VIEWPOINTS

Dissemination of Antibiotic-Resistant Bacteria across Geographic Borders

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The development of antibiotic-resistant (AR) bacteria in any country is of global importance. After their initial selection and local dissemination, AR bacteria can be transferred across international borders by human travelers, animal and insect vectors, agricultural products, and surface water. The sources and routes of importation of strains of AR bacteria are most often unknown or undetected, because many bacteria carrying resistance genes do not cause disease, and routine surveillance often does not detect them. Control of international dissemination of AR bacteria depends on methods to reduce selection pressure for the development of such bacteria and improved surveillance to detect their subsequent spread.

The risk of transmission of antibiotic-resistant (AR) bacteria from one country to another grows as the “global village” shrinks. Strains can be imported into a country and disseminated before their presence is recognized, and countries vary in their capacity to detect and deal with resistant bacteria once introduced. For these reasons, the emergence of an AR bacterial strain in one location becomes a global problem. In recent Scandinavian studies, greater genetic relatedness existed between Enterococcus faecium and Salmonella enterica isolated from humans in different countries than between strains isolated from humans and animals in the same country [1, 2]. These findings suggest that the transmission of some AR bacteria across borders may be even more important than the spread of AR resistant bacteria within countries.

An example of the international dissemination of clinically important AR bacteria is the introduction and spread of African and Asian penicillinase-producing Neisseria gonorrhoeae (PPNG) in Great Britain in the 1970s. Before then, PPNG was virtually unknown in Britain, and treatment of gonorrhea was usually carried out empirically with penicillin. In the subsequent decade, PPNG became endemic in Britain, and penicillin could no longer be used empirically [3]. More recently, Smith et al. [4] have shown that the majority of cases of infection due to quinolone-resistant Campylobacter in Minnesota in 1996–1997 were associated with international travel.

Other clinically important bacterial species that combine the dual risk of emerging antibiotic resistance and international transmission include staphylococci, Streptococcus pneumoniae, Mycobacterium tuberculosis, and both pathogenic and commensal enteric bacteria (reviewed in [5–8]). The transmission of nonpathogenic AR bacteria is also important because they can serve as reservoirs of resistance genes that may be transferred to pathogens. The magnitude of the problem is summarized by the World Health Organization: “antimicrobial resistance is a global problem, affecting developed and developing countries, and rapidly spreading between continents through international travel” [9]. In this article, we provide a review of and perspective on this expanding public health problem.

SELECTION OF AR BACTERIA IN INDUSTRIALIZED COUNTRIES

In many industrialized countries, overprescription of antibiotics [10, 11] and the increasingly popular use of disinfectants for routine hygiene have been shown to contribute to the selection pressure for AR bacteria [12, 13]. Perhaps even greater pressure is exerted by the use of approximately 50% of the antibiotics produced in developed countries for veterinary medication or growth pro-
motion in animal husbandry. Large-scale farming practices such as the inclusion of poultry waste in cattle fodder may provide conditions suitable for the exchange of AR organisms by livestock and consequently increase the chance that these organisms will be transmitted to humans [14, 15]. In hospitals, day-care centers, and nursing homes, AR bacteria are efficiently transmitted to inmates and their contacts, increasing local prevalence and the possibility that AR organisms will be exported [16–18].

TRANSMISSION OF NEWLY SELECTED AR BACTERIA FROM DEVELOPED TO DEVELOPING COUNTRIES

All of the antibiotics in clinical use today have been developed in industrialized countries. With rising costs of drug development, newer, patent-protected drugs are expensive and are used sparingly, if at all, in developing countries. However, AR organisms tend to spread rapidly in tropical developing countries, once introduced [19, 20]. As a result, AR bacterial strains selected in the developed world theoretically could be introduced into the developing world before the drug to which they are AR is available.

DEVELOPING COUNTRIES AS RESERVOIRS OF AR BACTERIA

For many bacterial genera, the problem of antibiotic resistance is more pronounced in developing countries, where several factors select for antibiotic resistance genes and encourage dissemination of AR strains (reviewed in [19, 21, 22]). Antibiotic pressure is enhanced by the use of subtherapeutic doses of antimicrobial agents, that are often of substandard quality. Poor infection control practices and sanitation allow AR organisms to be spread from person to person, magnifying the effect of their selection or importation. Infections are also likely to be improperly treated or untreated in developing countries, making it likely that AR organisms, when present, will spread. The warm and humid tropical climate is conducive to propagation of bacteria [23]. This, combined with the low level of sanitation in many developing countries, particularly in urban slums, provides an efficient means for the dissemination of these strains throughout the community, and thus increases the likelihood that they will be exported [19].

POSSIBLE ROUTES OF IMPORTATION

International Travel by Humans

• Short-term travelers. Because travel is quicker, more convenient, and cheaper than ever, the number of persons crossing borders has increased remarkably [24]. This provides greater opportunity for both pathogenic and nonpathogenic varieties of AR bacteria to be carried further distances and less chance that these bacteria will be detected before they are implanted in another country [24]. In addition, the high population densities in most port cities make it likely that AR bacteria will spread rapidly once introduced [25].

The importance of travel in the dissemination of AR bacteria is demonstrated by the study of Murray et al. [26], who showed that visitors to Mexico acquired AR flora without ingesting antibiotics and returned with these organisms to the United States. Similarly, Cobelens et al. [27] showed that the risk of infection with M. tuberculosis, which may be drug-resistant, was high among long-term travelers to areas of endemicity. Immigrants and other long-term travelers. Kenyon et al. [28] recently observed a correlation between the increase in pediatric tuberculosis patients and immigration from countries of endemicity into California. Most of the source cases, mainly parents of the children, were foreign-born, and 92% of cases were linked to a country where tuberculosis is endemic [28]. Other categories of travelers who are important as vehicles for the importation of AR organisms include refugees and relief workers [29, 30], as well as patients referred internationally for specialized health care [31].

Transmission aboard airplanes and ships. Transmission of pathogenic and AR microbes aboard airplanes can occur, as demonstrated by aerosol infection of multiply-resistant M. tuberculosis during long-distance air travel [32, 33]. Even though modern jet planes have air-purification systems superior to those found in most buildings, risk factors such as close proximity to highly infectious cases and long-distance travel appear to increase the chance of person-to-person transmission of M. tuberculosis [33, 34]. Foodborne bacteria, including Shigella sonnei and Vibrio cholerae, have been transmitted by contaminated meals served during international flights or aboard cruise ships [34–37].

Importation with Livestock or Agricultural Products

In Europe, the glycopeptide avoparcin, used in animal feeds, has provided selection pressure for vancomycin-resistant enterococci [15, 38]. Although avoparcin is not used in animal husbandry in the United States [39] or developing countries, the potential exists for importation of AR European strains with livestock or animal fodder [40].

AR commensal gastrointestinal flora is likely acquired from contaminated food. Up to 70% of fruits and vegetables eaten in the United States are imported from tropical countries, and many are consumed uncooked [41]. Food from developing countries is often contaminated with AR bacteria [42, 43]. Iceberg lettuce imported from Spain was responsible for outbreaks of AR S. sonnei dysentery in different parts of Europe [44]. Similar outbreaks occurred recently in the United States and Canada, with parsley from Mexico being strongly implicated [45].
Wildlife and Animal Pests

Wildlife provides a reservoir for potential transfer of AR bacteria across international borders. In a recent report, resistance among enteric bacteria from bank voles and wood mice—which presumably had no direct contact with antibiotics, humans, or antibiotic-exposed animals—was shown to be highly prevalent [46]. Souza et al. [47] also demonstrated that isolates of Escherichia coli from a wide variety of wild mammals were resistant to antibiotics, and Kadavy et al. [48] found multiply resistant Providencia species colonizing natural oil fly larvae. These data demonstrate the abundance of multiply resistant bacteria in the wild. Just as important, transfer across borders was demonstrated by migrating birds in Sweden that were found to carry enteric organisms resistant to multiple antibiotics [49]. Pet birds imported from tropical countries can also carry AR organisms, because they are frequently treated with antibiotics [50]. Insect and rodent pests have the capacity to act as vehicles for AR organisms as well [51]. The public health importance of such transfers depends on the frequency of contact between imported wildlife or pests and resident humans, livestock, or food.

Surface Water

Several studies have been conducted to identify environmental reservoirs of AR bacteria. In areas where such organisms exist in high densities, they may find their way into bodies of water via sewage runoff [52]. Sternes [53] identified vancomycin-resistant enterococci in the water of the Rio Grande, which runs along the border of the state of Texas. They speculated that Mexico was a possible source of the organisms because of the easy availability of antibiotics in that country. Further evidence of the role of flowing water in the dissemination of AR bacteria is provided by the observation that environmental organisms isolated downstream of wastewater discharge into the Arga River in Spain were more likely to carry resistance genes than those isolated from upstream areas [54].

Clinical or epidemiological evidence can also be used to infer transfer of AR organisms between countries. For example, AR pathogens endemic in many developing countries have been recovered from recent returnees in the United States and Europe who were presumed to be infected during their visits abroad (table 1) [3, 36, 56]. When strains causing infections show unusual antibiotic resistance patterns, they may have been imported from countries where such resistance is commonplace [57].

The reports listed in table 1 undoubtedly describe a small fraction of the actual number and variety of clinically significant importations of AR organisms that have occurred and do occur internationally. Confirmatory evidence of the transfer of antibiotic resistance is difficult to obtain. First, because surveillance of antibiotic resistance is difficult to obtain. First, because surveillance of antibiotic resistance by clinical laboratories in many countries is poor or lacking altogether, it is often impossible to prove that cross-transfer has occurred [62]. In some countries, because susceptibility testing is rarely conducted or documented, local resistance patterns are not known, and imported AR strains pass undetected. Second, even when more sophisticated molecular tests are available, the detection of identical resistance genes in strains from different countries may be insufficient to infer cross-transfer. Similar or identical genes may appear in different geographic locations as a result of separate evolutionary

Table 1. International transmission of antibiotic-resistant bacteria.

<table>
<thead>
<tr>
<th>Reference(s)</th>
<th>Resistant organism</th>
<th>Antibiotic resistance</th>
<th>Route of importation</th>
<th>Likely mode of importation</th>
</tr>
</thead>
<tbody>
<tr>
<td>[57]</td>
<td>Escherichia coli</td>
<td>β-Lactams, mediated by plasmid-borne SHV-5 β-lactamase gene</td>
<td>Indian subcontinent to United Kingdom</td>
<td>Human travel</td>
</tr>
<tr>
<td>[58, 59]</td>
<td>Salmonella typhi</td>
<td>Multiple antibiotics</td>
<td>Developing countries (mainly South Asia) to United States and Canada</td>
<td>Human travel</td>
</tr>
<tr>
<td>[31]</td>
<td>MRSA</td>
<td>Multiple antibiotics</td>
<td>Great Britain to The Netherlands</td>
<td>Human travel (health workers)</td>
</tr>
<tr>
<td>[60]</td>
<td>MRSA</td>
<td>Multiple antibiotics</td>
<td>Brazil to Portugal</td>
<td>Unknown</td>
</tr>
<tr>
<td>[49]</td>
<td>Shigella sonnei</td>
<td>Ampicillin, TMP-SMX, streptomycin</td>
<td>Mexico to United States</td>
<td>Imported food (parsley)</td>
</tr>
<tr>
<td>[4]</td>
<td>Campylobacter jejuni</td>
<td>Quinolones</td>
<td>Europe and Asia to United States</td>
<td>Human travel</td>
</tr>
<tr>
<td>[61]</td>
<td>Streptococcus pneumoniae</td>
<td>Multiple antibiotics</td>
<td>Spain to Iceland</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

NOTE. MRSA, methicillin-resistant Staphylococcus aureus; SHV-5, sulphydryl variable-5; TMP-SMX, trimethoprim-sulfamethoxazole.
events [63]. Finally, tracking important strains may be difficult, because bacterial strains are constantly evolving during dissemination [2].

Initial detection of antibiotic resistance is conventionally carried out by antibiotic susceptibility tests of cultured organisms. The inherent difficulty in cultivating some species and bacterial variants (such as small-colony variants of staphylococci [64] and viable but nonculturable bacteria [65, 66]) makes both detection and antibiotic susceptibility testing difficult. Genotypic identification of such organisms is not yet used routinely in most clinical laboratories [57, 67]. Even when bacteria can be cultivated, isolates from developing countries are often unavailable for analysis. Few developing countries have operational surveillance systems, and many do not have functional clinical microbiology laboratories [68, 69].

WHAT WE CAN LEARN FROM THE NOSOCOMIAL SPREAD OF AR BACTERIA?

Although the organisms causing AR hospital-acquired and community-acquired infections often differ, much can be learned from the dissemination of nosocomial AR bacteria, particularly as the organisms spread within and between different institutions [70]. Factors that have been instrumental in the nosocomial spread of AR bacteria are antimicrobial pressure, inadequate detection and reporting by clinical laboratories, asymptomatic carriage, environmental reservoirs, intrahospital and interhospital transfer of colonized persons, inadequate infection-control precautions, and inadequate compliance with hand washing and barrier precautions [71].

As in hospitals, the selection pressure in countries varies. The countries with higher prevalences of AR bacteria tend to have features similar to hospitals at risk of acquiring AR organisms. These features include indiscriminate use or overuse of antibiotics, high population density, environmental reservoirs, inadequate surveillance, and poor infection control.

The technology exists for screening every person, animal, or food item entering a country for bacteria resistant to antibiotics of clinical importance [69, 72]. Such screening, however, would be expensive, impractical, and unpopular among exporters and tourists [33]. There are also the difficult questions of whether to screen before or after travel and what to do when someone “fauls” the screening test. A far more practicable approach would be to provide support for (1) the global control of antimicrobial resistance (including reducing selection pressure and improving infection control and hygiene), (2) vaccination, (3) good surveillance, (4) and efficient travelers’ education [41, 73, 74].

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