New paradigm for improving outcomes from pneumonia and sepsis

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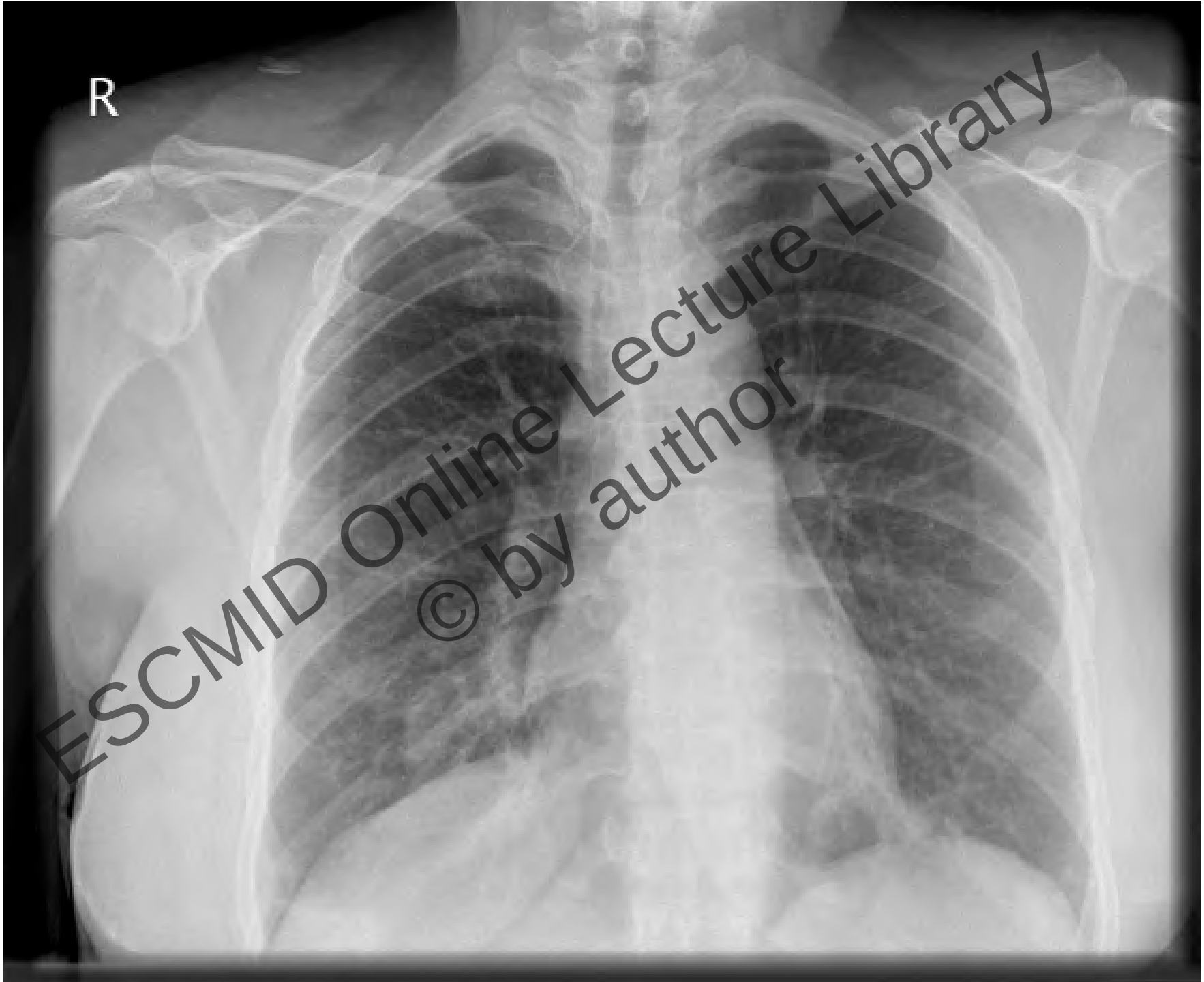
One Friday morning …..

- Asked to see 28yo woman
- Married, children aged 4 and 2
- No past medical history of note
- Cough for 2 days



Clinical progress

- Presented to ED at 0855, seen 1030
  - HR 115, RR22, BP 105/60, 0_2 94%
  - PSI I
  - Given iv ceftriaxone 1g and 500mg iv azithromycin at 1100
- At 1400 reviewed
  - HR 120, RR30, BP 105/55, 0_2 93%
  - PSI II

Clinical progress

- At 2200
  - HR 135, RR40, BP 95/55, 0_2 87%
  - PSI IV
- At 0300
  - HR 160, MV, BP 70/35, Fi02 1.0
  - PSI V
- At 0630
  - Deceased

Clinical progress

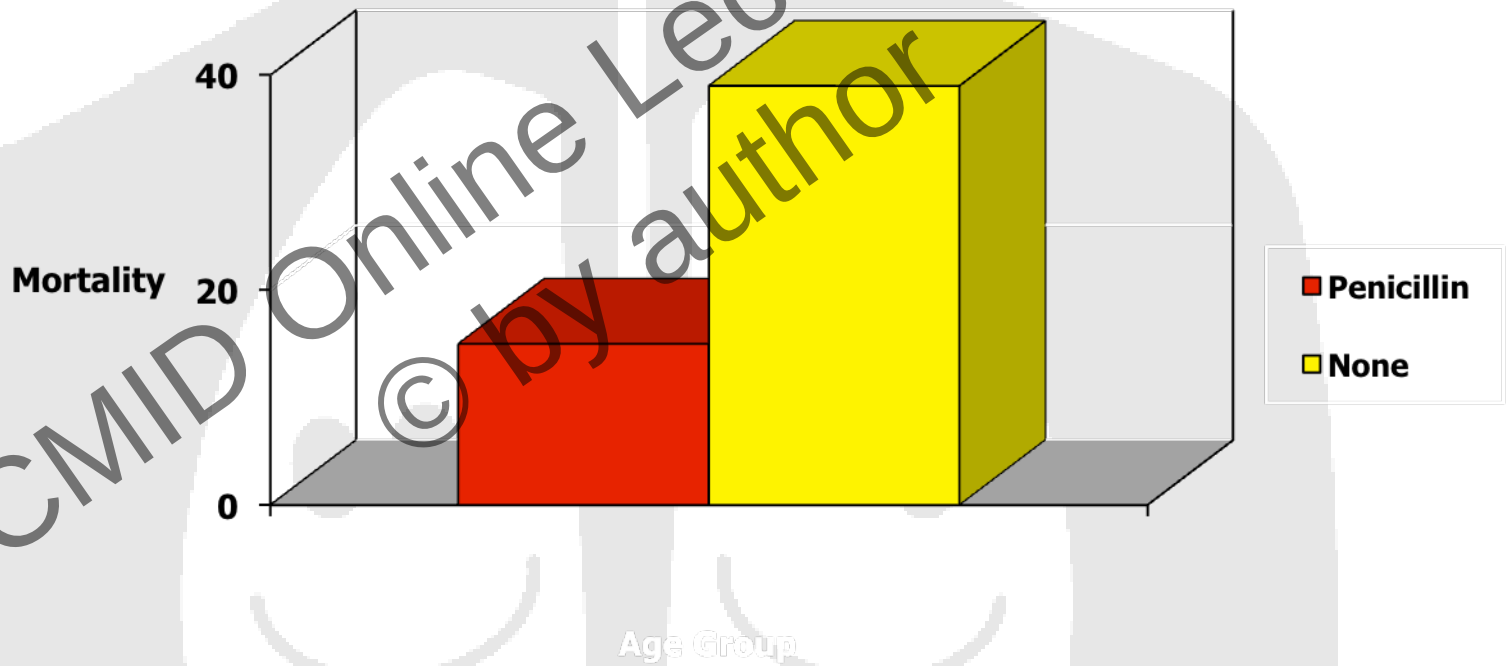
- +8 hours post death
  - Blood cultures positive for *Streptococcus pneumoniae*
- +30 hours post death
  - *S.pneumoniae* penicillin and erthryomcyin sensitive

Why?

Why couldn’t we do better?

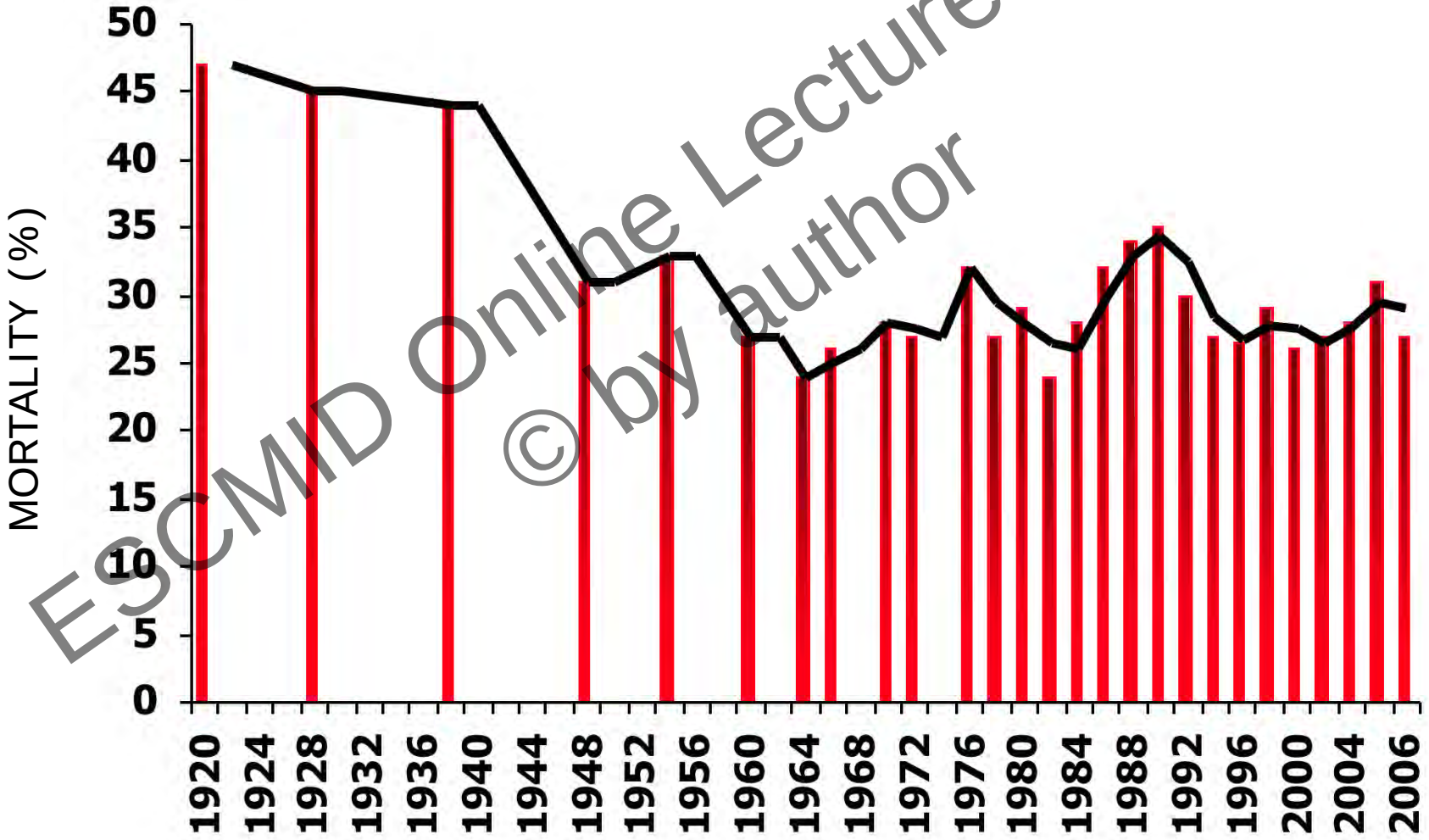
Why did she get so ill so quickly?

Penicillin vs Placebo Randomised Trial



Evans and Brim Lancet 1938; 2: 14-19

Mortality over time for bacteraemic pneumococcal pneumonia



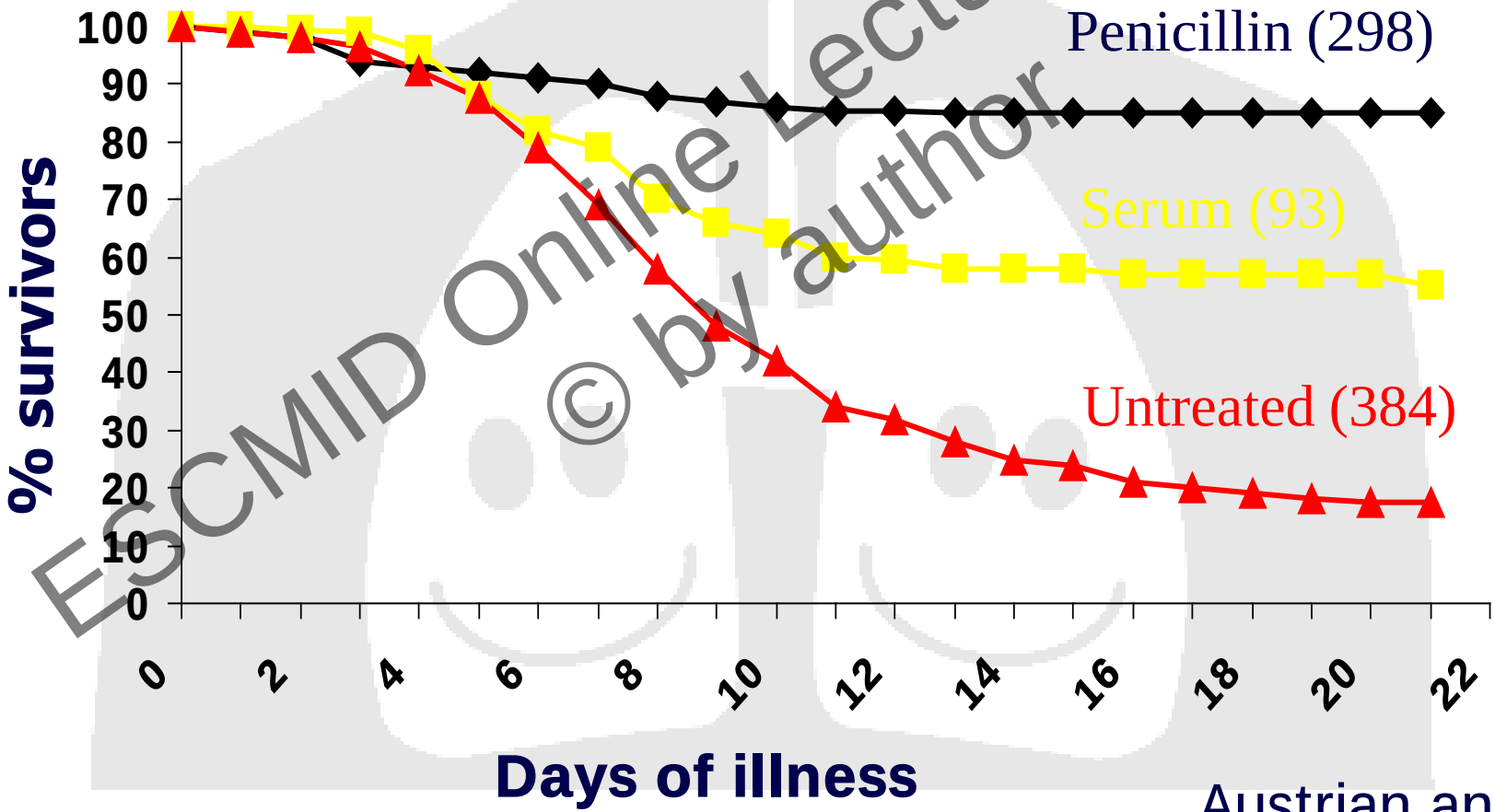
USA data compiled from published studies and Vital Statistics Reports

- Why can’t we do better?

Why can’t we do better?

- Antibiotics take time to work and some people present too late

Effect of antibiotics on mortality in pneumococcal bacteremia

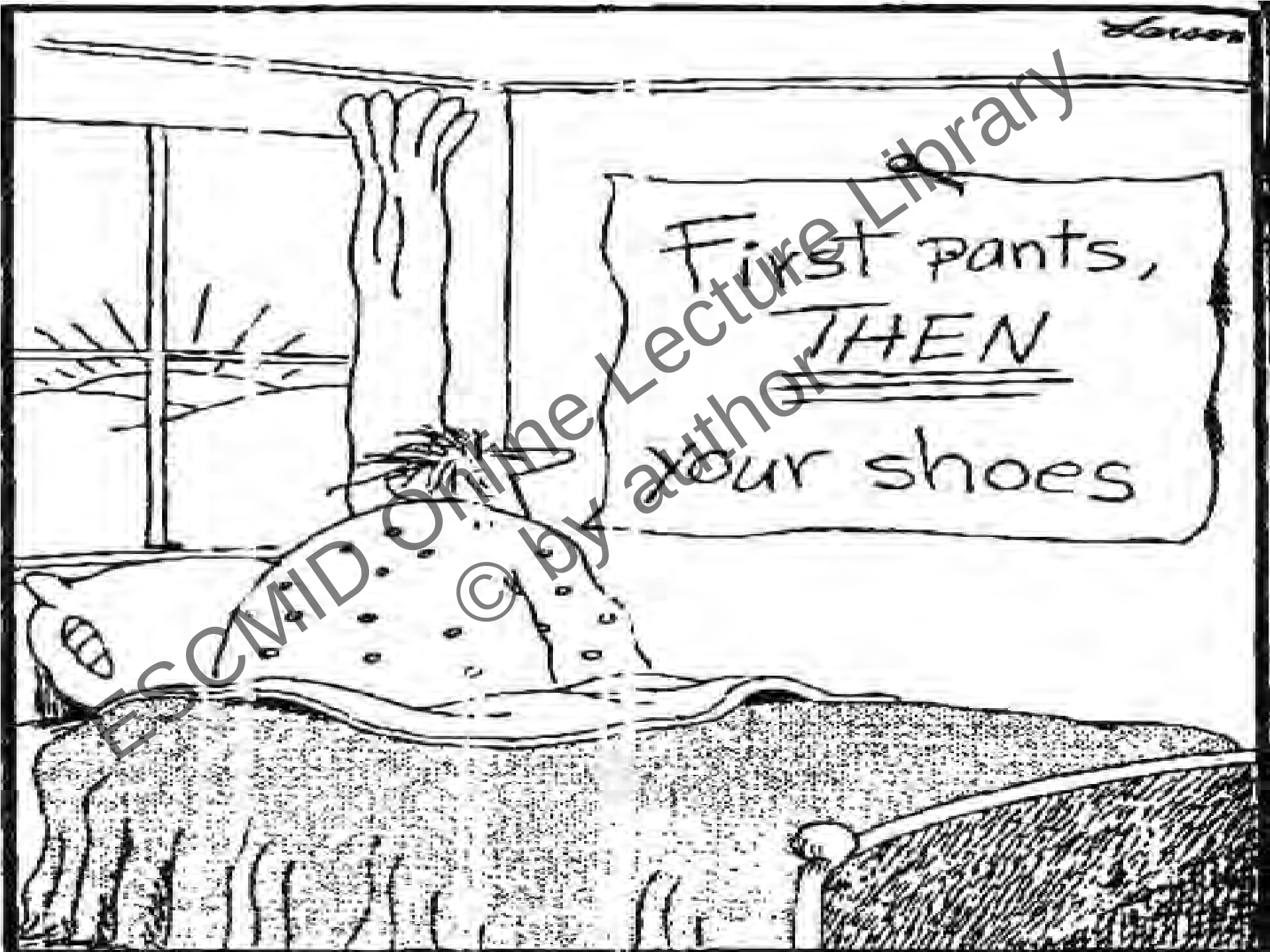


Austrian and Gold
Ann Int Med 1964

Why can’t we do better?

- Antibiotics take time to work and people present too late

- Picking people who will deteriorate is still an educated guess



Pneumonia Severity Index (PSI)

Fine MJ et al N Engl J Med 1997;336:243-50

Age: 1 point /year

Sex: female - 10 points

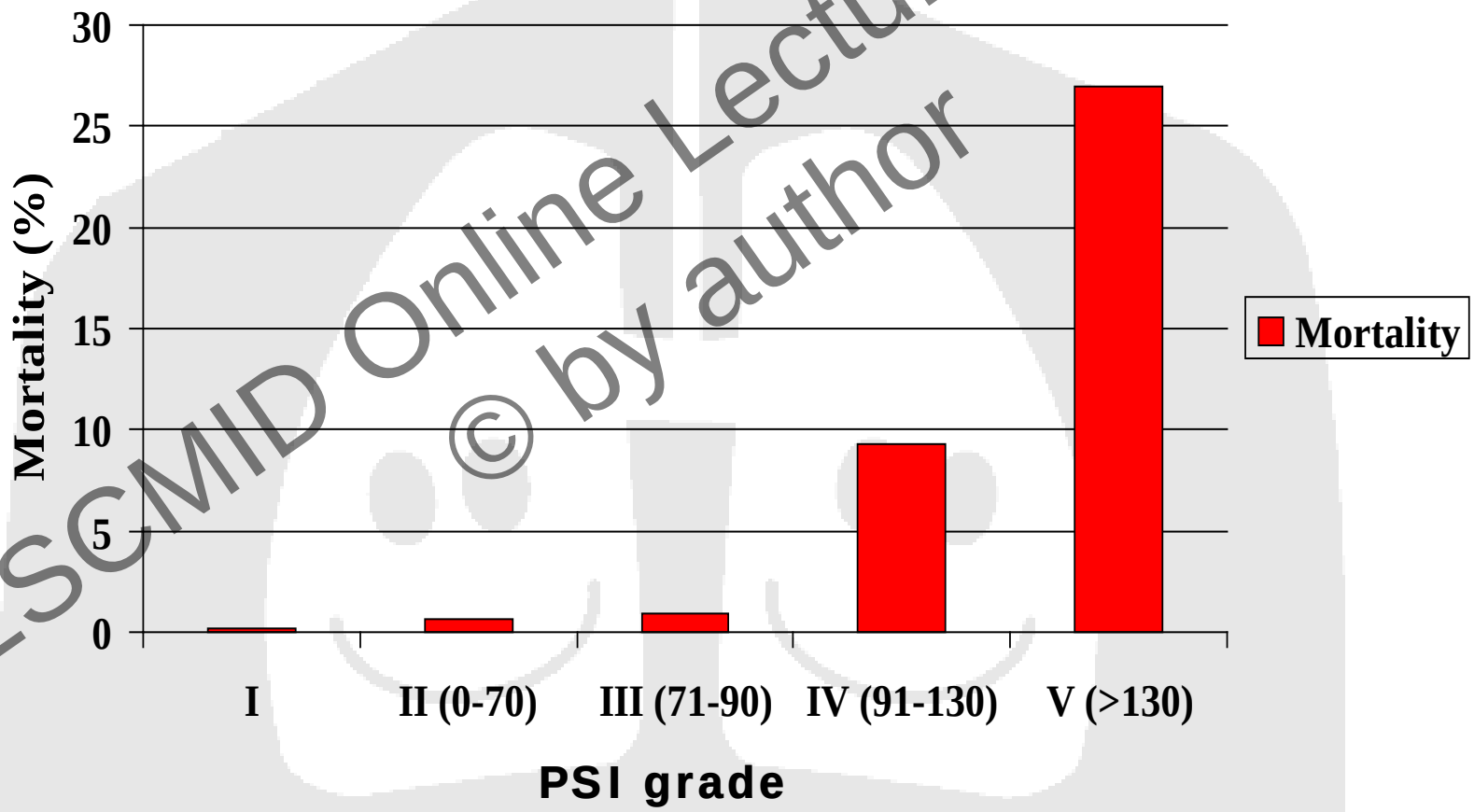
30 pts: arterial pH<7.35, Malignancy

20pts: BUN>30mg/dl (11mmol/l), Na^+<130, altered mental status, RR>30,SBP<90, liver disease

15pts: T<35°C (95°F) or >40°C (104°F)

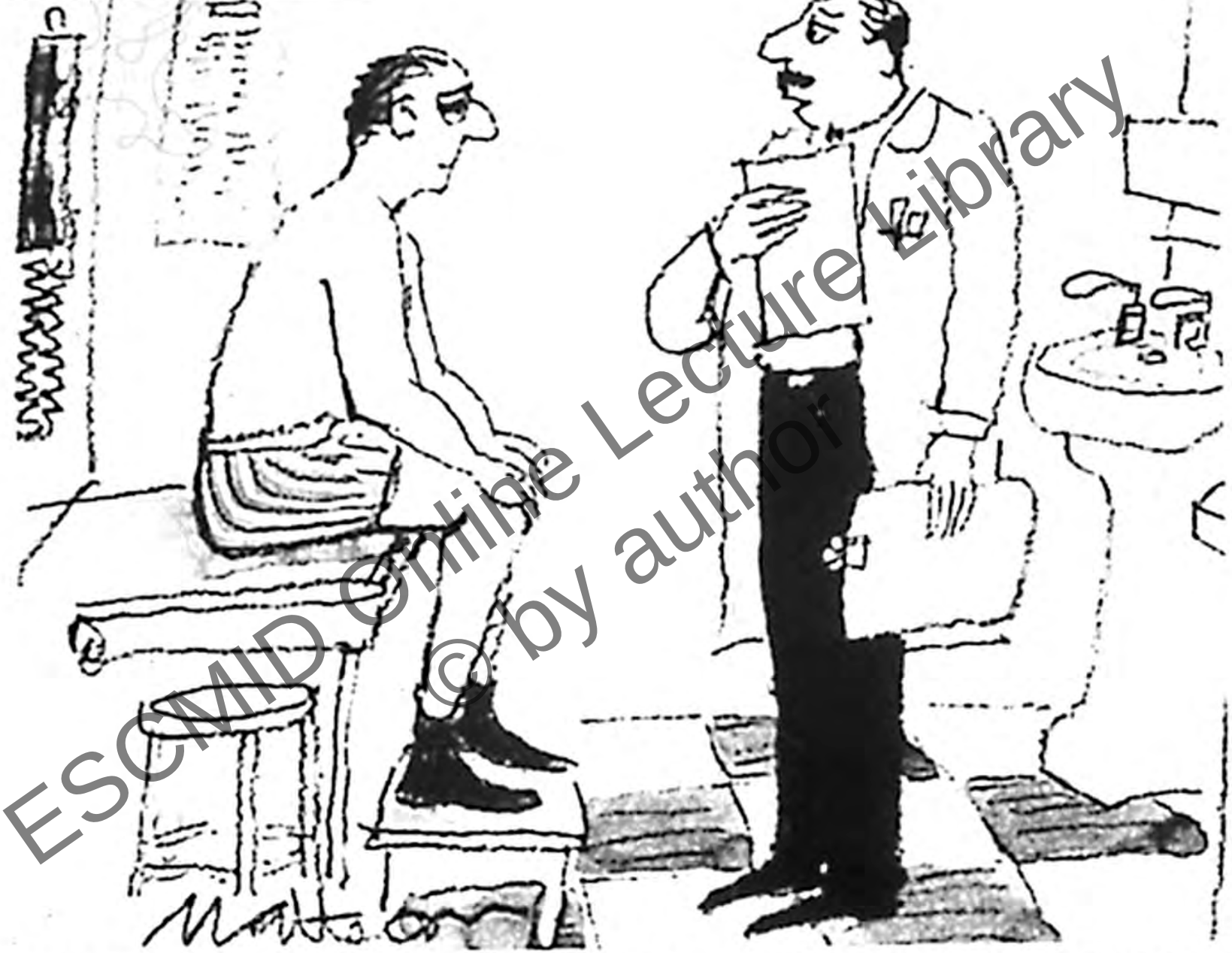
10pts: CCF, CVD, CRF, HR>125, glucose >250mg/dl, HCT<30%, paO2<60mmHg, pleural effusion

Mortality by PSI grade



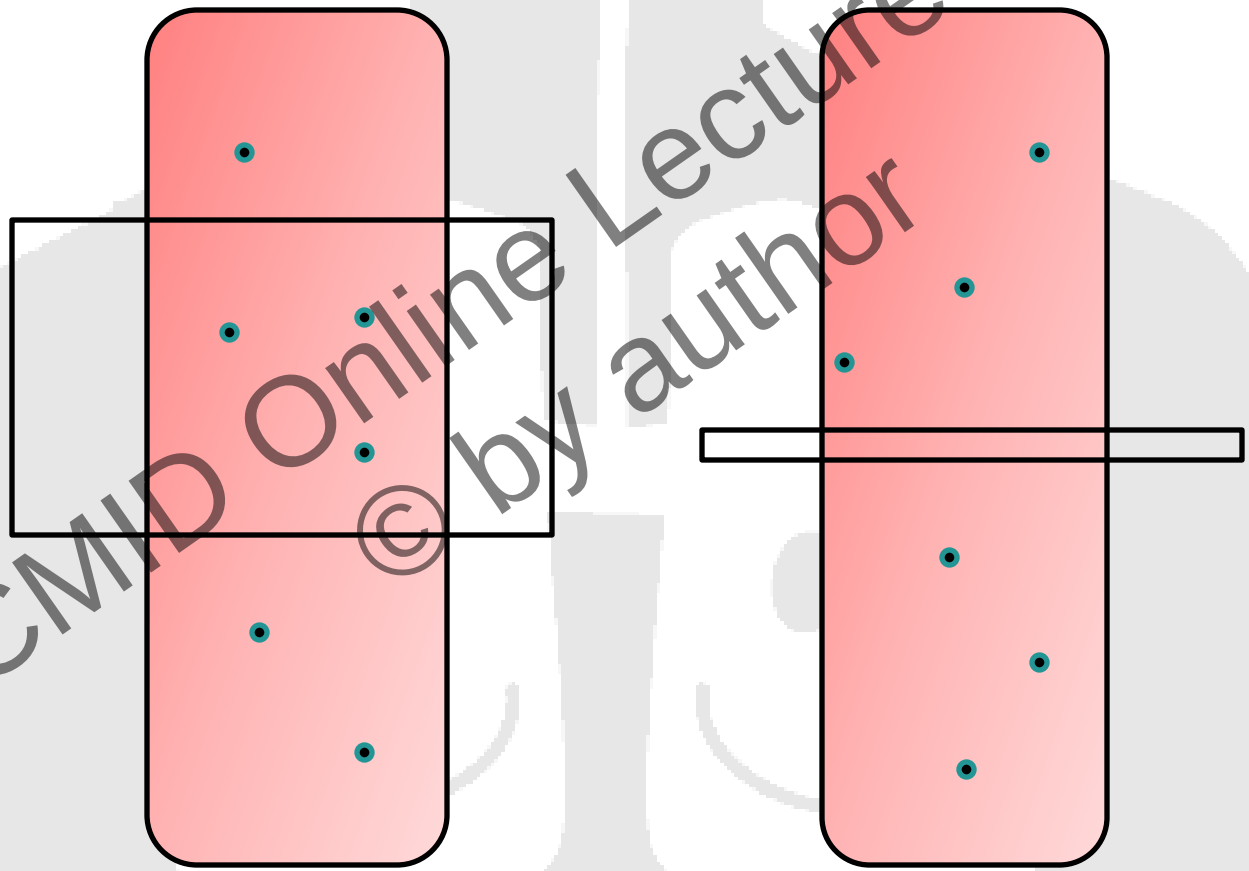
Why can't we do better?

- Antibiotics take time to work and people present too late
- Picking people who will deteriorate is still an educated guess
- Our ability to determine the 'bug' is still limited by 19th century technology



"We have a lot more tests to go through before we can say for certain we don't know."

Culture vs PCR



Blood culture 2 x 20mls

PCR 0.2ml

Serial improvements in PCR

- Targetting autolysin (lyt-A) better than pneumolysin
  - Van Haeften et al Diag Micro Clin Micro 2004
- Increased the volume to 1ml and improved autolysin probe
  - Kee et al Diag Micro Clin Micro 2008

Improved quantitative PCR

- Study of 450 patients with CAP
- Hypothesis: Bacterial Genomic Load

Rello et al Chest 2009

Excellent performance

	Blood culture Positive	Blood Culture Negative
PCR +	30	31
PCR -	5	287

Rello et al Chest 2009

Excellent performance

- Twice as sensitive as blood cultures
  - Better than anything published or commercially available by a factor > 2.0
- 5 PCR-ve, blood culture positive cases all mild disease, no fatalities
- Gold standard for the PCR+ve, blood culture negative cases?

Specificity superb

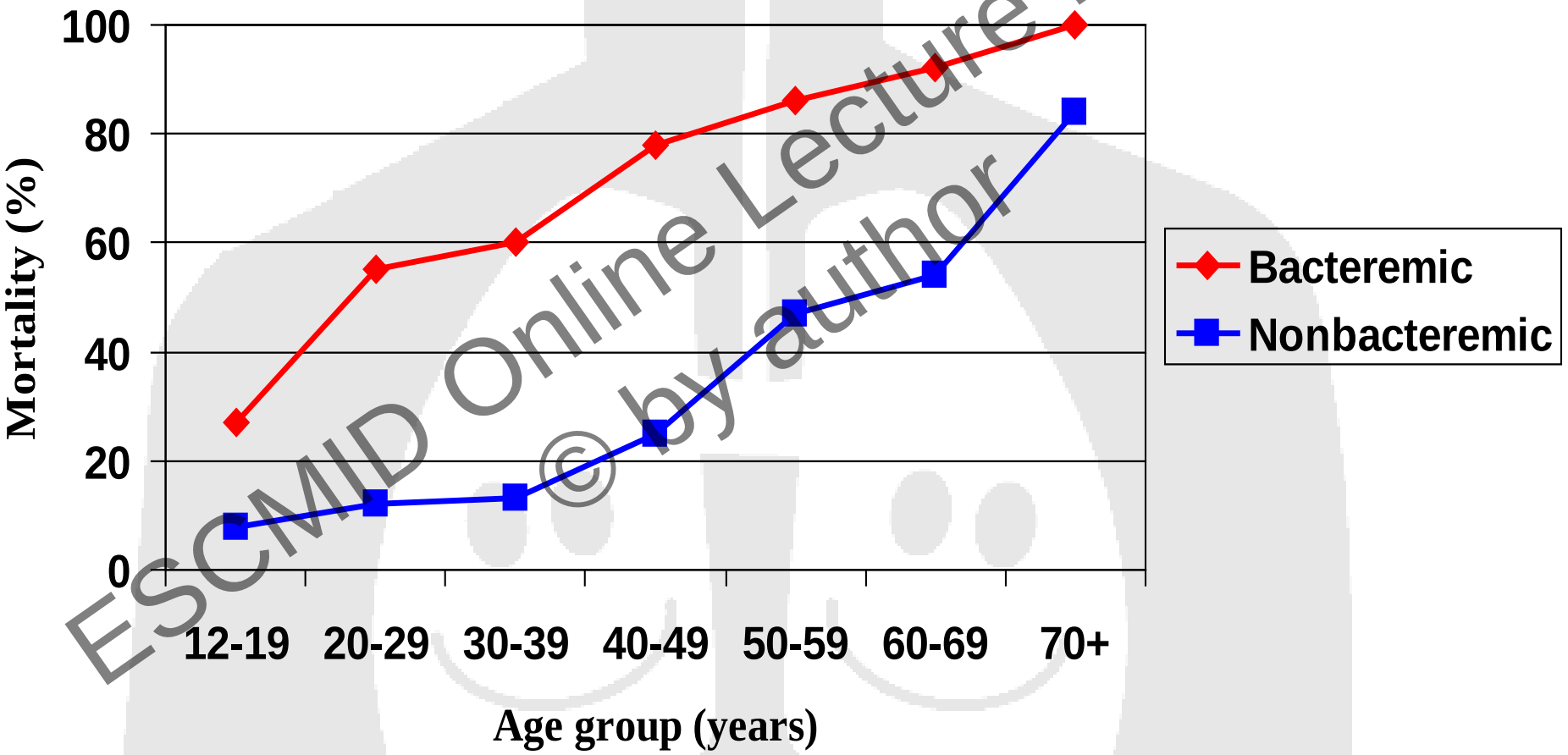
- 200 healthy controls
  - No false positives
- 1800 samples from RPH ED
  - 6 PCR +ve, culture negative results
  - 5 had pneumonia and no other positive culture
  - 1 had sepsis of unknown origin
- 99.9% -100% specificity

Kee et al Chest 2010

Measuring bacterial burden

- HIV infection
  - Viral ‘load’ determines prognosis and treatment
- Hepatitis C
  - Viral ‘load’ determines treatment
- Can we measure ‘bacterial load’?

Mortality from pneumococcal pneumonia in the pre-antibiotic era



Tilghman and Finland, Arch Intern Med 1937

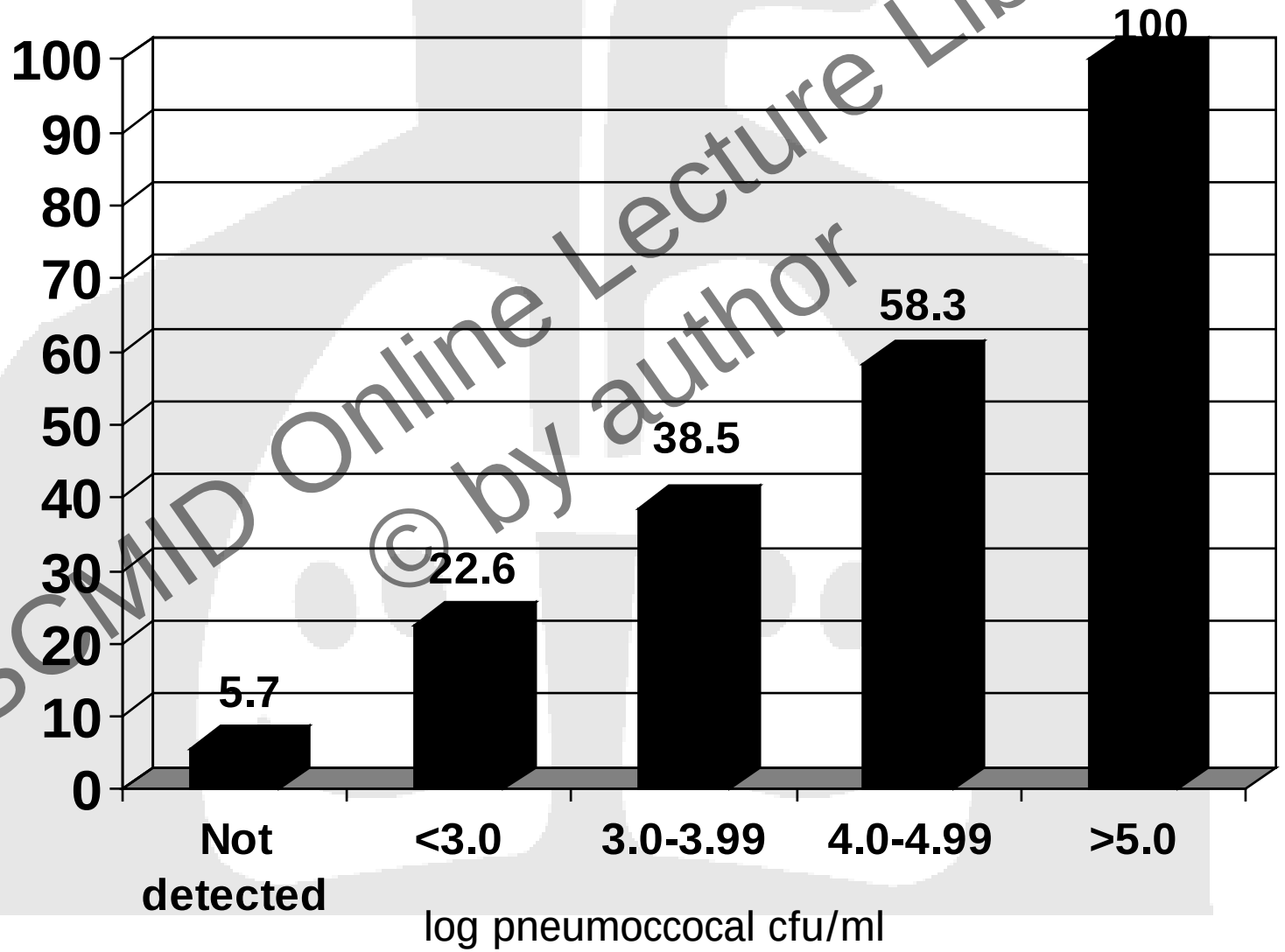
Bacterial burden

- Study of 450 patients with CAP
- CRIPS Net

- Quantitative counts varied from 15 cfu/ml to 1.8 million cfu/ml

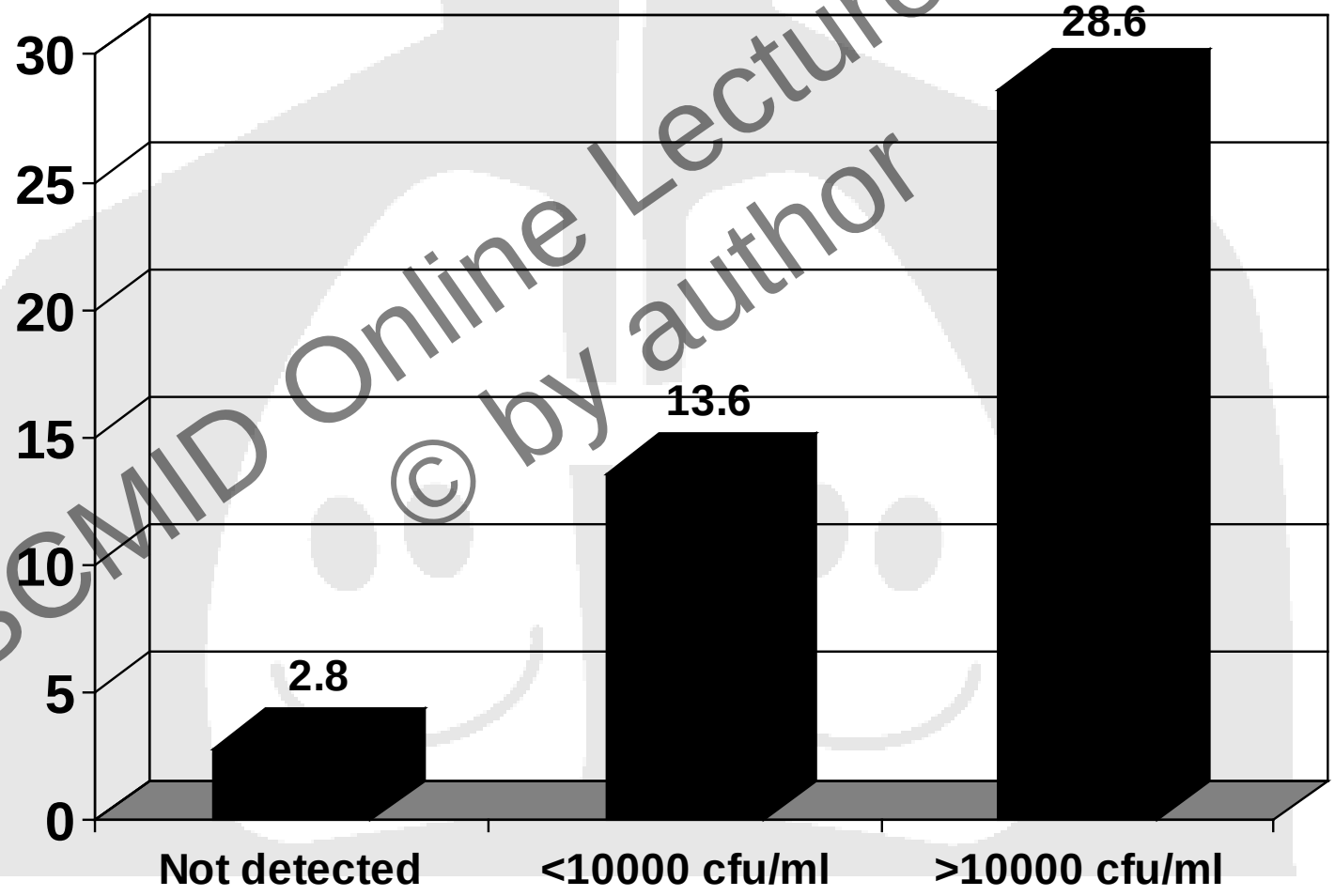
Rello et al Chest 2009

Risk of septic shock according to log pneumococcal burden



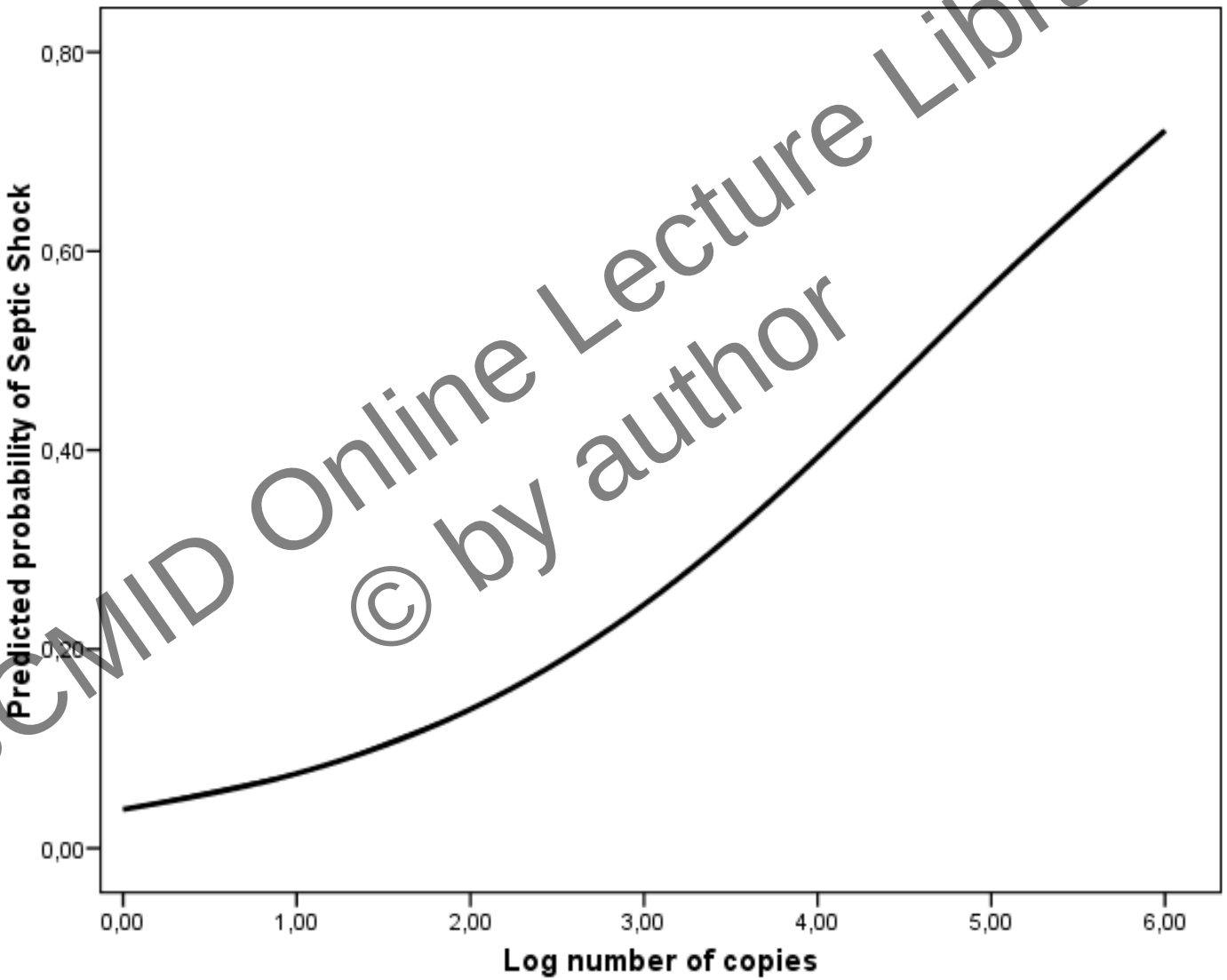
Rello et al Chest 2009

Risk of mortality by pneumoccal bacterial burden



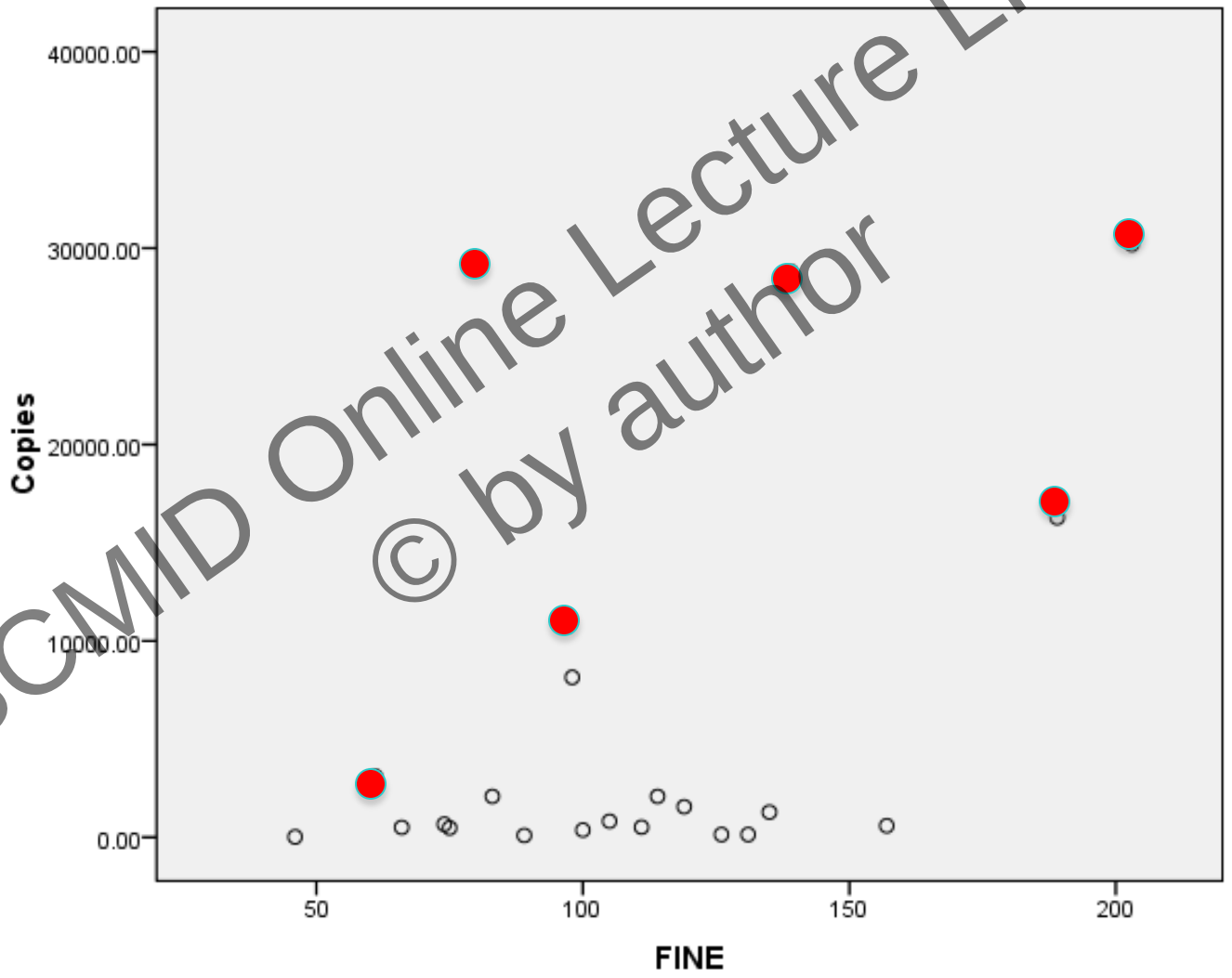
Rello et al Chest 2009

Risk of shock vs bacterial burden



Rello et al Chest 2009

New opportunities in risk stratification

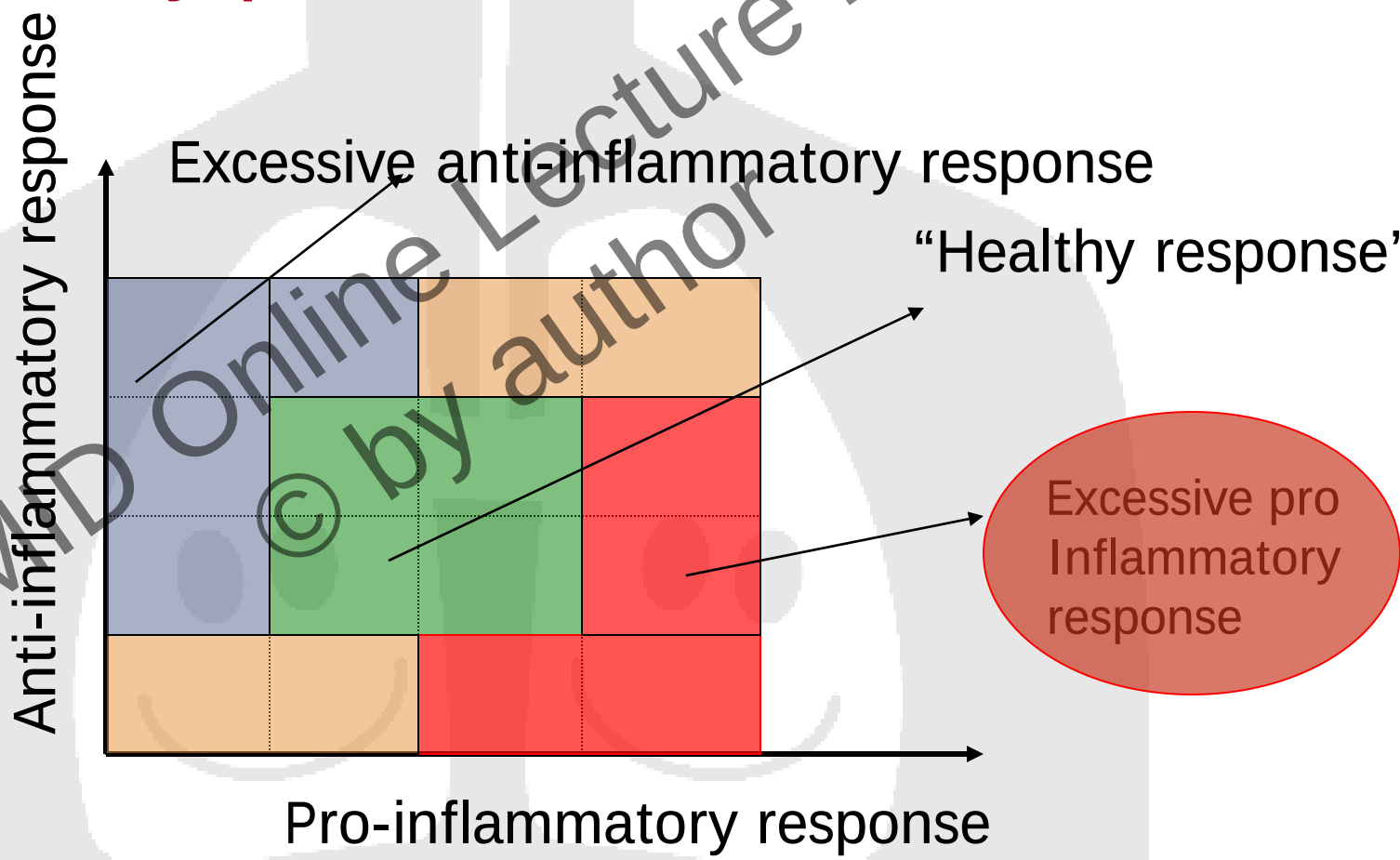


Bacterial burden is clinically relevant

- Predicts outcome
- More accurate than PSI in those who are PCR+ve
- Answer in under 2 hours

A new paradigm in pneumonia and sepsis

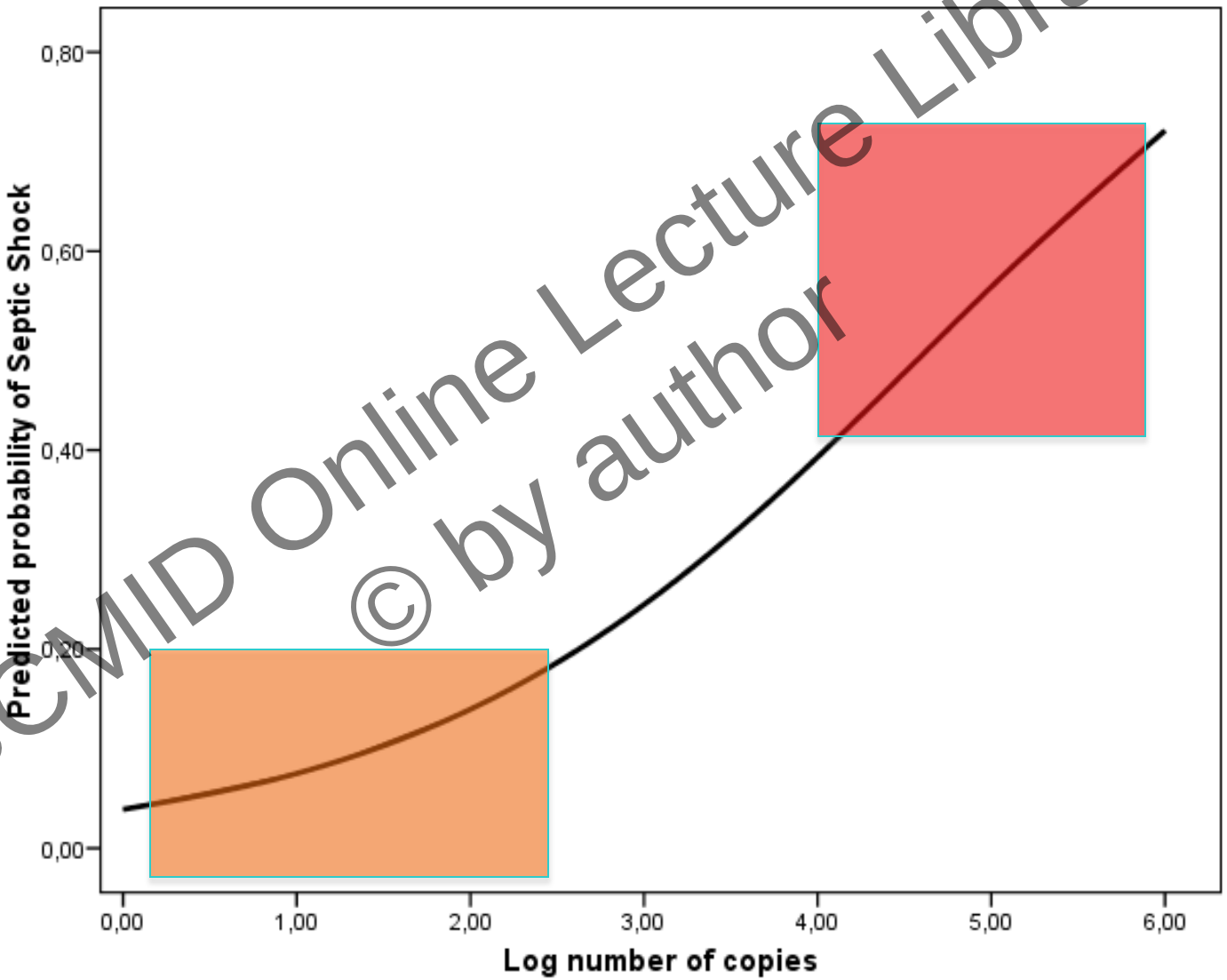
The paradigm: The sum of all your genetic influences gives you an inflammatory profile



The paradigm doesn't fit well with the data

- Most septic shock is associated with a high blood bacterial burden
  - The inflammatory response is probably proportionate
- Only a small minority have shock at low bacterial burdens
  - High likelihood of strong genetic influence
- Inflammation is proportional to the stimulus
  - If you are hunting genetic factors you need to look at deficient clearing or prevention of systemic invasion
- This opens up a whole new world of possibilities in triaging and treating patients with pneumonia

Risk of shock vs bacterial burden



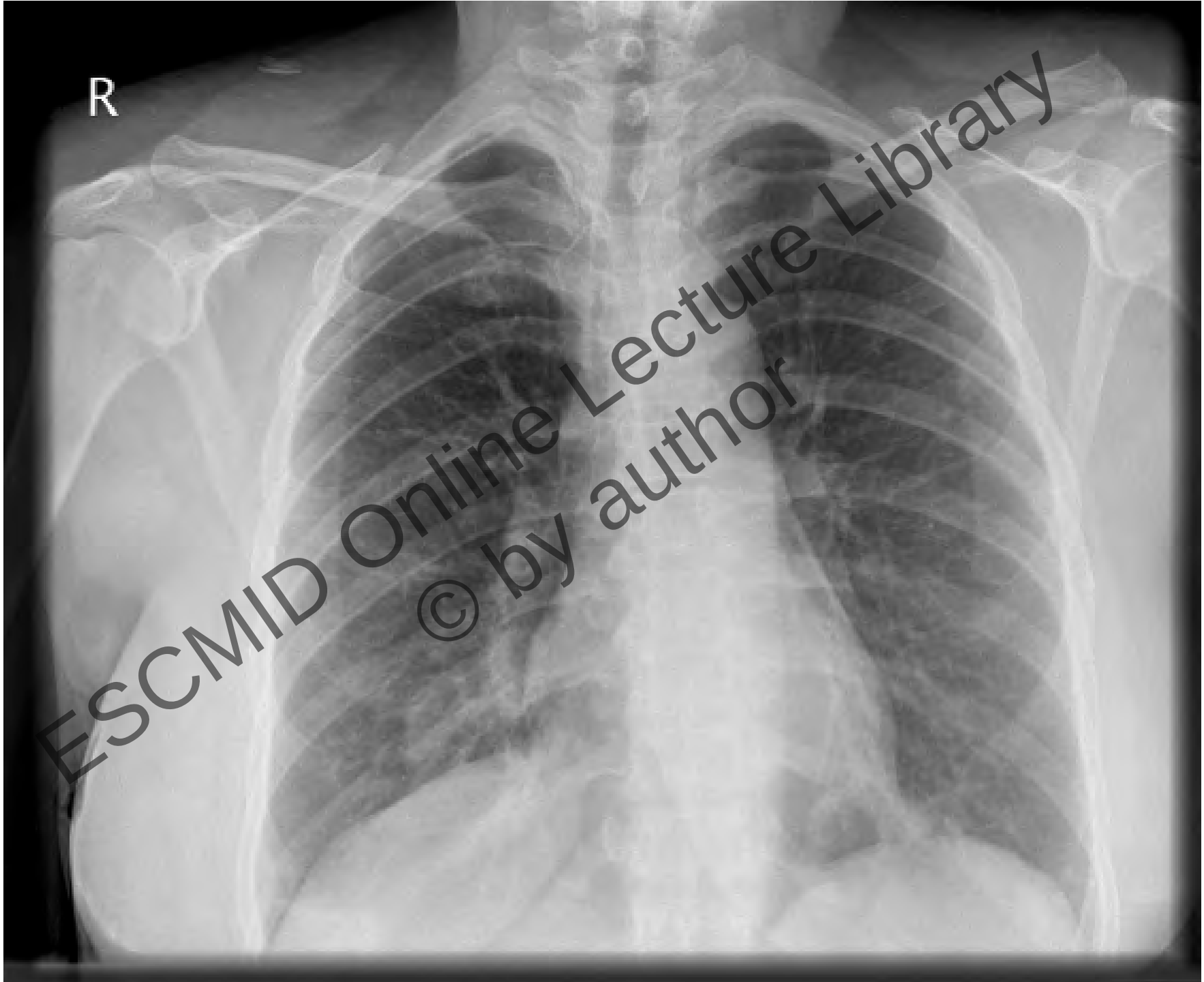
Rello et al Chest 2009

Moving ahead with new assays

- 16S generic ‘all bacteria’
- Generic antifungal
- MRSA/MSSA
- *E.coli*
- *P.aeruginosa*

A new paradigm in pneumonia and sepsis

- 16S would be the primary ‘warning’ of a high bacterial load
- When 16S positive, use a series of pathogen specific asssays (e.g. pneumococcus, staph etc depending on the setting)
- You CANNOT mix large numbers of assays into the one process (multiplexing) without a large loss of sensitivity



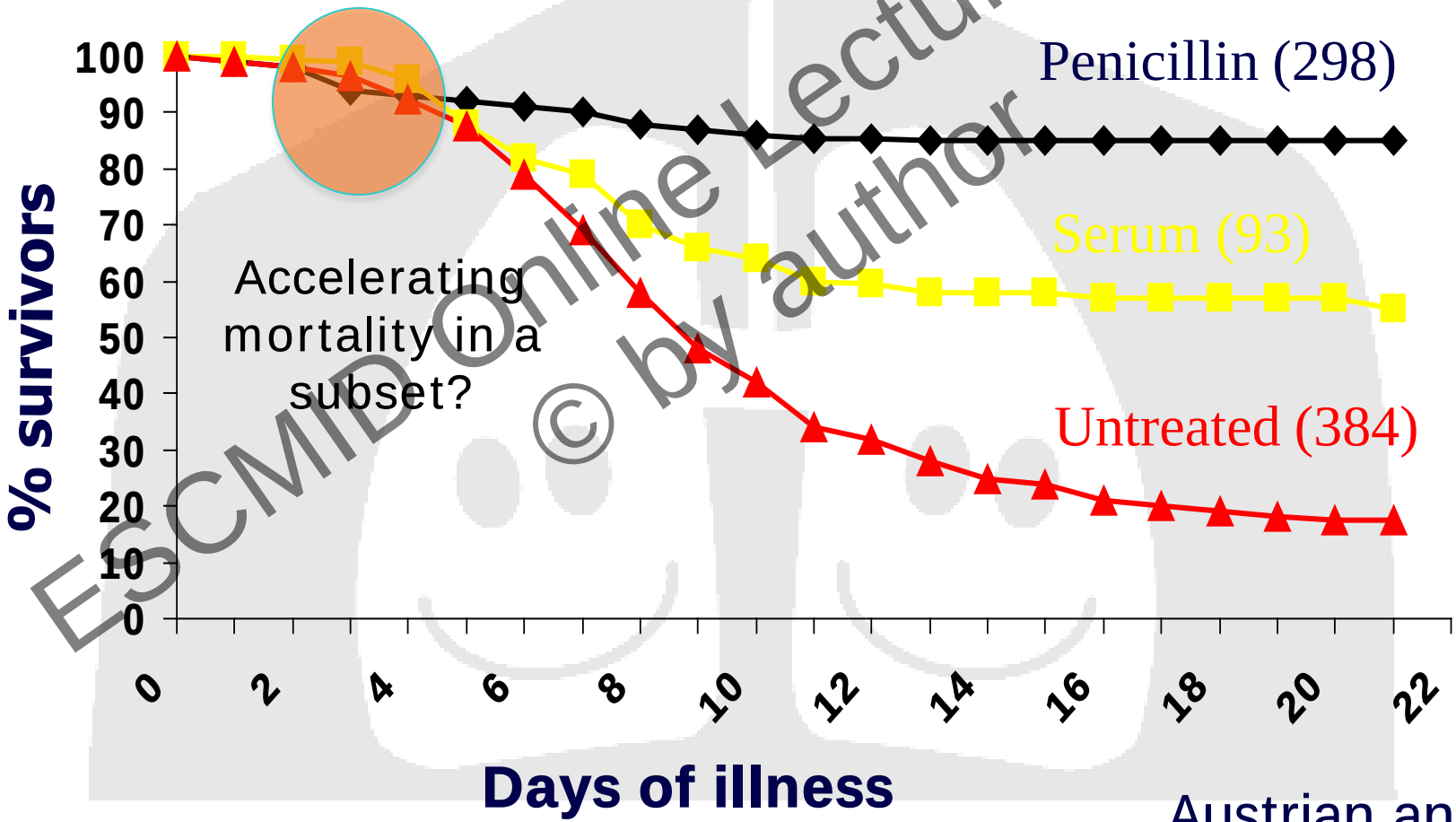
Young lady with fatal pneumonia

- 1.7 million copies/ml
- 24 hours before death
- 18 hours before septic shock
- 12 hours before ARDS

- Got the result at 13.30 – 4 hours after presentation and 18 hours before death

Antibiotics can set a fatal cytokine storm in motion

Effect of antibiotics on mortality in pneumococcal bacteremia



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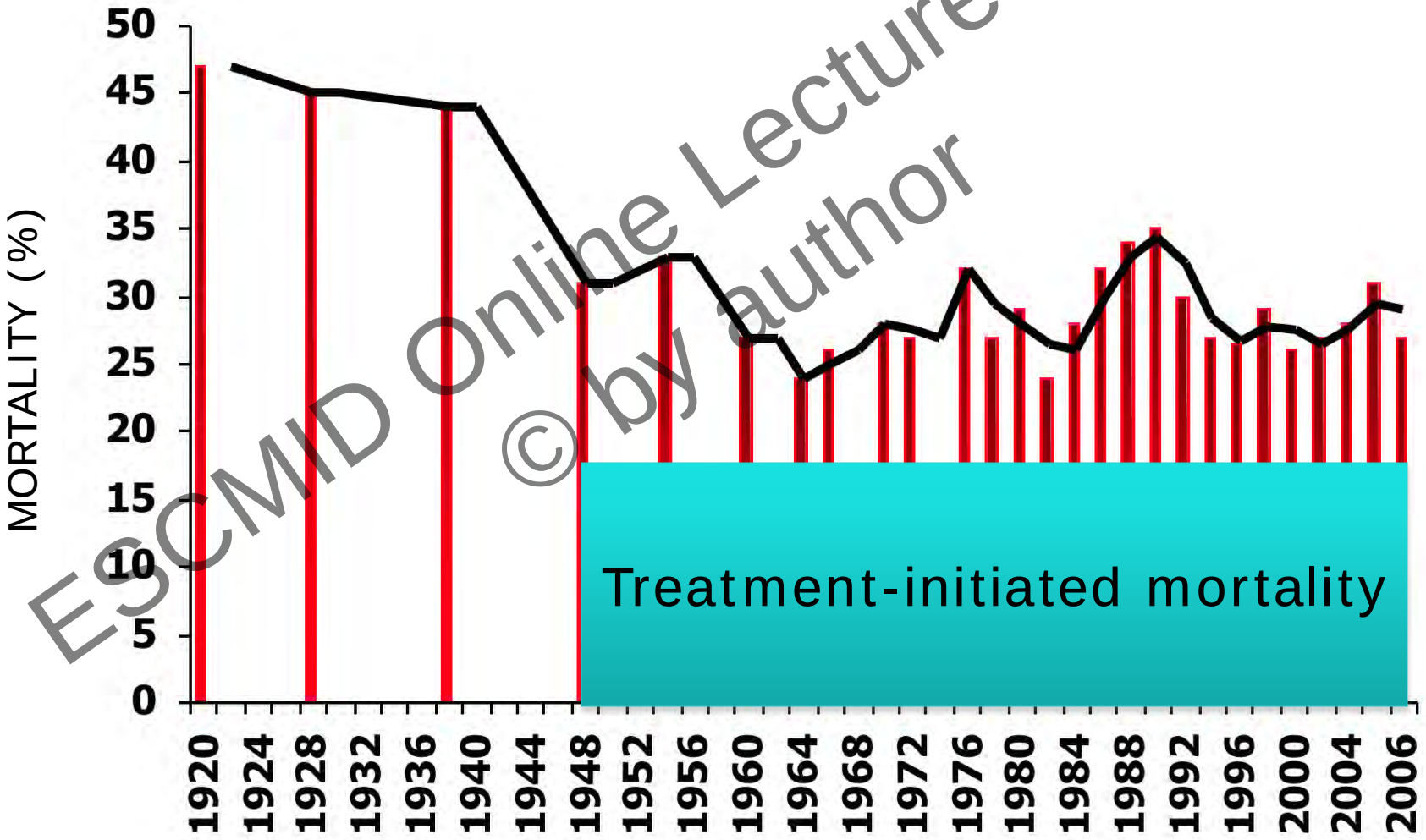
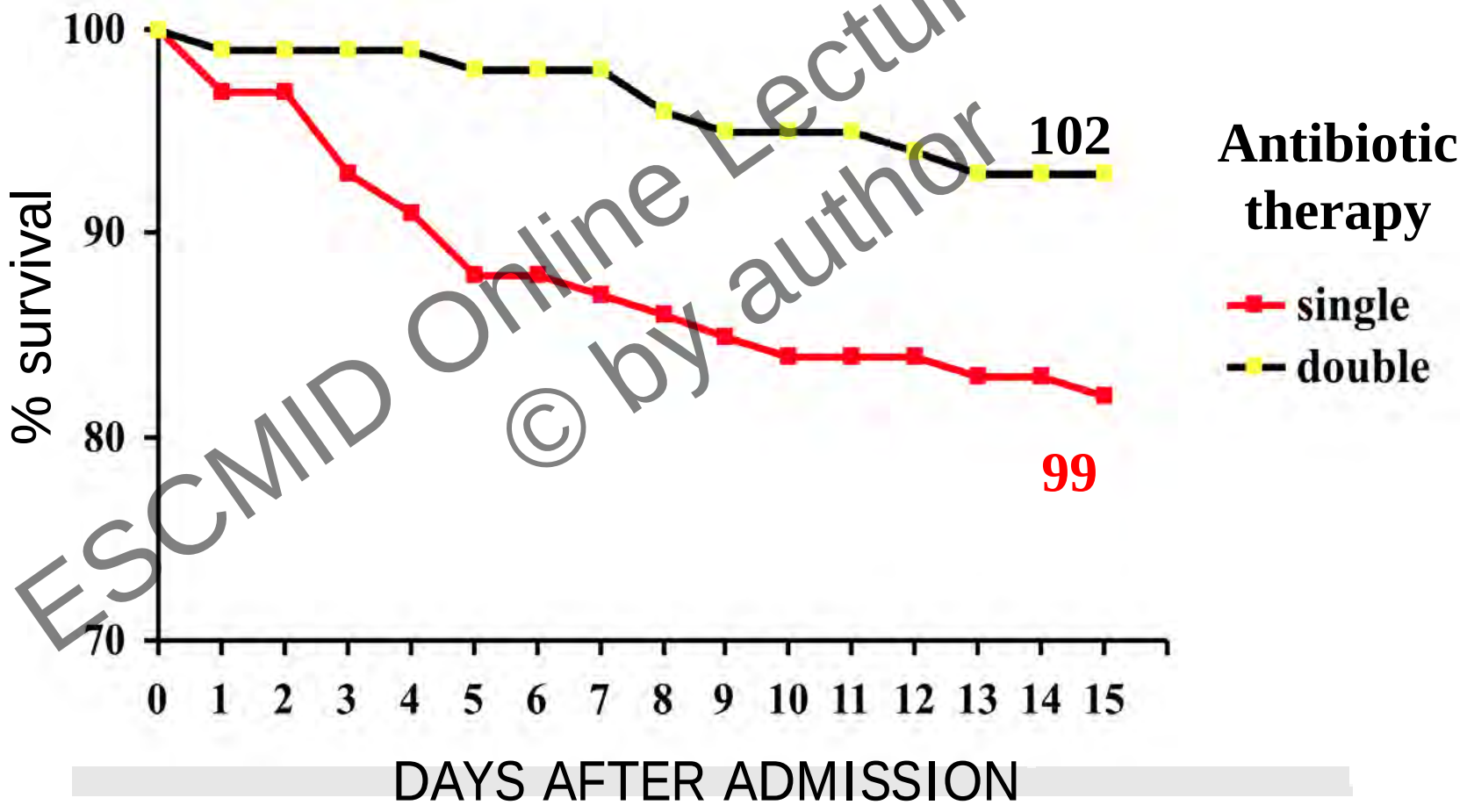


USA data compiled from published studies and Vital Statistics Reports

If antibiotics are part of the problem – what do we do?

- Reduce the virulence while waiting for bacterial clearance
- Improve the resilience of end organs to inflammatory mediated damage

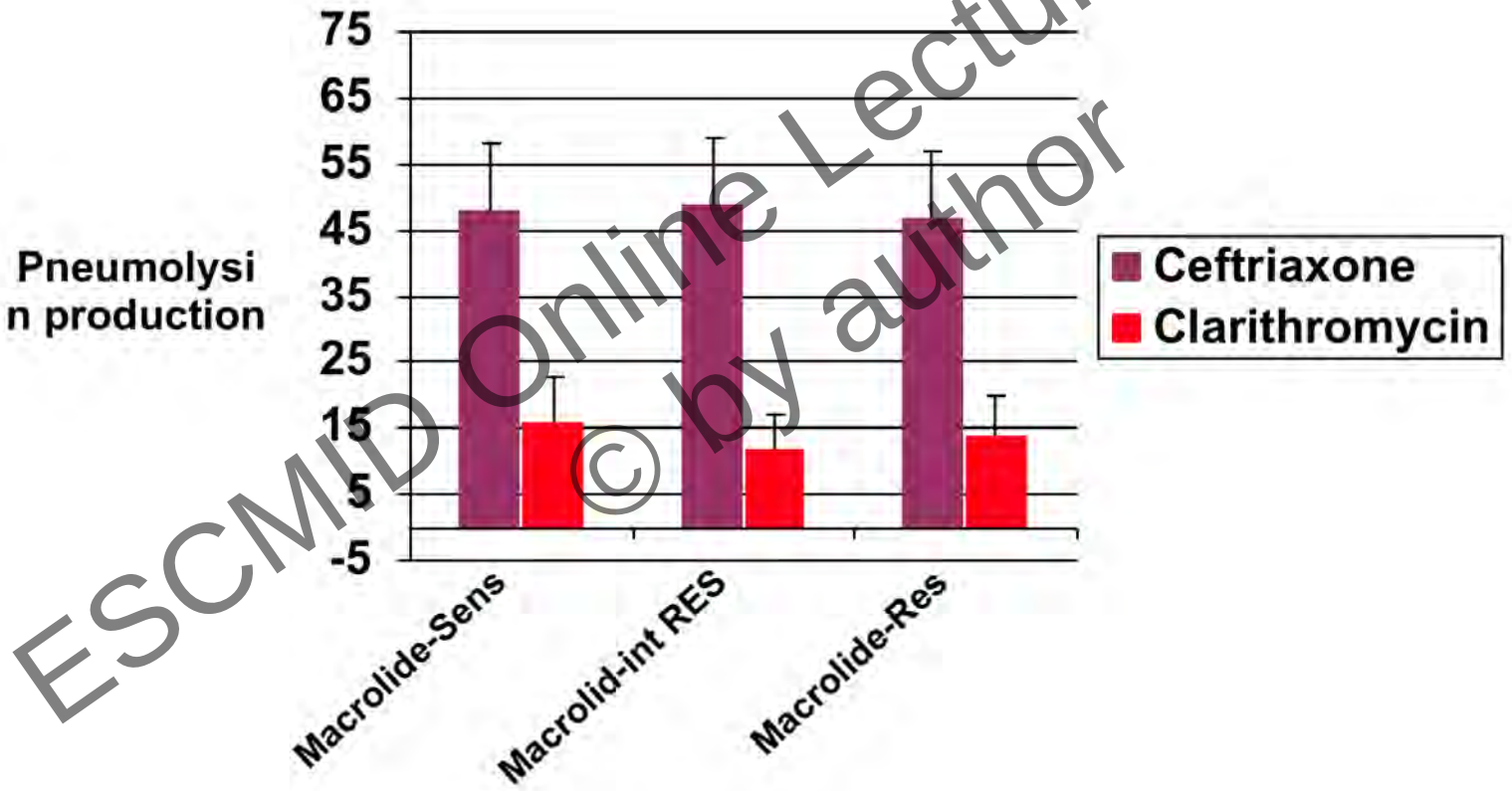
Survival in Patients with Bacteremic Pneumococcal Pneumonia



Waterer et al Arch Int Med 2001

Macrolides as non-lethal antimicrobials

Inhibition of pneumococcal pneumolysin production



Feldman et al J Antimicrob Chemother 2007

The research options are enormous

- Alternative antibiotic strategies for high vs low bacterial load
- Steroids
- Anti-TNF
- Prophylactic activated protein C
- Plasmapharesis
- etc etc

Many other potential uses of quantitative bacterial load

Other potential applications

- Febrile neutropenia
  - Generic anti-fungal and 16S PCRT
  - Bacterial vs fungal
- Early detection of nosocomial sepsis
  - When to change a CVL?
- MRSA vs MSSA

Summary

- These results challenge many of our treatment paradigms in CAP
- We need to explore the relevance of changes in bacterial load
  - e.g. treatment duration, complications etc
- This is likely to change the way we approach CAP and probably all patients with potential sepsis

The limit is in the horizon

- It’s a great time to be doing clinically orientated pulmonary infectious diseases research
- Need bigger clinical research networks to exploit the opportunities

Acknowledgements

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