Position Paper:

Recommended Design Features of Future Clinical Trials of Antibiotics for Community-Acquired Pneumonia

Infectious Diseases Society of America*

The Infectious Diseases Society of America (IDSA) is a national medical society representing infectious diseases physicians, scientists, and other health care professionals dedicated to promoting health through excellence in infectious diseases research, education, prevention, and patient care. The Society, which has more than 8,000 members, was founded in 1963 and is based in Arlington, VA. For more information, visit www.idsociety.org.

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Disclosures:

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Executive Summary

The efficacy of new antibiotics for the treatment of community acquired pneumonia (CAP) typically has been compared to established antibiotics in non-inferiority clinical trials. However, the U.S. Food and Drug Administration (FDA) is re-evaluating the appropriateness of a non-inferiority trial design for CAP. Resulting regulatory uncertainty as to appropriate trial design has contributed to uncertainty by industry sponsors of new antibiotics. The Infectious Diseases Society of America (IDSA) and its Antimicrobial Availability Task Force (AATF), as well as the FDA, recognized that clarity and consensus on appropriate trial designs for CAP were needed to reverse the trend of reduced investment in development of new anti-bacterial agents. To this end, on January 17 and 18, 2008, the IDSA and FDA jointly sponsored a workshop on the appropriate design of clinical trials of antibiotics for the treatment of CAP to provide a forum for scientific discussion.

An exhaustive review of available, pertinent data confirms that there is an unequivocal and substantial treatment effect of antibiotic therapy for CAP. The evidence supporting a treatment effect of antibiotics for CAP includes:

1) far higher mortality rates from CAP, regardless of disease severity or age, in the pre-antibiotic era
2) an immediate decline in the mortality of CAP for all age groups and disease severity within one year of the initiation of use of sulfa drugs for the treatment of CAP in humans
3) without exception, lower mortality rates with antibiotics versus no specific therapy in every clinical trial of CAP
4) higher rates of treatment failure in patients infected with organisms that are highly resistant to fluoroquinolones or macrolides
5) more treatment failure and increased mortality in patients receiving delayed antibiotics
6) strong correlation between antibiotic exposure and success rates
7) high rates of treatment failure in CAP patients treated with an antibiotic, daptomycin, that was found to be partially inactivated by surfactant, versus effective antibiotic therapy in randomized, double-blinded, registration-quality studies

In addition to mortality benefits, studies consistently demonstrate a treatment effect of antibiotics in time to resolution of fever, cough, chest pain, dyspnea, malaise, and/or shortened duration of hospitalization. The magnitude of the antibiotic treatment effect for clinical response at 72 h post initiation of therapy in patients with CAP ranges from 35-95%, depending on disease severity and etiologic agent.

Based on the reviewed data, the IDSA supports and encourages the following design features for registration trials of CAP:

1. a non-inferiority design with the margin of non-inferiority determined by the specific outcome measure and the severity of pneumonia of the enrolled patients, as suggested in Table 5.

2. use of the following severity of illness classification to establish clear and consistent definitions of the populations enrolled, and thereby harmonize clinical practice, clinical trial enrollment, and regulatory assessment.
   a. Mild = Pneumonia Severity Index (PSI) class I.
   b. Moderate = PSI class II-III.
   c. Severe = PSI class IV-V, or, PSI class I-III plus a requirement for mechanical ventilation, or other validated, physiological markers of severe disease (e.g. markers of severe sepsis/septic shock, use of pressors, etc.) in individual patients.
   d. Combination definitions to include: <u>mild to moderate</u> = PSI class I-III; <u>mild to severe</u> = PSI class I-V or I-III plus validated, physiological markers of severe disease; <u>moderate to severe</u> = PSI class II-V or II-III plus validated, physiological markers of severe disease.

3. Sponsors may wish to enrich their study populations for specific pathogens by increasing the use of modern tools of molecular biology. The impact of this enrichment should be taken into consideration when justifying non-inferiority margins for individual trials.

4. The following outcome measures are proposed in the context of an NI design:
   a. for trials exclusively enrolling patients with severe CAP (PSI IV-V), a 15-day "all cause" mortality outcome measure.
   b. for trials in which patients with mild (PSI I) or moderate (PSI II-III) CAP are enrolled (with or without patients with severe CAP), 15-day "all cause" mortality, either as the lead outcome in a hierarchical endpoint, or as a composite endpoint with morbidity variables that represent meaningful benefit to patients and are assessed by PRO instruments. In a hierarchical endpoint, morbidity outcomes may be assessed by time to event or dichotomous analyses. In a composite endpoint, mortality and morbidity outcomes may be assessed by dichotomous analyses at pre-specified time points. Potential morbidity endpoints include resolution of fever, cough, pain, dyspnea, or malaise. Hospital discharge is also a potential, relevant endpoint.

5. clinical trial assessment of procalcitonin or other biomarker of inflammation so as to determine their validity or lack thereof.

The current uncertainty in acceptable designs for clinical trials of CAP is contributing to dis-incentives in the discovery and development of new drugs for CAP. This crisis will be mitigated by the rapid approval and dissemination of clear and defensible guidelines for future clinical trials of new anti-bacterial agents for the treatment of CAP.

Introduction

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality in the United States (U.S.) and throughout the world [1, 2]. Four to six million cases of CAP occur per year in the U.S., resulting in 10 million physician visits, 600,000 hospitalizations, and tens of thousands of deaths [1, 3]. The total cost of CAP to the annual U.S. health care budget is in excess of $10 billion (in 2007-adjusted dollars) [4]. Furthermore, there is increasing antibiotic resistance among common pathogens, with a resultant critical need for new antibiotics [5].

In recent years, clinical trials of new antibiotics for CAP have tested the hypothesis that the new drugs were not inferior to established antibiotics by a pre-specified margin (i.e. non-inferiority clinical trials). The U.S. Food and Drug Administration (FDA) has initiated a re-evaluation of the appropriateness of a non-inferiority trial design for CAP. Resulting regulatory uncertainty as to appropriate trial design has contributed to uncertainty by industry sponsors. In turn, industry uncertainty about regulatory standards has exacerbated the already fragile market for antibiotic research and development [5].

The Infectious Diseases Society of America (IDSA) and its Antimicrobial Availability Task Force (AATF), as well as the FDA, recognized that clarity and consensus on appropriate trial designs for CAP were needed to reverse the trend of reduced investment in development of new anti-bacterial agents. To this end, on January 17 and 18, 2008, the IDSA and FDA jointly sponsored a workshop on the appropriate design of clinical trials of antibiotics for the treatment of CAP. The workshop was intended to allow experts from academe, industry, and the FDA to share pertinent knowledge.

This position paper is based on the data presented, discussions held, and opinions expressed at the workshop. Conclusions and suggestions presented in this document are those of the IDSA and its participating representatives. There is no intent to represent the views of industry or the FDA. The goal of the IDSA is to consider the data and represent the best interests of patients.

Herein six specific aspects of clinical trial design for CAP are addressed: 1) the basis of selection of non-inferiority vs. superiority trials for CAP; 2) severity of illness stratification for enrolled patients; 3) the basis of selection of margins for non-inferiority trials; 4) the value of microbiological confirmation of the etiologic organism; 5) appropriate clinical trial outcome measures; and 6) safety and other trial design concerns.

1. Non-inferiority vs. superiority trials for CAP, to include the ethics and feasibility of placebo controls

a. Are superiority trials feasible for CAP?

K. Higgins reviewed recent registration, phase III clinical trials of antibiotics for CAP [6]. There is a remarkable consistency of treatment effect across all trials and all drugs, with a ~90 +/- 5% clinical response rate in both experimental and comparator arms. Similarly, meta-analyses of multiple randomized clinical trials of antibiotic therapy for CAP found no significant

differences in mortality or clinical response, regardless of treatment activity versus atypical bacteria or duration of therapy [7-9].

In contrast, two clinical trials reported superior clinical response rates of CAP in patients treated with a fluoroquinolone (levofloxacin or moxifloxacin) versus treatment with a beta lactam +/- a macrolide [10, 11]. However, the first trial was not double-blinded, and the majority of therapy in the control arm was with oral cefuroxime rather than iv ceftriaxone. Furthermore, subsequent comparisons of moxifloxacin [12] or gatifloxacin [13] versus ceftriaxone +/- erythromycin found no difference in response rates. Finally, multi-centered, randomized comparisons of moxifloxacin or sparfloxacin versus amoxicillin also failed to show superiority of the fluoroquinolone [14, 15]. Hence, the vast majority of randomized clinical trials of antibiotics for CAP have failed to show superiority of new anti-microbial agents to the comparative antibiotic regimens. In light of the high rate of clinical success and relatively low mortality for CAP treated with standard antibiotics, demonstration of superiority of a new drug against an active comparator is unlikely. Hence, an active comparator superiority trial for CAP poses a considerable risk of failing to meet primary efficacy endpoints, even for an efficacious drug.

The possibility of a placebo-controlled superiority trial was discussed at the workshop. Such a trial would establish a precise estimate of antibiotic treatment effect size. However, a placebo-controlled trial is ethical only if there is equipoise as to the benefit of the treatment arms, or if withholding active treatment poses minimal risk to enrolled patients. A majority of participants at the workshop, and in particular virtually all of the physicians, concluded that it is unethical to use a placebo arm for a trial of moderate to severe CAP based on risk to the participants randomized to the placebo arm. It was acknowledged that the potential sequelae of placebo-treated CAP caused by "atypical" organisms, other than *Legionella* species, were unlikely to cause serious harm. Nevertheless, most clinicians believed that even "atypical" pneumonia requiring hospitalization should be treated with antibiotics, and that it is not ethical to administer a placebo to hospitalized patients with CAP.

Some workshop participants believed that a placebo-controlled trial might be justified in young, low-risk, clinically stable outpatients with mild CAP due to an atypical organism. Indeed such trials have already been performed. The only two randomized, double-blind, placebo-controlled trials of CAP identified in the literature were performed in young healthy adults. In 1961, Kingston et al. conducted a trial in 290 healthy Marine recruits (aged 17-22 years) with mild CAP who were randomized to receive treatment with tetracycline or placebo [16]. *Mycoplasma pneumoniae* was the etiology in 133 (46%) of the patients; no pathogen was identified in 122 (42%) patients; and respiratory viruses were the etiology in 35 (12%). Tetracycline significantly reduced the mean time to defervescence (temperature < 99°F), normalization of chest X-ray (CXR), and resolution of cough both in patients who had a confirmed diagnosis of *M. pneumoniae* as well as in patients in whom no microbiological diagnosis was established (Table 1). The fraction of patients remaining febrile on day 3 was dramatically lower in patients treated with tetracycline versus placebo, both in patients with confirmed *M. pneumoniae* infection (30% vs. 95% remained febrile in tetracycline vs. placebo arms respectively) and in patients in whom no microbiological diagnosis was established (30% vs. 65% remained febrile in tetracycline vs. placebo arms respectively). Significant differences

were also seen in Kaplan-Meier analyses of time to resolution of fever and time to normalization of CXR, both in patients with confirmed *M. pneumoniae* infection and in patients with no microbiological diagnosis. In contrast, tetracycline had no impact on time to defervescence, CXR resolution, or any other clinical parameter in patients with confirmed viral infections.

In a subsequent double-blind trial of 32 young, healthy Army recruits with CAP due to *M. pneumoniae*, patients were randomized to receive treatment with tetracycline, clindamycin, or placebo [17]. Patients receiving tetracycline had a significantly shorter time to defervescence than those receiving either clindamycin or placebo. Clindamycin was of no benefit compared to placebo. Hence, superiority of active antibiotics versus placebo has been demonstrated in two randomized trials of patients with mild pneumonia. It is unclear what benefit would accrue by repeating a placebo-controlled trial in a similar population.

The efficacy of macrolides, as well as tetracyclines, for CAP caused by *M. pneumoniae* was supported by results from three other clinical trials in U.S. Air Force trainees [18-20]. In the first trial, CAP caused by *M. pneumoniae* was serologically confirmed in 317 healthy young men aged 18-21 years. Patients "were treated at random" with erythromycin stearate, erythromycin ethylsuccinate, tetracycline, methacycline, troleandomycin, demeclocycline, penicillin, or no antibiotics. In the second trial, CAP caused by *M. pneumoniae* was serologically confirmed in 105 trainees alternately treated with erythromycin or tetracycline. Their outcomes were compared to those of 170 patients with *M. pneumoniae* seen during the previous five years who had been treated with no antibiotics or penicillin. In the third trial, patients with CAP caused by *M. pneumoniae* were treated with tetracyclines (n = 113) or with no antibiotics (n = 15). In all three trials, the mean duration of fever in patients treated with tetracyclines or macrolides was significantly shorter than for those treated with penicillin or no antibiotics. Of note, in all three trials the shortened duration of fever translated into significantly shorter hospital stays. Specifically, patients treated with demeclocycine, tetracycline, or erythromycin had an average hospital stay of five to seven days, versus nine to 14 days for patients receiving penicillin or no antibiotic. Shorter time to resolution of abnormal CXR was also seen in patients treated with a tetracycline or a macrolide. The authors of the first trial concluded, "The control group [of this trial] was not large because early in the investigation it was found that tetracycline and erythromycin reduced the length of illness, and thereafter it was considered inadvisable to withhold therapy" [18].

In addition to ethics, placebo-controlled trials for CAP, of any severity, face three practical hurdles [21]. First, treating physicians are unlikely to agree to enroll their patients in such trials. Second, Institutional Review Boards are unlikely to approve such protocols at individual sites given the current standard of care and literature documenting antibiotic efficacy. Lastly, patients with CAP are unlikely to give informed consent for a trial wherein they could be randomized to placebo. These three issues are particularly relevant to treatment trials of CAP in infants and children [22].

b. <u>Are non-inferiority trials appropriate for CAP?</u>

According to International Congress on Harmonization (ICH) guidance, non-inferiority trials are appropriate only when a comparator drug has been previously established to be superior

to placebo for the disease in question (the "historical evidence of sensitivity to drug effect", or HESDE, standard) [23]. Furthermore, the clinical settings in which the efficacy of the comparator was previously established must be relevant to the planned non-inferiority trial (the "constancy assumption" standard).

To determine if data exist to demonstrate HESDE and the accuracy of the constancy assumption, M. Singer analyzed studies from the 1920s-1940s of antibiotic use for the treatment of CAP [24]. Prior to the workshop, seven studies were identified that compared the effect of antibiotics to no therapy in patients with CAP (Table 2). Three of these studies compared the outcomes of consecutive patients treated with antibiotics to the outcomes of historical control, untreated patients prior to the availability of antibiotics. We refer to these studies as "historical control" studies. The other four studies enrolled patients to receive antibiotic treatment versus concurrent control patients who received no specific antibiotic therapy. We refer to these studies as "concurrent control" studies. Subsequent to the workshop, one addition concurrent control and three additional historical control studies were identified, for a total of 11 studies that compared antibiotics to no treatment for CAP (Table 2). In addition, several other studies were identified that exclusively evaluated and confirmed the efficacy of antibiotics in pediatric CAP. The pediatric studies are discussed by Bradley and McCracken [22].

The concurrent control studies were not randomized in the modern sense but rudimentary randomization strategies (e.g., enrollment by hospital ward, alternation of treatment regimen, alternation by day of enrollment) were used. The historical control studies predominantly evaluated patients with CAP caused by *S. pneumoniae*. In contrast, the concurrent control studies all included patients without confirmation of *S. pneumoniae* as the etiology, either because they enrolled patients with "lobar pneumonia" without specifying microbial etiology, or they included patients whose cultures did not identify *S. pneumoniae* [25-28].

In the historical control studies, the weighted average mortality was 38% without antibiotic treatment and 12% with antibiotic treatment, indicating a 26% (95% confidence interval = 24-28%) absolute reduction in mortality with antibiotic therapy (Table 2). In the concurrent control studies, the weighted average of mortality was 23% without antibiotics and 7% with antibiotics, indicating an absolute 16% (95% CI = 10-22%) reduction in mortality with antibiotics. These early studies established the efficacy of antibiotics for CAP, including CAP that is not confirmed to be caused by *S. pneumoniae*, and probably explain the absence of any recent placebo-controlled trials for this disease.

Stratification of the historical data by age demonstrates efficacy of antibiotics for CAP over a broad range of severity. For example, Tilghman and Finland [29] and Bullowa [30] reviewed the mortality of more than 2,000 patients with CAP caused by *S. pneumoniae* in the pre-antibiotic era, and stratified the results by age and the presence or absence of bacteremia. As expected, mortality was much lower in younger patients, and in particular in those without bacteremia. Today the majority of young patients with *S. pneumoniae* pneumonia but without bacteremia would be considered to have moderately severe disease, based on numerous studies [30-38] and a standard and well validated scoring system (the pneumonia severity index (PSI), discussed more fully below) [35, 39]. Nevertheless, untreated patients aged 12-19 and 20-29, including those who were not bacteremic, had mortality rates of ~10% in the pre-antibiotic era

(Table 3), which is far higher than the <1% mortality rate expected for such patients in the antibiotic era [39].

In 1928, Park et al. reported the results of a trial of anti-pneumococcal polysaccharide serum therapy in 223 consecutive patients with CAP caused by *S. pneumoniae* [40]. Every other patient was administered serum therapy or supportive care, and patients receiving serum therapy had an absolute 14% reduction in mortality (34% to 20%). Of note, patients who were in "good" baseline condition still had a mortality rate of 13% with no therapy, versus a 52% or 100% mortality, respectively, for patients in "fair" or "poor" condition at baseline. Again, those in "good" baseline condition likely reflected moderate CAP (i.e. PSI category II-III), and the mortality rate with no treatment was far higher than that which is reliably achieved with antibiotics in the modern era (< 1%).

In 1938 Evans and Gaiseford alternated patients with lobar CAP to receive sulfa versus no specific therapy [26]. Twenty-two percent of their cases were attributable to cultured *S. pneumoniae*; no microbiological etiology was identified for the remaining 78%. They reported that sulfa treatment caused a 16% reduction in mortality for patients aged <30, a 21% reduction for patients aged 30-59, and a 55% reduction for patients aged ≥ 60 years. Finland also compared the mortality of 1,220 patients with pneumococcal pneumonia treated with sulfa drugs from 1938-1941 versus 2,832 patients given no therapy from 1929-1940. The results confirmed that antibiotics had significant treatment effects in all age groups whether or not bacteremia was present [41]. The treatment effect was greater in older and in bacteremic patients. However, even in non-bacteremic patients aged 12-29, the mortality rates fell from 10% to 5% with antibiotic treatment. Similarly, in untreated patients aged <30 years, Dowling and Lepper reported an 8% mortality rate versus a 1% mortality with antibiotics [34].

In all the above studies, the benefits of antibiotics were larger for patients with more severe disease than for patients with moderate disease. Specifically, Finland reported an absolute 40% reduction in mortality of CAP patients ≥ 50 years, including a ~50% reduction in bacteremic and ~30% reduction in non-bacteremic patients [41]. Similar rates were reported by Evans and Dowling and Leper (Table 3) [26, 34].

Calculation of weighted averages from all five studies that reported mortality of treated versus untreated patients stratified by age reveals two critical insights (Table 3). First, specific estimates of antibiotic-mediated reduction in mortality can be generated for each age group. For patients aged <30, 30-59, or ≥ 60 years, the absolute reduction in mortality in patients treated with antibiotics was 11% (95% CI = 8-13%), 27% (25-30%), or 45% (39-54%), respectively. Second, the mortality rates of treated patients in each age group bear strong resemblances to the mortality rates of antibiotic treated patients stratified by the PSI scoring system from modern datasets (Table 4).

Collectively, these data establish a convincing reduction in mortality caused by antibiotics in the treatment of CAP, and provide point estimates of efficacy that can be used as the basis for justifying non-inferiority margins in CAP trials. Furthermore, the mortality rates of patient populations in historical datasets parallels closely the mortality rates of patients assigned specific PSI scores in modern datasets, providing evidence that the constancy assumption is valid

for non-inferiority trials for CAP. Additionally, while the historical control studies predominantly focused on CAP caused by *S. pneumoniae,* significant numbers of patients without confirmed *S. pneumoniae* infection were included in all of the concurrent control trials.

c. Additional data that support a benefit from antibiotic therapy for CAP

Adding credence to the historical datasets are recent studies of the effectiveness of antibiotic therapy in the setting of: discordant therapy (i.e. use of antibiotic against which the etiologic agent is resistant by in vitro testing); delayed initiation of therapy versus more rapid initiation of therapy; and subtherapeutic exposure to an antibiotic either as a result of inadequate pharmacokinetic-pharmacodynamic (PK-PD) parameters or in vivo drug inactivation.

Discordance. In vitro resistance to macrolides and fluoroquinolones is associated with documented clinical failure and increased mortality in patients with CAP [3, 42-51].

Delay in therapy. A delay in the initiation of active antibiotics is also associated with a higher mortality rate in patients with CAP [52-54]. The reduced mortality rate seen with rapid initiation of antibiotics is seen both for patients with moderate (PSI class II-III) and severe (PSI class IV-V) disease [52].

Subtherapeutic PK-PD parameters. As described in detail by P. Ambrose [55], data from PK-PD studies from both animal models and patients with CAP demonstrate that serum area-under-the-inhibitory-curve (AUIC) ratios for antibiotics (e.g. fluoroquinolones or macrolides) strongly correlate with clinical outcome. Indeed, lower fluoroquinolone AUIC ratios are associated with a 25% absolute reduction in clinical response in patients with CAP versus higher AUIC ratios. In a multinational trial of antibiotic efficacy in acute exacerbations of chronic bronchitis, lower AUICs predicted clinical progression to CAP [56]. Specifically 92% of patients with antibiotic AUIC of <100 progressed to CAP, versus only 35% of patients with AUIC ratios >100. Furthermore, as discussed by T. File and J. Schentag [57], patients presenting with mild CAP caused by *S. pneumoniae* are at higher risk of progressing to more severe CAP if they are not given effective antibiotic therapy than are patients given initial effective antibiotic therapy.

In vivo drug inactivation. Finally, pooled data from two recent, phase III, double-blind, randomized clinical trials also demonstrate a treatment effect of antibiotics [58]. In the two trials, a combined 936 patients with PSI class II-IV (1 patient had a PSI score of V) CAP were randomized to receive daptomycin versus ceftriaxone. Of the 834 patients in the intention-to-treat (ITT) population, 24% had microbiological confirmation of a diagnosis of *S. pneumoniae* as an etiologic agent. It was not realized until after the results of the first trial became available that daptomycin was inactivated by pulmonary surfactant, and hence loses considerable activity in lung tissue [59]. At that point enrollment in the second trial was terminated and the results were pooled with the first trial. In the pooled ITT population, there were nearly twice as many clinical failures in the daptomycin arm versus the ceftriaxone arm (n = 44 vs. 23), resulting in a cure rate of 71% in the daptomycin recipients vs. 77% in the ceftriaxone cohort (95% CI = -12.4% to -0.6%). Of the patients in the ITT population who did not have a microbiological confirmation of a gram-positive organism causing their CAP, the clinical response rates remained inferior for

daptomycin vs. ceftriaxone (69% vs. 77%). Hence, regardless of microbiological confirmation of the etiologic agent and over a broad range of disease severity (PSI class II-IV), standard antibiotic therapy was superior to a drug partially inactivated by surfactant.

In summary, four different approaches in the modern era generate data that are in concordance with historical data demonstrating that antibiotics are more effective than no treatment for CAP.

d. Demonstration of CAP antibiotic treatment effect using endpoints other than mortality.

A classic medical text by Osler indicated that in the natural history of untreated CAP, clinical improvement and defervescence was "very uncommon" before 72 hours [60]. This opinion is concordant with data from a large cohort reported in a 1937 text by Bullowa [30]. The cohort consisted of 662 untreated survivors of CAP. Since these patients were all survivors in an era where no effective therapy was available, they reflect a population selected for less severe disease on average than that represented by "all comers" with CAP. Nevertheless, only 1.4% of CAP patients in this untreated cohort defervesced by day 2 of therapy, and only 2.6% defervesced by day 3. Furthermore, both Bullowa and Cecil comment that the time course of normalization of pulse and respiratory rate parallel the time to normalization of fever in untreated CAP patients [30, 61].

In contrast, shortly after the availability of antibiotics, clinical trials found significantly shorter times to resolution of signs and symptoms of infection from that in the pre-antibiotic era. In 1939, only 2 years after Bullowa described his series of untreated CAP patients, Flippin reported that 83% of 100 patients with CAP treated with sulfa drugs defervesced by day 2 of treatment, and 99% of patients had defervesced by day 3 [62]. Raycraft et al. reported that 90% of children with CAP treated with antibiotics defervesced by day 2 of treatment [63]. Also in a previously mentioned trial of sulfa versus untreated controls in patients with lobar CAP, 54% of patients receiving sulfa drugs defervesced by day 3, versus only 4% of patients given no treatment [25]. Two decades later, Petersdorf et al. reported that 74-94% of CAP patients were clinically improved (by a composite of defervescence and symptom scores, including chest pain, cough, appetite, general feeling, etc.) by 72 hours after initiation of antibiotic therapy [64]. Hence, data available almost immediately after the introduction of sulfa drugs indicate that antibiotic treatment dramatically reduced the time to defervescence and/or clinical improvement of CAP. These data are concordant with the previously mentioned trials of tetracyclines or macrolides vs. placebo for mild CAP (PSI class I equivalent) in military recruits, in which the time to defervescence and clinical response rates were significantly shorter for antibiotics than placebo [16-20].

In individual studies, superiority of antibiotics against an active comparator for the treatment of CAP has been demonstrable by time to resolution of signs and symptoms of infection. Specifically, short-course, high dose (750 mg/day x five days) levofloxacin was shown to result in more frequent resolution of fever and improvement in a variety of clinical symptoms by day 3 of treatment as compared to a then standard dose (500 mg/day x seven days) of levofloxacin [65]. In another trial, moxifloxacin as compared to ceftriaxone with or without erythromycin produced defervescence in a higher proportion of patients on days 2-5 of antibiotic

therapy, improved time to resolution of clinical symptoms (e.g. cough, dyspnea, chest pain), and shortened hospital stay [12]. Of note, in both fluoroquinolone trials, patients with a PSI class ranging from I-IV were enrolled. Hence, time to clinical improvement is a feasible endpoint, and could apply to trials that evaluate the full spectrum of severity of CAP.

Collectively, all the data reviewed support a treatment effect of antibiotics versus placebo in time to defervescence, time to other clinical response endpoints, and reduction of mortality. The antibiotic treatment effect for defervescence or clinical response at 72 hours post initiation of therapy in patients with CAP ranges from 35-95%, depending on disease severity and etiologic agent.

In summary, the evidence supporting a treatment effect of antibiotics for CAP includes:

1) far higher mortality rates from CAP, regardless of disease severity or age, in the pre-antibiotic era
2) an immediate decline in the mortality of CAP for all age groups and disease severity within 1 year of the initiation of use of sulfa drugs for the treatment of CAP in humans
3) without exception, lower mortality rates with antibiotics versus no specific therapy in every clinical trial of CAP
4) higher rates of treatment failure in patients infected with organisms that are highly resistant to fluoroquinolones or macrolides
5) more treatment failure and increased mortality in patients receiving delayed antibiotics
6) strong correlation between antibiotic exposure and success rates
7) high rates of treatment failure in CAP patients treated with an antibiotic, daptomycin, that was found to be partially inactivated by surfactant, versus effective antibiotic therapy in randomized, double-blinded, registration-quality studies
8) extensive evidence of more rapid clinical improvement in patients with CAP treated with antibiotics compared to placebo or no specific therapy

2. Severity of illness stratification

According to ICH guidances, the patient population in current or future non-inferiority trials must be comparable to benchmark studies [23, 66]. Comparability can be addressed in part by stratifying patients using a validated marker of disease severity.

The two most widely used prognostic scoring systems for CAP are the PSI class, as already mentioned, and the CURB-65 score. From the perspective of defining disease severity for a CAP clinical trial, there are three advantages of the PSI scoring system over the CURB-65 scoring system. First, and most important, as discussed above, the PSI scoring system correlates with mortality despite antibiotic treatment in patients in both historical and modern datasets (Table 4). Thus, use of the PSI scoring system enables enrollment of populations that satisfy the patient population constancy requirement of non-inferiority trials. Second, the PSI score separates disease severity into more categories than does the CURB-65 score, and hence PSI is more flexible than CURB-65 in stratifying patients by severity of disease. Third, the PSI scoring system takes into account a continuous range of age, whereas the CURB-65 score dichotomizes age to <65 or ≥65 years.

From the prospective validation cohort of the PSI scoring system, mortality rates increased from 0.1% to 0.6% to 0.9% to 9.5% to 26.7% as the PSI class increased from I to V [39]. Note the six-fold increase in mortality between class I and class II, and the 10-fold increase between class III and IV. Furthermore, as mentioned, there is a correlation between mortality rates of treated patients in the historical datasets and the average mortalities of PSI class II-III, III-IV, and IV-V in the validation cohort (Table 4). Finally, the previously mentioned military studies of CAP due to *M. pneumoniae* were exclusively conducted in PSI class I-equivalent patients [16-20].

Therefore, the disease severity of patients enrolled into clinical trials can be defined by PSI class as: class I (mild), class II-III (moderate), and class IV-V (severe). In this context, trials that enroll patients across disease categories are concordantly designated as enrolling patients with mild to moderate (i.e. PSI class I-III), mild to severe (i.e. PSI class I-V), or moderate to severe (i.e. PSI II-V) disease. These designations are relevant as historical datasets provide evidence of antibiotic efficacy for populations crossing these disease categories (Tables 2-5).

The PSI scoring system provides the foundation for identification of populations with differing disease severity, but PSI does not capture all elements contributing to disease severity [36, 37, 67]. In individual clinical studies, protocol designers should have the ability to modify the definition of severe CAP based upon well-validated factors not accounted for in the PSI scoring system. For example, CAP with severe hemodynamic compromise or requirement for mechanical ventilation should be considered severe even in a young, otherwise healthy person who might not have enough comorbidities to achieve a PSI class IV-V. Care must be taken in creating such modifications to scoring disease severity so as not to undermine the predictive power of the PSI scoring system. Therefore, if the criteria are modified for individual studies, the modifications should be justified for the projected clinical trial patient population.

Finally, the PSI scoring system is not validated for use in children, and additional research is needed to better define populations for enrollment into trials of pediatric CAP.

3. IDSA Suggested Margins of Non-Inferiority

As summarized above, there is compelling evidence for a mortality benefit of antibiotic treatment in CAP. The overall effect size is a 26% (95% CI 24-28%) absolute reduction in mortality for CAP due to *S. pneumoniae*, and 16% (95% CI 10-22%) reduction in mortality for "all-comers" with CAP (Table 2). Furthermore, historical data indicate mortality reductions in antibiotic-treated patients of 11% (8-13%), 27% (25-30%), and 45% (39-54%) with, respectively, disease severities equivalent to PSI class II-III, III-IV, and IV-V CAP (Table 3).

According to the ICH E10 guidance, "The margin chosen for a non-inferiority trial cannot be greater than the *smallest effect size that the active drug would reliably be expected to have* compared with placebo in the setting of the planned trial" (italic emphasis from the original document) [23]. Therefore, the lower bound of the non-inferiority margin in a clinical trial for a new antibiotic is set based, in part, on the previously reported lower limits of efficacy of the comparator drug. Furthermore, the ICH guidance states, "In practice, the non-inferiority margin chosen usually will be smaller than that suggested by the smallest expected effect size of the active control because of interest in ensuring that some clinically acceptable effect size (or fraction of the control drug effect) was maintained."

Thus, the data justify conducting non-inferiority trials for CAP with an endpoint of mortality and a non-inferiority margin of five to 10% depending on the severity of disease of the enrolled population (Table 5). These proposals are based on the lower limit of the 95% CI of effect sizes in historical datasets, taking into consideration the need to preserve a significant effect size, particularly for more ill patients who have a higher risk of death. Furthermore, available data also support use of a non-inferiority trial design to evaluate time to resolution of clinical endpoints, such as fever and cough, or resolution of clinical endpoints as a dichotomous outcome for patients with the full spectrum of CAP severity, from mild to severe (PSI class I-V) (Table 5).

It is emphasized that resolution of fever, cough, chest pain, dyspnea, malaise, or hypoxia, are important clinical endpoints because: 1) faster resolution is closely linked to faster time to hospital discharge [12, 18, 19, 25]; and 2) they cause patients substantial discomfort and distress. Multiple clinical trials have demonstrated that achievement of "clinical stability", including defervescence and resolution of hypoxia, can be used to determine when it safe to switch a patient from intravenous to oral antibiotics, and/or when it is safe to discharge a hospitalized patient with CAP [68-73]. These studies underscore the close link between time to defervescence/clinical improvement and time to hospital discharge. Furthermore, use of clinical improvement to guide oral/iv antibiotic switch and hospital discharge decisions has been incorporated into national guidelines on the treatment of CAP [3].

Because the treatment effect of antibiotics for these clinical endpoints is so large compared to no treatment or placebo, and because the treatment effect is on clinical/symptomatic response rather than mortality, the precision with which the non-inferiority margin is selected for

future trials is less critical. For example, a 20% non-inferiority margin for a dichotomous endpoint of defervescence at day 3 of treatment is reasonable, since it is far below the treatment effect, and therefore is sufficient to maintain a substantial treatment effect relative to placebo.

Finally, we emphasize that Table 5 serves as a guideline for reasonable choices for non-inferiority margins in different clinical trial settings. However, the margins used may differ from one trial to another. Justification of specific endpoints should be carried out for each specific trial design, as the patient population and range of pathogens may alter the effect size and/or risk to benefit ratio, thereby affecting the appropriate non-inferiority margin.

4. The value of microbiological identification of the etiologic organism of the CAP

A prominent theme of the workshop was the value of identification of the microbiological etiology (or etiologies) of the pneumonia in patients enrolled in clinical trials. Although it is not always necessary to know the microbiological etiology of pneumonia to administer rational and effective empiric therapy for CAP in clinical settings, it is important to do so for a non-inferiority trial for CAP. The data that document a mortality benefit of antibiotic therapy for CAP derive, in large part, from trials that enrolled populations enriched for patients with CAP caused by *S. pneumoniae*. Therefore, for non-inferiority trials using mortality as an endpoint, it may be desirable to similarly enrich the enrolled population for CAP caused by *S. pneumoniae*.

However, as mentioned, substantial evidence does exist for a treatment benefit in patients with "lobar pneumonia" or pneumonia of unclear microbial etiology, as well as for patients with proven *M. pneumoniae* infection. Furthermore, in standard clinical practice treating physicians almost never know the etiologic organism when they choose empiric antibiotic therapy for CAP. Therefore, restricting primary endpoint analysis to those patients who are later confirmed to have an infection caused by a specific microbe does not reflect "real-world" practice. Hence while appropriate for some trials, it may not be necessary--and in some cases may be undesirable and misleading--to restrict the primary analysis to patients eventually confirmed to have pneumococcal pneumonia.

Nevertheless, another advantage of enriching the enrolled population in a CAP trial for those infected with *S. pneumoniae* is that the greater the homogeneity of the patient population, the greater the likelihood of clear clinical endpoints and reduced mortality. Pneumonia caused by viruses does not respond to antibiotics, and most other bacterial causes of CAP, with the exception of *Legionella*, are less likely to cause infectious complications. In a superiority trial, dilution of the population most likely to derive benefit from the therapeutic intervention biases the trial away from rejecting the null hypothesis (i.e. biases the trial away from finding a superiority outcome). In contrast, in a non-inferiority trial, dilution of the population most likely to derive benefit from the therapeutic intervention biases the trial towards rejecting the null hypothesis (i.e. biases the trial towards finding no difference between the two interventions). Enrichment for patients infected with *S. pneumoniae*—and hence most likely to benefit from antibiotic therapy—can therefore mitigate bias towards rejecting the null hypothesis in a non-inferiority trial.

Drs. Nolte and Klugman reviewed recent advances in the rapid, precise identification of the pathogens most often implicated as etiologies of CAP [74, 75]. Use of such methods could facilitate enrichment of an analyzable population for a target pathogen. Multiplex real time PCR is evolving rapidly and allows identification of bacteria and viruses in respiratory specimens in a few hours. Presently the technology is not generally available, but improved access is likely to emerge in a short time. The U.S. National Institutes of Health (NIH) could help by facilitating investigation of a wide range of diagnostic tests designed to identify the specific microbial etiology of CAP.

In short, even if not, at present, generally available clinically, the emerging methods of molecular diagnostics could, and perhaps should, be used in future clinical trials. However, to the degree that these methods provide greater sensitivity than classical microbiologic methods, they may identify patient cohorts different than those defined in the historical clinical trials that were used to define effect sizes for the active comparator arms. Hence the impact of molecular diagnostics on the anticipated event rate and enrolled population should be taken into consideration when justifying a non-inferiority margin for an individual trial.

Other microbiologic tests are readily available and should be performed: e.g. sputum Gram's stain and culture, blood cultures, urinary pneumococcal antigen, and *Legionella* urinary antigen. *Mycoplasma* IgM antibody has reasonable sensitivity and specificity. *Mycoplasma* and *Chlamydophila pneumoniae* can be identified by probing respiratory secretions by PCR. A positive sputum Gram's stain or culture, or blood cultures in the appropriate clinical setting (i.e. abnormal CXR with relevant signs or symptoms) are sufficient to identify patients with pneumococcal pneumonia. While positive serological or antigen test results for atypical pathogens do not exclude the possibility of pneumococcal pneumonia (because dual infection is well described), they do allow a greater understanding of the pathogen distribution in the trial population.

As discussed by Bradley and McCracken [22], the sensitivity and specificity, and the clinical significance, of diagnostic tests for pathogens of CAP may differ between adult and pediatric populations, and distinct tests may be required to assess infection in distinct age groups [76].

5) Appropriate outcome measures for CAP trials

a. Primary Endpoints

In accordance with ICH guidances, the primary endpoints in non-inferiority trials for CAP should reflect the endpoints of the trials used to justify the non-inferiority margin. Potential endpoints include mortality and/or clinical morbidity outcomes in hierarchical or composite endpoints, as discussed more fully below. Clinical outcomes could be time to event or dichotomous endpoints at a specific time point, including resolution of fever, cough, dyspnea, chest pain, malaise, or hypoxia, as well as duration of hospitalization. If defervescence is used as an endpoint, factors that can affect the temperature curve and validation of the definition of defervescence must be considered prospectively. For example, control of use of anti-pyretics must be built into the protocol. Similarly, prospective definition of the duration of normal

temperature required to achieve the "defervescence" endpoint is necessary (i.e., for how long must a patient maintain a normal temperature before he/she is considered to have defervesced?).

In a superiority trial design, as there is no need to match endpoints with historical precedents, selection of a primary endpoint for a superiority trial should follow ICH E9 guidance: "The primary variable ('target' variable, primary endpoint) should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial" [66]. It is recommended that time-to-event analyses be considered for superiority trials. Time-to-event analyses increase statistical power and informative analysis compared to dichotomous outcomes. Analyses might include time to: death, hospital discharge, transfer out of the intensive care unit, defervescence, cessation of pressors, cessation of supplemental oxygen, etc.

b. Mortality As An Endpoint

It is difficult to accurately assign cause of death for individual patients. Attempts to determine "attributable mortality" would likely introduce unmeasurable bias into the analysis. Hence, analysis of "all-cause mortality" is recommended in lieu of attributable mortality.

Historical datasets and recent evaluations of pneumonia demonstrate that deaths in patients with CAP typically occur within the first seven to 14 days after presentation [24, 31]. Deaths beyond 14 days are more likely due to comorbidities. Therefore, it is recommended that the primary mortality endpoint apply to all deaths occurring within 15 days after presentation, rather than deaths occurring after 30 or more days.

c. Patient Reported Outcome (PRO) Instruments (standardized questionnaires)

A PRO instrument is a tool used to measure a patient's health and well being. Information recorded on the PRO is provided by the patient, rather than by the health-care provider, and with no interpretation of the patient's answers by the health-care provider. An advantage of PRO instruments is that they "offer a structured interview technique that minimizes measurement error and ensures consistency, ultimately providing a more reliable measurement than one that can be obtained by informal interviews" [77]. There is considerable enthusiasm for increasing the use of PRO instruments to objectively quantify clinical response, especially in the context of time to event analyses. If a PRO is used, it should be appropriately validated [78], and the interview process must be standardized so as to remove interviewer bias from the results.

d. Surrogate Markers

In the context of CAP, clinical signs of infection, such as fever, are both biomarkers and surrogate markers for infection. An elevated WBC count is a laboratory surrogate marker for infection. Fever and elevated WBC count lack, by themselves, specificity for pneumonia. Neither separates bacterial from other causes of CAP (e.g. viral, fungal, etc.). Nonetheless, laboratory tests that indicate a bacterial, as opposed to a viral infection, could improve clinical

trials by excluding patients from enrollment who have a very high likelihood of viral as opposed to bacterial infection.

Elevated procalcitonin levels may increase the likelihood of a bacterial etiology of a patient's pneumonia. As discussed by Dr. Niederman, prospective clinical trials in adults demonstrate that antibiotics may be safely withheld from patients with pulmonary infiltrates who have a serum procalcitonin level of < 0.1 ng/ml [79]. If validated, procalcitonin may exclude patients with non-bacterial pneumonia from enrollment or primary endpoint analysis, thereby improving the population homogeneity and increasing the signal to noise ratio in the analysis of the primary endpoint.

e. Hierarchical Primary Endpoint Testing

Multiple primary endpoints are generally not appropriate for a clinical trial due to the concern of multiple comparisons testing. However, if multiple endpoints are hierarchically ranked such that the most important endpoint is tested first, and subsequent endpoints are tested only if significance is achieved with preceding endpoints, the issue of multiple comparisons is obviated [80].

Hierarchical testing may be particularly advantageous for a CAP clinical trial because it allows assessment of both non-inferiority and superiority primary endpoints in the same trial. Hierarchical testing can also allow sequential assessment of a dichotomous endpoint and time to event endpoints. For example, the first primary endpoint tested could be a dichotomous non-inferiority analysis of mortality. If statistical non-inferiority was met with the first primary endpoint, the second primary endpoint could be a superiority analysis of time to defervescence, time to clinical improvement by PRO, time to hospital discharge, etc. Thus the use of hierarchical testing enables superiority testing while still enabling a successful trial on a non-inferiority basis in case superiority is not achieved (i.e. the risks of not achieving superiority are mitigated).

If hierarchical primary endpoint testing is to be used in a clinical trial, three principles apply. First, the hierarchy of the endpoints must be pre-determined in the trial protocol, before initiation of the trial, and cannot be subsequently switched or bias will be introduced. Second, the hierarchy should set clinically more important/relevant endpoints to a more important hierarchical position (e.g. mortality should be tested before time to defervescence, etc.). Aside from clinical relevance, the hierarchical order should reflect loss of available information at each step in the hierarchy. For example, in a trial assessing both all-cause mortality and clinical endpoints (e.g. symptoms), mortality must be the first endpoint tested, because dead patients are not available for assessment of clinical endpoints [81]. Third, if the initial endpoint does not meet statistical significance, the trial is considered failed per the primary endpoint, and subsequent endpoints in the hierarchy can no longer be considered as primary endpoints. In the latter scenario, subsequent endpoints should either not undergo statistical testing, or if testing does occur, the results should be considered as secondary, hypothesis-generating endpoints rather than confirmatory endpoints.

f. Composite Outcome Measures

As stated in the Introduction, CAP results in considerable morbidity in addition to mortality. It is reasonable to determine the efficacy of antibiotics at reducing both mortality and morbidity due to CAP. For inclusion in a composite outcome measure, markers of morbidity must be clinically meaningful. Furthermore, evidence should be available demonstrating that antibiotics mitigate the severity of the individual components of the composite endpoint. Based on these criteria, a composite primary outcome measure for a non-inferiority CAP trial could include "all-cause" 15-day mortality and one of more dichotomous clinical morbidity endpoints, such as defervescence or other patient health status variables (e.g. cough, pain, shortness of breath, etc.) assessed by PRO instruments.

However, use of a composite endpoint has the potential to mask unfavorable mortality effects if the efficacy of the new antibiotic is driven by morbidity components. Therefore, if a composite endpoint is used, a secondary analysis of all-cause mortality should be performed to determine if the mortality effect is concordant or discordant with the overall composite endpoint and the other individual components of the endpoint.

Composite endpoints may be appropriate for CAP trials enrolling patients with mild (PSI I) or moderate (PSI II-III) CAP, with or without inclusion of severe (PSI IV-V) CAP in the study population. However, antibiotics mediate a very large reduction in mortality in patients with severe CAP (Table III), making assessment of non-inferiority with respect to mortality critical for any new drug directed at this population. Therefore, the preferred primary outcome assessment for trials that exclusively enroll patients with severe CAP (PSI class IV-V) is all-cause 15-day mortality. In trials that include CAP populations which include, but are not limited to, severe CAP, a secondary analysis should examine mortality in this subgroup to explore consistency with expected benefit (recognizing that the trial will not be powered to draw a definitive conclusion on this analysis).

g. Exclusions from the Analysis Population

In the past, patients in CAP trials were often excluded from the primary endpoint analysis if they received an insufficient number of days of therapy (usually ≤ 3 days), due to the assumption that patients dying within that time frame were sufficiently ill to have been unlikely to have benefited from any antibiotic therapy. However, in today's environment of early goal-directed therapy, and other critical care supportive measures, it is not clear that this assumption is valid. Furthermore, early deaths on therapy may reflect an exacerbation of underlying disease, toxicity of the trial drug, or worsening sepsis caused by sudden lysis of bacteria. Such data elements should not be excluded from the primary endpoint analysis. Therefore, it is recommended that the intent-to-treat population for efficacy analysis consist of all randomized patients.

6. Safety, blinding, prior antibiotics, pediatrics

a. Safety Issues

Patient safety should be a principal concern of all those participating in the design, conduct, and analysis of clinical trials, including those in CAP [82, 83]. The evaluation of known class or molecule toxicities is a standard component of this process. Antibiotic classes commonly used to treat CAP exhibit a number of known adverse events, such as QTc prolongation (e.g. fluoroquinolones) and gastrointestinal symptoms (e.g. macrolides). Furthermore, any antibiotic has the potential to affect the risk of developing *Clostridium difficile* enterocolitis. Trials should be designed and conducted to thoroughly evaluate the potential for such events, and to avoid them. Safety analyses should be conducted on an intent-to-treat basis using all patients randomized in the trial.

Patient safety also extends beyond the capture and analysis of adverse events [83]. Safety includes the impact of trial variables on efficacy. For example, suboptimal efficacy in a clinical trial can lead to many adverse patient "safety" outcomes, e.g. prolonged hospitalization, increased cost, complications, and even death. To increase the likelihood of efficacy, proper dose selection for the new antibiotic must be a primary focus. Other areas requiring rigorous attention in this context include: 1) the choice of active comparator; 2) the choice of adjunctive antibiotic therapy (i.e., antibiotics given as a part of the trial regimen, but not including the primary trial drug); 3) protocol-defined adjunctive non-antibiotic therapy; 4) the impact of prior antibiotic therapy; and 5) patient inclusion and exclusion criteria.

Impartial data safety monitoring boards (DSMBs) and interim analyses are important to protect against a clearly inferior treatment or unexpected adverse events. Finally, post-marketing studies should conduct active surveillance for safety issues that were not uncovered in earlier trials, and such studies should involve appropriate, rigorous design to enable meaningful conclusions.

b. Blinding

Double-blinding (i.e. blinding of the patient and all trial personnel who are involved with evaluations in the trial) should be incorporated into CAP clinical trials [84]. Double-blinding may require a double-dummy design if comparator antibiotic(s) are dosed with different frequency or by different routes from the trial drug, or if adjunctive therapy is planned in case of resistant gram-negative bacilli or other drug-resistant organisms. Expectation of a substantial portion of drug-resistant organisms, and MRSA in particular, may require use of an unblinded trial pharmacist, microbiologist, or other personnel, to provide therapeutic interventions (e.g, dose adjusting vancomycin, etc.) without unblinding the patient. However, the development of specific safety questions in individual patients may require unblinding to discern treatment assignment. Development of other clinical scenarios may also mandate unblinding of the patient or discontinuation of a patient from the trial protocol. For example, development of staphylococcal bacteremia necessitates initiation of a series of diagnostic (e.g. echocardiography) and therapeutic (i.e. prolonged IV antibiotics) interventions that are beyond the scope of most CAP clinical trials.

c. Prior AntibioticTherapy

The complexities involved in identifying, consenting, screening, and enrolling patients into clinical trials are such that enrollment within a few hours of presentation is extremely challenging. Because delayed initiation of therapy poses risks for patients with CAP, as well as for hospitals and individual physicians being monitored for compliance with national standards for quality care, clinical protocols may need to allow for a single dose, or perhaps short periods of antibiotic therapy prior to enrollment [83]. Nevertheless, striving to enroll patients prior to administration of antibiotics is an important goal to minimize the potential confounding effects of the antibiotic pre-treatment.

d. Pediatric Trial Design Concerns

The incidence of CAP in infants exceeds that in adults. Infants and children bring additional issues to the complexities of clinical trial design in CAP: e.g., ethical issues of placebo-controlled trials, the increased difficulty of identifying bacterial pathogens in pediatric CAP, and age-related differences in drug kinetics. Nevertheless, the historical evidence of antibiotic effectiveness in pediatric patients with CAP is sufficient to justify non-inferiority trials. These issues are discussed in this supplement by Bradley and McCracken [22].

Summary of the IDSA's Views

The following views and recommendations are those of the IDSA. The IDSA advocates for patients and their physicians. The positions presented are not motivated by advocacy for industry. IDSA leadership remains critically concerned about the converging problems of lack of antibiotic development and surging rates of antibiotic-resistance in lethal bacterial pathogens [5]. As physicians and public health advocates, we emphasize that patients need new drugs for CAP in the discovery and development pipeline. Furthermore, because it takes, on average, ≥10 years to complete development of a new drug, it is essential that the pipeline be strengthened now to meet anticipated needs a decade or more from now. An important step to enhance the discovery and development of new antibiotics is clarification of FDA guidance for future clinical trials of anti-bacterial agents for CAP.

An exhaustive review of available, pertinent data confirms that there is an unequivocal and substantial treatment effect of antibiotic therapy for CAP. Antibiotic therapy results in a reduction in mortality for patients with moderate CAP (i.e. PSI class II-III), and an even greater reduction in mortality for patients with severe CAP (i.e. PSI class IV-V). As demonstrated by placebo-controlled trials, antibiotic therapy also accelerates improvement in relevant clinical markers of morbidity in patients with mild CAP (i.e. PSI class I). Hence the ICH "historical evidence of sensitivity to drug effect" (HESDE) standard [23] is met for use of non-inferiority trials of antibiotics for the treatment of CAP of all severities of disease. Finally, the PSI scoring system enables correlation of mortality rates of antibiotic-treated patients in modern CAP trials and historical datasets, and thereby validates the constancy assumption needed for non-inferiority trials of CAP.

Given the available data, conduct of placebo-controlled trials of antibiotics for patients with CAP is both unnecessary and, we suggest, unethical. The IDSA favors a rapid and clear delineation of FDA guidance to industry on the design options for future registration clinical trials of CAP. Based on the reviewed data, the IDSA supports and encourages the following design features:

1. a non-inferiority design with the margin of non-inferiority determined by the specific outcome measure and the severity of pneumonia of the enrolled patients, as suggested in Table 5.
2. use of the following severity of illness classification to establish clear and consistent definitions of the populations enrolled, and thereby harmonize clinical practice, clinical trial enrollment, and regulatory assessment
   a. Mild = PSI class I.
   b. Moderate = PSI class II-III.
   c. Severe = PSI class IV-V, or, PSI class I-III plus a requirement for mechanical ventilation, or other validated, physiological markers of severe disease (e.g. markers of severe sepsis/septic shock, use of pressors, etc) in individual patients.
   d. Combination definitions to include: <u>mild to moderate</u> = PSI class I-III; <u>mild to severe</u> = PSI class I-V or I-III plus validated, physiological markers of severe disease; <u>moderate to severe</u> = PSI class II-V or II-III plus validated, physiological markers of severe disease.
3. Sponsors may wish to enrich their study populations for specific pathogens by increasing the use modern tools of molecular biology. The impact of this enrichment should be taken into consideration when justifying non-inferiority margins for individual trials.
4. The following outcome measures are proposed in the context of an NI design:
   a. for trials exclusively enrolling patients with severe CAP (PSI IV-V), a 15 day "all cause" mortality outcome measure.
   b. for trials in which patients with mild (PSI I) or moderate (PSI II-III) CAP are enrolled (with or without patients with severe CAP), 15-day "all cause" mortality, either as the lead outcome in a hierarchical endpoint, or as a composite endpoint with morbidity variables that represent meaningful benefit to patients and are assessed by PRO instruments. In a hierarchical endpoint, morbidity outcomes may be assessed by time to event or dichotomous analyses. In a composite endpoint, mortality and morbidity outcomes may be assessed by dichotomous analyses at pre-specified time points. Potential morbidity endpoints include resolution of fever, cough, pain, dyspnea, or malaise. Hospital discharge is also a potential, relevant endpoint.
5. Clinical trial assessment of procalcitonin or other biomarker of inflammation so as to determine their validity or lack thereof.

The current uncertainty in acceptable designs for clinical trials of CAP is contributing to dis-incentives in the discovery and development of new drugs for CAP. This crisis will be mitigated by the rapid approval and dissemination of clear and defensible guidelines for future clinical trials of new antibacterials for the treatment of CAP.

References:

1. Mandell LA. Epidemiology and etiology of community-acquired pneumonia. Infect Dis Clin North Am 2004;18:761-76
2. Deaths by cause, sex and mortality stratum in WHO Regions, estimates for 2002. World Health Report-2004. Geneva: World Health Organization, 2004:Annex Table 2
3. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44 Suppl 2:S27-72
4. Niederman MS, McCombs JS, Unger AN, Kumar A and Popovian R. The cost of treating community-acquired pneumonia. Clin Ther 1998;20:820-37
5. Spellberg B, Guidos R, Gilbert D, et al. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. Clin Infect Dis 2008;46:155-64
6. Higgins K. Overview of Recent CAP Trials: Non-inferiority trial Design and Endpoints. In: Issues in the Design and Conduct of Clinical Trials of Antibacterial Drugs in the Treatment of Community-Acquired Pneumonia: A workshop co-sponsored by the FDA and IDSA. Silver Spring, MD, January 17th, 2008
7. Shefet D, Robenshtok E, Paul M and Leibovici L. Empirical atypical coverage for inpatients with community-acquired pneumonia: systematic review of randomized controlled trials. Arch Intern Med 2005;165:1992-2000
8. Mills GD, Oehley MR and Arrol B. Effectiveness of beta lactam antibiotics compared with antibiotics active against atypical pathogens in non-severe community acquired pneumonia: meta-analysis. Bmj 2005;330:456
9. Li JZ, Winston LG, Moore DH and Bent S. Efficacy of short-course antibiotic regimens for community-acquired pneumonia: a meta-analysis. Am J Med 2007;120:783-90
10. File TM, Jr., Segreti J, Dunbar L, et al. A multicenter, randomized study comparing the efficacy and safety of intravenous and/or oral levofloxacin versus ceftriaxone and/or cefuroxime axetil in treatment of adults with community-acquired pneumonia. Antimicrob Agents Chemother 1997;41:1965-72
11. Finch R, Schurmann D, Collins O, et al. Randomized controlled trial of sequential intravenous (i.v.) and oral moxifloxacin compared with sequential i.v. and oral co-amoxiclav with or without clarithromycin in patients with community-acquired pneumonia requiring initial parenteral treatment. Antimicrob Agents Chemother 2002;46:1746-54
12. Welte T, Petermann W, Schurmann D, Bauer TT and Reimnitz P. Treatment with sequential intravenous or oral moxifloxacin was associated with faster clinical improvement than was standard therapy for hospitalized patients with community-acquired pneumonia who received initial parenteral therapy. Clin Infect Dis 2005;41:1697-705
13. Dean NC, Sperry P, Wikler M, Suchyta MS and Hadlock C. Comparing gatifloxacin and clarithromycin in pneumonia symptom resolution and process of care. Antimicrob Agents Chemother 2006;50:1164-9
14. Petitpretz P, Arvis P, Marel M, Moita J and Urueta J. Oral moxifloxacin vs high-dosage amoxicillin in the treatment of mild-to-moderate, community-acquired, suspected pneumococcal pneumonia in adults. Chest 2001;119:185-95
15. Aubier M, Verster R, Regamey C, Geslin P and Vercken JB. Once-daily sparfloxacin versus high-dosage amoxicillin in the treatment of community-acquired, suspected

pneumococcal pneumonia in adults. Sparfloxacin European Study Group. Clin Infect Dis 1998;26:1312-20
16. Kingston JR, Chanock R, Mufson MA, et al. Eaton agent pneumonia. JAMA 1961;176:118-23
17. Smilack JD, Burgin WW, Jr., Moore WL, Jr. and Sanford JP. Mycoplasma pneumoniae pneumonia and clindamycin therapy. Failure to demonstrate efficacy. Jama 1974;228:729-31
18. Shames JM, George RB, Holliday WB, Rasch JR and Mogabgab WJ. Comparison of antibiotics in the treatment of mycoplasmal pneumonia. Arch Intern Med 1970;125:680-4
19. Rasch JR, Mogabgab WJ. Therapeutic effect of erythromycin on Mycoplasma pneumoniae pneumonia. Antimicrob Agents Chemother 1965;5:693-9
20. Gooch WM, 3rd, Mogabgab WJ. Therapeutic effect of doxycycline upon Mycoplasma pneumoniae pneumonia. Antimicrobial Agents Chemother (Bethesda) 1970;10:291-5
21. Echols RM, Tillotson GS, Song JX and Tosiello RL. Clinical Trial Design for Mild to Moderate Community Acquired Pneumonia – An Industry Perspective. Clin Infect Dis 2008;In Press
22. Bradley JS, McCracken GHJ. Unique Considerations for the Evaluation of Antibacterials in Clinical Trials of Pediatric Community-Associated Pneumonia. Clin Infect Dis 2008;In Press
23. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Guidance for Industry. E10, Choice of Control Group and Related Issues in Clinical Trials, 1998
24. Singer M, Nambiar S, Valappil T, Higgins K and Gitterman S. Historical and Regulatory Perspective on the Treatment Effect of Antibacterial Drugs in Community Acquired Pneumonia. Clin Infect Dis 2008;In Press
25. Agranat AL, Dreosti AO and Ordman D. Treatment of pneumonia with 2-(p-aminobenzenesulphonamido) pyridine. Lancet 1939;233(6024):309-317
26. Evans GM, Gaisford WF. Treatment of pneumonia with 2-(p-aminobenzenesulphonamido) pyridine. Lancet 1938;232(5992):14-19
27. Graham D, Warner WP, Dauphinee JA and Dickson RC. The treatment of pneumococcal pneumonia with dagenan (M. & B. 693). Can Med Assoc J 1939;40:325-332
28. Ormiston G, Woodman D and Lewis FJW. Pneumonia in infants, children, and adults. Quarterly J Med 1942;48:155-180
29. Tilghman RC, Finland M. Clinical significance of bacteremia in pneumococcal pneumonia. Arch Intern Med 1937;59:602-619
30. Bullowa JGM. Chapter II. The course, symptoms and physical findings. The management of pneumonias. NY, NY: Oxford University Press, 1937
31. Marrie TJ, Carriere KC, Jin Y and Johnson DH. Factors associated with death among adults <55 years of age hospitalized for community-acquired pneumonia. Clin Infect Dis 2003;36:413-21
32. Kaplan V, Angus DC, Griffin MF, Clermont G, Scott Watson R and Linde-Zwirble WT. Hospitalized community-acquired pneumonia in the elderly: age- and sex-related patterns of care and outcome in the United States. Am J Respir Crit Care Med 2002;165:766-72
33. Baik I, Curhan GC, Rimm EB, Bendich A, Willett WC and Fawzi WW. A prospective study of age and lifestyle factors in relation to community-acquired pneumonia in US men and women. Arch Intern Med 2000;160:3082-8

34. Dowling HF, Lepper MH. The effect of antibiotics (penicillin, aureomycin, and terramycin) on the fatality rate and incidence of complications in pneumococcic pneumonia. A comparison with other methods of therapy. Am J Med Sci 1951;222
35. Musher DM, Alexandraki I, Graviss EA, et al. Bacteremic and nonbacteremic pneumococcal pneumonia. A prospective study. Medicine (Baltimore) 2000;79:210-21
36. Marras TK, Gutierrez C and Chan CK. Applying a prediction rule to identify low-risk patients with community-acquired pneumonia. Chest 2000;118:1339-43
37. Arnold FW, Ramirez JA, McDonald LC and Xia EL. Hospitalization for community-acquired pneumonia: the pneumonia severity index vs clinical judgment. Chest 2003;124:121-4
38. Marrie TJ, Huang JQ. Low-risk patients admitted with community-acquired pneumonia. Am J Med 2005;118:1357-63
39. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997;336:243-50
40. Park WH, Bullowa JGM and Rosenbluth MB. The treatment of lobar pneumonia with refined specific antibacterial serum. JAMA 1928;91:1503-1509
41. Finland M. Chemotherapy in bacteremias. Connecticut State Med J 1943;7:92-100
42. Davidson R, Cavalcanti R, Brunton JL, et al. Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia. N Engl J Med 2002;346:747-50
43. Dylewski J, Davidson R. Bacteremic pneumococcal pneumonia associated with macrolide failure. Eur J Clin Microbiol Infect Dis 2006;25:39-42
44. Endimiani A, Brigante G, Bettaccini AA, Luzzaro F, Grossi P and Toniolo AQ. Failure of levofloxacin treatment in community-acquired pneumococcal pneumonia. BMC Infect Dis 2005;5:106
45. Ho PL, Yung RW, Tsang DN, et al. Increasing resistance of Streptococcus pneumoniae to fluoroquinolones: results of a Hong Kong multicentre study in 2000. J Antimicrob Chemother 2001;48:659-65
46. Kelley MA, Weber DJ, Gilligan P and Cohen MS. Breakthrough pneumococcal bacteremia in patients being treated with azithromycin and clarithromycin. Clin Infect Dis 2000;31:1008-11
47. Lonks JR, Garau J, Gomez L, et al. Failure of macrolide antibiotic treatment in patients with bacteremia due to erythromycin-resistant Streptococcus pneumoniae. Clin Infect Dis 2002;35:556-64
48. Musher DM, Dowell ME, Shortridge VD, et al. Emergence of macrolide resistance during treatment of pneumococcal pneumonia. N Engl J Med 2002;346:630-1
49. Peterson LR. Penicillins for treatment of pneumococcal pneumonia: does in vitro resistance really matter? Clin Infect Dis 2006;42:224-33
50. Rzeszutek M, Wierzbowski A, Hoban DJ, Conly J, Bishai W and Zhanel GG. A review of clinical failures associated with macrolide-resistant Streptococcus pneumoniae. Int J Antimicrob Agents 2004;24:95-104
51. Iannini PB, Paladino JA, Lavin B, Singer ME and Schentag JJ. A case series of macrolide treatment failures in community acquired pneumonia. J Chemother 2007;19:536-45
52. Houck PM, Bratzler DW, Nsa W, Ma A and Bartlett JG. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. Arch Intern Med 2004;164:637-44

53. Kahn KL, Rogers WH, Rubenstein LV, et al. Measuring quality of care with explicit process criteria before and after implementation of the DRG-based prospective payment system. Jama 1990;264:1969-73
54. Meehan TP, Fine MJ, Krumholz HM, et al. Quality of care, process, and outcomes in elderly patients with pneumonia. Jama 1997;278:2080-4
55. Ambrose PG. Use of pharmacokinetics-pharmacodynamics in a community-aquired pneumonia failure analysis: implications for future clinical trial study design. Clin Infect Dis 2008;In Press
56. File TM, Jr., Monte SV, Schentag JJ, et al. RTI Response in the Community; Observations on the Transition State Between COPD and CAP. In: Abstract #1047: 45th Annual Meeting of the Infectious Diseases Society of America (IDSA). San Diego, CA, 2007
57. File TM, Jr., Schentag JJ. Community-acquired pneumonia in adults not requiring hospitalization: a clinical perspective on superiority and non-inferiority trials. Clin Infect Dis 2008;In Press
58. Pertel PE, Bernardo P, Fogarty C, et al. Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. Clin Infect Dis 2008;In Press
59. Silverman JA, Mortin LI, Vanpraagh AD, Li T and Alder J. Inhibition of daptomycin by pulmonary surfactant: in vitro modeling and clinical impact. J Infect Dis 2005;191:2149-52
60. Osler W. XV. Lobar Pneumonia. The principles and practice of medicine, 7th edition. NY, NY: Appleton and Co., 1910:179
61. Cecil RL. A Textbook of Medicine, 5th Edition. In: Cecil RL, Kennedy F, eds. Philadelphia, PA: W.B. Saunders and Co., 1942:149
62. Flippin HF, Lockwood JS, Pepper DS and Schwartz L. The treatment of pneumococcic pneumonia with sulfapyridine. JAMA 1939;112:529-534
63. Raycraft WB, Motel W and Greegard J. Chemotherapy of pneumonia in infants under one year of age. Am J Dis Child 1941;61:898-903
64. Petersdorf RG, Cluff LG, Hoeprich PD, Hopkins FT and McCann WP. Pneumococcal pneumonia treated with penicillin and aspirin. Bull Johns Hopkins Hospital 1967;101:1-12
65. Dunbar LM, Wunderink RG, Habib MP, et al. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. Clin Infect Dis 2003;37:752-60
66. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Guidance for Industry. E9, Statistical Principles for Clinical Trials, 1998
67. Ortega L, Sierra M, Dominguez J, et al. Utility of a pneumonia severity index in the optimization of the diagnostic and therapeutic effort for community-acquired pneumonia. Scand J Infect Dis 2005;37:657-63
68. Ramirez JA, Vargas S, Ritter GW, et al. Early switch from intravenous to oral antibiotics and early hospital discharge: a prospective observational study of 200 consecutive patients with community-acquired pneumonia. Arch Intern Med 1999;159:2449-54
69. Rhew DC, Weingarten SR. Achieving a safe and early discharge for patients with community-acquired pneumonia. Med Clin North Am 2001;85:1427-40

70. Aliyu ZY, Aliyu MH and McCormick K. Determinants for hospitalization in " low-risk" community acquired pneumonia. BMC Infect Dis 2003;3:11
71. Samsa GP, Matchar DB, Harnett J and Wilson J. A cost-minimization analysis comparing azithromycin-based and levofloxacin-based protocols for the treatment of patients hospitalized with community-acquired pneumonia: results from the CAP-IN trial. Chest 2005;128:3246-54
72. Drummond MF, Becker DL, Hux M, et al. An economic evaluation of sequential i.v./po moxifloxacin therapy compared to i.v./po co-amoxiclav with or without clarithromycin in the treatment of community-acquired pneumonia. Chest 2003;124:526-35
73. Cabre M, Bolivar I, Pera G and Pallares R. Factors influencing length of hospital stay in community-acquired pneumonia: a study in 27 community hospitals. Epidemiol Infect 2004;132:821-9
74. Klugman KP. Novel approaches to the diagnosis of Streptococcus pneumoniae as a cause of community acquired pneumonia. Clin Infect Dis 2008;In Press
75. Nolte FS. Molecular diagnostics for bacterial and viral pathogens in community acquired pneumonia. Clin Infect Dis 2008;In Press
76. Dowell SF, Garman RL, Liu G, Levine OS and Yang YH. Evaluation of Binax NOW, an assay for the detection of pneumococcal antigen in urine samples, performed among pediatric patients. Clin Infect Dis 2001;32:824-5
77. Bren L. The Importance of Patient-Reported Outcomes.It's All About the Patients. Rockville, MD: U.S. Department of Health and Human Services. Food and Drug Administration., 2006
78. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration, 2006
79. Niederman MS. Biologic Markers to Determine Eligibility for Community-Acquired Pneumonia (CAP) Trials: A Focus on Procalcitonin. Clin Infect Dis 2008;In Press
80. Powers J. Primary and secondary and composite endpoints. In: Issues in the Design and Conduct of Clinical Trials of Antibacterial Drugs in the Treatment of Community-Acquired Pneumonia: A workshop co-sponsored by the IDSA and FDA. Silver Spring, MD, January 18th 2008
81. Lubsen J, Kirwan BA. Combined endpoints: can we use them? Stat Med 2002;21:2959-70
82. Psaty BM. Clinical-trial design and selected drug safety issues for community acquired pneumonia. Clin Infect Dis 2008;In Press
83. Talbot GH. Efficacy: An Important Facet of "Safety" in Clinical Trials: How Can We Do Our Best for Our Subjects. Clin Infect Dis 2008;In Press
84. Boucher HW. Is It Possible to Blind a Trial of Community Acquired Pneumonia? Clin Infect Dis 2008;In Press
85. Austrian R, Gold J. Pneumococcal bacteremia with especial reference to bacteremic pneumococcal pneumonia. Ann Int Med 1964;60:759-776
86. Heintzelman JHL, Hadley PB and Mellon RR. The use of p-aminobenzenesulphonamide in type 3 pneumococcus pneumonia. Am J Med Sci 1937;193:759-763
87. Anderson T, Cairns JG. Treatment of pneumonia with sulphapyridine and serum. Lancet 1940;236:449-451
88. Gaisford WF. Results of the treatment of 400 cases of lobar pneumonia with M & B 693. Proc Royal Soc Med 1939;32:1070-1076

89. Dixon WJ, Massey FJ. Introduction to Statistical Analysis. 4th ed. New York: McGraw Hill, 1983:463
90. Deeks JJ, Altman DG and Bradburn MJ. Statistical methods for examining heterogeneity and combining trials. In: Egger M, Davey Smith G and Altman DG, eds. Systematic Reviews in Healthcare: Meta-analysis in Context. Londgon: BMJ Books, 2001

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Table 1. Effect of Tetracycline on Mean Time to Resolution (days) in Patients with CAP

	***Mycoplasma* Confirmed (n = 133)**		**No Microbiological Diagnosis (n = 122)**		**Confirmed Viral Infection (n = 35)**	
	Placebo	Tetracycline	Placebo	Tetracycline	Placebo	Tetracycline
Fever (T >99° F)	10	3*	7	3*	6	4
CXR+	20	9*	15	11*	16	15
Cough	22	10*	15	9*	18	14
Fatigue/Malaise	9	3*	4	3	4	5

Data are from [16].

*$p < 0.05$

Table 2. Historical Studies Demonstrating Antibiotic Mediated Reduction in Mortality in Patients with CAP

First Author [ref]	Non-*S. pneumoniae* included?*	Untreated Mortality†	Mortality With Antibiotics†
	Historical Control Studies		
Finland [41]	No	1161/2832 (41%)	207/1220 (17%)
Dowling [34]	No	331/1087 (31%)	47/920 (5%)
Austrian [85]	No	405/480 (84%)	90/527 (17%)
Heinztelman [86]	No	8/10 (80%)	2/9 (22%)
Anderson [87]	No	86/462 (19%)	26/217 (12%)
Gaisford [88]	Yes	193/876 (22%)	26/400 (7%)
	Total (Weighted Average)	2184/5747 (38%)	398/3293 (12%)
Absolute Mortality Reduction (95% CI)‡		**26% (24-28%)**	
	Concurrent Control Studies		
Evans [26]	Yes	27/100 (27%)	8/100 (8%)
Graham [27]	Yes	7/30 (23%)	4/80 (5%)
Agranat [25]φ	Yes	16/86 (19%)	6/71 (8%)
Agranat [25]φ	Yes	6/27 (22%)	2/27 (7%)
Ormiston [28]	Yes	2/11 (18%)	1/30 (3%)
	Total (Weighted Average)	58/254 (23%)	21/308 (7%)
Absolute Mortality Reduction (95% CI)‡		**16% (10-22%)**	

*Indicates if patients were included in the trial who did not have laboratory confirmed *S. pneumoniae*; †Number of patients that died divided by all patients (% dead); ‡Mortality reduction is summarized over studies as the differences between antibiotic and non-antibiotic groups weighted by numbers of patients. Confidence intervals are calculated using standard linear combination variance formulas [89]. This method allows inclusion of one-arm studies and non-randomized two-arm studies that is not possible with meta-analytic techniques [90]. φTwo distinct patient populations were considered separately in this trial.

Table 3. Historical Mortality Rates by Age or Baseline Status

1st Author [ref]	<30 Years or "Good"* (i.e. PSI II-III equivalent)		30-59 years or "Fair" * (i.e. PSI III-IV equivalent)		≥ 60 Years or "Poor"* (i.e. PSI IV-V equivalent)	
	No Abx	**+ Abx**	**No Abx**	**+ Abx**	**No Abx**	**+ Abx**
Tilghman [29]	32/301 (11%)	N/A	154/563 (27%)	N/A	96/140 (69%)	N/A
Bullowa [30]	103/739 (14%)	N/A	371/1090 (34%)	N/A	80/135 (59%)	N/A
Heinzelman [86]	N/A	N/A	5/7 (71%)	0/7 (0%)	3/3 (100%)	2/2 (100%)
Evans [26]	6/34 (18%)	1/51 (2%)	18/52 (35%)	6/44 (14%)	3/4 (75%)	1/5 (20%)
Dowling [34]	23/287 (8%)	3/226 (1%)	199/613 (32%)	24/565 (4%)	109/187 (58%)	20/129 (16%)
Weighted Average	164/1361 (12%)	4/277 (1%)	747/2325 (32%)	30/616 (5%)	291/469 (62%)	23/136 (17%)
Absolute Mortality Reduction (95% CI) †	**11% (8-13%)**		**27% (25-30%)**		**45% (39-54%)**	

*Some studies scored baseline severity of illness as "good", "fair", or "poor"; if scoring was not available, age was used; †Mortality reduction is summarized over studies as the differences between antibiotic and non-antibiotic groups weighted by numbers of patients. Confidence intervals are calculated using standard linear combination variance formulas [89]. This method allows inclusion of one-arm studies and non-randomized two-arm studies that is not possible with meta-analytic techniques [90]. One small trial (Heinzelman, N=19) was not included in the summary statistics due to 0% or 100% mortality in some subgroups. Also, the large, historical control study by Finland was not included because he reported only the percent mortality by age and did not list the numerator and denominator of patients in each age group [41].

Table 4. Comparison of the Influence of Age on Mortality Rates of Antibiotic-Treated Patients in Historical and Contemporary Datasets

Age	Historical Data*	Average Mortality by PSI Class from Validation Cohort*
< 30 years	1%	0.75% (PSI class II-III)
30-59 years	5%	5.3% (PSI class III-IV)
≥60 years	17%	18.1% (PSI class IV-V)

*Historical data taken from Table 3. PSI = Pneumonia Severity Index. PSI mortality rates reflect averages of 0.6% & 0.9% for PSI II & III, 0.9% & 9.5% for PSI III & IV, and 9.5% & 26.7% for PSI IV & V [39].

Table 5. Examples of Possible Non-Inferiority Margins for CAP Clinical Trial

Population	Established Lower Limit of Antibiotic Effect *	Proposed NI Margin
	Mortality	
PSI II-V : *S. pneumoniae* only	24%	10%
PSI II-V	10%	10%
PSI II-III	8%	5%
PSI III-IV	25%	10%
PSI IV-V	39%	10%
	Defervescence by Day 3 (dichotomous)	
PSI I : *M. pneumoniae* only	65%	20%
PSI I	35%	15%
PSI II-V	50%	20%
	Composite Clinical Response†	
Any	Varies	10-20%

*Based on data reviewed in Tables 2-3 and in the text.

†Composite clinical responses could include either time to event or dichotomous endpoints at a specific time point. Data exist to support components including mortality, defervescence, resolution of cough, resolution of dyspnea, resolution of chest pain, resolution of malaise, and duration of hospitalization. PRO instruments should be considered for clinical response endpoints. The appropriate patient population and selection of NI margin should be appropriately justified based on available data and the principles outlined above and in ICH E9 and E10 guidances.