Appropriate Use of Antibiotics in Lower Respiratory Tract Infections

Infectious Diseases

- **Infectious disease remains a major cause of mortality and morbidity but the development of antimicrobials has greatly reduced the mortality and morbidity** [1]
- **Almost 10% of the worldwide burden of morbidity & mortality relates to respiratory tract infections** [2]
- **There are still serious problems in defining and choosing the most appropriate antimicrobials for clinical therapy** [1]

The goals of antimicrobial therapy, International Journal of infectious diseases, Vol. 7 Supplement 1, March 2003

Peter Ball etal, Journal of Antimicrobial chemotherapy (2002) 49, 31 - 40

Lower Respiratory Tract Infections

Pneumonia

Pneumonia has been recognized as a common and potentially lethal condition for nearly two centuries. It is regarded as the most common cause of death due to infectious disease

Symptoms include

Fever

Cough, sputum production

Pleurisy

Dyspnea

Signs include respiratory rate > 20/min, crackles are heard on auscultation in 80% and upto 30% have signs of consolidation

Bartlett JG & Mundy, New England Journal of Medicine, 1995: 1618 - 1622

Lower Respiratory Tract Infections

Acute Exacerbation of Chronic Bronchitis

Patients with AECB have bronchitis as an underlying condition and the acute exacerbation represents a progression along a continuum rather than a sudden break from the norm.

There is increased dyspnea in already dyspneic patients and increased sputum volume in patients who already have a significant amount of mucus but sputum purulence is the most important sign in differentiating between chronic bronchitis & an acute exacerbation

Bartlett JG & Mundy, New England Journal of Medicine, 1995: 1618 – 1622

Southhard. J. The American journal of managed care 1999: 333:1618-1624

Lower Respiratory Tract Infections

- **Objective**

  Optimize therapy to reduce morbidity, therapeutic failure and cost, and prevent resistance emergence

Peter Ball etal, Journal of Antimicrobial chemotherapy (2002) 49, 31 - 40

OPTIMIZE diagnosis / severity assessment

- **Correct diagnosis of bacterial infection is the key to limiting unnecessary prescribing. However, lack of availability of cost effective diagnostic tests ensures the persistence of grey areas of confusing etiology** [1]

- **Accurate assessment of the patients condition is vital if an appropriate antibiotic is to be prescribed** [2]

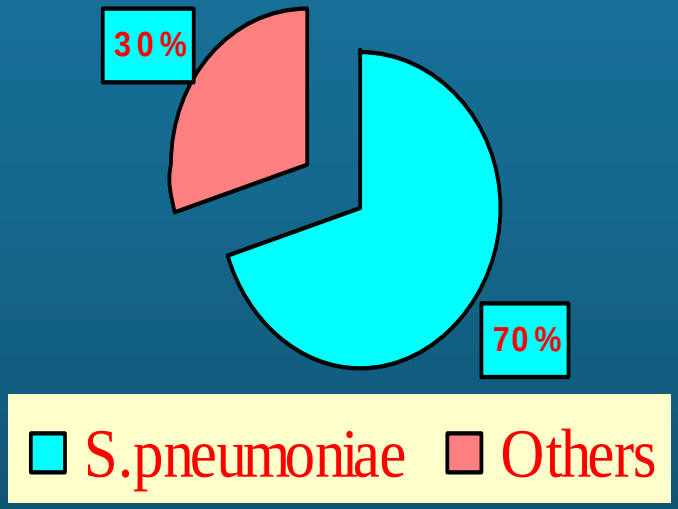
Peter Ball etal, Journal of Antimicrobial chemotherapy (2002) 49, 31 - 40
Current Opinion in Infect Diseases **2002**; **15**:149–150

LRTI

The main bacterial pathogens implicated in Lower respiratory tract infections (LRTI) are Streptococcus pneumoniae, Haemophilus influenzae & Moraxella catarrhalis

Anthony White, Journal of antimicrobial chemotherapy (2004)

Major pathogens in LRTI (CAP)



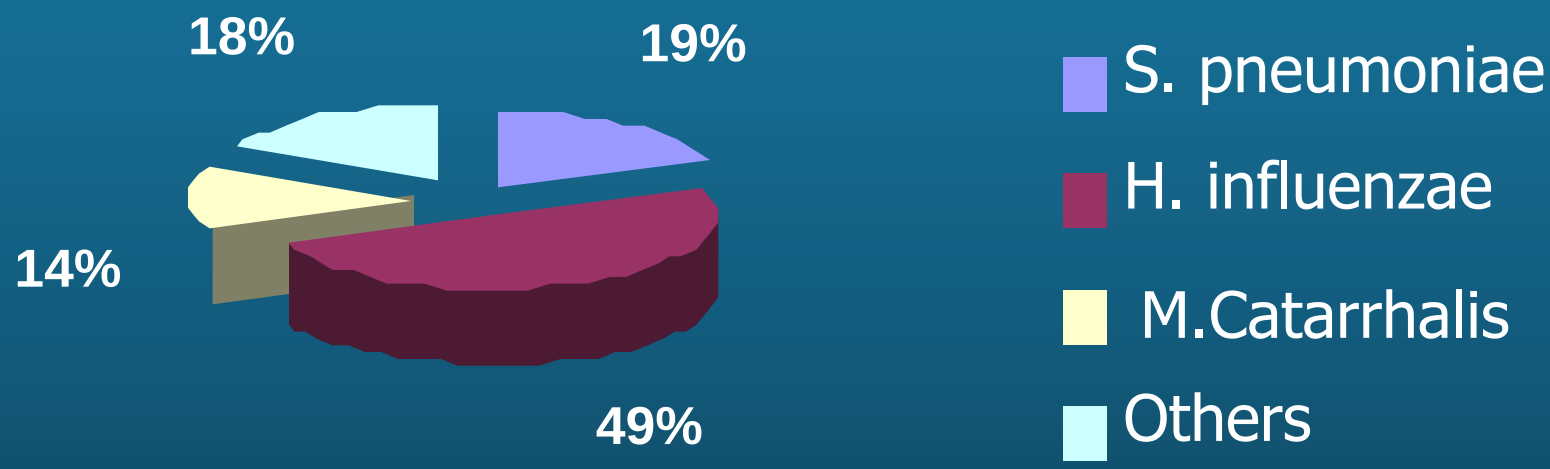
- S.pneumoniae the leading pathogen in CAP [1]

  Only 7.5% patients had an atypical pathogen detected [2]

Bartlett Jg & Mundy LM./new England Journal of Medicine (1995)333:1618-1624. *Average of prevalence figures from North American studies & British Thoracic Society. Other bacteria include S. aureus, gram -ive bacilli and M. catarrhalis.

Linda M.Mundy et al, Implications for macrolide treatment in CAP Chest (1998);113:1201-06

Major pathogens in LRTI (AECB)



H. Influenzae - the pre-dominant pathogen in AECB

Southard J. The American Journal of Managed Care (1999) 5/11 Suppl:S677-S684

Major pathogens in LRTI

Emergence of beta lactamase producing H.Influenzae & M.Catarrhalis has rendered many antimicrobials inactive [1]

Emergence of Drug resistant Streptococcus pneumoniae (DRSP) has led to increased numbers of treatment failures [2]

Amoxicillin/clavulanate for infections in infants & children, Vol. 22, No 8, August 2003

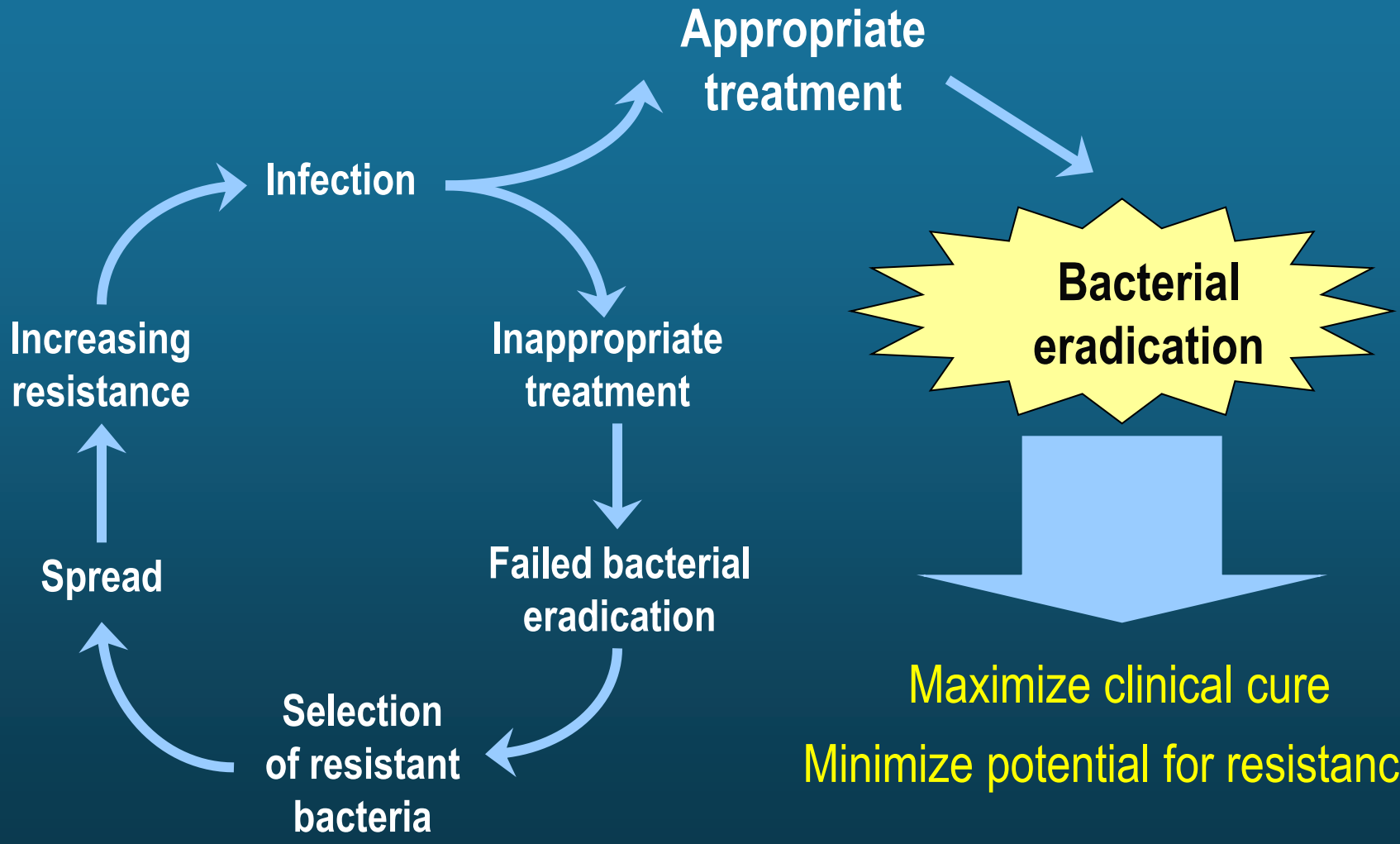
Bacteriologic efficacy in patients with DRSP, J.Garau, European society of clinical microbiology & infectious diseases 2004

We need

Reliability against beta lactamase

Reliability against DRSP

MAXIMIZE bacterial eradication in LRTI



MAXIMIZE bacterial eradication in LRTI

There is accumulating evidence to confirm bacterial eradication as the primary goal of antibiotic therapy and the main determinant of therapeutic outcome. Antibiotic therapy that allows bacterial persistence risks not only early recurrence or relapse but also resistance selection.

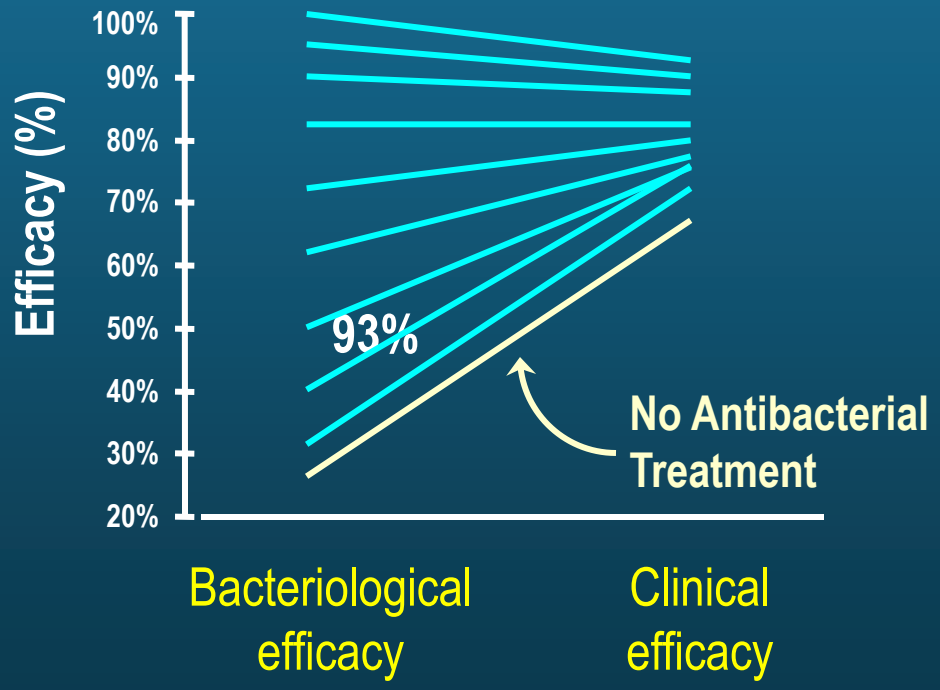
Peter Ball etal, Journal of Antimicrobial chemotherapy **(2002)** 49, 31 - 40

Limitations of clinical assessment: the ‘Pollyanna phenomenon’

“Agents with poor bacteriologic efficacy can appear clinically almost as good as those with optimal efficacy”- Pollyana effect

Calculation of success rates in patients with AOM

Bacteriological efficacy	**100%**
Clinical success	
Bacteriological efficacy	**27%**
Clinical success	**71%**



Peter Ball etal, Journal of Antimicrobial chemotherapy (2002) 49, 31 - 40

International Journal of infectious diseases / Vol. 7, Supplement 1, 2003

Bacteriological eradication maximizes clinical success: evidence in acute otitis media

Bacteriological success → **93% clinical success**
faster resolution of signs and symptoms

Bacteriological failure → **71% clinical success**
slower resolution of signs and symptoms

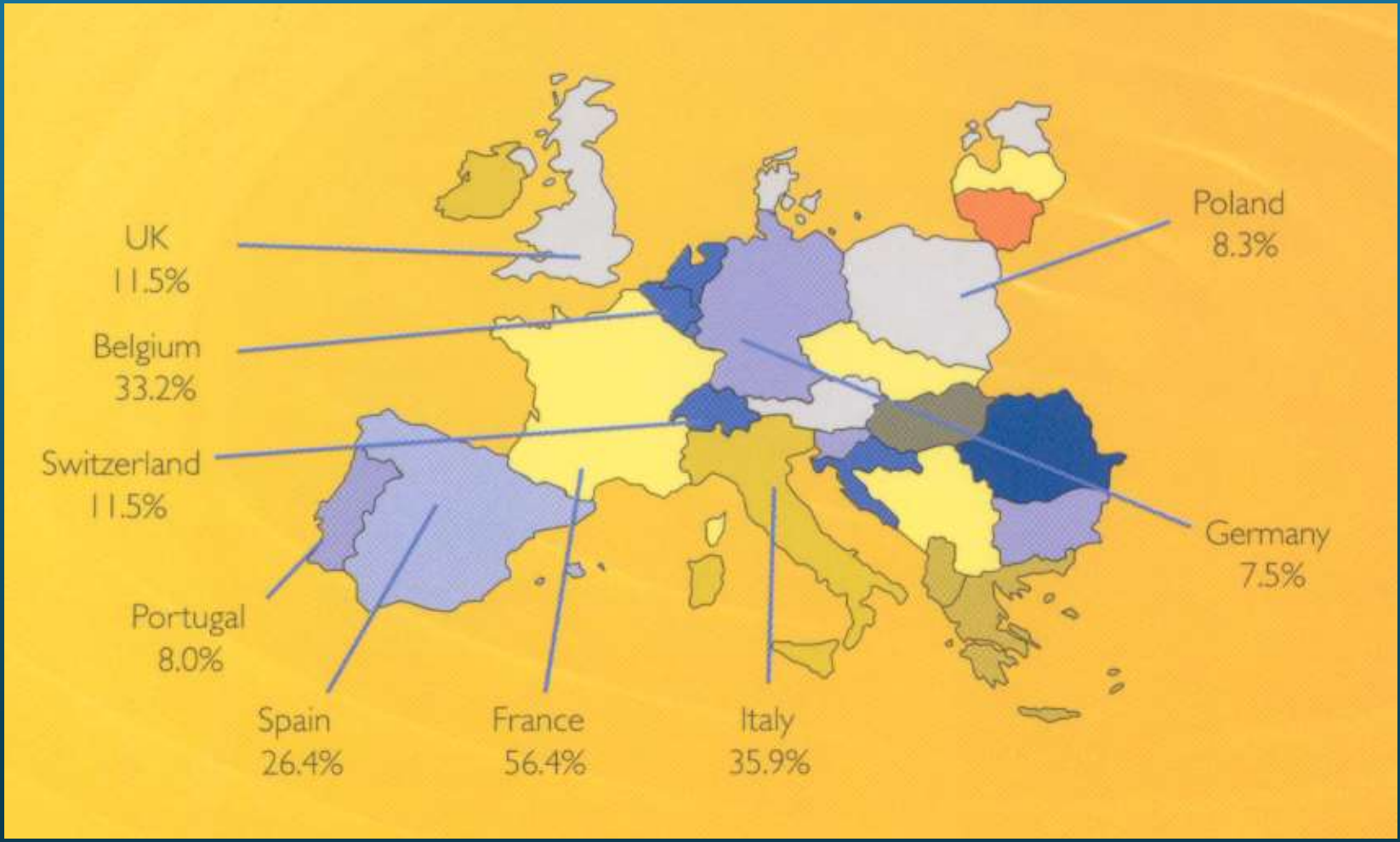
International Journal of infectious diseases / Vol. 7, Supplement 1, 2003

RECOGNIZE resistance prevalence

We are in the age of increasing bacterial resistance & antibiotic therapy should be appropriate in type and in context of local resistance prevalence

Javier Garau, Treatment of pneumococcal pneumonia. Vol 2, 7 July **2002, pg. 404 -415**

S.Pneumoniae, erythromycin resistance



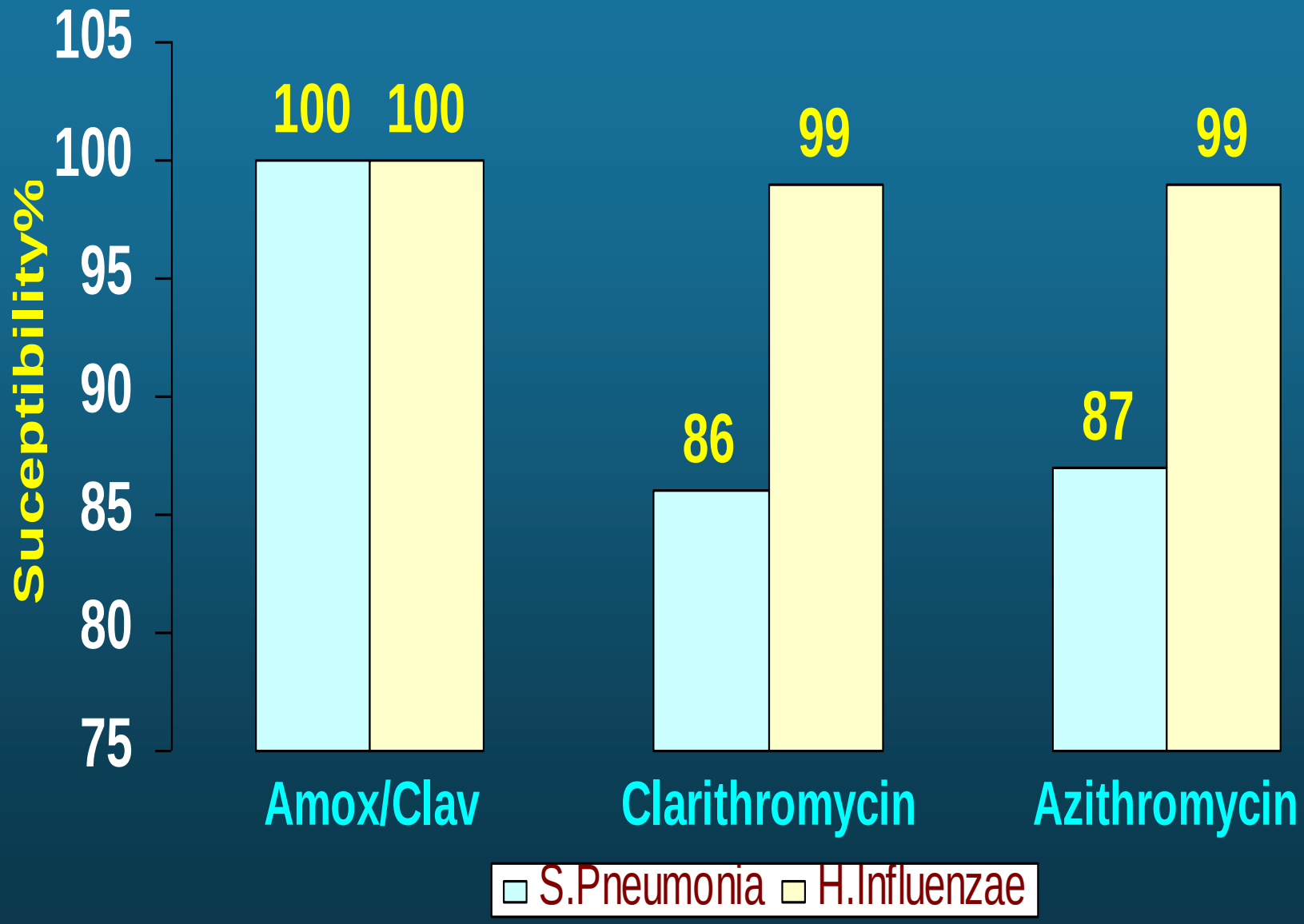
Alexander Project, 2000

SOAR Study (2002 - 2003)

- **To monitor the prevalence & spread of resistance to commonly prescribed antimicrobials , respiratory tract isolates of S.Pneumoniae and H.Influenzae were collected from patients in 3 African countries, 7 Middle eastern countries and Pakistan in the 2002/03 winter season**

- **MICs for various antimicrobials were determined using Etest and susceptibility assessed on NCCLS breakpoints**

SOAR Study (2002 - 2003) Pakistan



SOAR Study, Antimicrobial resistance among Strep.Pneum and H.Inf **2003**

Resistance patterns in LRTI

- DRSP (Drug Resistant *Strep. pneumoniae*) Therapeutic working Group does not recommend the newer Fluoroquinolones as first line treatment because resistance among pneumococci will rapidly emerge with their widespread use(27)

Karnath B et al,Pneumococcal pneumonia;Update on Therapy in the era of Antibiotic resistance, Consultant, March 2003

Resistance patterns in LRTI

- Recent reports from Hong Kong,Canada and the USA indicate emergent quinolone resistant pneumococci
- Clinical failures in pneumonia caused by levofloxacin-resistant *s.pneumoniae* confirm that emergent resistant is becoming clinically relevant

Journal of Antimicrobial Chemo therapy (2002) 49,34-35

UTILIZE PD for effective therapy in LRTI

PK/PD relationship for effective therapy

Pharmacokinetics

means the way in which body handles the drug. It includes absorption, distribution, metabolism & elimination of drug

Pharmacodynamics

means the effects of drug on body & includes mechanism of action & biochemical & physiological effects of drug

Lippincotts Pharmacological basis of therapeutics 2000;

UTILIZE PD for effective therapy in LRTI

Determining potency of antimicrobial agents

- **Minimal Inhibitory concentration (MIC) determination**
- **Minimal Bactericidal concentration (MBC) determination**

M.Jacobs, International Journal of infectious diseases / Vol. 7, Supplement 1, 2003

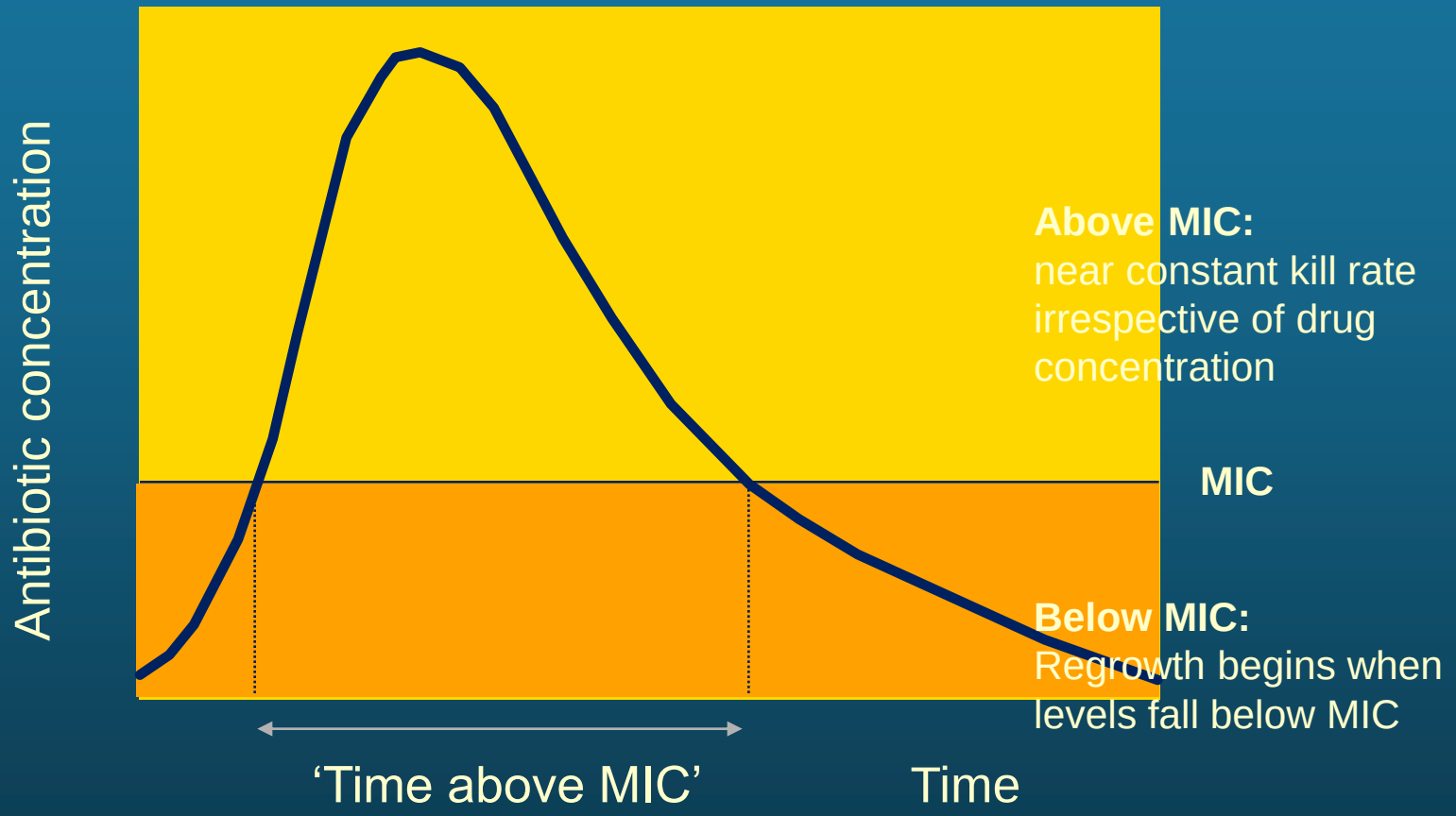
UTILIZE PD for effective therapy in LRTI

PK/PD indices include

- **the time for which non protein bound concentrations exceed the MIC (T>MIC)**
- **the ratio between peak serum concentration (Cmax) amd MIC (Cmax/MIC)**
- **the relationship between drug exposure (AUC) and MIC (AUC/MIC).**

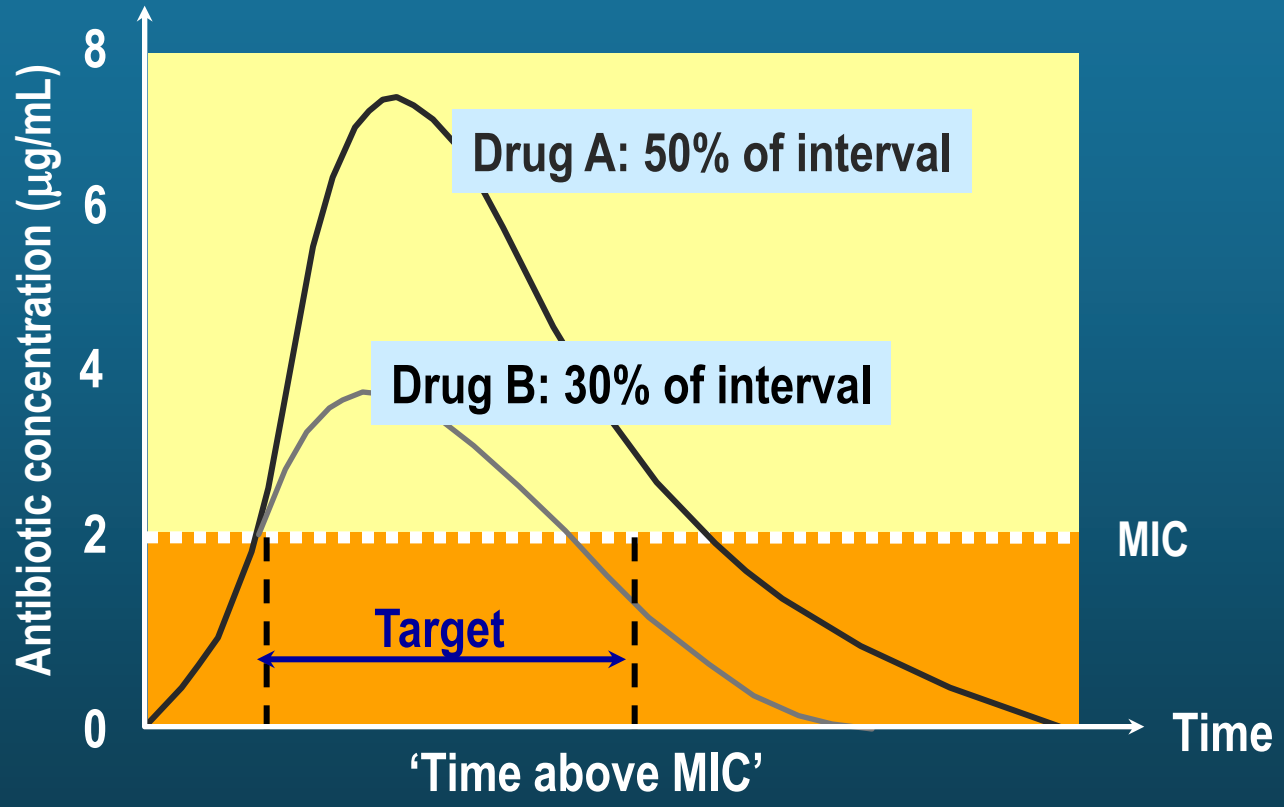
Peter Ball etal, Journal of Antimicrobial chemotherapy (2002) 49, 31 - 40

‘Time above MIC’



‘Time above MIC’ = the time that serum concentrations of free antibiotic exceed MIC

Target for β-lactams = 'Time above MIC'



'Time above MIC' > 40% correlates with clinical and bacteriological outcome
Drug B does not achieve this pharmacodynamic target

Peter Ball etal, Journal of Antimicrobial chemotherapy (2002) 49, 31 - 40

PK / PD Indices

Using PK/PD indices, it is easier to predict the efficacy of a regimen in terms of

- **Clinical outcome**
- **Bacteriological eradication**
- **Prevention of resistance emergence**

Peter Ball etal, Journal of Antimicrobial chemotherapy (2002) 49, 31 - 40

Conclusions:
ABC (the goal of antibiotic therapy in LRTI)

Appropriate antibiotic therapy guided by PD

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Bacteriological eradication

Reduces:
- clinical failure
- recurrence or relapse
- selection of resistance

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Clinical cure

Reduces:
- morbidity
- mortality
- resource utilization / cost

THANK YOU