Prevalence of fluoroquinolone resistance and QRDR mutations in S. pneumoniae in Toronto, Canada, 1995-2006

A. McGeer1,2, K. Green1, R. Melano3, S. Drews2,3, S. Pong-Porter1, A. Plevneshi1, D. E. Low1,2,3, on behalf of the Toronto Invasive Bacterial Diseases Network (TIBDN)
Mount Sinai Hospital1, University of Toronto2, Ontario Public Health Laboratory3, Toronto, Ontario, Canada

Abstract
Background: The emergence of fluoroquinolone resistance (FQR) in S. pneumoniae (SP) is a concern. We examined FQ use, FQR and QRDR mutations in pneumococci in Toronto, Canada.

Methods: From 1995-2006, the Toronto Invasive Bacterial Diseases Network (TIBDN) collected all sterile site isolates of pneumococci isolated from residents of Toronto/Peel, CA (pop 4m); from 2002-2006, all respiratory tract isolates were also collected. Broth microdilution susceptibility testing to CLSI standards is performed on all isolates, sequencing of QRDR regions was performed on all FQR isolates, and a representative sample of FQ susceptible isolates. Pop’n FQ use was obtained from IMS Health Canada. Demographic and medical data were collected for all patients.

Results: From 1995 to 2006, overall FQ use increased from 67 to 94 scripts/1000 pop/yr; levofloxacin use increased from 0 to 12.6 scripts/1000 pop/yr, and moxifloxacin use increased from 0 to 15.3 scripts/1000 pop/yr. The prevalence of mutations in gyrA and parC by fluoroquinolone susceptibility is more than 2 isolates with gyrA mutations (2% of such isolates), and 20-30 parC mutations were sequenced in all FQ resistant isolates and a representative sample of pneumococcal isolates. 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.

Results: 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 44% from 1995 to 2007.

Results (cont’d)

Table 1: Prevalence of QRDR mutations by fluoroquinolone susceptibility

<table>
<thead>
<tr>
<th>Isolate susceptibility</th>
<th>Number sequenced/Total (1995-2006)</th>
<th>Number (%) with gyrA mutation</th>
<th>Number (%) with parC mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxi MIC&gt;.25ug/ml</td>
<td>157/157 (100%)</td>
<td>0 (0%)</td>
<td>124 (79%)</td>
</tr>
<tr>
<td>Levofloxacine MIC&gt;2ug/ml</td>
<td>3331/7649 (44%)</td>
<td>20 (0.6%)</td>
<td>98 (62%)</td>
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Conclusions: Despite increasing use of FQ antibiotics FQR is stable or decreasing in Toronto. Isolates with mutations in gyrA and parC remain very rare in FQ susceptible isolates. Similarly, mutations in gyrA alone remain exceedingly uncommon, suggesting the moxifloxacin exerts minimal selective pressure for 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’n 4m) since January 1, 1995. The emergence of fluoroquinolone resistance in S. pneumoniae and its impact on empiric therapy for pneumococcal disease continues to be a concern. We examined isolated and data from this surveillance to determine the prevalence of fluoroquinolone resistance and QRDR mutations in these pneumococcal isolates, and the relationship between the emergence of resistance and fluoroquinolone use in the human population.

Figure 1. TIBDN population area

Figure 2. Resistance of pneumococci to fluoroquinolones over time, TIBDN

Figure 3. Prevalence of isolates with QRDR mutations over time, TIBDN

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.