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OqxAB, a Quinoline and Olaquindox Efflux Pump, Is Widely Distributed among Multidrug-Resistant Klebsiella pneumoniae Isolates of Human Origin

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Use of antibiotics among livestock contributes to the selection and dissemination of multidrug resistant (MDR) bacteria (1). Olaquindox and carbadox are quinoline derivatives with antibacterial properties that prevent dysentery and enhance weight gain in suckling pigs (2). Resistance to quinoxalines is mediated by the efflux pump OqxAB, which also extrudes antibiotics such as chloramphenicol and fluoroquinolones (3). The gene encoding this efflux pump, oqxAB, was initially detected within plasmid pOLA52, which was found in Escherichia coli isolated from swine manure (4). Dissemination of oqxAB has been noted in Salmonella species, and the original genetic reservoir of oqxAB was traced to the chromosome of Klebsiella pneumoniae (5, 6). Surprisingly, OqxAB has been reported only in clinical isolates of K. pneumoniae from China, South Korea, and Spain (7–9).

Like other Enterobacteriaceae, K. pneumoniae is able to colonize and cause infection in animals and humans. As isolates harboring extended-spectrum β-lactamases (ESBLs) and Klebsiella pneumoniae carbapenemases (KPCs) have become so prevalent, we hypothesized that OqxAB may be widely present among these clinically relevant types of K. pneumoniae.

Isolates were screened by PCR for the oqxA gene (forward primer, 5′-GGGTTCGGGAGTACATTGAT-3′; reverse primer, 5′-GGGGATTCTTTATGTGGA-3′) and, if positive, were also screened for oqxB (forward primer, 5′-CTGGGCTTTTCCTGCTGA ATAC-3′; reverse primer, 5′-CAGGTACACCGAAAACACTG-3′). Known positive strains were used as controls. Resistance to ciprofloxacin (as a representative fluoroquinolone) was recorded for each isolate, using a breakpoint of ≥4 μg/ml (10). Sequence type was established using the multilocus sequence typing (MLST) scheme developed at the Institut Pasteur (http://www.pasteur.fr/recherche/genopole/POF/mlst/Kpneumoniae.html).

The following sets of isolates were studied (Table 1): (i) K. pneumoniae isolates harboring bla_KPC (n = 12) collected in a pediatric long-term-care facility in northeast Ohio in 2004 (11), (ii) K. pneumoniae isolates harboring bla_KPC (n = 36) obtained from acute-care hospitals in northeast Ohio in 2012, (iii) K. pneumoniae isolates harboring bla_KPC (n = 43) obtained between 2004 and 2011 from the mid-Atlantic states of the United States (New Jersey, New York, Pennsylvania), and (iv) ESBL-producing K. pneumoniae isolates (n = 16) with a variety of blalβ, blalTEM, and blalCTX-M genes, collected in the 1990s from Taiwan, Australia, Argentina, Belgium, Turkey, South Africa, and the United States (12).

The prevalence of oqxAB varied widely in the different sets of strains (Table 1). Among KPC-producing K. pneumoniae isolates from northeast Ohio, oqxAB was present in 100%. This included contemporary isolates from acute-care facilities that were also quinolone resistant and belonged to sequence type (ST) 258, as well as isolates from a pediatric long-term-care facility that were quinolone susceptible and belonged to ST 36. Among KPC-producing K. pneumoniae isolates from the mid-Atlantic, the genes

### TABLE 1 Presence of oqxAB in diverse clinical isolates of Klebsiella pneumoniae

<table>
<thead>
<tr>
<th>Location, yr of isolation</th>
<th>No. of isolates</th>
<th>Source(s)</th>
<th>Sequence type(s)</th>
<th>Acquired β-lactamase (bla) gene type(s)</th>
<th>Prevalence of oqxAB (%)</th>
<th>% with ciprofloxacin resistance (MIC ≥ 4 μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric long-term-care facility, northeast Ohio, 2004</td>
<td>12</td>
<td>Stool</td>
<td>ST 36</td>
<td>KPC-3</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Acute-care hospitals, northeast Ohio, 2012</td>
<td>36</td>
<td>Blood, urine, sputum</td>
<td>ST 258</td>
<td>KPC-2, KPC-3</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Hospitals in Taiwan, Australia, Argentina, Belgium, Turkey, South Africa, and the United States, 1996–1997</td>
<td>16</td>
<td>Blood</td>
<td>Not determined</td>
<td>TEM-10, SHV-2, SHV-5, CTX-M-2, CTX-M-3</td>
<td>87.5</td>
<td>Not determined</td>
</tr>
</tbody>
</table>

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were present in 71% (22/31) of ST 258 isolates and 91.7% (11/12) of other non-ST 258 types; 96.8% and 58.3% of these isolates were ciprofloxacin resistant, respectively. Also, oqxAB was present in 87.5% (14/16) of international ESBL-producing K. pneumoniae isolates.

Our survey indicates that OqxAB, an efflux pump found in isolates of veterinary origin, is highly prevalent in diverse clinical MDR K. pneumoniae strains isolated from humans, including KPC-producing K. pneumoniae isolates of ST 258. Furthermore, its presence in K. pneumoniae isolated more than a decade ago suggests widespread dissemination. The association of the OqxAB efflux pump with a diverse set of substrates, including fluoroquinolones, commonly used in humans, may contribute to the MDR profile of K. pneumoniae. The occult dissemination of this efflux pump gene adds to the constellation of resistance determinants already circulating in Enterobacteriaceae.

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