The role of international travel in the worldwide spread of multiresistant Enterobacteriaceae

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From international tourists to war-displaced refugees, more people are on the move than ever before. This provides the opportunity for a variety of antimicrobial-resistant bacteria to be carried from one geographic location to another. The Enterobacteriaceae are among the most important causes of serious hospital-acquired and community-onset bacterial infections in humans, and resistance to antimicrobial agents in these bacteria has become an increasingly relevant problem. International travel and tourism are important modes for the acquisition and spread of antimicrobial-resistant Enterobacteriaceae, especially CTX-M-producing Escherichia coli. Infections with KPC-, VIM-, OXA-48- and NDM-producing Enterobacteriaceae in developed countries have been associated with visiting and being hospitalized in endemic areas such as the USA, Greece and Israel for KPCs, Greece for VIMs, Turkey for OXA-48, and the Indian subcontinent for NDMs. To combat the spread of antimicrobial-resistant Enterobacteriaceae, the French Healthcare Safety Advisory Committee recently issued national recommendations for screening and contact isolation precautions for patients transferred from, or hospitalized outside, France. For effective public and patient health interventions, it is important to understand the role of international travel in the spread of antimicrobial-resistant Enterobacteriaceae. We urgently need well-designed studies to evaluate the transmission potential and risks for colonization and infections due to multiresistant Enterobacteriaceae in travellers who have recently visited or have been hospitalized in endemic areas. The emergence of CTX-M-, KPC- and NDM-producing bacteria is a good example of the role that globalization plays in the rapid dissemination of new antibiotic resistance mechanisms.

Keywords: antibiotic resistance, β-lactamases, globalization

Introduction

Easy access to air and ground transportation is making it possible for people to travel to different countries and continents in a matter of hours or days, either as tourists, immigrants, refugees, asylum seekers or migrant workers. Since the late 1990s, international air travel has grown by ~6% per year, and the International Air Transport Association reported that ~900 million passengers were transported over international borders during 2010.1 The United Nations World Tourism Organization published on their web site that a total of 940 million international tourist arrivals were recorded in 2010 (which is a 7% increase from 2009). This continued growth has been driven strongly by tourists visiting new destinations in Asia, South America, Africa and the Middle East.2

As the global population continues to grow, and economic and social disparities between rich and poor countries intensify, the world will continue to witness rapidly growing numbers of migrants in search of employment and a better quality of life. The International Labour Organization (ILO) estimated that in 2004, ~81 million migrant workers (excluding refugees) were present in different parts of the world. The ILO also reported that certain developed countries, such as Australia, Canada, New Zealand, Spain and the USA, each received an influx of >100,000 legal foreign workers during 2005.3

A number of people from some European countries, the USA, Canada, Japan and the Middle East choose to undergo several types of surgical procedure in developing countries, such as India or China, in order to avoid long waiting times for surgery in their respective home countries and to take advantage of the relatively low cost associated with the treatment elsewhere. This is referred to as medical tourism.4 It is estimated that medical tourism to India will grow by 30% each year over the next 5 years.5

This increasing population mobility of travellers and migrant workers between countries is playing an important role in the...
Antimicrobial resistance is an underappreciated threat to public health in nations around the globe. The consequences of antimicrobial resistance have resulted in treatment failures with adverse outcomes for patients and dramatic cost implications for healthcare systems. The prevalence of antimicrobial-resistant bacteria is generally higher in developing countries due to poor control in the use of antimicrobial agents, overcrowding and improper sewage disposal due to the increasing urbanization.

Overseas travel as a risk factor for the acquisition of infections due to antimicrobial-resistant enterobacteria has recently been described for infections due to quinolone-resistant *Salmonella* spp., *quinolone-resistant* *Shigella* spp. and *trimethoprim/sulfamethoxazole-resistant* *Escherichia coli*. The Enterobacteriaceae, most notably *E. coli* and *Klebsiella pneumoniae*, are among the most important causes of serious hospital-acquired and community-onset bacterial infections in humans, and resistance to antimicrobial agents in these bacteria has become an increasingly relevant problem. Since β-lactam antibiotics are a major drug class used to treat serious community-onset or hospital-acquired infections caused by Enterobacteriaceae, resistance to these agents will continue to challenge clinical therapeutic choices.

Recent reviews have addressed some general aspects of antimicrobial resistance and global mobilization, including the transfer of patients between countries. With globalization booming, it is important to understand the international spread of resistant bacteria. The aim of this review is to explore the role of travellers and the spread of antimicrobial-resistant Enterobacteriaceae, specifically those that produce newer β-lactamases. We believe this is an important but largely unrecognized issue facing public health systems and that implementation of control measures, specifically those directed at returning travellers from certain high-risk areas, will help to curtail the spread of these organisms.

**Enterobacteriaceae that produce newer β-lactamases**

In Enterobacteriaceae, β-lactamase production remains the most important mediator of β-lactam resistance. β-Lactamases are bacterial enzymes that inactivate β-lactam antibiotics by hydrolysis, which results in inactive compounds. Most important within the Enterobacteriaceae is the increasing recognition of isolates producing ‘newer’ β-lactamases that consist of plasmid-mediated AmpC β-lactamases (e.g. CMY types), extended-spectrum β-lactamases (ESBLs) (e.g. CTX-M types)), carbapenem-hydrolysing enzymes or carbapenemases (e.g. class A (KPC types) and class B [e.g. the metallo-β-lactamases (MBLs), such as VIM, IPM and NDM types]) and class D oxacilllines (e.g. OXA-48-like enzymes). The production of newer β-lactamases (with the exception of OXA-48-like enzymes) often results in broad-spectrum resistance to most of the β-lactam antibiotics. The characteristics of the Enterobacteriaceae that produce newer β-lactamases are summarized in Table 1. A report from the Infectious Diseases Society of America listed ESBL- and carbapenemase-producing Enterobacteriaceae as priority drug-resistant microbes to which new therapies are urgently needed.

**The role of international travel in the worldwide spread of CTX-M-, KPC-, VIM-, OXA- and NDM-producing Enterobacteriaceae**

ESBLs have the ability to hydrolyse the penicillins, cephalosporins and monobactams, but not the cephamycins and carbapenems, and are inhibited by ‘classical’ β-lactamase inhibitors, such as clavulanic acid, tazobactam and sulbactam, respectively (Table 1). The majority of ESBLs identified in clinical isolates during the 1980s and 1990s belonged to the SHV or TEM types, which evolved from parent enzymes such as TEM-1, TEM-2 and SHV-1. A different type of ESBL, named CTX-M β-lactamases, which originated from environmental *Kluyvera* spp., gained prominence during the 2000s with reports of clinical isolates of predominantly *E. coli* producing these enzymes; CTX-M are currently the most widespread and common type of ESBL throughout the world.

International travel as a possible risk factor for infections due to ESBL-producing bacteria in returning travellers has been implicated in various countries, including the UK and the USA. Specific ESBLs that have been identified in returning travellers with subsequent infections include SHV-12-producing *Salmonella* typhi in a Dutch patient returning from the Philippines and CTX-M-14-producing *Salmonella enterica* serotype *Choleraesuis* in a Danish patient who visited Thailand and CTX-M-15-producing *Shigella sonnei* in a Czech traveller returning from Asia. The Danish study also investigated CTX-M-14-producing *S. enterica* serotype *Choleraesuis* obtained from Thailand and showed that the Danish isolate had a PFGE pattern that was indistinguishable from those of Thai isolates, suggesting that the Danish isolate was most likely acquired while visiting Thailand.

The first sufficient evidence that travellers are also involved in the spread of CTX-M-producing *E. coli* between different countries originated from studies conducted during the mid-2000s in Calgary, Canada and in Auckland, New Zealand (Table 2). The study from New Zealand described a series of patients who presented to an Auckland hospital with community-associated genitourinary tract infections due to CTX-M-15-producing *E. coli* with a history of recent travel to or recent emigration from the Indian subcontinent. All the patients lacked the traditional risk factors associated with urinary tract infections (UTIs). The study from Calgary demonstrated that travel to the Indian subcontinent [relative risk (RR) 145.6, 95% CI 77.7–252.1], Africa (RR 7.7, 95% CI 2.8–17.2) and the Middle East (RR 18.1, 95% CI 8.1–35.2) was associated with a high risk of community-onset infections with ESBL-producing *E. coli* in returning travellers. A follow-up study in Calgary showed that these infections were mostly due to the acquisition of ST131 that produce CTX-M-15. A recent case-control study from a tertiary care centre in Switzerland showed that risk factors for infections due to ESBL-producing *E. coli* and *K. pneumoniae* included the recent consumption of antibiotics while travelling in high-risk countries.
Colonization with ESBL-producing Enterobacteriaceae was demonstrated for patients presenting with traveler’s diarrhoea in studies from Sweden, the UK and Canada. The Swedish study demonstrated that 36% (50/138) of people who travelled outside Europe and presented with diarrhoea on their return to Sweden were found to have ESBL-producing *E. coli* in their stools, compared with 3% (2/63) of those who had travelled within Europe. The UK study showed that the genetic environment around the *bla*CTX-M-15 gene of ESBL-producing *E. coli* isolated from stools of returning travellers differed from those seen in clinical isolates from non-travellers in the UK. This suggested that the isolates were acquired while travelling overseas. The Canadian study found that 5/107 (5%) of patients without a history of recent travel had CTX-M-producing *E. coli* in their stools while 26/107 (24%) of returning travellers were positive for CTX-M-producing *E. coli* (P<0.0001).

The colonization of asymptomatic returning travellers with ESBL-producing *E. coli* has been addressed in prospective studies from Sweden and Australia. The Swedish study enrolled 100 healthy volunteers who travelled outside Northern Europe and found that 24 participants were colonized with CTX-M-producing *E. coli* on their return to Sweden. Interestingly, travel to India was associated with the highest risk for the acquisition of CTX-M-producing *E. coli* (seven out of eight travellers). The Australian study showed that the presence of antibiotic-resistant *E. coli* in stool cultures increased from 7.8% pre-travel to 49% post-travel and occurred most frequently in travellers returning from Asia.

### KPC-producing Enterobacteriaceae

The most clinically significant class A carbapenemases comprise the KPC types (where KPC stands for *K. pneumoniae* carbapenemase). KPC was first reported in the late 1990s from a *K. pneumoniae* isolated in North Carolina, USA and, to date, >10 different KPC variants have been described. These enzymes provide resistance to carbapenems, cephaporphins, cephapyrins and monobactams, and are weakly inhibited by ‘classical’ β-lactamase inhibitors, such as clavulanic acid and tazobactam (Table 1). KPC β-lactamases (especially KPC-2 and -3) have been described in several enterobacterial species, especially *Klebsiella* spp. and *E. coli*. KPC-producing bacteria are considered to be endemic in certain parts of the world, such as the North-East USA, Puerto Rico, Colombia, Greece, Israel and China, and are important causes of nosocomial infections in some parts of these countries.

The genes responsible for the production of KPC enzymes are located on transferable plasmids and are associated with the mobile element transposon Tn4401, explaining their spread among clinically relevant pathogens. Plasmids that encode KPC enzymes often contain several genes that encode resistance to other antimicrobial agents, such as aminoglycosides, quinolones, trimethoprim, sulphonamides and tetracyclines. In a scenario very similar to that of ST131 with CTX-M-producing *E. coli*, it seems that a certain international sequence type, namely ST258, has played an important role in the worldwide distribution of KPC-producing *K. pneumoniae*.

### Table 1. Characteristics of Enterobacteriaceae that produce ‘newer’ β-lactamases

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Classification</th>
<th>Examples</th>
<th>Resistance spectrum</th>
<th>Inhibition</th>
<th>Bacteria</th>
<th>Endemic areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended-spectrum β-lactamases</td>
<td>Class A</td>
<td>TEM, SHV CTX-M</td>
<td>penicillins, cephalosporins, monobactams</td>
<td>clavulanic acid, tazobactam, subbactam</td>
<td><em>K. pneumoniae</em>, <em>E. coli</em>, others</td>
<td>worldwide</td>
</tr>
<tr>
<td>Plasmid-mediated AmpC β-lactamases</td>
<td>Class C</td>
<td>CMY, FOX, ACT, MOX, ACC, DHA</td>
<td>penicillins, cephalosporins, monobactams, cephamycins</td>
<td>cloxacillin, boronic acid</td>
<td><em>K. pneumoniae</em>, <em>E. coli</em>, others</td>
<td>worldwide</td>
</tr>
<tr>
<td>Metallo-β-lactamases</td>
<td>Class B</td>
<td>IMP, VIM, NDM</td>
<td>penicillins, cephalosporins, cephamycins, carbapenems</td>
<td>metal chelators, e.g. EDTA and dipicolinic acid</td>
<td><em>K. pneumoniae</em>, <em>E. coli</em>, others</td>
<td>Greece (VIM), Japan (IMP), Taiwan (IMP), Indian subcontinent (NDM), Balkan states (NDM)</td>
</tr>
<tr>
<td>KPC carbapenemases</td>
<td>Class A</td>
<td>KPC</td>
<td>penicillins, cephalosporins, cephamycins, carbapenems</td>
<td>clavulanic acid (weak), tazobactam (weak), boronic acid</td>
<td><em>K. pneumoniae</em>, <em>E. coli</em>, others</td>
<td>USA, Greece, Israel, China</td>
</tr>
<tr>
<td>OXA β-lactamases</td>
<td>Class D</td>
<td>OXA-48, OXA-181</td>
<td>penicillins, temocillin, β-lactamase inhibitor combinations, carbapenems</td>
<td>NaCl</td>
<td><em>K. pneumoniae</em>, <em>E. coli</em></td>
<td>Turkey, Morocco</td>
</tr>
</tbody>
</table>
Table 2. The role of travel in the worldwide spread of multiresistant Enterobacteriaceae

<table>
<thead>
<tr>
<th>Country (year of study)</th>
<th>Type of study</th>
<th>Infections</th>
<th>Travellers/patients</th>
<th>Country visited</th>
<th>Organisms</th>
<th>β-Lactamases</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Zealand (2004–06)</td>
<td>retrospective case study</td>
<td>community-onset UTIs</td>
<td>13</td>
<td>India (10/13 patients), China, USA</td>
<td>E. coli</td>
<td>CTX-M-15</td>
<td>29</td>
</tr>
<tr>
<td>Canada (2004–06)</td>
<td>prospective population-based surveillance case–control</td>
<td>several, including community-onset UTIs</td>
<td>247</td>
<td>India, Middle East, Africa</td>
<td>E. coli</td>
<td>CTX-M-14, -15 and others</td>
<td>30</td>
</tr>
<tr>
<td>Switzerland (2005–07)</td>
<td>colonization of travellers</td>
<td>travellers’ diarrhoea</td>
<td>58</td>
<td>NS</td>
<td>K. pneumoniae, E. coli</td>
<td>ESBLs</td>
<td>32</td>
</tr>
<tr>
<td>Sweden (2007–08)</td>
<td>colonization of travellers</td>
<td>travellers’ diarrhoea</td>
<td>242</td>
<td>various</td>
<td>E. coli</td>
<td>CTX-M-1 and -9 groups</td>
<td>33</td>
</tr>
<tr>
<td>UK (2006–08)</td>
<td>colonization of travellers</td>
<td>travellers’ diarrhoea</td>
<td>182</td>
<td>various, including India</td>
<td>E. coli</td>
<td>CTX-M-14</td>
<td>34</td>
</tr>
<tr>
<td>Canada (2009)</td>
<td>colonization of travellers</td>
<td>travellers’ diarrhoea</td>
<td>113</td>
<td>various, including India</td>
<td>E. coli</td>
<td>CTX-M-14 and -15</td>
<td>35</td>
</tr>
<tr>
<td>Sweden (2007–09)</td>
<td>colonization of travellers</td>
<td>asymptomatic</td>
<td>100</td>
<td>various, including India (7/8 patients)</td>
<td>E. coli</td>
<td>CTX-M-14, -15 and others</td>
<td>36</td>
</tr>
<tr>
<td>Australia (2008–09)</td>
<td>colonization of travellers</td>
<td>asymptomatic</td>
<td>102</td>
<td>various, including India (11/14 patients)</td>
<td>E. coli, others</td>
<td>CTX-M-1 and -9 groups</td>
<td>37</td>
</tr>
<tr>
<td>France (2005)</td>
<td>case report</td>
<td>upper UTI</td>
<td>1</td>
<td>USA</td>
<td>K. pneumoniae</td>
<td>KPC-2</td>
<td>43</td>
</tr>
<tr>
<td>France (2005)</td>
<td>case report</td>
<td>IAI</td>
<td>1</td>
<td>USA</td>
<td>E. cloacae</td>
<td>KPC-3</td>
<td>44</td>
</tr>
<tr>
<td>Israel (2006)</td>
<td>characterization of resistance</td>
<td>various</td>
<td>100</td>
<td>USA</td>
<td>K. pneumoniae</td>
<td>KPC-3</td>
<td>45</td>
</tr>
<tr>
<td>Greece (2007)</td>
<td>case report</td>
<td>rectal colonization</td>
<td>1</td>
<td>USA</td>
<td>K. pneumoniae</td>
<td>KPC-2</td>
<td>46</td>
</tr>
<tr>
<td>Colombia (2008)</td>
<td>case reports</td>
<td>various</td>
<td>84 (32 infected)</td>
<td>Greece, Israel</td>
<td>K. pneumoniae</td>
<td>KPC-2 and -3</td>
<td>47</td>
</tr>
<tr>
<td>Norway and Sweden (2007–08)</td>
<td>case reports</td>
<td>various</td>
<td>7</td>
<td>Greece, Italy</td>
<td>K. pneumoniae</td>
<td>KPC-2 and -3</td>
<td>48</td>
</tr>
<tr>
<td>The Netherlands (2009)</td>
<td>case report</td>
<td>pneumonia</td>
<td>1</td>
<td>Greece</td>
<td>K. pneumoniae</td>
<td>KPC-2</td>
<td>49</td>
</tr>
<tr>
<td>Switzerland (2009–10)</td>
<td>case reports</td>
<td>NS</td>
<td>4</td>
<td>Greece, Italy</td>
<td>K. pneumoniae</td>
<td>KPC-2 and -3</td>
<td>50</td>
</tr>
<tr>
<td>Canada (2008)</td>
<td>case reports</td>
<td>UTI, IAI</td>
<td>3</td>
<td>USA</td>
<td>K. pneumoniae</td>
<td>KPC-2</td>
<td>51</td>
</tr>
<tr>
<td>UK (2009)</td>
<td>case report</td>
<td>UTI</td>
<td>2</td>
<td>Curacao</td>
<td>K. pneumoniae</td>
<td>KPC-2</td>
<td>52</td>
</tr>
<tr>
<td>Scandinavia (2005–08)</td>
<td>characterization of resistance</td>
<td>various</td>
<td>8</td>
<td>Greece, Turkey</td>
<td>K. pneumoniae</td>
<td>VIM-1</td>
<td>53</td>
</tr>
<tr>
<td>USA (2010)</td>
<td>case report</td>
<td>sepsis</td>
<td>1</td>
<td>Greece</td>
<td>K. pneumoniae</td>
<td>VIM</td>
<td>54</td>
</tr>
<tr>
<td>Ireland (2010)</td>
<td>case report</td>
<td>wound infection</td>
<td>1</td>
<td>Greece</td>
<td>K. pneumoniae</td>
<td>VIM-1</td>
<td>55</td>
</tr>
<tr>
<td>Luxembourg (2010)</td>
<td>case report</td>
<td>wound infection</td>
<td>1</td>
<td>Greece</td>
<td>K. pneumoniae</td>
<td>VIM-27</td>
<td>56</td>
</tr>
<tr>
<td>Sweden (2008)</td>
<td>case report</td>
<td>UTI</td>
<td>1</td>
<td>India</td>
<td>K. pneumoniae, E. coli</td>
<td>NDM-1</td>
<td>57</td>
</tr>
<tr>
<td>UK (2008–09)</td>
<td>characterization of resistance</td>
<td>various, including UTIs</td>
<td>37</td>
<td>India</td>
<td>K. pneumoniae, E. coli</td>
<td>NDM-1</td>
<td>58</td>
</tr>
<tr>
<td>The Netherlands (2009)</td>
<td>case reports</td>
<td>rectal colonization</td>
<td>2</td>
<td>India</td>
<td>K. pneumoniae</td>
<td>NDM-1</td>
<td>59</td>
</tr>
<tr>
<td>USA (2010)</td>
<td>case report</td>
<td>UTI</td>
<td>1</td>
<td>India</td>
<td>E. coli</td>
<td>NDM-1</td>
<td>60</td>
</tr>
<tr>
<td>Australia (2010)</td>
<td>case report</td>
<td>pneumonia</td>
<td>1</td>
<td>Bangladesh</td>
<td>E. coli</td>
<td>NDM-1</td>
<td>61</td>
</tr>
<tr>
<td>France (2010)</td>
<td>case report</td>
<td>UTI</td>
<td>1</td>
<td>India</td>
<td>Citrobacter freundii</td>
<td>NDM-1</td>
<td>62</td>
</tr>
<tr>
<td>Japan (2009)</td>
<td>case report</td>
<td>bacteraemia</td>
<td>1</td>
<td>India</td>
<td>E. coli</td>
<td>NDM-1</td>
<td>63</td>
</tr>
</tbody>
</table>

Continued
The role of travel and the spread of Enterobacteriaceae that produce KPC β-lactamases are mostly limited to case reports (Table 2). The first case of the intercontinental spread of KPC-producing Enterobacteriaceae occurred in France, where an 80-year-old man who had previously been hospitalized in New York was admitted to a hospital in Paris during February 2005. A KPC-2-producing *K. pneumoniae* resistant to all antimicrobial agents except colistin and fosfomycin was isolated from his blood and urine. A very similar scenario was described a few months later when a KPC-3-producing *Enterobacter cloacae* was isolated from abdominal pus taken from a 31-year-old Parisian man who was previously hospitalized in New York. No secondary spread occurred in both instances. A highly epidemic clone of KPC-3-producing *K. pneumoniae* emerged in Israel during 2006, causing several nosocomial outbreaks with high mortality among patients. This clone was later identified as ST258 and was most likely introduced into Israel via travellers from the USA during the early to mid-2000s. The next report of KPC-producing Enterobacteriaceae occurred in Greece during 2007, causing nosocomial outbreaks in Athens; the genetic analysis of the *bla*KPC-2 gene suggested that the *K. pneumoniae* most likely originated from New York. In 2008, 32 patients presented with infections due to carbapenem-resistant *K. pneumoniae* in a Columbian hospital; the index case was a medical tourist who travelled from Israel to undergo a liver transplantation. The *bla*KPC was identified as KPC-2 and the isolates had PCR-generated DNA fingerprints similar to that of ST258. These were followed by various case reports describing the importation of KPC-producing Enterobacteriaceae by travellers who had recently visited endemic areas: in Norway and Sweden there were case reports of patients who were recently admitted to hospitals in Greece and Israel; in France after visiting Greece; in The Netherlands after visiting Greece; in Switzerland after visiting Italy and Greece; in Canada after visiting USA; and in the UK after visiting Curacao (i.e. the Dutch Caribbean). Secondary spread occurred in the Norwegian, Canadian and UK cases.

### Enterobacteriaceae producing MBLs (VIM, IMP and NDM)

**VIM- and IMP-producing Enterobacteriaceae**

The production of MBLs of the IMP and VIM types has mostly been detected in *Pseudomonas aeruginosa* and remains relatively rare in members of the Enterobacteriaceae, except for *K. pneumoniae* and *E. coli* present in Mediterranean Europe (VIMs in Greece, Italy and Spain), Taiwan and Japan (IMPs). It is possible that *P. aeruginosa* can act as a potential reservoir for VIMs in Enterobacteriaceae, as suggested by a study from Greece. The MBLs have the ability to hydrolyse a wide variety of β-lactams, such as penicillins, cephalosporins and carbapenems, but not the monobactams (i.e. aztreonam) (Table 1). IMP- and VIM-type MBLs are often associated with class 1 integrons that contain various gene cassettes that often render isolates resistant to various groups of antimicrobial agents.  

*K. pneumoniae* that produce VIMs were first reported during 2002, from patients admitted to intensive care units (ICUs) of three teaching hospitals located in Athens, Greece. VIM-producing Enterobacteriaceae (especially *K. pneumoniae* with VIM-1) are endemic in certain hospitals situated in Greece.
and nosocomial infections caused by these bacteria constitute a major public health problem for this Mediterranean country.\textsuperscript{57} A recently published study investigating Enterobacteriaceae responsible for bloodstream infections from three hospitals in Athens revealed that 37.6\% of all \textit{K. pneumoniae} isolates from blood were \textit{bla}\textsubscript{VIM-1} positive; 77.8\% of those isolates were isolated from patients in ICUs.\textsuperscript{58} Outbreaks of Enterobacteriaceae that produce VIM-type \(\beta\)-lactamases have also been reported in Italy\textsuperscript{59} and Spain.\textsuperscript{60}

The molecular epidemiology of \textit{K. pneumoniae} that produces VIM-1 showed multiclonal outbreaks in Athens (Greece)\textsuperscript{58} and Rawalpindi, Pakistan.\textsuperscript{61} Plasmids harbouring \textit{bla}\textsubscript{VIM-1} varied in size, displayed different restriction patterns and most often belonged to the broad-host range \textit{N} incompatibility replicon group.\textsuperscript{57} VIM-27, a single-point variant of VIM-1, has been described in \textit{K. pneumoniae} ST147 recovered from hospitals in Greece.\textsuperscript{63}

Sporadic cases of VIM-producing \textit{K. pneumoniae} have been reported in several European countries (including Portugal, France, Germany, Belgium, Poland, Hungary, Norway, Sweden, Denmark, the UK and Ireland), Turkey, Lebanon, South America (including Brazil, Argentina and Columbia), the USA, Africa (including Tunisia, Algeria and South Africa), Asia (including Japan, China, South Korea and India) and Australia.\textsuperscript{20} The role of travel and the spread of Enterobacteriaceae that produce VIM- and IMP-type MBLs are not well defined. However, the majority of sporadic cases in Europe and Ireland, due to VIM-producing \textit{K. pneumoniae}, were traced back to patients who were recently admitted to hospitals while visiting Greece or Turkey (Table 2).\textsuperscript{57,64–67}

\section*{NDM-producing Enterobacteriaceae}

Recently, a new type of MBL, named NDM, has been described in \textit{K. pneumoniae} and \textit{E. coli} recovered from a Swedish patient who was previously hospitalized in New Delhi, India.\textsuperscript{68} Kumarasamy et al.\textsuperscript{69} provided compelling evidence that NDM-producing Enterobacteriaceae (mostly \textit{K. pneumoniae} and \textit{E. coli}) are prevalent in India and Pakistan. They also found patients from the UK who were infected with NDM-producing bacteria and had recently travelled to India to undergo several types of medical procedures. These patients presented with a variety of hospital- and community-associated infections, with UTIs being the most common. Recent reports from the Indian subcontinent (including India, Pakistan and Bangladesh) show that NDM \(\beta\)-lactamases are widespread among Enterobacteriaceae in these countries\textsuperscript{70–72} and also among environmental bacteria.\textsuperscript{73} A hospital in Varanasi in northern India reported a prevalence of 6.9\% of NDM producers among 780 consecutive, non-duplicate enterobacterial species isolates between February 2010 and July 2010,\textsuperscript{74} while the prevalence was 8\% among Enterobacteriaceae from a major hospital in Mumbai, India\textsuperscript{75} and 18.5\% of patients in Rawalpindi, Pakistan carried NDM-1-producing bacteria in their gut flora.\textsuperscript{74}

Sporadic cases of infections due to bacteria that produce NDMs have subsequently been reported from different parts of the world, including several countries in Europe, North America, the Middle East, Asia, Africa and Australia.\textsuperscript{77}

The majority of NDM-1-producing bacteria are broadly resistant to various drug classes and also carry a diversity of other resistance mechanisms (e.g. 16S RNA methylases with resistance to the aminoglycosides and other \(\beta\)-lactamases such as CTX-M, CMY, OXA-48 and VIM), which leaves very limited treatment options.\textsuperscript{20} NDM \(\beta\)-lactamases have been identified most often in \textit{E. coli} and \textit{K. pneumoniae}, but are also present in various other members of the Enterobacteriaceae.\textsuperscript{77} Although \textit{bla}\textsubscript{NDM} have been identified in internationally successful sequence types, such as \textit{E. coli} ST101 and ST131, it seems that mobile, broad-host range plasmids that belong to various replicon types (e.g. IncA/C, IncF and IncL/M) are mostly responsible for the spread of this carbapenemase.\textsuperscript{77}

The role of travel and the spread of Enterobacteriaceae that produce NDM-type \(\beta\)-lactamases are also limited to case reports (Table 2). The majority of the patients from North America, Europe and Australia infected with NDM-producing bacteria were previously hospitalized in the Indian subcontinent.\textsuperscript{77} They include tourists who were hospitalized for medical emergencies and medical tourists who underwent various medical procedures, including cosmetic surgery and renal dialysis. NDM-producing bacteria have also been isolated from the stools of travellers returning from the Indian subcontinent while undergoing microbiological investigation for unrelated diarrhoeal symptoms.\textsuperscript{78} Recent reports suggest that other areas, such as the Balkan states and the Middle East, might also act as reservoirs for the spread of these bacteria.\textsuperscript{77}

\section*{OXA-48-producing Enterobacteriaceae}

OXA-48 was first identified in 2001 from \textit{K. pneumoniae} isolated in Turkey\textsuperscript{79} and since then, bacteria that produce these \(\beta\)-lactamases have been important causes of nosocomial outbreaks in this country.\textsuperscript{80} The first report of OXA-48-producing \textit{K. pneumoniae} outside of Turkey was in 2007 from Belgium,\textsuperscript{81} and bacteria that produce OXA-48 have spread rapidly to several Belgian hospitals.\textsuperscript{82} Since then, sporadic cases of infections due to Enterobacteriaceae that produce OXA-48 have been detected in several countries in Europe (e.g. France, Germany, Spain, The Netherlands and the UK) and North Africa.\textsuperscript{80} Several recent reports indicate that OXA-48-producing Enterobacteriaceae are endemic in Turkey and North African countries, such as Morocco and Tunisia.\textsuperscript{20} The spread of this carbapenemase is mostly due to a mobile 62.5 kb plasmid that belongs to the \textit{IncL/M} replicon group, as well as the presence of \textit{Tn1999}.\textsuperscript{83} Interestingly, the 62.5 kb plasmid does not carry additional resistance genes. \textit{K. pneumoniae} that produce OXA-181, which is a point mutation of a variant of OXA-48, had recently been identified in India.\textsuperscript{20}

OXA-48 and OXA-181 have good activity against the penicillins, weakly hydrolyse the carbapenems, and show very weak activity against the oximino-cephalosporins (e.g. ceftaxime, ceftriaxone and ceftazidime) and aztreonam.\textsuperscript{20} These enzymes have mostly been identified in \textit{K. pneumoniae} and \textit{E. coli}, and are not inhibited by metal chelators, such as EDTA, or ‘classical’ \(\beta\)-lactamases inhibitors, such as clavulanic acid or tazobactam (Table 1). The production of ESBLs and/or permeability barriers in bacteria that coproduce OXA-48 will increase the level of resistance to the cefalosporins and carbapenems.\textsuperscript{20}

As noted with KPC-, VIM- and NDM-producing bacteria, the role of travel and the spread of Enterobacteriaceae that produce OXA-48-type \(\beta\)-lactamases are mostly limited to case
reports (Table 2): from France there are case reports of patients who were admitted to hospitals in Morocco, and Turkey from Slovenia of a patient who was admitted to a hospital in Libya; and a study from Israel showed that medical tourism was responsible for the introduction of OXA-48-producing Enterobacteriaceae into Israeli hospitals due to patients who were transferred from Georgia and Jordan. K. pneumoniae ST395 that produce OXA-48 were recently identified in The Netherlands, and this sequence type with OXA-48 had also been described in France and Morocco, suggesting importation into The Netherlands from either of these countries.

Discussion

The continuous movement of people over international borders is playing an integral role in globalization. A century ago, it took ~365 days to circumnavigate the globe; today it can take <36 h. From international tourists to war-displaced refugees, more people are on the move than ever before. This provides the opportunity for a variety of antimicrobial-resistant bacteria to be carried rapidly from one geographic location to another.

The importance of travel in the global spread of antimicrobial-resistant bacteria becomes apparent when people move from countries with high levels of antimicrobial resistance to countries with lower levels of antimicrobial resistance, including areas where bacteria with novel resistance mechanisms (e.g. NDM-producing isolates) are absent or rare. The clinical microbiology laboratory acts as an early warning system, alerting the medical community to new resistance mechanisms present in clinically important bacteria. In regions with low levels of antimicrobial resistance, it will be reasonably easy for clinical microbiology laboratories to recognize the importation of novel multiresistant bacteria by travellers. It is important to understand the role of international travel in the spread of antimicrobial-resistant bacteria in order to implement effective public and patient health interventions. Our review shows that international travel and tourism are important modes for the acquisition and spread of antimicrobial-resistant Enterobacteriaceae. The evidence that international travel is a risk factor for rectal colonization and infections due to Enterobacteriaceae that produce newer β-lactamases is strongest for CTX-M-producing E. coli. Several case–control studies from New Zealand, Canada, Sweden, Switzerland and Australia clearly show that international travellers have a higher risk for rectal colonization and infection due to CTX-M-producing E. coli than people without a recent history of overseas travel. The Indian subcontinent is associated with the highest risk of colonization with CTX-M-producing E. coli. The combination of the temporal changes in the gastrointestinal flora of travellers due to the consumption of antibiotics for traveller’s diarrhoea, with the presence of inappropriate sewage systems, poor levels of healthcare services and high carriage rates of multiresistant bacteria in the Indian population provides the ideal opportunity for the rectal colonization of visiting travellers with CTX-M-producing E. coli.

The emergence of CTX-M-producing E. coli across different continents, especially isolates that produce CTX-M-15, is an excellent example of the important role that travel to certain high-risk areas (i.e. the Indian subcontinent) plays in the global spread of antimicrobial-resistant bacteria. CTX-M-15, which was first described in E. coli from India during 2001, are important pathogens causing worldwide community-associated infections. The initial colonization of travellers with CTX-M-producing E. coli and the subsequent worldwide distribution occurred most likely during the late 1990s and early 2000s. Since reports from India indicated that >70% of E. coli collected from the community are ESBL producers, it is conceivable that foreign travel to high-risk areas, such as the Indian subcontinent, potentially played an important role in the initial spread of CTX-M-producing E. coli across different continents. However, certain studies from The Netherlands and France failed to identify recent international travel as a risk factor for infection due to CTX-M-producing E. coli.

The association of overseas travel with the risk for colonization or infections due to KPC-, VIM-, NDM- and OXA-48-producing Enterobacteriaceae is mostly limited to case reports. However, there is very little doubt that infections with KPC-, VIM-, OXA-48- and especially NDM-producing enterobacteria in non-endemic countries have been associated with visiting or being hospitalized in endemic areas, such as the USA, Greece and Israel for KPCs, Greece for VIMs, Turkey and Morocco for OXA-48, and the Indian subcontinent for NDMs (Table 2).

In order to prevent the introduction and spread of multiresistant bacteria by returning travellers in their respective home countries, it is essential to rapidly identify patients colonized or infected by these bacteria. This can be accomplished by rectal screening for colonization with multiresistant enterobacteria in patients who have recently visited or been admitted to hospitals in endemic areas. Adequate infection control measures, such as contact isolation precautions, should then be implemented for colonized or infected patients. In 2010, the French Healthcare Safety Advisory Committee issued national recommendations for screening and contact isolation precautions for patients transferred from, or hospitalized outside, France. These recommendations target vancomycin-resistant enterococci (VRE) and carbapenemase-producing enterobacteria (CPE). Healthcare facilities have to notify regional health authorities about patients who are colonized or infected with VRE or CPE, and laboratories are requested to refer isolates to the antimicrobial resistance referral centre or an expert laboratory for additional testing and confirmation of the resistance mechanisms.

It is also recommended that adequate infection control measures be implemented once the VRE and/or CPE status is confirmed as positive. These include the reinforcement of standard contact precautions, contact tracing and cohorting of patients.

The pandemics caused by CTX-M-, KPC- and NDM-producing Enterobacteriaceae during the 2000s highlight, yet again, the desperate need for publicly funded global antimicrobial resistance surveillance systems, especially in resource-limited countries, where novel resistance mechanisms are more likely to emerge. These surveillance systems will help to determine the scope of the antimicrobial resistance in resource-limited countries, ensure the early recognition of novel resistance mechanisms and aid the implementation of measures to curb the worldwide spread of antibiotic resistance. Additionally, there is a need for a timely sharing of international data to ensure the monitoring of resistance trends and the recognition of emerging antimicrobial resistance mechanisms. The European Centre for Disease Prevention and Control has developed a communication
platform tool dedicated to antimicrobial resistance (AMR) in healthcare-associated infections (HAIs), and is referred to as the Epidemic Intelligence Information System (EPIIS) AMR-HAIs. EPIS AMR-HAIs allows experts from national risk assessment bodies within the European Union (EU) to rapidly and securely exchange information related to microorganisms with emerging antimicrobial resistance that have a potential impact in the EU. EPIS AMR-HAIs will be a potentially very useful tool for information exchange and subsequent rapid interventions, so long as confidentiality is guaranteed. Similar communication platforms should also be established and developed in resource-limited countries.

The emergence of NDM-producing bacteria is a good example of the early recognition of a novel resistance mechanism associated with travel and the role of globalization in the rapid dissemination of such a new antibiotic resistance mechanism. We urgently need well-designed prospective, case–control studies to investigate the risk factors for acquiring multiresistant bacteria in travellers to high risk areas and to evaluate the risks for infection due to travel-associated multiresistant Enterobacteriaceae. These studies should also explore the transmission potential in people colonized with antimicrobial-resistant organisms when they return to their home countries. These issues are still largely unexplored and need to be addressed.

Antimicrobial resistance is a global problem that requires local, national and global responses. Surveillance systems that provide epidemiological and molecular information about antimicrobial resistance in pathogens among humans, animals and plants are the key to understanding the magnitude of antimicrobial resistance. This information in combination with epidemiological background data will help in developing publicly funded targeted interventions aimed at controlling antibiotic resistance globally.

Funding
This work was supported by a research grant from the Calgary Laboratory Services (#73-6350).

Transparency declarations
J. D. P. had previously received research funds from Merck and Astra Zeneca. A. KvdB. has nothing to declare.

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