MAJOR ARTICLE

Risk Factors for Acquisition of Levofloxacin-Resistant *Streptococcus pneumoniae*: A Case-Control Study

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A case-control study was conducted to identify the risk factors associated with levofloxacin-resistant *Streptococcus pneumoniae* (LRSP) colonization or infection. Twenty-seven case patients (patients with LRSP) were compared with 54 controls (patients with levofloxacin-susceptible *S. pneumoniae*). Risk factors that were significantly associated with LRSP colonization or infection, according to univariate analysis, included an older age (median age, 75 years for case patients versus 72.5 years for controls), residence in a nursing home (odds ratio [OR], 7.2), history of recent (OR, 4.6) and multiple (OR, 4.4) hospitalizations, prior exposure to fluoroquinolones (OR, 10.6) and β-lactams (OR, 8.6), presence of chronic obstructive pulmonary disease (COPD; OR, 5.9), and nosocomial origin of the bacteria (OR, 5.7). Multivariate analysis showed that presence of COPD (OR, 10.3), nosocomial origin of the bacteria (OR, 16.2), residence in a nursing home (OR, 7.4), and exposure to fluoroquinolones (OR, 10.7) were independently associated with LRSP colonization or infection. Thus, a distinct group of patients with COPD is the reservoir of LRSP.

A major issue in pneumococcal infection in recent years is the emergence and global dissemination of multiply resistant strains of *Streptococcus pneumoniae*. In many countries, currently >40% of isolates are resistant to penicillin [1–5]. Among the penicillin-resistant *S. pneumoniae* isolates, 60%–90% are also resistant to chloramphenicol, clindamycin, cotrimoxazole, erythromycin, and tetracycline. In coincidence with this escalating drug resistance problem among the pneumococci in the 1990s was the launching of a number of new fluoroquinolones with enhanced activity against gram-positive bacteria. Generally speaking, this group of agents has good safety profiles and favorable pharmacokinetic properties. Given these desirable characteristics of the newer fluoroquinolones and the significance of penicillin-resistant *S. pneumoniae* in community-acquired pneumonia, the newer quinolones are being prescribed with increasing frequency for initial treatment of respiratory tract infections [6, 7]. As the rate of use increases, resistance to the newer fluoroquinolones will likely rise. Indeed, in the past few years, fluoroquinolone-resistant *S. pneumoniae* have been reported from many countries, although the prevalence still remains low in general [1, 7–10]. In an attempt to understand better the epidemiological and clinical aspects of fluoroquinolone-resistant *S. pneumoniae*, a retrospective, multicenter study was conducted in Hong Kong, a region with a 5.5% rate of levofloxacin-resistant *S. pneumoniae* (LRSP) [11].

PATIENTS AND METHODS

Settings. This study was conducted at 3 hospitals (A, B, and C) in Hong Kong. Hospitals A and C are

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acute regional medical centers, including a university hospital with intensive care, burn, liver, kidney, and bone marrow transplantation units. The remaining hospital (B) is a convalescent institute. These hospitals serve approximately one-quarter of the population of Hong Kong. The microbiology laboratories of these hospitals handle clinical specimens from both inpatients and outpatients.

Study design and patient description. This retrospective study included an 18-month period from June 1998 through November 1999. A case-control study was done to compare the frequency of exposure and the features of case patients with those of control patients and to identify and quantify potential risk factors associated with LRSP colonization or infection. Both case and control patients were identified by means of a systematic review of the laboratory results in the microbiology laboratories. Because both infected and colonized patients might play a role in the transmission of LRSP, both patient groups were considered to be case patients. A "case patient" was defined as one who was either clinically infected with or colonized by *S. pneumoniae* that was resistant to levofloxacin. For instances of multiple isolations of LRSP from the same patient, the initial isolation was used. One case patient was matched with 2 control patients according to hospital location (for all adults) and date of bacterial isolation. "Control patients" were either clinically infected with or colonized by levofloxacin-susceptible *S. pneumoniae.*

Patient records were reviewed, and relevant data were entered onto predesigned forms. All diagnoses and underlying diseases had been previously documented in the patient charts and were independently verified by a clinician by use of predetermined criteria. To identify the patients' exposure to antibiotics during hospital admissions and attendance at emergency departments and outpatient clinics, the networked, computerized records in the pharmacies were reviewed. The following data were obtained for all patients: age, sex, type of ward, prior hospitalization, residence in a nursing home, underlying diseases, site of bacterial isolation, status of bacterial isolation (infection or colonization), infective syndrome–associated bacterial isolation, origin of the infection or colonization (community- or hospital-acquired), length of hospitalization, prior exposure to antibiotics, and outcome (survival or death).

Microbiological data, including the date of initial isolation, site of isolation, and antimicrobial susceptibilities, were collected. During the study period, there were 1366 isolations of *S. pneumoniae* from 1060 patients. LRSP was identified in 29 hospitalized patients. Medical records were available for 27 of these patients.

Definition of terms. The "type of ward" (e.g., medical, surgical, or orthopedic) was defined as the place where the patient was staying on the day that the bacteria were isolated. All past events and prior exposures were dated back from the day of admission. "Prior hospitalization" was defined as any inpatient treatment that lasted for >1 day in the 12 months prior to admission. "Recent hospitalization" was defined as any inpatient treatment that lasted for >1 day in the 6 weeks prior to hospitalization. "Multiple hospitalizations" were defined as >3 admissions during the 12 months prior to hospitalization.

"Underlying diseases" included all those that might increase patients' predisposition to infection and adversely affect their life expectancies. All diagnoses of chronic obstructive pulmonary disease (COPD) were made by the clinicians in charge of the patients and were confirmed by the investigators by use of a combination of clinical and laboratory criteria, as described elsewhere [12]. The site of bacterial isolation was categorized as "respiratory," "blood," and "other." Colonization was diagnosed when *S. pneumoniae* was isolated from sputum specimens in the absence of clinical, laboratory, and/or radiological features that were suggestive of infection. Infective syndromes were determined according to a combination of criteria. "Pneumonia" was defined by the clinical, radiographic, and laboratory criteria described by the Centers for Disease Control and Prevention [13]. "Acute exacerbation of COPD" was defined as a worsening of clinical symptoms that included increases in cough, sputum production, and dyspnea.

"Bacteremia" was defined as the isolation of *S. pneumoniae* in ⩾1 culture of blood specimens in association with clinical features of sepsis. An interval of 48 h between the time of admission and day that bacteria were isolated was used to define the origin of infection or colonization as community-acquired (⩽48 h) or hospital-acquired (>48 h). "Prior exposure to antibiotics" was defined as administration of any oral or parenteral antimicrobial agent for >1 day. "Previous exposure to antibiotics" was categorized according to time (any exposure that lasted for >1 day during the 6-week and 12-month intervals prior to admission) and class of agents (fluoroquinolones, β-lactams, macrolides, and other). The β-lactam/β-lactamase inhibitor combinations were grouped under the term "β-lactams."

Microbiological methods. *S. pneumoniae* was identified by use of Gram's stain, colony morphology, bile solubility, and sensitivity to optochin. Susceptibility testing was done by use of the disk diffusion method, according to the National Committee for Clinical Laboratory Standards [14]. Antibiotic disks that included chloramphenicol (30 μg), cotrimoxazole (trimethoprim-sulfamethoxazole; 1.25/23.75 μg), erythromycin (15 μg), levofloxacin (5 μg), and oxacillin (1 μg) were obtained from commercial sources (BBL; Becton Dickinson). Initial screening for reduced susceptibility to penicillin was done by use of the oxacillin disk (1 μg). For those strains with oxacillin zone diameters of ⩽19 mm, the MIC of penicillin was determined by use of the Etest (AB Biodisk), performed according to the manufacturer's recommendations. For determination of levofloxacin resistance, strains with zone diameters of ⩽13 mm

Table 1. Potential risk factors associated with colonization or infection with levofloxacin-resistant *Streptococcus pneumoniae*.

Factor	Case patients (n = 27)	Control patients (n = 54)	OR (95% CI)	P
Age, y[a]	72.5 (62.3–78.3)	75 (70–85)	—	.01
Nursing home residence	14 (52)	7 (13)	7.2 (2.4–21.6)	<.001
COPD	17 (63)[b]	12 (22)	5.9 (2.2–16.3)	.001
Nosocomial origin	18 (66)	14 (26)	5.7 (2.1–15.6)	.001
Interval from day of admission to isolation of LRSP, d[a]	7 (1–20)	1 (1–3)	—	<.001
No. of prior admissions[a]	4 (2–7)	1 (0–3)	—	<.001
Recent hospitalization	16 (59)	13 (24)	4.6 (1.7–12.3)	.003
Multiple hospitalization	15 (56)	12 (22)	4.4 (1.6–11.8)	.004
Previous exposure to antibiotics[c]				
Fluoroquinolones	8 (30)/14 (52)	0 (0)/5 (9)	—/10.6 (3.2–34.7)	<.001/<.001
β-Lactams	24 (89)/25 (93)	20 (37)/32 (59)	14.7 (3.9–55.4)/ 8.6 (1.8–40)	<.001/.006

NOTE. Data are no. (%) of patients, unless otherwise indicated. COPD, chronic obstructive pulmonary disease; LRSP, levofloxacin-resistant *S. pneumoniae*.

[a] Median (interquartile range).

[b] Colonization in 3 patients.

[c] Exposure to antibiotic therapy during the 6 weeks prior to hospitalization/12 months prior to hospitalization.

(corresponding to an MIC of ≥ 8 μg/mL) were interpreted as resistant. All 27 strains from the case patients had levofloxacin zone diameters of <13 mm. The MICs of levofloxacin for 3 strains were confirmed to be 16 μg/mL by use of the National Committee for Clinical Laboratory Standards broth microdilution method [14].

Statistical analysis. Potential risk factors for colonization or infection with LRSP were identified by means of univariate analysis. Either the χ^2 test or Fisher's exact test was used for categorical variables. Continuous variables were tested by use of Student's t test or the Mann-Whitney U test. The 12 variables that were significant in the univariate analysis and those variables that could increase the risk of LRSP colonization or infection from a clinical point of view were further tested by means of logistic regression done by the use of the forward conditional method. $P < .05$ was considered to be statistically significant. A statistical package (SPSS 10.0; SPSS Hong Kong) was used for all analyses.

RESULTS

Of the 27 hospitalized patients with LRSP, 9 were identified from hospital A, 6 from hospital B, and 12 from hospital C. Sex and types of wards did not differ between the case patients and the 54 control patients. Twenty-four case patients were men, compared with 43 control patients. Types of wards (data are presented for case vs. control patients) were mostly medical (24/27 vs. 43/54) in both groups; the remaining wards were surgical (1/24 vs. 8/54), orthopedic (2/24 vs. 1/54), and oncology (0/24 vs. 2/54). Case patients were slightly older than controls. The overall median age of all patients was 73 years (interquartile range, 65–80.5 years). In both groups, isolation of *S. pneumoniae* was associated with a similar proportion of infective syndromes, including acute exacerbation of COPD (10/27 vs. 30/54), pneumonia (11/27 vs. 9/54), and respiratory colonization (6/27 vs. 15/54). The median duration of hospital stay was longer among the case patients (11 days [interquartile range, 4–47 days]) than it was among the control patients (5.5 days [interquartile range, 2–20.1 days]; $P = .05$). Bacteremia occurred in 1 case patient and in 4 control patients. One control with bacteremic pneumonia also had clinical evidence of meningitis. Four (19.1%) of 21 patients with infection with LRSP died, compared with 5 (12.8%) of 39 controls ($P = .7$)

Potential risk factors for infection or colonization with LRSP are shown in table 1. The following risk factors were significantly different between groups, according to univariate analysis: age, residence in a nursing home, COPD, nosocomial origin of bacteria, interval between day of admission and isolation of LRSP, number of prior admissions, and recent and multiple hospitalizations. The occurrences of other underlying diseases, including malignancy (3/27 vs. 12/54) and heart (6/27 vs. 9/54) and cerebral (9/27 vs. 8/54) diseases, were similar for case patients and controls. Exposure to 2 antibiotic groups (fluoroquinolones and β-lactams) occurred significantly more frequently among the case patients. In contrast, the groups did not differ in terms of exposures to macrolides during both the

6 weeks prior to admission (3/27 vs. 0/54) and 12 month prior to admission (3/27 vs. 6/54).

Exposure to fluoroquinolones in the group of case patients amounted to 27 treatment courses and 291 days, compared with 7 courses and 55 days for the control group. The main characteristics of the 14 case patients who had recent and/or remote exposure to fluoroquinolones are summarized in table 2. Of note, 11 of the 14 patients had COPD. The most common daily doses were 400 mg (range, 200–600 mg) for levofloxacin, 1000 mg (range, 400–1000 mg) for ciprofloxacin, and 600 mg (range, 200–800 mg) for ofloxacin. Three case patients had isolation of LRSP while they were receiving therapy with fluoroquinolones for pneumonia (patient 12, oral levofloxacin, 400 mg q.d.) or acute exacerbation of COPD (patient 13, oral levofloxacin 400 mg q.d.; patient 18, oral ciprofloxacin 500 mg b.i.d.). All 3 patients who were treated with fluoroquinolones and who were infected with LRSP had clinical failure. They improved after treatment with iv vancomycin (patients 12 and 18) and high-dose oral ampicillin-sulbactam (patient 13).

The logistic regression model showed that presence of COPD (OR, 10.3; 95% CI, 1.6–66.2; $P = .01$), nosocomial origin of the bacteria (OR, 16.2; 95% CI, 2.1–122.2; $P = .007$), residence in a nursing home (OR, 7.4; 95% CI, 1.5–35.1; $P = .01$), and exposure to a fluoroquinolone during the 12 months prior to admission (OR, 10.7; 95% CI, 1.6–71.2; $P = .01$) were factors that were independently associated with LRSP infection or colonization. Data regarding susceptibilities of the sputum isolates to penicillin, erythromycin, cotrimoxazole, and chloramphenicol are shown in table 3. LRSP isolates were more likely than levofloxacin-susceptible *S. pneumoniae* to have resistance to penicillin and non–β-lactam agents.

DISCUSSION

Recognition of patients who have an increased risk of exposure to LRSP is important in the battle against the epidemic dissemination of these multiply resistant pneumococci. It is believed that the global emergence of drug-resistant *S. pneumoniae* has occurred in stages and that those stages involved selection of resistant mutants and clonal expansion [15]. This study showed that risks of infection with LRSP are increased among those who are institutionalized in nursing homes, those who have hospital-acquired pneumococcal infection, those who have received fluoroquinolones previously, and those who have COPD as comorbidity. Prior treatment with a fluoroquinolone is relevant because it provides the necessary selection pressure for mutations. Because prolonged carriage of *S. pneumoniae* can allow for persistence of early-step mutants that were induced by multiple courses of fluoroquinolone treatment [16], we chose to examine exposure to fluoroquinolones in the 12 months prior to admission. Our data demonstrated that the majority of the case patients (63%) had COPD. This suggests that elderly patients with COPD are the main reservoir of LRSP. This situation is different from that of penicillin-resistant *S. pneumoniae,* for which children are widely believed to be the reservoir. In agreement with our observation, an increase in resistance to fluoroquinolones, from <1% in 1995 to >3% in 1998, has been reported among older Canadians [9].

Our findings show that the presence of COPD in patients who were treated with fluoroquinolones could play a role in the selection of fluoroquinolone resistance. An examination of some reports of previous studies might help to explain this observation. The first explanation related to the limited antipneumococcal activities of ciprofloxacin and ofloxacin. The MIC_{90} values of both agents were 2–4 μg/mL in most previous studies. Levofloxacin is the *S*-isomer of ofloxacin. Although it is more active than ofloxacin, its MIC for pneumococci is only 2 times lower than that of ofloxacin. In Hong Kong, the MIC_{50} and MIC_{90} values of levofloxacin for pneumococci were 1 μg/mL and 1.5 μg/mL, respectively [11]. For ofloxacin, the mean sputum level of ofloxacin was 1.2 μg/mL after administration of a 300-mg dose [17]. The levels that were reported for ciprofloxacin were 3.41 μg/L (mean peak level) and 1.11 μg/L (mean trough level) when the drug was given at a dosage of 750 mg b.i.d. [18]. Data on the sputum level of levofloxacin after the usual 500-mg dose are not available. After a single oral dose of 200 mg, peak sputum levels of 4 μg/mL and 4.7 μg/mL were reported in 2 patients [19]. In this study, 9 of the 14 case patients with exposure to fluoroquinolones had received ciprofloxacin and/or ofloxacin. Among the 8 case patients who were treated with levofloxacin, the dosage was potentially suboptimal (<500 mg, given daily) in 15 of the 16 treatment courses. Therefore, exposure to levels of these fluoroquinolones that are below the MIC is to be expected in the sputum, leading to de novo selection of resistant mutants. In vitro, resistant mutants can be easily selected at a frequency of 10^{-5} after exposure of *S. pneumoniae* to subinhibitory concentrations of most fluoroquinolones.

The next question to ask is whether these counts of pneumococci are to be encountered in the airways of patients with pneumococcal infections. In patients with COPD, the average sputum count of *S. pneumoniae* was reported to be 10^7 cfu/mL, during both the periods of exacerbation and remission [16]. Notwithstanding these data, resistance that occurred in *S. pneumoniae* isolates that persisted after fluoroquinolone treatment has not been evaluated in clinical trials of treatment of patients who have acute bacterial exacerbation of chronic bronchitis [20–29]. In the study by Davies and Maesen [21] on the effectiveness of levofloxacin in treatment of patients with acute bacterial exacerbation of chronic bronchitis, a high rate of treatment failure (13 [65%] of 20) was reported in association with *S. pneumoniae* [21].

Table 2. Summary of clinical data for 14 patients with levofloxacin-resistant *Streptococcus pneumoniae* (LRSP) and their previous exposure to fluoroquinolones.

Patient, hospital	Chest disease(s)	Other medical condition(s)	Date of acquisition of LRSP, mo/y	Fluoro-quinolone	No. of treatment courses	Duration of treatment, d[a]
1, B	None	Ischemic heart disease, chronic renal failure, hypertension	07/99	Lvfx	1	10 (10)
5, B	Recurrent aspiration	Stroke, Parkinson's disease	10/99	Lvfx	1	10 (—)
11, C	COPD	Congestive heart failure, ischemic heart disease	07/98	Cpfx, Lvfx	4	36 (—)
12, C	COPD	None	08/99	Cpfx, Lvfx	3	27 (25)
13, C	COPD, old TB	None	12/99	Lvfx	1	5 (5)
14, C	COPD	Ischemic heart disease	09/98	Ofx	1	4 (—)
15, C	COPD, old TB	Benign prostatic hypertrophy	09/98	Lvfx	1	7 (7)
16, C	COPD	None	09/98	Cpfx, Lvfx	6	58 (10)
17, C	COPD	None	10/98	Cpfx, Ofx	2	24 (7)
18, C	COPD, old TB	None	10/98	Cpfx	2	34 (34)
21, A	COPD	None	04/99	Lvfx	2	14 (7)
24, A	None	Dementia, hypertension	08/99	Ofx	1	7 (—)
25, A	COPD	Ischemic heart disease, hypertension	11/99	Ofx	1	10 (—)
26, A	COPD, old TB	Hypertension	11/99	Ofx	1	18 (—)

NOTE. COPD, chronic obstructive pulmonary disease; Cpfx, ciprofloxacin; Lvfx, levofloxacin; mo, month; Ofx, ofloxacin; TB, tuberculosis.
[a] Data are no. of days of treatment during 12 months prior to admission (no. of days of treatment during 6 weeks prior to admission).

An alternative hypothesis to explain the link between fluoroquinolone resistance and COPD is that nosocomial spread of pneumococci is biased toward the most vulnerable patients—those with COPD. During an interhospital outbreak of infection with multidrug-resistant *S. pneumoniae* in The Netherlands, COPD was identified as a major risk factor for acquisition of multidrug-resistant pneumococci [30]. Results of staff screening were negative. The authors concluded that patient-to-patient spread was the most likely mechanism of dissemination. After the implementation of several measures, including screening of patients with COPD for carriage of drug-resistant pneumococci, pneumococcal eradication therapy, and barrier nursing of those persons who tested positive for carriage in a separate nursing room, the epidemic ceased immediately [30].

The case patients in our study were not epidemiologically linked with regard to their nursing home residence, geographic locations, and period of admission. However, the possibility that case patients in our study were part of a complicated interinstitutional outbreak cannot be excluded. Patients with COPD who have been colonized with *S. pneumoniae* have been reported to play a role in patient-to-patient transmission of pneumococci [30]. During the study period, there were no attempts to identify carriage of LRSP in the hospitalized patients with COPD. Moreover, a preliminary analysis of 10 strains of LRSP that we reported elsewhere revealed that they all shared an indistinguishable DNA pattern, which was determined by use of pulsed-field gel electrophoresis [31]. Prospective epidemiological studies are indicated to validate this outbreak hypothesis. Meanwhile, isolation precautions, such as screening of the patients with COPD and cohort nursing of those with LRSP, are justified in the institutions that treat a high number of patients who have strains with fluoroquinolone resistance.

Fluoroquinolone resistance among clinical isolates of pneu-

Table 3. Comparison of resistance to agents other than fluoroquinolones among levofloxacin-resistant and levofloxacin-susceptible *Streptococcus pneumoniae*.

Agent	Levofloxacin-resistant (n = 27)	Levofloxacin-susceptible (n = 54)	P
Penicillin	25/27 (92.5)	27/54 (50)	<.001
Chloramphenicol	14/15 (93.3)	9/30 (30)	<.001
Cotrimoxazole	16/16 (100)	17/30 (56.7)	.002
Erythromycin	27/27 (100)	27/54 (50)	<.001
Multiple[a]	17/17 (100)	14/33 (42.4)	<.001

NOTE. Data are no. of nonsusceptible strains/total no. of strains tested (%).
[a] Nonsusceptible to ⩾3 of above agents.

mococci occurred mainly as a result of point mutations in the topoisomerase genes [8]. For most fluoroquinolones, a single mutation generally causes only a ≤8- to 16-fold increase in the MIC. On the basis of this and other in vitro and vivo findings, a therapeutic index (ratio of drug level at site of infection to MIC) of 10–16 has been suggested to be required for prevention of the emergence of resistant mutants during treatment with fluoroquinolones [32–34]. The MIC breakpoint of levofloxacin for the pneumococci was set at 2 μg/mL. On the basis of this breakpoint, sputum levofloxacin levels of 20–32 μg/mL will be required to prevent fluoroquinolone resistance in the case of airway infection. Such levels are not reached in the sputum after the currently recommended dose of 500 mg.

On the other hand, the therapeutic index for prevention of resistance is reached in alveolar macrophages. In the study by Andrews et al. [35], the mean alveolar macrophage level was 41.9 μg/mL after a single 500-mg oral dose of fluoroquinolones. Alveolar concentration might be more relevant than sputum level for pneumococcal pneumonia, although this is controversial for the extracellular pathogens. In clinical trials, development of resistance rarely occurred after treatment of community-acquired pneumonia [36]. Nonetheless, the fluoroquinolones appear to differ in their potentials for selection of first-step mutants with mutations in the *par*C genes. Drugeon et al. [37] examined 2 strains of *S. pneumoniae* and found that the relative potential of levofloxacin is lower than that of ciprofloxacin, ofloxacin, and sparfloxacin. Interpretation of these data, however, is difficult, because most studies have involved only a small number of strains. The major clones of *S. pneumoniae* that are currently prevalent in various countries have not yet been studied [38]. It is uncertain whether the potential to yield resistant mutants depends on the strain. This is further complicated by the use of different methodology for selection of resistant mutants. Moreover, data are not available on this topic for the newer fluoroquinolones that are more active against pneumococci, such as moxifloxacin, clinafloxacin, and gemifloxacin. Comparisons of the effects of different fluoroquinolones on clinical strains from different countries need to be conducted by use of the same method.

The present study shows that pneumococcal resistance to levofloxacin is associated with resistance to penicillin, chloramphenicol, cotrimoxazole, and erythromycin. In a previous study of 181 pneumococci strains obtained from 7 hospitals in Hong Kong, levofloxacin resistance was more common among strains that were not susceptible to penicillin (8%) than it was among penicillin-susceptible strains (0%) [11]. These findings differ from those in reports from other countries, which found that fluoroquinolone susceptibilities of pneumococci were independent of the MIC of penicillin [39, 40]. In our study, the use of a β-lactam was a risk factor for fluoroquinolone resistance in the univariate analysis, but this risk factor disappeared in the multivariate analysis. This finding suggests that the fluoroquinolones, rather than the β-lactams, provide the major selective pressure for fluoroquinolone resistance. Therefore, the emergence of fluoroquinolone resistance appears to be dominated by fluoroquinolone use, but the long-term selection of these multiresistant strains may well include selection with any of the other agents to which they are resistant. In any case, infection control measures and the judicious use of antibiotics will remain major defenses against these multiply resistant pneumococci. In children, conjugated pneumococcal vaccines have been shown to be able to reduce carriage of vaccine serotypes [41, 42]. Given that LRSP belongs to 2 of the vaccine serotypes, 19F and 23F [31], studies of the roles of the conjugated vaccines, with regard to their ability to eliminate pneumococcal carriage in patients with COPD, should be done now.

In conclusion, a distinct group of patients with COPD appears to be an important reservoir of LRSP in Hong Kong. These LRSP isolates appeared to have emerged both de novo after suboptimal use of fluoroquinolones and by means of person-to-person transmission in hospitals or nursing homes. Use of fluoroquinolones should be restricted for these patients who are at increased risk of getting LRSP. Our findings call for international attention and collaborative strategies to prevent these strains from intercontinental dissemination.

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