Lower respiratory tract infections have been a major cause of morbidity and mortality among humans since the dawn of history. The initial hope that the era of antibiotics would remove this scourge has been replaced by the more realistic view that although antimicrobial agents represent a major therapeutic advance, they have not yet solved all of the problems of lower respiratory tract infections. The pneumococcus, for example, causes mortality in a certain number of patients despite antimicrobial therapy. An even greater challenge is being imposed by the emergence of antimicrobial resistance among important bacterial pathogens, especially Streptococcus pneumoniae.

Throughout recorded history, pneumonia has been a major cause of morbidity and mortality among humans. Indeed, despite all the advances made by medical science, lower respiratory tract infections are still the most frequent among infectious causes of mortality worldwide. In 1998, the World Health Organization reported >3.7 million deaths due to lower respiratory tract infections [1]. Of all the common causes of human respiratory tract infections, lobar pneumonia, usually due to Streptococcus pneumoniae, is potentially the most dangerous. Indeed, it has likely been a consistent cause of serious infection for thousands of years. Throughout history, there have been intermittent epidemics of other serious pulmonary infections, including the Plague of Athens in the third century B.C., the Black Death due to Yersinia pestis in the Middle Ages, and the Great Influenza Pandemic in 1918 [2]. Recent evidence suggests, but does not prove, that the influenza virus causing the pandemic of 1918 may have been unusually virulent, but to date, it has been impossible to prove that on the basis of DNA samples from victims of that epidemic [3].

With the dawn of the era of antibiotics in the late 1930s and early 1940s, it was widely hoped that serious bacterial pulmonary infections would soon become a thing of the past. Pneumococci were exquisitely susceptible to penicillin and a whole host of new agents including erythromycin, chloramphenicol, tetracycline, and the sulfonamides (especially when combined with trimethoprim). Despite the susceptibility to antimicrobial agents of the pneumococcus, however, antibiotics were not completely successful in preventing early deaths in patients with severe pneumococcal pneumonia [4]. As a result, Dr. Robert Austrian and others championed pneumococcal vaccination as a way to both prevent pneumococcal disease and abrogate the early mortality that antimicrobial agents seemed unable to prevent [4].

It was with some disbelief and then growing concern that the first reports of penicillin-resistant pneumococci began to emerge, initially from New Guinea, then from South Africa [5]. Penicillin resistance in these early strains was only relative, because the MIC of penicillin that inhibited the majority of these relatively resistant strains was still <2 μg/mL. Nonetheless, these modest elevations in MIC resulted in clinical failures when penicillin was used to treat infections in areas relatively deficient in host defenses and into which penicillin pen-
It also appeared highly likely that penicillin (and penicillin derivatives such as ampicillin) and many of the cephalosporins remained effective against these relatively resistant pneumococcal strains, provided the drugs were given in sufficient doses [7]. Concomitant with the widespread emergence of penicillin resistance in pneumococci, multiply resistant strains began to appear, and indeed, strains with resistance not only to β-lactams, but also to macrolides, chloramphenicol, tetracyclines, and cotrimoxazole have been appearing with increasing frequency in various parts of the world [8].

The advent of macrolide resistance in pneumococci was of particular concern because the macrolides have been considered first-line agents in many parts of the world for the treatment of community-acquired pneumonia. As was the case with the relatively penicillin-resistant strains, it was not immediately clear that macrolide resistance was clinically significant. A number of clinical investigators felt that macrolides could still be effective against the majority of “macrolide-resistant” pneumococcal strains, suggesting either that the resistance was irrelevant or that the susceptibility breakpoints were incorrect [9, 10]. Part of the confusion here may have been the result of the fact that there are several mechanisms of resistance to macrolides in pneumococci. Resistance due to efflux mechanisms is often of low level, and indeed, strains with this mechanism may respond to macrolide therapy. Ribosomal modification (usually by methylation of the 23S rRNA binding site for macrolides, or, less commonly, mutations at this site) typically leads to strains that are highly resistant, and most investigators feel that such strains would likely not respond [11, 12]. Differences in geographic distribution of such resistant strains are quite striking. In North America, the majority of macrolide-resistant pneumococci owe their resistance to an efflux mechanism, whereas in Europe, the majority of strains are highly macrolide resistant as a result of ribosomal alteration [13].

Until recently, the majority of resistant pneumococci have remained susceptible to the fluoroquinolones. Although the earlier generations of fluoroquinolones such as norfloxacin and ciprofloxacin had less intrinsic activity against the pneumococcus than did the newer compounds, even ciprofloxacin was successful in treating the majority of pneumococcal respiratory tract infections in the early 1990s. The advent of the newer “respiratory” fluoroquinolones, including levofloxacin, gatifloxacin, moxifloxacin, and others, resulted in a group of compounds that had excellent activity against the pneumococcus and indeed covered all the major respiratory pathogens that cause community-acquired pneumonia. To date, the development of resistance to the fluoroquinolones among pneumococci has been infrequent, but there are areas of the world where resistant isolates have emerged, albeit in relatively low frequency at the present time [14, 15]. Moreover, there have been several anecdotal reports of clinical failure when fluoroquinolones have been used in infections due to fluoroquinolone-resistant pneumococci [16, 17].

The potential emergence of fluoroquinolone resistance among pneumococci is of considerable concern because the fluoroquinolones, as previously noted, provide excellent coverage against the majority of respiratory tract pathogens. Indeed, in addition to standard bacteria such as the pneumococcus and H. influenzae, the fluoroquinolones also have outstanding activity against the agents that cause so-called atypical pneumonia, including Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella pneumophila. It has been somewhat difficult to assess the contribution of activity against the atypical pathogens in the management of community-acquired pneumonia, but a recent study suggests that fluoroquinolones may be superior to cephalosporin therapy in this setting, and part of that superiority may relate to the activity of these compounds against atypical pathogens [18].

The 3 articles that follow define clearly the important issues faced by researchers and clinicians who study and attempt to devise solutions to the problems posed by increasing resistance among pneumococci and other important respiratory tract pathogens. In the first article, Clyde Thornberry and his colleagues present data from the TRUST Surveillance Program [19]. This program began monitoring antimicrobial resistance among important respiratory pathogens in the United States in 1996 and now contains valuable longitudinal data on resistant pathogens in the United States. The authors clearly show that there are differences in prevalence of antimicrobial resistance among pneumococci by region in the United States. Penicillin resistance is lowest in New England and highest in the South Atlantic region. They also clearly show that penicillin-resistant pneumococci tend to exhibit resistance to multiple antimicrobials including macrolides and trimethoprim sulfamethoxazole.

In the second article, Thomas M. File Jr. documents the explosive increase in penicillin resistance among pneumococci in the United States that has occurred during the past decade [20]. In addition, he cites data that suggest that the mortality from pneumococcal pneumonia in the United States is unchanged during the past decade. Moreover, he provides evidence that suggests (but falls short of proving) that patients infected with penicillin-resistant pneumococcal strains have a greater risk of supplicative complications and in-hospital death due to pneumonia than those infected with susceptible strains. However, only the risk of supplicative complications reached statistical significance when adjustments were made for baseline differences in severity of illness.

Finally, Joseph P. Lynch III and Fernando J. Martinez discuss the contribution of macrolide resistance to outcome in patients with pneumococcal respiratory tract infections [21]. They examine carefully the factors that contribute to mortality in pa-
tents with bacterial pneumonia and note that these factors also contribute to the difficulty in proving the clinical significance of macrolide resistance. They provide data on 21 patients with bacteremic pneumococcal infections that failed to respond to therapy with macrolides and subsequently responded to other antibiotics, strongly suggesting (but falling just short of absolutely proving) the clinical significance of macrolide resistance in pneumococci. Nonetheless, their data suggest that it should be taken seriously. There can be little doubt that growing resistance to antimicrobials among respiratory pathogens is a serious problem.

Numerous studies detail the relationship between antimicrobial use and the emergence of resistance in pneumococci and other streptococci [22, 23]. Studies from France clearly demonstrate that prolonged courses of subtherapeutic concentrations of penicillins are associated with emergence of penicillin resistance in pneumococci in children in day-care centers [22]. It is also clear that much of our outpatient use of antimicrobials for “respiratory tract infections” in both adults and children is inappropriate [24]. A recent survey of doctors clearly suggests that there are a number of factors that drive the inappropriate use of antibacterial agents for nonbacterial infections [25]. Factors such as purulent discharge, diagnostic uncertainty, patient request, and fever were all cited by doctors as reasons to give antimicrobial agents for respiratory tract infections. Interestingly, in this study [25], drug “detailing” by pharmaceutical representatives was cited by only 7%. Although this may be an underestimate, it was clear that much of the blame for overuse of antimicrobial agents can be placed directly at the doorstep of the medical profession. We clearly need to do a better job of finding and heeding criteria for appropriate use of antimicrobials if we wish to prolong the lives of these important and life-saving drugs.

References