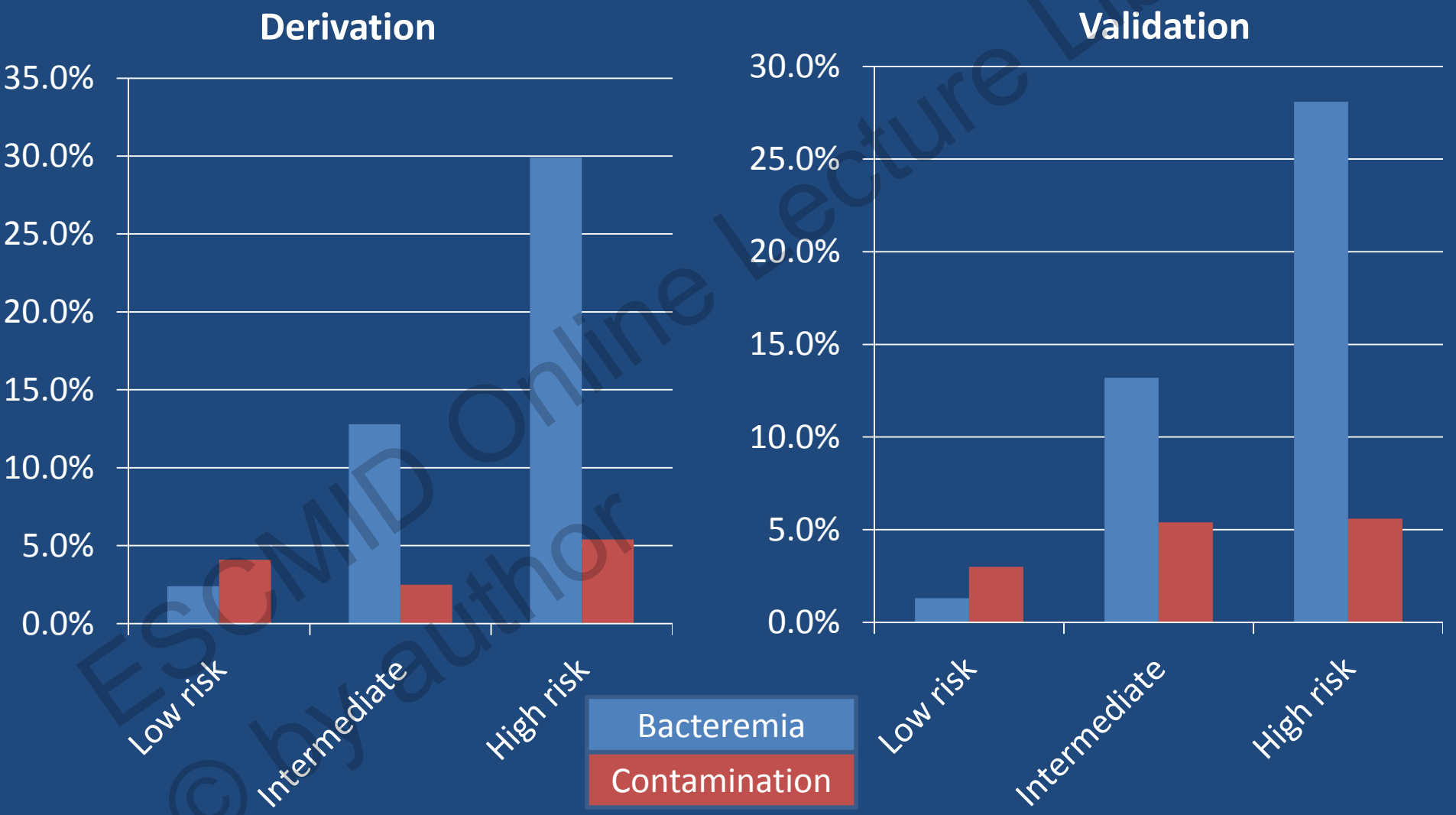
Prospective cohort studies using same methods. Rabin Medical Center

TREAT model for empirical antibiotic treatment

- Causal probabilistic network for diagnosis of bacterial infections in inpatients
  - Does the patient have an infection?
  - Infection severity
  - Pathogens causing infection
  - Antibiotics covering each pathogen
- Cost benefit model to decide on antibiotic treatment

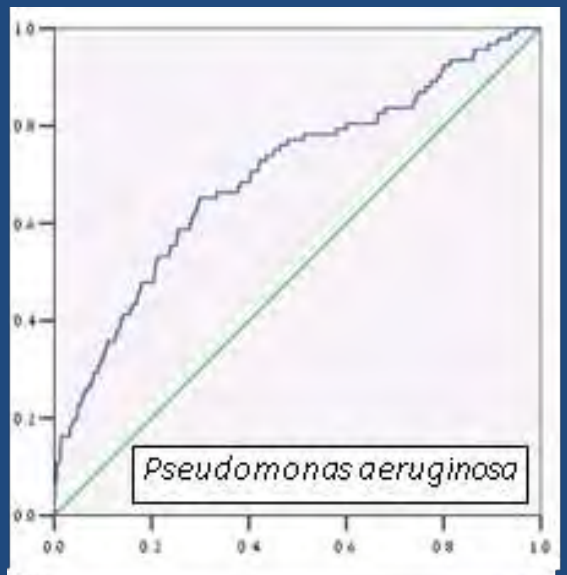
Paul et al. J Antimicrob Chemother. 2006; 58(6): 1238-45

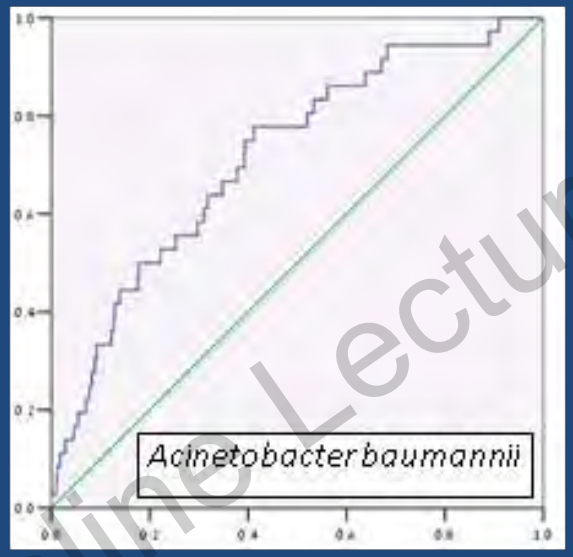
Prediction of bacteremia

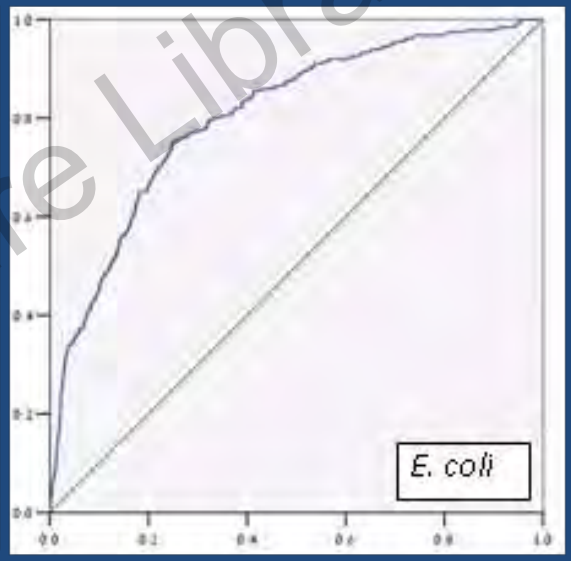


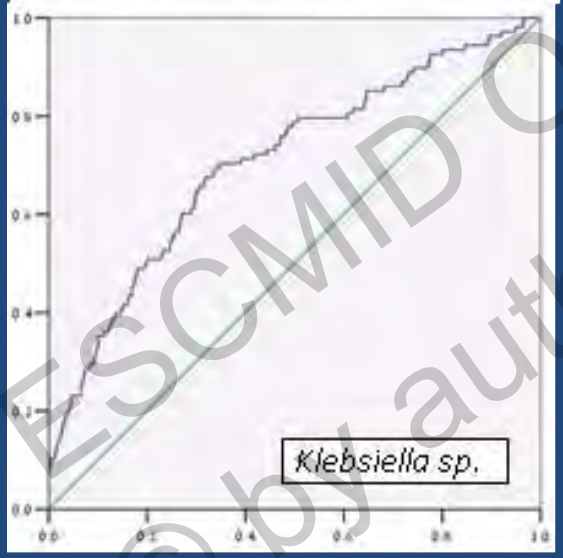
Paul et al. Clin Infect Dis. 2006; 42(9): 1274-82

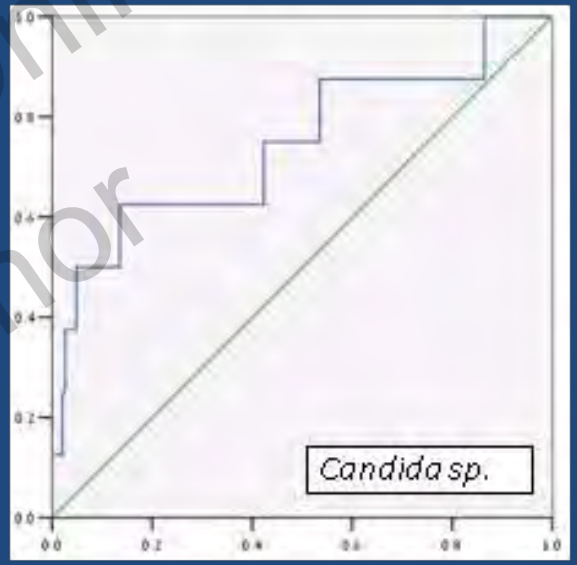
Pathogen prediction

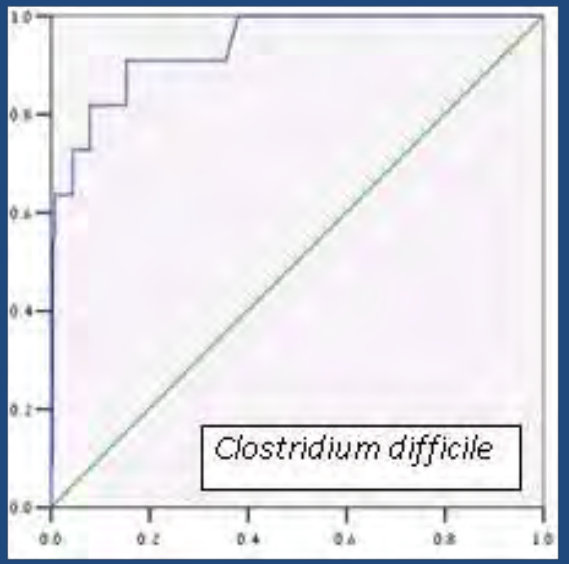












Paul et al. J Antimicrob Chemother. 2007; 59(6) :1204-7

TREAT model for empirical antibiotic treatment

- Causal probabilistic network for diagnosis of bacterial infections in inpatients

  - Antibiotics covering each pathogen
- Cost benefit model to decide on antibiotic treatment

Cost-benefit model

- Benefit
  - Appropriate antibiotic reduces mortality risk by ~1.6
  - Reduces hospital stay by ~2 days
- Cost
  - Direct drug, administration and monitoring costs
  - Adverse events costs
  - Ecological costs

Benefit: survival

Inappropriate

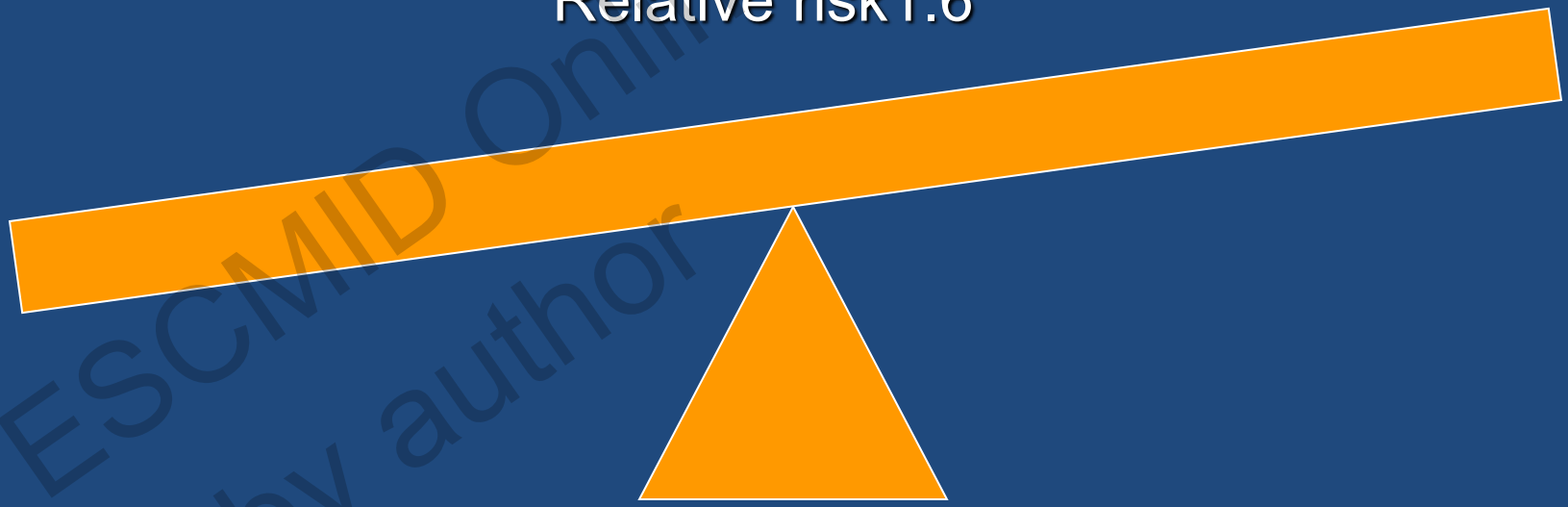
Appropriate

All-cause mortality

20.2%

12.6%

Relative risk1.6



Time horizon 5 years: absolute gain 4.56 months (0.38 LY)
Life year cost 50,000$: absolute gain 19,000 $

Benefit: reduced hospital stay

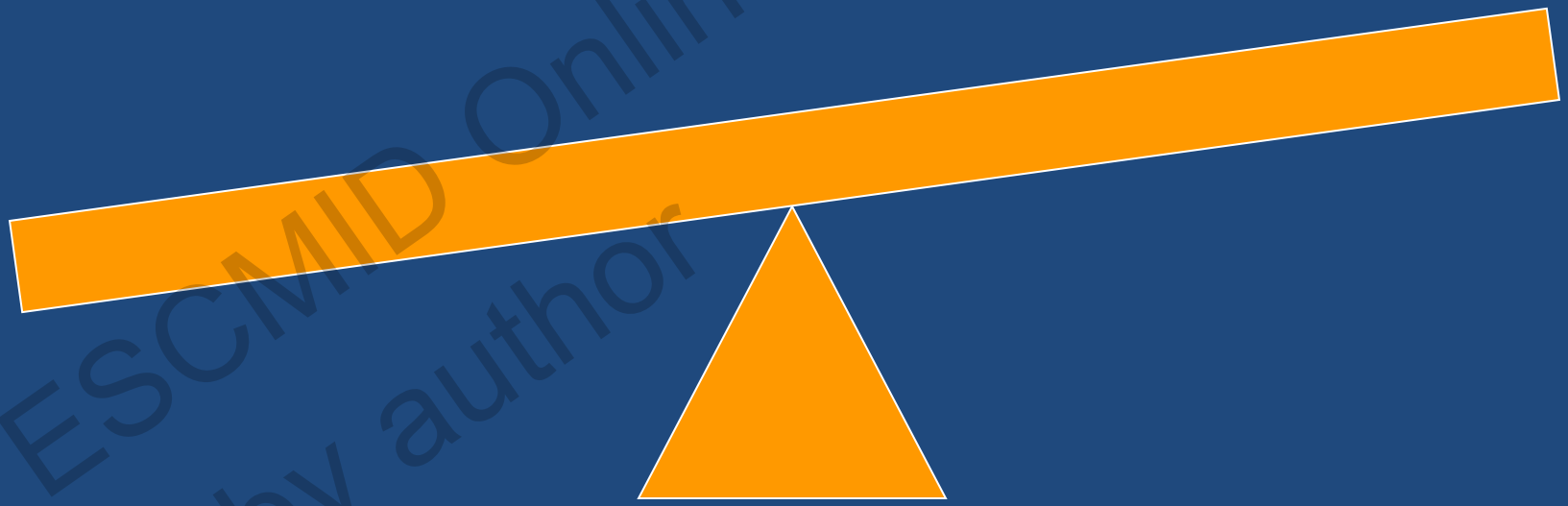
Inappropriate

Appropriate

Mean duration of hospital stay (survivors)

12.87 days

10.64 days



Absolute gain: 2.23 days

Hospital day cost 350$: absolute gain of 780$

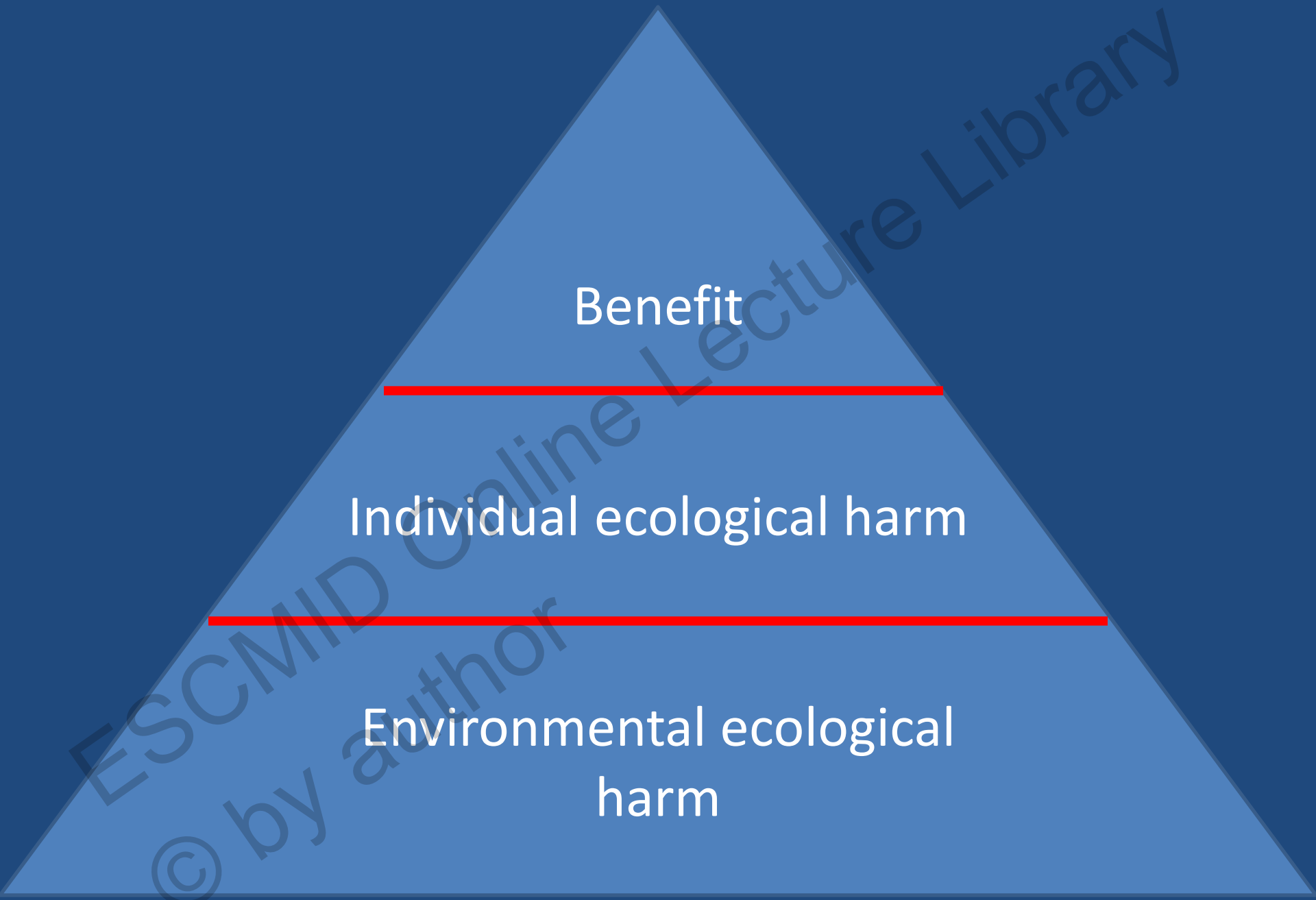
Cost-benefit model

- Benefit
  - Appropriate antibiotic reduces mortality by X1.6 and hospital stay by 1 day
- Cost
  - Direct drug, administration and monitoring costs
  - Adverse events costs
  - Ecological costs

Ecological costs

- Model follows the economic theory of depletable resources
- Separate costs assigned for the loss of the individual treated and the costs to the environment
  - Costs to the individual model the patient's next infection
  - Costs to the environment assume a policy of using the specific antibiotic
- An additional cost for "penalty"

Leibovici et al. Int J Antimicrob Agents 2007



Ecological costs: empirical treatment

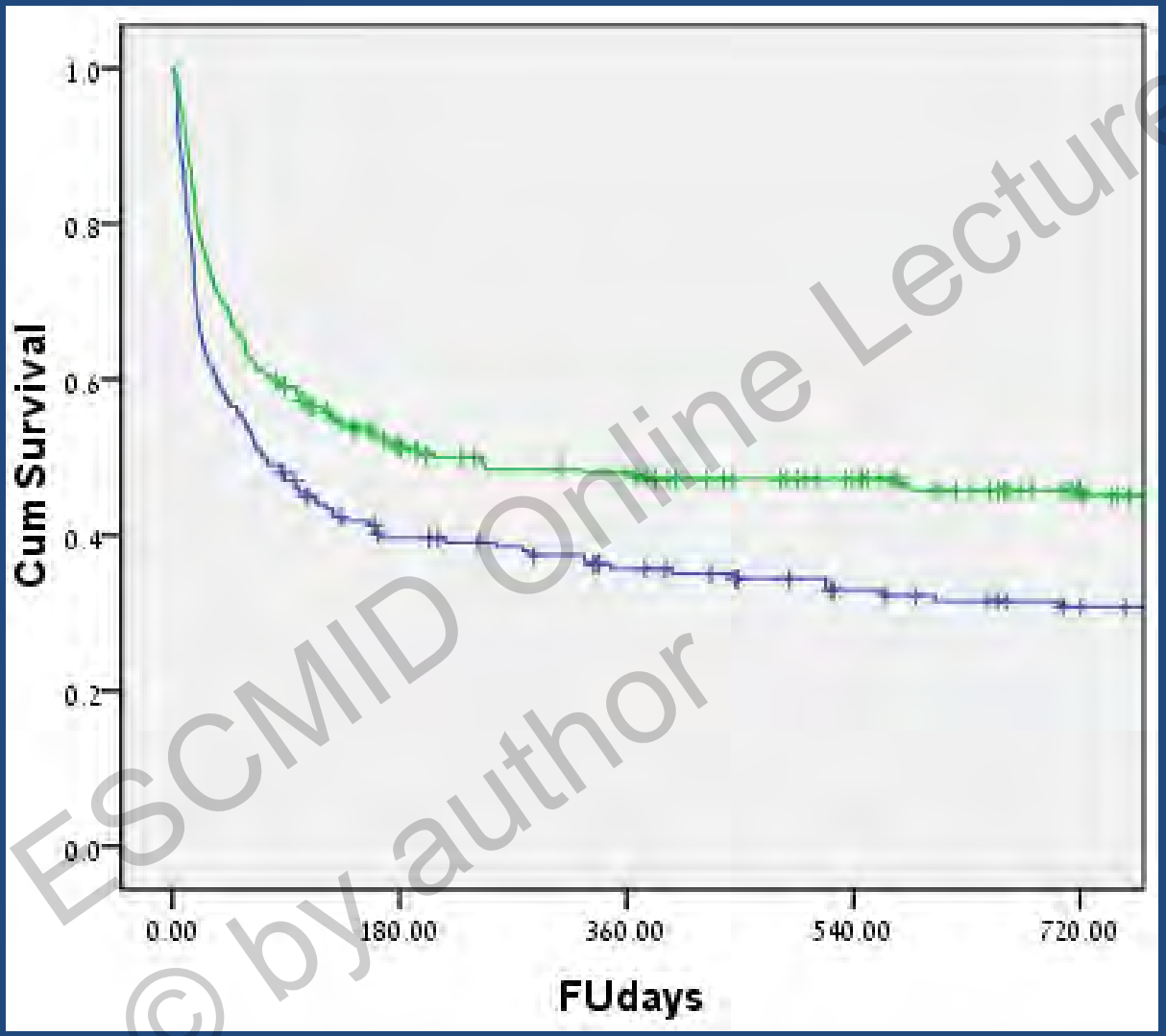
	Ecological cost/ benefit	Coverage	DDDs used meropenem empirically	DDDs used colistin empirically
Physicians' treatment	45.6%	49.2%	14	4
DSS with ecological costs	28.3%	61.8%	12	0
DSS without ecological costs	53.4%	81.1%	988	4

- Prospective cohort of 1348 inpatients with suspected sepsis; mortality 16.5%
  ESBLs: 38% of documented Gram negative infections; 5.7% of all patients
- Carbapenem resistant GNB: 6.8% of documented Gram negative infections; 1% of all patients

Colistin vs. carbapenem/ AS: 30-day mortality

Risk factor	Odds ratios (95% confidence intervals)	
	All patients, N=495	**Bacteremia, N=220**
Colistin arm of study	1.44 (0.91-2.26), p=0.116	1.99 (1.06-3.77), p=0.033
Age [b]	1.04 (1.03-1.06), p<0.001	1.04 (1.02-1.07), p<0.001
MacCabe score No fatal disease Ultimately fatal disease Proximately fatal disease	 0.42 (0.23-0.79), p=0.007 0.52 (0.27-1.00), p=0.051 Reference	Not significant
Independent functional capacity on admission	0.51 (0.31-0.84), p=0.008	0.44 (0.22-0.88), p=0.021
Bacteremia	1.95 (1.25-3.05), p=0.003	Not relevant
SOFA score at onset of infection [b]	1.28 (1.18-1.38), p<0.001	1.32 (1.19-1.47), p<0.001
Albumin at onset of infection [b]	0.65 (0.42-1.01), p=0.057	Not significant

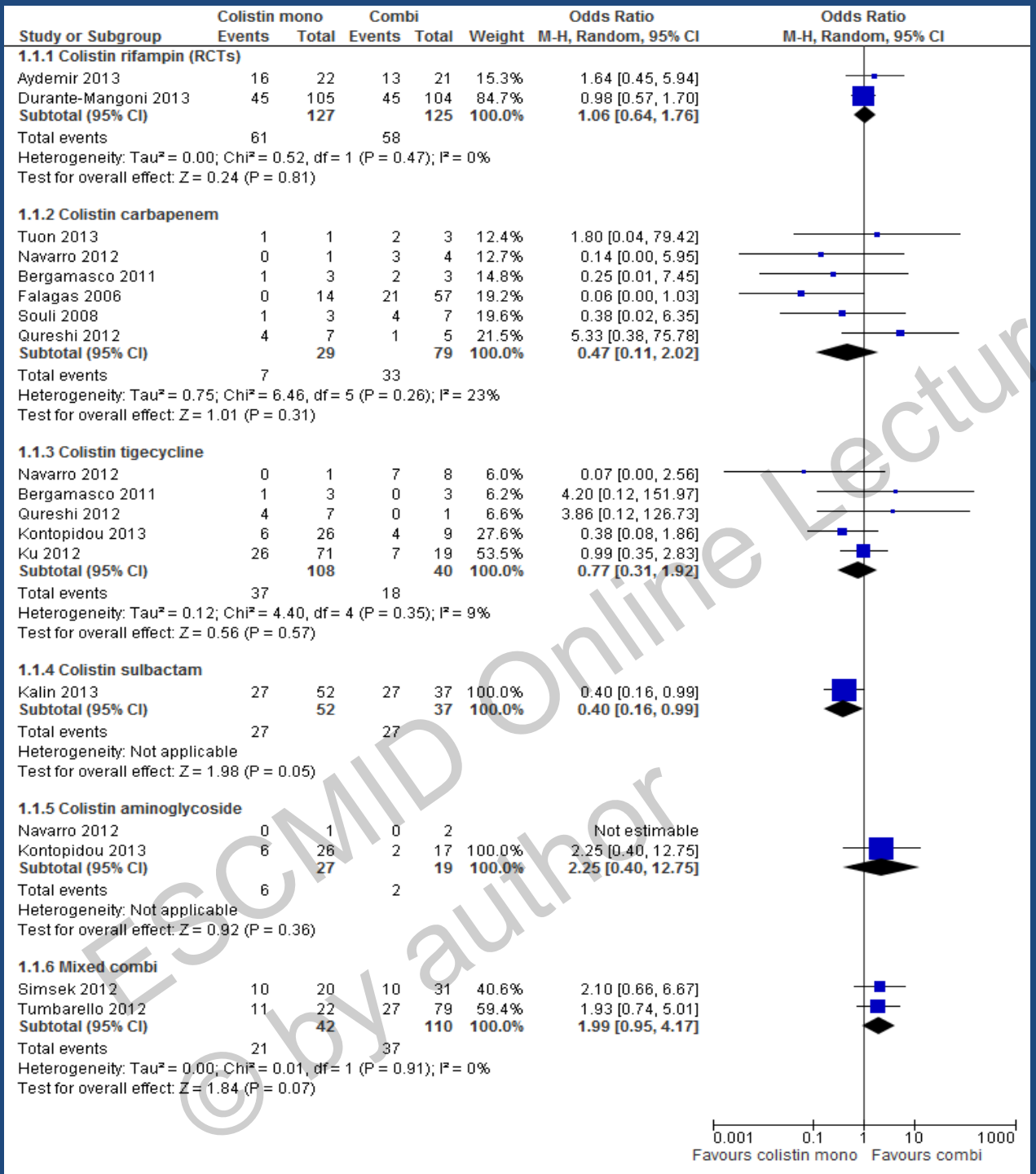
Cumulative mortality, end of follow-up



Median survival
72 days with colistin
vs.
245 with comparators

Cox regression adjusted OR 1.27 (1.01-1.60), p=0.049

Paul et al. J Antimicrob Chemother 2010; 65(5): 1019-27



Colistin monotherapy vs. colistin combination therapy: observational studies/ case series

Paul et al. accepted for publication. J Antimicrob Chemother

Summary

- Appropriate empirical antibiotic treatment maintains its benefit for MDR/XDR bacteria
- Rates of appropriate empirical treatment probably decline with increasing resistance
- A formal model can balance benefit and harm
  - Largely driven by benefit
- Need for improved prediction models
  - Starting at bed-side at onset of infection

Thank you

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