IDSA Headquarters
1300 Wilson Boulevard
Suite 300
Arlington, VA 22209
TEL: (703) 299-0200
FAX: (703) 299-0204
EMAIL ADDRESS:
info@idsociety.org
WEBSITE:
www.idsociety.org

IDSA
Infectious Diseases Society of America

July 16, 2007

Dennis M. Dixon, PhD
Chief, Bacteriology and Mycology Branch
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases
6610 Rockledge Drive, Room 4111
Bethesda, MD 20817

Dear Dr. Dixon:

We are writing on behalf of the Infectious Diseases Society of America (IDSA) to discuss the urgency of the antimicrobial resistance problem and to propose several antimicrobial therapy study recommendations to pursue. This letter is in response to a January 2007 meeting convened between Dr. Louis Rice, Chair of IDSA's Research on Resistance Working group (RRWG), Dr. Barry Eisenstein, member of IDSA's RRWG, yourself, and other National Institute of Allergy and Infectious Diseases (NIAID) representatives. The group discussed the National Institute of Health's (NIH's) antimicrobial resistance research portfolio and identified areas where IDSA input may be beneficial. While IDSA and NIAID efforts to accurately characterize the NIH portfolio on antimicrobial resistance continue, we reached a consensus about the importance of clinical research on antibacterial therapy and the current limitations of the portfolio in this area. NIAID representatives welcomed suggestions from the RRWG on specific studies that would help clarify the optimal antimicrobial therapy for common infectious diseases. Enclosed with this letter is IDSA's proposal for three, randomized, multi-centered controlled trials, which aims to address this goal.

By way of background, IDSA represents more than 8,000 physicians, scientists, and other health professionals who specialize in infectious diseases in the United States and internationally. These members include many who oversee clinical trials related to anti-infective drug development. Our infectious diseases experts view the emergence and spread of antimicrobial resistance as the "next big public health problem." IDSA applauds NIH's leadership and commitment in the field of HIV/AIDS research—we believe the same level of support and commitment is needed to address antimicrobial resistance and its clinical impact on patient care and outcomes.

In 2004, IDSA launched a "Bad Bugs, No Drugs" initiative on behalf of our patients to call attention to the lack of new antibacterial development, the rise in antimicrobial resistance, and the critical need to spur anti-infective development to address our patients' needs. In 2006, as part of this initiative, IDSA leaders established the RRWG to characterize the current federal portfolio in antimicrobial resistance research and to make recommendations on ways to

optimize this portfolio to address the present and future threats posed by resistance to antimicrobial agents. Numerous major medical advances achieved over the past three decades owe their feasibility to the availability of effective antimicrobial agents. The administration of antibiotics has minimized the morbidity and mortality associated with many types of surgeries, premature births, and common diseases of old age. Their ready availability and effectiveness also has promoted the development of more aggressive cancer chemotherapies and a wide variety of transplantations. In many ways, modern medicine would not be possible without antibiotics. Unfortunately, the wide variety and remarkable safety of antimicrobial agents developed over the past few decades has led to widespread use and the predictable problem of antimicrobial resistance. Many hospitals in the United States now face major challenges in the treatment of common infections caused by routine bacteria that have developed resistance to many, and in some cases virtually all, currently available antibiotics. Moreover, the widespread use of antibiotics in hospitals has led to the emergence and spread of aggressive strains of *Clostridium difficile*. Nosocomial infections, particularly those caused by resistant bacteria, have emerged as the number one patient safety issue of our time.

Although antimicrobial resistance has received increased attention at NIAID over the past few years, the present portfolio is deficient in clinical studies on the optimal use of antimicrobial agents. In order to promote the intelligent and defensible use of antibiotics to minimize the selective pressure for resistance, we need robust prospective, randomized controlled trials to define therapies that are safe and effective while minimizing antimicrobial selective pressure. Supporting such studies is well within the purview of NIAID, as evidenced by numerous such studies examining optimal therapeutic regimens of licensed and available compounds used for treating HIV and tuberculosis.

Although there is an almost limitless number of studies that could be proposed to better define optimal therapy, we propose three specific initial studies, each of which addresses a major deficiency in our knowledge of optimal antimicrobial use (described in detail in the enclosed document):

1. A trial comparing the efficacy of three days versus seven-to-10 days of therapy for the treatment of uncomplicated, community-acquired cellulitis. The antibiotic to be used has not been decided, but vancomycin or clindamycin are reasonable options.
2. A three-armed trial comparing ceftriaxone alone with ceftriaxone plus azithromycin for the treatment of mild-to-moderate community-acquired pneumonia. Two arms of the study will employ a standard seven-day course of therapy. A third arm of the trial will test the efficacy of a three-day course of ceftriaxone alone.
3. A placebo-controlled trial of amoxicillin for the treatment of otitis media.

The hypothesis to be tested in each of these studies is that treatment regimens constituting reduced antibiotic exposure compared with standard courses will be equally effective in curing the illness and will result in fewer emergences of resistance and greater patient and physician satisfaction. These studies will provide a proof-of-principle that such trials can be carried out with NIH support and will facilitate development of the infrastructure to conduct further studies. Each trial will employ generic antimicrobial agents. Embedded within each of these trials will be natural history studies to provide critical information for defining therapeutic

outcome for these and future studies. The short- or no-treatment arm of each of these studies also will be used to define the natural history of each disease. Surveillance cultures will be performed to define the relative risks of colonization by resistant bacteria in each treatment group. In addition, patient and physician surveys can be embedded within these randomized trials to determine satisfaction with the different treatment regimens and assess patient and physician attitudes and trade-offs toward factors that influence antibiotic prescribing and antimicrobial resistance. These questionnaires also can yield physician and patient acceptable failure rates that can be used as surrogate outcomes in future randomized, nonrandomized and equivalence trials.

These recommendations constitute a beginning, serving as a base for additional trials that not only will provide information on natural history and lengths of therapy, but also will promote studies on surrogate markers to better define the need for further antibiotic therapy, so that we may one day arrive at individualized regimens for treating bacterial infections.

IDSA values our close working relationship with NIH, and specifically, NIAID. Given our shared expertise in the field of antimicrobial resistance, we look forward to working with you on these and other issues.

Should you have any questions, please feel free to contact Beth Rada, MS, IDSA's program officer for science and research, at brada@idsociety.org or (703) 299-1216.

Sincerely,

Edward N. Janoff, MD
Chair, IDSA Research Committee

Louis B. Rice, MD
Chair, IDSA Research on Resistance Work Group

cc: Anthony Fauci, MD, Director, National Institute of Allergy and Infectious Diseases (NIAID)
H. Clifford Lane, MD, Acting Deputy Director, NIAID
Carole Heilman, PhD, Director, Division of Microbiology and Infectious Diseases (DMID)/NIAID
Barbara Mulach, PhD, Acting Chief, Policy, Legislation and Communications Section, Office of Scientific Coordination and Program Operations, DMID/NIAID

Enclosure: IDSA proposal for three randomized, multi-centered controlled trials to be sponsored by NIAID, with the goal of defining optimal antimicrobial therapy of common bacterial infections

Proposal for three randomized, multi-centered controlled trials to be sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), with the goal of defining optimal antimicrobial therapy of common bacterial infections

Infectious Diseases Society of America (IDSA)

July, 2007

Developed by the IDSA Research on Resistance Work Group Members:

Louis B. Rice, MD, Chair

Henry F. Chambers, MD, FIDSA

Barry I. Eisenstein, MD, FIDSA

Anthony Harris, MD, MPH

John H. Powers, III, MD, FIDSA

Lisa Saiman, MD

Richard P. Wenzel, MD, MSc, FIDSA

Background

This proposal was developed by the IDSA Research on Resistance Work Group (RRWG) in response to a request from National Institute of Allergy and Infectious Diseases (NIAID) representatives for suggestions on specific studies that would help clarify the optimal antimicrobial therapy for common infectious diseases. This request originated from a January 2007 meeting convened between Dr. Louis Rice, Chair of IDSA's RRWG, Dr. Barry Eisenstein, member of IDSA's RRWG, and NIAID representatives where IDSA and NIAID reached a consensus about the importance of clinical research on antibacterial therapy and the need for a robust portfolio in this area.

Although there is an almost limitless number of studies that could be proposed to better define optimal therapy, the RRWG proposes three specific randomized, multi-centered controlled trials, each of which addresses a major deficiency in the existing knowledge of optimal antimicrobial use:

1. A trial comparing the efficacy of three days versus seven-to-10 days of therapy for the treatment of uncomplicated, community-acquired cellulitis. The antibiotic to be used has not been decided, but vancomycin or clindamycin are reasonable options.
2. A three-armed trial comparing ceftriaxone alone with ceftriaxone plus azithromycin for the treatment of mild-to-moderate community-acquired pneumonia. Two arms of the study will employ a standard seven-day course of therapy. A third arm of the trial will test the efficacy of a three-day course of ceftriaxone alone.
3. A placebo-controlled trial of amoxicillin for the treatment of otitis media.

The hypothesis to be tested in each of these studies is that treatment regimens constituting reduced antibiotic exposure compared to standard courses will be equally effective in curing the illness and will result in fewer emergences of resistance and greater patient and physician satisfaction. These studies will provide a proof-of-principle that such trials can be carried out with National Institutes of Health (NIH) support and will begin to develop the infrastructure to conduct further studies. Each of these trials will employ generic antimicrobial agents. Embedded within each of these trials will be natural history studies to provide critical information for defining therapeutic outcome for these and future studies. The short- or no-treatment arm of each of these studies will be used to define the natural history of each disease. Surveillance cultures will be performed to define the relative risks of colonization by resistant bacteria in each treatment group. In addition, patient and physician surveys can be administered to determine satisfaction with the different treatment regimens.

These recommendations constitute a beginning, serving as a base for additional trials that not only will provide information on natural history and lengths of therapy, but also will promote studies on surrogate markers to better define the need for further antibiotic therapy, so that we may one day arrive at individualized regimens for treating bacterial infections.

Trial #1: Skin and Soft Tissue Infection

A trial comparing the efficacy of three days versus seven-to-10 days of therapy for the treatment of uncomplicated, community-acquired cellulitis.

Define the disease state to be studied – Community-acquired infection and inflammation of the skin and subcutaneous tissue.

State the question(s) that need to be asked – Is three days of antimicrobial therapy sufficient for treating community-acquired cellulitis?

Describe the gap in our current knowledge regarding these questions - The optimal duration of therapy for routine community-acquired cellulitis has not been defined. The IDSA guideline for treatment of skin and soft tissue infections published in 2005 lists no optimal duration of antimicrobial therapy, http://www.journals.uchicago.edu/CID/journal/issues/v41n10/37519/37519.html.

This reticence likely stems from the fact that there are no good studies looking at the question of duration of therapy. As stated by Hepburn, Dooley, et al, in the introduction to their 2004 study comparing five with 10 days of antibiotic therapy for cellulitis: "On literature review, we did not encounter a previous study that compared a short course (<1 week of therapy) with a standard course of therapy, using the same antibiotic, for skin and soft tissue infections." [1] To their credit, these investigators attempted to answer the question and concluded that five days of therapy was similar in effectiveness to 10 days. However, there were several deficiencies in the study. The major problem was that the study took place at a single center, making it difficult to accrue enough patients to be confident that the lack of differences observed were real. Given the relatively small sample size, the 95% CI around the difference of 5 d minus 10 d was -11.4% to +11.7%. This means that we are 95% confident based on the data from this one sample that the true difference between the groups could be as much as 11.4% in favor of the 10 day group to as much as 11.7% in favor of the five day group. There were other issues of inclusion and exclusion criteria that made the study suboptimal. Moreover, the antibiotic that was used in this study was levofloxacin, which most experts would agree is far too broad in its spectrum to be used routinely for simple cellulitis with sub-optimal *Staphylococcus aureus* coverage. Still, it is tantalizing that reducing therapy by 50% may be similarly effective to the standard duration. It is therefore critical that this study be followed by a multi-center, randomized controlled trial to define the minimum duration of therapy for cellulitis. Evaluating the time to resolution of symptoms as part of this trial would allow even more precise estimates of treatment duration.

Describe issues that have complicated study of these questions in the past, and suggest ways in which those issues can be overcome with different study design, etc. – The major problem with this previous study was that it occurred at a single center. In order to study this syndrome correctly, one will need enough patients to detect a less than 10% difference with sufficient power. The Hepburn, et al. study[1] occurred at a single medical center, Brooke Army Medical Center. Although they did not specify the period of enrollment of the study, they were able to evaluate for enrollment 169 patients, 87 of

whom were ultimately evaluated. As they state in their introduction: "The US military alone observed 104,738 cases of cellulitis from January 1998 to December 2001."[1] Using a multi-center design of committed centers, there should be no trouble enrolling the number of patients needed to achieve sufficient power.

A second issue may be the definition of cellulitis. In this instance, we propose that it be defined as non-suppurative skin infection characterized by erythema, warmth, edema, and pain. A small focus of drainable material accompanied by a much larger area of cellulitis, particularly if there are associated systemic signs of inflammation, would be acceptable to include in the cellulitis category. However, the inclusion of abscesses that may respond to incision and drainage or for which the major therapy would be incision and drainage would constitute a heterogeneous mix of cases, including those that zero (0) days of antibiotics might be best.

Define the bottom line need that these studies will address – the yield at the end that will make the study a worthwhile endeavor – This study will allow us to make evidenced-based recommendations for the treatment of cellulitis. This extraordinarily common infection is responsible for the use of large quantities of antibiotics in the U.S., many of which have considerably broader spectra than is required (fluoroquinolones and inhibitor combinations, for example), thereby promoting the emergence and spread of antimicrobial resistance and resulting in potentially unnecessary adverse events for patients. Carefully done studies using generic, narrow-spectrum antimicrobial agents will provide an evidence-based rationale to reduce the use of broad-spectrum antimicrobial agents in the community and hospitals (since patients will frequently be admitted with this condition), thereby reducing both economic and ecological and adverse event-associated costs associated with treating these infections.

Trial #2: Community-Acquired Pneumonia (CAP)

A three-armed trial comparing ceftriaxone alone with ceftriaxone plus azithromycin for the treatment of mild-to-moderate community-acquired pneumonia. Two arms of the study will employ a standard seven-day course of therapy. A third arm of the trial will test the efficacy of a three-day course of ceftriaxone alone.

Define the disease state to be studied – Community-acquired pneumonia defined as infection of the lung parenchyma acquired in the community setting in CAP patients without recent hospitalization.

State the question(s) that need to be asked – There are two questions to be asked. The first is whether three days of antimicrobial therapy is similar in effectiveness to the standard seven-to-10 day course. The second question is whether outcomes are improved by adding antimicrobial coverage for atypical pathogens (*Chlamydia pneumoniae*, *Legionella pneumoniae* and *Mycoplasma pneumoniae*).

Describe the gap in our current knowledge regarding these questions – The optimal duration of antimicrobial therapy for CAP remains unknown. For many years, 10-14 days of therapy was standard. IDSA published CAP guidelines in 1998, 2000, 2003, and 2007. The 2007 guidelines were co-authored with the American Thoracic Society (2007 IDSA/ATS).

When IDSA published its first guidelines for the treatment of CAP in 1998, they stated: "We are not aware of any controlled trials that have specifically addressed the questions of how long pneumonia should be treated." This statement was followed by the statement that patients should be treated for 72 hours after they have become afebrile (evidence level C-III), http://www.journals.uchicago.edu/CID/journal/issues/v26n4/ap63_811/ap63_811.web.pdf. These statements were repeated in the IDSA guidelines published in 2000.

In the most recent IDSA guidelines (2007) which were co-authored with the American Thoracic Society, http://www.journals.uchicago.edu/CID/journal/issues/v44nS2/41620/41620.html, the recommendation had changed: Patients with CAP should be treated for a minimum of 5 days (level I evidence), should be afebrile for 48–72 hours, and should have no more than 1 CAP-associated sign of clinical instability before discontinuation of therapy (level II evidence). (Moderate recommendation.)

A longer duration of therapy may be needed if initial therapy was not active against the identified pathogen or if it was complicated by extrapulmonary infection, such as meningitis or endocarditis. (Weak recommendation; level III evidence.)

These more recent recommendations were not based on randomized controlled trials comparing the same regimen for different lengths of time but rather on a hodgepodge of studies using antimicrobials of different half-lives, licensing studies of new

antimicrobials, and studies funded by pharmaceutical firms to justify different dosing of their agents. In 2006, el Moussaoui et al[2] published a study comparing three days of amoxicillin therapy with eight days. This study, which was carried out in nine Dutch hospitals over a two-year period, randomized 121 patients. Cure rates were similar in the two groups, despite the fact that the pneumonia severity scores were worse in the three-day group at baseline. However, in the intention—to—treat analysis, the difference between the three-day and eight-day groups was consistent with a difference of greater than 10% less effectiveness for the three-day group given the relatively small sample size. However, these initial data are compelling, and need to be confirmed with additional studies in our country with a larger sample size and drugs that are commonly used in the U.S.

Additional circumstantial evidence for the potential efficacy of short-course therapy for serious pneumonias can be found in the recent registration trial for daptomycin in the treatment of pneumonia. In European trials, daptomycin was found to be inferior to comparator for the treatment of pneumonia, whereas in the U.S. it was found to be non-inferior. The primary difference in the trials in the two locations was the extent to which the study population had received a potentially effective antimicrobial agent prior to the administration of daptomycin. In most cases this effective antimicrobial agent was 24 hours or less treatment with ceftriaxone or a respiratory fluoroquinolone. If, as is now understood, daptomycin is ineffective in treating pneumonia because of interaction with alveolar surfactant, then these data suggest that a single dose of an effective antimicrobial agent may be sufficient to treat the majority of pneumonias.

Regarding the type of antimicrobial therapy to be administered, the 2007 IDSA/ATS guidelines for CAP patients admitted to the hospital are shown below:

Inpatient, non-ICU treatment. The following regimens are recommended for hospital ward treatment.

- A respiratory fluoroquinolone (strong recommendation; level I evidence)
- A beta-lactam **plus** a macrolide (strong recommendation; level I evidence) (Preferred beta-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem for selected patients; with doxycycline [level III evidence] as an alternative to the macrolide. A respiratory fluoroquinolone should be used for penicillin-allergic patients.)

These recommendations reflect the consensus on the part of the guideline authors that therapy directed at atypical pathogens is required for CAP. Yet the above results of the Netherlands study would suggest that may not be the case (93% cure rate in each group, none of whom received therapy active against atypical, intracellular pathogens)[2]. Moreover, a systematic review of randomized controlled trials published in 2005 concluded that there was no benefit of atypical coverage in survival or clinical efficacy when treating hospitalized patients with community-acquired pneumonia.[3] On the other hand, a recently published secondary analysis using two comprehensive international databases indicated that atypical pathogens were identified in 20-25% of cases of CAP and that advantages in time to clinical stability, length of stay, total mortality and CAP-

related mortality were demonstrable with combination therapy.[4] The obvious and unavoidable flaws in both study designs (meta-analysis, secondary analysis) make it clear that there is not yet a definitive answer to this question. Under these circumstances, a well-designed, randomized, double-blinded controlled trial is required.

Describe issues that have complicated study of these questions in the past, and suggest ways in which those issues can be overcome with different study design, etc. – As noted above, a randomized, double-blinded controlled trial comparing lengths of therapy has recently been completed. It required a multi-center design and two and one-half years to complete. There is nothing about the design that should be prohibitive for a similar study to be conducted in the United States. It is interesting that a trial comparing beta-lactam therapy with beta-lactam plus a macrolides for CAP has never been attempted. The strength of the IDSA and ATS recommendation for therapy of CAP may create reluctance to enroll patients in this trial. Nevertheless, it will be important to undertake, as we may be substantially over-treating our patients at the present time. Moreover, the perceived need to cover atypical pathogens has been a major driver of overuse of the fluoroquinolones, with the consequent rapid rise in resistance to this class of agents in a variety of Gram-negative rods. The data from such a trial would be important in providing the data for future treatment guidelines.

One issue that has complicated past pneumonia trials has been the issue of surrogate microbiological markers. When testing a new drug, it is important to determine the efficacy of the test agent against the microbe at the site of infections. Since we will be using known effective agents, the need for documentation of microbiological response will be minimized. It will be the clinical response that will be the primary outcome measure.

Define the bottom line need that these studies will address – the yield at the end that will make the study a worthwhile endeavor – This study will inform us about how intensively, and for how long, we need to treat CAP. CAP is a very common illness, and is responsible for a substantial number of hospitalizations in this country. Reductions in our antimicrobial usage for this diagnosis will reduce the selective pressure favoring the emergence and spread of antimicrobial resistance in both the hospital and the community.

Trial #3: Acute bacterial otitis media (ABOM)

A trial comparing the effectiveness (time to resolution of symptoms) of amoxicillin plus analgesics versus azithromycin plus analgesics versus placebo plus analgesics in children aged >6 months of age with middle ear infections.

Define the disease state to be studied – Bacterial infection of the middle ear in children ages ≥6 months.

State the question(s) that need to asked – Is the time to resolution of symptoms in AOM shorter with various antimicrobials plus analgesics versus analgesics plus placebo? If so, what is the magnitude of the treatment effect compared to placebo and which populations are most likely to benefit? If there is a benefit, what is the optimal duration of therapy? How do any benefits of therapy compare to potential harms (e.g. diarrhea, rash, etc.)?

Describe the gap in our current knowledge regarding these questions – Whether antimicrobials are effective in the treatment of acute otitis media remains an unanswered question based on the results of previous placebo controlled trials and meta-analyses. Exploratory subgroup analyses from previous trials have hinted at a greater benefit for children under the age of two years, but this finding has never been confirmed in randomized trials specifically designed to answer this question. In addition, the lack of detailed information on the potential harms of therapy from previous trials has hindered an adequate weighing of risks and benefits in this disease. Finally, if antimicrobials are beneficial, there is little data on the optimal duration of therapy. Limiting the duration of therapy may decrease adverse events as well as decrease the spread of resistance. Given that AOM is the single most common reason for a child to receive antimicrobials as well as one of the most common reasons for anyone in the U.S. to receive an antimicrobial, the public health impact of answering these questions would be large.

Describe issues that have complicated study of these questions in the past, and suggest ways in which those issues can be overcome with different study design, etc. – Five of 10 randomized placebo-controlled trials, which evaluated clinical endpoints in children have failed to provide evidence of a benefit of antimicrobials over placebo in this disease.[5] In trials that did show an effect, the effect size was small (with point estimates on the order of 2%-3% over placebo). Studies of the strategy of "watchful waiting" have had the primary purpose of evaluating parental acceptability of withholding antimicrobials. Therefore, these trials were not blinded and may overestimate the treatment effect of antimicrobials. These "watchful waiting" trials did show that parents would accept withholding antimicrobials, and there were no complications in children who did not receive an immediate course of therapy. Previous meta-analyses combining these trials increased the precision of estimates of effect but did not address the issue of biases inherent in these trials, therefore leaving uncertainty regarding the reliability of their conclusions. The trials that have shown an effect of antimicrobials in AOM as well as those that did not show an effect have had flaws in their design and analysis, including lack of adequate criteria to select subjects with the

disease, lack of standardization of concomitant medications, lack of blinding, unclear and imprecise outcome measures, and exclusion of subjects from the analysis/missing data. All of these issues leave considerable uncertainty regarding the effect of antimicrobials in the treatment of AOM.

While concerns could be raised about the ethics of including a placebo arm in a disease that has, in the past, been associated with severe sequelae (specifically, mastoiditis and meningitis), it should be emphasized that the landscape of downstream complications has changed since the introduction of conjugated vaccines against *Haemophilus influenzae* B and *Streptococcus pneumoniae*. One study showed the incidence of suppurative complication in the absence of antimicrobial therapy to be on the order of 0.12% to 0.24% in developing countries, making the risk to children in a single trial quite small.[5] Previous placebo controlled trials did not show evidence of a difference in suppurative complications between the active treatment and placebo groups, and such complications were rare in both groups. Moreover, there should be ample time to treat a child with antimicrobial agents if the otitis is persistent or worsens, making severe suppurative infections very unlikely. The extent to which antimicrobial agents in the short term would prevent severe suppurative complications is not well established.

Define the bottom line need that these studies will address – the yield at the end that will make the study a worthwhile endeavor – A comparison of various antimicrobials plus standardized analgesics vs. placebo plus analgesics will allow a measurement of the effect of antimicrobials compared to placebo in ABOM. Amoxicillin is the drug of choice in ABOM so should be one of the drugs tested. Azithromycin is a newer drug that is used in children allergic to penicillin and there are questions about the clinical relevance of the relatively weaker *in vitro* potency of this drug against *Haemophilus influenzae*. (Note: An alternative would be to test standard dose amoxicillin versus high dose amoxicillin clavulanate to determine the added benefit of the latter in children infected with *H. influenzae* and penicillin "resistant" *Streptococcus pneumoniae.*) Using time to resolution of symptoms based on patient/caregiver reported outcome criteria would allow determination of the median time to resolution of disease in order to design future trials regarding duration of therapy, if an effect of antimicrobials is measured. The trial should be stratified by age and appropriately powered and designed to evaluate the effects of the two antimicrobials in children above and below the age of two years. Appropriate analysis of adverse events will allow calculation of the number needed to treat to benefit compared to the number needed to treat to harm in order to balance risks and benefits. Measuring of pre- and post-therapy throat swabs in children treated with antimicrobials versus placebo would allow an estimate of the effect of antimicrobials on normal host flora and an estimate of the effect of the potential for spread of resistance.[5]

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