

Predicting Hospital Rates of Fluoroquinolone-Resistant *Pseudomonas aeruginosa* from Fluoroquinolone Use in US Hospitals and Their Surrounding Communities

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Rates of fluoroquinolone resistance among *Pseudomonas aeruginosa* in hospitals are increasing, but inter-hospital variability is great. We sought to determine whether this variability correlated to fluoroquinolone use in hospitals and in the surrounding community. Hospital quinolone use in 1999 (24 hospitals) through 2001 (35 hospitals) was determined from billing records. The number of fluoroquinolone prescriptions within a 10-mile (~16-km) radius of each hospital was determined for 1999 and 2000. Hospital fluoroquinolone use increased from 1999 through 2001, from 137 to 163 defined daily doses (DDD)/1000 patient-days ($P = .01$). The rate of community fluoroquinolone use also increased, from 2.3 to 2.8 DDD/1000 inhabitant-days ($P < .001$). Rates of fluoroquinolone-resistant *P. aeruginosa* increased from 29% in 1999 to 36% in 2001 ($P = .003$). Both community and hospital fluoroquinolone use were predictive of rates of fluoroquinolone-resistant *P. aeruginosa*. Levofloxacin was associated with resistance, but ciprofloxacin was not. Most of the variability in resistance rates is explained by volume of fluoroquinolone use, both in the hospital and the surrounding community.

Fluoroquinolone antibiotics have potent activity against a broad spectrum of pathogenic bacteria and are safe and effective for many community- and hospital-acquired infections [1]. Ciprofloxacin, in particular, is effective for treatment of serious nosocomial infections, including those caused by *Pseudomonas aeruginosa* [1, 2]. Newer fluoroquinolones, including levofloxacin, gatifloxacin, and moxifloxacin, have improved activity against *Streptococcus pneumoniae*, including strains that

are resistant to penicillin, and use of these fluoroquinolones has increased substantially in the community for treatment of respiratory tract infections [3–5].

Epidemiologic investigations and case reports link community fluoroquinolone use to fluoroquinolone-resistant *S. pneumoniae* [6–8]. In US hospitals, there is also an association between community sales of fluoroquinolones and the prevalence of ciprofloxacin-resistant *P. aeruginosa* in intensive care units [9]. Furthermore, retrospective studies in multiple-hospital networks have found a positive association between increasing use of fluoroquinolones and fluoroquinolone-resistant *P. aeruginosa* [10, 11]. The Centers for Disease Control and Prevention (CDC) reports that the increase in hospital rates of fluoroquinolone-resistant *P. aeruginosa* is second only to the rate for methicillin-resistant *Staphylococcus aureus* [12]. This is especially worrisome, because fluoroquinolone resistance in *P. aeruginosa* is linked to resistance for unrelated antibiotics [9, 13, 14].

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Unfortunately, there are few new drugs in development for the treatment of resistant gram-negative bacterial infection [15].

Antimicrobial resistance in a hospital is believed to reflect the impact of 3 variables: hospital antimicrobial use, cross-transmission of resistant strains, and introduction of antimicrobial-resistant organisms from the community [16]. However, these relationships have been difficult to quantify, in part because antimicrobial use data in the community and in hospitals are not readily available. We measured fluoroquinolone use in a network of US hospitals during a 3-year period (1999–2001). We also measured fluoroquinolone use in the communities surrounding these hospitals for 2 years, from March 1999 through February 2001. The purpose of this study was to determine whether both sites of use were independently and significantly associated with hospital rates of fluoroquinolone-resistant *P. aeruginosa*.

METHODS

Hospital antibiotic use in the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE)–MediMedia Information Technology (MMIT) Antimicrobial Monitoring Network. SCOPE is a nosocomial bacteremia surveillance network involving ~40 medical-surgical hospitals throughout the United States [17]. SCOPE is coordinated at Virginia Commonwealth University in Richmond, Virginia. MMIT (Yardley, PA; <http://www.mminfotech.com>) performs detailed patient-level analyses of drug use in ~70 US nongovernment hospitals and links drug use to hospital and patient demographic data. The SCOPE-MMIT Antimicrobial Surveillance Network is an alliance between SCOPE and MMIT, and the network has measured inpatient antibiotic use, beginning with 19 MMIT hospitals in 1999 and expanding to 45 hospitals in 2004. All inpatient antibiotic dispensing data are electronically extracted from billing records. Drug identity is determined from recognition of codes from the Uniform System of Classification (IMS). Antibiotic use is identified by recognition of antibacterial drugs (code 15000), antiviral drugs (code 82000), and antifungal drugs (code 38000). For this report, patient-level data were aggregated for “hospital wide” antimicrobial use. The total number of grams of individual antibiotics and total patient-days (PD) are used to calculate the defined daily dose (DDD)/1000 PD [18, 19]. The DDVs for ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin used in this study were 1000 mg, 500 mg, 400 mg, and 400 mg, respectively.

The database is validated at each new hospital from random patient profiles that detail all demographic characteristics, diagnoses, procedures, and drugs used by the patient. These sample profiles are sent to each hospital to confirm that all recorded information for individual patients has been received by MediMedia and interpreted accurately.

This study received an expedited review and was approved

by the Institutional Review Board of Virginia Commonwealth University.

Hospital demographic data. Demographic data for the year 2000 were obtained from the MediMedia database, the American Hospital Directory [20], and Hospital Select [21]. Hospitals are geographically dispersed over the whole United States, with 33% of hospitals in the East, 13% in the West, 13% in the Midwest, and 41% in the South [22]. Members of the Council of Teaching Hospitals and Health Systems [23] were designated as teaching hospitals.

Community fluoroquinolone use. The number of community prescriptions in the United States for fluoroquinolone antibiotics and the mean number of doses prescribed from March 1999 through February 2001 were obtained from IMS Health (<http://www.imshealth.com>) in conjunction with its Xponent database. IMS Health measures and assesses prescription and nonprescription drug use world wide. Xponent provides aggregated information about use trends and total prescription volume. Fluoroquinolone prescriptions were tabulated by individual zip codes. Fluoroquinolone use during January and February 1999 was estimated from the slopes of drug use during March and April 1999. Fluoroquinolone use for March 2001 was estimated by extrapolating use from January and February 2001.

The density of community fluoroquinolone use surrounding each hospital was estimated using Zipfind.net (Bridger Systems). All zip codes within a 5-mile (~8-km) and 10-mile (~16-km) radius of the zip code of each SCOPE-MediMedia hospital were identified. The mean number of tablets per prescription, number of prescriptions, and tablet strength were used to estimate total number of grams dispensed. The population in each zip code was determined from data from the 2000 Census and used to calculate the number of DDDs per 1000 inhabitant-days for each antibiotic, as recommended by the World Health Organization (<http://www.whocc.no/atcddd/>).

Measurements of fluoroquinolone susceptibility for *P. aeruginosa*. Antibiograms for 1999–2001 were requested from all hospitals. We requested the methodology used to determine antimicrobial susceptibility, as well as policy toward duplicate isolates and surveillance cultures in the construction of the annual antibiogram. Antibiograms were constructed using NCCLS guidelines for the Kirby-Bauer disk diffusion method or by Vitek (bioMérieux) or MicroScan (Dade Behring) automated susceptibility testing. For hospitals that reported susceptibilities by unit or infection site (e.g., blood), data were aggregated so that rates of resistance included all clinical sources. Most hospitals reported fluoroquinolone susceptibility for *P. aeruginosa* using ciprofloxacin. Levofloxacin susceptibility was reported by 2 hospitals during 1999, by 4 hospitals during 2000, and by 3 hospitals during 2001.

Statistical analysis. Repeated-measures analysis of vari-

ance assessed the significance of changes in antibiotic use and changes in fluoroquinolone susceptibility in hospitals for which data were available from 1999–2001. Least-squares linear regression was used to examine the univariate relationship between fluoroquinolone use in hospitals and in communities, as well as selected hospital demographic data, to rates of fluoroquinolone-resistant *P. aeruginosa*. We then used multiple linear regression to assess the significance of combined hospital and community fluoroquinolone use and the rates of fluoroquinolone-resistant *P. aeruginosa* during 1999 and 2000. The program JMP IN, version 4.0.4 (SAS Institute), was used for all analyses. A *P* value of <.05 was considered to be statistically significant. All tests were 2-tailed.

RESULTS

Hospital demographic data. All hospitals were general medical-surgical institutions, except for 1 women and children’s hospital (table 1). Data from this hospital are not included in the statistical analysis but do appear in the figures to contrast fluoroquinolone use and rates of resistance. There were no significant associations between hospital demographic data and rates of fluoroquinolone-resistant *P. aeruginosa*.

Hospital fluoroquinolone use. The mean hospital fluoroquinolone use across all hospitals, by quarter, is seen in figure 1. The mean total amount of fluoroquinolone use (\pm SD) during 1999 was 132 ± 54 DDD/1000 PD (24 hospitals). Use increased to 140 ± 71 DDD/1000 PD in 2000 (35 hospitals) and to 155 ± 69 DDD/1000 PD in 2001 (35 hospitals). Paired fluoroquinolone use data was available for 18 hospitals from 1999–2001, and the increase from 137 ± 57 DDD/1000 PD in 1999 to 163 ± 75 DDD/1000 PD in 2001 was statistically significant (*P* = .01). There is a seasonal increase in total fluoroquinolone use during the fourth quarter of each year and the subsequent

first quarter. There was marked variability across hospitals in total fluoroquinolone use and in use of specific agents. From 1999 through 2001, levofloxacin use increased from 88 ± 55 to 132 ± 77 DDD/1000 PD, and ciprofloxacin use decreased from 39 ± 35 to 28 ± 25 DDD/1000 PD. In hospitals for which paired data were available, the increase in levofloxacin use was significant (*P* = .0006), but the decrease in ciprofloxacin use was not (*P* = .14). As a percentage of total fluoroquinolone use, the rate of levofloxacin use increased from 64% in 1999 to 82% in 2001; ciprofloxacin use decreased from 28% to 17% during the same period.

Community fluoroquinolone use. The mean rate of community fluoroquinolone use surrounding all 35 hospitals, by quarter, is seen in figure 2. The mean total rate of fluoroquinolone use in communities increased from 2.59 DDD/1000 inhabitant-days in the first quarter of 1999 to 3.39 DDD/1000 inhabitant-days in the first quarter of 2001. Ciprofloxacin use remained steady over this time and exceeded use of levofloxacin until the first quarter of 2001. Levofloxacin use gradually increased over the same period, with the greatest increases in use occurring during the fourth quarter and the subsequent first quarter of the following year. Gatifloxacin and moxifloxacin use increased after their introduction into the US market, contributing to the increase in total fluoroquinolone use.

The mean total rate of fluoroquinolone use during 1999 within a 10-mile radius of each hospital was 2.3 ± 0.6 DDD/1000 inhabitant-days and increased during 2000 to 2.8 ± 0.7 DDD/1000 inhabitant days (*P* < .0001). The mean rate of ciprofloxacin use (\pm SD) did not change significantly between 1999 and 2000 (1.5 ± 0.4 to 1.5 ± 0.4 DDD/1000 inhabitant days). The mean rate of levofloxacin use (\pm SD) during the same period increased significantly, from 0.8 ± 0.4 to 1.1 ± 0.4 DDD/1000 inhabitant-days (*P* = .0001). The volume of to-

Table 1. Hospital demographic data during the year 2000 for 34 hospitals in the Surveillance and Control of Pathogens of Epidemiologic Importance–MediMedia Network.

| Characteristic | Mean \pm SD | Median (range) |
|--|-----------------------|----------------------------|
| No. of admissions | 15,741 \pm 10,750 | 13,320 (1,593–42,417) |
| No. of patient-days | 77,459 \pm 61,060 | 61,785 (12,115–239,147) |
| Age, years | 53.2 \pm 5.4 | 55 (41.2–65.2) |
| Case mix index | 1.52 \pm 0.26 | 1.55 (0.92–2.10) |
| Length of hospital stay, days | 6.23 \pm 1.05 | 6.00 (4.0–8.4) |
| No. of staffed beds | 331 \pm 190 | 290 (62–866) |
| No. of occupied beds | 230 \pm 159 | 182 (28–658) |
| No. of intensive care unit beds | 24 \pm 24 | 16 (0–119) |
| No. of surgeries per 1000 admissions | 288 \pm 101 | 294 (70–500) |
| Population in 10-mile (i.e., ~16-km) radius around each hospital | 724,622 \pm 768,938 | 519,938 (11,820–3,078,812) |

NOTE. Table excludes data from a single women and children’s hospital at which the mean age of patients was 14.3 years.

tal fluoroquinolone use in the community (the number of DDDs per 1000 inhabitant-days in a 10-mile radius) was unrelated to total hospital fluoroquinolone use (number of DDDs per 1000 PD) during 1999 ($R^2 = .004$; $n = 23$) or 2000 ($R^2 = .002$; $n = 34$).

Fluoroquinolone-resistant *P. aeruginosa* and fluoroquinolone use. Antibigrams that reported rates of fluoroquinolone-resistant *P. aeruginosa* were available from 21 hospitals for 1999, 28 hospitals for 2000, and 32 hospitals in 2001. The median number of fluoroquinolone-resistant *P. aeruginosa* isolates was 263 (range, 41–1600) for year 2001. Rates of resistance in these hospitals increased from a mean of 29% in 1999 (median, 27%; range, 11%–45%) to 36% in 2000 (median, 35.5%; range, 12%–61%) and to 38% in 2001 (median, 36%; range, 12%–60%). Paired antibigrams were available for 18 hospitals, and rates of resistance increased significantly, from 29% in 1999 to 33% in 2000 and 36% in 2001 ($P = .003$).

Univariate analysis revealed a significant association between total hospital fluoroquinolone use and rates of fluoroquinolone-resistant *P. aeruginosa* for the years 2000 ($R^2 = .34$; $P = .001$; 28 hospitals) and 2001 ($R^2 = .35$; $P = .001$; 27 hospitals). This relationship did not reach significance for 1999 ($R^2 = 0.21$; $P = .066$), but only 17 hospitals had data available for analysis. When individual fluoroquinolones were examined, ciprofloxacin use was not associated with resistance. However, for the years 2000 and 2001, the association between levofloxacin use and resistance was statistically significant ($R^2 = .38$ [$P = .0006$] and $R^2 = .39$ [$P = .0008$], respectively) (figure 3).

Community fluoroquinolone use was also associated with fluoroquinolone-resistant *P. aeruginosa*. The correlations be-

tween fluoroquinolone use and resistance were consistently greater for a 10-mile radius than for a 5-mile radius (data not shown). Although ciprofloxacin was the dominant fluoroquinolone, its use did not correlate with rates of resistant *P. aeruginosa* for 1999 ($R^2 = .12$) or 2000 ($R^2 = .08$). There was, however, a significant correlation between levofloxacin use in the community and hospital rates of resistant *P. aeruginosa* for the years 1999 ($R^2 = .56$; $P = .001$) and 2000 ($R^2 = .25$; $P = .008$) (figure 4).

For 1999–2001, the women and children’s hospital had the lowest rate of fluoroquinolone use and a low rate of fluoroquinolone-resistant *P. aeruginosa* (figure 3). In contrast, the rate of community fluoroquinolone use surrounding this hospital was average (figure 4).

A multiple regression model showed that 2 predictor variables (total rate of fluoroquinolone use [i.e., sum of levofloxacin and ciprofloxacin use rates] in hospitals and in communities) were significantly associated with rates of fluoroquinolone-resistant *P. aeruginosa* in 1999 ($R^2 = .63$; $P = .0009$; $n = 17$) and 2000 ($R^2 = .43$; $P = .0009$; $n = 28$). In 1999, fluoroquinolone use was independently associated with resistance in both the community ($P = .001$) and the hospital ($P = .031$). In the year 2000, hospital fluoroquinolone use was significantly associated with resistance ($P = .0004$), and community use was not ($P = .068$).

A multiple regression model with 4 independent variables (ciprofloxacin and levofloxacin use both in hospitals and in communities) was analyzed for 1999. The model was predictive of rates of resistance ($R^2 = .78$; $P = .0014$; $n = 16$). Levofloxacin use in the community was statistically significant ($P =$

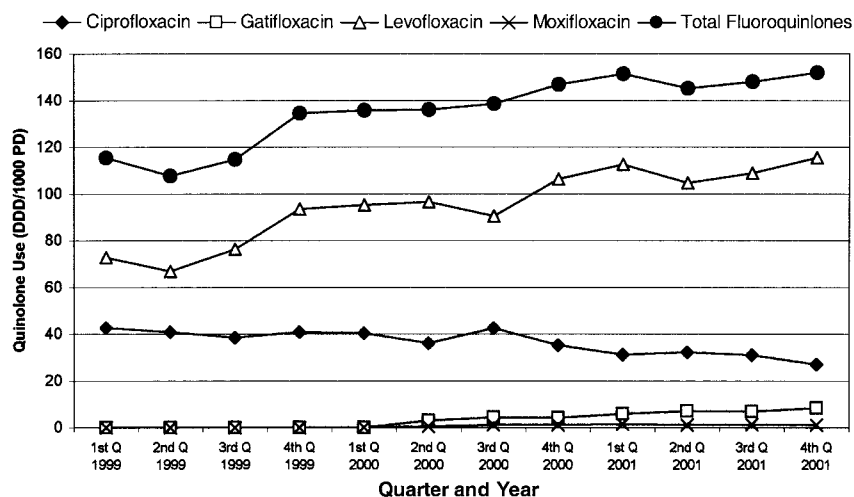


Figure 1. Trend analysis of hospital fluoroquinolone use. Each point represents the aggregated mean of hospital usage by quarter, expressed as defined daily doses (DDD) per 1000 patient-days (PD), across all hospitals between 1999 and 2001. Individual data for trovafloxacin, norfloxacin, and ofloxacin are not shown to improve clarity but are included in the trend line of total use. In hospitals at which paired data were available for all 3 years, total annual fluoroquinolone use increased significantly over this period ($P = .01$). Levofloxacin use increased significantly ($P = .0006$), and ciprofloxacin use decreased ($P =$ not significant).

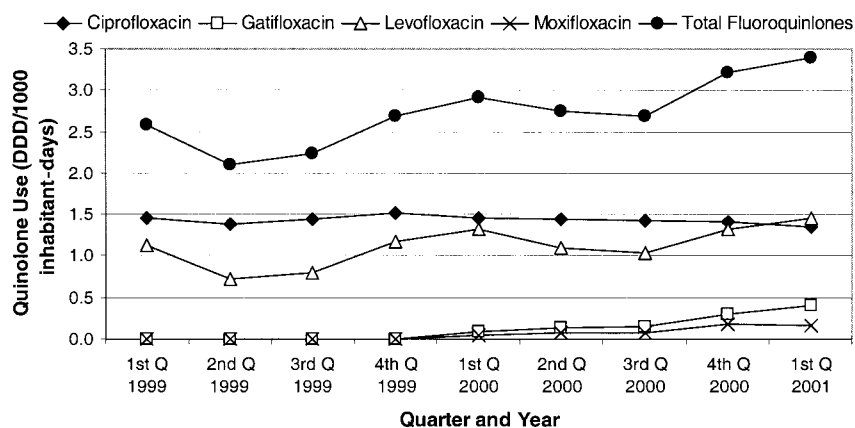


Figure 2. Trend analysis of community fluoroquinolone use. Each point represents the aggregated mean of community use for the specified drug, expressed as defined daily doses (DDD) per 1000 inhabitant-days, within a 10-mile (~16-km) radius surrounding all 35 SCOPE-MMIT hospitals. Total fluoroquinolone use and levofloxacin use increased significantly over this period; ciprofloxacin use did not change significantly.

.0006), but community usage of ciprofloxacin was not statistically significant ($P = .37$). Hospital use of levofloxacin and ciprofloxacin was not predictive of resistance in 1999. In the year 2000, the model explained one-half of the variation in rates of resistance ($R^2 = .50$; $P = .003$; $n = 27$), and levofloxacin use both in the community ($P = .031$) and in the hospital ($P = .029$) contributed significantly to the model. Ciprofloxacin use was not predictive of rates of resistance in the community ($P = .83$) or in the hospital ($P = .75$).

DISCUSSION

Resistance of *P. aeruginosa* to fluoroquinolones is mediated by multiple mechanisms, and the organism is often multidrug resistant [13]. Such strains cause endemic infections and are only susceptible to colistin (colistimethate sodium) [13, 24]. These strains have evolved when there are few drugs under development that are active against multidrug-resistant gram-negative bacteria [13, 15].

The mean rates of fluoroquinolone-resistant *P. aeruginosa* in our hospital network (29% in 1999, increasing to 38% in 2001) are similar to those in other reports. Surveillance from 250 US hospitals in the year 2000 found that 29% of *P. aeruginosa* were fluoroquinolone resistant [14], a rate similar to that from the CDC Project ICARE hospitals (~24% in 1998/1999) [12]. These reports of the mean rates of resistance, however, underemphasize marked variability between hospitals, from 16% to 60% during 2001 in our network. The women and children's hospital consistently had the lowest rates of resistance, from 11% in 1999 to 13% in 2001, as well as the lowest rates of fluoroquinolone use. This is the first report that antibiotic use in the hospital and surrounding communities explains much of this variability—something that has not been possible in previous studies that lack local antibiotic use data [9–11, 25–27].

Fluoroquinolone use is a significant risk factor for selection of resistant *P. aeruginosa* in individual patients and in populations [9–11, 27–29]. Richard et al. [28] found that prior receipt of a fluoroquinolone was the main risk factor for infection with a quinolone-resistant gram-negative bacterium. They also reported that, of 206 hospitalized patients, the gastrointestinal tracts of 63 were colonized with fluoroquinolone-resistant bacteria [29]. One-half of these organisms were *P. aeruginosa*, and receipt of a fluoroquinolone within the preceding month, either in the hospital or in the community, was the main risk factor.

The observation that community antimicrobial use may contribute to antimicrobial resistance in hospitals is a relatively

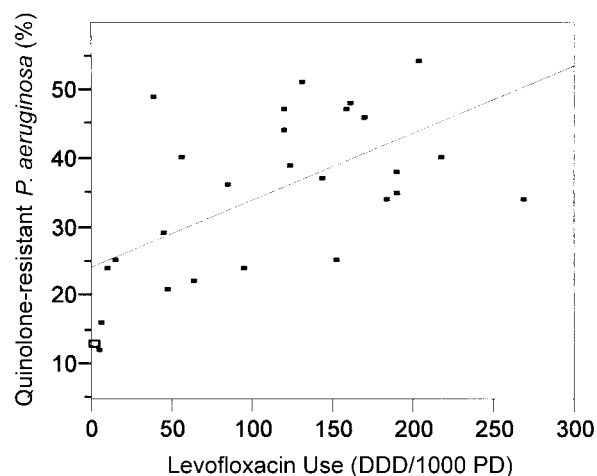


Figure 3. Individual hospital levofloxacin use during the year 2000, expressed as defined daily doses (DDD) per 1000 patient-days (PD), versus hospital rates of fluoroquinolone-resistant *Pseudomonas aeruginosa*. The relationship is significant ($R^2 = .38$; $P = .0006$; 27 hospitals). Box, A women and children's hospital, which was not included in calculation of the regression line but is shown for contrast.

new phenomenon. Before the availability of fluoroquinolones, the antibiotics used most often in the community were not used in hospitals to treat serious infections. The exception has involved patients admitted from a long-term care facility at which use of potent antimicrobial agents is common [30]. In 1999, Fridkin et al. [31] reported from the National Nosocomial Surveillance System that fluoroquinolone resistance in *P. aeruginosa* was higher in community isolates than in hospital isolates. They speculated that this may be related to community use of fluoroquinolones. A report that the increase in fluoroquinolone-resistant *P. aeruginosa* in intensive care units in the United States is correlated with community fluoroquinolone use is consistent with our observations [9]. However, the relative rate of use of fluoroquinolones in the community (~3 DDD/1000 inhabitant-days) is considerably lower than that in the hospital (~150 DDD/1000 PD), strongly suggesting that hospital use is more likely to contribute to fluoroquinolone resistance in the hospital than is community use.

The finding that fluoroquinolone resistance is most closely linked to levofloxacin use (and not to ciprofloxacin use) is intriguing. Rates of fluoroquinolone resistance in *P. aeruginosa* were increasing before levofloxacin was widely used, so use of this agent cannot be solely responsible. However, levofloxacin may be more likely to select for resistant strains of *P. aeruginosa* than is ciprofloxacin. Peterson et al. [32] reported that the monthly prevalence of ciprofloxacin-resistant *P. aeruginosa* at Northwestern Memorial Hospital (Chicago, IL) increased from ~7% in June 1992 to 25% by October 1995. This was more closely linked to ofloxacin use than to ciprofloxacin use. Bhavnani et al. [11] found that hospital expenditures for levofloxacin were associated with fluoroquinolone resistance in *P. aeruginosa*, whereas ciprofloxacin expenditures were not. When levofloxacin was approved for use in the United States in 1996, ciprofloxacin was more active against *P. aeruginosa* [1], but recent surveillance reports indicate that susceptibility is now essentially identical [14]. There are, however, subtle differences between these 2 drugs that may explain these observations. Fluoroquinolone-resistant *P. aeruginosa* are most likely to originate in the gastrointestinal tract [29]. The bioavailability of levofloxacin is nearly 100%, whereas the bioavailability of ciprofloxacin is 60%–70% [1]. The higher gastrointestinal concentrations of ciprofloxacin may eliminate borderline fluoroquinolone-susceptible organisms, whereas lower gastrointestinal concentrations of levofloxacin may select for fluoroquinolone-resistant strains. Furthermore, in vitro serial passage studies by Gilbert et al. [33] report that levofloxacin is consistently more likely than ciprofloxacin to select for fluoroquinolone-resistant strains of *P. aeruginosa*.

There are limitations to our observations. First, hospitals did not use uniform methods to construct and report antibiograms.

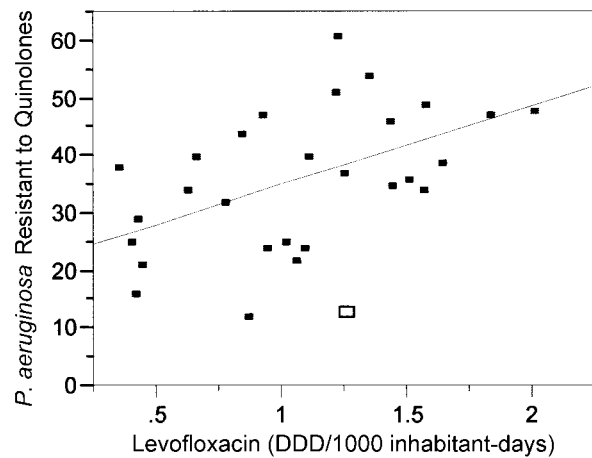


Figure 4. Individual community levofloxacin use during the year 2000, expressed as defined daily doses (DDD) per 1000 inhabitant-days, within a 10 mile radius of each hospital, versus hospital rates of fluoroquinolone-resistant *P. aeruginosa* ($R^2 = .28$; $P = .004$; $n = 28$). Box, A women and children's hospital, which was not included in calculation of the regression line but is shown for contrast.

Failure to eliminate duplicate isolates, for example, tends to increase the rate of reported resistance [34]. Second, there is potential for information bias, selection bias, and confounding during investigations that link aggregate antibiotic use to resistance [35]. Although we found no relationship of selected hospital demographic data to rates of resistance, there are other variables that may contribute to resistance in *P. aeruginosa*. In particular, patient-to-patient transmission is a frequent confounder of the relationship between drug use and resistance [12, 35, 36]. This, however, appears to be an unlikely explanation of our observations, because patient-to-patient transmission of drug-resistant *P. aeruginosa* is uncommon and is less important than drug exposure [37]. Finally, associations cannot by themselves prove causal relationships. However, the association between community fluoroquinolone use and hospital rates of resistance has now been replicated: the variability in rates of resistance correlated with use, antibiotic use preceded increasing resistance, and the results are biologically plausible.

Whether a return to more modest use of fluoroquinolones or preferential use of fluoroquinolones with a lower propensity to select for resistant strains will delay or reverse the rates of increasing resistance remains unclear. What is clear is that we are rapidly losing a valuable class of antibiotics for the treatment of serious nosocomial infections.

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