

Trends in Ciprofloxacin Nonsusceptibility and Levofloxacin Resistance among *Streptococcus pneumoniae* Isolates in North America

Jones and Pfaller recently reported on macrolide and fluoroquinolone resistances among *Streptococcus pneumoniae* isolates from 36 North American laboratories participating in the SENTRY Antimicrobial Surveillance Program from 1997 to 1999 (3). Their report is one of several recent publications claiming to support the observations of Canadian investigators Chen et al. (1), who found associations between ciprofloxacin nonsusceptibility (MIC ≥ 4 $\mu\text{g/ml}$) and penicillin resistance in elderly patients (age ≥ 65 years) and increased fluoroquinolone prescription volumes (1). The work of Chen et al. (1) has met with considerable response from the medical community and is now commonly cited by authors of studies describing fluoroquinolone activities against pneumococci. A closer examination of the Jones and Pfaller study, however, demonstrates why care must be exercised when comparing data from disparate surveillance studies.

The Jones and Pfaller study found that among pneumococcal isolates, ciprofloxacin nonsusceptibility was essentially unchanged between 1997-1998 (mean nonsusceptibility, 1.9%; range, 1.7 to 2.4%) and 1999 (mean nonsusceptibility, 2.0%; $P = 0.82$; χ^2 analysis), while levofloxacin resistance increased significantly, from 0.2 to 0.3% in 1997-1998 to 0.9% in 1999 ($P = 0.002$) (3). Although Chen et al. reported similar rates of ciprofloxacin nonsusceptibility in 1997 (1.7%) and 1998 (1.8%) (1), Jones and Pfaller's finding that ciprofloxacin nonsusceptibility and levofloxacin resistance are evolving at different rates is perplexing and may not correlate with the data of Chen et al., which showed that of 75 isolates with reduced susceptibility to ciprofloxacin, only one-third were levofloxacin-resistant (MIC ≥ 8 $\mu\text{g/ml}$), a resistance rate of 0.3% (25 of 7,551 isolates) (1). Chen et al. did not discuss yearly trends in levofloxacin resistance for isolates included in their study (1). One possible explanation for the above-mentioned disparity may be the low numbers of levofloxacin-resistant isolates (<15 isolates/year) in the Jones and Pfaller study, which may make meaningful analysis difficult and certainly requires some caution in its interpretation.

A major finding of Chen et al. was the association between ciprofloxacin nonsusceptibility and fluoroquinolone prescription volumes based on IMS prescription rate data (1). The Jones and Pfaller report cannot support this finding, as it did not contain any usage data. Nor can two other publications cited by Jones and Pfaller in support of Chen et al. (based on a trovafloxacin surveillance study conducted in 1997-1998 and 1998-1999 in the United States) (3; R. N. Jones, D. J. Biedenbach, D. M. Johnson, and The Trovafloxacin Study Group, Abstr. 99th Gen. Meet. Am. Soc. Microbiol., abstr. C-421, p. 191, 1999), as these also provide no usage data. Moreover, these studies appear to report only four ciprofloxacin MICs for the 3,049 isolates tested in 1997-1998 (4) and none for the 4,588 isolates from 1998-1999 (Jones et al., Abstr. 99th Gen. Meet. Am. Soc. Microbiol., 1999). It should also be noted that the fluoroquinolone prescription data described by Chen et al. (1) did not include levofloxacin, as it was not marketed in Canada during the period in which the data were collected (1988-1997) (1). The effects (if any) of these inconsistencies on meaningful analysis and comparison are unclear; however, the

value of Jones and Pfaller's contribution would be greatly enhanced if these differences were noted and explained.

Another problem arises in comparing a wholly Canadian study like that of Chen et al. with a study that combines Canadian and U.S. data like the Jones and Pfaller study. There is evidence to suggest that clear differences may exist between pneumococcal isolates from Canada and the United States (1, 6, 7), as Pfaller et al. were careful to point out for other pathogens in a previous publication (5). It would have been interesting to see the Jones and Pfaller data from Canada and the United States analyzed separately, as well as together, as this conflation could have contributed to some of the inconsistencies in the study.

The Chen et al. study itself has been challenged recently. In a 1997-1998 surveillance study, it was found that among 5,640 pneumococcal isolates collected from across the United States, only 0.3% had ciprofloxacin MICs of ≥ 4 $\mu\text{g/ml}$ (6), and ciprofloxacin MIC distributions appeared essentially unchanged compared to those reported in the 1980s (6). A second Canadian surveillance study conducted during 1997-1998 found that 1% of isolates (12 of 1,180 isolates) were ciprofloxacin nonsusceptible (a finding similar to that of Chen et al.) but did not identify differences in fluoroquinolone activities against *S. pneumoniae* stratified into penicillin-susceptible, -intermediate, and -resistant groups; in fact, levofloxacin resistance was not identified among penicillin-resistant or -intermediate isolates (7). The results of both of these studies contrast sharply with those of Chen et al. The suggestion by Jones and Pfaller that this second Canadian study supports the Chen et al. observation that elevated quinolone resistance rates occur among older patients also appears unfounded. Further inconsistencies identified in the analysis of Chen et al. (5), as well as their acknowledgment by the Canadian investigators, have been previously published (2).

As we seek to improve our understanding of antibiotic resistance mechanisms and trends, researchers must be willing to examine preceding reports critically, avoid the assumption that all new data will follow earlier observations and trends, and appreciate that subtly or overtly overstating resistance may have as negative an impact as understating it. This is especially important in the complex and often misunderstood area of the antipneumococcal activities of fluoroquinolones.

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Authors' Reply

We agree with the concerns of Karlowsky et al. that surveillance data must be analyzed critically and that resistance trends should not be overstated. However, we do not agree with their (over) analysis of our recent report (4). Simply stated, we presented data representing consecutive isolates of *Streptococcus pneumoniae*, all of which were from the same participant sites each year and tested in a central laboratory using reference methods (6). Our data regarding resistance rates for ciprofloxacin and levofloxacin and the relationship with levels of penicillin susceptibility do in fact parallel those of Chen et al. (1). Furthermore, we confirmed the levofloxacin-resistant phenotype by identifying specific point mutations in the quinolone-resistance determining region of the isolates genome. We chose to report our results as North American data (United States and Canada combined), but the same trend was noted upon further stratification and steady trends toward resistance were observed in all SENTRY-monitored hospitals in the Western Hemisphere from 1997 to 2000 (8,364 strains), although the numbers of isolates were modest (3). It is curious that Karlowsky et al. criticized our report for comparing combined U.S. and Canadian data with strictly Canadian data and then state that a U.S. study (performed by Sahm et al., i.e., a study of which several of them were coauthors) (7, 8) does not support the emerging fluoroquinolone resistance trends described by Chen et al. (1). In fact, their publication (7) clearly demonstrates a statistically significant increase in levofloxacin resistance (0.1 to 0.6%; $P < 0.05$) from the 1997-1998 season to the 1998-1999 season. Also, the data presented by Zhanel and colleagues (8) principally illustrated that ciprofloxacin resistance among *S. pneumoniae* had emerged in Canada in their sample, confirming the work of Chen et al. (1), who also noted the well-recognized association with older patients (2). Further, their analysis of two trovafloxacin surveillance

studies (1997-1998 and 1998-1999; more than 6,000 strains from the same sites (more than 200 sites in the United States) was not correct (6; R. N. Jones, D. J. Biedenbach, D. M. Johnson, and The Trovafloxacin Study Group, Abstr. 99th Gen. Meet. Am. Soc. Microbiol., abstr. C-421, p. 191, 1999). In this trial only trovafloxacin-resistant strains were referred for molecular analysis and the trovafloxacin resistance among *S. pneumoniae* increased from <0.2% (four strains; mutations in *gyrA* and *parC*) to 0.5% (14 strains) in only 1 year.

It is true that our study and most of the other studies demonstrating increased resistance rates of any drug class did not have antimicrobial use data, but this does not invalidate the resistance rates that were observed. This is especially true if the study sites are kept stable over the longitudinal sampling intervals; few studies have accomplished this task (3-5; Jones et al., Abstr. 99th Gen. Meet. Am. Soc. Microbiol.). It is well known that fluoroquinolone usage has increased markedly (in the United States and Canada) because of the broad-spectrum applicability and potency of these drugs against pathogens causing community-acquired respiratory tract infections. Usage of these drugs has been escalated by the recent introduction of agents highly active against *S. pneumoniae* (gatifloxacin, moxifloxacin, and trovafloxacin). It is not a far stretch to suggest that there may be a relationship between usage and resistance, as was implied by the Canadian study (1) and by several studies in the United States (3-5; Jones et al., Abstr. 99th Gen. Meet. Am. Soc. Microbiol.).

The bottom line here is that fluoroquinolone resistance data from surveillance studies in addition to that of Chen et al. (1) have also documented fluoroquinolone resistance creep. The fact (if true?) that other studies might fail to show this same trend is worth noting and deserving of further analysis. The crux of antimicrobial resistance surveillance is the observance of what happens over time (i.e., trends), so continued efforts using reference-quality testing methods (not less-controllable commercial system results), validation of reported quantitative resistance data, and molecular confirmation of phenotypic resistance must continue, with cooperation among the monitoring networks. This should lead to the rapid sharing of derived information with the interested parties in clinical practice (4), federal agencies, professional societies, and industry.

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