Valadas and Antunes also raise questions regarding the history of HIV-2 discovery, which we wish to clarify. HIV-2 was first identified in a group of healthy Senegalese commercial sex workers by Barin and colleagues in 1985 on the basis of serologic cross-reactivity to simian T-lymphotropic virus–3 with altered seroreactivity to human T-lymphotropic virus–3 [6]. As noted by Clavel and colleagues in 1986, serologic reagents from reactive Senegalese women were used to type the described isolates [7]. In 1987, a special WHO working group designated HIV-2 to accommodate the variety of virus names including lymphadenopathy-associated virus–2, SBL-6669, and human T-lymphotropic virus–4 [8]. The original Senegalese sex workers described in 1985 have been part of a 19-year prospective study of HIV-2 pathogenesis, immunity, and, more recently, antiretroviral treatment. In fact, the lowered transmission potential and decreased time to disease progression with HIV-2 infection was first described in this cohort of HIV-2 infected women, along with many other unique biological and clinically relevant features of HIV-2 infection [9–12]. We are in complete agreement with Valadas and Antunes on the need for further studies to determine the optimal course of treatment for HIV-2-infected individuals.

Acknowledgment


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References


Snr—In his recent editorial in the journal, McGowan [1] noted the emergent situation regarding antimicrobial resistance among bacteria in both the hospital and other patient care settings. He recognized that bacterial drug resistance has many consequences to patients and to society. Increased infection-associated morbidity and mortality, decreased utility of antimicrobial agents for future generations of infected patients, and the consequent eco-
nomic impact of caring for patients infected with drug-resistant bacteria are extremely important issues.

Antibacterial resistance places a particularly high financial burden on private and governmental health payer systems in the United States. Alarmingly, at the same time that we are recognizing the importance of increasing antimicrobial resistance to individual patients and to society as a whole, there has been a diminishing effort in research and development of new antimicrobial agents to combat such bacteria. Presently, fewer than 5 antimicrobial agents are in phase 3 clinical development, and there are only ~10 undergoing preclinical assessment. Few large pharmaceutical companies remain interested in developing new antimicrobial agents [2].

Fluoroquinolones are one of the few antibacterial classes predictably active against Streptococcus pneumoniae, an organism long known as the “old man’s friend.” This may be a misguiding assumption, however, if one believes data being promulgated by some studies. The reason behind the perception of maintained levofloxacin activity (as well as the activity of other “respiratory” fluoroquinolones) is the yardstick used to determine drug susceptibility and resistance. Current NCCLS interpretive criteria state that only pneumococci with an MIC of ≥8 μg/mL are considered to be levofloxacin resistant, whereas those with an MIC of ≤2 μg/mL are considered to be susceptible to levofloxacin [3].

Recent evidence from Canada by Lim et al. [4] demonstrated that, of the strains that are regarded as levofloxacin susceptible, 59% possessed a single-step mutation in their quinolone resistance–determining region (QRDR), which can easily mutate to further levels of fluoroquinolone nonsusceptibility with MICs of >4 μg/mL. Microbiological surveillance studies, such as the SENTRY Antimicrobial Surveillance Program and the TRUST Surveillance Program, have expressed these data as a function of their MIC population statistics. SENTRY program data have shown a steady increase in levofloxacin nonsusceptibility (from 0.5% to 1.5% of isolates) during a 4-year period; however, the percentage of levofloxacin-intermediate strains and the level of single-step mutants within the population of susceptible strains are rarely reported [5]. Susceptibility levels of S. pneumoniae to levofloxacin, as measured by the MIC90 (TRUST III-VI), increased from 0.5 to 1 μg/mL [6]. Data from the IPD survey of S. pneumoniae corroborate these findings [7], further highlighting the unrecognized emergence of decreasing susceptibility of pneumococci in lower respiratory tract infections in the community. Moreover, Bhavnani et al. [8] demonstrated an association between decreased pneumococcal susceptibility to levofloxacin and increased levofloxacin use within institutions and geographic areas participating in the SENTRY program (1997–2002), with median MICs being as much as 126% higher in areas with greater levofloxacin consumption, compared with regions with lower consumption.

As pneumococci gather mutations, from either fluoroquinolone selection pressure or possible horizontal gene transfer from viridans group streptococcal species [9], they become less susceptible to the more potent members of the class, such as gatifloxacin, gemifloxacin, and moxifloxacin [10]. Davidson et al. [11] have shown the development of fluoroquinolone cross-resistance after clinical exposure to less potent members of the class that raises the possibility of clinical failure even when more-potent agents are prescribed. There have been >25 clinical case reports in the literature describing clinical failures with ciprofloxacin and levofloxacin while the patient had been receiving therapy; these have been concurrent with the emergence of highly resistant strains following suboptimal initial therapy [12–14]. None of these isolates would have been detected, even after their initial QRDR target mutation, using the current NCCLS MIC susceptibility breakpoints for levofloxacin [3].

Brueggemann et al. [15] have longitudinally examined strains of S. pneumoniae since 1994 from over 25 sites in the United States, and they have noted a continual increase in both single-step mutations and multiple-step mutants. The latter likely render most fluoroquinolones, with the possible exception of gemifloxacin, clinically inadequate. The worst-case scenario would be if we allowed this inexorable increase to continue unabated without any effort to recognize the changes or to recommend an alternative diagnostic and therapeutic approach.

McGowan [1] listed several measures to help us turn the resistance tide in our favor. These included promoting a vaccine against multidrug-resistant S. pneumoniae, validating laboratory methods to detect resistance, bench-marking resistance patterns, improving educational programs, decreasing antimicrobial selective pressure by improving antimicrobial use, and encouraging the development of new antimicrobials to fill emerging therapeutic gaps. The latter is proving extremely unlikely, because many large pharmaceutical companies have ceased such efforts. It has been the smaller research-based companies that have stepped up in an effort to fill these gaps [2].

Because the effort being put into new antimicrobial research is diminishing and the microbes appear to be winning the battle that started with the introduction of penicillin more than a half-century ago, we must address these cited issues before we run out of adequate empirical agents for use against community-acquired respiratory tract infections. Time is not on our side, and let us hope that it is not already too late for the fluoroquinolones and the treatment of infections caused by the “old man’s friend.”

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**References**


**Reply to Ambrose et al.**

Sir—Ambrose et al. [1] present detailed information about the emergence of resistance to fluoroquinolones in *Streptococcus pneumoniae*. They highlight 2 aspects that I agree are of critical concern, especially from a public health point of view. These are (1) minimization of adverse medical events that are associated with laboratory testing and reporting of antimicrobial agent susceptibility, and (2) improvement in the development of new antimicrobial agents.

Problems in interpreting susceptibility testing results for *S. pneumoniae* are discussed by Ambrose et al. [1]. Difficulties in testing and interpretation of susceptibility data also continue to develop for other bacteria [2]. For example, organisms with some resistance profiles are difficult to detect using automated susceptibility testing and disk diffusion [3–5]. Likewise, resistance to expanded-spectrum cephalosporins in strains of *Enterobacteriaceae* containing extended-spectrum β-lactamases (ESBLs) can be difficult to detect using routine antimicrobial susceptibility test methods [5], and many other types of non-ESBL β-lactamases, such as AmpC enzymes, continue to pose problems of detection and interpretation [6]. These problems illustrate how new facets of clinical resistance continue to challenge microbiology service providers [2]. When resistance is not accurately detected or reported, patient care may well suffer, as Ambrose et al. [1] describe for infections with *Streptococcus pneumoniae*. This laboratory-related aspect of preventing medical errors deserves more attention than it has received to date.

Second, Ambrose et al. [1] highlight the crucial need for development of new antimicrobials by focusing on *S. pneumoniae* resistance to fluoroquinolones. I am concerned as well about the lack of new drugs for treatment of infection with strains of *Acinetobacter baumanii* and *Pseudomonas aeruginosa* that are resistant to all of the antimicrobial agents that usually are tested [7]. The pharmaceutical industry and the private sector traditionally have done a superb job of developing new antimicrobials. However, many companies now are abandoning development of these drugs [8]. In a setting in which maximum (“blockbuster”) profit is the major determinant of industry action, this decision is said to be reasonable and proper. Nevertheless, this free-market approach ignores the needs of patients and public health [9].