Re-establishment of Susceptibility to Respiratory Fluoroquinolones (FQ) in *Streptococcus pneumoniae* in Toronto, Canada

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Abstract (revised)

Background: FQ resistance (FQR) emerged in *S. pneumoniae* (SPN) in the 1990's, shortly after the introduction of ciprofloxacin. FQR increased from 1995 to 2002, and was associated with older age, recent use of FQ, and hospital/nursing home-acquired infection. We examine trends in FQR in SPN in Toronto since 2002.
Methods: From 1995-2007, TIBDN collected all SPN isolated from sterile sites from residents of Toronto/Peel (pop 4M); from 2002-2007, all respiratory tract isolates were also collected, and the population area expanded. Broth microdilution susceptibility testing to CLSI standards is performed on all isolates. Popn FQ use was obtained from IMS Health Canada. Demographic and medical data were collected from consenting patients.
Results: From 1995-2006, FQ use increased from 67 to 97 scripts/1000pop/yr; Levo use from 0 to 12.6 scripts/1000pop/yr, and Moxi use from 0 to 17.7 scripts/1000pop/year. 7212/8070 (89%) of SPN isolates were available for testing. From 2000-2006, FQR decreased significantly for isolates in all subgroups (see Table), with the exception of isolates from respiratory specimens in patients currently receiving FQ and isolates which were hospital acquired. From 2006 to 2007, there was a further decrease in resistance in respiratory isolates: Lev R from 3.5% to 1.7% (P=.11), and Mox R from 2.1% to 0.1% (P=.19). Serotype shifts associated with vaccine use do not explain these changes.

	Lev R	Mox R	Lev R	Mox R	Lev R	Mox R
Invasive disease	**2000-2002 (N=1076)**		**2003-2005 (N=1136)**		**2006-2007 (n=825)**	
All adults	1.8%	0.5%	1.3%	0.3%	0.3%	0
Adults >65y	3.2%	1.0%	1.2%	0.5%	0.3%	0
Hospital-acquired	6.2%	4.6%	3.7%	3.7%	0	0
Nursing home acquired	8.9%	2.5%	2.5%	0	2.1%	0
Failing FQ therapy	21.4%	7.1%	27.3%	9.1%	0	0
FQ prior 3 months	6.2%	3.1%	4.4%	0.9%	1.5%	0
Respiratory isolates	**2002 (N=252)**		**2003-2005 (N=1220)**		**2006-2007 (N=841)**	
All adults	5.7%	1.2%	3.4%	1.6%	2.4%	1.3%
Adults >65y	9.4%	2.6%	4.0%	1.8%	3.5%	2.1%
Hospital-acquired	6.7%	2.2%	0.8%	0.4%	3.4%	2.7%
Nursing home acquired	9.1%	0	9.7%	6.5%	4.0%	0
Current FQ therapy	60.0%	20%	24.2%	9.1%	42.9%	28.6%
FQ prior 3 months	18.5%	0	8.5%	3.9%	5.5%	2.8%

Conclusion: Despite increasing use of FQ since 1995, in 2006 and 2007 all sterile site isolates of *S. pneumoniae* were susceptible to moxifloxacin. Mox R continues to decrease despite increasing moxifloxacin use.

Introduction:

The Toronto Invasive Bacterial Diseases Network (TIBDN) has performed population-based surveillance for invasive pneumococcal disease in metropolitan Toronto and Peel region (pop'n 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 fluroquinolone resistance in SPN in Toronto since 2002 and re-examined these previously identified risk factors**.**

Methods:

From 1995 to 2006, all sterile site isolates of pneumococci identifed through population-based surveillance for pneumococcal disease in Metropolitan Toronto and Peel region were collected. From 2002 to 2006, 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.

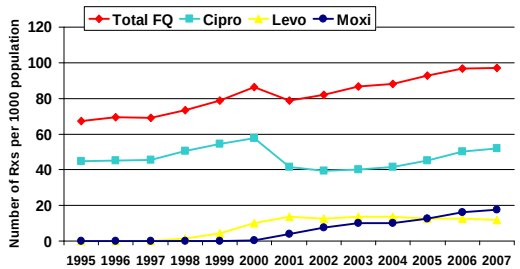
Acknowledgements:

We are grateful to the infection control practitioners, microbiology technologists, public health staff and our tireless TIBDN staff for their ongoing contributions to this surveillance. This work has been supported in part by an unrestricted grant from Bayer Healthcare AG.

Results:

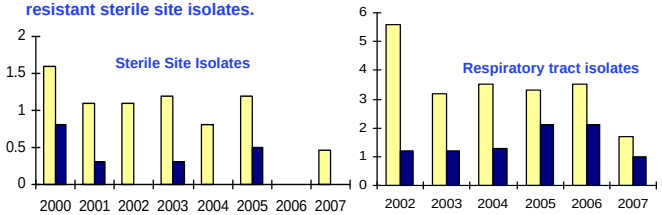
From 1995 to 2007, outpatient fluoroquinolone use increased from 67 to 97 prescriptions/1000pop/year. Per capita out-patient fluoroquinolone use during the study period is shown in Figure 1. Formulary restrictions in the provincial drug benefit formulary resulted in a decrease in ciprofloxacin use between 2000 and 2001. Total FQ use increased by 31% from 1995 to 2007.

Figure 1. Rate of outpatient fluoroquinolone prescriptions by year



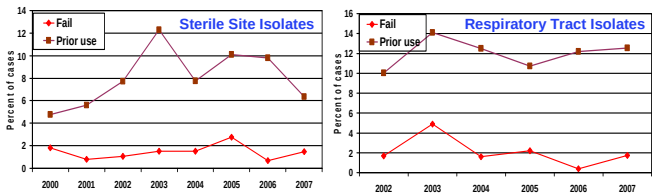
Between 2000 and 2007 there were 3217 cases of pneumococcal bacteremia and 2655 patients with respiratory isolates of *S. pneumoniae* reported to the study. 91 % of these isolates were available for susceptibility testing. Levofloxacin and moxifloxacin resistance rates appear to be decreasing in both sterile site (Lev P=0.02, Mox P=0.06) and respiratory (Lev P=0.03, Mox P=0.69)(Figure 2). In 2006/7 there were no moxifloxacin resistant sterile site isolates.

Figure 2. Levofloxacin (yellow) and moxifloxacin (blue) resistance in respiratory and sterile site isolates of *S. pneumoniae*. In 2006/7 there were no moxifloxacin resistant sterile site isolates.



101 (1.7%) of the cases met our definition for failure of FQ outpatient therapy and an additional 550 (9.4%) 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 therapy remained stable in sterile sites but 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 those 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



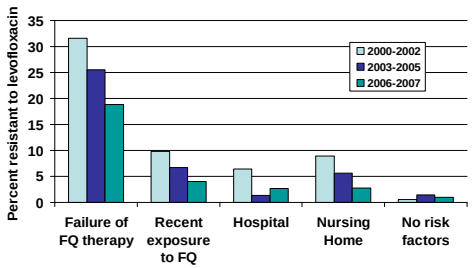
Results con't:

Overall, 105 (2%) pneumococcal isolates were resistant to levofloxacin, and 42 (0.8%) were resistant to moxifloxacin. Of the 105 patients with levofloxacin resistant isolates, 34 (32%) had been exposed to fluoroquinolones in the previous three months (12 cipro,15 lev0, 5 moxi, 1 gati and 1 oflox), 29 (28%) had acquired their infections in healthcare institutions (hospitals or nursing homes), 24 (23%) had incomplete data available for risk factors, and 11 (11%) had no risk factors identified.

Of 42 patients with moxifloxacin resistant isolates, 12 (29%) had been exposed to fluoroquinolones (4 cipro, 5 levo, 2 moxi and 1 ofloxacin), and 10 (24%) had acquired their infections in hospitals or nursing homes. 20 (48%) had no identified risk factors.

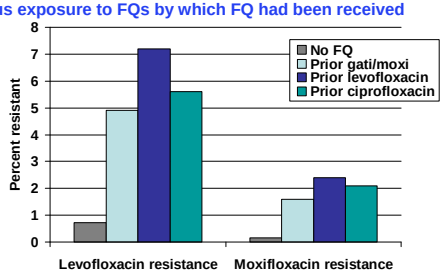
The proportion of resistant isolates in patients with identified risk factors decreased over time (9% in 2000 to 3.2% in 2007, P=0.003) (Figure 4).

Figure 4. Levofloxacin resistance by risk factors and time



26% (23/90) isolates from patients with pneumococcal disease who were failing out-patient therapy were resistant to levofloxacin, and 10% (9/90) were resistant to moxifloxacin. There was no difference in the rate of resistance by which fluoroquinolone was being used for therapy. Patients with previous exposure to more active respiratory fluoroquinolones appear to have a somewhat reduced risk of resistance in their infecting isolate, compared to patients who have been exposed to levofloxacin or ciprofloxacin. However, this difference is not statistically significant .

Figure 5. Rates of levofloxacin and moxifloxacin resistance in patients with previous exposure to FQs by which FQ had been received



Conclusions:

Despite increasing use of FQ since 1995, resistance to levofloxacin and moxifloxacin is decreasing most notably in sterile site isolates where we have not seen Mox R since 2005.