Susceptibility to Respiratory Fluoroquinolones in *Streptococcus pneumoniae* in Toronto, Canada

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Abstract

Background: Fluoroquinolone resistance (FQR) emerged in *S. pneumoniae* (SPN) shortly after the introduction of ciprofloxacin. FQR increased from 1995 to 2002, and by 2002 was clinically significant in the elderly, and those with recent exposure to FQ and healthcare institutions. We examined trends in FQR in SPN in at-risk populations in Toronto since 2002.

Methods: Since 1995, TIBDN has collected all SPN isolated from sterile sites in residents of Toronto/Peel (pop 4M); from 2002, respiratory tract isolates were collected and the population area expanded. Broth microdilution susceptibility testing to CLSI standards is performed on all isolates. Pop'n FQ use is obtained from IMS Health. Demographic and medical data were collected from patients.

Results: From 1995-2008, FQ use increased from 67.3-97.3 scripts/1000pop/yr; Levo use from 0 to 12.0 scripts/1000pop/yr, and Moxi use from 0 to 17.7 scripts/1000pop/year. 8645/9796 (88%) of SPN isolates were available for testing. After 2002, FQR decreased significantly for isolates in all subgroups (see Table), with the exception of isolates from respiratory specimens from patients currently receiving FQ. In 2008/10, FQR appeared to increase marginally, but the differences are not statistically significant.
In 2009, moxifloxacin resistance rates were less than 2% in all patients except those patients failing fluoroquinolone therapy and residents of nursing homes.

	Lev R	Mox R	Lev R	Mox R	Lev R	Mox R	Lev R	Mox R
Invasive disease	**2000-2002 (N=1148)**		**2003-2005 (N=1168)**		**2006-2007 (N=904)**		**2008-2010 (N=1336)**	
All adults	1.7%	0.5%	1.3%	0.3%	0.3%	0	0.9%	0.2%
Adults >65y	3.3%	1.0%	1.2%	0.5%	0.3%	0	1.4%	0.5%
Hospital-acquired	6.2%	0	3.6%	0	0	0	5.1%	0
Nursing home acquired	8.9%	2.5%	2.5%	0	2.1%	0	5.8%	2.0%
Failing FQ therapy	21%	7.1%	26.1%	8.7%	0	0	7.7%	7.7%
FQ prior 3 months	4.8%	1.6%	1.8%	0.9%	1.4%	0	1.4%	1.4%
Respiratory isolates	**2002 (N=360)**		**2003-2005 (N=1343)**		**2006-2007 (N=951)**		**2008-2009 (N=1329)**	
All adults	6.1%	1.2%	3.4%	1.6%	2.6%	1.4%	2.4%	1.2%
Adults >65y	8.9%	1.8%	4.1%	1.9%	4.0%	2.4%	1.8%	0.48%
Hospital-acquired	8.7%	2.2%	0.8%	0.4%	3.3%	2.6%	2.2%	1.1
Nursing home acquired	9.1%	0	9.4%	6.3%	3.9%	0	12.5%	6.3%
Current FQ therapy	50%	16.7%	25.8%	9.7%	42.9%	28.6%	14.3%	14.3%
FQ prior 3 months	15%	7.0%	7.4%	3.7%	3.8%	1.9%	5.0%	1.4%

Conclusion: Despite increased use of respiratory fluoroquinolones, fluoroquinolone resistance in pneumococcal isolates is not increasing. Only nursing home patients and patients failing treatment with fluoroquinolones at presentation are at risk of fluoroquinolone resistance.

Introduction

The Toronto Invasive Bacterial Diseases Network (TIBDN) has performed population-based surveillance for invasive pneumococcal disease in metropolitan Toronto and Peel region (pop 4M) since January 1, 1995. The emergence of fluoroquinolone resistance in *S. pneumoniae* from 1995 to 2002 was associated with older age, recent use of FQ, and hospital/nursing home-acquired infection. We examined trends in fluoroquinolone resistance in SPN in Toronto since 2002 and re-examined these previously identified risk factors**.**

Methods

From 1995 to 2009, all sterile site isolates of pneumococci identified through population-based surveillance for pneumococcal disease in Metropolitan Toronto and Peel region were collected. From 2002 to 2009, all respiratory site isolates from hospital laboratories were also collected. Broth microdilution antimicrobial susceptibility testing was performed to CLSI standards. Population fluoroquinolone use was obtained from IMS Health Canada. Demographic and clinical data were collected from review of health records and interviews with patients and attending physicians. Details of previous antibiotic treatment has been collected since 2000. Patients currently on antimicrobials or who finished a course of antibiotics within 48 hours of positive culture were classified as failing therapy.

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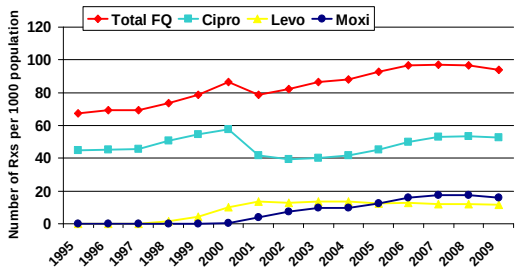
Results

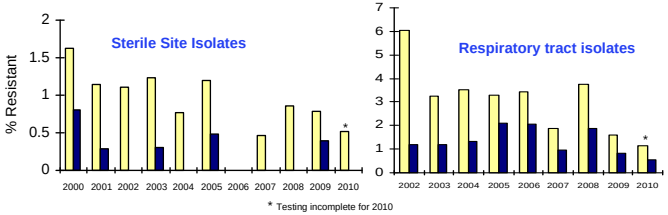
0utpatient fluoroquinolone use increased from 67 to 97 prescriptions/ 1000pop/year between 1995 and 2007, and has remained stable since (Figure 1). Formulary restrictions in the provincial drug benefit formulary resulted in a decrease in ciprofloxacin use between 2000 and 2001; use has since increased to pre-restriction levels. In 2009, levofloxacin usage was 11.7 prescriptions per 1000, and moxifloxacin use was 16.9 prescriptions per 1000 population.

Figure 1. Rate of outpatient fluoroquinolone prescriptions by year



Between 2000 and 2010, there were 4456 cases of invasive pneumococcal disease (e.g. bacteremia, meningitis, empyema) and 3983 patients with respiratory isolates of SPN reported to the study. Ninety percent (7660/8539) of these isolates were available for susceptibility testing. Levofloxacin and moxifloxacin resistance rates have not changed significantly since 2000 (Figure 2). Since January 2006, only 2 of 1997 (0.1%) sterile site isolates of pneumococci have been moxifloxacin resistant.

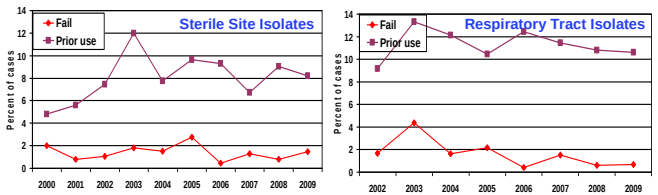
Figure 2. Levofloxacin (yellow) and moxifloxacin (blue) resistance in respiratory and sterile site isolates of *S. pneumoniae*



* Testing incomplete for 2010

Of the cases, 119 (1.4%) met our definition for failure of FQ outpatient therapy and an additional 765 (9%) patients had received a fluoroquinolone for a previous infection in the three months before presentation. Despite the increasing use of fluoroquinolones, the proportion of cases that were failures of fluoroquinolone therapy remained stable in sterile sites and decreased significantly in respiratory isolates (p=0.02). The proportion of patients with sterile site isolates who had been exposed to fluoroquinolones in the previous 3 months decreased in 2006/7 (p=0.06), but remained stable in patients with respiratory isolates (p=0.7).

Figure 3. Proportion of *S. pneumoniae* cases that were either failure of FQ therapy or had received a FQ in the previous 3 months



Results cont.

Overall, 142 (1.9%) pneumococcal isolates were resistant to levofloxacin, and 57 (0.75%) were resistant to moxifloxacin.

Figure 4. Levofloxacin resistance by risk factors and time

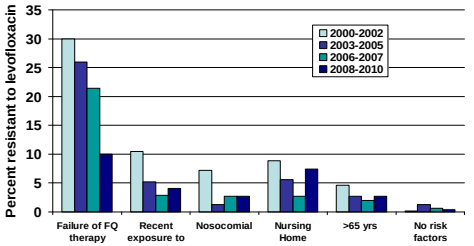
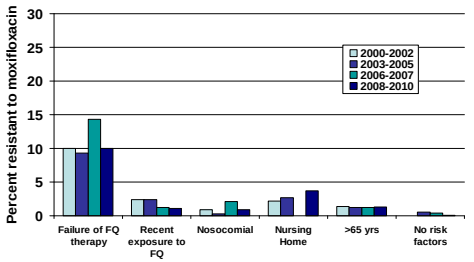
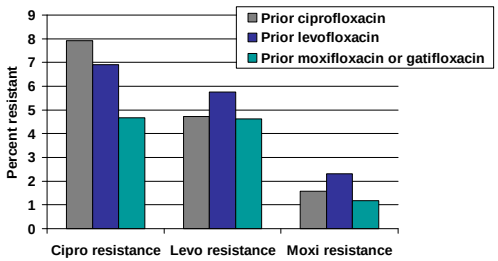


Figure 5. Moxifloxacin resistance by risk factors and time



Patients with prior exposure to more active respiratory fluoroquinolones have a slightly reduced risk of fluoroquinolone resistance compared to patients with prior exposure to levo/ciprofloxacin. This difference is not statistically significant.

Figure 6. Fluoroquinolone resistance in patients with previous exposure to fluoroquinolones



From 2006-2010, only 2 of 1977 (0.1%) patients with invasive pneumococcal disease had an isolate resistant to moxifloxacin: an 84-year-old nursing home resident who was failing ciprofloxacin therapy at diagnosis, and an 82-year-old patient with COPD who had recently been treated with levofloxacin.

Conclusions

Pneumococcal resistance to respiratory fluoroquinolones has not emerged despite increasing use of ciprofloxacin and a decade of use of respiratory fluoroquinolones. Patients failing fluoroquinolone therapy at the time of diagnosis of their pneumococcal infection are the only patients for which moxifloxacin resistance is a risk.