Population-based approaches: Regulatory issues and Population simulations

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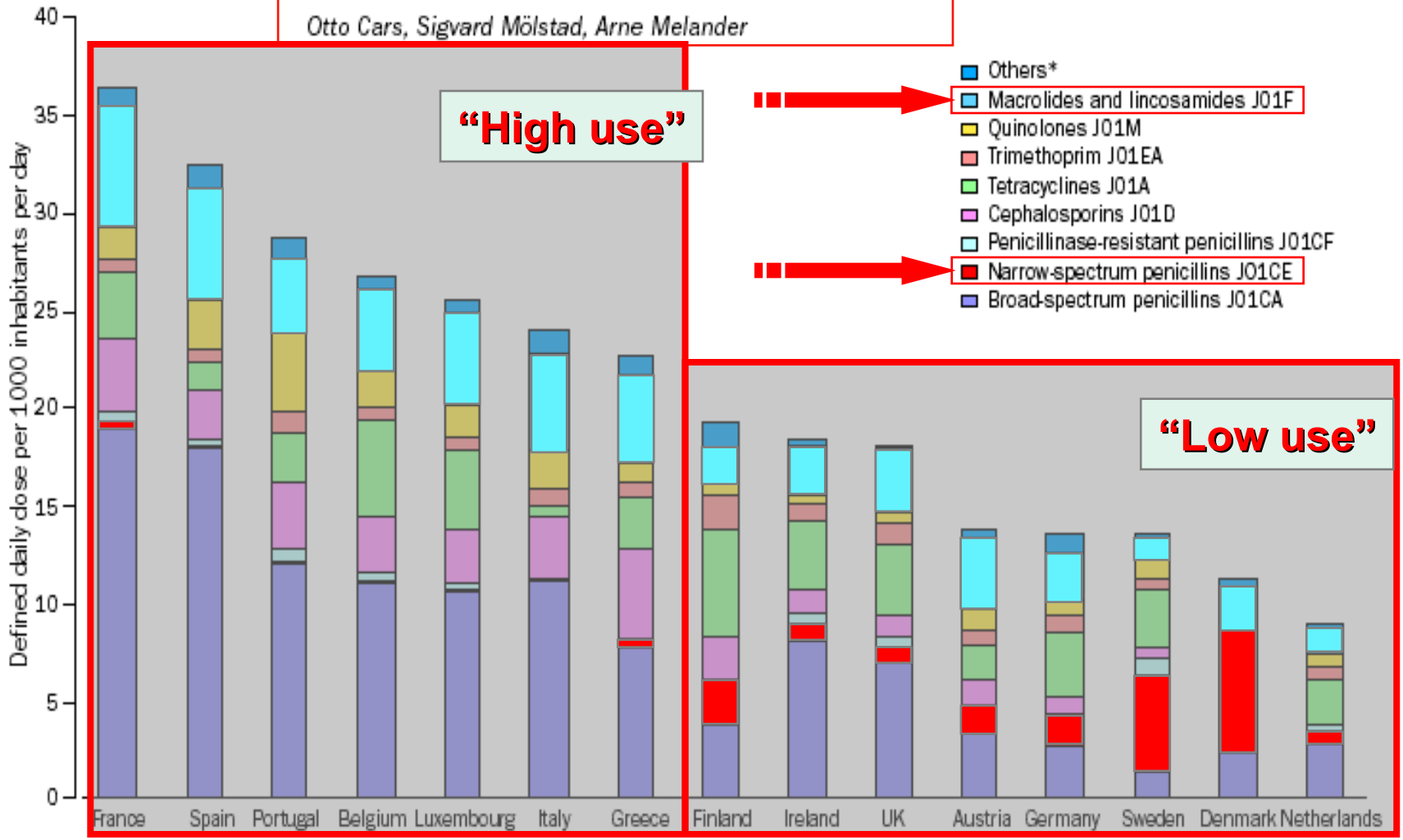
Topics

- Regulatory issues
  - Regulatory agents require demonstration of safety and therapeutic non-inferiority to suitable comparator/s for licensing
  - "Non-inferiority" in most RTIs is very easy to demonstrate as most RTIs are self-limiting
- Population-based simulations
  - In the absence of adequate data, computer simulations of outcome of infection can be determined using a statistical model that determined the outcome of infection based on MIC distributions and PK distributions – referred to as "Monte Carlo simulations"
  - "Therapeutic outcome model"

Variation in antibiotic use in the European Union

Otto Cars, Sigvard Mölstad, Arne Melander



Outpatient antibiotic sales in 1997 in the European Union

*Includes sulphonamides, penicillinase-resistant penicillins, amphenicols, aminoglycosides, and glycopeptides.

Lancet 357:1851-1853, 2001

Outpatient clinical studies in respiratory tract infections

- High-rate spontaneous resolution makes it difficult to show differences between agents
- Bacteriologic outcome studies are not often performed due to necessity for invasive procedure (ear, sinus or lung tap) to obtain specimen
- Most studies are therefore designed to show equivalent clinical outcome between established and new agents
- Inadequacies of agents studied are therefore often not apparent

Regulatory issues

- Regulatory agents require demonstration of safety and therapeutic non-inferiority to suitable comparator/s for licensing
- Placebo-controlled studies are almost never conducted
- Formulas used to calculate sample sizes needed in clinical studies contain assumptions about the outcome of the disease being studied
- Formulas also contain values chosen to represent the difference between study arms that is considered “acceptable” and is typically set at 10% to 20%

Assuring Assay Sensitivity in Non-Inferiority Trials

In a non-inferiority trial, assay sensitivity is not measured in the trial. That is, the trial itself does not show the study's ability to distinguish active from inactive therapy. Assay sensitivity must, therefore, be deduced or assumed, based on historical experience showing sensitivity to drug effects, a close evaluation of study quality and, particularly important, the similarity of the current trial to trials that were able to distinguish the active control drug from placebo.

Assay sensitivity can be measured in an active control trial if there is an "internal standard," a control vs placebo comparison as well as the control vs test drug comparison (i.e., a three-arm study).

RJ Temple, MD, CDER, FDA, Feb 19, 2002

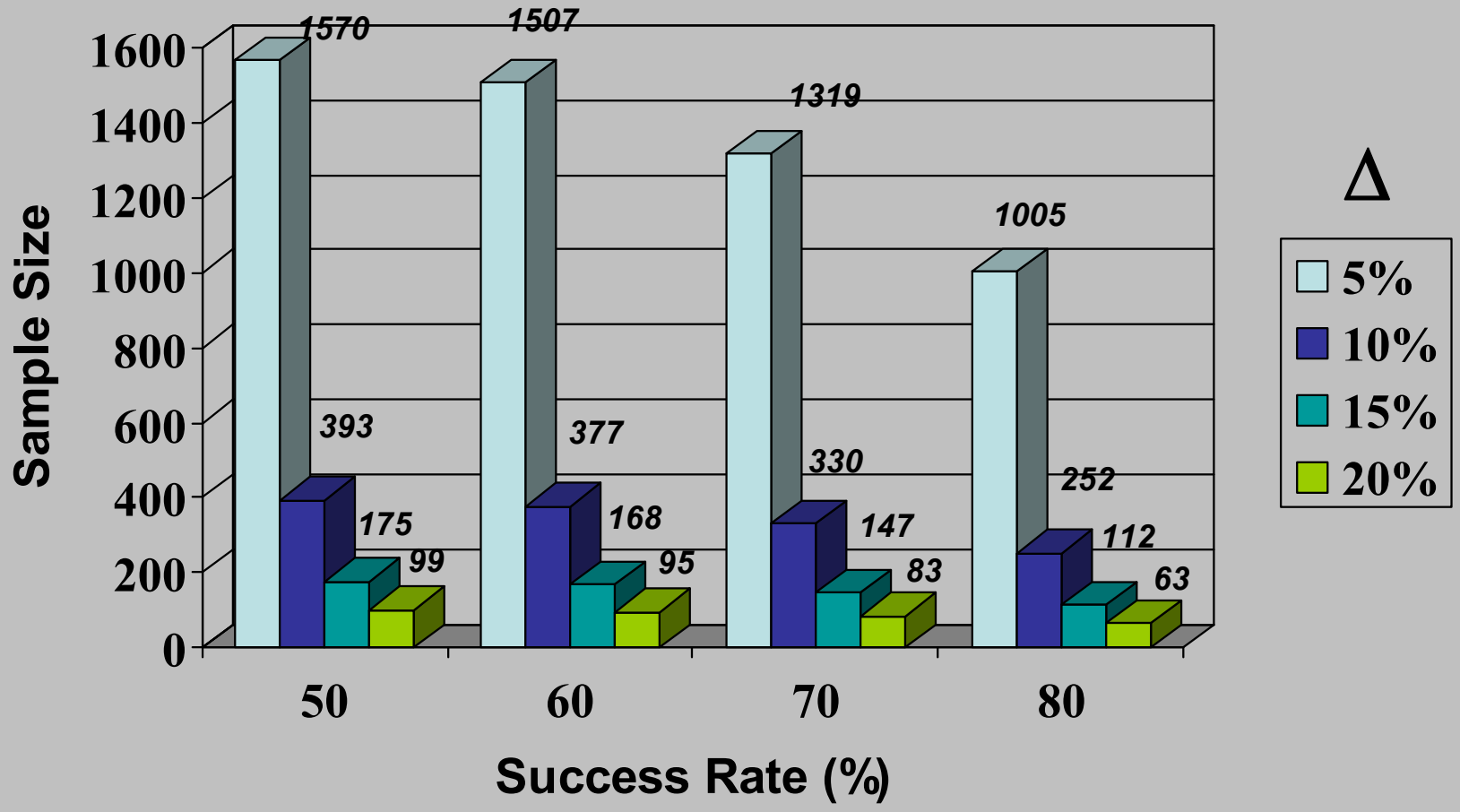
Historical Evidence of Sensitivity to Drug Effects

To people's surprise, there are many effective drugs that cannot be said to have HESDE, i.e., that are not regularly superior to placebo in well-done studies of adequate size

To illustrate, about 46% of well-done trials of effective antidepressants cannot distinguish drug from placebo. No one knows how to choose a population, sample size, or design that will alter this state

RJ Temple, MD, CDER, FDA, Feb 19, 2002

Clinical Trial Implications:
Sample size per arm to achieve 80% power based on differences between study arms



R Albrecht, MD. CDER, FDA, Feb 19, 2002

Consequence to Patients

- If accept a delta of 15% instead of delta of 10% as evidence of non-inferiority, the consequence is that
  - *the drug is potentially 5% less effective*
  - *an extra 5000 patients may potentially fail therapy for each 100,000 patients treated*

R Albrecht, MD. CDER, FDA, Feb 19, 2002

Why are conclusions of clinical trials apparently (sometimes and apparently) contradictory ?

- insufficient separation of covariables
  - only one or a few dosage regimens

Correct but incomplete conclusion

- not enough true failures
  - self-limiting diseases
  - study design
- intercurrent variables influencing outcome and not recognized as such

No conclusions possible

- insufficient or inappropriate collection of PK data
  - only “peaks” or troughs...

Conclusions of poor value (shed confusion…)

H. Sun, ISAP-FDA Workshop, 1999

Regulatory issues

- "Non-inferiority" in most RTIs is very easy to demonstrate as most RTIs are self-limiting
- Clinical studies of RTIs can be improved if patients are stratified by disease severity or other factors that have been shown to be associated with outcome
  - PORT criteria in CAP
  - Stratification of AECB patients
  - Age in acute otitis media

Patient Stratification in Community Acquired Pneumonia (CAP)

Pneumonia Outcomes Research Team (PORT) Study

- Stratified patients into 5 Pneumonia Severity Index (PSI) risk classes based on risk of mortality at 30days
- PSI can be used to guide decision to hospitalize patients with CAP

A PREDICTION RULE TO IDENTIFY LOW-RISK PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

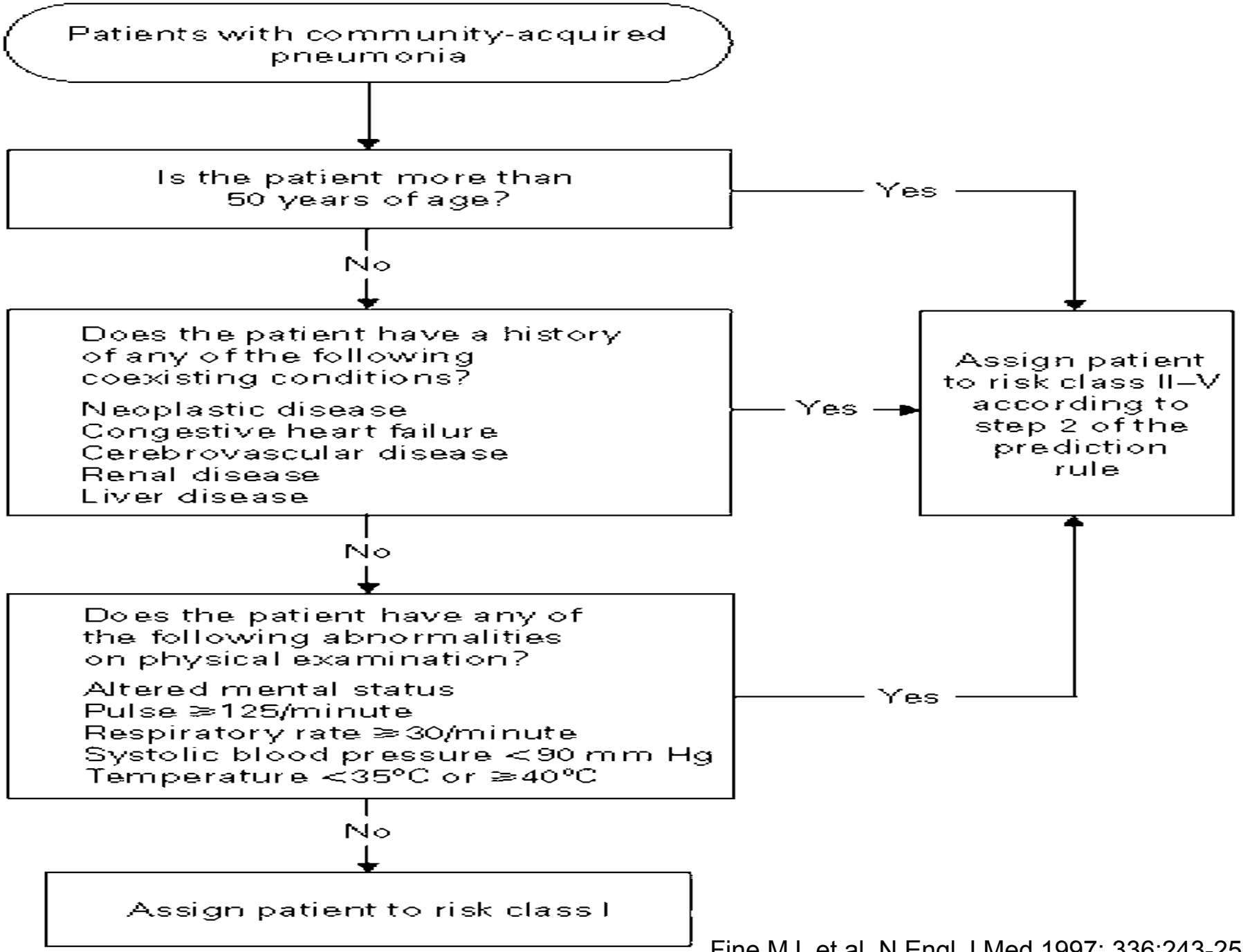
MICHAEL J. FINE, THOMAS E. AUBLE, DONALD M. YEALY, BARBARA H. HANUSA, LISA A. WEISSFELD, DANIEL E. SINGER, CHRISTOPHER M. COLEY, THOMAS J. MARRIE, ANDWISHWA N. KAPOOR, N Engl J Med 1997; 336:243-250.

PORT study

The following were independently associated with mortality:

- **An age of more than 50 years**
- **Five coexisting illnesses**
  - **neoplastic disease**
  - **congestive heart failure**
  - **cerebrovascular disease**
  - **renal disease**
  - **liver disease**
- **Five physical examination findings**
  - **Altered mental status**
  - **Pulse ≥125 per minute**
  - **Respiratory rate ≥30 per minute**
  - **Systolic blood pressure < 90 mm Hg**
  - **Temperature < 35°C or ≥ 40°C**

Fine MJ, et al. N Engl J Med 1997; 336:243-250.



Fine MJ, et al. N Engl J Med 1997; 336:243-250.

PORT study Pneumonia Severity Index point allocation

Demographic factor	Points
Age	
Men	Age (yr)
Women	Age (yr) -10
Nursing home resident	+10
Coexisting illnesses†	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Physical-examination findings	
Altered mental status‡	+20
Respiratory rate≥30/min	+20
Systolic B press <90mmHg	+20
Temperature <35°C o r≥40°C	+15
Pulse ≥125/min	+10

Demographic factor	Points
Laboratory and radiographic findings	
Arterial pH <7.35	+30
Blood urea N ≥30 mg/dl (11mmol/liter)	+20
Sodium <130 mmol/liter	+20
Glucose ≥250mg/dl	+10
Hematocrit <30%	+10
Arterial p02 <60 mm Hg or Pulseox <90%	+10
Pleural effusion	+10

Fine MJ, et al. N Engl J Med 1997; 336:243-250.

PORT study Pneumonia Severity Index definitions

†Neoplastic disease is defined as any cancer except basal- or squamous-cell cancer of the skin that was active at the time of presentation or diagnosed within one year of presentation. Liver disease is defined as a clinical or histologic diagnosis of cirrhosis or another form of chronic liver disease, such as chronic active hepatitis. Congestive heart failure is defined as systolic or diastolic ventricular dysfunction documented by history, physical examination, and chest radiograph, echocardiogram, multiple gated acquisition scan, or left ventriculogram. Cerebrovascular disease is defined as a clinical diagnosis of stroke or transient ischemic attack or stroke documented by magnetic resonance imaging or computed tomography. Renal disease is defined as a history of chronic renal disease or abnormal blood urea nitrogen and creatinine concentrations documented in the medical record.

‡Altered mental status is defined as disorientation with respect to person, place, or time that is not known to be chronic, stupor, or coma.

Fine MJ, et al. N Engl J Med 1997; 336:243-250.

PORT Study Pneumonia Severity Index classes and Mortality

Class	*Points*	*Mortality(%)*
I	na	0.1
II	=<70	0.6
III	71-90	2.8
IV	91-130	8.2
V	>130	29.6
All patients		10.6

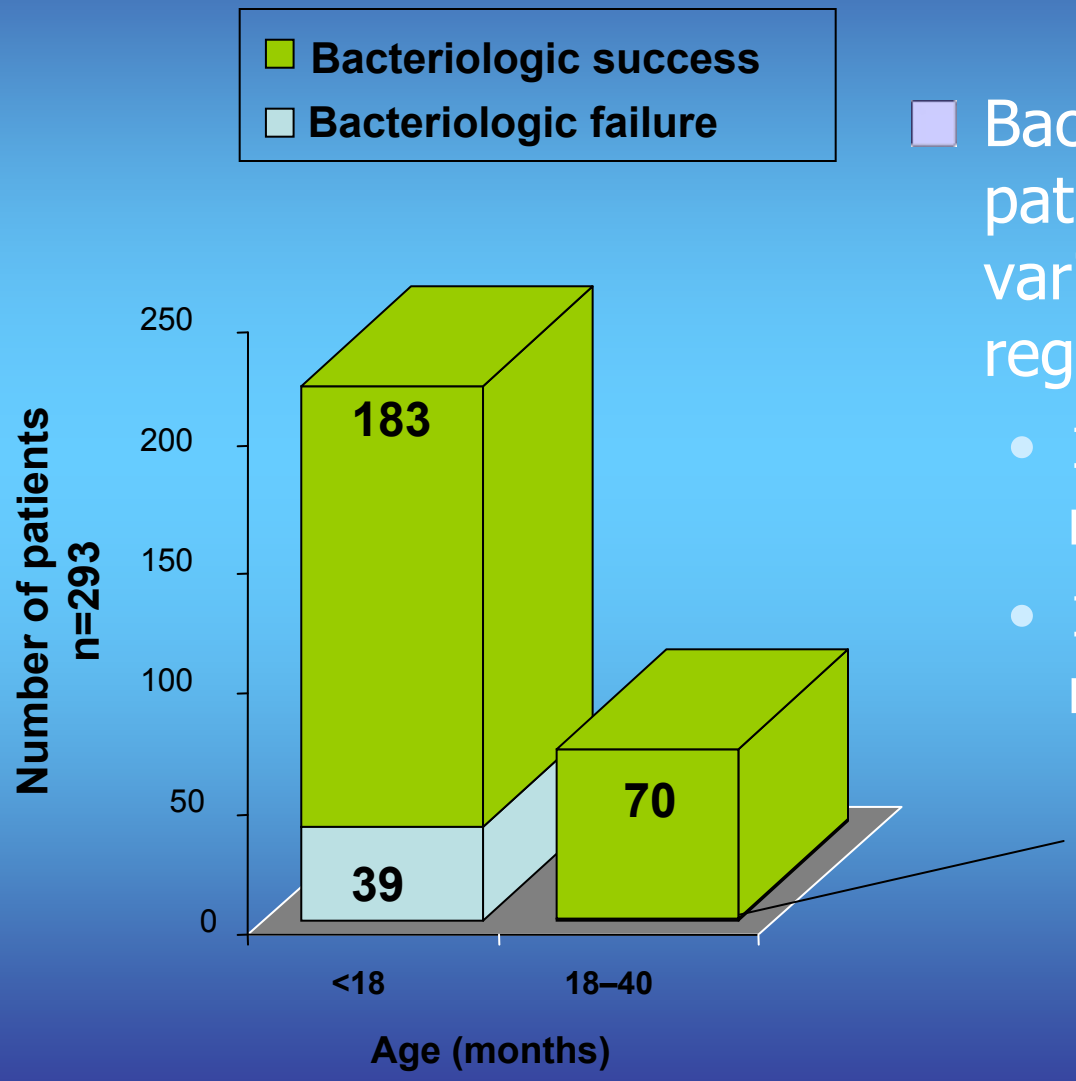
Fine MJ, et al. N Engl J Med 1997; 336:243-250.

Patient Stratification in Acute Otitis Media (AOM)

Correlation of clinical studies with antimicrobial efficacy in AOM

- Bacteriologic outcome during therapy and clinical outcome at end of therapy have been shown to be the most useful time points to assess therapy
- Outcome by 30 days shows no relationship to treatment due to frequent new viral and bacterial infections
- Outcome is worst in patients with risk factors:
  - <2 years old
  - Prior AOM
  - Prior antibiotics
  - Day care
  - Siblings

Effect of Age on Outcome of AOM



- Bacteriologic failure rate in patients treated with various antibiotic regimens:
  - 18% (39/222) if <18 months
  - 1% (1/71) if 18–40 months

P <0.001[1]

Carlin SA, et al. *Pediatr.* 1991;118:178-183.

Amoxicillin vs Placebo in AOM

Effect of Age on Initial Clinical Failure

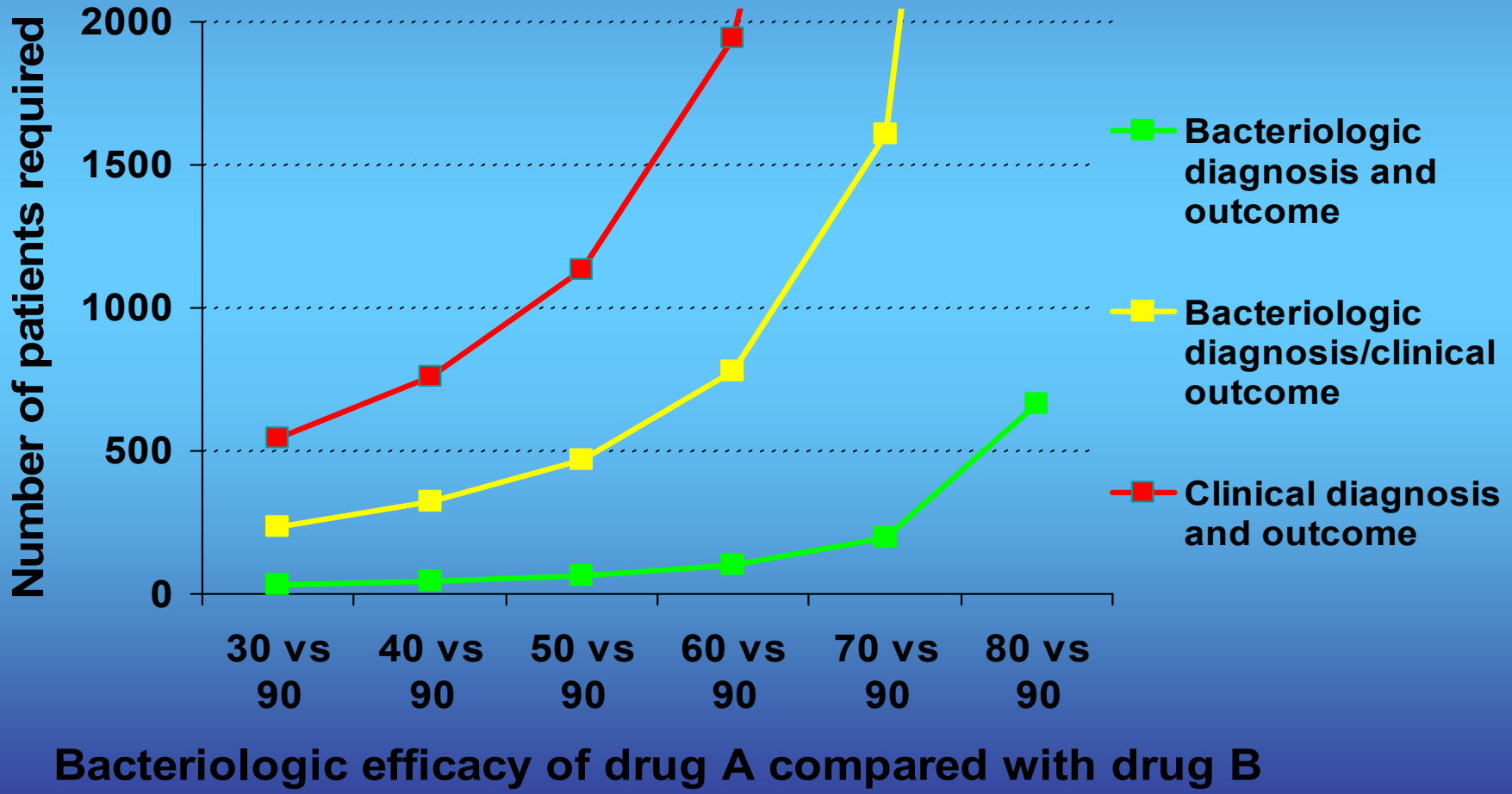
Initial Rx Failure

	Amox	Placebo
Age < 2 yrs	6.5%	9.8%
Age > 2 yrs	0.5%	5.5%

Kaleida et. al. Pediatrics 1991;87:466

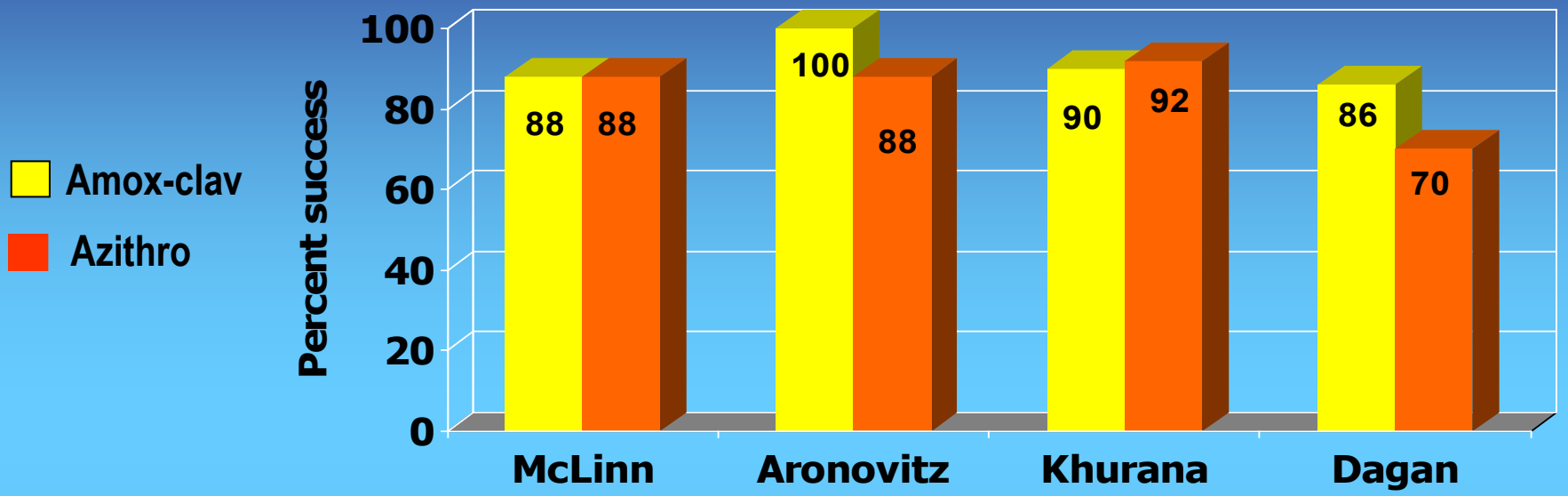
Sample sizes required to detect differences between antibacterial drugs for acute otitis media

Comparison of bacteriologic versus clinical outcomes in trials of two drugs (half the patients would be in each arm of a study)



Marchant *et al. J Pediatr* 1992; **120**:72–77

Azithromycin vs amox-clav in AOM: clinical outcome at end of treatment



Mean age (range) years	? (1-15)	4.0 (2-15)	5.7 (0.5-12)	1.3 (0.5-4)
N evaluable at EOT	553 (82%)	92 (54%)	444 (84%)	143 (60%)
P value for clin. outcome	0.64	0.10	0.42	0.023
No. of patients needed to show:				
60% vs 90% bact. efficacy	2000	800	2000	800 clin/100 bact
30% vs 90% bact. efficacy	542	234	542	100 clin/30 bact

Effect of study design on comparative efficacy of placebo and antimicrobials in AOM

Characteristics of patients included in study designs:

*** Only patients younger than 2 years old are included, 70% of all cases are bacterial cases and only those with bacterial infections are included in the bacteriologic efficacy evaluation.**

† Clinical failure occurs in only 40% of those with bacteriologic failure after 3 to 5 days of treatment; maximal clinical success occurs in 90% of patients because even with the best drugs, persistence of symptoms or newly acquired symptoms (mainly viral infections) will occur in up to 10% of patients.

‡ The 30% who were initially culture-negative also are included in this group. On the basis of clinical experience, patients improve quickly, even without treatment.

§ If some children >2 years of age and >3 years of age are included.

¶ In most studies, with clinical diagnosis only, up to 20% do not have acute otitis media but rather upper respiratory infections only.

Dagan R, McCracken GH. PIDJ 2002: 21:894

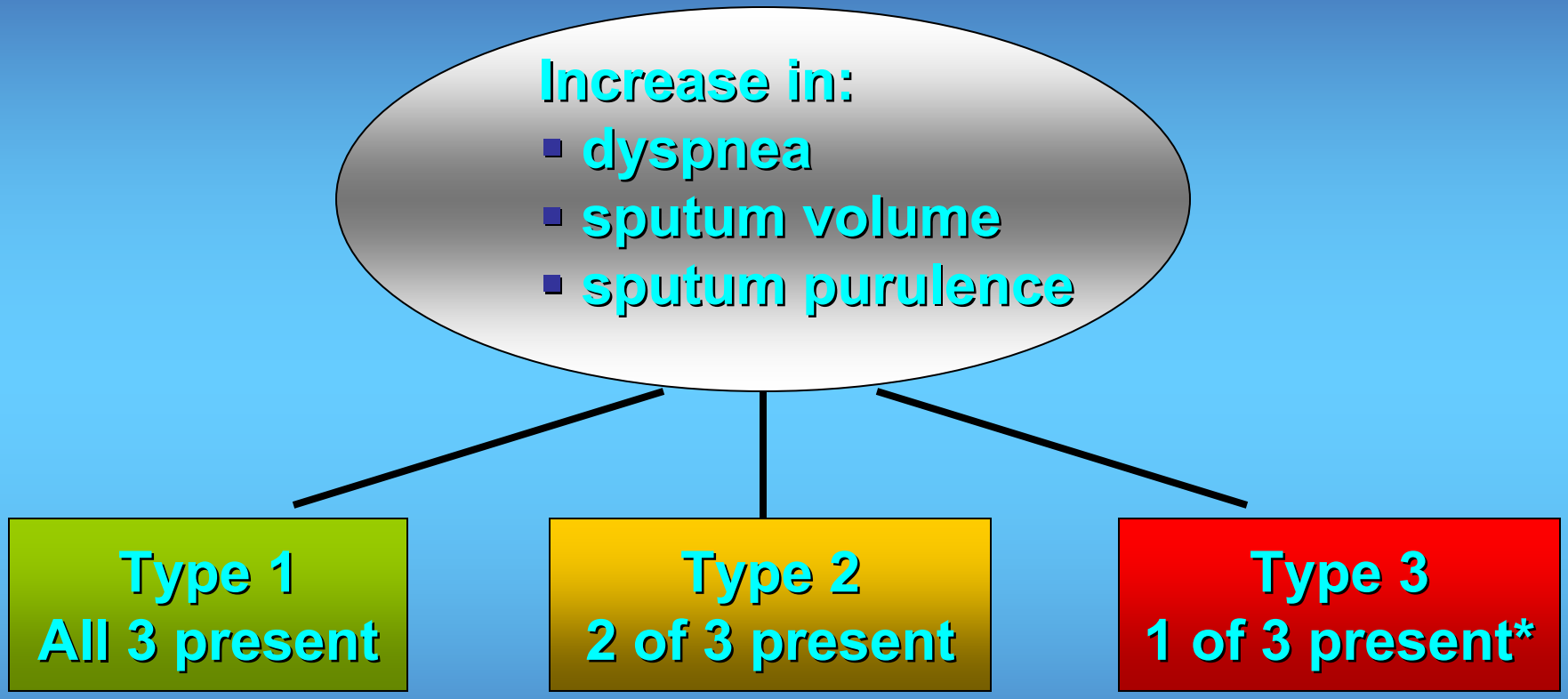
Effect of study design on comparative efficacy of placebo and antimicrobials in AOM

Treatment	Bacteriologic Efficacy (%) in Culture-positive Cases (Days 4–6) – all patients under 2 years old*	Clinical Efficacy (Days 12–14) in culture positive patients – all patients under 2 years old † (%)	Clinical efficacy including Patients with Negative Baseline Culture (30%)‡ (%)	Cliinical efficacy including 30% of Patients Older Than 2 yr and 10% Older Than 3 yr§ (%)	Clinical efficacy including 10–20% of Patients with Simple Upper Respiratory Tract Infection¶ (%)
Placebo	30	76	> 80	> 85	≈ 90
Agent A	60	84	> 85	≈ 90	≈ 90
Agent B	90	≈ 90	≈ 90	≈ 90	≈ 90

Dagan R, McCracken GH. PIDJ 2002: 21:894

Patient Stratification in Acute Exacerbations of Chronic Bronchitis

AECB Stratification Based on Exacerbation Characteristics



*plus upper respiratory tract infection in the prior 5 days, fever, increased wheezing, cough, and respiratory and/or heart rates.

Anthonisen et al. *Ann Intern Med* 1987;106:196.

Antibiotics in AECB

- 362 exacerbations in 173 patients were treated with either placebo or antibiotics (TMP/SMX, doxycycline or amoxicillin)
- Cardinal symptoms of exacerbation were increased dyspnea, sputum volume, sputum purulence

Anthonisen et al, Ann Intern Med 1987;106:196-204

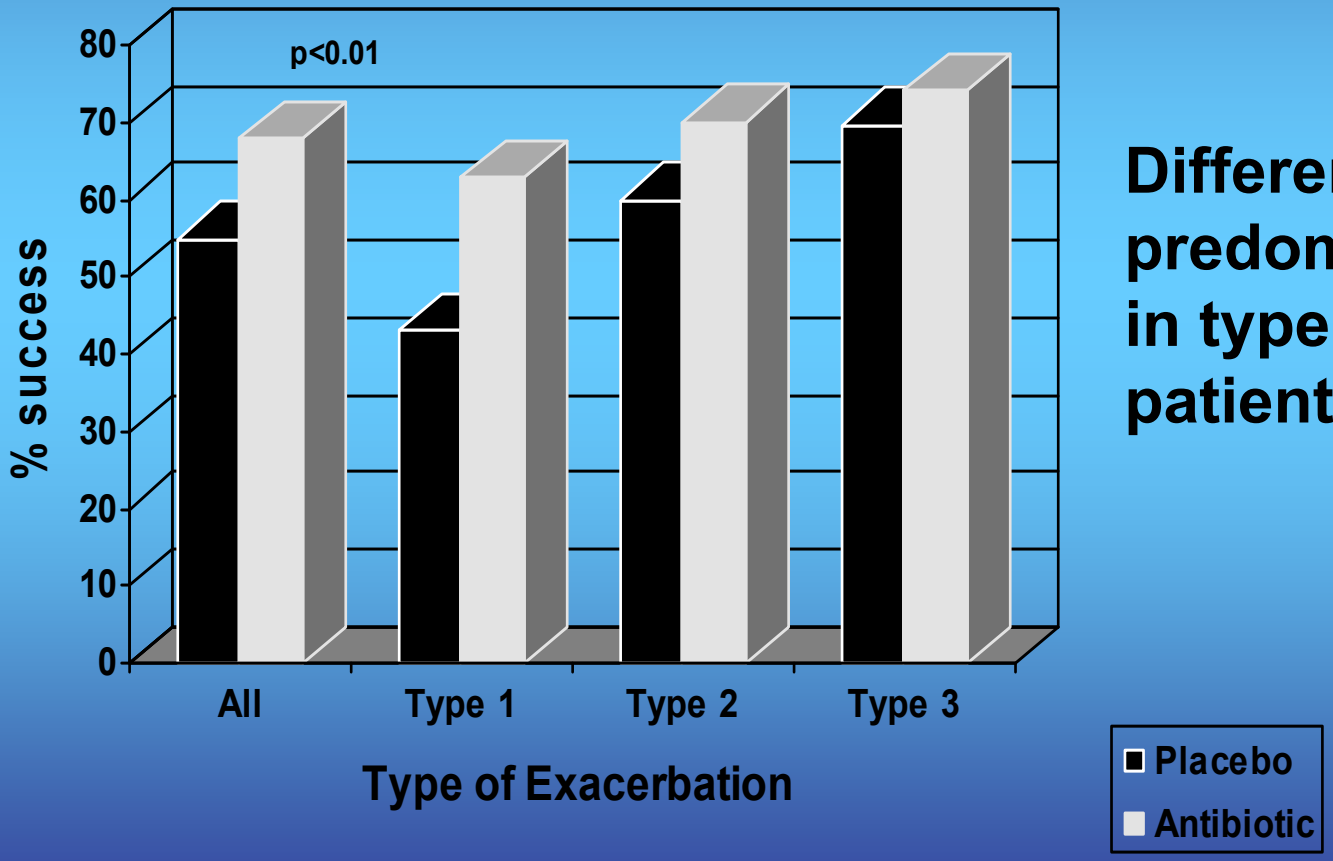
Antibiotics in AECB

Exacerbations were classified as Type 1, 2 or 3 according to the number of cardinal symptoms

- **Type 1: All 3 cardinal symptoms (increased dyspnea, sputum volume, sputum purulence)**
- **Type 2: 2 of the 3 present**
- **Type 3: 1 of the 3 symptoms plus URTI, fever, cough, wheeze or a 20% increase HR or RR**

Anthonisen et al, Ann Intern Med 1987;106:196-204

Antibiotics in AECB Results



Difference predominantly in type 1 patients

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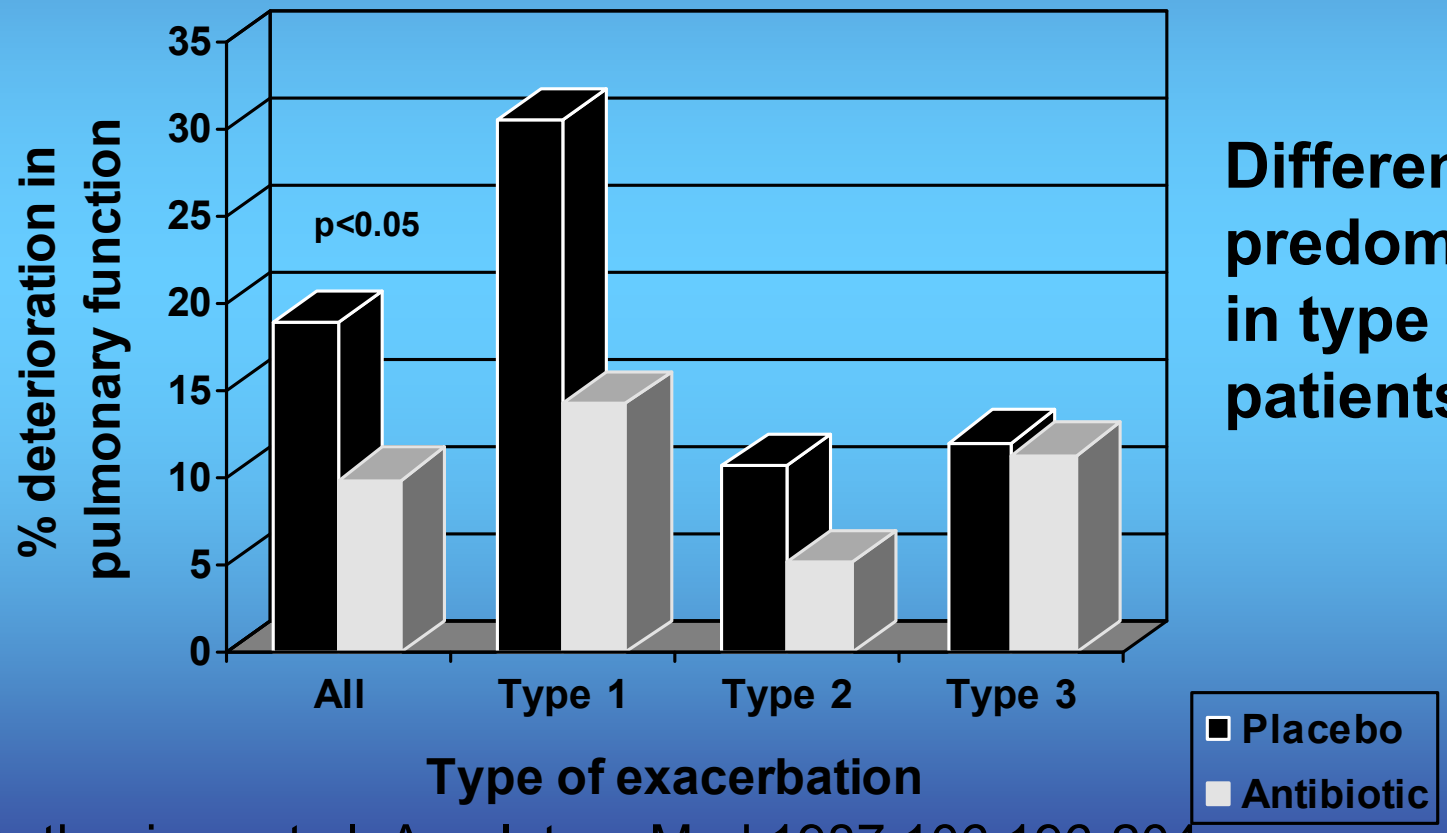
Antibiotics in AECB Results



Difference predominantly in type 1 patients

Anthonisen et al, Ann Intern Med 1987;106:196-204

Stratification Based on Patient Characteristics

Group 1 (acute viral bronchitis)
No previous respiratory problems

Group 2 (simple chronic bronchitis)
Age ≤65 years; <4 exacerbations/year; FEV_1 >50%

Group 3 (complicated chronic bronchitis)
Age ≥65 years; ≥4 exacerbations/year; FEV_1 <50%

Group 4 (complicated chronic bronchitis) Above criteria plus: congestive heart failure, diabetes, chronic renal failure, chronic liver disease, or other chronic disease

Balter et al. *Can Med Assoc J* 1994;151(suppl 10):5;
Adams and Anzueto *Semin Respir Infect* 2000;15:234.

Antimicrobial Therapy for AECB

Category	Probable Pathogen	Therapy
Group 1	Viral	Symptomatic
Group 2	*H. influenzae*, *S. pneumoniae*, *M. catarrhalis* possibly atypical organisms	Doxycycline, newer macrolide newer cephalosporins
Group 3 & 4	As above with the possible addition of *Pseudomonas* spp Enterobacteriaceae, and other Gram-negative pathogens	Amoxicillin/clavulanate, fluoroquinolones*

*If at risk for infection with *Pseudomonas* spp, use ciprofloxacin.

Balter et al. *Can Med Assoc J* 1994;151(suppl 10):5; Adams and Anzueto. *Semin Respir Infect* 2000;15:234.

Consequences of Inappropriate Guidelines: A Natural Experiment in Australia

- Australian government directive targeted at reducing amoxicillin/clavulanate (amox/clav) prescribing
- Recommendation that amox/clav should only be used in infections where resistance to amox was known or suspected
  - Nonsusceptible pneumococci (1997) amox/clav 0.3%, cefaclor 21.4%, erythromycin 16.3%, tetracycline 15.9%, TMP/SMX 45.8%
- No guidance given as to alternative to amox/clav
- Data collected on 4 GP practices, 34,242 patients and 15,303 antibiotic prescriptions for RTIs over 4 years (1994–1998)

Beilby J, et al. *Clin Infect Dis.* 2002;34:55–64.

Changes in Prescribing

- Shift away from best practice prescribing e.g., amoxicillin for otitis media and sinusitis
- Decrease in prescription share of amoxacillin/clavulanate: 13.8 $\Rightarrow$ 8.6%
- Increase in prescription share particularly of macrolides*, tetracyclines, cephalexin and cefaclor

* Roxithromycin and erythromycin

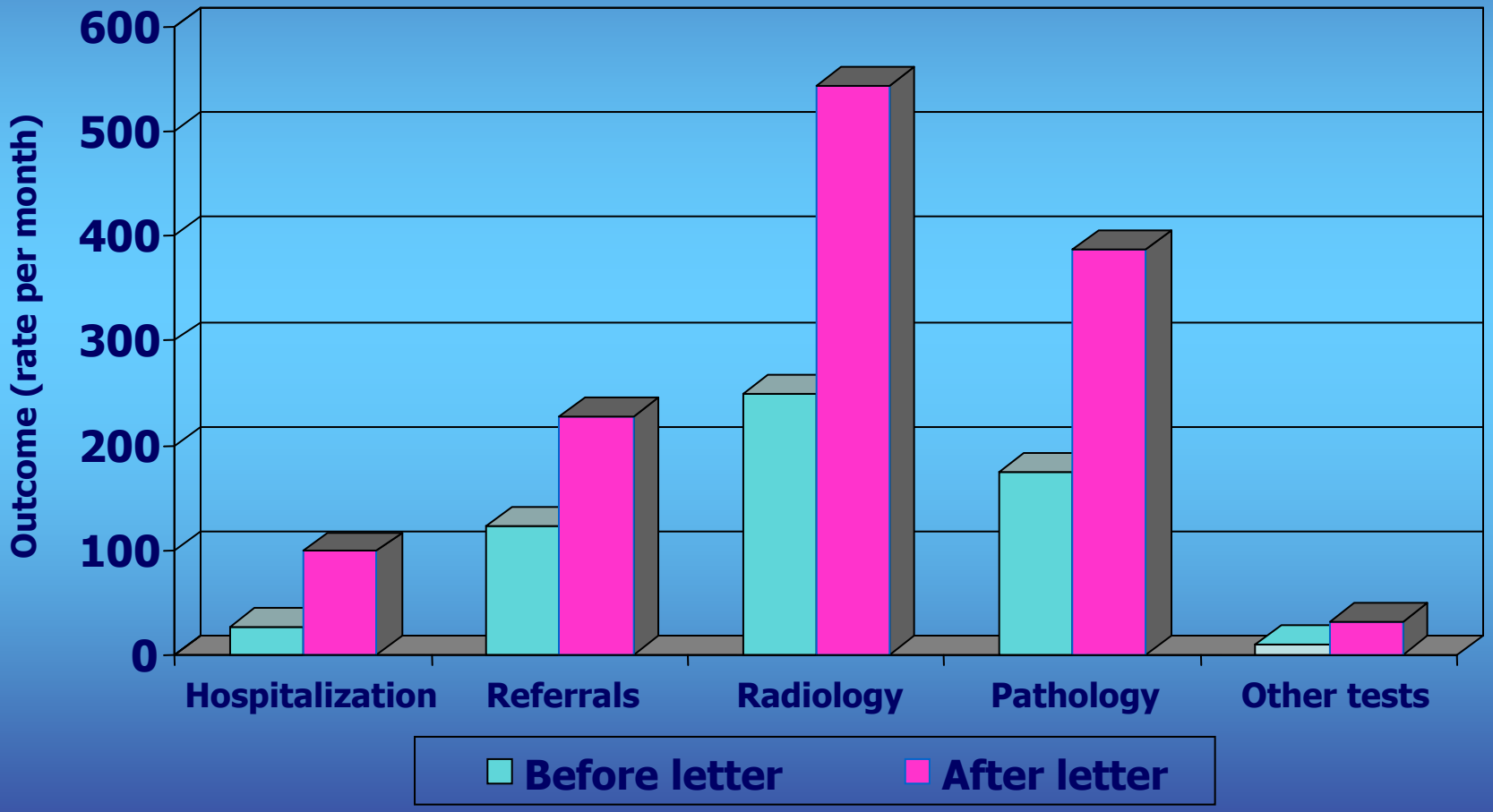
Beilby J, et al. *Clin Infect Dis.* 2002;34:55–64.

Changes in Outcomes

- Amoxicillin/clavulanate use shifted to sicker patients (decreased use for sinusitis)
- Increased cost of care
- Management became more conservative:
  - More radiologic (P=0.00001) investigations
  - More pathologic (P=0.005) investigations
- More hospitalizations (P=0.005)
  ? conservatism, ? therapeutic failures

Beilby J, et al. *Clin Infect Dis.* 2002;34:55–64.

Changes in Outcomes



Beilby J, et al. *Clin Infect Dis.* 2002;34:55–64.

Summary: A Natural Experiment in Australia

- There was a shift away from best practice prescribing
- There was a significant association between the rate and cost of process-of-care and patient outcomes and the decrease in amoxicillin/clavulanate share
- This policy created unintended changes in prescribing behavior, increased cost of care and resulted in a trend towards poorer patient outcomes

Beilby J, et al. *Clin Infect Dis.* 2002;34:55–64.

Population based pharmacokinetics

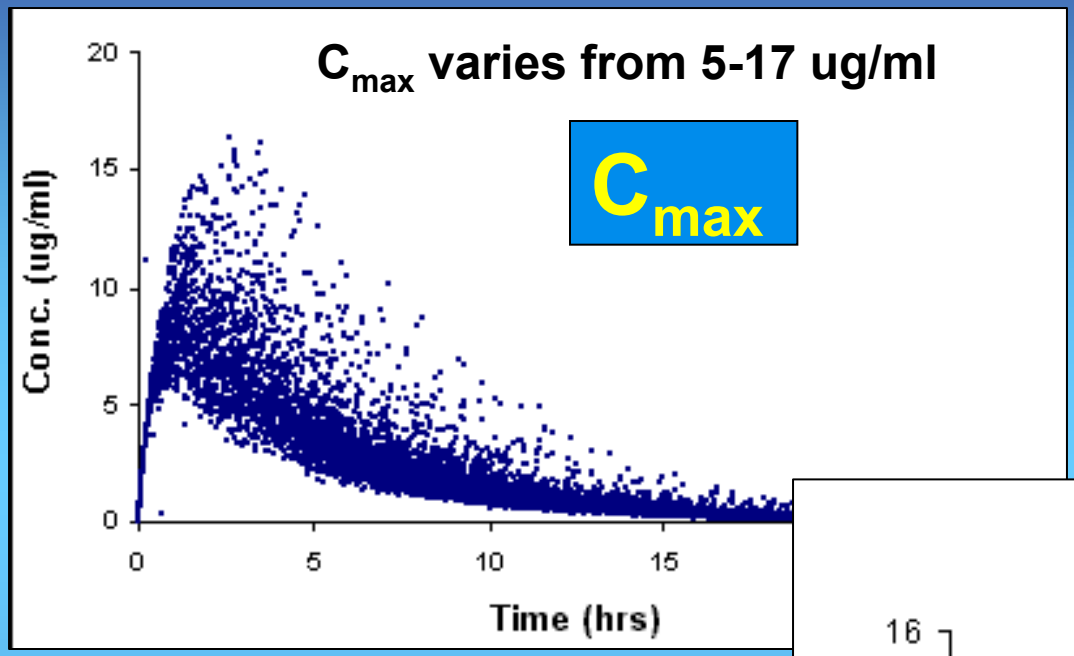
- Product labelling gives mean PK values approved by regulatory agencies
- These values are typically obtained in healthy volunteers
- Values in actual patients can vary considerably from these values, and measurement in patients is desirable

Preston SL, Drusano GL et at. AAC 1998;42:1098-1104

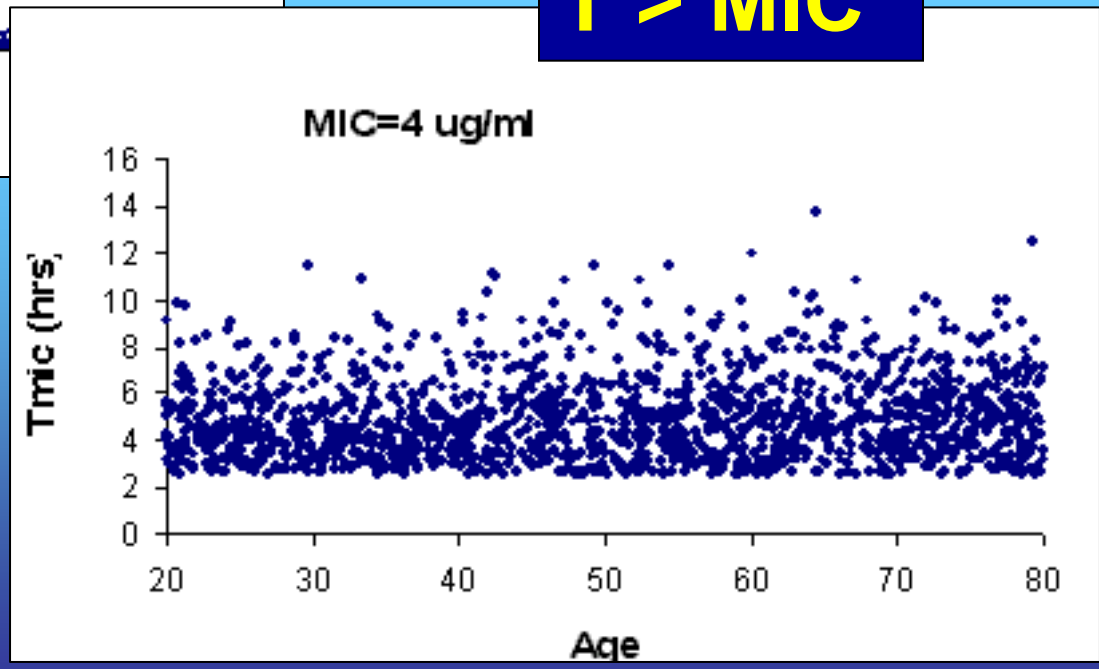
Ambrose PG, Grasela D. ICAAC 1999

Ambrose PG et al Chapter 17 in Antimicrobial Pharmacodynamics in Theory and Clinical Prectice, eds Nightingale CH, Murakawa T, Ambrose PG. 2002. Marcel Decker, NY

Population pharmacokinetics: examples of variations



T > MIC



H. Sun, ISAP-FDA Workshop, 1999

Monte Carlo Simulation 1

- Monte Carlo simulation is a mathematical technique for numerically solving differential equations.
- The technique tends to be computer intensive, with many problems taking minutes or hours to solve on a high speed computer. For this reason, Monte Carlo simulation is avoided when simple solutions exist for a problem.
- Monte Carlo simulation, however, has the advantage that it is a "brute force" technique that will solve many problems for which no other solutions exist. Because many problems are highly complex, this "method of last resort" is used frequently.

Monte Carlo Simulation 2

Monte Carlo simulation is typically used to solve problems which require that one or more statistics of a probability distribution be calculated by

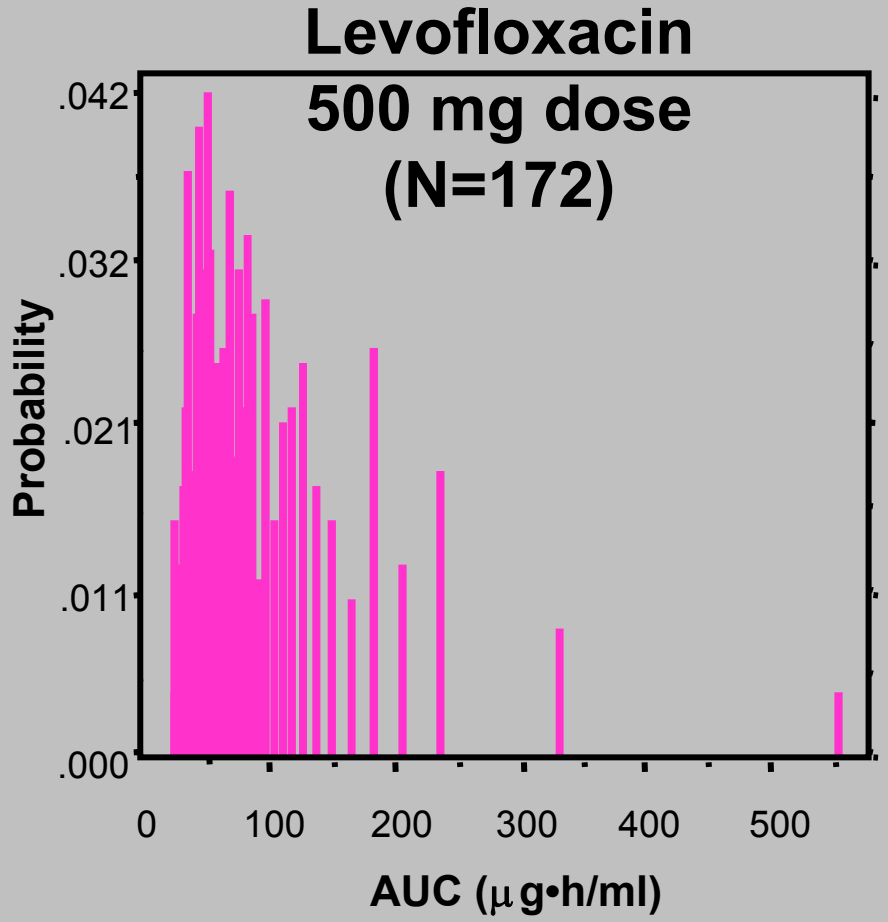
- **"randomly" generating 10,000 scenarios for the data sets being evaluated**
- **Determining what the values would be under each of the 10,000 scenarios**
- **Forming a histogram of those results. This represents a discrete approximation for the probability distribution of the data.**
- **This solution only yields an approximate answer. By using more scenarios—say 20,000 instead of 10,000—the precision of the result could be improved. Typically, the precision of a Monte Carlo simulation is proportional to the square root of the number of scenarios used.**

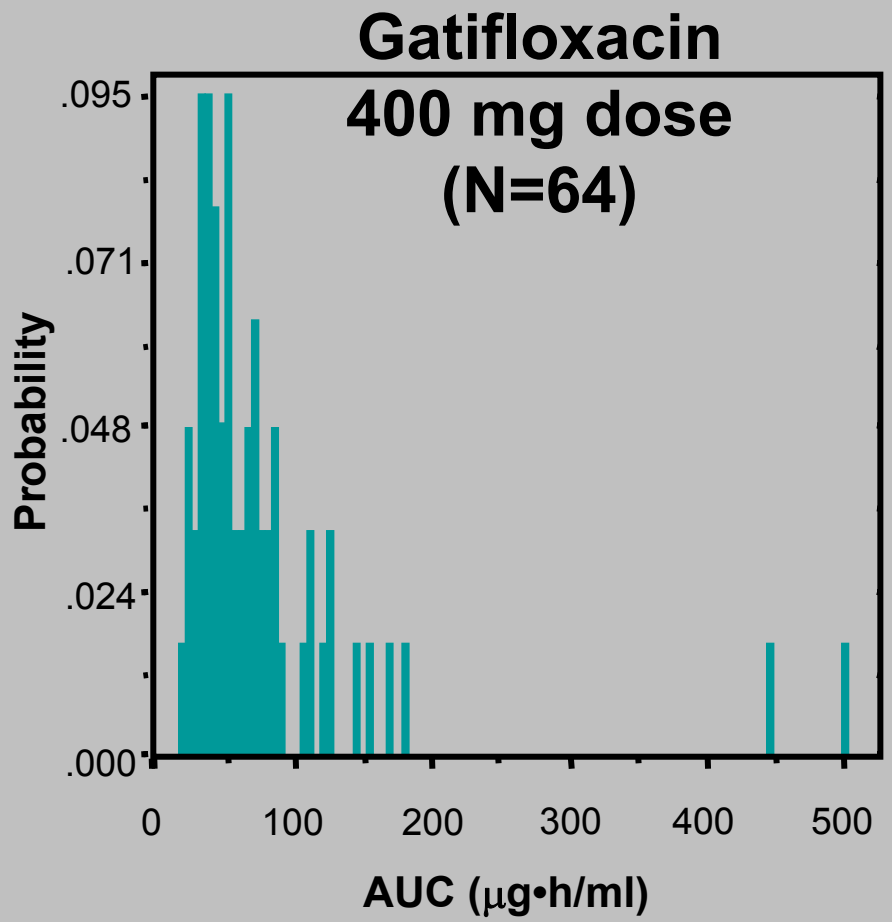
Monte Carlo Simulation of Distribution of AUC: MIC Ratios of Gatifloxacin and Levofloxacin Against *S. pneumoniae*

- AUC values determined in adult patients enrolled in clinical studies
- MICs of 2000 isolates of *S. pneumoniae* from surveillance studies determined
- Monte Carlo simulation run on these data using a 5000 patient simulation randomly pairing AUC and MIC values
- A probability distribution is then generated that reflects the chance that a pharmacodynamic target will be achieved in a patient

Ambrose PG, Grasela D. ICAAC 1999

AUC values in acutely ill patients





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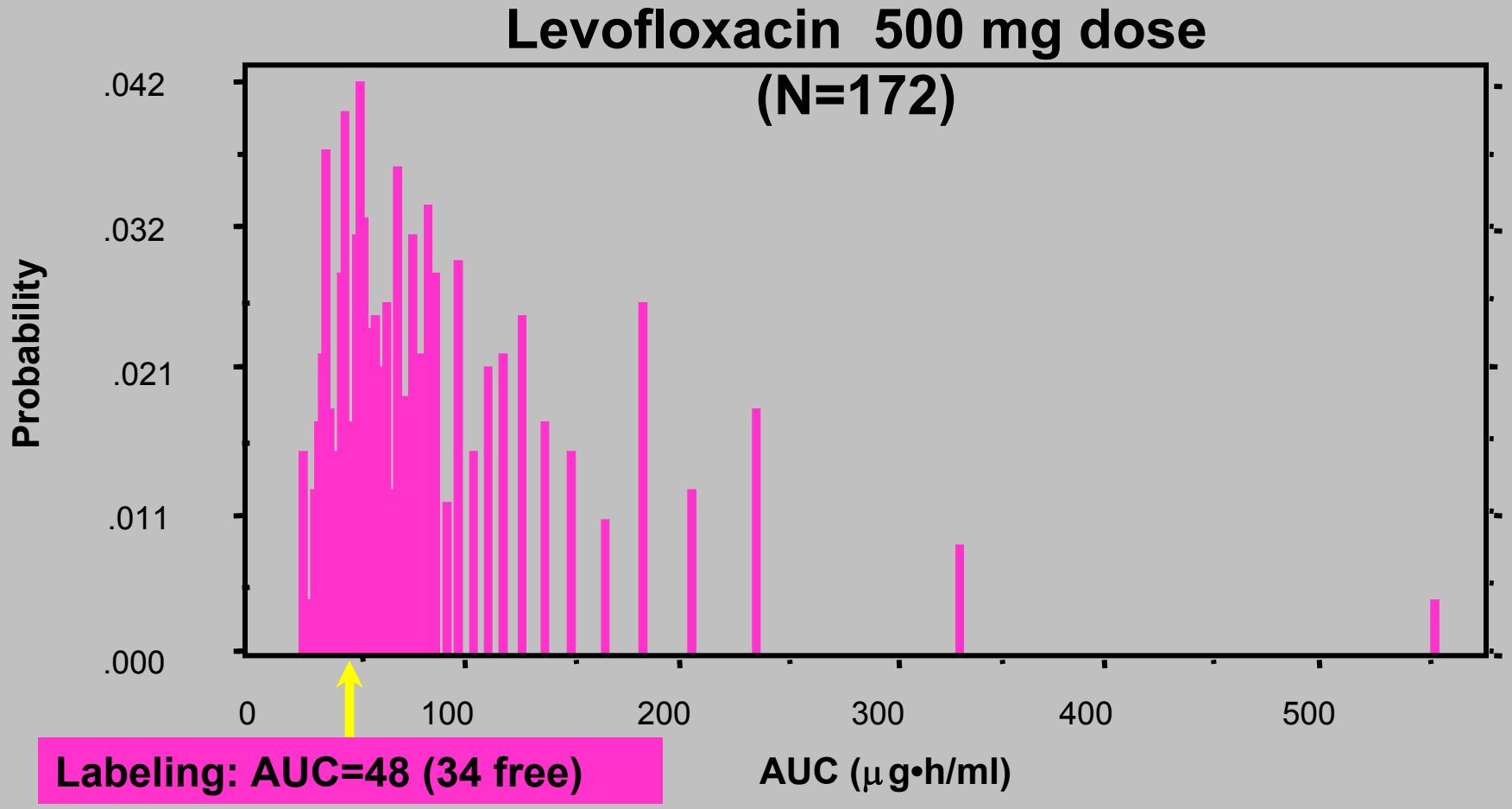

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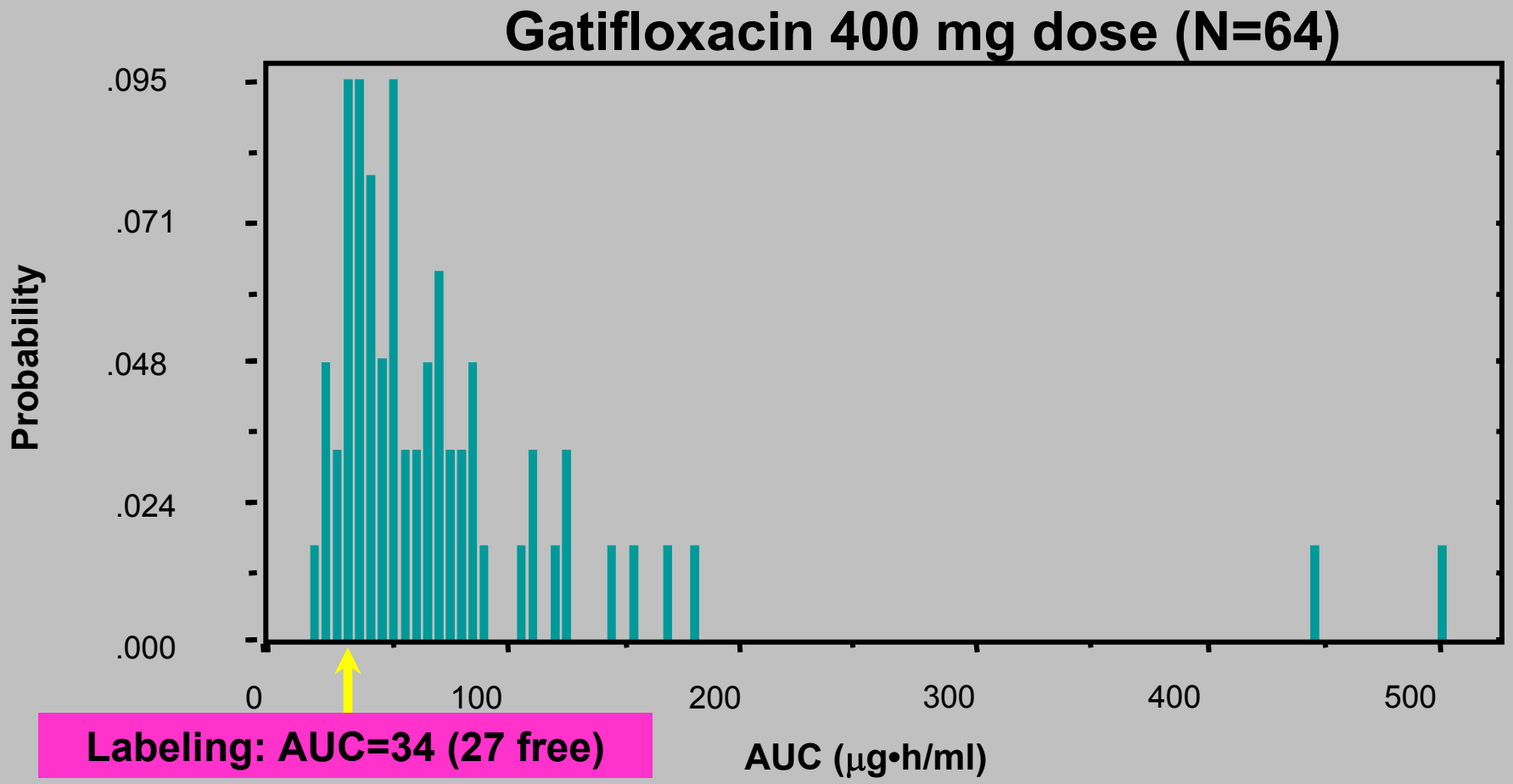

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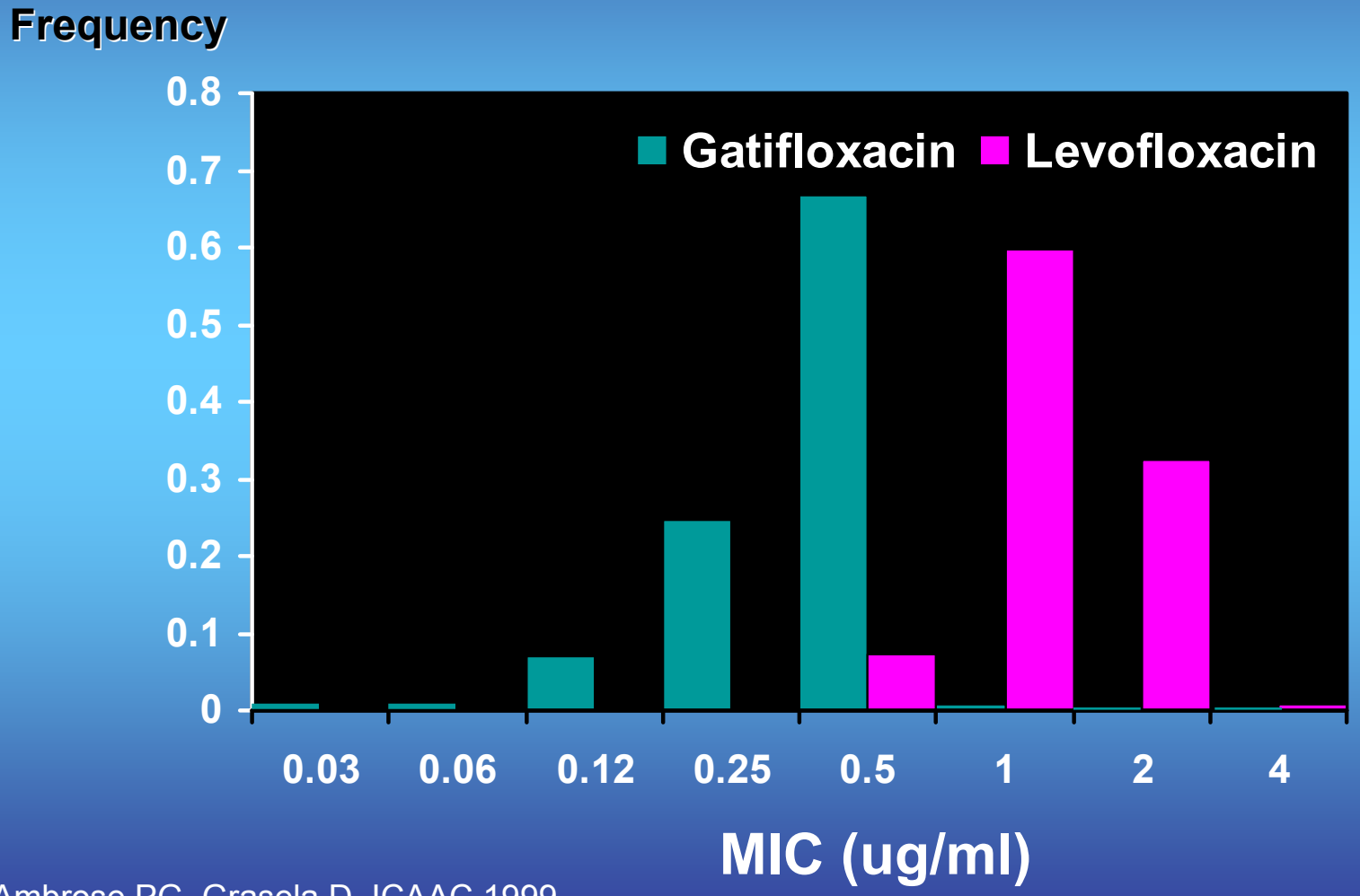
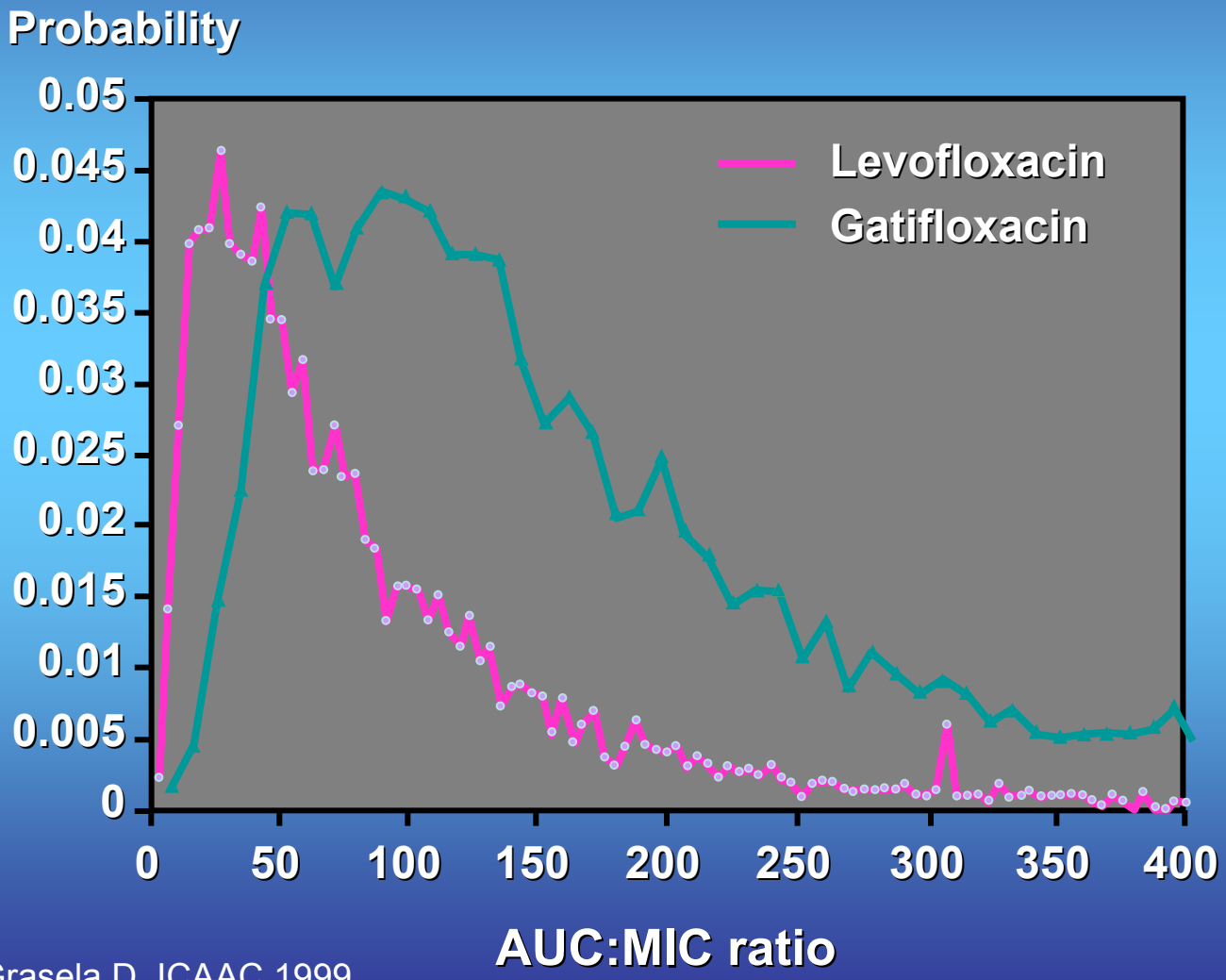
S. pneumoniae MIC Distribution
Gatifloxacin and Levofloxacin
N=2000



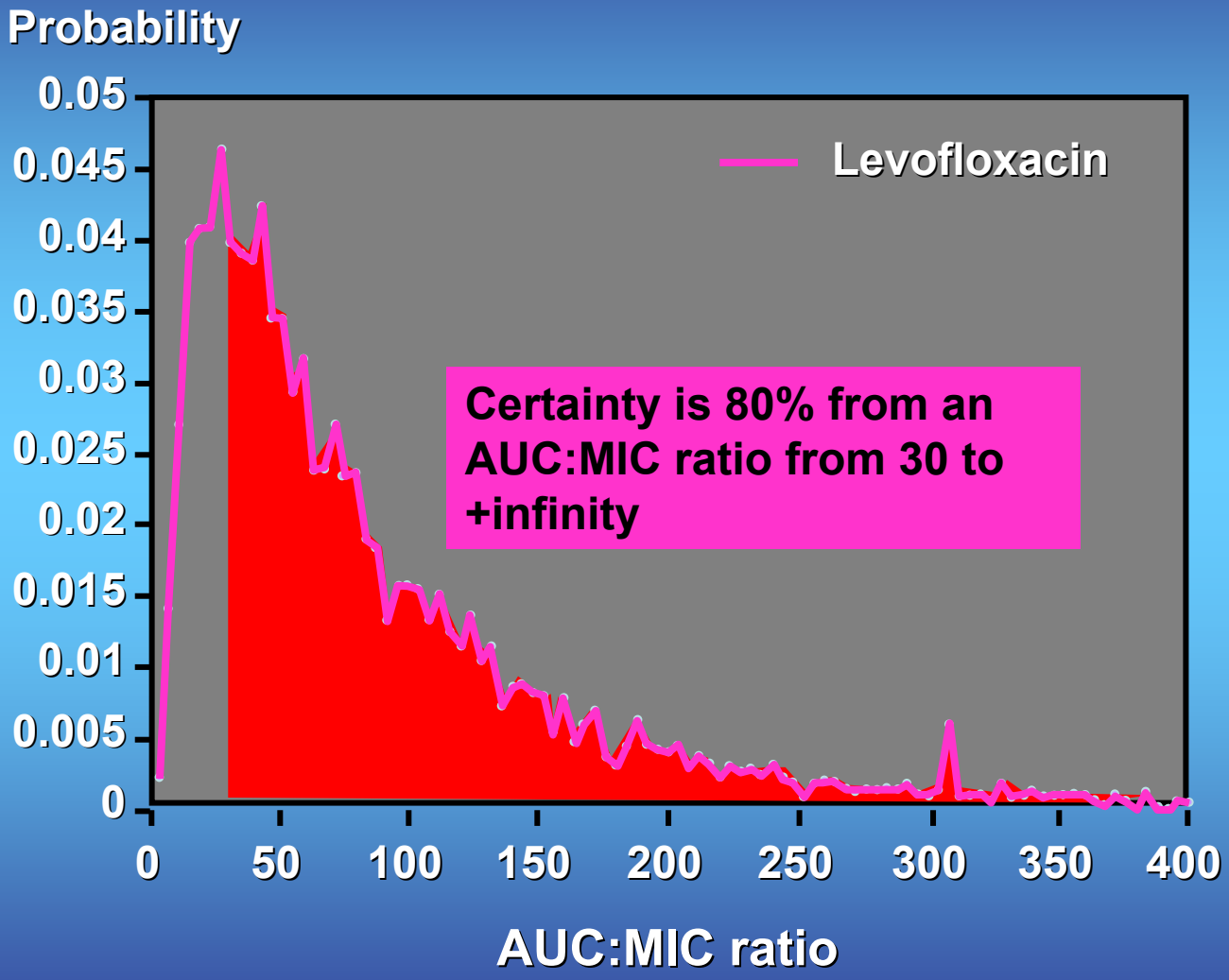
Ambrose PG, Grasela D. ICAAC 1999
Jones RN. SENTRY Surveillance Program 1997

Monte Carlo Simulation of Distribution of AUC: MIC Ratios of Gatifloxacin and Levofloxacin Against *S. pneumoniae*



Ambrose PG, Grasela D. ICAAC 1999

Probability of Achieving Target AUC:MIC Ratio Levofloxacin Vs *S. pneumoniae*



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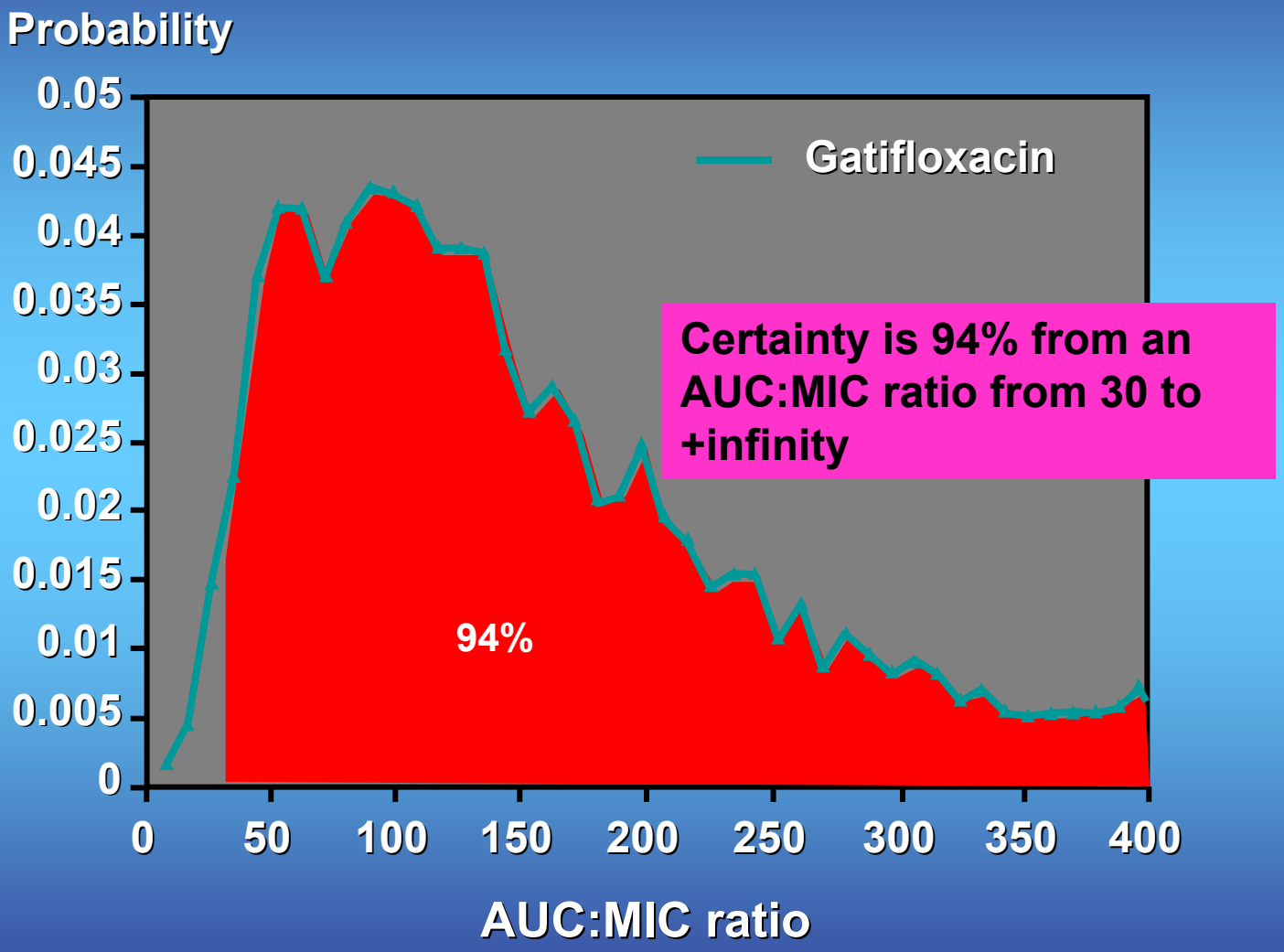
Ambrose PG et al Chapter 17 in Antimicrobial Pharmacodynamics in Theory and Clinical Prectice, eds Nightingale CH, Murakawa T, Ambrose PG. 2002. Marcel Decker, NY

Probability of Achieving Target AUC:MIC Ratio Gatifloxacin Vs *S. pneumoniae*



Preston SL, Drusano GL et at. AAC 1998;42:1098-1104; Ambrose PG, Grasela D. ICAAC 1999

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Using PK/PD parameters to develop treatment guidelines

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ANTIMICROBIAL TREATMENT GUIDELINES FOR ACUTE BACTERIAL RHINOSINUSITIS

Sinus and Allergy Health Partnership

Supported by an educational grant from the Sinus and Allergy Health Partnership, an organization created through the joint efforts of the American Academy of Otolaryngic Allergy, the American Academy of Otolaryngology–Head and Neck Surgery, and the American Rhinologic Society

Mosby

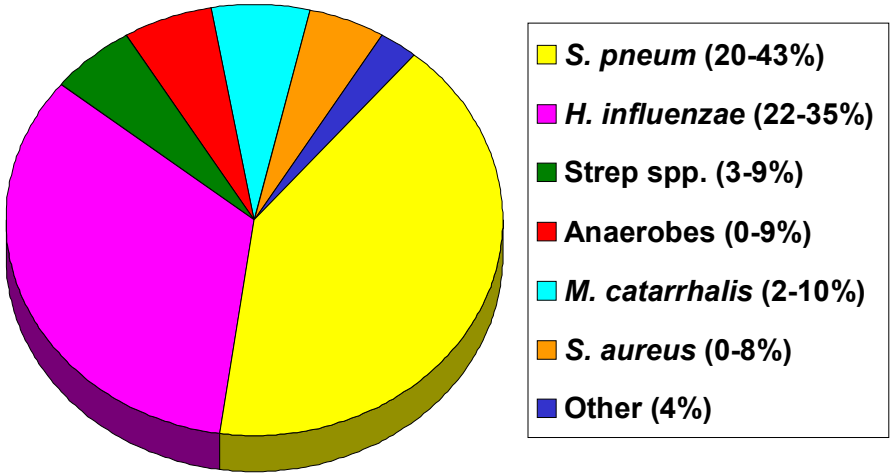
Using PK/PD parameters to develop sinusitis treatment guidelines

Therapeutic outcome model developed based on:

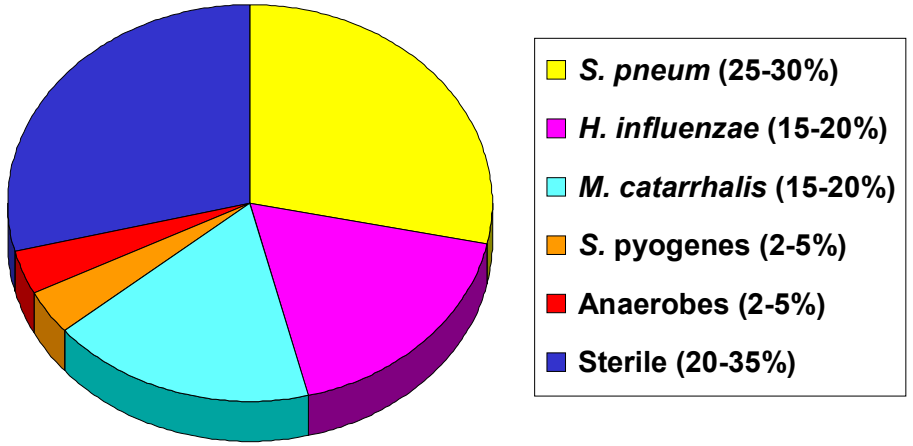
- Prevalence of pathogens in acute sinusitis
- Spontaneous resolution of each pathogen
- Bacterial eradication of each pathogen based on susceptibility at PK/PD breakpoints

Prevalence of pathogens in acute sinusitis

Microbiology of Acute Bacterial Rhinosinusitis (Adults)



Microbiology of Acute Bacterial Rhinosinusitis (Children)



Sinus and Allergy Health Partnership. *Otolaryngol Head Neck Surg* 2000; **123**(supp 1 part 2):S1–S32

Pharmacodynamic breakpoints for oral agents used for RTIs

	PK/PD breakpoint (µg/ml)
	ALL ORGANISMS
Amoxicillin	2
Amox/clav	2
Cefuroxime axetil	1
Cefprozil	1
Cefixime	0.5
Cefaclor	0.5
Loracarbef	0.5
Azithromycin	0.12
Clarithromycin	0.25

Based on M100-S11, National Committee for Clinical Laboratory Standards, 2001; Sinus and Allergy Health Partnership. *Otolaryngol Head Neck Surg* 2000; **123**(supp 1 part 2):S1–S32.

Pharmacodynamic vs. NCCLS breakpoints (µg/ml)

	NCCLS		PK/PD
	S. pneumoniae	*H. influenzae*	ALL ORGANISMS
Amoxicillin	2	4	2
Amox/clav	2	4	2
Cefuroxime axetil	1	4	1
Cefprozil	2	8	1
Cefixime	–	1	0.5
Cefaclor	1	8	0.5
Loracarbef	2	8	0.5
Azithromycin	0.5	4	0.12
Clarithromycin	0.25	8	0.25

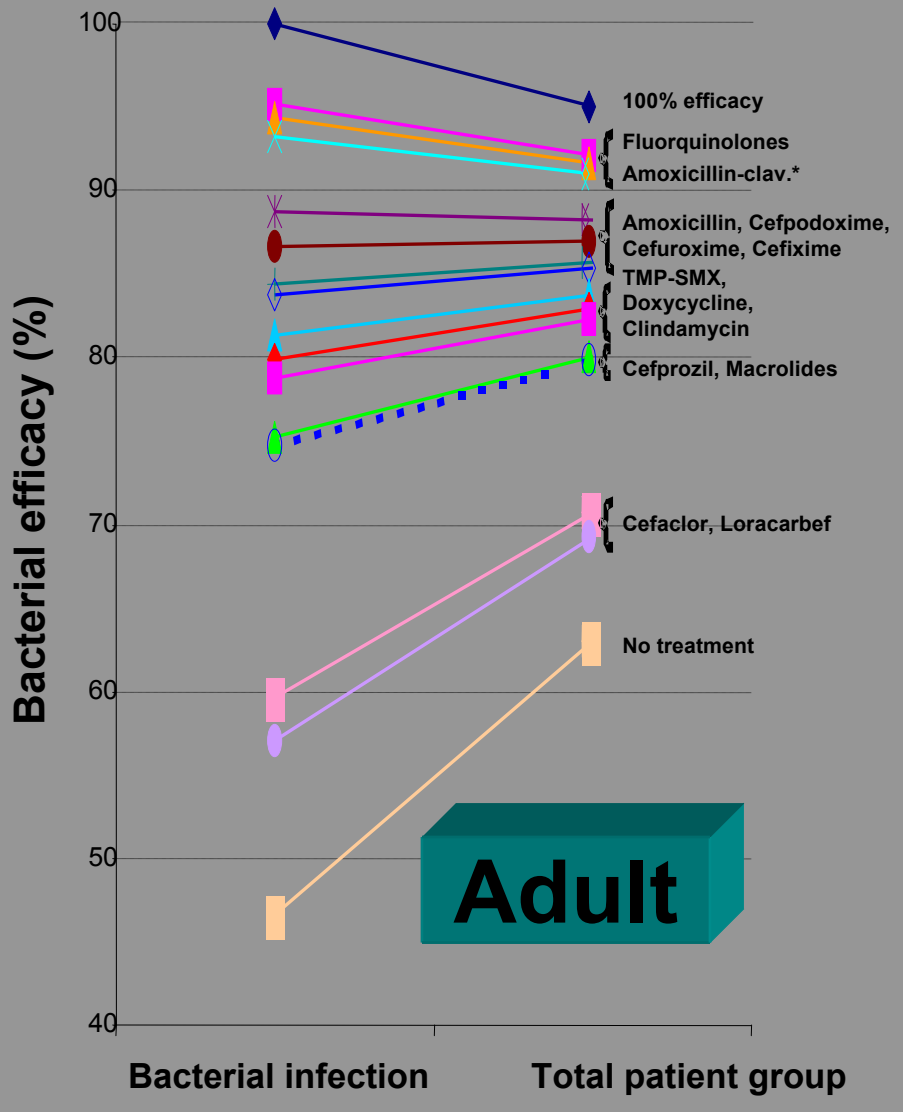
Based on M100-S11, National Committee for Clinical Laboratory Standards, 2001; Sinus and Allergy Health Partnership. *Otolaryngol Head Neck Surg* 2000; **123**(supp 1 part 2):S1–S32.

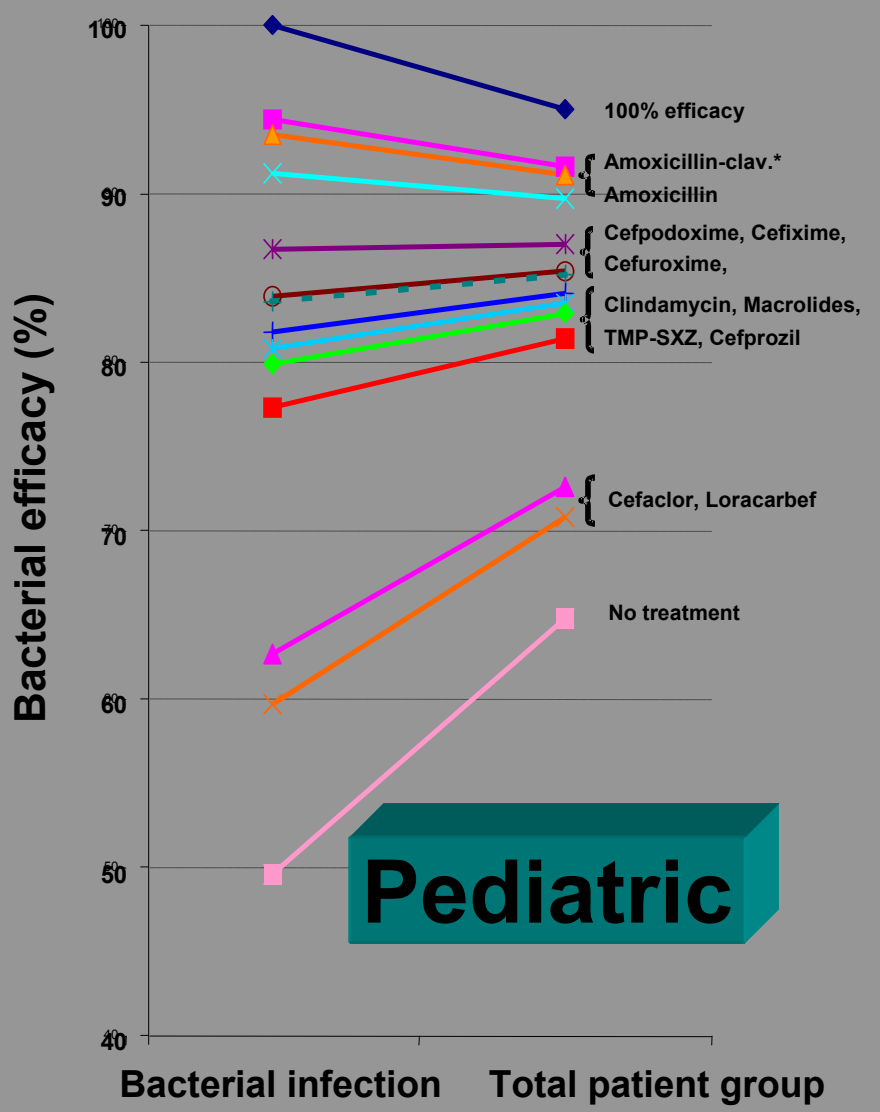
Susceptibility of US Isolates at PK/PD breakpoints

	Percentage of strains susceptible		
Agent	***S. pneumoniae***	***H. influenzae***	***M. catarrhalis***
Amox/clav	90	97	100
Amoxicillin	90	61	14
Cefaclor	27	2	5
Cefixime	57	99	100
Cefpodoxime	63	99	64
Cefprozil	64	18	6
Cefuroxime	64	79	37
Cefdinir‡	61	97	100
Azithromycin	67	0	100
Clindamycin*	89	NA	NA
Doxycycline	76	20	96
Levofloxacin	99.8	100	99
TMP/SMX*	57	75	9

Based on M100-S11, National Committee for Clinical Laboratory Standards, 2001; Sinus and Allergy Health Partnership. *Otolaryngol Head Neck Surg* 2000; **123**(supp 1 part 2):S1–S32. ‡Jacobs M. (unpublished)

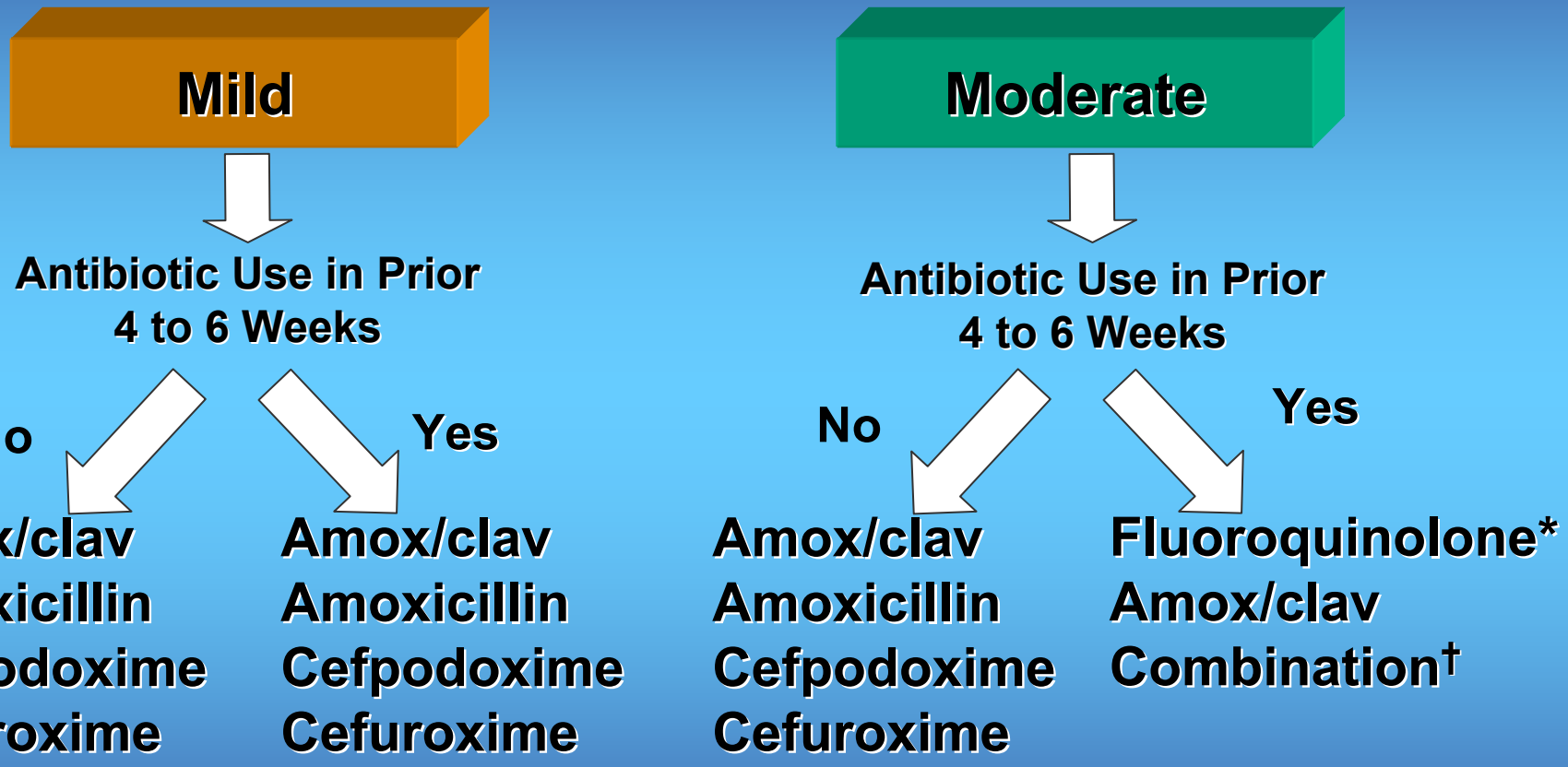
Sinusitis Therapeutic Outcome Model





Sinus and Allergy Health Partnership. Antimicrobial Treatment Guidelines for Acute Bacterial Rhinosinusitis *Otolaryngol Head Neck Surg* 2000;123(supp 1 part 2):S1–S32

Antimicrobial Recommendations for Acute Sinusitis



*Fluoroquinolone=gatifloxacin/levofloxacin/ moxifloxacin; currently not approved for use in children. †Amoxicillin or clindamycin plus cefixime.

Sinus and Allergy Health Partnership. *Otolaryngol Head Neck Surg* 2000;123(1 part 2):S1.

Conclusions

- Determining the real efficacy of antibiotics is not easy to obtain as studies are designed to show "non-inferiority"
- Avoiding use of good agents may not be the best policy
- Statistical modeling can provide some additional information
- Therapeutic outcome models are very useful
- We need a better way to evaluate antibiotics, especially in RTIs