Invasive *Haemophilus influenzae* isolates with decreased levofloxacin susceptibility in Hong Kong

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Sir,

Although *Haemophilus influenzae* with phenotypic resistance to fluoroquinolones remains rare, recent studies suggested that decreased susceptibility due to first-step mutations in *gyrA* or *parC* may be more common.¹² First-step mutants with reduced susceptibility generally remain undetected when fluoroquinolone susceptibility tests are interpreted using current breakpoints. However, it is important to detect first-step mutants because they may be associated with clinical failures and high-level resistance may emerge during treatment with fluoroquinolones.³ In this regard, nalidixic acid has been found to be a useful indicator compound for the detection of quinolone resistance in *H. influenzae*.¹² By using nalidixic acid, we previously reported an incidence of 0.9% for decreased susceptibility to levofloxacin among 563 *H. influenzae* isolates carried by children.¹

In an attempt to define the incidence of decreased susceptibility to levofloxacin among *H. influenzae* causing invasive infections in Hong Kong, we retrospectively tested all *H. influenzae* isolated from blood samples of patients admitted to three hospitals during 1998–2003. The three hospitals are estimated to provide an inpatient service for approximately one-quarter of the 6.5 million population in Hong Kong. The MICs of nalidixic acid and levofloxacin were determined by the MIC microbroth dilution method.¹ Nalidixic acid resistance was defined as an MIC of ≥32 mg/L.¹ Quality control strains *H. influenzae* ATCC 49247 and ATCC 49766 were included with each run. A multiplex PCR procedure was used for capsular typing.⁵ The subset of isolates with reduced susceptibility to levofloxacin was examined further by multi-locus sequence typing (MLST).⁶ Previously described primers and methods were used to define mutations in *gyrA* and *parC* genes.¹

Of 29 invasive isolates three (10.3%) were resistant to nalidixic acid with an MIC of 128 mg/L; the MICs ranged from 0.5 to 4 mg/L for nalidixic acid-susceptible isolates. Levofloxacin MICs for the three nalidixic acid-resistant isolates were 0.06–0.12 mg/L, compared with an MIC range of 0.004–0.0016 mg/L for the nalidixic acid-susceptible isolates. The three nalidixic acid-resistant isolates were non-capsulated. All three patients with infection by nalidixic acid-resistant isolates had underlying disease (Case 1, recurrent pyogenic cholangitis; Case 2, adenocarcinoma of lung; and Case 3, multiple myeloma). Case 3 had a history of exposure to fluoroquinolones (levofloxacin) while the other two did not. The quinolone resistance determining regions of *gyrA* and *parC* for the three isolates were sequenced and a Ser-84→Lys substitution was found in *GyrA* in all three. No substitution was found in ParC. MLST analysis of these three isolates revealed three distinct allelic profiles: 14-4-1-1-22-1-5 (ST183), 1-1-1-64-42-5 (ST136) and 1-24-36-14-45-1-5 (a novel ST), indicating that they were not clonally related.

It is noteworthy that fluoroquinolone resistance in *Streptococcus pneumoniae* is also high in Hong Kong. Since both *H. influenzae* and *S. pneumoniae* are often found in the respiratory tract, the two organisms may be subjected to a common antibiotic selection pressure. In this regard, a relationship between resistance in *H. influenzae* and *S. pneumoniae* has also been noted by others.⁷ In conclusion, this study suggests that low-level quinolone resistance in *H. influenzae* may be an under-recognized phenomenon.

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Transparency declarations

None to declare.

References