GIG CYMRU NHS WALES

Iechyd Cyhoeddus Cymru

Public Health Wales

23rd August 2016

Why we perform susceptibility testing

Robin A Howe

Why do we do susceptibility tests?

- Clinical
  - Choose antimicrobial

Prediction of outcome

Definitions of antimicrobial susceptibility and resistance in relation to clinical breakpoints

- **Clinically Susceptible (S)**
  - –a micro-organism is defined as susceptible by a level of antimicrobial activity associated with a high likelihood of therapeutic success

- **Clinically Intermediate (I)**
  - –a micro-organism is defined as intermediate by a level of antimicrobial activity associated with indeterminate therapeutic effect

- **Clinically Resistant (R)**
  - –a micro-organism is defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure.

Micro-organism SIR is defined by applying the appropriate breakpoint in a defined phenotypic test system

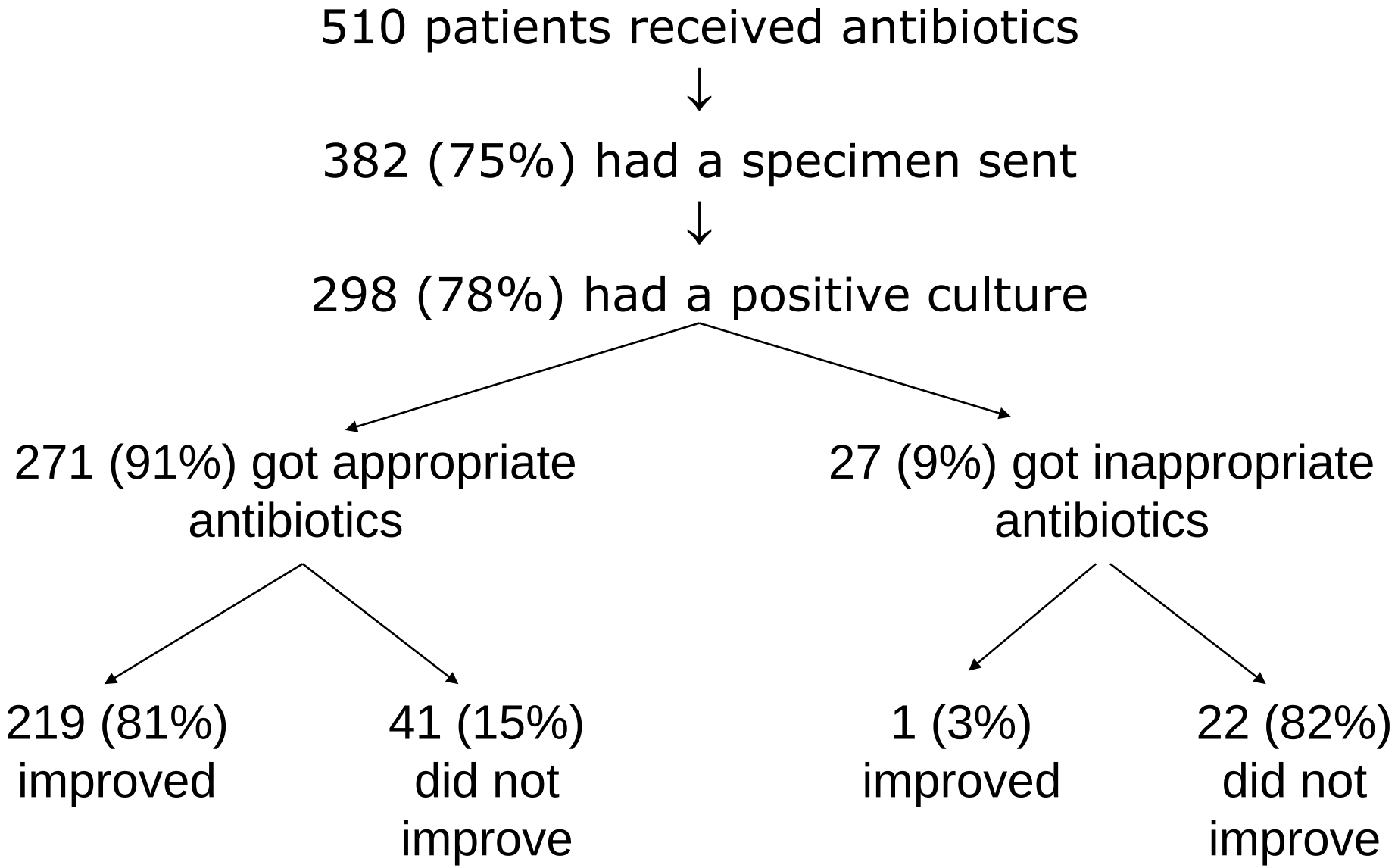
Is susceptibility testing useful?

Victor Lorian (1990)

Journal of Antimicrobial Chemotherapy

Vol 25, 175-181.

Predictive value of susceptibility tests for the outcome of antimicrobial therapy


510 patients received antibiotics
382 (75%) had a specimen sent
298 (78%) had a positive culture
271 (91%) got appropriate antibiotics
27 (9%) got inappropriate antibiotics
219 (81%) improved
41 (15%) did not improve
1 (3%) improved
22 (82%) did not improve

Why do we do susceptibility tests?

- Clinical
  - Choose antimicrobial
  - Direct empiric therapy
  - Optimise therapy

Community-acquired bloodstream infections admitted to ITU

- 30 ITUs in Spain - 339 CA-BSI
- Inappropriate initial therapy in 14.5% patients

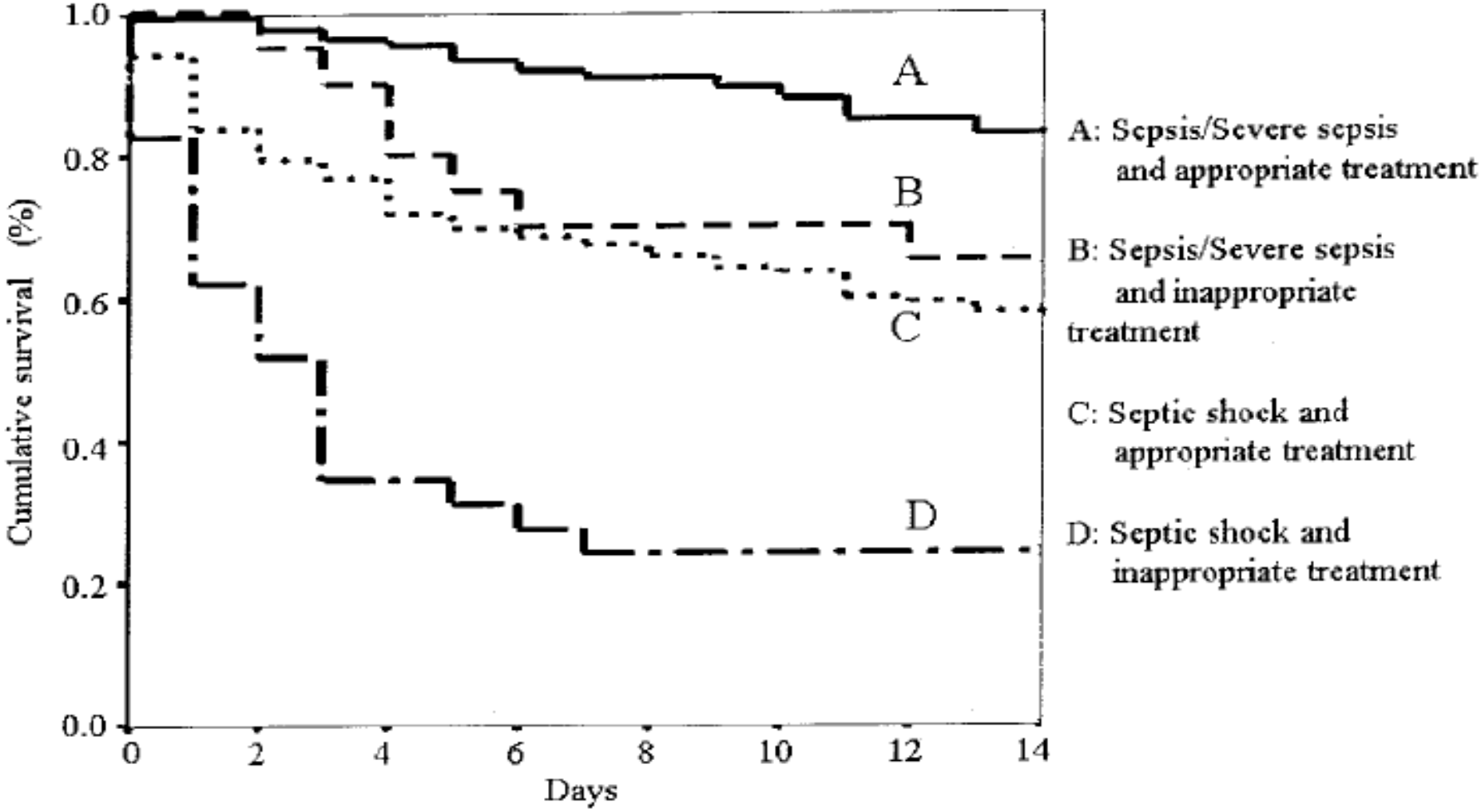
Organism	No. of patients	No. with Septic shock (%)	No. with inappropriate therapy (%)	No. died (%)
S. pneumoniae	55	20 (36.4)	4 (7.3)	18 (33.3)
S. aureus	46	26 (56.5)	15 (32.6)	27 (58.6)
All Gram positives	148	62 (41.9)	25 (16.9)	61 (41.5)
E.coli	86	55 (64)	8 (9.3)	34 (39.5)
All Gram negatives	143	88 (61.5)	14 (9.8)	55 (38.5)

Valles et al (2003) Chest 123: 1615

	Overall	Appropriate therapy	Inappropriate therapy
Mortality	43.1%	37%	69.4%

Multivariate analysis:

inappropriate therapy independently predicted mortality (OR, 4.11; 95% CI 2.03 – 8.32)



The Value of Routine Microbial Investigation in Ventilator-Associated Pneumonia

JORDI RELLO, MIGUEL GALLEGO, DOLORS MARISCAL, ROSARIO SOÑORA, and JORDI VALLES

Intensive Care, Respiratory and Microbiology Departments, Hospital de Sabadell, Sabadell, Barcelona, Spain

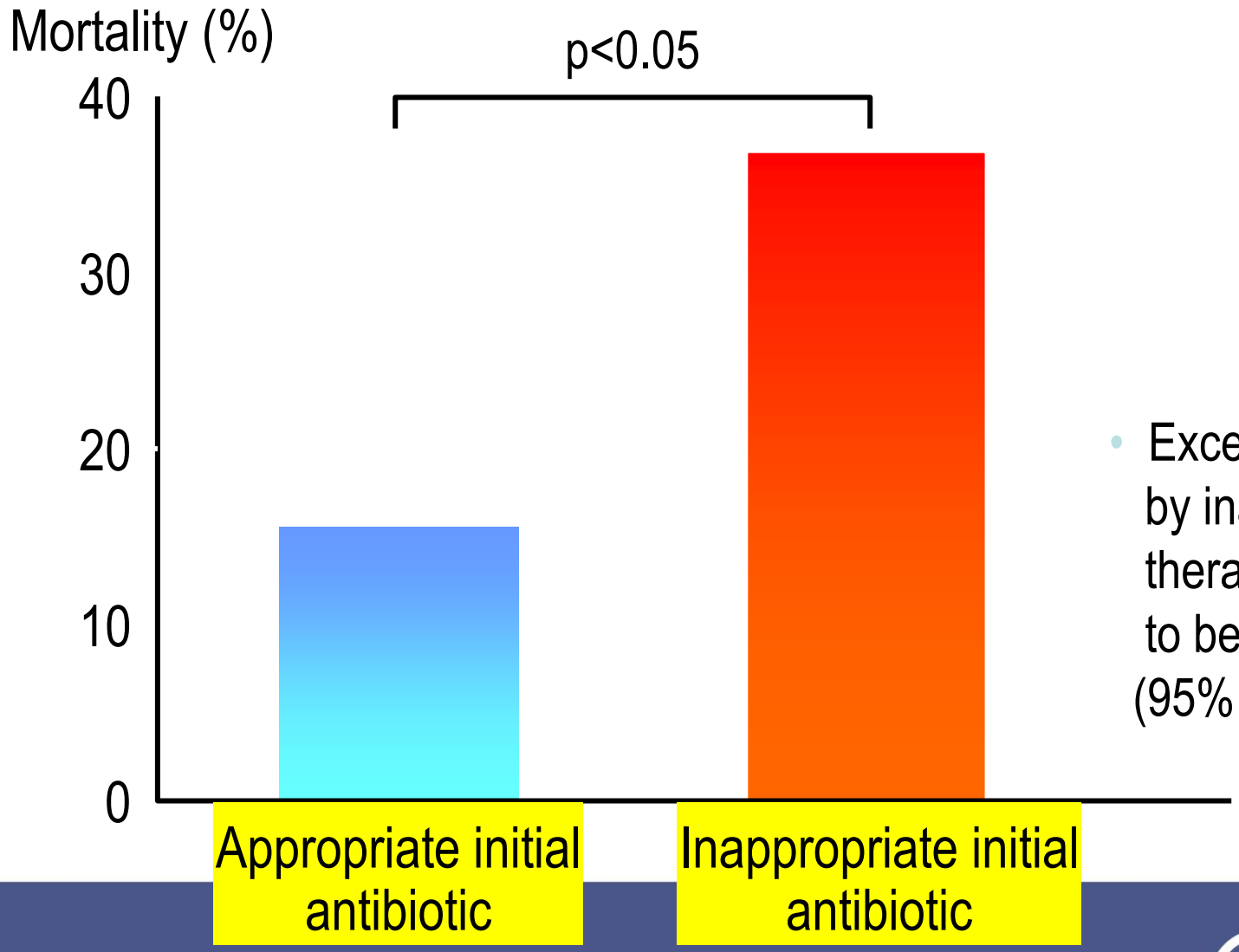
- A prospective study of 113 patients with VAP assessed
  - utility of micro investigations in guiding A/B use
  - influence of micro investigations on clinical outcome
- Microbial investigations included:
  - blood culture (78.7% of cases)
  - culture of protected brush specimens (95.5% of cases)
  - BAL culture (45.5% of cases)
- Immediately after diagnosis, empiric antibiotic therapy was either initiated or modified
- Antibiotic therapy could subsequently be changed based on culture and susceptibility studies

Rello et al. Am J Respir Crit Care Med 1997;156:196–200

The Value of Routine Microbial Investigation in Ventilator-Associated Pneumonia

JORDI RELLO, MIGUEL GALLEGO, DOLORS MARISCAL, ROSARIO SOÑORA, and JORDI VALLES

Intensive Care, Respiratory and Microbiology Departments, Hospital de Sabadell, Sabadell, Barcelona, Spain



- Excess mortality caused by inappropriate initial therapy was estimated to be 21.4% (95% CI, 43.2 to -0.03)

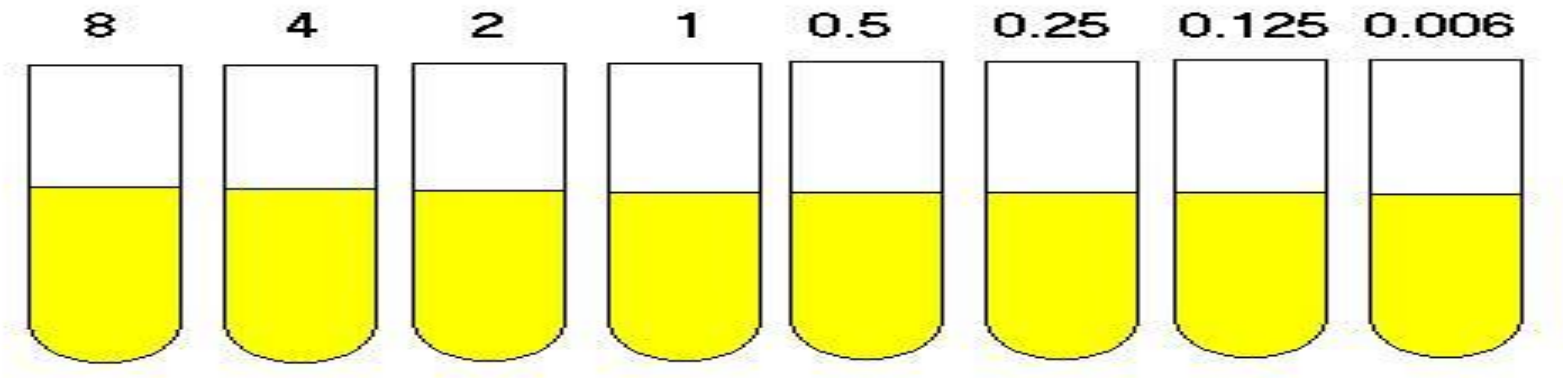
Rello et al. Am J Respir Crit Care Med 1997;156:196–200

Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

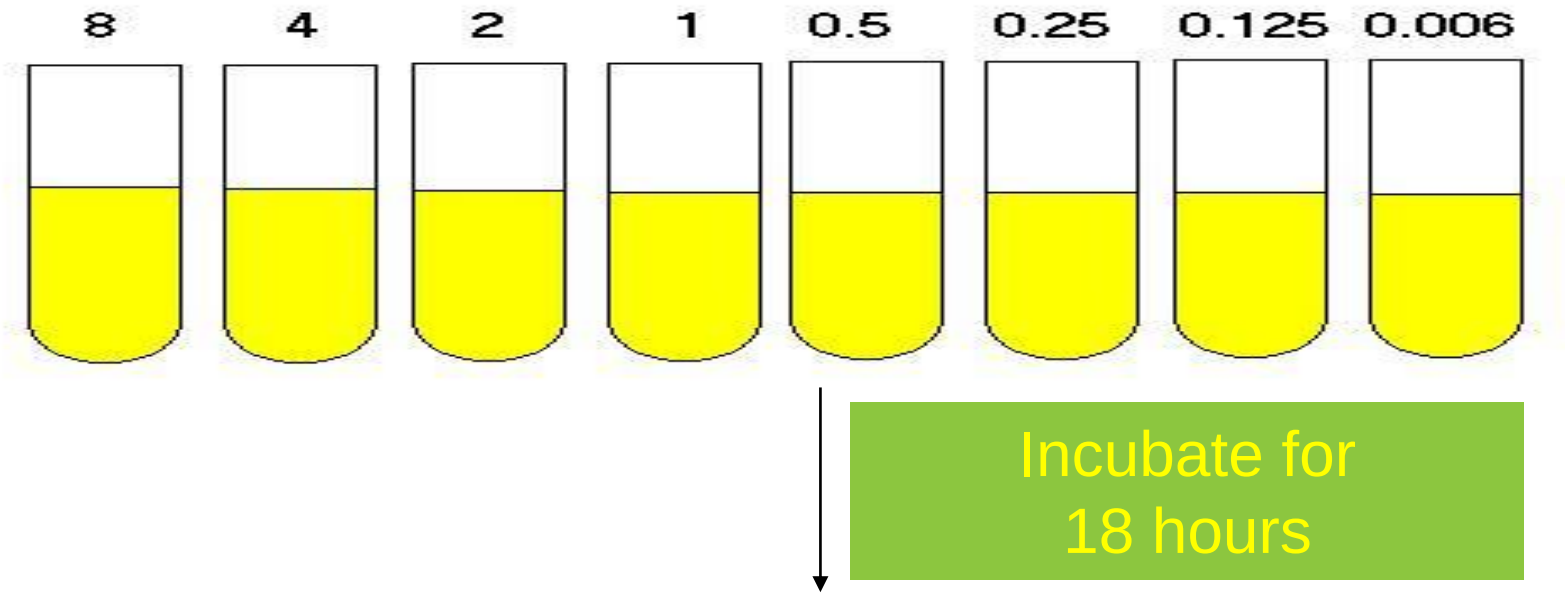
Dellinger et al. (2004) Critical Care Medicine 32(3): 858-873

1. Intravenous antibiotic therapy should be started within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained.
2. Initial empirical anti-infective therapy should include one or more drugs that have activity against the likely pathogens and that penetrate into the presumed source of sepsis.
   - The choice of drugs should be guided by the susceptibility patterns of microorganisms in the community and in the hospital.
   - The initial selection of an empirical antimicrobial regimen should be broad enough, according to these criteria, covering all likely pathogens since there is little margin for error in critically ill patients. There is ample evidence that failure to initiate appropriate therapy promptly (i.e., therapy that is active against the causative pathogen) has adverse consequences on outcome

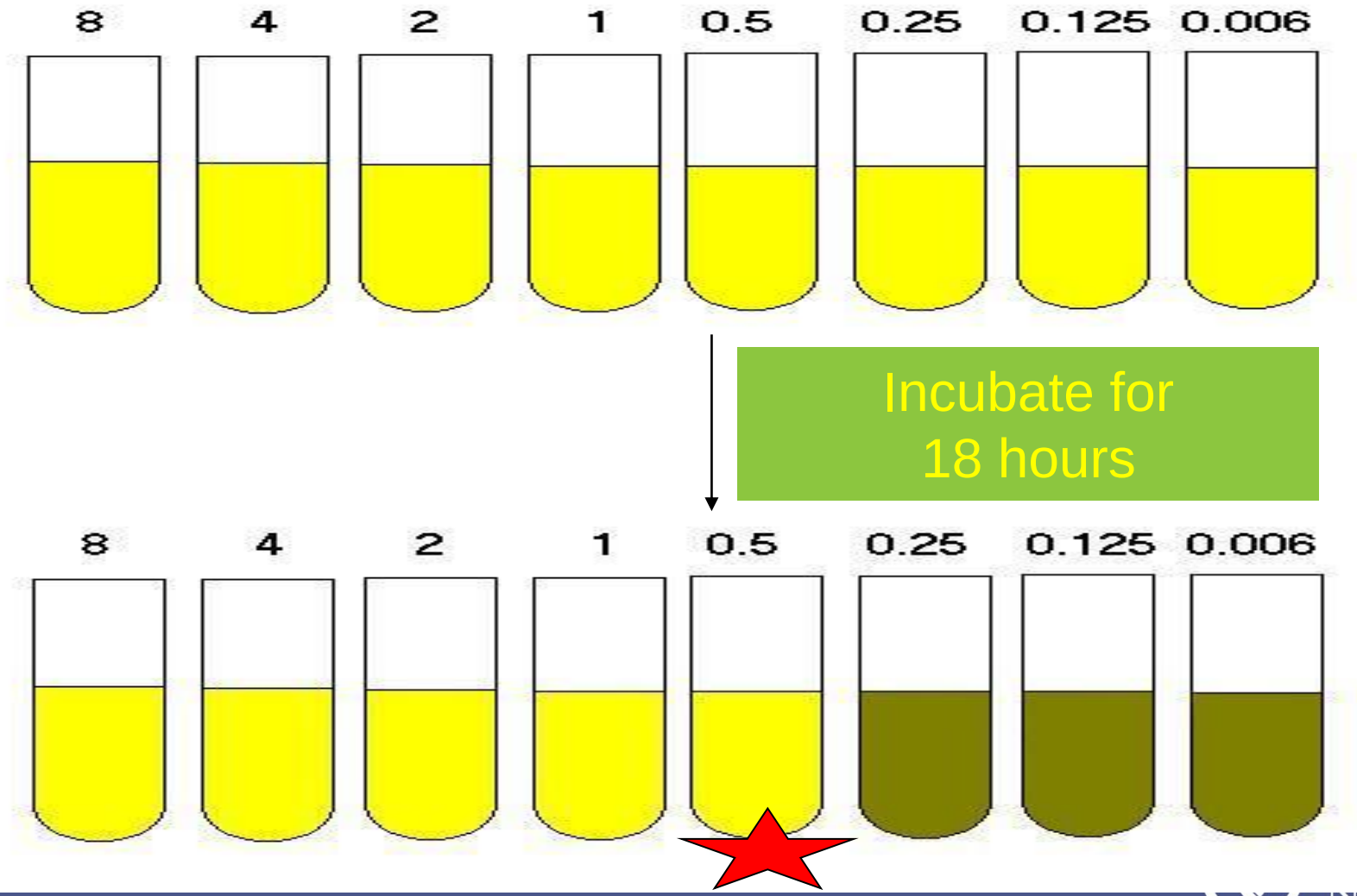
MIC (minimum inhibitory concentration)– the gold standard for susceptibility testing



MIC (minimum inhibitory concentration)– the gold standard for susceptibility testing



MIC (minimum inhibitory concentration)– the gold standard for susceptibility testing



Why do we do susceptibility tests?

- Clinical
  - Choose antimicrobial
  - Direct empiric therapy
  - Optimise therapy
- Epidemiological tracking of resistance
- Research

MIC wild type distributions, ECOFFs and their usefulness.

MIC distributions

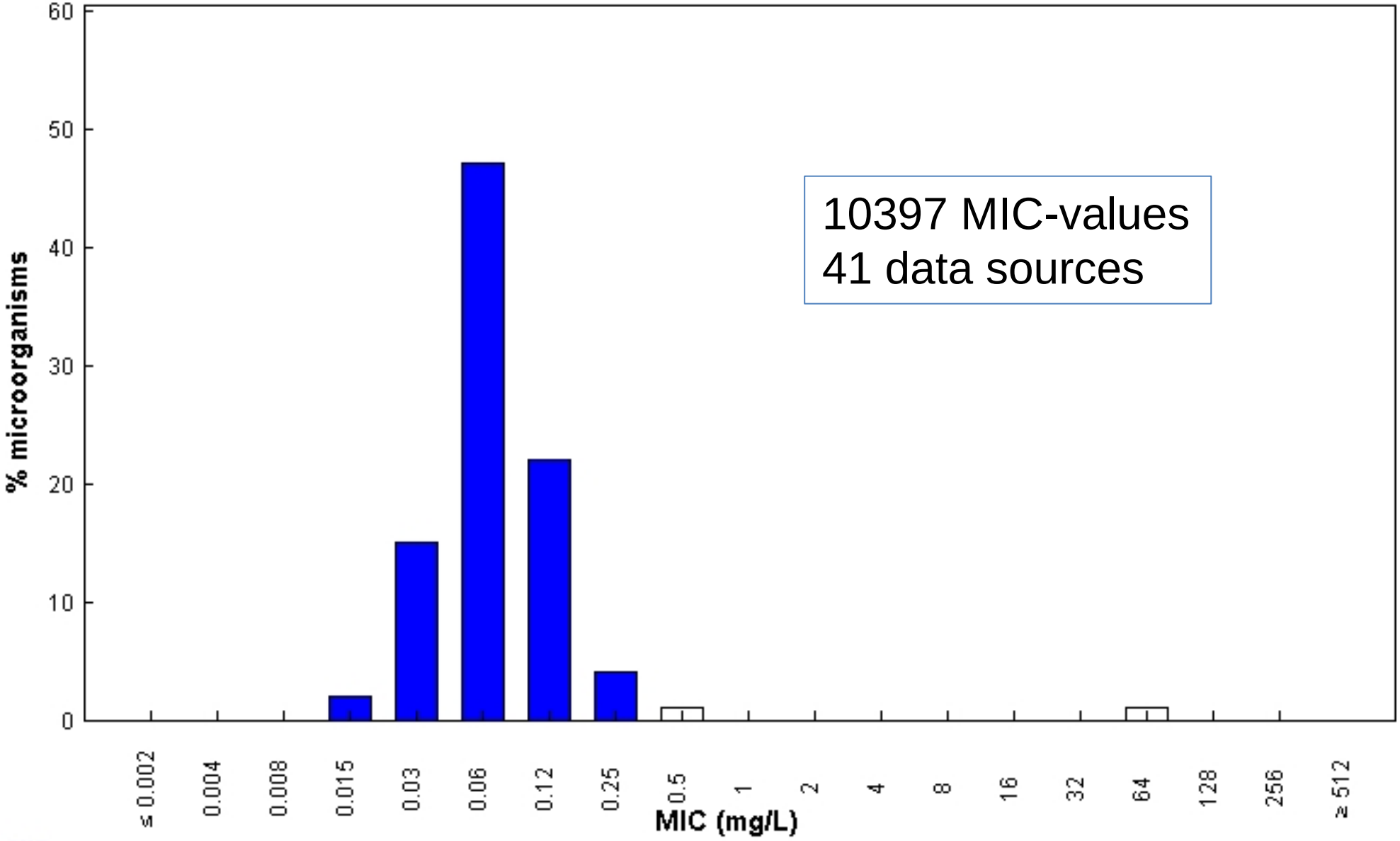
- If you ask many investigators from many countries
  - in different settings,
  - some working with humans,
  - some working with animals,
  - using the same standardised method,

to contribute 100 – 1000 MIC-values each to a common “MIC-bank”, this is what you get:

Cefotaxime / Escherichia coli

International MIC Distribution - Reference Database 2015-02-22

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



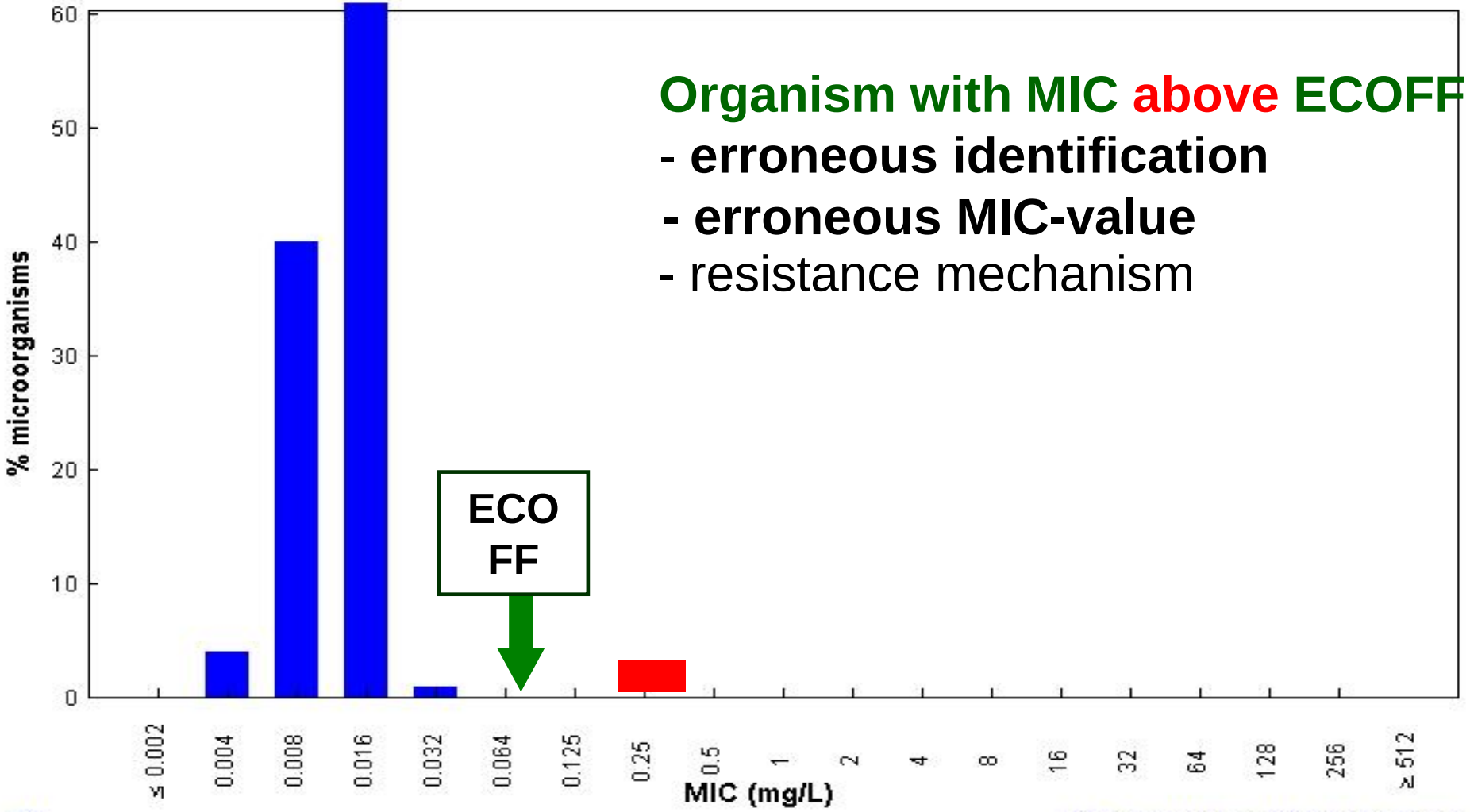
10397 MIC-values
41 data sources

MIC
Epidemiological cut-off (ECOFF): 0.25 mg/L
Wildtype (WT) organisms: ≤ 0.25 mg/L

10397 observations (41 data sources)

Benzylpenicillin / Streptococcus pyogenes
EUCAST MIC Distribution - Reference Database

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



Organism with MIC above ECOFF:
- erroneous identification
- erroneous MIC-value
- resistance mechanism

MIC
Epidemiological cut-off: WT ≤ 0.064 mg/L

3615 observations (11 data sources)
Clinical breakpoints: S ≤ 0.25 mg/L, R > 0.25 mg/L

Epidemiological cutoff

For a species and an agent, the MIC value which will distinguish between organisms without (wild type) and with (non-wild type) phenotypically detectable resistance mechanisms.

- The ECOFF is the highest MIC value of isolates devoid of phenotypically expressed resistance.
- The ECOFF is also the lowest possible S-breakpoint once it is decided that the species is a good target for the agent.

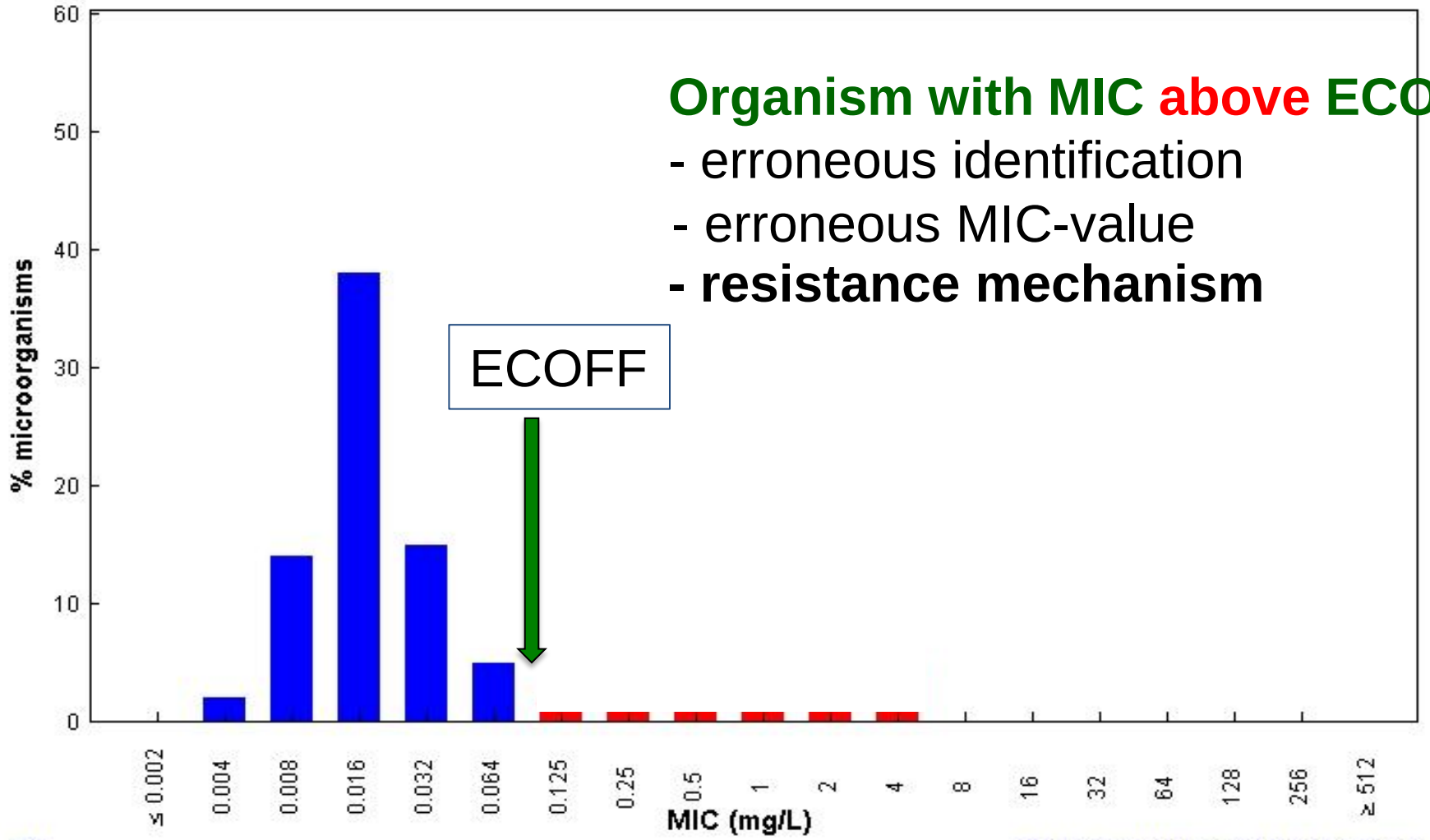
- Wild type ≤X mg/L
- Non wild type >X mg/L

Where X = the ECOFF

Benzylpenicillin / Streptococcus pneumoniae

EUCAST MIC Distribution - Reference Database

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



Organism with MIC above ECOFF:

- erroneous identification
- erroneous MIC-value
- **resistance mechanism**

MIC

Epidemiological cut-off: WT ≤ 0.064 mg/L

37642 observations (32 data sources)

Clinical breakpoints: S ≤ 0.064 mg/L, R > 2 mg/L

The concept of Wild Type MIC distribution and ECOFFs
is based on the fact that all individuals within a wild type are very similar and that the major difference is between those that are inside and those that are outside the wild type and that the distribution is not affected by the …

1. geographical origin of the isolates
2. temporal origin of the isolates
3. whether isolates originate from the human or the animal field

Systematic differences between clones of a species inside the wild type (growth rate, growth requirements, virulence, etc) may affect the perceived sensitivity of the organism to the agent in question.

The use of ECOFFs

- As a tool in the determination of clinical breakpoints
  - To avoid dividing wild type MIC distributions of important target organisms
  - As a surrogate clinical breakpoint when Pk/Pd data is incomplete and clinical data pertain only to wild type organisms

- For **sensitive detection of (to screen for) resistance**
  - oxacillin to detect all penicillin-R in *S. pneumoniae*
  - cefoxitin to detect methicillin resistance in *S. aureus*
  - benzylpenicillin to detect all betalactam resistance in *H.influenzae*
  - pefloxacin to detect quinolone resistance in Salmonella spp
  - meropenem to screen for KPC in Enterobacteriaceae

- For **surveillance of antimicrobial resistance** when clinical breakpoints…
  - are not sensitive enough
  - have not been determined
  - change over time
  - differ between systems (CLSI, FDA, EUCAST etc)
  - differ between humans, cows, pigs, birds, fish and camels.

- to **exclude resistance**
  - food safety – in the development of functional foods

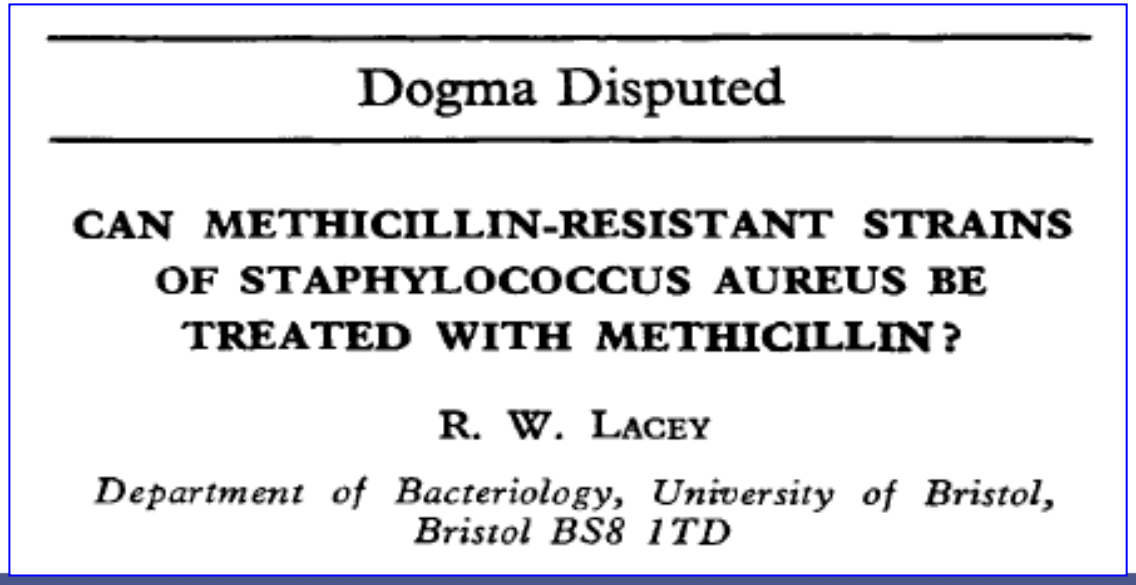
Expert rules

- Phenotypic tests may not identify resistance mechanisms (variable expression) and therefore may not corellate with clinical efficacy…

MRSA

- The presence of mecA has been associated with clinical failure

  ...although there were dissenters



Dogma Disputed

CAN METHICILLIN-RESISTANT STRAINS OF STAPHYLOCOCCUS AUREUS BE TREATED WITH METHICILLIN?

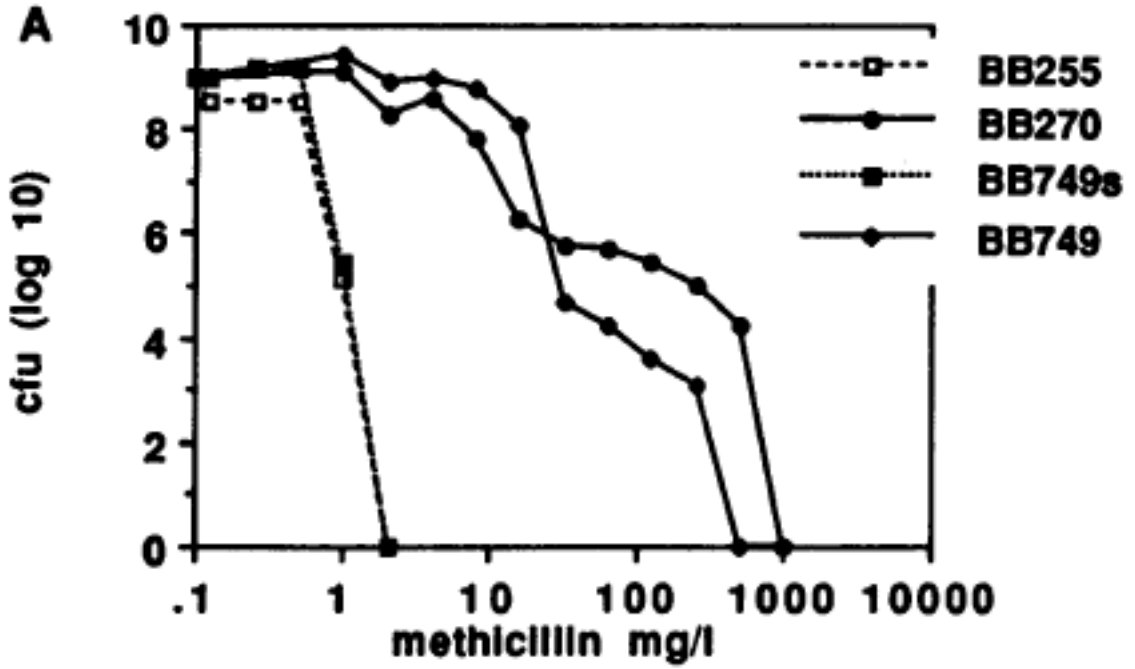
R. W. LACEY

Department of Bacteriology, University of Bristol, Bristol BS8 1TD

MRSA

- Methicillin resistance is heterogeneously expressed by many strains

- When using methicillin to test need to optimise expression of resistance by addition of salt and/or incubation at 30^{0C}



Ryffel et al (1994) AAC 38: 724

MRSA

- Even with optimisation, results with different beta-lactams are unreliable

TABLE 1. Effect of addition of 2% NaCl to CSMHB with 50 MRSA strains

Antibiotic	No. of $\log_2$ MIC differences[a] (CSMHB+S compared with CSMHB)										% Resistant (moderately susceptible)	
	−1	0	+1	+2	+3	+4	+5	+6	+7	Indeterminate[b]	CSMHB	CSMHB+S
Methicillin		3	13	18	8	1	1			6	66	98
Oxacillin		1	12	12	7	8	2	2	1	5	84	100
Cephalothin		1	7	4	11	23	4				18 (4)	72 (18)
Cefazolin			11	5	13	9	7	1		4	34 (10)	92 (6)
Cefamandole		6	25	17	1	1					4 (14)	30 (34)
Cefonicid			9	22	6	3				10	64 (28)	100 (0)
Cefotaxime		1	7	17	16	3				6	22 (56)	90 (10)
Imipenem		3	13	15	10	6				3	6 (4)	12 (2)
Amoxicillin-clavulanate		14	29	6	1						98	100
Ticarcillin-clavulanate	1	20	20	9							14 (48)	24 (70)

[a] Includes some values off the scale in one medium, i.e., > highest test concentration or ≤ lowest test concentration.
[b] Indeterminate because of MICs off the scale in both media.

Jorgensen et al. (1988) JCM. 26: 1675

MRSA

- Expert rule:

IF resistant to isoxazolyl-penicillins (as determined with oxacillin, cefoxitin, or by detection of mecA-gene or of PBP2a), THEN report as resistant to all b-lactams except those specifically licensed to treat infections caused by methicillin-resistant staphylococci owing to low affinity for PBP2a

Conclusions

- AST is performed primarily to predict the likely clinical outcome of treatment.
- MICs & ECOFFs provide additional epidemiological information
- Phenotypic tests perform well
  - Expert rules can refine clinical information