Office of Antimicrobial Products

FDA Briefing Document

Meeting of the Anti-Infective Drug Advisory Committee

April 1 - 2, 2008

Section A:
Clinical Trial Design Issues in Antibacterial Studies of Community Acquired Pneumonia. (59 pages)

Section B
Exposure-Response Analysis of Community-Acquired Pneumonia (23 pages)

Section C:
FDA-IDSA January 17 & 18, 2008 Workshop materials (29 files)

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Clinical Trial Design Issues in Antibacterial Studies of Community Acquired Pneumonia

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I. INTRODUCTION

The purpose of this briefing document is to provide background information regarding clinical trial design issues in antibacterial studies of community acquired pneumonia (CAP). A brief overview of CAP and the use of predictive scoring systems in CAP is followed by a succinct summary of the design of non-inferiority trials. Subsequent sections discuss issues specific to estimation of the treatment effect of antibacterial treatment for CAP, including review of natural history studies, observational and controlled trials from the pre-antibiotic era and alternative approaches from more recent active control studies of CAP. The final section discusses the conclusions drawn and limitations of these data, and the questions for the committee. A summary of the recent IDSA/FDA workshop on CAP held on January 17th and 18th, 2008, is also included.

II. BACKGROUND

a. Community-acquired pneumonia

"The most widespread and fatal of all infectious diseases, pneumonia is now the 'Captain of the Men of Death' to use the phrase applied by John Bunyan to consumption."

- Sir William Osler, 1902 (who succumbed to pneumonia at age 71)

"She was one of five women to graduate from Johns Hopkins University in 1931 with medical degrees. She became a pediatrician and practiced in Washington, D.C., for 35 years. During a Bell Club meeting in the early 1990s, Ms. Grosvenor was asked by a nurse what the greatest medical advancement had been during the span of her career. 'Antibiotics,' she said without hesitation."

- From the obituary notice of Mabel Grosvenor, a granddaughter of famed telephone inventor Alexander Graham Bell and likely the last person who had personal memories of him, and who died last year at age 101.

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality. It is estimated that approximately one million episodes of CAP occur annually in adults ≥ 65 years of age in the United States. Overall mortality remains relatively high, ranging from 5.1% for those hospitalized or treated in an ambulatory setting to 36.5% for those treated in an ICU (Fine et al., 1996). Mortality is affected by several factors such as increasing age, nursing home residence, preexisting chronic lung disease, and bacteremia at diagnosis.

In a recent retrospective case-control study, Kaplan, et al. (2003) compared in-hospital and 1-year mortality in 158,960 patients with CAP to 794,333 hospitalized controls matched by age, gender and race. In-hospital mortality rates for the CAP and hospitalized control cohorts were 11.0% and 5.5%, respectively, while 1 year mortality was 40.9% and 29.1% in the respective cohorts. As discussed by Niederman (2007), these data suggest that "CAP is much more than a self-limited illness for those who survive, and that the 1-year mortality rate of elderly patients with CAP is four times higher than the in-hospital mortality rate, with one in three survivors of CAP dying in the subsequent year following hospital discharge."

Specific antibiotic recommendations are included in all CAP treatment guidelines, including the joint recommendations of the Infectious Disease Society of America (IDSA) and the American Thoracic Society Guidelines (Mandell, et al. 2007). These guidelines also emphasize the importance of early administration of antibacterials after hospitalization based on retrospective studies showing that early treatment is associated with a reduction in mortality.

Common infectious pathogens for CAP in adults are listed in the following table. Estimates for different etiologies vary widely depending on age, underlying disease status, and microbiologic testing performed:

Table 1. Common Microbiological Causes of CAP*

'Typical' Bacterial Pathogens (present on gram stain or routine sputum culture): [1]	
• *S. pneumoniae*	20-60%
• *H. influenzae*	3-10%
• *S. aureus*	3-5%
• *M. catarrhalis*	Uncommon except in COPD
• Other gram-negative bacteria	Uncommon
'Atypical' Bacterial Pathogens (not present on gram stain or routine culture media):	
• *M. pneumoniae* • *L. pneumophila* • *C.pneumoniae*	10-20% including all atypical organisms
Viral:	
• Influenza • Parainfluenza • RSV • Adenovirus • Metapneumovirus	2-15% including all respiratory viruses
No documented pathogen:	30-60%
Others (uncommon): *M. tuberculosis, Chlamydophila psittaci* (psittacosis), *Coxiella burnetii* (Q fever), *Francisella tularensis* (tularemia), *Bordetella pertussis* (whooping cough), and endemic fungi (*Histoplasma capsulatum, Coccidioides immitis, Cryptococcus neoformans,* and *Blastomyces hominis*)	

*Adapted from Bartlett JG. Approach to the patient with pneumonia (CH 53) in Gorbach SL, Bartlett JG, Blacklow NR. Infectious Diseases, 2nd Ed. W. B Saunders, Philadelphia. 1998. pp. 553-564

Microbiologic etiology based on whether or not patients are treated as inpatients/outpatients is outlined in the following table:

Table 2. CAP Etiology in Outpatient and Inpatient Settings*

Outpatients	Inpatients (non-ICU)	ICU
S. pneumoniae	*S. pneumoniae*	*S. pneumoniae*
M. pneumoniae	*M. pneumoniae*	*Legionella* spp
H. influenzae	*C. pneumoniae*	*H. influenzae*
C. pneumoniae	*H. influenzae*	Gram-negative bacilli
Respiratory viruses	*Legionella* spp	*S. aureus*

*Adapted from File, 2003

b. Pneumonia Prognosis

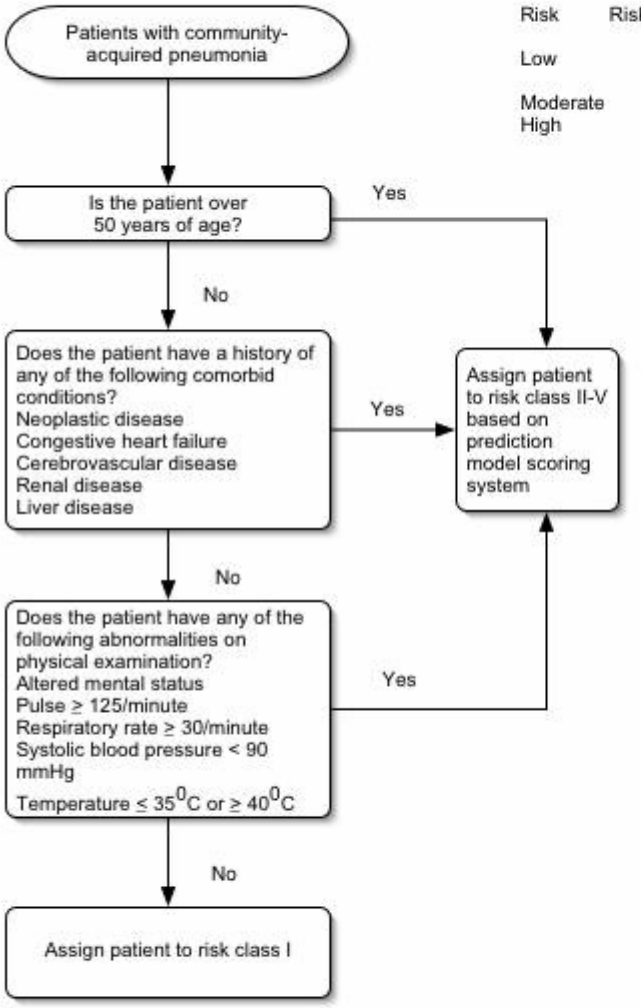
Important recent developments in the treatment of CAP have included the development of measures to assess the overall prognosis of patients with CAP; these measures have been used when assessing whether hospital admission is needed. Although these measures have been suggested as measures of 'severity,' they are more correctly interpreted as prediction rules which describe mortality risk based on certain variables. These rules have been developed and validated solely in patients who were treated with antibacterials for pneumonia. These measures are discussed here since they are often used as enrollment criteria for CAP studies or for classifying patients at enrollment into a study.

The Pneumonia Severity of Illness (PSI) score was developed from studies of the Pneumonia Patient Outcomes Research Team (PORT). This prediction rule stratifies patients into one of five categories based on 20 items including demographic features, coexisting illnesses, physical examination, laboratory, and radiographic findings (Figure 1). On the basis of associated mortality rates, it has been suggested that risk class I and II patients should be treated as outpatients, risk class III patients should be treated in an observation unit or with a short hospitalization, and risk class IV and V patients should be treated as inpatients (Fine et al., 1997).[1]

[1] PORT score, Fine score, and PSI (pneumonia severity index) score are used synonymously in this document.

Figure 1. PORT (PSI) Score Decision Tool[2]

Community Acquired Pneumonia
Decision Tool for Site of Care
Pneumonia Severity Index / PSI



Risk	Risk Class	Points	Site of Care
	I	0	outpatient
Low	II	≤70	outpatient
	III	>71-90	Inpatient (briefly)
Moderate	IV	>91-130	Inpatient
High	V	>130	Inpatient

Patient Characteristics		Points
A. Demographics		
Age:		
Male	age (yrs)	____
Female	age(yrs -10)	____
Nursing Home Resident		+10
B. Cormorbidities		
Neoplastic disease		+30
Liver disease		+20
Congestive heart failure		+10
Cerebrovascular disease		+10
Renal disease		+10
C. Exam Findings		
Altered mental status		+20
Respiratory rate ≥ 30/minute		+20
Systolic B/P < 90 mmHg		+20
Temperature < 35⁰C or > 40⁰C		+15
Pulse ≥ 125/minute		+10
D. Lab Findings		
pH < 7.35(do ABG only if hypoxic or COPD)		+30
BUN > 10.7 mmol/L		+20
Sodium < 130 mEq/L		+20
Glucose > 13.9 mmol/L		+10
Hematocrit < 0.30		+10
PO_2 < 60 mmHg or O2 Sats < 90%		+10
Pleural effusion		+10
Total A + B + C + D		_____

Note: This tool is a guide only to assist in decision making on site of care for CAP patients. It does not supercede physician direction or individualized patient care

Fine, M. et al. A Prediction Rule To Identify Low-Risk Patients with Community Acquired Pneumonia. New England Journal of Medicine (1997) 336(4),243-250.

[2]Available at http://pda.ahrq.gov/clinic/psi/psicalc.asp.

The following table summarizes the risk of mortality and need for hospitalization in patients treated for CAP based on PORT scores:

Table 3. MortalityRisk by PORT Classification*

PORT class	Mortality Risk	Hospitalization
I	0.1%	No
II	0.6%	No
III	0.9%	Consider
IV	9.3%	Yes
V	27%	Yes

*Adapted from Fine, et al., 1997

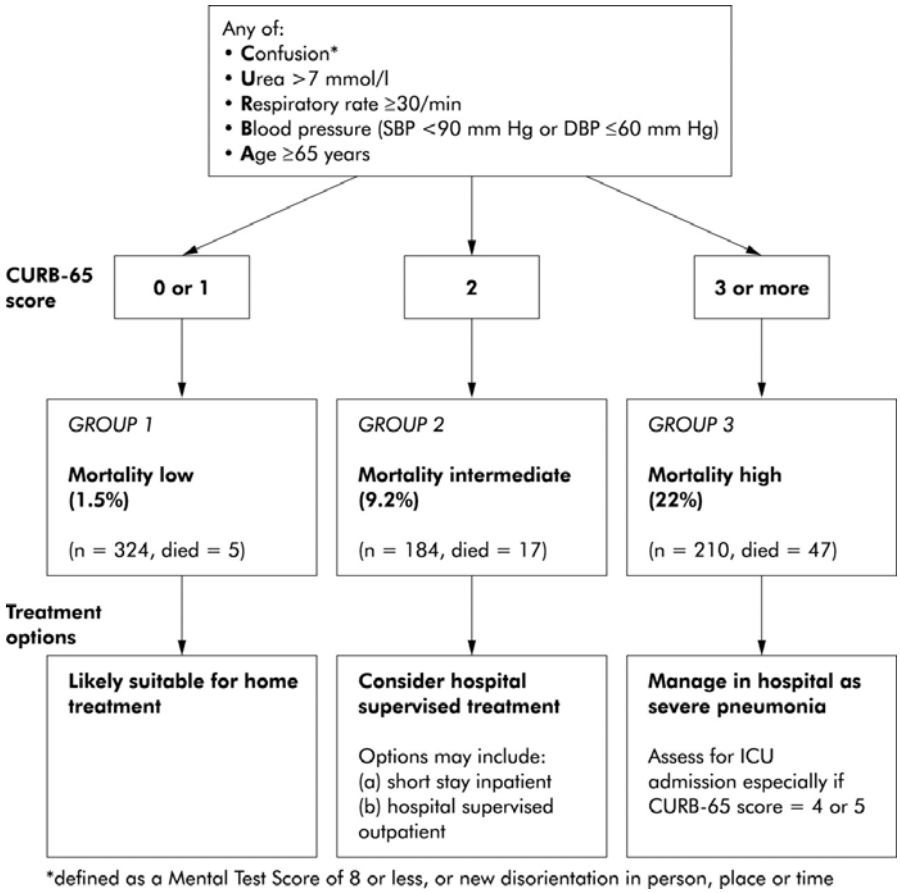
The CURB index (Neill et al.,1996) is another tool that uses four clinical features: confusion of new onset (or worsening of existing state for those with background cognitive impairment), serum urea >7 mmol/l, respiratory rate ≥30/min, and blood pressure (systolic blood pressure <90 mm Hg or diastolic blood pressure ≤ 60 mm Hg). The presence of two or more of these four criteria leads to a "severe" classification.

The CURB-65 index (Lim et al., 2003) is a modification of the CURB score with age ≥65 years was added as a fifth variable to the prediction score (Figure 2). A patient with three or more of the five criteria is classified as having severe disease. Mortality risk by the presence of these factors was confirmed in a validation cohort. Table 4 summarizes the risk of mortality and management recommendations based on CURB-65 classification:

Table 4. MortalityRisk and Management recommendations based on CURB-65

CURB-65 class	Mortality Risk	Management
0	0.7%	Low risk; consider home treatment
1	3.2%	
2	3.0%	Short inpatient hospitalization or closely supervised outpatient treatment
3	17.0%	Severe pneumonia; hospitalize and consider admitting to intensive care
4	41.5 %	
5	57%	

Figure 2. Curb-65 Score Algorithm



Limitations of Prediction Scores for CAP: Both the PSI and CURB-65 scores are heavily weighted by age. One strength of the PSI score, i.e. the inclusion of comorbid illnesses in the prediction model is a weakness of the CURB score which includes only the four factors mentioned earlier (Niederman, 2007). However, as noted earlier, both predictors reflect prognosis rather than severity in patients treated for CAP.

III. REGULATORY BACKGROUND FOR DESIGNING CAP STUDIES

Approximately 30 drugs are approved for the indication of CAP and its predecessor indication, Lower Respiratory Tract Infection (LRTI). Ten of these exist only as oral preparations.

Every clinical trial that has been submitted to FDA in support of a CAP indication has been a non-inferiority trial. This is consistent with the FDA 1992 Points-to-Consider document on

Antimicrobial Drug development[3] where ethical concerns regarding placebo-controlled studies are specifically addressed:

> In clinical trials of antimicrobial drug products, we only occasionally have the luxury of placebo controlled trials, because it is often felt to be ethically unacceptable not to treat infected patients when effective therapy is available. Therefore, we have most often relied upon active-controlled studies to establish effectiveness of a new antimicrobial drug product, usually using comparator agents already approved for similar indications in the United States…...
>
> With the increasing effectiveness of antimicrobial drug products in many infections, high cure rates make it nearly impossible or impractical for a new antimicrobial drug product to demonstrate statistical or clinically-relevant superiority to an approved comparator agent.

The 1992 FDA Points-To-Consider document also recommended a step function (i.e., sliding scale) approach for choosing a non-inferiority (NI) margin in antimicrobial trials. For non-inferiority studies of diseases where the successful outcome rate was 90% and above for the active control, an NI margin of 10% was recommended; for an 80% - 90% success rate, an NI of 15% margin was recommended; when the success rate for the control was below 80%, a 20% NI margin was considered acceptable.

There are several issues with this approach: the seriousness of the disease and the consequence of treatment failure are not taken into account, the possible effect from a lack of assay sensitivity is not addressed, and the large change in the NI margin for a small change in the success rate, e.g., from 80% to 79%, may not be justified. These and other concerns with the sliding scale approach were discussed at a number of public meetings.

It has subsequently been determined that the sliding scale method would no longer be used for NI clinical trials in systemic anti-infectives. Instead the principles discussed in section 1.5.1.1 of ICH E10 guidance, "Historical Evidence of Sensitivity to Drug Effects and Choosing the Non-inferiority Margin," should be utilized for determining an NI margin in clinical studies.[4] FDA issued draft guidance on the use of active-controlled non-inferiority studies for approval of anti-bacterial agents in October, 2007, to further articulate FDA's thinking regarding appropriate clinical study designs to evaluate antibacterial drugs. Currently, sponsors are asked to provide adequate evidence to support the proposed NI margin for any indication being studied with active-control non-inferiority studies.[5]

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[3] See http://www.fda.gov/cder/guidance/old043fn.pdf.

[4] See http://www.fda.gov/cder/guidance/4155fnl.pdf,

[5] See http://www.fda.gov/cder/guidance/7884dft.pdf.

IV. NON-INFERIORITY STUDY DESIGN CONSIDERATIONS

All clinical trials recently submitted to the FDA for an indication of CAP have been non-inferiority trials where the test drug has been compared to a drug currently approved for CAP. Efficacy of the new drug has been concluded by showing the test drug is 'non-inferior' to (i.e., 'not too much worse than') the approved drug in a well designed and conducted clinical trial. A conclusion of non-inferiority of the new drug is accepted if the lower bound of the 95% confidence interval for the treatment difference between the test drug and the active control is within a pre-specified margin. A basic tenet of this approach is that the treatment effect of the active control relative to placebo is known. For CAP, the evidence that the active control is superior to placebo in CAP is limited because no CAP studies comparing antibacterial drugs to no antibacterial treatment have been conducted since the 1940s.

In non-inferiority trials, the treatment benefit of active control over placebo (M1)[7,8] must be demonstrated based on reliable historical evidence, while controlling for variability and discounting for uncertainties in the treatment effect (i.e., recognizing that estimates of even a strong 'treatment effect' may vary between studies). After M1 has been determined, then M2[7] should be determined: M2 is defined as an acceptable loss of effect relative to control while preserving a substantial fraction of M1, i.e., the difference in treatment effect that would be clinically acceptable for a specific trial.

Assay sensitivity is a property of a clinical trial and is defined as the ability to distinguish an effective treatment from a less effective or ineffective treatment. Assay sensitivity is important in any clinical trial but has different implications for superiority trials (i.e., trials designed to show differences between study arms) than for trials intended to show non-inferiority (i.e., 'similarity' of study arms). A trial that successfully demonstrates superiority has simultaneously demonstrated assay sensitivity, A superiority trial that lacks assay sensitivity will fail to show that the test treatment is superior to control, the appropriate conclusion. Conversely, if a trial intended to demonstrate efficacy by showing a test treatment to be noninferior to an active control lacks assay sensitivity, the trial may find an ineffective treatment to be non-inferior, possibly leading to an erroneous conclusion of efficacy (ICH E10). In a non-inferiority trial, the trial itself does not have the ability to distinguish the active control from placebo, i.e., that the active control is 'active'; assay sensitivity must therefore be deduced or assumed from historical evidence demonstrating sensitivity to drug effects, with good study quality and similarity of the current trial to trials that were able to discriminate the active control drug from placebo.

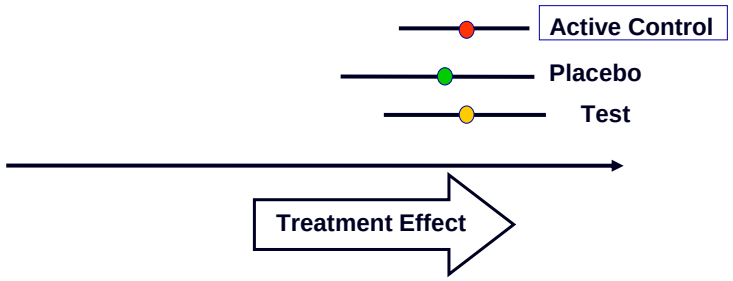
The primary statistical hypothesis in a non-inferiority trial is as follows:

$$\mathbf{H0: P_T - P_C \leq -\delta \text{ (T is inferior to C)}}$$
$$\mathbf{H1: P_T - P_C > -\delta \text{ (T is non-inferior to C)}}$$

P_T = Clinical response rate with test drug (T)
P_C = Clinical response rate with control drug (C)
δ = Pre-specified non-inferiority margin

Examples of different interpretations of non-inferiority trials are illustrated in the three figures below. The circles represent the point estimates of the treatment effect, and the lines represent the 95% confidence intervals. In Figure 3, it is evident that it would be difficult to differentiate the placebo response from either the 'active control' (active comparator) or test drug; a conclusion that the test drug has activity by comparison to the 'active control' alone would be incorrect. To establish non-inferiority, an effect of the control drug compared to placebo (or no treatment) has to be established prior to an NI study; as NI studies generally do not include a placebo arm, and therefore activity of the test drug can only be inferred by the assumption that the control drug would have been superior to placebo by a previously defined effect size. The NI margin is used to determine how much less efficacious the test drug could possibly be in comparison to the active control yet still be active (M1) and clinically acceptable (M2). In a scenario such as Figure 1, estimating a non-inferiority margin is not feasible and a non-inferiority design would not be appropriate.

Figure 3. NI Trial Inappropriate (Uncertain treatment effect [M1])



In Figure 4, there is a substantial active control effect over placebo and determining a non-inferiority margin from an adequate and well-controlled study is possible.

Figure 4. Large Treatment Effect (M1 can be estimated)

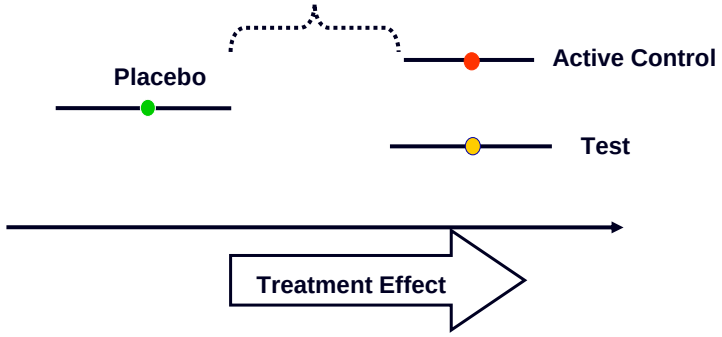
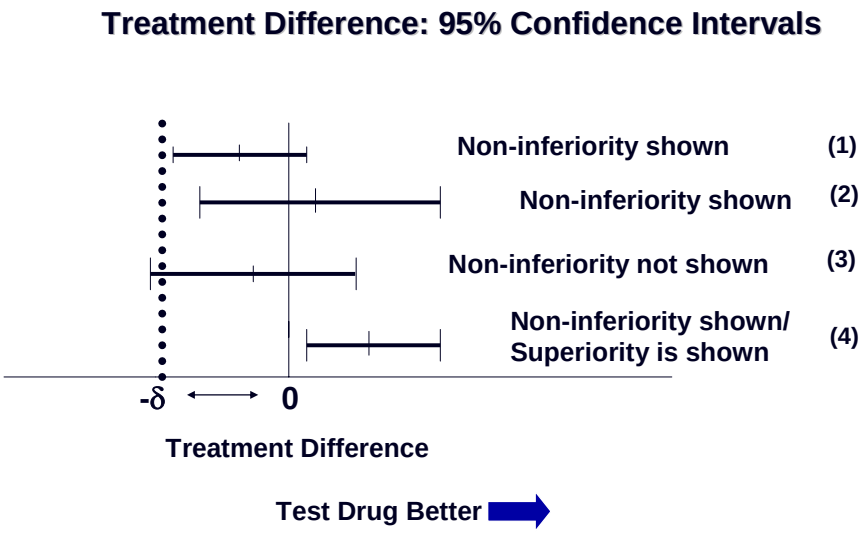


Figure 5 illustrates statistical inference applied to hypothetical results for a 95% confidence interval for the difference in clinical response between an active control and the test drug. Outcomes (1) and (2) clearly establish non-inferiority, although in outcome (2), the point estimate for the difference is above zero and provides stronger evidence than outcome 1.

Outcome (3) fails to demonstrate non-inferiority, and item (4) demonstrates an outcome of both non-inferiority and superiority.[6]

Figure 5. Hypothetical Non-inferiority Trial Outcomes



V. OVERVIEW OF RECENT CAP STUDIES

a. Outpatient studies (oral only)

To characterize patient populations, endpoints, pathogens, and outcomes observed in recent CAP studies submitted to the FDA, seven comparative studies which were submitted to the Office of Antimicrobial Products within the last eight years to support a claim for the indication of CAP are summarized here. All studies were randomized, double-blind active controlled non-inferiority trials designed to show similar effectiveness to an approved product and closely followed the 1998 FDA draft guidance, *Community-Acquired Pneumonia — Developing Antimicrobial Drugs for Treatment*.

Typical enrollment criteria, definitions of outcome, and analysis populations used in these CAP studies are summarized in Table 5:

[6] This is discussed further in ICH documents E9 and E10.

Table 5. Characteristics of Oral CAP Trials.

Enrollment criteria:	• Men and women at least 18 years of age
	• Clinical diagnosis of CAP characterized by:
	  • Fever (oral/tympanic temperature >38° C or rectal temperature >38.5° C)
	  • At least 2 of the following:
	  – New or increased cough
	  – Purulent sputum or a change in sputum characteristics
	  – Auscultatory findings of rales and/or evidence of pulmonary consolidation (e.g., bronchial breath sounds, or dullness on percussion)
	  • Dyspnea
	  • A new or progressive infiltrate(s) on chest radiograph
	• Willingness (and ability) to comply with the study protocol

Primary Endpoint:	Clinical outcome (test of cure visit, usually 7-21 days after end of therapy):
	• Success: Complete resolution or improvement of all signs and symptoms of pneumonia and improvement or lack of progression of abnormalities on chest radiograph such that no additional antibacterial therapy was required.
	• Failure was defined as:
	  • Persistence or worsening in signs or symptoms of the acute process after 3 to 5 days of therapy
	  • Failure to show improvement in at least three of the clinical findings after 3 days of therapy
	  • Initial improvement in at least three of the clinical signs and symptoms followed by clinically significant worsening in one or more of these clinical findings after 3 to 5 days of therapy
	  • Development of new pulmonary infection or extrapulmonary infection requiring antimicrobial therapy other than or in addition to the study drug
	  • Persistence or progression of chest radiographic abnormalities
	  • Death due to pneumonia
	
	All failures at the end of therapy were carried forward and considered failures at the TOC visit.

Microbiological evaluation/response:	Culture obtained at entry and test of cure. • Eradication: absence of original pathogen from the test of cure culture • Presumed eradication: clinical cure without specimen for culture • Persistence: presence of original pathogen in the TOC culture • Presumed persistence: clinical failure without culture of specimen.
Analysis Populations:	• Intent to treat (ITT) population: all randomized patients • Per protocol population (PP) or the clinically evaluable (CE) population: all ITT patients who did not have any major protocol violations • Microbiological ITT (MITT): all ITT patients in whom a pathogen was isolated • Microbiologically evaluable population: all MITT patients who did not have any major protocol violation
Primary Analysis:	Non-inferiority in these studies was assessed by constructing a two-sided 95% confidence interval for the difference in cure rates (test drug – control drug) for both the ITT and the PP populations. The non-inferiority margins for these studies were generally pre-specified as -10% or -15% and were determined on the basis of clinical judgment.

The size of the studies ranged from approximately 300 to 500 patients; patient ages ranged from 18 to 98 years old, with a mean and median of 46 and 45 years, respectively and the middle 50% of the population between 35 and 55 years old. The active controls used included clarithromycin, amoxicillin/clavulanate, and levofloxacin.

Cough and sputum production at entry were reported by 97-100% and 75-100% of patients respectively. A smaller percentage of patients had fever (19% to 98%); the study with 98% was an outlier since fever was an entry criterion for that particular study. Approximately 20% of patients had multilobar disease. Bacteremia was seen in 0-8% of patients, with 0 to 2% having *S. pneumoniae* bacteremia. Most patients enrolled were categorized as PORT I or PORT II. The percentage of patients with PORT scores of III or higher ranged from approximately 5 to 10%. In some studies PORT scores were not reported.

Figure 6 shows that the percentage of all randomized patients with a bacterial pathogen identified at baseline ranged from 45% to 75%, including subjects diagnosed by serology. These subjects define the MITT analysis population for each study. Overall (i.e., including subjects without a pathogen identified), patients with *S. pneumoniae* isolated from blood or sputum at baseline ranged from approximately 6 to 20% of patients enrolled.

Figure 6. Percentage of Study Patients with a Bacterial Pathogen Identified

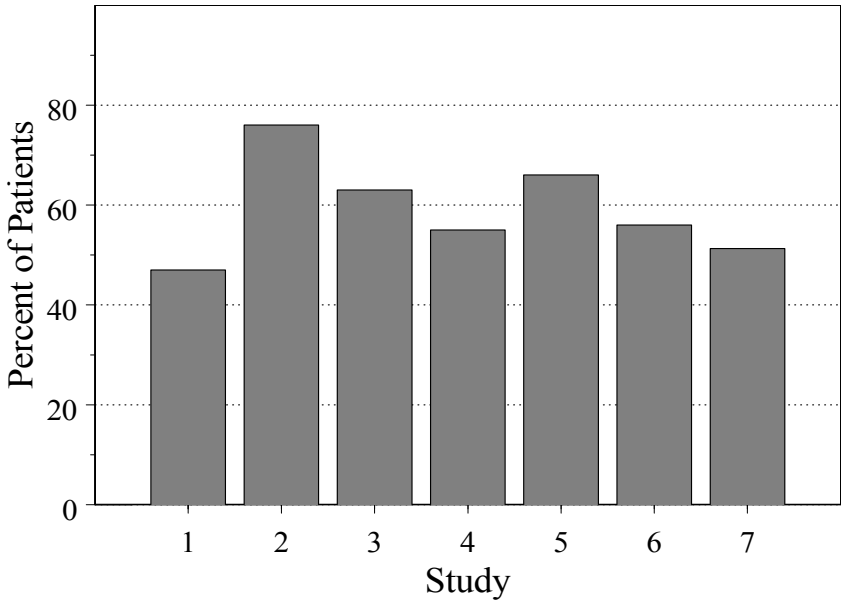
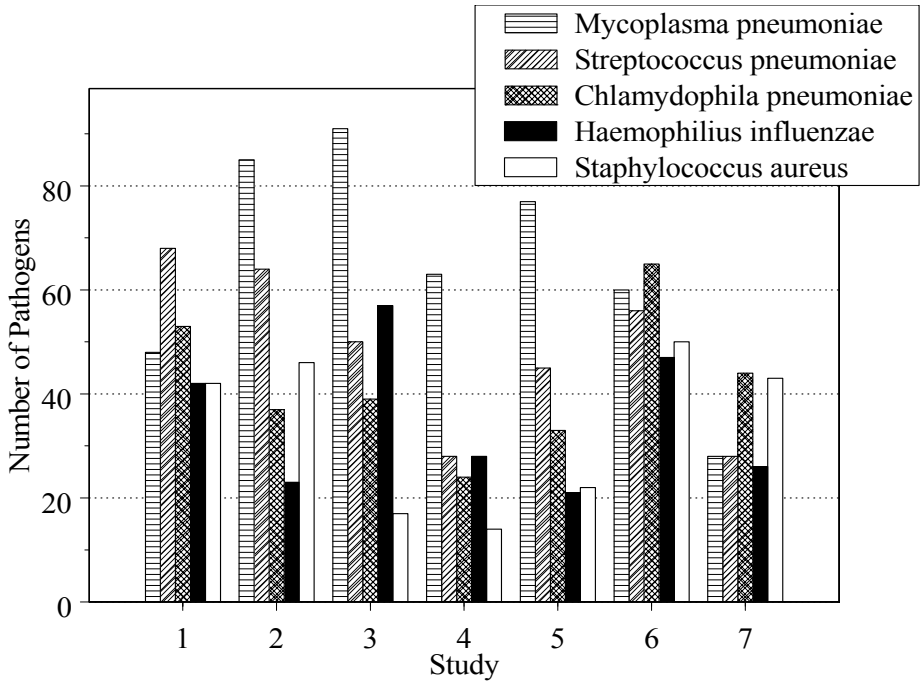


Figure 7 shows the baseline pathogens in these studies. The y-axis represents the actual number of patients with a particular pathogen rather than the percentage since patients could have had more than one pathogen. Although there is variability across studies, in general *S. pneumoniae, M. pneumoniae,* and *Chlamydophila pneumoniae* were most commonly identified. (Both *Mycoplasma* and *Chlamydophila* were identified serologically.)

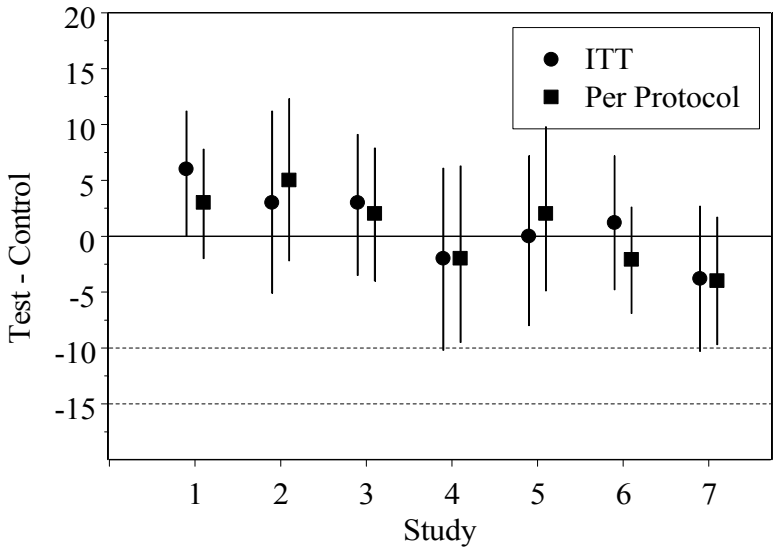
Figure 7. Number of Bacterial Pathogens Identified in Each Study



Clinical cure rates were generally very similar between studies with success rates greater than 80% in all treatment arms. Cure rates in the PP population were ≥ 90%, and mortality was low (<2%).

Figure 8 shows the treatment difference between the test and controls in the ITT and PP populations based on clinical cure. In all of these studies the results in the ITT and PP populations were very similar. All of these studies would have been able to claim non-inferiority with a 15% margin, and all but two would have been able to claim non-inferiority with a 10% margin. Each study is shown twice. The circles are the point estimates of the difference for the ITT population and the squares are for the per protocol population. Each line is the 95% confidence interval of the difference between test and control.

Figure 8. Treatment Difference Between Test Drug and Active Control



Although microbiological response is an important endpoint, microbiologic specimens are usually unavailable at the end of study to confirm eradication. Accordingly, the large majority of microbiological responses are presumed eradication. The percentage of presumed eradication (out of all eradications) was 94% or higher for 6 of the 7 studies and 83% in the seventh study. Among the failures, presumed persistence ranged from 78% to 100%.

b. Hospitalized Studies (IV treatment)

Fewer studies using intravenous (IV) antibacterial agents were submitted to the Office of Antimicrobial Products over the past eight years. In general, study designs were similar to those for the oral antibacterial drug studies although some studies were not blinded. Patients were required to be newly hospitalized, usually within 24 hours prior to enrollment in the study. The endpoints, definition of analysis populations, and primary analysis were the same as for the oral studies (see Table 5).

Study sizes ranged from 300 to 700 patients. Patients were older than those in the oral studies, with a mean age of 56 years and the middle 50% of the population between 40 and 70 years. PORT scores were higher than with the oral studies: 20% of patients had PORT scores of III, 20% had PORT scores of IV, and <5% had PORT scores of V. The remaining 55% had PORT scores of I and II. The percentage of patients with a baseline pathogen isolated was 30 – 55%. The types of pathogens varied greatly between studies, with 20% overall having *S. pneumoniae* isolated from blood or sputum. Eight to ten percent had bacteremia at baseline and 4-9% had *S. pneumoniae* bacteremia. These rates are higher than that seen in the oral studies.

The clinical response rates were approximately 80% for ITT and 90% for the PP populations respectively. Mortality was approximately 2 – 4%.

VI. SUMMARY OF FDA/IDSA WORKSHOP

A workshop on "Issues in the Design and Conduct of Antibacterial Dugs in the Treatment of Community-Acquired Pneumonia," was co-sponsored by the U.S. Food and Drug Administration and the IDSA and held on January 17 and 18, 2008. Two common clinical scenarios served as the focus for discussion of clinical trial designs at the meeting. The first was a relatively healthy adult with clinical and radiological evidence of pneumonia who met criteria for outpatient treatment with an oral antibacterial drug. The second scenario described an elderly woman with diabetes, COPD and history of CHF who was hospitalized for left lower lobe pneumonia. These scenarios represented two common patient populations seen in antibacterial drug studies: outpatients in oral antibacterial drugs studies, and hospitalized patients in IV antibacterial studies.

The presentations covered various topics relevant to clinical trial designs for CAP, including:

- Statistical considerations for trial designs
- Clinical perspectives on trial design for CAP
- A summary of recent non-inferiority trials for CAP submitted to FDA
- Development of the pneumonia severity index as a predictor of mortality in treated CAP patients
- Historical data on the use of antibacterials for pneumonia
- PK/PD analyses of current CAP clinical trials with emphasis on outcomes for patients with low drug exposure.

Much of the information from these presentations is discussed elsewhere in this briefing package, and will be presented at the upcoming Advisory Committee meeting.

Other presentations addressed clinical endpoints, collection of safety data, new diagnostic methods under study, and procalcitonin as a biological marker. These presentations provided discussion points for better methods to be used in future clinical trials, e.g., use of molecular diagnostics may lead to trials enriched for patients with pneumococcal pneumonia; procalcitonin may allow better selection of patients with bacterial pneumonia; and patient-reported outcome tools might allow more objective assessment of changes in pneumonia symptoms. However, additional research is needed on the development of these tools, and their implementation in clinical trials.

At the end of each day, the workshop format provided opportunities for different perspectives to be discussed and debated. For patients with moderate to severe pneumonia, there appeared to be general agreement that non-inferiority trials could be supported by the available scientific data, though the endpoints and definitions of severity for patients in these trials engendered greater discussion. Various endpoints (mortality, symptom resolution, occurrence of complications, days of hospitalization/ days in ICU, and composite endpoints) were discussed. Mortality was considered by some as the main endpoint of interest because it is the most important effect of treatment, and the historical data of treatment effect are based on mortality. Others viewed a primary endpoint of mortality as impractical, though they included mortality as part of any composite measure. The use of patient-reported outcome measures was endorsed by many for

pneumonia studies (regardless of severity), though it was unclear that the PRO tools for CAP had been "validated" and whether there is enough historical data to support a treatment effect based on this measure. The pneumonia severity index and CURB-65 were suggested as reasonable measures of severity, based on their use as decision tools for hospitalization. However, it was pointed out that these tools were developed as predictors of higher mortality in antibiotic-treated patients, not as predictors of patients who would have worse outcomes if untreated. These scales are not measures of disease severity, though some of the elements of each scale include factors related to severity (e.g., respiratory rate >30). These scores are heavily weighted toward elderly patients, and this raised concerns in some about creating greater differences between clinical trial populations and patients treated in clinical practice.

For mild pneumonia, there was discussion of defining disease severity, endpoints and methods to enrich for patients with pneumococcus. There was greater debate about whether non-inferiority trials were appropriate in this population, and whether superiority studies that would provide meaningful results could be designed. Many participants considered the limitations of non-inferiority to be a significant problem for this population. Some stated that it was unlikely that newer antibacterials would be able to demonstrate superiority to penicillin in treatment of CAP. One of the most prominent concerns expressed by participants was related to the ethics of placebo groups or delayed treatment in these trials. It was clear that the ethics of such trials was a significant concern. Statements regarding use of placebo ranged from "it would be inappropriate to not treat that patient" to emphasis on the risks of giving a drug, when its effectiveness is unclear.

In the end, there was emphasis placed on improvement of non-inferiority trials through better diagnostics, better selection criteria, and more objective measures of outcome. However, many of these methodologies are still in development, and there was an emphasis on the need to be able to move forward today with the development of newer drugs.

VII. APPROACH TO DETERMINATION OF ANTIBACTERIAL DRUG TREATMENT EFFECTS IN CAP

The quantitative estimate of "treatment effect" (the difference in efficacy between an active control and placebo) necessary for designing a non-inferiority study is usually determined from prior placebo-controlled trials. This estimate is required when designing a noninferiority study to ensure that the active comparator is more effective than placebo. A clinically acceptable non-inferiority margin is determined from the difference in efficacy between active control and placebo so that activity of the test drug can be inferred by similarity to the active control.

To determine the treatment effect of antibacterial drugs for CAP, literature searches were performed to identify natural history and "no treatment" controlled studies of CAP from the pre-antibiotic era and in the decades immediately following the introduction of antibacterial drugs for treatment of pneumonia. Literature searches were performed using PubMed to identify CAP studies published from approximately 1950 to the present; studies published prior to 1950 were

identified from citations in published literature and textbooks. This information is reviewed in the section "Historical Information" below.

An alternative approach was to identify evidence of superiority from modern CAP trials as a minimum estimate of a treatment effect. This included:

- Active control studies where superiority was demonstrated
- Studies that evaluated the effectiveness of guideline-concordant CAP antibiotic treatment compared to antibiotic treatment which was not guideline-concordant
- Studies that evaluated the effect of discordant therapy on CAP outcomes (e.g. comparison of treatments which included empirical coverage for atypical pathogens vs. those which covered only typical bacterial pathogens)
- Studies with treatments that covered resistant pathogens versus those that did not
- Studies that evaluated the effect of delayed vs. immediate antibiotic therapy on outcomes,
- Studies that demonstrated dose-response, and/or pharmacokinetic/pharmacodynamic relationships as evidence of an antibacterial treatment effect.

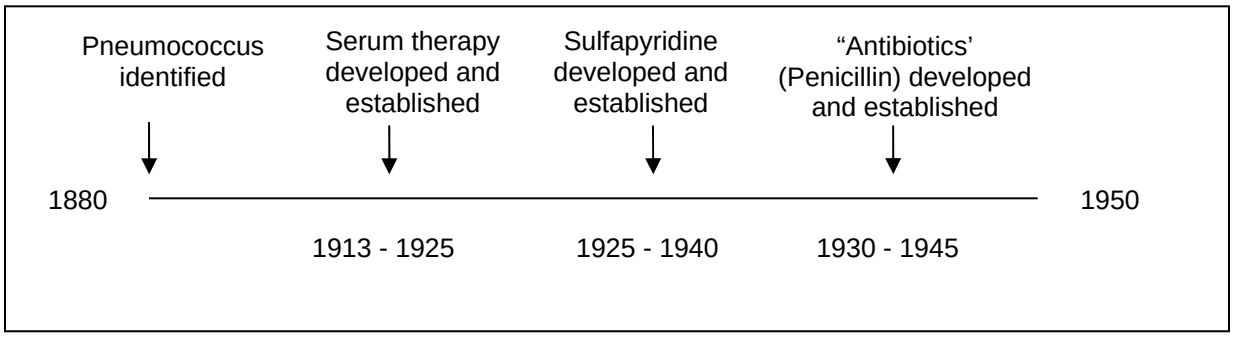
Sources of information included published articles, reviews (e.g., Cochrane reviews), and the FDA New Drug Application database. The goal of evaluating these alternative sources of data was to estimate a "minimum" treatment effect to support the information available from the 'historical,' i.e., pre-1950, data. This approach is described in the section "Alternative approach to determination of Antibacterial Drug Treatment Effect in CAP".

a. Historical Information on Treatment of CAP

Pneumonia, once considered the "Captain of the Men of Death" by Sir William Osler has been treated with antibacterial drugs since the late-1930s. Sulfapyridine, the first antibacterial agent shown to be effective against pneumococcal pneumonia, was followed rapidly by penicillin and other drugs that redefined pneumonia as a manageable clinical entity. Although preceding the 'birth' of modern clinical trials by a decade, the effectiveness of antibacterial therapy for pneumonia was shown in early controlled trials and careful observational studies.

S. pneumoniae was first identified as a cause of pneumonia in 1881 when it was separately isolated by George Sternberg ("Father of American Bacteriology") and Louis Pasteur. Figure 9 summarizes the timeline from the identification of the pneumococcus to development of specific treatments for pneumonia.

Figure 9. Treatment of Pneumococcal Pneumonia Timeline



Many detailed histories on the evolution of treatment for pneumococcal pneumonia have been published including Heffron (1939), Cecil (1939), Finland (1979), Austrian (1981). Dowling (1972), and Podolsky (2006). Serum therapy, the first generally recognized effective treatment specifically targeted at pneumococcal pneumonia, was first used in 1913 and refined over the subsequent 25 years. Observational studies comparing serum treatment to untreated historical controls showed reduced mortality. Subsequent studies with concurrent controls confirmed a reduction in mortality with the use of concentrated antiserum in type I pneumococcal pneumonia, and to a lesser extent, in type II pneumococcal pneumonia (Cecil and Larsen (1922) Cecil and Sutliff, (1928) Park, et al. (1928) and Finland (1930)). As discussed by Podolosky (2006) rapidly providing serum to patients with pneumococcal pneumonia was a major public health initiative of the late 1930s.

Sulfonamides were first synthesized and noted to have antibacterial activity *in vitro* and in animals in the early 1900s. Sulfapyridine (M&B 693) was the first well-tolerated, soluble sulfonamide with anti-pneumococcal activity. By 1939, sulfapyridine was widely adopted for use in clinical practice after a number of early clinical studies with sulfapyridine reported decreased mortality in patients with lobar or pneumococcal pneumonia, Penicillin, the "miracle drug for pneumococci, staphylococci and syphilis" (Dowling, 1972) was first available for commercial use in 1942 and rapidly supplanted sulfonamides for treatment of pneumonia by the mid-1940s.

Soon after sulfapyridine became available, observational studies demonstrated decreased mortality in patients who received antibacterial therapy when compared to patients who received no specific therapy or serum therapy. H.F. Dowling, in his 1972 description of the beginnings of the "antibiotic era of therapy", noted the dramatic effect of antibacterials on pneumonia: "Deaths from influenza and pneumonia dropped from about 200/100,000 population for the year 1900 to 31/100,000 for each year from 1949 to 1951." He also noted that "empyema practically disappeared; (and) endocarditis and meningitis as complications of pneumonia were rarely seen."

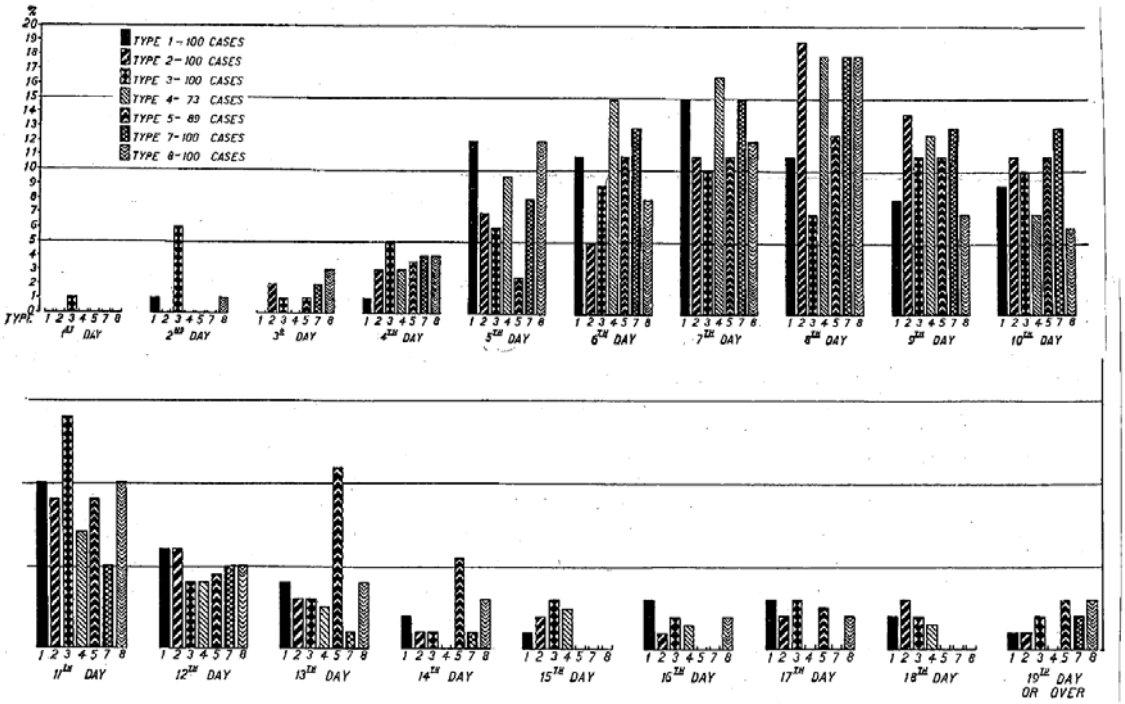
b. Natural History of Pneumococcal Pneumonia

Several publications addressed the natural history of pneumococcal pneumonia prior to the availability of effective treatment. In "The Management of the Pneumonias," Bullowa (1937) described the course of a 'typical' untreated patient with severe pneumonia.

> "The typical picture of a patient is a man about 30 years of age, who, after a cold in the head lasting 3 or 4 days is suddenly taken with a shaking chill and stabbing pain in the side of the chest……Fever and malaise continue day after day and prostration progresses. After four or five days, the patient who has become irritable and peevish begins to 'see things' … After eight or nine days the temperature falls following a drenching sweat. The patient then convalesces over several weeks, unless, after a few days there is an exacerbation of fever with the onset of suppurative complication. In one of four cases, …. the breathing becomes more labored and shallow… There are periods of apnea increasing in length until breathing ceases."
>
> "It is usually stated that the temperature continues high without intermission until it breaks on the eighth or ninth day by crisis or gradually descends day by day (lysis)…. The duration of temperature in pneumonia varies considerably… with the mode (for the day of temperature termination) on the eighth or ninth day. A graph of the frequency of termination resembles the bell shaped curve of the distributions from the mean. It will be seen that some types of pneumococcus pneumonias tend to terminate earlier than others."

Figure 10 from Bullowa's chapter on "Course, Symptoms and Physical findings" (Bullowa, 1937) illustrates the proportion of patients without purulent complications who have "terminated by recovery." These 662 patients spontaneously recovered from pneumococcal pneumonia with no specific treatment. The percentage of patients who "terminated by recovery" on each day varied by pneumococcal type. Though the data suggest that very few patients "recover" before day 4, this figure seems to refer only to resolution of fever rather than resolution of other signs and symptoms of pneumonia. In current CAP trials, outcome assessment, generally performed at some point after the end of therapy and fever resolution, is only one part of the definition of cure (see Table 5). Thus, the applicability of these data to determination of a non-inferiority margin for current CAP trials is limited. However, these data may be useful for trials in which time to fever resolution is used as an endpoint.

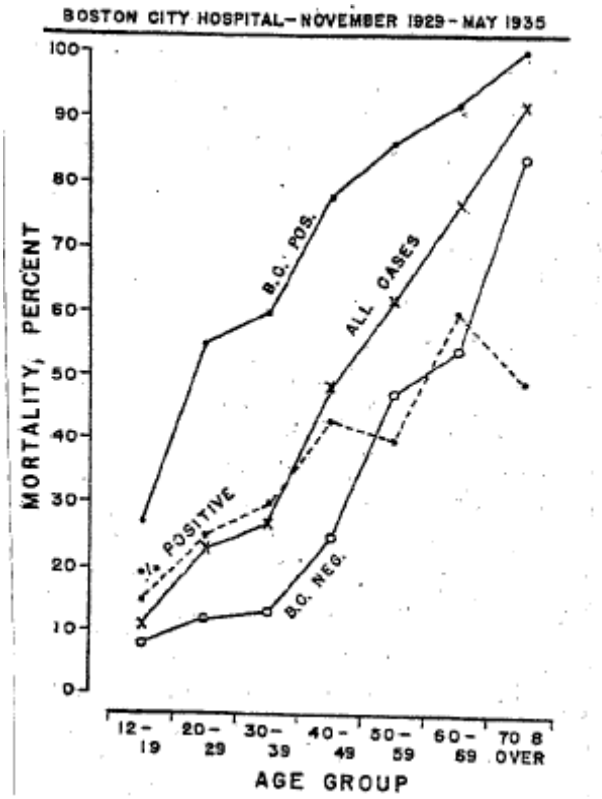
Figure 10. Percentage of Untreated Patients "Terminating by Recovery" by Each Day in Seven Different Pneumococcal Types (from Bullowa, 1937)



An additional description on the duration of acute symptoms in lobar pneumonia comes from Osler (1910): “After persisting from 7 to 10 days the crisis occurs, and with a fall in temperature the subject passes from the condition of extreme distress and anxiety to one of comparative comfort.” Crisis was an abrupt drop in temperature which was considered one of the most characteristic features of pneumonia. Osler also noted: “The day of crisis is variable. It is very uncommon before the third day and rare after the twelfth. I have seen it as early as the third day.”

Tilghman and Finland (1937) reported the mortality of pneumococcal pneumonia by age and presence or absence of bacteremia in 1586 cases seen at Boston City Hospital from 1929-1935. These patients received only symptomatic treatment but no specific anti-pneumococcal therapy. . Their data (Figure 11) show increasing mortality with age, regardless of the presence of bacteremia (although the incidence of bacteremia similarly rises with age). Even patients with the better outcomes, i.e., blood culture negative patients, had 8% mortality at ages 10-19, rising to 50% at age 50 and over 80% at age 70.

Figure 11. Mortality in Untreated Pneumococcal Pneumonia



As further discussed by Tilghman and Finland (1937), termination of the acute disease by crisis, lysis or death occurred most frequently between the 7th and 9th day in patients who received no specific serum therapy, regardless of the presence of bacteremia. In patients treated with specific anti-serum, "recovery" usually occurred between the 4th and 6th day, regardless of the presence of bacteremia. In both treated and untreated groups few patients had resolution of acute disease within the first three days, similar to the findings of Bullowa (1937) described earlier.

Figure 12. Duration of Acute Illness in Patients Treated With or Without Serum Therapy

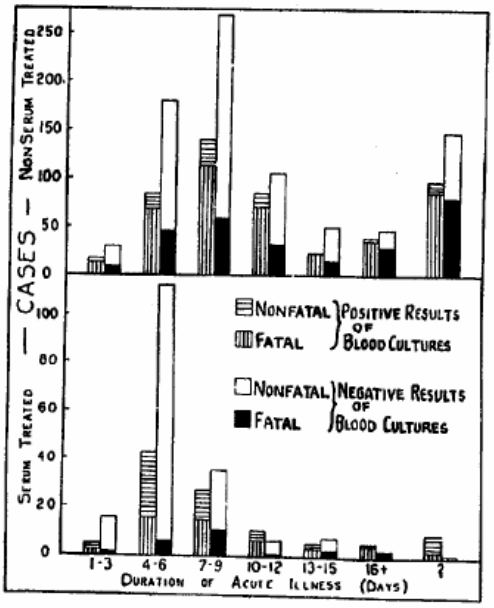


Chart 3.—Comparison of the duration of the acute illness, the mortality, the incidence of bacteremia and the type of treatment for various age groups. The height of the columns represents the number of cases.

Observational data summarized by Bullowa (1937) from Harlem Hospital showed a similar trend of age-related increased mortality and bacteremia. Bullowa also found prognosis to be dependent on pneumococcal serotype, an important consideration for the clinical use of serum therapy.

c. Serum Therapy for Pneumococcal Pneumonia

The first publications on serum therapy for pneumococcal pneumonia date to 1913, with subsequent improvements over the next 2 decades (primarily adding more serum types). Serum therapy was established through what was described as ‘one of the first collaborative controlled clinical trials,’ partially funded by the Metropolitan Life Insurance Company to address the rapid increase in claims for pneumonia-related illness. The following table from Cecil (1939) summarizes data published to that time on the effectiveness of serum therapy. Percent mortality is reported by pneumococcal serotype for serum treated versus untreated subjects:

Table 6. Serum Therapy for Pneumococcal Pneumonia

TABLE III
RESULTS OF SERUM THERAPY IN BACTERIEMIC CASES OF PNEUMONIA

	Serum Treated			*No Serum*		
Pneumococcus	*No. Cases*	*Deaths*	*Mortality Per Cent*	*No. Cases*	*Deaths*	*Mortality Per Cent*
Type I	651	225	34.5	325	225	69.6
II	189	105	55.5	381	282	74.0
V	36	26	72.2	113	87	76.9
VII	13	2	15.4	71	61	85.9
VIII	15	5	33.3	126	57	45.2
TOTAL	904	363	42.2	1016	712	70.0

These cumulative observational results provided evidence of a reduction in mortality with serum therapy. However, additional important observations from this study were that earlier administration of serum therapy dramatically affected mortality (see table below), and that there was an apparent dose response for serum therapy, with <60,000 units being less effective (data not shown). Another aspect of serum therapy, also seen in other publications, was that the treatment effect was primarily seen in younger patients, with less benefit observed in older patients.

Table 7. Mortality in Pneumococcal Pneumonia Patients Treated Within or After 72 Hours

TABLE II
FATALITY RATES FOR PNEUMOCOCCUS TYPES I & II TREATED WITHIN AND AFTER SEVENTY-TWO HOURS

	Cases Treated Within 72 hours of onset			*Cases Treated 72 hours, or more, after onset*		
Pneumococcus	*No. Cases*	*Deaths*	*Mortality Per Cent*	*No. Cases*	*Deaths*	*Mortality Per Cent*
Type I	844	79	9.3	979	170	17.3
II	62	10	16.1	40	16	40.0

A number of other observational studies, including Davies, et al. (1935a) and Davies, et al. (1935b) also reported a mortality benefit for specific serotherapy in the treatment of pneumococcal pneumonia.

Although serum therapy was considered dramatic for its impact on mortality, none of these controlled studies can be used for quantifying a treatment of antibacterial treatment effect for CAP for this review. Different effect sizes observed across different pneumococcal types, non-standardization of the antiserum source between studies, and differences in antiserum dose and duration of treatment within and between studies render any estimate of effect unreliable even if an effect is evident.

Park et al. (1928) also compared serotherapy with standard treatment in patients with lobar pneumonia. As discussed for similar studies noted above, this study is also of limited value for quantifying a treatment effect for serum therapy. Nonetheless, the study described outcome by

disease severity at baseline, an analysis not reported for most of the studies at that time. Patients were assigned in an alternating fashion to receive either polyvalent pneumococcal antiserum (to pneumococcal types I, II, and III) or standard treatment (fluids, pain relief with adhesive plaster, restriction of opiates, no drastic catharsis, oxygen for cyanosis or rapid breathing and digitalization for heart rate > 120 beats per minute). Patients with type I pneumococcal pneumonia were classified by baseline condition as good, fair, or poor, although the specific criteria characterizing each of the severity groups were not described in any detail. Outcomes were reported by baseline condition, as shown in Table 1, although the actual numbers of patients in each of the severity groups was not reported.

Table 8. Case Fatality Rate in Patients with Type I Pneumococcal Pneumonia[1]

Condition at baseline	Serum-treated (N=114)	Standard Treatment (N=109)	Treatment Difference (standard-serum therapy)
Any condition	20%	34%	14%
Good	9%	13%	4%
Fair	29%	52%	23%
Poor	64%	100%	36%

[1] Adapted from (Park, et al., 1928)

Overall, the case fatality rate was 34% in patients who received standard therapy and 20% in those who received serum therapy, regardless of baseline condition. Whether the interventions of standard therapy may have had detrimental effects resulting in higher mortality in that treatment group is not clear. However, the important suggestion was made that mortality and the effect of treatment increased with severity, and that the observed treatment difference was greatest in patients considered to be in poor condition at baseline.

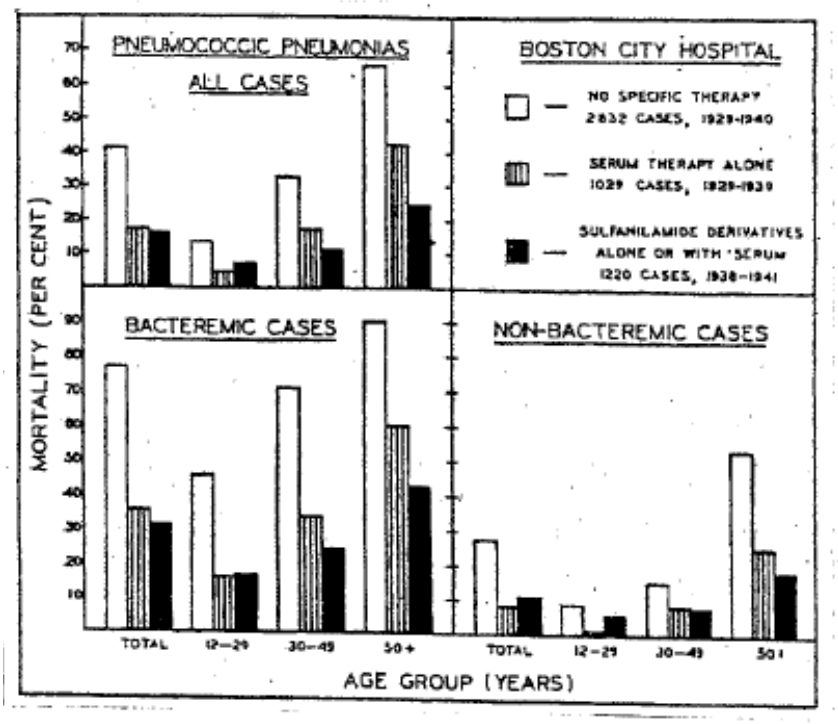
d. Treatment of Pneumococcal Pneumonia with Antibacterial Drugs

i. Observational Studies

Finland (1943; 1960) summarized mortality in patients with pneumococcal pneumonia seen at Boston City Hospital from 1929-1941. This cohort included patients who received no specific therapy between the years of 1929-1940 (N=2832), patients treated with serum between 1929 and1938 (N=1029) and patients treated with sulfonamides between 1939 and 1941 (N=1220).

As shown in Figure 13, the overall difference in mortality between patients who received no specific therapy and those who received a sulfonamide derivative was 24% (41% minus 17%,). Similar to serum therapy, there was a greater difference in bacteremic patients, 48% (78% minus 30%) than non-bacteremic patients at 17% (28% minus 11%). Mortality increased substantially with age in both bacteremic and non-bacteremic patients. These data are summarized in Table 9.

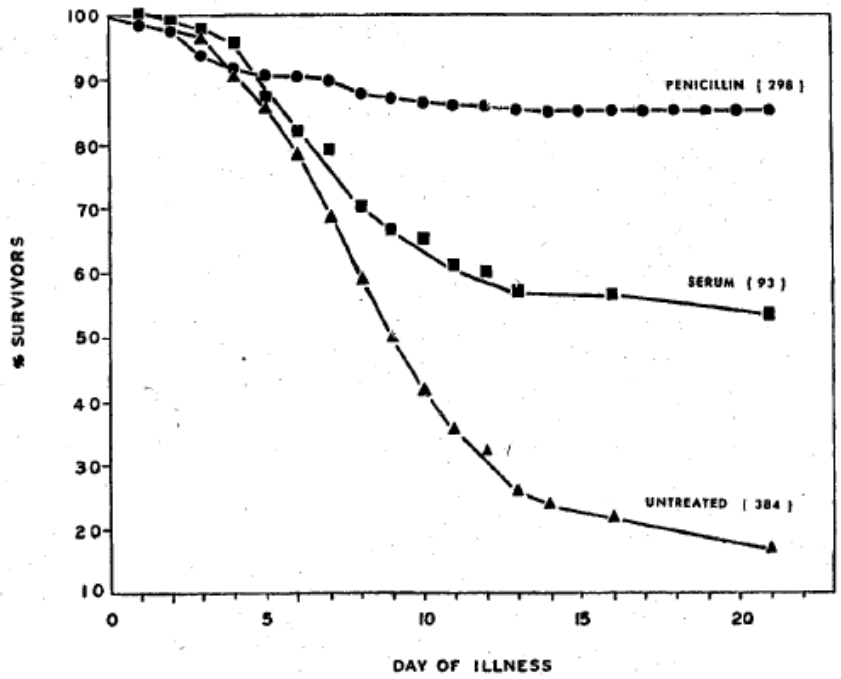
Figure 13. Mortality in Pneumococcal Pneumonia (from Finland, 1943 and 1960)



Dowling and Lepper (1951) compared case fatality rates in patients who received no specific treatment (N= 1087) to those treated with pneumococcal antiserum (N= 889), sulfonamides (N=1274), or penicillin and other antibiotics e.g., tetracyclines (N=920). The no specific treatment and serum treatment groups were historical controls studied at Boston City Hospital between 1939 and 1940 reported in earlier publications [Brown 1939, Finland 1939, Finland 1940, Ruegsegger 1940]. Overall case fatality rates (i.e., regardless of bacteremia or age) were 30.5% for patients without specific treatment and 16.9%, 12.3%, and 5.1% for patients receiving serum, sulfonamide, or antibiotic (penicillin or tetracyclines) therapy respectively as summarized in Table 9. In this report mortality was again shown to increase with age and the presence of bacteremia regardless of treatment.

Austrian and Gold (1964) reported survival by days of illness for patients with bacteremic pneumococcal pneumonia treated with penicillin between 1952 and 1962 (N= 298), pneumococcal antiserum (N=93), or with no specific therapy (N= 384). The latter two groups were historical controls reported by Tilghman and Finland (1937). As shown in Figure 14, at 21 days, survival was 85% for those treated with penicillin, 50% in those treated with pneumococcal antiserum, and 17% in patients who received no specific anti-pneumococcal therapy. The difference in survival between the groups treated with penicillin and the untreated (historical control) group was 68% at day 21, 60% at day 14, and 22% at day 7. No difference was observed in the first 5 days of illness.

Figure 14. Effect of Therapy on % Survival in Bacteremic Pneumococcal Pneumonia (From Austrian and Gold, 1964)



In the same publication, Austrian and Gold (1964) also reported mortality by treatment in a different group of patients which included 454 cases of bacteremic pneumococcal pneumonia without an extrapulmonary focus of infection. In patients treated with penicillin, 57/338 (17%) died; while 10/55 (18%) patients treated with tetracyclines died; 8/44 (18%) patients treated with other antibacterials died; while 14/17 (82%) concurrent patients who received no specific treatment, died. For all antibiotic-treated cases, there were 75 deaths/437 patients (17.1%) overall. These data are summarized in Table 9.

Overall mortality and treatment effect (the mortality difference between untreated controls and antibacterial drug-treated) obtained from several of the observational studies described above is summarized in Table 9. Although anti-pneumococcal serum could be considered an antibacterial drug, the treatment difference was determined only from data which evaluated ‘conventional’ antibacterial drugs such as sulfonamides or antibiotics such as penicillin.

Table 9. Summary of Mortality and Antibacterial Drug Treatment Effect from Observational Studies*

Publication	Year	Population	Mortality Untreated	Mortality Serum-Treated	Mortality Antibacterial Drug-Treated	Mortality Difference Untreated - Antibiotic (95% confidence interval)
Finland [16, 17]	1929 - 1941	Pneumococcal pneumonia ≥ 12 years old:	N = 2832 (1929-1940) 41%	N = 1029 (1929-1938) 18%	N = 1220 (1939-1941) 17% (sulfonamides)	24% (21, 27)
			Bacteremic: 78% Non-bacteremic: 28%	Bacteremic: 36% Non-bacteremic: 8%	Bacteremic: 30% Non-bacteremic: 11%	Bacteremic: 48% Non-bacteremic: 17%
Dowling and Lepper [18]	1938 - 1950	Pneumococcal pneumonia ≥ 10 years old Bacteremic and non-bacteremic	Historical control** N =1087 30.5%	Historical Control** N = 889 16.9%	N =1274 12.3% (sulfonamides)	Sulfonamides: 18.5% (15, 21)
					N=920 5.1% (penicillin or tetracyclines)	Penicillin or tetracyclines: 25.4% (22, 28)
Austrian and Gold [24]	1952 - 1962	≥ 12 years old Bacteremic pneumococcal pneumonia (uncomplicated)	N = 17 82%		N = 437 17% (multiple antibacterials***)	65% (41, 79)

* Dosing information for antibacterial drugs was not provided in these publications.
** Brown and Finland (1939); Finland and Brown (1939); Finland, et al.. 1939); Ruegsegger, et al. (1940)
*** Multiple antibacterials included penicillin, tetracyclines, erythromycin, chloramphenicol, and streptomycin

In a small observational study at Boston City Hospital (Meads et al., 1945), patients with pneumococcal pneumonia were treated with either penicillin alone or with penicillin following failure of or intolerance to sulfonamide therapy. Thirty-seven of the 54 patients in the study were characterized as severely ill by study criteria, 56% (21/37) of patients receiving penicillin and 94% (16/17) of subjects with penicillin following sulfonamide therapy. Outcomes reported in this study are shown in Table 10.

Table 10. Outcomes in Penicillin-Treated Patients with Pneumococcal Pneumonia

Parameter	Penicillin N=37	Penicillin after sulfonamide failure or sulfonamide intolerance N=17
Survival	30 (81%)	14 (82%)
Relapse	2/30	1/14
Pyogenic complications	0	0
Bacteremia	0/12	4/6
Resolution of acute symptoms in < 48 hours**	27/30 (90%)	9/14 (64%)
Resolution of fever in < 48 hours	24/30 (80%)	8/14 (57%)

*[f]From Meads, et al., 1945
**Acute symptoms included delirium, prostration, and dyspnea.

Although survival was similar in both treatment arms, this study provides information on certain clinical outcome measures other than mortality. In the group treated with penicillin alone, no patients had pyogenic complications or bacteremia after receiving penicillin. In this group, fever and acute symptoms resolved within 48 hours for 80% and 90% of patients, respectively. In the group that received penicillin following sulfonamide treatment, a smaller proportion of patients had rapid resolution of acute symptoms and fever; and a higher proportion had bacteremia even after penicillin therapy was started. However, most patients in the latter group did not receive penicillin until after 4 days of illness, were somewhat older, and were classified as severity grades 3 or 4 (acutely ill or irrational, or shock or congestive failure, respectively) prior to receipt of penicillin in comparison to the former group.

Although there are many limitations to this study, i.e. small size, observational design, and variety of penicillin doses and durations used for treatment, in comparison to earlier studies penicillin apparently had an effect on clinical outcome measures other than mortality in patients with moderate-severe pneumococcal pneumonia.

ii. *Treatment of pneumonia with antibacterial drugs: 'No treatment' controlled clinical trials*

Several controlled clinical trials of pneumonia were performed which led to generalized acceptance of antibacterial treatment of pneumonia. These studies compared groups assigned to antibacterial treatment to those assigned to receive no specific antipneumococcal therapy; however, there was no blinding of patients or investigators, and the methods for randomization were not what we would expect in contemporary clinical trials.

Evans and Gaisford (1938) studied hospitalized patients with lobar pneumonia. Patients were assigned to either sulfapyridine or no specific therapy on alternate days of admission. Patients who died within 24 hours of admission were excluded from analysis. As summarized in Table 11., among the untreated controls 27/100 (27%) patients died, compared to 8/100 (8%) who received M&B 693 (sulfapyridine).

Graham et al. (1939) similarly studied hospitalized patients with pneumococcal pneumonia. Patients who had type I, II, V, VII and VIII pneumococcal pneumonia were treated with sulfapyridine, no specific therapy or specific antiserum. Alternate patients without these specific serotypes were treated with sulfapyridine or with no specific therapy (controls). The proportion of patients with bacteremia was higher in the sulfapyridine-treated group (34%) than in the control group (20%) or in the serum treated group (14%). As summarized in Table 11, mortality was 24% (19/80) in the untreated control group, compared to 5% (4/80) in the sulfapyridine group, and 12% (6/50) in the serum-treated group. Among bacteremic patients, case fatality was 50% (3/6) in the control group, 18% (3/17) in the sulfapyridine group, and 57% in the serum-treated group in this study.

Agranat et al. (1939) studied sulfapyridine for the treatment of lobar pneumonia in Johannesburg, South Africa. There were four different study sites, and results were reported separately for each. At three sites, patients were treated with sulfapyridine or control (no specific therapy), and only sulfapyridine at a fourth site. The authors state that "no selection whatever was made of patients preliminary to their being allocated to control or treated series in each group." Only two study locations are discussed here because the results were not described in the text of the article for one site and another lacked a control group. At the Johannesburg Hospital site, control cases were allocated to one hospital ward while treated cases were allocated to another. Results were also reported separately for European and non-European patients at that site.

Disease severity was described as mild, moderate or severe on admission based on respiratory rate, pulse, and symptoms such as restlessness and delirium. In both the European and non-European groups treated with sulfapyridine, approximately one-third of patients had severe disease at baseline, while in the control groups 26% of the European patients had severe disease in comparison to 17% of the non-European patients. Overall, European patients were older and had more severe disease in the control group than non-European patients.

As summarized in Table 11 among non-European patients, the case fatality rate was 18.6% in the control group and 8.5% in the treated group. Among European patients mortality was 22.2% and 7.4%, and in the untreated and treated groups, respectively.

At the second site, also located in Johannesburg, City Deep, Ltd. Central Native Mine Hospital, sulfapyridine or control (without sulfapyridine) was evaluated for treatment of lobar pneumonia. Patients were all 'healthy' male native mine workers between the ages of 20-40 years and were generally younger and appeared to have less severe disease than at the Johannesburg hospital site. At this site, only 1/100 treated cases was considered severe at entry compared to 10/96 severe cases in the control group. Case fatality rate was 4% in the control group and 0% in the treated group. The results from this study site (City Deep Ltd. Central Native Mine Hospital) have not been included in Table 11 because of the significant differences in patient population studied, with respect to age and severity at baseline, to the Johannesburg Hospital study site.

Table 11 summarizes the case fatality rates and treatment effect (difference between untreated controls and sulfapyridine-treated patients) observed in the controlled clinical trials described above. None of these was truly randomized, and thus are subject to selection bias.

Table 11.Summary of Case Fatality Rates and Antibacterial Treatment Effect in Early Controlled Clinical Trials

Publication	Year	Population	Case Fatality Rate Control	Case Fatality Rate Sulfapyridine- Treated	Treatment Difference and (95% CI) Untreated minus Sulfapyridine-Treated
Evans and Gaisford (1938)	1938	Lobar pneumonia 26% severe disease 8 – 68 years old	N =100 27%	N =100[a] 8%	19% (8.8, 29.2)
Graham, Warner et al. (1939)	1938 - 1939	Pneumococcal pneumonia Bacteremic and non-bacteremic Age 14-89 years old	N =80 (Jan. 1939) 24% ---------- Bacteremic subset: 3/6 (50%)	N = 80[b] (1938-1939) 5% ---------- Bacteremic subset: 3/17 (18%)	19% (8.3, 29.2) ---------- Bacteremic subset:32%
Agranat et al. (1939)	1938	Lobar pneumonia of < 120 hours duration	Johannesburg: non-Europeans[d] N=86 18.6% ---------- Johannesburg- Europeans[f] N=27 22.2%	Johannesburg: non-Europeans[e] N=71[c] 8.5% ---------- Johannesburg- Europeans[g] N=27[c] 7.4%	10% (-0.3, 20.6) ---------- 15% (-6.2, 35.5)

[a] Sulfapyridine dosing regimen early in study was (1) 0.5g tablet every 4 hours for 3-4 days, followed by 1 tablet twice daily for 2-3 days for average total dose of 12 g. Later in the study, sulfapyridine was dosed as 2g (4 tablets) initial dose, then 1 g every 4 hours thereafter, for a total dose of approximately 25g. In a few cases, a total of 9 g sulfapyridine was administered in the first 24 hours.
[b] Sulfapyridine was dosed 2 g every 4 hours for 6 doses, then 1.5g every 4 hours for 6 doses, then 1 g every 4 hours for 6 doses. If temperature remained normal for 36-73 after starting treatment, and the WBC was "toward" normal, then sulfapyridine dosing was continued at 0.5g every 4 hours for 3-4 days.
[c] Sulfapyridine dosing regimen: (2) 0.5 g tablets every 4 hours for 48 hours, then 2 tablets 3 times daily early in the study. Later in the study sulfapyridine dosing regiment was (4) 0.5g tablets every 4 hours for 72 hours, then 2 tablets twice thrice daily until temperature was normal for 3 days.
[d] Age range: 20 to ≥ 50 years old, with 2.3% > 50 years old.
[e] Age range: 20 to ≥ 50 years old, with 2.8% > 50 years old.
[f] Age range: 20 to ≥ 50 years old, with 14.8% > 50 years old.
[g] Age range: 20 to ≥ 50 years old, with 22.2% > 50 years old.

e. Conclusions and Limitations of Early Studies of Pneumococcal Pneumonia

Early studies of serum and antibacterial treatment provide rich and reproducible evidence that specific antiserum and antibacterial drugs reduced mortality in patients with pneumococcal pneumonia. Although treatment effect varied between studies, the effect of treatment on survival was consistently greater in older patients and in patients with bacteremia. In the observational studies of pneumococcal pneumonia, the point estimates of treatment difference based on mortality ranged from 19-25% for patients treated with sulfonamides, penicillin, or tetracyclines compared to historical controls who received no specific therapy regardless of age or bacteremia. In bacteremic patients, the point estimates of treatment difference based on mortality ranged from 48-65% (Table 2). In the early controlled clinical trials in which patients were treated with sulfapyridine or no specific therapy, the point estimates of treatment difference based on mortality ranged from 10-19% regardless of age (Table 4).

Despite the strength of these findings, direct extrapolation of these data to contemporary CAP clinical studies is challenging. Aside from the readily apparent methodological 'deficiencies' in study design when viewed by current clinical trial standards (i.e., blinding, randomization, analysis, etc.), there are differences in patient populations, the spectrum of bacteria and viral etiologies now identified as causing CAP, and differences in the standard of care. On the other hand, as noted by the authors, sub-optimal sulfapyridine dosing may have been used early in the conduct of two of these studies [26, 28], reducing the observed treatment effect relative to what may have been observed had dosing been optimized.

Modern non-inferiority studies demand accurate estimation of the treatment effect. The challenge in generalizing estimates of efficacy from older studies of pneumococcal pneumonia to current studies of CAP is summarized below:

Severity: Although some early studies did attempt to grade illness at entry, descriptions of how severity was assessed were very limited. Assessing how patients in these early studies would compare to patients enrolled in current CAP trials is difficult.

Etiology: For almost all the early studies, pneumococcal pneumonia was considered synonymous with CAP. Although *S. pneumoniae* remains the most common etiology of CAP, it is identified as the causative agent in only a minority of patients enrolled in current clinical trials. For pathogens such as such as *M. pneumoniae*, and *C. pneumoniae* the size of the treatment effect remains unknown.

Cohort: In many respects it is difficult, if not impossible, to compare patients enrolled in CAP studies in the 1930s to patients enrolled in current CAP trials. Overall health of the population, including co-morbidities, earlier diagnosis, more readily available access to care, and current practice guideline recommendations for early treatment, all substantially contribute to the likelihood that patients enrolled in any of the studies described above would not be comparable to patients enrolled in a modern CAP trial, even if controlled for age. Higgins and colleagues have summarized data from recent CAP registrational trials. The majority of studies was conducted in outpatients and evaluated oral antibacterial therapy. Though the studies enrolled patients older than 65 years of age, the mean age tended to be in the 4-5th decade. *S. pneumoniae* was identified as the etiologic agent in a fraction of the cases and mortality in these studies was also very low. [29]

Endpoint: Mortality was used as the endpoint in the historical studies described in this review. In the majority of studies the timing for the assessment of mortality was not specified, i.e. it is not clear whether mortality was measured at 30 days, during hospital stay, or at some unspecified time period after hospital discharge. Mortality has not been used as an endpoint in contemporary CAP clinical trials. In current clinical trials, patients who are not improving on therapy would be considered clinical failures and alternative treatment would be initiated long before death was likely. Extrapolating quantitative estimates of treatment benefit from a mortality endpoint to newer definitions of 'clinical failure' raises additional questions for non-inferiority trials. The availability of newer supportive therapies, as well as prior pneumococcal vaccination [30, 31] has also likely decreased CAP mortality.

In summary, despite the many limitations of the historical studies, a substantial effect on mortality from treatment with antibacterial drugs is seen in pneumococcal pneumonia. However, this same information is limited for estimating the expected treatment effect for an active control in a contemporary study of CAP outside of well-defined populations, e.g., elderly patients with pneumococcal pneumonia or bacteremic patients.

VIII. OTHER APPROACHES TO ESTIMATING THE ANTIBACTERIAL DRUG TREATMENT EFFECT IN CAP

a. Phase 3 Studies that failed to demonstrate noninferiority of daptomycin for treatment of CAP

Daptomycin is a cyclic lipopeptide antibacterial approved for the treatment of complicated skin and skin structure infections (cSSSI), *S. aureus* bloodstream infections and right-sided infective endocarditis. Daptomycin activity is restricted to certain Gram-positive bacteria.

Intravenous daptomycin was studied in hospitalized patients with CAP due to Gram-positive organisms in two phase 3 studies; however, the second study was halted when the first study showed inferiority to the control arm in the treatment of CAP due to *S. pneumoniae* and *S. aureus* pneumonia. The study enrolled patients with PORT scores from II – IV (PORT V patients were excluded).

In the pooled studies, the population of all randomized patients who took one or more dose of randomized therapy and had CAP (defined as the ITT population by the authors constituted 89% of all randomized patients) included 413 and 421 daptomycin- and ceftriaxone-treated patients, respectively, while the clinically evaluable (CE) population (patients who took 3 or more days of correct study drug, had CAP and had a clinical response assessed) included 369 and 371 patients, respectively. PORT scores were as follows: 42% PORT II, 30% PORT III, and 28% PORT IV. A Gram-positive pathogen was isolated at baseline in 132 and 116 daptomycin and ceftriaxone treated patients respectively. (Pertel, et al., 2008)

What is of particular relevance is that following these studies it was shown that daptomycin is inactivated by pulmonary surfactant, substantially lowering the free daptomycin drug concentration at the site of infection. (Silverman et al., 2005). As such, although an antibiotic effect is still likely, these studies may have been closer to placebo-controlled trials than any in the post-antibiotic era.

Clinical cure rates for the daptomycin arm were significantly worse than the control arm for both the ITT and the CE analysis populations (Table 4). In the ITT population, the clinical success rates dropped from 78.0% (128/164) to 68.5% (89/130) to 64.4% (76/118) for PORT classes II, III, and IV, respectively in daptomycin-treated patients. In ceftriaxone-treated patients clinical success rates dropped from 80.1% (149/186) to 78.9% (97/123) to 71.4% (80/112) for PORT classes II, III, and IV, respectively (data on file, Cubist). Mortality was 21 (4.6%) in daptomycin and 12 (2.6%) in ceftriaxone-treated patients during the studies.

Table 12. Clinical Cure Rates by Pooled Study Population in Phase 3 Daptomycin Studies[a].

	Daptomycin		Ceftriaxone		
Population	**n/N**	**Cure rate %**	**n/N**	**Cure rate %**	**Treatment difference (95% CI[b])**
ITT	293/413	70.9	326/421	77.4	-6.5 (–12.4 to –0.6)
mITT	98/132	74.2	92/116	79.3	-5.1 (–15.6 to 5.4)
CE	293/369	79.4	326/371	87.9	-8.5 (–13.8 to –3.2)

[a]Table modified from Pertel et al. (2008).
[b] 95% confidence interval (CI) around the difference in cure rates (daptomycin minus ceftriaxone).

Patients in these studies could have received antibiotic treatment for up to 24 hours prior to enrollment; when analyzed post-hoc by prior 'effective' antibiotic, no difference in outcome between daptomycin and ceftriaxone-treated patients was observed. However, for patients who received no antibiotic before entry, results showed a greater difference in favor of the active control in the CE population. (**Table 13**) The authors conclude that as little as 24 hours of prior therapy may greatly affect outcome and therefore, limiting enrollment of future studies to those subjects without prior therapy may be necessary.

Table 13. Clinical cure rates for patients by prior effective antibacterial therapy in the pooled CE population[a]

	Daptomycin		Ceftriaxone		
Prior effective therapy	**n/N**	**Cure rate %**	**n/N**	**Cure rate %**	**Treatment Difference (95% CI[b])**
Yes	88/97	90.7	81/92	88.0	2.7 (–6.1 to 11.5)
No	205/272	75.4	245/279	87.8	-12.4 (–18.8 to –6.0)

[a] Table modified from Pertel et al. (2008).
[b] 95% confidence interval (CI) around the difference in cure rates (daptomycin minus ceftriaxone).

This effect was further explored for days of persistence in *S. pneumoniae* in those patients without prior effective therapy for one study. This is really a post-hoc analysis (days of persistence) of a subset (those without prior effective therapy) in Study 05 only. Table 14 summarizes differences in *S. pneumoniae* persistence by treatment group for study DAP-00-05.

Table 14. Persistence of *Streptococcus pneumoniae* in sputum on or Beyond day 2 by prior effective antibacterial therapy in Study DAP-00-05 [a,b]

	Daptomycin		Ceftriaxone		
Prior effective therapy	**n/N**	**Persistence rate, %**	**n/N**	**Persistence rate, %**	**95% CI, P value[c]**
Yes	1/23	4.3	0/24	0.0	(-22.0, 11.4), 0.489
No					
Persistence ≥2 days	22/69	31.9	5/53	9.4	(-36.3, -7.5), 0.004
Persistence ≥3 days	15/69	21.7	4/53	7.5	(-27.1, -1.2), 0.043
Persistence ≥4 days	10/69	14.5	1/53	1.9	(-23.4, -2.6), 0.023

[a] Table modified from Pertel et al. (2008).
[b] Only patients in the ME population with adequate follow-up sputum cultures;
[c] 95% exact confidence intervals on the difference (daptomycin – ceftriaxone), Fisher's exact test p-value.

Despite limitations of these data e.g. pooling across studies, use of sub-group and post-hoc analyses, a treatment difference was seen between daptomycin and ceftriaxone-treated patients in many of the analyses presented, confirming that in modern studies less effective antibiotics can be identified. Another important finding is that in the subgroup of patients who received no prior antibiotics as defined by the authors, the treatment difference was 12.4 (95% CI 6.0 to18.8). Whereas in the patients who received a minimal amount of prior antibiotic therapy, the ability to differentiate between treatment arms was completely eliminated, emphasizing that methodological rigor is necessary for non-inferiority studies.

It is important to note that although these studies were conducted in hospitalized patients, 42% of patients had a PORT score of II. The difference between clinical cure rates in ceftriaxone and daptomycin-treated patients increased as PORT score increased from PORT II to PORT III, emphasizing that a treatment effect will likely be smaller for studies enrolling patients with lower PORT score. In addition, although a post hoc and subset analysis, evidence of *S. pneumoniae* persistence in sputum supports a clinical-pathological correlation that would be expected for a disease such as CAP.

b. Studies of *Mycoplasma pneumoniae* pneumonia

M. pneumoniae is the most common cause of "atypical" pneumonia in CAP studies. Pneumonia caused by *Mycoplasma* is generally milder in severity than that caused by "typical" bacterial pathogens such as *S. pneumoniae*, *S. aureus*, and *H. influenzae*, and is a common cause of CAP treated in the outpatient setting. Other causes of atypical pneumonia include *C. pneumoniae*, respiratory viruses, such as influenza and adenovirus, and less common bacterial pathogens such as *Legionella spp*., *C. psittaci*, and *Coxiella burnetii*.

Kingston, et al. (1961) studied primary atypical pneumonia caused by the "Eaton agent" (prior to identification as *M. pneumoniae*) in military recruits 17-22 years of age. The study was a randomized, double-blind study, of 290 "bacteriologically-negative" patients who received either demethylchlortetracycline or placebo. Enrollment criteria included illness less than 5 days duration, temperature > 100º F, an x-ray suggestive of atypical pneumonia, and nose/throat cultures negative for streptococci and pneumococci. Chest x-ray was repeated every three days until infiltrates cleared. Serological testing was performed on the day of admission and 17-21 days after admission. A fluorescent antibody technique was used to demonstrate the development of antibodies to the Eaton agent, with a four-fold rise in titer considered diagnostic. Possible viral pathogens were also identified serologically. Each patient was examined daily and questioned for the occurrence of cough, sputum, fatigue, malaise, headache, and anorexia. Temperatures were recorded 4 times daily.

One-hundred thirty-three patients were identified as 'Eaton positive, including 109 where this was the sole pathogen found, and 24 patients with respiratory viruses (influenza A and B, parainfluenza, adenovirus, and RSV) identified in addition to the Eaton agent. The majority of patient had minimal pulmonary infiltration. Duration of fever was significantly reduced in patients with Eaton-positive pneumonia treated with demethylchlortetracycline. In 21/50 placebo-treated patients and 5/59 demethylchlortetracycline- treated patients, the extent of pulmonary infiltration increased after hospitalization. The difference in mean days of fever and other symptoms between treated (demethylchlortetracycline) and placebo groups in patients with Eaton-positive pneumonia and virus-negative group (no identified pathogen) is shown in the following table, adapted from Kingston, et al. (1961).

Table 15. Treatment Difference in Days between treatment and placebo groups in Eaton-positive (*Mycoplasma*) pneumonia and virus-negative pneumonia*

Parameter	Mean Days Duration Treated	Mean Days Duration Placebo	Treatment Difference (Days Duration)
Temperature 99º F	3.02	10.04	7.02
Temperature 100 ºF	2.13	8.14	6.01
Positive CXR	9.46	20.00	10.54
Rales	6.89	15.54	8.65
Cough	9.69	21.98	12.29
Bed rest	5.82	9.22	3.40
Fatigue, malaise	2.70	8.54	5.84
Anorexia	1.97	7.04	5.07

* Adapted from Kingston, et al., 1961.

Duration of fever (≥ 99 º F) and duration of "positive" x-ray by treatment group is shown in Figures x and xx below:

Figure 15. Duration of Fever by Treatment Group for *Mycoplasma* Pneumonia (Kingston, et al., 1961)

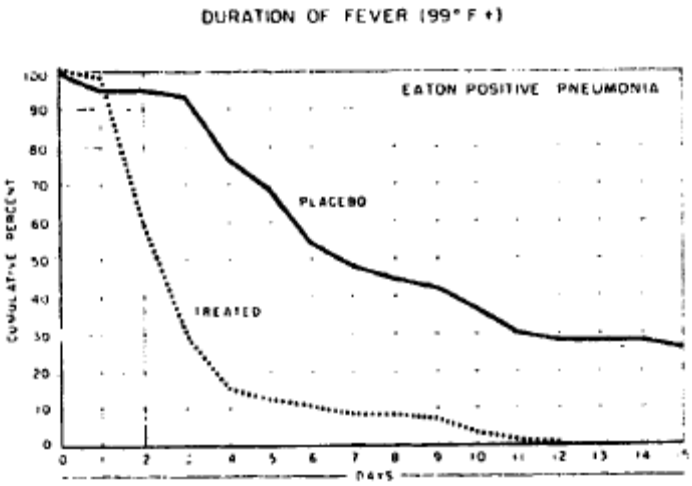
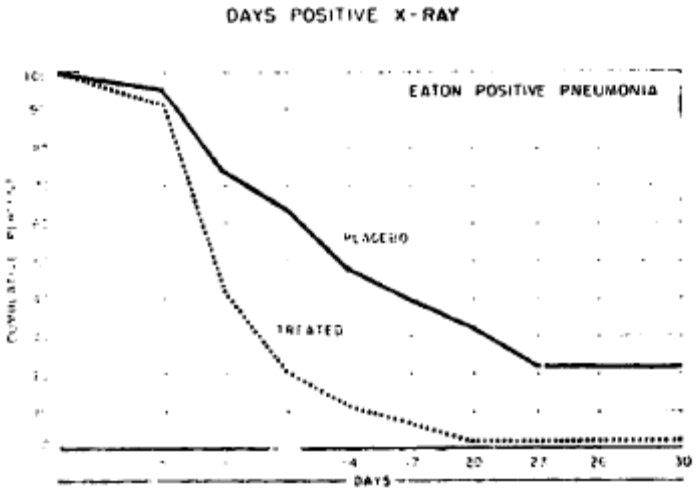


Figure 16. Duration of CXR Abnormalities by Treatment Group for *Mycoplasma* Pneumonia (Kingston, et al., 1961)



The authors concluded that demethylchlortetracycline significantly reduced the duration of fever, rales, cough, malaise, and fatigue in Eaton-positive pneumonia, reduced progression and accelerated the clearing of pulmonary infiltrates. Point estimates for the treatment difference for each of the variables studied ranged from 3.4 days (bed rest) to 12.3 days (cough).

The double-blind study by Kingston et al. (1961) demonstrates a significant treatment effect for demethylchlortetracycline when used for mycoplasma pneumonia in a group of young military recruits. However, this study has several limitations in the present context. As the single study in this domain, no information is available to confirm the treatment effect, nor can the variability of the effect they observed be assessed. In addition, the treatment effect they describe is for endpoints other than mortality: no mortality was seen

for mycoplasma pneumonia, indicative of a dramatically different prognosis than seen with pneumococcal pneumonia.

c. Guideline concordant/discordant studies and resistance studies

Several epidemiological studies have addressed the issue of 'guideline' concordant therapy versus guideline discordant therapy, i.e., outcomes in patients whose treatment was retrospectively determined to be concordant with published guidelines compared to patients whose treatment was not consistent with guideline recommendations. These have addressed the specific agents being used (e.g., a non-recommended antibiotic or monotherapy in circumstances where combination treatment is recommended) and the timing of treatment (e.g., delayed administration of antibacterials after diagnosis). In most cases non-discordant therapy reflected use of a beta-lactam antibiotic alone where guidelines recommended combination therapy (or use of quinolone monotherapy).

In a retrospective cohort study, Mortensen et al. (2004) assessed the association between guideline-concordant therapy and 30-day mortality in patients with pneumonia. Patients were identified based on ICD-9 discharge diagnoses of pneumonia, respiratory failure, or sepsis with a secondary diagnosis of pneumonia. Information on antimicrobial therapy given in the first 48 hours of admission was collected and was considered to be guideline concordant if it agreed with either the 2000 IDSA/2001 ATS guidelines. For a therapy to be considered guideline concordant, the patient must also have received at least one dose of one of the recommended combinations within the first 48 hours of admission. A propensity score technique was used to balance covariates (e.g., PORT score, history of COPD, admission through emergency room, etc.) associated with choice of antimicrobial therapy between concordant and discordant groups.

Overall, forty-one of 420 patients (9.8%) died by day 30; in the guideline-concordant group 30-day mortality was 6.2% (20/323) compared to 21.7 % (21/97) in the non concordant group. The difference in mortality persisted even after adjusting for confounders using the propensity score.

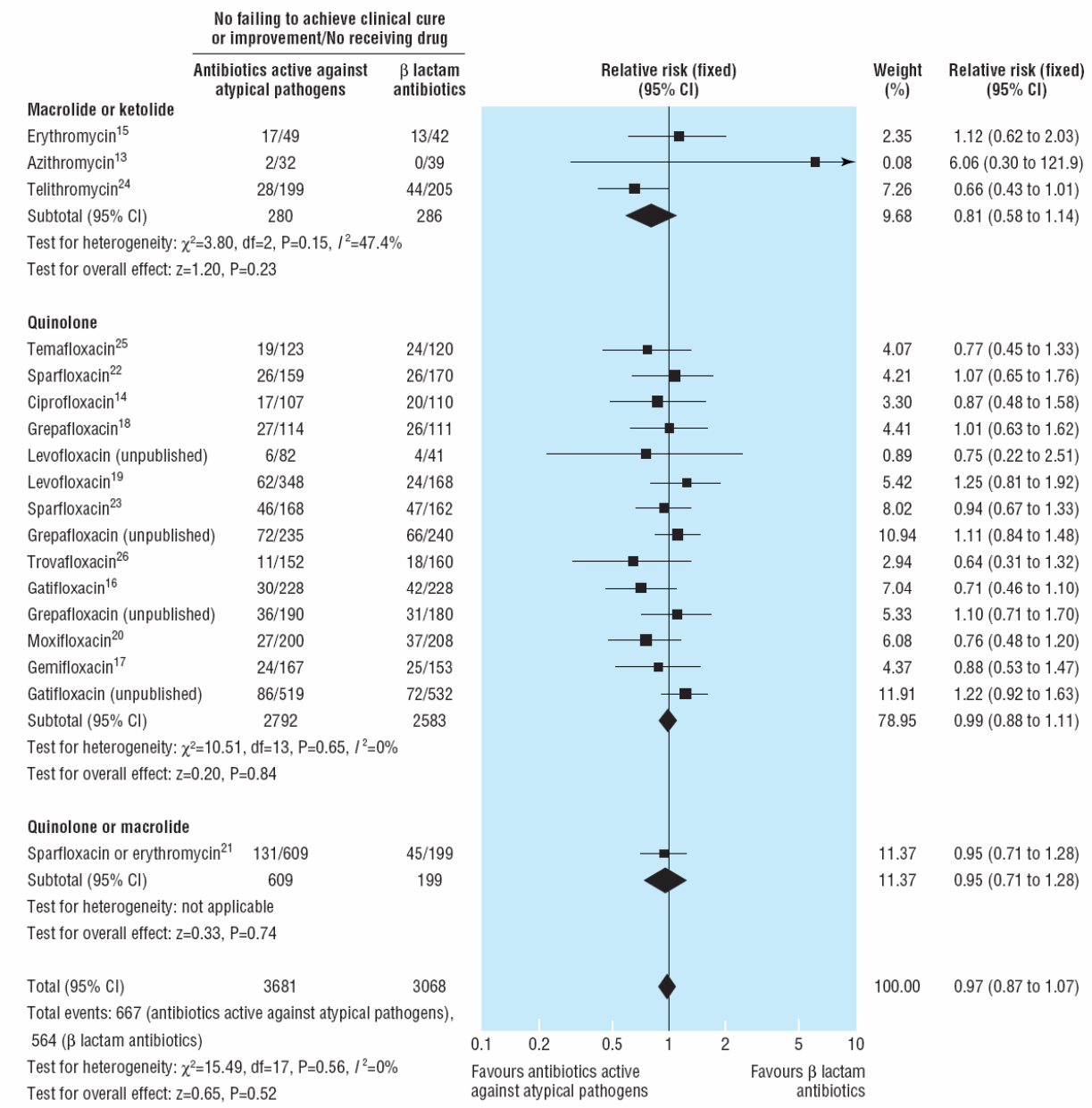
Though the study seems to suggest that use of guideline concordant therapy within the first 48 hours of admission is associated with lower 30-day mortality, there are several limitations. Most apparent is the retrospective design and the possibility of bias despite correction for obvious covariates.

A similar study by the same group of authors also showed that use of initial empiric guideline-concordant antimicrobial therapy was associated with decreased mortality at 48 hours (Mortensen 2006).

Two published summary reviews (Mills et al., 2005; Shefet et al., 2005) have also addressed the question whether 'broader spectrum' agents with coverage of atypical pathogens (e.g., macrolide or quinolone antibacterials) are superior to antibacterials with a more narrow treatment spectrum (e.g., beta-lactam antibacterials). Neither review found

evidence of superiority of a specific antibiotic regimen or drug class as compared to other possible treatments. The figure below, reproduced from Mills et al., 2005 illustrates this result for agents being studied against a beta-lactam comparator:

Figure 17. Summary of Studies of CAP Including Agents with Activity Against Atypical Pathogens (from Mills et al., 2005)



Number of patients failing to achieve clinical cure or improvement with β lactam antibiotics compared with antibiotics active against atypical pathogens in all cause community acquired pneumonia

A unique case of 'discordant' therapy is treatment of antibiotic resistant organisms where presumably clinical response would be closer to placebo treatment than an active

comparator; however, this is limited by substantial uncertainty regarding the clinical relevance of current breakpoints that define *S. pneumoniae* resistance to beta-lactam antibacterials. Further, the pharmacokinetics and pharmacodynamic characteristics of beta-lactams at current dosing regimens are sufficient to often obtain bacteriologic eradication of organisms that have higher *in vitro* MICs. Data on organisms with very high MICs where discordant therapy may be more relevant are very limited. Studies of guideline discordant therapy and antibiotic resistance are summarized in Appendix 2 and 3.

Overall, resistance studies have similarly yielded little information directly relevant for aiding in the determination of a non-inferiority margin for current CAP trials.

d. Time to Resolution of Signs and Symptoms in CAP

An alternative approach to determining a treatment effect for antibacterial drugs is to identify non-inferiority studies which demonstrate superiority of one antibacterial drug over another for an endpoint other than mortality. These studies lack comparability to earlier studies with an antibacterial arm since none reported outcomes other than mortality in detail.

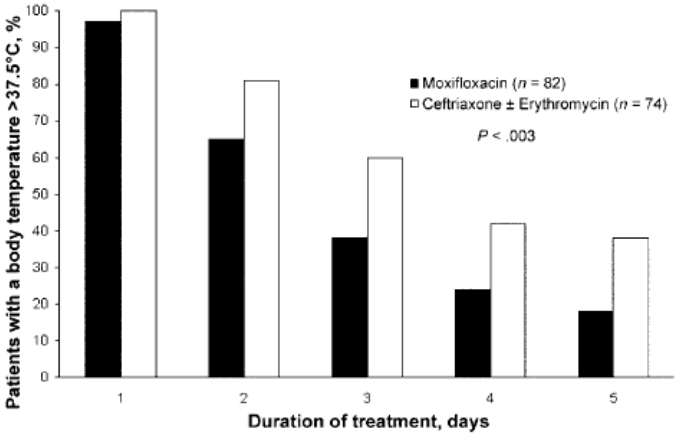
Halm et al. (1998) described time to resolution for vital signs, and a number of other parameters in 686 hospitalized adults who were enrolled in the PORT study, a prospective, observational multicenter study of outcomes in hospitalized and ambulatory patients treated for CAP. The median time to stability was 2 days for heart rate (≤ 100 beats/min) and systolic blood pressure (≥ 90 mm Hg), and 3 days for respiratory rate (≤ 24 breaths/min), oxygen saturation (≥ 90%), and temperature (≤ 37.2ºC). Patients with more severe pneumonia (classes IV and V) at presentation took longer to reach stability.

In a more recent prospective, multicenter, randomized controlled, open-label study (Welte et al., 2005), hospitalized patients ≥ 18 years old with CAP who required parenteral therapy were randomized to receive moxifloxacin (400 mg daily, intravenously, possibly followed by oral tablets) or ceftriaxone (2g intravenously once daily) with or without erythromycin (1 g IV every 6-8 hours) for 7-14 days. The study was heavily weighted to patients with PSI scores of I, II, or III at baseline in both treatment groups, and no microbiological analysis was reported.

At the test of cure visit 5-20 days after last dose of study drug(s), 138/161 (85.7%) patients in the moxifloxacin treatment group and 135/156 (86.5%) of patients in the ceftriaxone treatment group had clinical resolution (defined as resolution or improvement of clinical signs and symptoms related to the infection that did not require any antibiotic therapy) in the per protocol population. The treatment difference was 0.8% (95% confidence interval -7.92, 7.09) in the per protocol population, and 4% in the intent to treat population (95% confidence intervals -4.71, 12.2); however, for the subset of patients with fever on entry (approximately 50% of subjects), fever resolved faster in the moxifloxacin treatment group (Figure 18). The difference between treatment groups was considered statistically different ($p < .003$) by the Wilcoxon rank-sum test stratified by

region. Analysis of fever was a secondary endpoint in this trial, not the primary study endpoint, and only a subset of patients (those with fever on enrollment) was included in this analysis.

Figure 18. Percentage of Patients with Fever by Treatment Duration (Welte, et al. 2005)



In addition to temperature, time to resolution of other signs and symptoms of pneumonia were also reported based on patient diary entries. Patients treated with moxifloxacin had more rapid improvement in chest pain, weakness and sputum color, but without a difference observed for cough, dyspnea, or sputum quantity. This study was not blinded and use of concomitant antipyretic medications was not reported in this publication.

In a randomized, open-label study of moxifloxacin vs. amoxicillin-clavulanate with or without clarithromycin in adult patients with CAP who required hospitalization, (approximately half had severe pneumonia by ATS criteria), clinical cure at 5-7 days post-treatment was 241/ 258 (93.4%) in the moxifloxacin group, and 239/ 280 (85.4%) in the comparator group for a treatment difference of 8% with a 95% confidence interval of (2.91, 13.19) (Finch et al., 2002). Although this study demonstrated superiority of moxifloxacin over comparator, this was not a consistent finding in other studies. This study also measured time to resolution of fever (first day of peak temperature ≤ 37.5ºC). The median time to resolution was 2 days in the moxifloxacin group, and 3 days in the comparator group. Mean temperature on enrollment was similar for both treatment groups, and more patients in the comparator groups received antipyretic medications such as acetaminophen, aspirin, NSAIDs, or corticosteroids.

These data suggest that alternative endpoints such as time to fever resolution or resolution of other symptoms which are clinically meaningful as primary endpoints need further exploration in the setting of a superiority trial.

Table 16. Studies Addressing Clinical Outcome based on Concordance or Discordance with Published Treatment Guidelines

Publication	Study Design	Hypothesis	Population	Data	Comments
Mortensen et al. (2004)	Retrospective n = 420	ATS Guideline vs non-guideline treatment	Hospitalized patients with diagnosis of pneumonia	30-day Mortality: • Concordant 20/323 • Non-concordant 21/97 Group OR 5.7 (2.0-16)	Significant effect on time of administration, i.e.,< 8 hours; propensity score to balance covariates
Mortensen et al. (2006)	Retrospective n = 787	ATS/IDSA Guideline vs non-guideline treatment	Hospitalized patients at 2 institutions	48-hour mortality • Propensity-adjusted concordant survival 0.975 • Propensity-adjusted discordant survival 0.925 Group OR 0.37 (0.14-0.95)	Propensity score to balance covariates. Overall mortality at 48 hours was low (2.7%)
Malone et al. (2001)	Retrospective, n = 330; 51 were non-concordant	ATS Guideline vs non-guideline treatment	Hospitalized patients at 5 institutions	In hospital mortality: 23/330 overall (not separated by concordance) OR 4.46 (1.38-14.43) for concordance	37/51 had severe disease. No adjustment for severity of illness
Menendez et al. (2002)	Prospective observational n = 295; 65.8% adhered to SEPAR and 87.8% adhered to ATS.	ATS/SEPAR Guideline vs non-guideline treatment	Hospitalized patients at 1 institution	In hospital mortality: RR 0.3 (0.14-0.9) for adherence to ATS guideline. No association with adherence to SEPAR.	No adjustment of severity of illness or other covariates except PORT score
Gleason et al. (1999)	Retrospective n = 12, 945	ATS/IDSA guidelines treatment	Hospitalized patients using Medicare database	30-day mortality: 2nd generation cephalosporin plus macrolides, non-pseudomonal 3rd generation cephalosporin plus a macrolides or a fluoroquinolone alone were independently associated with a lower 30-day mortality.	Association between empirical antimicrobial therapy and outcome was assessed.
Waterer et al, (2001)	Retrospective n = 225	Single effective therapy compared with dual effective therapy	Patients with bacteremic pneumococcal disease within a healthcare system	Mortality: OR for death in SET vs. DET was 6.4 (1.9-21.7)	

Table 17. Discordance based on Antibiotic Resistance

Publication	Study Design and Years	Hypothesis	Population	Data	Comments
Falagas et al. (2006)	Meta analysis n = 317	Effect of Antibiotic Resistance on Outcome	All cause mortality	• 51/275 (19%) vs. 9/42 (21.4%) (p=0.66)	No difference in clinical success; only discordance with beta-lactam therapy assessed
Feikin et al. (2000)	Population-based active surveillance n = 2168	Effect of beta-lactam resistance on mortality	'Invasive' pneumococcal disease'	All deaths • No effect for penicillin or cefotaxime resistance overall For subgroups with highest MIC, OR between 4.3 – 7.1 for penicillin and cefotaxime	Did not control for empiric therapy, likely biased negatively
Song et al. (2004)	Retrospective (2000-2001) n = 233	Effect of Antibiotic Resistance on Outcome	Patients with Pneumococcal Pneumonia Caused by Antibiotic-Resistant Strains in Asian	Mortality vs. resistance • Penicillin-susceptible strains - 12.4% • Penicillin-nonsusceptible strains (14.1%) • Penicillin-resistant strains - 15.9%; MIC 2 - 4 mg/L) • High-level resistant strains - 13.6%; MIC, 4 mg/L Mortality by concordance • Concordance (n = 170) – 13.5% Discordance (n = 37) – 14.1%	No effect on outcome, but definition of 'resistance' for pneumococcus uncertain.
Lujan et al. (2004)	Prospective (single site, 1999-2002) n = 95	Concordance with 2002 NCCLS Guidelines	Bacteremic pneumococcal pneumonia	28-day Mortality • Concordance (n = 85) – 6/85 • Discordance (n = 10) – 5/10	Small number. Of these 10 patients, 6 had PORT score of V. 5/6 deaths in the discordant group had PORT score of V.
Lonks et al. (2002)	Case-control;n=76 cases and 136 controls	Probability of more macrolide use in patients with erythromycin resistant *S. pneumoniae*	Patients with bacteremic pneumococcal pneumonia	18/76 (24%) with erythromycin resistant *S. pneumoniae* bacteremia were taking macrolides compared to 0/136 with non-resistant isolates	

e. Pharmacokinetic/Pharmacodynamic Analyses of *S. pneumoniae* Response to Antibacterial Therapy.

In several publications and at the recent IDSA/FDA workshop, Dr. Paul Ambrose has presented analyses linking the free AUC/MIC ratio from patients in clinical trials of CAP to clinical and microbiological response using a pharmacokinetic/pharmacodynamic (PK/PD) model. Dr. Ambrose's methodology identified a minimum estimate of 25% for a 'treatment' response against *S. pneumoniae* when compared to individuals with sub-therapeutic treated patients with free AUC/MIC ratios below 30. FDA undertook an analysis to similarly test the hypothesis that clinical outcome could be associated with drug exposure, and that response at the lowest ranges of drug exposure could be used as an estimate of response in an 'untreated' control. This analysis was restricted to select recent studies with fluoroquinolone antibacterials.

Although this work replicated previous studies of the free-drug AUC/MIC ratio breakpoint that separates sub-therapeutic and therapeutic drug exposure, because of the limited number of subjects with low free-drug AUC/MIC ratios, the 95% confidence intervals for sub-therapeutic and therapeutic treated patients overlap and could therefore not be used to derive a non-inferiority margin.

With more clinical PK/PD data available, these findings may provide quantitative support for the choice of a non-inferiority margin for future CAP studies involving fluoroquinolone antibiotics. This analysis is discussed in more detail in an appended report.

f. Conclusions regarding Alternative Approaches to Estimation of Antibacterial Treatment Effect

Although the alternative approaches used suggest that antibacterials are effective in the treatment of CAP, no quantitative estimation of a non-inferiority margin was possible. Despite the limitations of the daptomycin data discussed these data are the closest to placebo data in the post-antibiotic era and the treatment effect estimated from that data could be viewed as a minimum treatment effect in the population studied. Studies which assessed time to resolution of fever may provide an alternative approach to choice and timing of endpoints for CAP trials.

IX. ISSUES REGARDING CLINICAL TRIALS OF CAP

The single most important issue for clinical trials of CAP is study design, i.e. is there sufficient information available to rigorously define a non-inferiority margin for studies of CAP. As discussed earlier, to fully address this question fully requires consideration of several important prerequisites, specifically:

- Study Population/Severity
- Inclusion criteria
- Clinical Endpoints
- Analysis populations
- Microbiology

These will be discussed separately below, although all of these concerns are fundamentally interdependent.

Study population: Patients enrolled in modern CAP trials are differentiated by whether patients are hospitalized or treated in an outpatient setting. Hospitalized patients are enrolled in studies of intravenous therapy and patients with 'milder' disease are enrolled in outpatient studies that, by definition, use oral therapy. Most often the PORT or CURB-65 score is used for this purpose; however, these scoring systems reflects prognosis (i.e., expected mortality on treatment based on risk factors) and not disease severity. An obvious circumstance is a more clinically 'severe' pneumonia in a younger person that may have a lower PORT score than a 'milder' illness in an elderly person. However, the distinction between 'outpatient' and 'inpatient' treatment is sometimes blurred in clinical trials; patients may be enrolled in an IV study if no oral form of an antibacterial is available simply to be a study participant, and several IV studies have relatively high number of PORT II subjects.

As discussed earlier, data are available supporting a non-inferiority margin based on mortality from the early controlled studies of pneumococcal pneumonia. These data are most directly applicable to hospitalized patients since we can assume by the mortality rates observed that many of these patients had a poor prognosis and were relatively ill; further, because age is a major contributor to PORT score, the higher mortality seen with increasing age in early studies (e.g., Finland, 1943) can be roughly equated with the increase in mortality observed in patients with higher PORT scores. The additional evidence from daptomycin studies of CAP support an NI estimate in this population.

The issue of patient severity is entwined with the choice of study population. Although 'mild pneumonia' has been characterized as defining patients appropriate for 'outpatient' therapy, the data for this recommendation is based solely on study results from treated patients. Our understanding of the natural history of pneumonia in the contemporary setting is insufficiently reliable to predict which 'mild' patients would develop progressive disease if untreated. All data from controlled studies with serum, sulfapyridine, or penicillin reflects hospitalized patients; the characteristics of patients who would have sought medical care in that era compared to those treated as outpatients today are unknown.[7]

[7] It is important to note that although 'outpatient' and 'inpatient' treatment is roughly equated with oral and intravenous therapy, respectively; early studies with sulfapyridine were all oral treatment of hospitalized patients. Unfortunately, there are insufficient details in the early studies to yield assay sensitivity when comparing patients studied with sulfapyridine to current outpatient populations; it is very difficult to even assess the criteria for hospitalization in 1930 as compared to 2008. As one observer has noted, even the

Pragmatic concerns with the use of 'severity' are also apparent; since clinical status and 'severity' reflect a dynamic state, the absence of definitive markers to predict progression precludes a meaningful definition of severity. For example, if it could be predicted that 50% of patients with "mild" pneumonia were to progress to more severe disease, a non-inferiority margin could likely be extrapolated from historical studies of more severely ill patients. Unfortunately, conflicting information regarding anticipated progression rates, and the lack of any recent study with an untreated cohort makes justifying a non-inferiority margin for studies patients with a better prognosis (i.e., lower PORT scores) at the time of presentation difficult.

Inclusion criteria: In the early studies discussed above, 'pneumonia' was virtually synonymous with pneumococcal pneumonia. To generalize results from pneumococcal disease for modern CAP trials requires specifying the microbiological etiologies where the course of disease (and response to treatment) can be considered similar, if not identical, to that for pneumococcal pneumonia. Observational studies of pneumonia other than pneumococcal pneumonia have not been identified, nor have any controlled placebo trials been identified for bacterial causes for pneumonia other than *S. pneumoniae* with the exception of Kingston et al. (1961) for mycoplasma. Accordingly, defining an overall non-inferiority margin for studies where patients have different etiologies of CAP are enrolled is problematic.[8]

The double-blind study by Kingston et al. (1961) demonstrates a significant treatment effect for demethylchlortetracycline when used for mycoplasmal pneumonia in a group of young military recruits. However, this study has several limitations in the present context. As the single study in this domain, no information is available on the variability or confirmation of the treatment effect they observed; in addition, the treatment effect they describe is for endpoints other than mortality. No mortality was seen for mycoplasma pneumonia, a dramatically different prognosis than seen with pneumococcal pneumonia.

Despite this, the Kingston et al. (1961) study is important for consideration of endpoints other mortality. If it can be assumed that treatment of pneumococcal pneumonia, a more severe disease, would have at least similar, if not greater effects on the same endpoints described by Kingston, then use of endpoints other than mortality may be acceptable in current CAP studies. This is further discussed below.

This issue of inclusion criteria is even more difficult when no specific bacterial etiology of pneumonia is ultimately identified after a patient is enrolled, and a bacterial etiology must be presumed.[9]

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classic studies of serum treatment for pneumonia fail to mention virtually any of the components of the PORT score, many of which were difficult to measure in 1930.

[8] Although estimating an NI margin for CAP due to *Legionella* or *Staphylococcus* may be feasible, these are relatively infrequent causes of CAP in any single clinical trial.

[9] Since most patients are enrolled before bacterial culture (or other tests) confirm a specific bacterial etiology, this is a common occurrence and has led to separate ITT and MITT (modified or microbiological

One advantage of approaching studies where patients are enrolled by prognosis (i.e., PSI scores) is that patients who are more ill are more likely to have outcome influenced by clinical status. For example, even if *Mycoplasma* pneumonia is generally milder than pneumococcal pneumonia, outcomes in hospitalized patients with severe *Mycoplasma* pneumonia more likely approximate the outcomes observed in historical studies of pneumococcal pneumonia than do outcomes in outpatients with clinically mild *Mycoplasma* pneumonia.

Clinical Endpoints, including clinical 'failure': Although the reports from early studies of pneumonia sometimes included descriptions of clinical endpoints other than mortality (e.g., fever), no study sufficiently quantified the results such that these could be used to estimate a treatment effect for determining a non-inferiority margin. A non-inferiority margin for current studies based on mortality is problematic for the reasons cited previously under *study population*: it is unknown if the observed treatment effect observed in a cohort in the 1930s would have mortality similar to a prospectively enrolled cohort today, even if restricted solely to pneumococcal pneumonia.

There is, however, an additional consideration for current studies. Early studies could use mortality as an endpoint since there were no effective therapies other than sulfapyridine or serum therapy. In contrast, it can be assumed that patients in current trials would be switched to known effective antibacterials before clinical progression made death inevitable. By defining 'clinical failure' as an early endpoint such that death may be obviated by 'rescue therapy,' clinical failure essentially serves as a surrogate for death. Although definitions of clinical failure have face validity and usually reflect professional consensus, none have been evaluated in clinical trials as a 'surrogate' for mortality, and non-inferiority margins from mortality studies would need to be extrapolated to this intermediate endpoint. The daptomycin studies are important in this context since they strongly suggest both an effect on mortality and clinical failure. Assuming that clinical failure and mortality co-vary is acceptable in studies where untreated mortality is expected to be relatively high (e.g., patients with higher PSI scores), but adds additional assumptions for studies where the overall untreated mortality may be low (e.g., oral outpatient studies).

The use of endpoints other than overall outcome, e.g., fever, was described earlier; the data from Kingston et al. (1961) are important in strongly suggesting that endpoints than mortality could be used for demonstrating non-inferiority, as the moxifloxacin studies cited earlier also do. However, the data on which to base placebo response for many of these measures is unknown, and although data suggest that superiority in outcome may be seen in some trials and could be used for estimating M1, the number of studies that have shown superiority based on endpoints other than mortality is small and is against a background of a large number of clinical studies that have shown no difference.

ITT) analysis populations. However, most studies are powered for an NI margin on the ITT population rather than the MITT population.

Other clinical endpoints, e.g., Patient Reported Outcome instruments, have been advocated as better measurements of clinical outcome than other possible outcomes. However, PRO instruments can only partially address response (e.g., the clinical signs of respiratory failure will be an important component of clinical failure regardless of PRO instruments), and the use of a PRO instrument still does not address non-inferiority studies where the treatment effect for a PRO outcome would still need to be defined.

Where a PRO instrument may be valuable is when used for a more sensitive, validated measure of clinical response. For studies where outcomes on less discriminatory measures are unlikely to distinguish a test drug from control (e.g., 'investigator assessed outcome at 21 days'), a more sensitive PRO instrument may be able to show superiority of a test drug versus active control. For a validated instrument, it is possible that superiority for a PRO outcome while in the setting of non-inferiority for mortality and other measures (e.g., bacteriological outcome) may be sufficient to confirm effectiveness.[10]

Analysis populations: A mentioned earlier, patients in CAP trials are enrolled and treatment started on study therapy before a microbiological etiology is confirmed; this yields studies with varying percentages of microbiologically confirmed subjects. This is addressed by separate ITT (all enrolled) and MITT (modified or microbiological intent-to-treat) analysis populations. Although it can reasonably assumed that hospitalized patients (or patients who are more ill at presentation) are more likely to have a pneumococcal pneumonia even if *S. pneumoniae* is not isolated, analysis of ITT populations adds additional uncertainty in the interpretation of an NI margin.[11]

Microbiology: Although microbiological etiology was discussed previously, unique aspects of pneumococcal pneumonia potentially limit assay sensitivity from past studies to studies in 2008. A major public health initiative of the early 1930s involved typing pneumococcal strains so that specific antiserum could be administered; substantial research was devoted to assessing the prognosis (and response to serum) for different pneumococcal serotypes so that the benefits of antiserum could be maximized. The distribution of serotypes in an era where pneumococcal vaccination is common, especially in the elderly, may influence expected outcome relative to studies in the 1930s. Several large studies have shown effects consistent with the hypothesis that pneumococcal vaccination may not alter the incidence of pneumococcal pneumonia but may affect the likelihood of invasive disease and therefore outcome.

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[10] See FDA draft guidance on patient reported outcomes at http://www.fda.gov/cder/guidance/5460dft.htm

[11] The problem of patients enrolled where a microbiological etiology is not documented could be reduced by use of additional diagnostic criteria, e.g., excluding patients with documented viral pneumonia or influenzae. It is possible that additional diagnostic testing in the future (e.g., procalcitonin levels) may further reduce uncertainty in the diagnosis of bacterial pneumonia.

X. CONCLUSIONS

Early studies of serum and antibacterial treatment provide strong evidence that antibacterial drugs reduced mortality in patients with pneumococcal pneumonia. Although treatment effect varied between studies, the effect of treatment on survival was consistently greater in older patients and in patients with bacteremia. In the observational studies of pneumococcal pneumonia, the point estimates of treatment difference based on mortality ranged from 19-25% for patients treated with sulfonamides, penicillin or tetracyclines compared to historical controls who received no specific therapy. In bacteremic patients, point estimates of treatment difference based on mortality ranged from 48-65%. In the early controlled clinical trials in which patients were treated with sulfapyridine or no specific therapy, the point estimates of treatment difference ranged from 10-19% overall regardless of age.

Despite the strength of these findings, direct extrapolation of this data to contemporary CAP clinical studies is challenging. Aside from the readily apparent methodological 'deficiencies' in study design when viewed by current clinical trial standards (i.e., blinding, randomization, analysis, etc.), differences in patient populations, the spectrum of bacterial and viral etiologies now identified as causing CAP, and differences in the standard of care may be of even greater relevance when comparing historical studies to contemporary trials. Factors that may bias the estimate of treatment effect in both directions likely exists; for example, some of the earlier studies [26, 28] may have used sub-optimal sulfapyridine dosing, reducing the observed treatment effect had dosing been optimized whereas the almost exclusive enrollment of patients with *S. pneumoniae* in early studies likely increased the treatment margin observed relative to contemporary studies. In this context, the recent Phase 3 daptomycin studies provide evidence of a treatment effect for antibacterials for pneumococcal pneumonia, albeit with a lower estimate of treatment effect. These concerns may be particularly acute for patients with lower PORT scores treated as outpatients with oral therapy.

XI. DRAFT ADVISORY COMMITTEE QUESTIONS

1. Does the committee concur that evidence provided from the "historical" studies and more recent studies support non-inferiority studies of CAP due to *S. pneumoniae*? In your response please discuss whether this evidence is applicable to current clinical trials of CAP.

2. If the committee concurs that there is evidence to support a non-inferiority margin from earlier studies, what non-inferiority margin is supported by this information?

    a. Please discuss the population to which this margin would apply, specifically addressing severity of illness.

    b. Please discuss how the evidence which showed a treatment effect based on mortality can be generalized or modified to the endpoints which are used in current non-inferiority trials, (i.e. clinical response or other endpoints).

    c. If the available evidence for setting a non-inferiority margin in current CAP trials is limited to treatment of *S. pneumoniae,* should non-inferiority studies enroll patients with other etiologies for CAP? If not, what additional data/studies are needed to show that antibacterial drugs are effective for specific organisms? Please specifically address this question with regard to the following organisms:
        - *Chlamydophila pneumoniae*
        - *Haemophilus influenzae*
        - *Klebsiella pneumoniae*
        - *Legionella pneumophila*
        - *Mycoplasma pneumoniae*
        - *Staphylococcus aureus*

3. Can placebo-controlled trials be performed safely in patients with CAP?

    a. If yes, what selection criteria or study procedures are needed to minimize risk for study participants?

    b. If no, what alternative study designs can be used to measure the treatment effect of antibacterial drugs in these patients?

4. Please discuss the following issues in CAP trial design for antibacterials available as only oral or intravenous formulations:

    a. Should only patients with more severe pneumonia be enrolled in studies of intravenous antibacterial therapy, and if so, how should severity be defined (e.g., clinical exam, CURB-65, or PORT scores)?

b. Should a microbiological diagnosis be necessary for enrollment in CAP trials, and if so, what organisms should be permitted for enrollment (or analysis)?

c. Since the historical evidence for a treatment effect was based on studies which evaluated penicillin and sulfonamides, are these the only appropriate comparators for CAP studies? If no, then what information is needed to extrapolate the treatment effect for other antibacterial drugs?

d. What primary endpoint should be used for clinical studies of CAP?

e. What secondary endpoints should be included?

5. For a drug with both an IV and oral formulation, is study of inpatients with the IV formulation sufficient to support approval of the oral formulation for outpatient use? Alternatively, would separate studies using oral therapy alone be necessary to demonstrate safety and/or effectiveness of the oral drug?

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EXPOSURE-RESPONSE ANALYSIS OF COMMUNITY-ACQUIRED PNEUMONIA

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1 EXECUTIVE SUMMARY

Recent studies of CAP have all been non-inferiority designs that do not allow estimation of the expected treatment effect for the active control relative to placebo. The purpose of this exposure-response analysis was to identify the size of the treatment effect in studies of community-acquired pneumonia (CAP) using PK/PD data from trials that included a fluoroquinolone treatment arm. This analysis was undertaken to test the hypothesis that clinical outcome could be associated with drug exposure, and that response at the lowest ranges of drug exposure could be used as an estimate of response in an 'untreated' control.

Fluoroquinolone antibiotics have consistently demonstrated efficacy in the treatment of CAP and have been reported to exhibit concentration-dependent killing with the ratio between free-drug area under the concentration-time curve (AUC) and the minimum inhibitory drug concentration (MIC) being the PK/PD parameter that correlates with therapeutic efficacy.

The free-drug AUC/MIC ratio breakpoint that separates sub-therapeutic and therapeutic drug exposure was estimated to be 37, which is in agreement with what previous studies have reported. The estimated probability of clinical response (i.e. resolution of signs and symptoms of pneumonia at test-of-cure visit) for patients with sub-therapeutic fluoroquinolone exposure was 60% (95% CI 15-95%), whereas patients with a free AUC/MIC ratio above 37 had an estimated clinical response rate of 97% (95% CI 90-100%). Due to the limited number of subjects with free-drug AUC/MIC below 37, the 95% confidence intervals for sub-therapeutic and therapeutic treated patients overlap and can therefore not be used to derive a non-inferiority margin.

With more clinical PK/PD data available, these findings may provide quantitative support for the choice of a non-inferiority margin for future CAP studies involving fluoroquinolone antibiotics.

2 INTRODUCTION

2.1 BACKGROUND

Over the past several years a major effort by the Office of New Drugs has been to justify the non-inferiority margins used in active control studies of antibacterial products. This presents a particular problem for diseases such as community-acquired pneumonia (CAP) where antibacterial use became the standard of care long before careful placebo-controlled or dose-response studies became accepted practice during drug development.

For patients treated with oral antibacterials, there is very limited information regarding what the expected 'placebo-rate' or treatment effect would be in these patients; accordingly, justification of an appropriate non-inferiority margin for an active-control study of CAP in these patients is difficult.

Fluoroquinolone antibacterial drugs have consistently demonstrated efficacy in the treatment of CAP and have been reported to exhibit concentration-dependent killing with the ratio between free-drug area under the concentration-time curve (AUC) and the minimum inhibitory drug concentration (MIC) being the PK/PD parameter that correlates with therapeutic efficacy [Ambrose 2007].

A recent presentation by Dr. Paul Ambrose at the IDSA-FDA workshop on Clinical Trial Design for Community-Acquired Pneumonia [IDSA-FDA workshop] suggested an alternative approach to determining a non-inferiority margin. Dr. Ambrose presented analyses linking the free AUC/MIC ratio from patients in clinical trials of oral therapy of CAP to clinical and microbiological response using a sigmoidal E_{max} model. Dr. Ambrose's methodology identified a minimum estimate of 25% for a 'treatment' response against *Streptococcus pneumoniae* when compared to individuals with sub-therapeutic treated patients with free AUC/MIC ratios below 30 [Ambrose 2001].

2.2 AIMS OF ANALYSIS

The key objectives of this analysis are:

1. Perform exposure-response analysis using available PK/PD data from CAP studies using fluoroquinolones.
2. Calculate treatment response against *Streptococcus pneumoniae* for patients with adequate and sub-therapeutic drug exposure.
3. Identify non-inferiority margin for CAP using the difference between the calculated response rates for patients with adequate and sub-therapeutic drug exposure.

3 STUDIES

Table 1 summarizes phase 2/3 studies over the past decade that included fluoroquinolone treatment arms and contained PK/PD data available to FDA. The data from these studies are described in the following sections.

Table 1. Clinical studies in the treatment of CAP over the last decade that involved the use of fluoroquinolones and contained pharmacokinetic/pharmacodynamic (PK/PD) data.

Drug (NDA no.) **Dose**	**Study** **Location/ Date/ Protocol**	**Population** **(ITT patients/ Patients with PK/PD)**	**Administration route** **Hospitalized** **Treatment duration**	**Primary Endpoint (TOC)**	**Clinical response (ITT/PP)**
Garenoxacin (NDA 21931)	Multinational 1999-2000	Mild-severe	Oral Out patients	7-14 days post Rx	
400 mg daily	AI464-004	N=199/106	10 days		0.84/0.91
Gatifloxacin (NDA 21061)	US 1997-1998	Mild-severe	IV→Oral, Oral In/Out patients	7-14 (5-28) days post Rx	
Gati 400 mg daily	AI420-038	N=203/12	7-14 days		0.89/0.90
Levo 500 mg daily		N=197/16	7-14 days		0.95/0.93
Gemifloxacin (NDA 21158)	Multinational 1998-1999	Mild-moderate	Oral In/Out patients	14-21 days post Rx	
320 mg daily	049/ 061	N=290/46 N=216/71	7-14 days 7 days		0.88/0.94 0.83/0.92

3.1 DRUG CLASS

Fluoroquinolone antibiotics have been of particular interest in active controlled studies since quinolone products have a spectrum of activity that includes ‘atypical’ pathogens, and thereby may theoretically demonstrate ‘superiority’ as an empiric therapy to more narrow spectrum beta-lactam drugs. Fluoroquinolone antibiotics are considered first-line agents for the treatment of CAP in current IDSA-ATS guidelines.

A total of four CAP studies (one phase 2 and three phase 3 studies) that involved the use of fluoroquinolones and contained PK/PD data submitted in support of three fluoroquinolone NMEs (garenoxacin, gatifloxacin, and gemifloxacin) from 1998-2005 were reviewed for this exposure-response analysis.

3.2 ENROLLMENT CRITERIA

Enrollment of patients was based on clinical signs and symptoms of CAP (e.g., fever, cough, chest pain, sputum production) and the presence of a new or progressive infiltrate on chest x-ray.

The age of the enrolled patients ranged from 18 - 90 years, with most subjects between 40 and 65 years.

3.3 PATIENT POPULATION

The studies included patients of either gender above 18 years of age with a clinical diagnosis of mild-moderate CAP. In general, trials using oral therapy only enrolled patients with mild to moderate disease and intravenous/oral formulations were used in moderate to severe disease patients.

Patients in the gatifloxacin and gemifloxacin studies were treated as either inpatients or outpatients based on clinical status.

3.4 TREATMENT AND ADMINISTRATION

Treatment duration ranged from 7 - 14 days with once daily administration. The majority of patients received oral (PO) therapy while some patients in the gatifloxacin study initially received IV treatment and later switched to PO therapy.

4 DATA

A measure of drug exposure and drug potency for a given pathogen as well as clinical or microbiological response is needed to perform the exposure-response analysis. The available pharmacokinetic, microbiological susceptibility and clinical/microbiological response data are described in the following sections.

4.1 PHARMACOKINETIC DATA

Sparse PK samples were obtained in the studies and the clearance estimates were obtained from sponsor's population PK modeling.

The protein binding information for the fluoroquinolones of interest was obtained from the drug labels or other sources (see Table 2).

Table 2. Protein binding for four fluoroquinolones**.**

Drug	Protein binding
Gatifloxacin	20%
Garenoxacin	75%
Gemifloxacin	65%
Levofloxacin	30%

The mean (range) free-drug AUC, MIC, and free AUC/MIC for each of the five most commonly identified bacterial pathogens are shown in Table 4.

4.2 MICROBIOLOGICAL SUSCEPTIBILITY DATA

Sputum/blood was collected by the patients over the 24 h before their clinic visits. Volume was measured, and an aliquot was analyzed for cell numbers, cell types, and culture to identify organisms. If a respiratory pathogen or predominant organism was isolated from a sample, bacterial susceptibility to the drug and other fluoroquinolones, as an MIC, was determined.

Antimicrobial susceptibility testing of isolates was typically performed by reference broth microdilution methods.

The five most commonly identified bacterial pathogens in the CAP studies with PK/PD data are listed in Table 3 along with the levofloxacin *in vitro* activity (MIC). It is noticed that there is a 500-fold difference between the lowest and highest levofloxacin MIC.

Table 3. Mean (range) levofloxacin MIC for the five most commonly identified bacterial pathogens in the CAP studies with PK/PD data.

Pathogen	**N**	**Levofloxacin MIC**
Streptococcus pneumoniae	74	0.2 (0.002-1)
Haemophilus parainfluenzae	35	0.1 (0.004-2)
Haemophilus influenzae	32	0.01 (0.001-0.12)
Staphylococcus aureus	33	0.05 (0.004-1)
Moraxella catarrhalis	12	0.02 (0.01-0.06)

4.3 CLINICAL/MICROBIOLOGICAL RESPONSE DATA

4.3.1 Clinical Outcome

The primary efficacy parameter in these studies was clinical response, usually assessed 1 - 3 weeks after the end of treatment (EOT) at the test of cure (TOC) visit. Clinical response rates ranged from 84 - 95% for the ITT analyses and from 90 - 94% in the Per Protocol (PP) analyses.

All studies used an endpoint of clinical outcome which was determined by comparing the patient's baseline signs and symptoms of infection with those at the TOC visit, i.e.

> ***Clinical Cure*:** Complete resolution of all signs and symptoms of pneumonia and improvement or lack of progression of all abnormalities on chest radiograph as assessed at the 7- to 21-day test-of-cure visit.
>
> ***Clinical Failure*:** The patient should be considered to have failed therapy under the following conditions:
>
> - Persistence or worsening in signs or symptoms of the acute process after 3 to 5 days of therapy.
> - Failure to show improvement in at least three of the clinical findings after 3 days of therapy.
> - Initial improvement in at least three of the clinical signs and symptoms followed by clinically significant worsening in one or more of these clinical findings after 3 to 5 days of therapy.
> - Development of new pulmonary infection or extrapulmonary infection requiring antimicrobial therapy other than or in addition to the study drug.
> - Persistence or progression of chest radiographic abnormalities.
> - Death due to pneumonia.

Patients with clinical evaluations of cure and improvement were classified as clinical responders whereas clinical failures were considered clinical non-responders for the exposure-response analysis whereas patients classified as indeterminate were not used.

4.3.2 Microbiological outcome

All baseline isolated pathogens were evaluated for microbiological response to treatment and test of cure as follows:

- Eradicated – Eradication of baseline pathogen in TOC culture.
- Presumed eradicated – Presumed eradication of baseline pathogen in TOC culture based on clinical response and due to the patient not being able to produce sputum.
- Persisted – Continued presence of baseline pathogen in the TOC culture.
- Presumed Persisted – Presumed continued presence of baseline pathogen in the TOC culture based on clinical failure and patient unable or unavailable to produce sputum.
- Unknown – No test of cure culture available because patient was unavailable to follow-up.

For the microbiological outcome evaluation, eradication and presumed eradication of the organism were considered successful outcomes while persistence and presumed persistence of the organism were considered unsuccessful outcomes. Patients classified as unknown were not used for the exposure-response analysis.

5 METHODS

5.1 PHARMACOKINETIC DATA ANALYSIS

The most commonly chosen measure of drug exposure for a given pathogen is calculated by dividing the AUC_{0-24} with the drug potency MIC against the identified pathogen.

The total-drug AUC_{0-24} was calculated by:

$$AUC_{0-24}=Dose/(CL*\tau)$$

where 'Dose' is the daily dose, CL is the drug clearance estimate and τ is the dosing frequency (i.e. 24 hr).

Differences in protein binding also need to be taken into consideration when combining data from drugs with markedly different protein binding. The free-drug AUC_{0-24} was calculated by multiplying the total-drug AUC_{0-24} for each patient with the drug-specific protein-binding information (see Table 2).

The free-drug AUC_{0-24} was then divided by the MIC for the identified pathogen with the highest MIC for each individual to get a measure of drug exposure against the pathogen of interest (e.g. *Streptococcus pneumoniae*) which will be drug-independent and can be used in a pooled exposure-response analysis.

5.2 EXPOSURE-RESPONSE ANALYSIS

The basic idea behind performing exposure-response analysis is to use the y-intercept of the exposure- response relationship as a sub-therapeutic treatment effect to be used to support the choice of a reasonable non-inferiority margin.

Two methods were used to investigate the relationship between drug exposure (free AUC/MIC) and the clinical/microbiological response in patients with CAP associated with *Streptococcus pneumoniae*.

5.2.1 Classification and Regression Tree (CART) Analysis

Classification and Regression Tree (CART) analysis is used to select the optimal breakpoints for the predictor variable (i.e., free AUC/MIC) that maximally distinguishes the response variable (i.e. clinical/microbiological response). The procedure uses recursive partitioning, multiple stepwise linear regression and the Kruskal–Wallis non-parametric one-way analysis of variance and is implemented in S-PLUS v. 7.0.

5.2.2 Logistic Regression Analysis

Logistic regression with drug exposure as a continuous predictor variable was also considered using a sigmoidal E_{max} model to link free-drug AUC/MIC with clinical/microbiological response.

6 RESULTS

A total of 1009 patients with CAP were identified in the four CAP studies treated with fluoroquinolones (see Table 1) of which 257 patients had PK information. Of these 257 patients, 81 had *Streptococcus pneumoniae* identified at the screening visit with a determined MIC, and 74 of these 81 patients had a clinical outcome determination at the test of cure visit.

This group of 74 patients was used for the exposure-response analysis in an attempt to link the free-drug AUC/MIC ratio to the probability of a clinical response to support the choice of non-inferiority margin. Only 4 out of these 74 patients were clinical failures.

6.1 PHARMACOKINETIC RESULTS

Only creatinine clearance (CrCL) was found to be a significant demographic covariate for AUC (see Figure 1), whereas body weight, age, sex, and race did not influence AUC (see Figure 7).

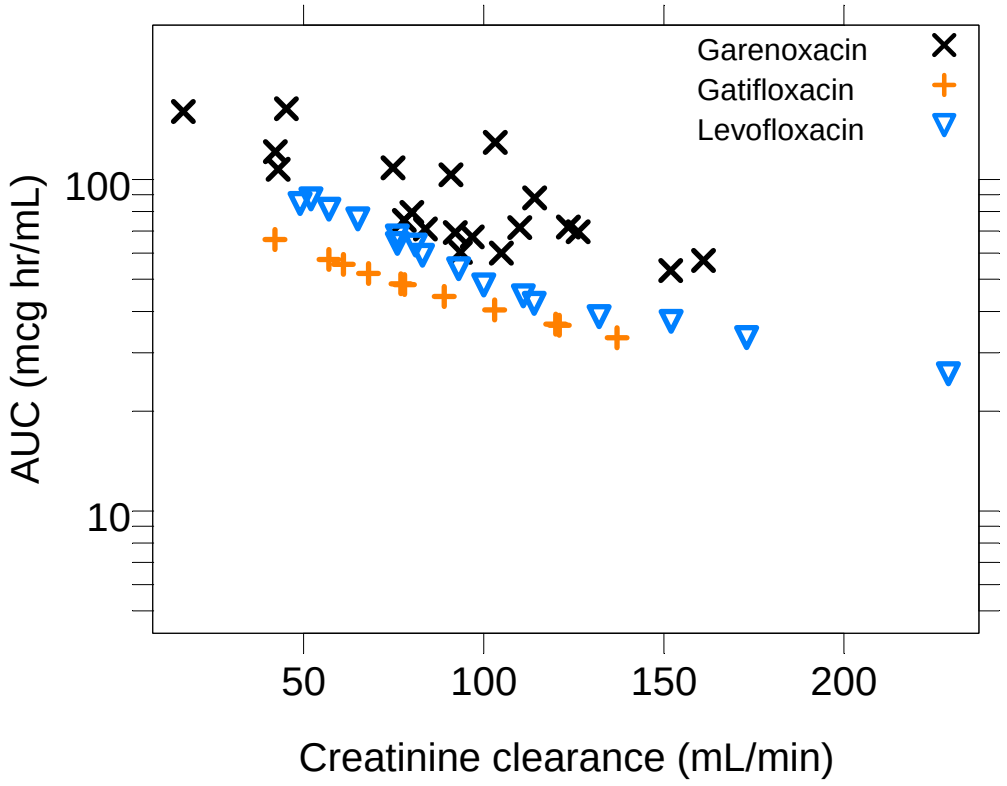

Figure 1. AUC vs. creatinine clearance for garenoxacin (black), gatifloxacin (orange), and levofloxacin (blue).

Gatifloxacin and levofloxacin AUCs were calculated by regression analysis using demographic covariates including CrCL as predictor variables; this explains the lack of variability in AUC vs. CrCL compared to garenoxacin, where AUCs were calculated using a population PK clearance estimate. No CrCL estimates were available for gemifloxacin [Ambrose 2001].

The distribution of free AUC for each drug is illustrated in Figure 2 together with the clinical/microbiological failures shown as symbols.

There was a 2-3-fold difference between the lowest and highest AUCs for garenoxacin, gatifloxacin, and levofloxacin whereas a 9-fold difference was observed for gemifloxacin.

A total of 4 out of 74 patients with *Streptococcus pneumoniae* were reported as clinical failures. The two levofloxacin failures occurred at the 15th and 40th AUC percentile whereas the two garenoxacin failures were at the 45th and 95th AUC percentiles. No clear pattern was apparent suggesting that that the patients with the lowest AUCs were at greater risk of clinical failure. .

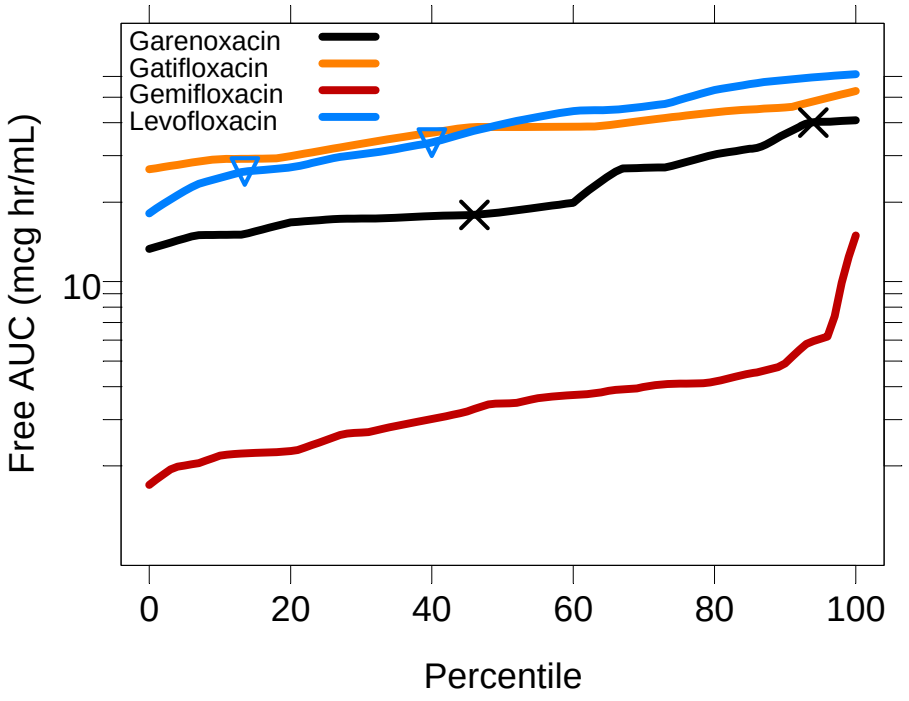

Figure 2. Plot of free AUC on log-transformed scale vs. free AUC percentile for garenoxacin (black), gatifloxacin (orange), gemifloxacin (red), and levofloxacin (blue) from the 0th to the 100th free AUC percentile. The symbols (black cross=garenoxacin, blue triangle=levofloxacin) indicate clinical/microbiological non-responders' AUC.

6.2 MICROBIOLOGICAL SUSCEPTIBILITY RESULTS

The microbiological susceptibility results for *Streptococcus pneumoniae* are visualized in Figure 3 for the investigated drugs (left) and for levofloxacin (right).

An 8-30 fold difference between the lowest and highest MICs was observed which is substantially larger than what was observed for the free-drug AUCs. The two levofloxacin failures occur at the highest observed MIC of 1 mcg/mL while the garenoxacin failures occurred at 0.03 mcg/mL (0.5 mcg/mL levofloxacin MIC).

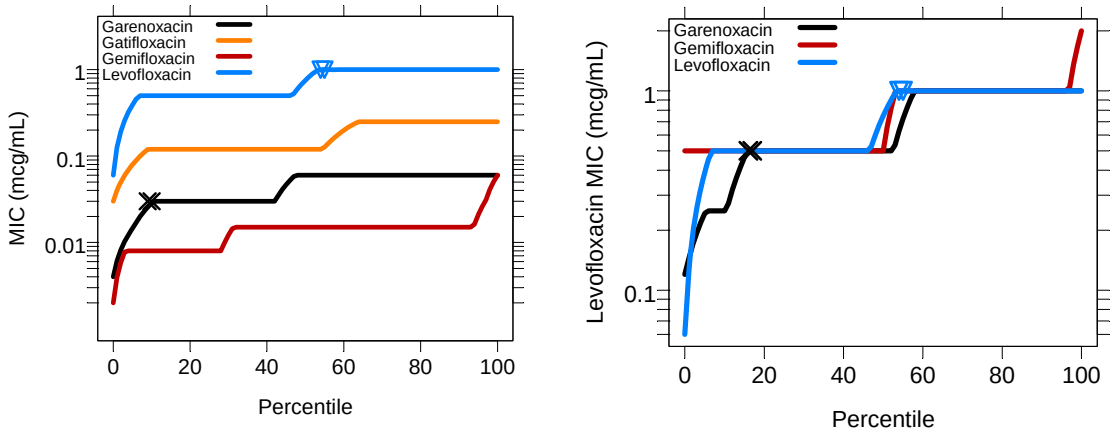

Figure 3. Plot of MIC for investigated drug (left) and levofloxacin (right) on log-transformed scale vs. MIC percentile for garenoxacin (black), gatifloxacin (orange), gemifloxacin (red), and levofloxacin (blue) from the 0th to the 100th MIC percentile. The symbols (black cross=garenoxacin, blue triangle=levofloxacin) indicate clinical/microbiological non-responders' MIC.

6.3 EXPOSURE-RESPONSE RESULTS

6.3.1 Streptococcus pneumoniae

The distribution of free-drug AUC/MIC for each drug is illustrated in Figure 4 together with the clinical/microbiological failures shown as symbols. A 12-50 fold difference between the lowest and highest free-drug AUC/MIC was observed. The variability in free-drug AUC/MIC ratios is primarily due to variability in MIC and not free-drug AUC. Only levofloxacin treated patients had free-drug AUC/MIC ratios below 30.

The two levofloxacin failures both occurred in the lowest free AUC/MIC quartile whereas the two garenoxacin failures are above the 50th free AUC/MIC percentile.

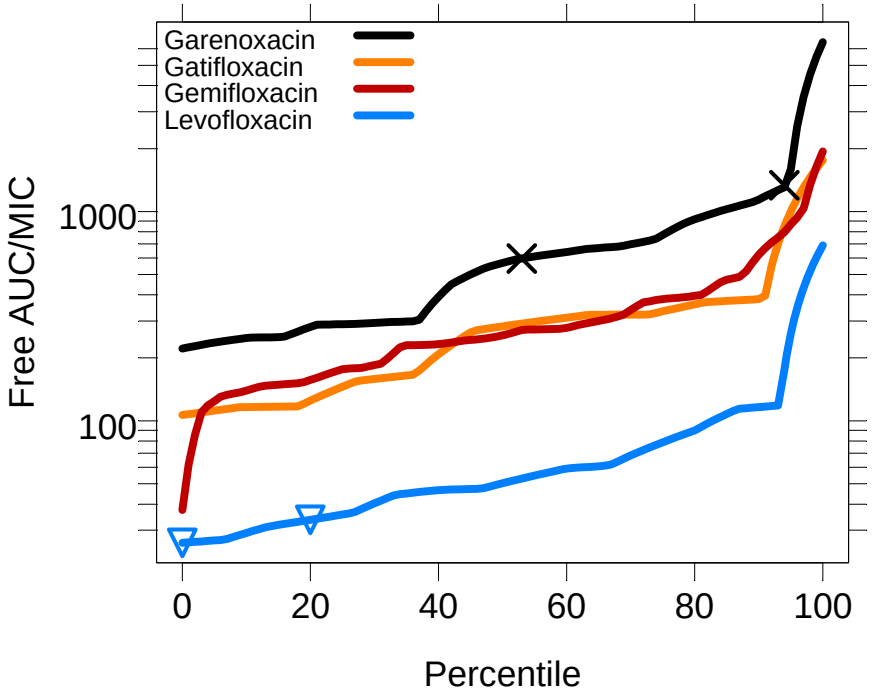

Figure 4. Plot of free-drug AUC/MIC on log-transformed scale vs. free AUC/MIC percentile for garenoxacin (black), gatifloxacin (orange), gemifloxacin (red), and levofloxacin (blue) from the 0th to the 100th free AUC/MIC percentile. The symbols (black cross=garenoxacin, blue triangle=levofloxacin) indicate clinical/microbiological non-responders' AUC.

The estimated breakpoint from the CART analysis was 37. The exposure-response relationship for the treatment of CAP associated with *Streptococcus pneumoniae* is visualized in Figure 5.

The estimated probability of clinical response for sub-therapeutic treated patients was 60% (95% CI 15-95%) whereas patients with free AUC/MIC above 37 had an estimated clinical response rate of 97% (95% CI 90-100%). Due to the limited number of subjects with free-drug AUC/MID below 37, the 95% confidence intervals for sub-therapeutic and therapeutic treated patients overlap and can therefore not be used to derive a non-inferiority margin.

The demographic information for sub-therapeutic treated patients and clinical failures are shown in Table 5 and Table 6. No confounding factors were identified for these patients that could help explain their low free-drug AUC/MIC ratio (e.g., age, body weight, CrCL) or their clinical response status (e.g. comorbidities).

Most fluoroquinolones are dosed in a manner that result in very few patients having exposures consistent with that associated with failure in animal infection models involving pneumococci. It is therefore expected that very few patients will have free-drug AUC/MIC ratios below 30, which has been reported as the breakpoint between responders and non-responders [Ambrose 2001]. In the data used for this exposure-response analysis, only 5 patients had free-drug AUC/MIC ratios below 37.

Logistic regression using AUC/MIC as a continuous predictor variable was not found to contribute to any further information due to the limited number of subjects in the lower range of AUC/MIC ratios.

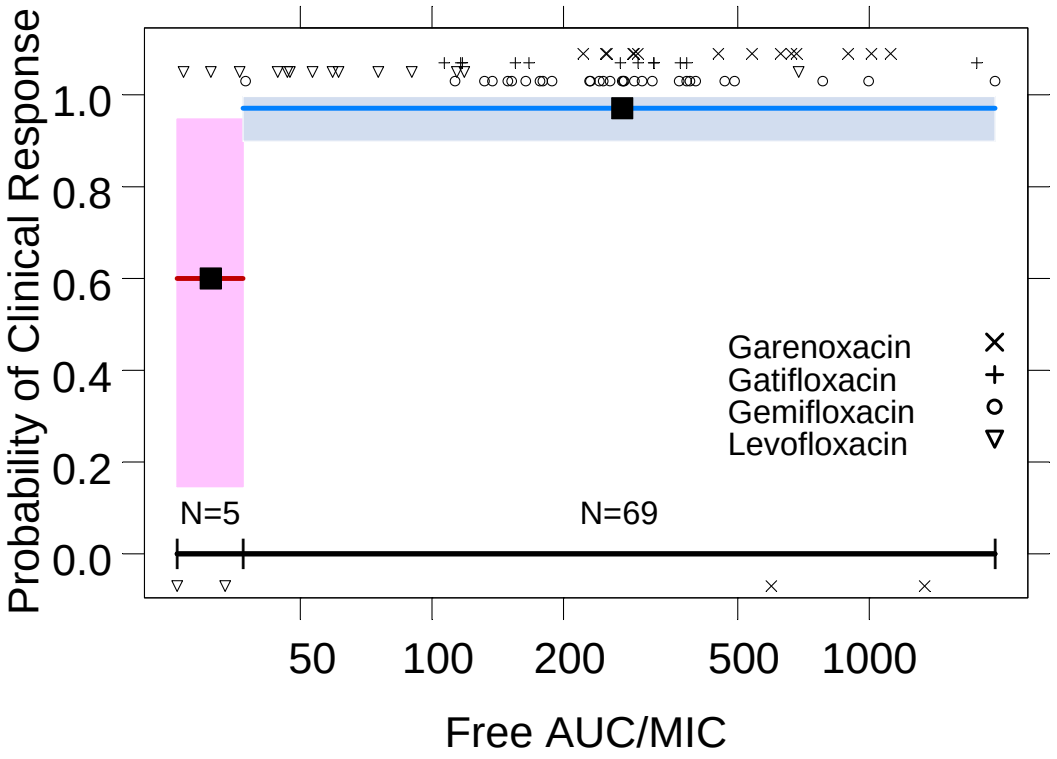

Figure 5. Estimated exposure-response relationship using PK/PD data from 4 fluoroquinolones (garenoxacin, gatifloxacin, gemifloxacin, and levofloxacin) in 74 patients with CAP associated with *Streptococcus pneumoniae*. Clinical response was 97% (95% CI 90-100%) (blue solid line and blue shaded area) in patients with a free AUC/MIC ratio >37 compared to patients with values below 37 with a sub-therapeutic clinical response rate of 60% (95% CI 15-95%) (red solid line and pink shaded area). The solid black squares indicate the median free-drug AUC/MIC ratio in each group with the corresponding clinical response rate on the y-axis. The horizontal bar shows that there are a total of 5 patients in the sub-therapeutic range with free AUC/MIC below 37 and 69 patients above. The grey symbols at the top and bottom of the graph are the individual free AUC/MIC ratios for responders and non-responders, respectively. Confidence intervals were calculated using the normal approximation to the binomial distribution.

6.3.2 Other pathogens

The estimated exposure-response relationships for the other 4 most common pathogens (*Haemophilus influenzae, Haemophilus parainfluenzae, Staphylococcus aureus, and Moraxella catarrhalis*) are shown in Figure 6. The low number of patients and clinical failures do not allow for estimation of any meaningful breakpoints between responders and non-responders except for *Haemophilus parainfluenzae* where the breakpoint was 200.

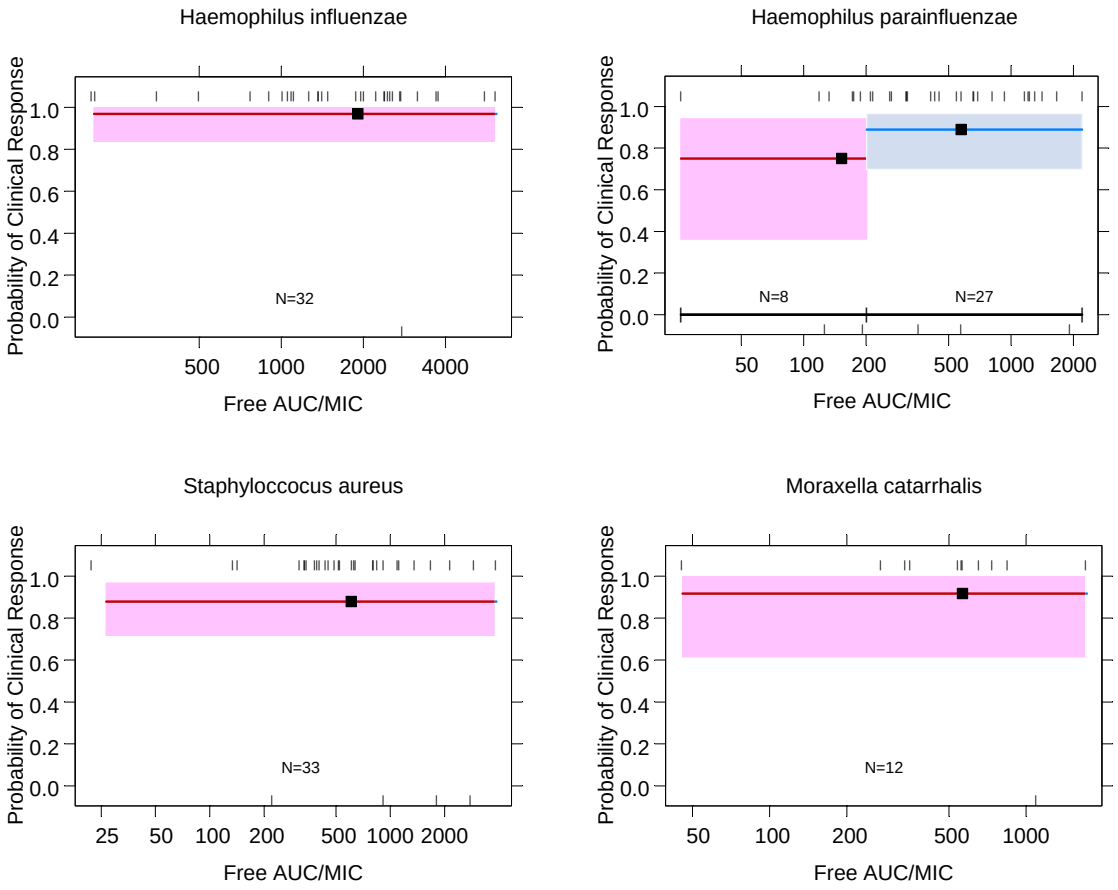

Figure 6. Estimated exposure-response relationships for *Haemophilus influenzae* (Top Left), *Haemophilus parainfluenzae* (Top Right), *Staphylococcus aureus* (Bottom Left), and *Moraxella catarrhalis* (Bottom Right).

7 CONCLUSIONS

In conclusion, a relationship between free-drug AUC/MIC ratio and clinical response in patients with community-acquired pneumonia involving *Streptococcus pneumoniae* was identified using pooled PK/PD data from four clinical studies with fluoroquinolone antibiotics.

The free-drug AUC/MIC ratio breakpoint that separates sub-therapeutic and therapeutic drug exposure was estimated to be 37, which is in agreement with what has been reported in previous studies.

The estimated probability of clinical response for sub-therapeutic treated patients was 60% (95% CI 15-95%) whereas patients with free AUC/MIC above 37 had an estimated clinical response rate of 97% (95% CI 90-100%). Due to the limited number of subjects with free-drug AUC/MIC below 37, the 95% confidence intervals for sub-therapeutic and therapeutic treated patients overlap and can therefore not be used to derive a non-inferiority margin.

With more clinical PK/PD data available, these findings may provide quantitative support for the choice of a non-inferiority margin for future CAP studies involving fluoroquinolone antibiotics.

8 REFERENCES

Ambrose2001: Ambrose PG, Grasela DM, Grasela TH, Passarell J, Mayer HB, Pierce PF. *Pharmacodynamics of Fluoroquinolones against Streptococcus pneumoniae in Patients with Community-Acquired Respiratory Tract Infections.* Antimicrobial Agents and Chemotherapy. 45(10):2793-2797 (2001).

Ambrose2007: Ambrose PG, Bhavnani SM, Rubino CM, Louie A, Gumbo T, Forrest A, Drusano GL. *Pharmacokinetics-Pharmacodynamics of Antimicrobial Therapy: It's Not Just for Mice Anymore.* Antimicrobial Resistance. 44:79-86 (2007).

IDSA-FDA Workshop: IDSA-FDA workshop on Clinical Trial Design for Community-Acquired Pneumonia. January 17-18, 2008 (http://www.fda.gov/cder/meeting/CAP.htm).

9 APPENDIX

9.1 PHARMACOKINETIC COVARIATE ANALYSIS

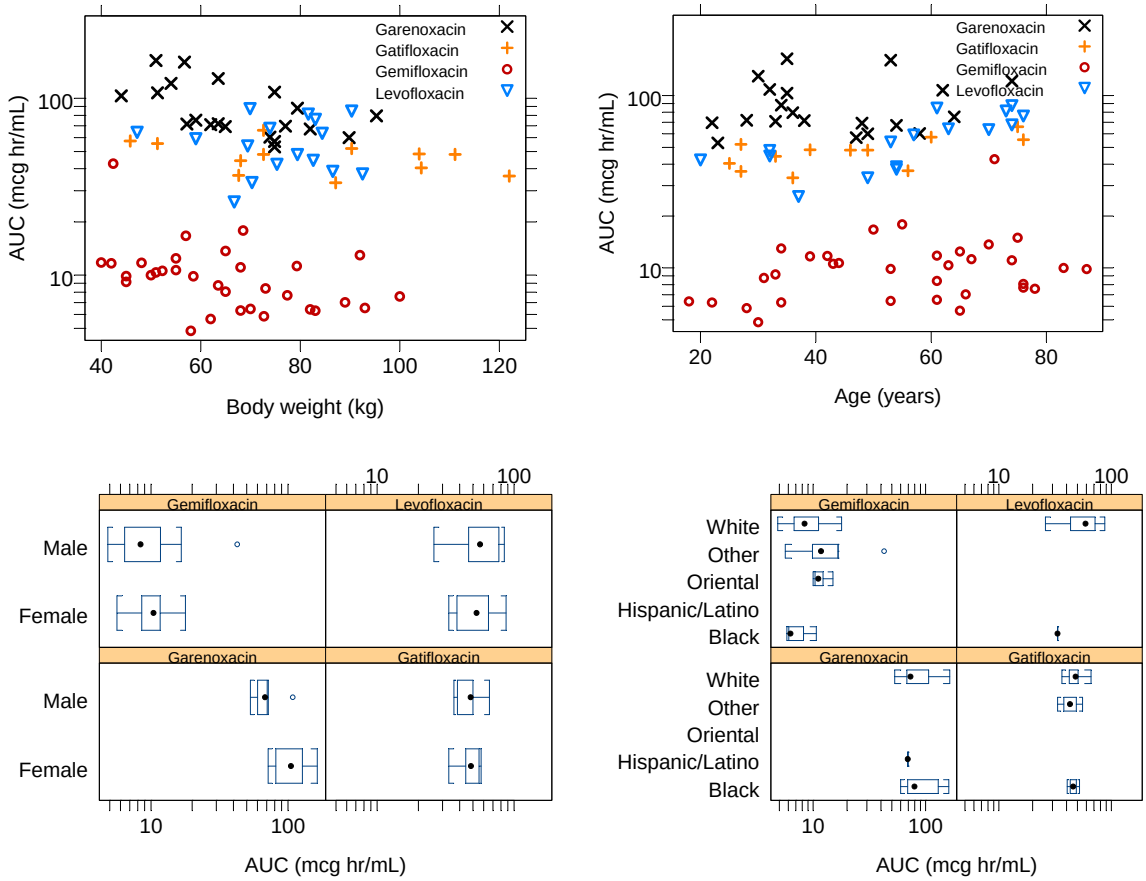

Figure 7. Scatter plot of AUC vs body weight (Top Left) and age (Top Right) and boxplots of AUC for gender (Bottom Left) and race (Bottom Right).

9.2 MICROBIOLOGICAL SUSCEPTIBILITY DATA

Table 4. Mean (range) AUC, MIC, and free AUC/MIC for each of the five most commonly identified bacterial pathogens.

Pathogen	Drug	N	Free AUC	MIC	Free AUC/MIC
	Garenoxacin	16	23 (13-41)	0.05 (0.01-0.06)	595 (222-1337)
Streptococcus	Gatifloxacin	12	38 (27-53)	0.17 (0.03-0.25)	365 (107-1759)
pneumoniae	Gemifloxacin	30	3.8 (1.7-15)	0.01 (0.002-0.06)	352 (38-1938)
	Levofloxacin	16	40 (18-61)	0.72 (0.06-1.00)	97 (26-689)
	Garenoxacin	26	23 (13-51)	0.13 (0.01-2.00)	716 (26-2202)
Haemophilus	Gatifloxacin	-	-	-	-
parainfluenzae	Gemifloxacin	9	3.4 (1.9-4.6)	0.01 (0.004-0.03)	401 (119-932)
	Levofloxacin	-	-	-	-
	Garenoxacin	316	23 (15-43)	0.03 (0.004-0.12)	1903 (206-5562)
Haemophilus	Gatifloxacin	-	-	-	-
influenzae	Gemifloxacin	16	4.4 (2.2-7.5)	0.003 (0.001-0.01)	2158 (212-6101)
	Levofloxacin	-	-	-	-
	Garenoxacin	19	26 (14-54)	0.08 (0.01-1.00)	1302 (27-3823)
Staphylococcus	Gatifloxacin	NA	-	-	-
aureus	Gemifloxacin	14	3.4 (2.0-5.8)	0.01 (0.004-0.01)	396 (134-923)
	Levofloxacin	-	-	-	-
	Garenoxacin	7	20 (16-26)	0.03 (0.01-0.03)	877 (540-1710)
Moraxella	Gatifloxacin	-	-	-	-
catarrhalis	Gemifloxacin	9	3.0 (2.1-4.6)	0.02 (0.01-0.06)	315 (46-568)
	Levofloxacin	-	-	-	-

- : Not available

9.3 CLINICAL FAILURES

Table 5. List of patients who were classified as clinical failures.

Drug	Study	Weight	Height	Age	CrCL	Sex	Free AUC	MIC	Free AUC/MIC	Clinical status	Micro status
Levo	038	93	168	54	152	F	26.1	1.0	26.1	Failure	Failure
Levo	038	79	180	32	100	M	33.7	1.0	33.7	Failure	Failure
Gar	004	57	170	53	17	F	40.1	0.03	1337	Failure	Presumed Persisted
Gar	004	57	163	38	110	F	17.9	0.03	597	Failure	Presumed Persisted

9.4 PATIENTS WITH AUC/MIC RATIOS BELOW SUB-THERAPEUTIC BREAKPOINT

Table 6. List of patients with free-drug AUC/MIC ratio below sub-therapeutic breakpoint of 37.

Drug	Study	Weight	Height	Age	CrCL	Sex	Free AUC	MIC	Free AUC/MIC	Clinical status	Micro status
Levo	038	93	168	54	152	F	26.1	1.0	26.1	Failure	Failure
Levo	038	79	180	32	100	M	33.7	1.0	33.7	Failure	Failure
Levo	038	67	185	37	229	M	18.2	0.5	36.3	Success	Eradicated
Levo	038	87	160	54	132	F	27.0	1.0	27.0	Success	Eradicated
Levo	038	83	163	32	111	F	31.2	1.0	31.2	Success	Eradicated

9.5 STUDY SYNOPSIS

9.5.1 Garenoxacin

Study AI464-004: An Open-Label, Multicenter, Non-Comparative Study of Oral BMS-284756 in the Treatment of Community-Acquired Pneumonia

Study AI464-004 was an open label multi-center, Phase II trial designed to asses the clinical efficacy of a 10-day course of oral garenoxacin at a dose of 400 mg one daily in the treatment of community-acquired pneumonia. Physical examinations (including a chest exam) and pregnancy tests were performed at the pre-treatment (prior to dosing) and post-treatment visits (7 to 14 days following the last dose of study medication or at the time of termination of therapy for patients who discontinue from the study); a chest exam was also performed during treatment (Days 3 to 5) and if there was evidence of clinical relapse was repeated at the final follow-up visit (21 to 28 days following the last dose of study medication). Chest X-rays were performed at the pre-treatment and post-treatment visits, and were repeated if clinically indicated during treatment and again at the final follow-up visit if there was evidence of clinical relapse. Clinical laboratory tests and vital signs were performed at the pre-treatment, during treatment, and post-treatment visits. A sputum smear and culture was evaluated at the pre-treatment visit and was repeated during treatment and at the post-treatment and final follow-up visits if sputum production persisted. A blood culture was performed at the pre-treatment visit and if clinically indicated (previous blood culture tested positive) additional cultures were performed at the during treatment, post-treatment, and final follow-up visits. Serology tests (antibody titers for *M. pneumoniae*, *C. pneumoniae* and *L. pneumophila*) were performed at the pre-treatment, post-treatment and final follow-up visits. Clinical signs and symptoms were evaluated at the pre-treatment visit and were performed along with an assessment of adverse events, medication use, and resource use at the during treatment, end of treatment (1 to 3 days following the last dose of study medication), post-treatment, and final follow-up visits (medication use not assessed at the final visit). Oxygen saturation was measured at the pre-treatment and during treatment visits.

9.5.2 Gatifloxacin/Levofloxacin

Study AI420-038: Randomized, Double-Blind, Multicenter, Comparative Phase III Study of Gatifloxacin Versus Levofloxacin in the Treatment of Community-Acquired Pneumonia

Study AI420-038 was a double-blind phase III study comparing levofloxacin and gatifloxacin for the treatment of community-acquired pneumonia (CAP) Ambulatory or hospitalized patients 18 years of age and older with a clinical diagnosis of CAP were eligible for enrollment into the study. The clinical diagnosis of CAP required evidence of a new pulmonary infiltrate on chest radiograph and two or more of the following clinical findings: fever; leukocytosis; cough; chest pain; purulent sputum; transtracheal aspirate, bronchial brushings, or biopsy material demonstrating neutrophils and a predominate pathogen on Gram staining. Patients were excluded from the study for any of the following reasons: if more than one dose of a systemic antibiotic was administered within 7 days prior to enrollment, if the requirement for another systemic antibiotic seemed likely during the study period, if there were clinical reasons necessitating more than 14 days of antibiotic therapy, or if patients were likely to die of intercurrent disease within 3 days. Patients were randomly assigned to receive either 500 mg of levofloxacin or 400 mg of gatifloxacin every 24 h for 7 to 14 days. Gatifloxacin was administered either orally or as an intravenous infusion over 1 h. Levofloxacin was administered either orally or as an intravenous infusion over 1 h. At the investigator’s discretion, patients received either oral therapy alone or intravenous therapy followed by oral therapy.

Clinical response was determined by comparing the patient’s baseline signs and symptoms of infection with those after therapy and then categorized as either cure or failure. Cure was defined as resolution or improvement of all signs and symptoms present at study entry at the test-of-cure visit (7 to 14 days after the end of therapy) without need of further antibiotics. Failure was defined as any one or more of the following circumstances: persistent or worsened signs and symptoms after at least 3 days of therapy, new clinical findings consistent with progression of infection, progressive radiological abnormalities, additional antibiotic therapy needed for the study indication, and/or death due to the study indication.

Microbiologically evaluable patients were those clinically evaluable patients with a susceptible pretreatment pathogen. The microbiological response to therapy was determined 7 to 14 days after the completion of study drug therapy and was classified as either eradicated, presumed eradicated, persistent, or presumed persistent. “Eradicated” was defined as the absence of the pretreatment pathogen from the posttreatment sputum. If a patient’s clinical response was classified as a cure and no material was available for culture, the pretreatment pathogen was presumed eradicated. “Persistent” was defined as the presence of the pretreatment pathogen in the posttreatment culture. If a patient’s clinical response was classified as a failure and no material was available for culture, the pretreatment pathogen was considered presumed persistent.

9.5.3 Gemifloxacin

Study 049: Gemifloxacin 320 mg Once Daily Versus Oral Trovafloxacin 200 mg Once Daily for 7 or 14 Days in the Treatment of Bacterial Community-acquired Pneumonia (CAP) in Adults

The primary objective of this study was to demonstrate that oral gemifloxacin 320 mg (equivalent to 400 mg gemifloxacin mesylate) o.d. is at least as good as trovafloxacin 200 mg o.d., for 7 or 14 days for the treatment of community-acquired pneumonia (CAP) in adults. This was a randomised, double-blind, double-dummy, multicentre, parallel group, two arm comparative study of 320 mg gemifloxacin o.d. for 7 days (or 14 days if severe infection) versus 200 mg trovafloxacin o.d. for 7 days (or 14 days if severe infection) in patients with CAP. Centres across North America participated in this clinical trial. The study consisted of a screening visit followed by a 7 day (or 14 day) treatment period and a follow-up period. Doses were taken without regard to food intake. Patients attended the clinic 4 times over a duration of approximately 6 weeks to evaluate their clinical and bacteriological response to treatment. A blood sample for the evaluation of population pharmacokinetics was collected at the On Therapy visit (Visit 2, 1 day between Days 2 - 5) between 0.5 and 12 hours after the morning dose of study medication. A blood sample was also collected prior to the morning dose of study medication on 1 day between Days 2 - 6. A total of 573 patients were randomised into the study. Gemifloxacin plasma concentrations from 179 patients (62% of the total patients who received gemifloxacin) were included in the population pharmacokinetic dataset, contributing 338 observations to the dataset.

Study 061: Gemifloxacin 320 mg Once Daily Open Label Study in the Treatment of Lower Respiratory Tract Infections in Adults

The primary objective of this study was to evaluate the clinical efficacy of oral gemifloxacin 320 mg o.d. for 7 days, in patients with lower respiratory tract infections. A secondary objective was to evaluate the bacteriological efficacy and safety of oral gemifloxacin 320 mg o.d. for 7 days, in patients with lower respiratory tract infections. This was an open, non-comparative, multicentre study to evaluate the clinical efficacy of oral gemifloxacin 320 mg o.d. for 7 days, in patients with lower respiratory tract infections. Centres across the world participated in this clinical trial. The study consisted of a screening visit followed by a 7 day treatment period and a follow-up period. Doses were taken without regard to food intake. Patients attended the clinic four times over a duration of approximately 4 weeks to evaluate their clinical and bacteriological response to treatment. A blood sample for the evaluation of population pharmacokinetics was collected at the On Therapy visit (Visit 2, 1 day between Days 2 - 4) between 0.5 and 12 hours after the morning dose of study medication. A blood sample was also collected prior to the morning dose of study medication on 1 day between Days 2 - 6. A total of 477 patients were eligible for the study. Gemifloxacin plasma concentrations from 456 patients (96 % of the total patients in this open-label, non-comparative study) were included in the population pharmacokinetic dataset, contributing 864 observations to the dataset.

Office of Antimicrobial Products

FDA Briefing Document

Meeting of the Anti-Infective Drug Advisory Committee

April 1 - 2, 2008

Section C:
FDA-IDSA January 17 & 18, 2008 Workshop materials

- Please click on the "Attachments" tab on the left for the list of all documents from the FDA-IDSA Workshop.
- The same files can also be found on the backgrounder CD in a folder named: "FDA January 2008 CAP Workshop materials"