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REVIEWS

Risk of Highly Resistant Bacteria Importation from Repatriates and Travelers Hospitalized in Foreign Countries: About the French Recommendations to Limit Their Spread

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The rapid development of transport and communication, environmental exchanges, and migration of populations creates opportunities for the spread of infectious diseases. The emergence and spread of pathogenic and epidemic pathogens is a major emerging phenomenon of the past 30 years. Some species of bacteria have become resistant to multiple antibiotics and, sometimes, to all antibiotics available: multidrug-resistant bacteria (MDR), extensively drug-resistant bacteria (XDR), or pan drug-resistant bacteria (PDR).[1–3] These terminologies have drawn attention to the evolution of multidrug resistance and the potential difficulties in treating bacterial infections now and in the future.[4]

The very high levels of resistance that are currently observed result from massive exposure to antibiotics, to which humans and animals have been subjected over the past 50 years.[5] Resistance to antibiotics concerns not only pathogens but also, and probably even more importantly, the commensally bacteria colonizing individuals (humans and animals). These are less easily detected because the carriage is asymptomatic.

More than 80 million foreign visitors travel in France each year. In the same period, 19.4 million French peoples travel to foreign countries, more often in Europe.[6] In addition, 1.4 million French peoples live in foreign countries (i.e., 48% Europe, 20% America, 15% Africa, 8.5% in Asia-Oceania, and 6.6% in the Near and Middle East).[7] The repatriation of French patients from foreign hospitals, but also health care provided to foreigners traveling in France, whatever their nationality, then expose the French population to highly resistant bacteria acquired in high resistance prevalent areas.

The risk of the emergence and spread of highly resistant bacteria from migration has been recently evaluated in France because sporadic or limited epidemic situations have occurred in the recent past with pathogens such as *Clostridium difficile* ribotype 027,[8,9] carbapenemase-producing Enterobacteriaceae (CPE),[10–12] vancomycin-resistant *Enterococcus* (VRE),[13,14] or multidrug-resistant *Acinetobacter baumannii*.[15]

French guidelines to control the hospital spread of CPE and VRE from patients repatriated and travelers hospitalized in French hospitals were published in August 2010.[16] They are so far available in French only but an official translation into English is under consideration. This article reviews the highly resistant bacteria at risk of importation from high prevalence foreign countries, having only spread to France on sporadic or limited epidemic situations, and describes the recent French guidelines to control their spread.

Carbapenemase-Producing Enterobacteriaceae

The emergence of CPE since the early 1990s is alarming, and carries the risk for therapeutic failures.[17] The carbapenems are now often used for the treatment of severe infections caused by Enterobacteriaceae producing extended-spectrum β-lactamases (ESBL). The large increase of ESBL prevalence and the exposure of hospitalized population to carbapenems appear to be a major factor favoring the emergence of carbapenem-resistant bacteria via

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selective pressure, particularly in *Klebsiella pneumoniae* species, also in other species such as *Escherichia coli*.[18] Resistance is due to carbapenemases, of which there are three types: *K pneumoniae* carbapenemases (KPC), metallo-β-lactamases, and oxacillinases.[19] The production of metallo-β-lactamases has mostly been associated with *Pseudomonas aeruginosa* and *Acinetobacter* spp. and is rare in Enterobacteriaceae, except in isolates from Mediterranean Europe.[20] New Delhi metallo-β-lactamase (NDM) 1 was identified in *K pneumoniae* and *E coli* recovered from a Swedish patient who was admitted in a hospital in New Delhi, India.[21]

The first CPE strain described was a *Klebsiella* isolate recovered in North Carolina, United States in 1996, and the enzyme was called KPC-1.[22] Subsequently, other KPC-type enzymes have been described throughout the United States (KPC-2 to KPC-7) by sporadic or epidemic spread.[23] The first outbreak of KPC outside the United States was reported in Israel, from passengers and/or patients having traveled between the two countries.[24] Since then, many continents, such as South America and Asia, have reported the emergence of CPE. In Europe, the phenomenon appears to be rare, but CPE strains were isolated sporadically in Sweden, Ireland, UK,[25] and Greece, which currently represents a high prevalence area.[2,26] Most of the CPE episodes observed in France were related to cross-border transfer, mainly after hospitalization in countries abroad where CPE are endemic. Moreover, the origin of index cases was highly consistent with population migration routes and countries most frequently visited by French tourists.[11,12,27,28] Because OXA-48 remains difficult to detect, especially when it is not associated with an ESBL, enhanced surveillance and rapid identification are essential to prevent cross-transmission.[29]

The European Antimicrobial Resistance Surveillance System (EARSS) began collecting antimicrobial susceptibility data for invasive *K pneumoniae* in 2005.[30] In 2008, 12,227 isolates were reported from 31 countries, and for the first time, the EARSS network was able to provide trends in time, as results are available now from the last 4 years. Carbapenem resistance is still absent in most countries (Figure 1).[30] Seven countries reported from 1 to 5% resistance: Bosnia and Herzegovina (3%), Italy (2%), Latvia (3%), Norway (1%,), Portugal (1%), Turkey (3%), and the UK (1%). In three countries, carbapenem resistance is considerably higher: Cyprus (10%), Greece (37%), and Israel (19%).

In the August 2010 issue of *The Lancet Infectious Diseases*, Kumarasamy and colleagues provided evidence that NDM-producing Enterobacteriaceae (mostly *K pneumoniae* and *E coli*) are widespread in India and Pakistan.[31] They also identified patients in the UK infected with NDM-producing bacteria who had recently traveled to India for various types of medical procedures. Since 2008, there has been repeated import of NDM-1-positive bacteria from the Indian subcontinent to Europe, the United States, Canada, Asia, and Australasia, which was often mediated via transfers of patients, as well as some direct transmission in Europe and some unaccounted clusters linked to the Balkans.[32,33]

Vancomycin-Resistant *Enterococcus*

Enterococci belong to the resident flora of the gastrointestinal tract of humans. Under normal circumstances, they are harmless commensals and are even believed

Figure 1 Proportion of carbapenems resistant *Klebsiella pneumoniae* isolates in participating countries in 2009.[30]

to have positive effects on a number of gastrointestinal and systemic conditions. Resistance to glycopeptides has emerged first in the United States, and more recently, in Europe.[34] The emergence of VRE in Europe is alarming because of the pan drug-associated resistance involving difficulties to treat infected patients. Moreover, glycopeptides are one of the last lines of treatment for methicillin-resistant *Staphyloccocus aureus* (MRSA) infections and the resistance gene can spread from VRE to MRSA strains. The transmission of this glycopeptides resistance to other bacteria such as MRSA, which is highly pathogenic and widespread, is quite rightly feared. Seven cases of VRSA have already been described in the United States.[35] VRE currently represents over 30% cases of enterococcal infections in the United States[36] despite the publication of guidelines for control of VRE.[37] In Europe, the situation is heterogeneous, as shown by the EARSS network data (Figure 2).[30] Three countries reported resistance rates above 25% (Ireland, Luxembourg, and Greece) and five countries reported resistant rates between 10 and 25%, whereas the majority of countries (18 of 26) reported resistant rates below 10%; rates below 1% were reported from seven countries (Bulgaria, Estonia, Finland, France, Norway, Romania, and Sweden). From 2005 to 2009, a significant decrease in vancomycin resistance was observed in France (from 2 to 0.8%),[38] Greece (from 37 to 27%), and Italy (from 19 to 4%). Greece, in particular, has managed to downsize the very high levels of vancomycin resistance, but still has higher resistance levels than most of the other countries under surveillance.

The prohibition of glycopeptides' derivatives use as growth promoters in animals in Europe since 1997 and the moderate use of vancomycin (particularly as oral formulation) in human medicine in Europe have protected France from VRE high endemic emergence, as only few cases of colonization were reported. However, since 2004, several outbreaks have been reported in French healthcare facilities.[13,14] This emergence seems unpredictable and all institutions may be affected. The rapid implementation of infection control measures, such as outlined in the French guideline published in 2010, remains a key factor to controlling a sporadic case, before a major outbreak occurs.[39,40] The VRE prevalence is actually changing in some European countries, and the risk to move from a sporadic to an endemic situation is real in France from repatriated French people or foreign travelers requiring hospital care.

Multiresistant *A baumannii*

The worldwide spread of multidrug-resistant *A baumannii* seems different from other pathogens. It is a saprophytic bacteria that lives mainly in the environment and its epidemiology varies from one country to another and from one institution to another.[41] The species *A baumannii* is naturally resistant to many antibiotics. Moreover, strains have acquired additional resistance mechanisms using hospital antibiotic selective pressure. Some strains are pan-resistant to all available antibiotics, exposing patients to therapeutic failures, particularly when resistance to imipenem is present. *Acinetobacter baumannii* often affects patients in intensive-care unit and spreads mostly by cross-transmission, with environmental reservoirs often playing a major role. A multidrug-resistant *A baumannii* epidemic spread in non-ICU area is possible, as it has been observed in several hospitals in Northern France in 2005.[15] Thus, *Acinetobacter* is an old friend but a new enemy.[42] A large number of European countries have reported

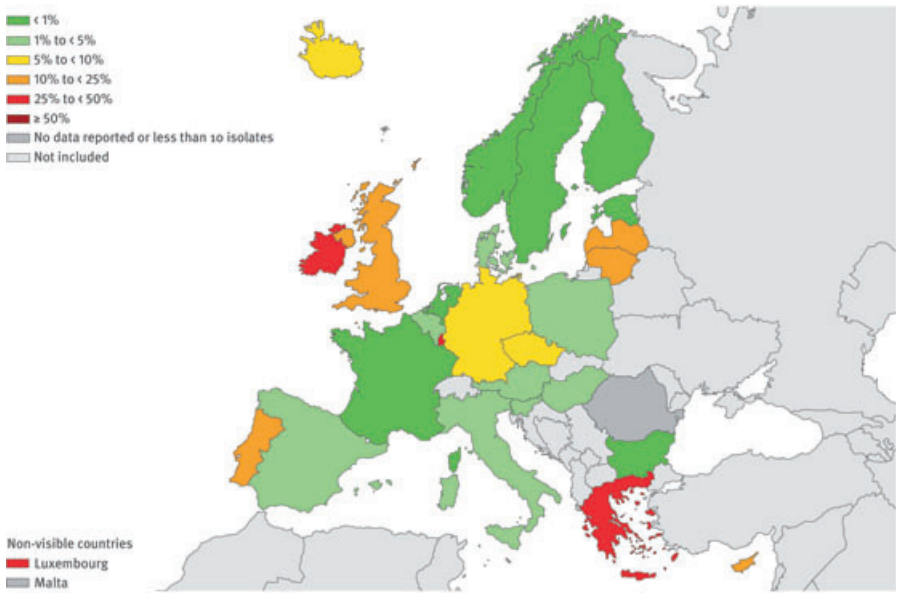

Figure 2 Proportion of vancomycin-resistant *Enterococcus faecium* in participating countries in 2009.[30]

outbreaks of imipenem-resistant *A baumannii*.[2] Several episodes of imported multidrug-resistant *A baumannii* have already been reported in specific situations, such as natural disasters[43] or situations of war, particularly among American and Canadian soldiers repatriated from Afghanistan or Iraq.[44–47] The risk of importation of multidrug-resistant *A baumannii* seems difficult to assess because clones carrying genes for resistance are already circulating in France.

French Guidelines to Control the Spread of CPE and VRE

The French Health Authorities published in 2010 guidelines to limit the spread of highly resistant bacteria. These French guidelines were developed by the members of a national working group, from their experiences and following the international literature.[16] The guidelines target two main commensally MDR, CPE and VRE, that have only been observed in France sporadically, but may spread on a sporadic or epidemic way when introduced in the hospital by carriers needing medical or surgical cares in French hospitals The aims of these guidelines are to control and limit the hospital spread of these two pathogens among (1) repatriated patient hospitalized more than 24 h in foreign hospitals, whatever the medical or surgical wards in high-level resistance prevalence areas; or (2) among travelers hospitalized in foreign countries within the last year. The CPE culture media recommended in these guidelines are also able to detect other Gram-negative MDR such as *A baumannii* and *P aeruginosa*. However, these media perform rather poorly to detect some bacteria that produce enzymes, which confer only low levels of carbapenem resistance (e.g., OXA-48). This flaw underlines, however, the urgent needs to make available new generation of tests, most probably molecular that will allow detection of such resistance mechanisms. Even if some countries are well known to present high-level rates of multidrug resistance, as outlined above, the French guidelines do not provide a list of "suspected" countries, as the epidemiological situation is changing continuously and few countries have no risk of multidrug resistance.

These guidelines include six recommendations (1–6) to be taken upon patients' hospital admission and four recommendations (7–10) when the patient is detected positive for CPE or VRE carriage after systematic rectal screening (Table 1). Upon hospital admission of patients at risk of CPE and VRE carriage, the French guidelines recommend to inform the Infection Control Team and the patient about the situation. The best way to detect repatriated patients is through an automatic alert system. During the first 48 h after admission and before the microbiological results of the screening (rectal swab or stool sample) are obtained, it is recommended to put the patient in contact isolation precautions.[48] When CPE or VRE is detected on screening sample, it is recommended (1) to maintain the contact precautions; (2) to identify the mechanism of resistance (e.g., resistance to imipenem: VIM, KPC, OXA-48); and (3) to alert the French Public Health Authorities for the national Healthcare-Associated Infections Early Warning and Response System.[12] If control measures have not been implemented upon admission, a systematic screening for CPE or VRE of patients hospitalized in the same ward and cared for by the same personnel is recommended to identify the

Table 1 French guidelines to control the emergence and spread of carbapenemase producing *Enterobacteriaceae* (CPE) producing carbapenemase and vancomycin-resistant *Enterococcus* (VRE) among repatriated patients or travelers hospitalized in foreign countries[16]

Recommendations
Upon patient admission
1. Hospital administration must alert the Infection Control Team to identify the situation by an automatic alert system.
2. The Infection Control Team or the medical staff must inform the patient of the situation to explain the control measures.
3. Medical staff must notify the situation in the medical record of the patient.
4. The Infection Control Team must implement the control measures upon patient's admission, following the French Guidelines "Prevention of cross-transmission: contact precautions" published in 2009.[48] These measures will be reevaluated after the results of the microbiological testing.
5. The patient must be screened immediately and systematically to detect CPE and VRE digestive carriage by rectal swab or stool sample.
6. If the control measures were implemented upon admission, it is not necessary to perform a systematic screening of the contact patient (defined as patients cared for by the same health-care workers).
When the patient or the traveler is detected positive for KPC-producing bacteria or VRE
7. The hospital laboratory must alert the Infection Control Team and the medical staff of the CPE or VRE positive screening.
8. The Infection Control Team must alert the French Health Authorities by using the national Healthcare-Associated Infections Early Warning and Response System.
9. The resistance mechanism (e.g., resistance to imipenem: VIM, KPC, OXA) must be identified at the local laboratory or otherwise by transferring the strain to the National Reference Centre for Antibiotic Resistance.
10. Infection control measures and epidemiological survey must be maintained until the repatriate or traveler has three successive negative rectal swabs (performed every week). In case of an epidemic spread, the national program initially designed to contain the spread of VRE must be applied to each outbreak.[40]

reservoir and secondary cases that might have developed via cross-transmission during the time elapsed when the patient was not in contact isolation precautions. If at least one secondary case is detected, all carriers must then be cohorted in a dedicated area and cared for by a dedicated staff. If transferred to another ward or hospital, contact patients must be maintained under control measures in other wards or hospitals and must be screened every week. If remaining in the hospital, control measures must be maintained until three negative rectal swabs for CPE and VRE are obtained. The French Ministry of Health has endorsed and enforced these recommendations through a directive for all hospitals.[49]

Discussion

Over the last 10 years, international health authorities observed the emergence and rapid spread throughout the world of new strains of the influenza virus, *C difficile* or multidrug-resistant tuberculosis.[50] The modern transport and increased tourism, business travel, and migration population have contributed to the spread of these pathogens with high epidemic impacts.[51–55] Data on systematic screening of repatriated patients hospitalized in foreign hospitals are scarce and relatively old.[56,57] Fifteen percent[58] to sixty-four percent[59] of travelers report health complaints during travel, and 5 of 1000 are admitted in foreign hospital during their travels.[58]

The global spread of resistance has not escaped this phenomenon. CPE and VRE have increasingly been isolated worldwide. The spread of these highly resistant bacteria is alarming, from a public health point of view, because this species is prone to be the source of many hospital-acquired infections in severely ill patients, and is well known for its ability to accumulate and transfer resistance determinants as illustrated with ESBLs. Current reports indicate that CPE (mainly KPC-producing bacteria)[60,61] and VRE[34,36] are widespread in many continents or countries such as Asia, Israel, Greece, South America, Canada, and the United States. Fortunately, in western and northern Europe, CPE and VRE are still rare. So, why worry?

Highly resistant and even pan drug-resistant (i.e., resistant to all available classes) CPE may be the source of therapeutic dead-ends, because novel anti-Gram-negative molecules are not expected in the near future.[62] Careful and conservative use of antibiotics, combined with good infection control practices, is therefore mandatory.[63]

Little is known about the repatriates- or travelers-related risk factors other than hospitalization in foreign hospitals, but the description of outbreaks indicates that producer strains seem to benefit from selective advantages in hospitals where antimicrobial use is much higher and opportunities for transmission are more frequent than in the community.[64]

In this complex and evolving epidemiological situation, and because France is so far less affected by this phenomena than other countries, the French Health Authorities published guidelines to limit the spread of CPE and VRE in 2010. Choices were made to select the types of patients that should be screened and the types of bacteria that must be sought. The choices are, as always, the result of a compromise between what appeared absolutely necessary and, at the same time, possible. The strategy of the French recommendations is based on the rapid detection and isolation upon admission, in any medical or surgical wards, of repatriates and travelers hospitalized for more than 24 h in foreign countries within the last year.

The rapid detection of CPE and VRE digestive carriage will also help to prescribe antibiotic treatment if the patients are infected, even if difficulties are also encountered by laboratories when trying to detect carbapenemase production during routine diagnostic procedures due to an often heterogeneous expression of resistance.

To ensure the application of these recommendations by French hospitals, a directive was published recently by the French Ministry of Health.[49] This directive reiterates the control measures to limit or delay the spread of CPE and the need to limit the use of carbapenems. In case of an epidemic spread, control measures adopted in a national program initially designed to contain the spread of VRE[40] must be applied to each outbreak caused by CPE or VRE. This consists in the rapid implementation of a step-by-step containment plan within the affected hospital; constant support by local infection control teams, regional experts and health authorities; and feedback to the medical community at the national level. The hospital containment strategy has the following components: (1) stopping transfer of cases and contacts within and between hospitals; (2) cohorting separately case and contact patients with dedicated healthcare workers; (3) screening all contact patients; and (4) continuous vigilance through surveillance.

Other countries also recommend strict infection control measures to prevent the further spread of CPE, based on Israeli or US experiences. For example, the Nosocomial Infections Committee of Quebec recently published guidelines to prevent and control the spread of KPC-producing bacteria in acute healthcare facilities, although no strain of NDM-1 producing Enterobacteriaceae has been identified in Quebec, and only 14 KPC-producing isolates have been identified in the past.[65] These recommendations are similar to the French guidelines and recommend to screen all patients admitted directly from a healthcare facility located outside of Canada in last year during 24 h or more or from a Canadian hospital setting with an outbreak situation. In the same way, the Netherlands published guidelines to control the spread of highly resistant microorganisms, specifically defined.[66] The guidelines recommend that patients should be screened for carriage of highly resistant microorganisms specifically in the event of admission in a high-risk ward, such as the intensive-care unit. This applies to the following patients: (1) patients

who were treated in a foreign hospital for more than 24 h within 2 months before admission, or who underwent surgery or were given a drain or a catheter abroad, or who were intubated, or who have skin lesions or possible. This concerns the following patients: (1) patients who were treated in a foreign hospital for more than 24 h within 2 months before admission, or who underwent surgery or were given a drain or a catheter abroad, or who were intubated, or who have skin lesions or possible sources of infection such as abscesses or furuncles; (2) a patient from another Dutch hospital, from a department experiencing a highly resistant microorganisms epidemic that has not yet been brought under control; and (3) a patient who has been in contact with another patient with highly resistant microorganisms.

In conclusion, antimicrobial resistance is increasing worldwide with geographical variations. The introduction of sporadic or primary cases of highly resistant bacteria from repatriates or travelers hospitalized in foreign hospitals is not predictable. It may also concern travelers without a history of hospitalization in the visited countries. These initial cases can provide the sources for the next outbreaks, with local, regional, or national spread. Although their efficacy will likely be partially effective, these guidelines provide a real opportunity to develop an automatic alert system upon hospital admission, to increase our knowledge concerning the repatriated patients' proportion in hospitals, and to determine the risk factors associated with highly resistant bacteria digestive carriage. They must also include consensus approaches with agreed screening and detection protocols, and mandatory reporting at a national or international level to alert other countries.[67] A medical and economic evaluation is needed to asses the efficacy of such recommendations as a response to the worldwide spread of antimicrobial resistance and to assess the link between travels, antibiotic use, and globalization of medical care and antibiotic resistance.

Declaration of Interests

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The other authors state they have no conflicts of interest to declare.

References

1. Falagas ME, Karageorgopoulos DE. Pandrug resistance (PDR), extensive drug resistance (XDR), and multidrug resistance (MDR) among Gram-negative *bacilli*: need for international harmonization in terminology. Clin Infect Dis 2008; 46:1121–1122.
2. Souli M, Galani I, Giamarellou H. Emergence of extensively drug-resistant and pandrug-resistant Gram-negative *bacilli* in Europe. Euro Surveill 2008; 13:1–11.
3. Magiorakos AP, Srinivasan A, Carey RB. Multidrug resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. (Accepted). doi: 10.1111/j.1469-0691.2011.03570.x.
4. Livermore DM. Has the era of untreatable infections arrived. J Antimicrob Chemother 2009; 64(Suppl 1): i29–i36.
5. American Society for Microbiology. Antibiotic resistance: an ecological perspective on an old problem. 2009. Available at: http://www.asm.org/. (Accessed 2011 May).
6. Institut national de la statistique et des études économiques (INSEE). 2007. Available at: http://www.insee.fr/
7. Ministère des Affaires Etrangères. 2008. Available at: http://www.diplomatie.gouv.fr/. (Accessed 2010 Sep).
8. Coignard B, Barbut F, Blanckaert K, et al. Emergence of *Clostridium difficile* toxinotype III, PCR-ribotype 027-associated disease, France, 2006. Euro Surveill 2006; 11: E060914.1.
9. Birgand G, Blanckaert K, Carbonne A, et al. Investigation of a large outbreak of *Clostridium difficile* PCR-ribotype 027 infections in northern France, 2006–2007 and associated clusters in 2008-2009. Euro Surveill 2010; 15: pii.19597.
10. Naas T, Nordmann P, Vedel G, Poyart C. Plasmid-mediated carbapenem-hydrolyzing β-lactamase KPC in a *Klebsiella pneumoniae* isolate from France. Antimicrob Agents Chemother 2005; 49:4423–4424.
11. Carbonne A, Thiolet JM, Fournier S, et al. Control of a multi-hospital outbreak of KPC-producing *Klebsiella pneumoniae* type 2 in France, September to October 2009. Euro Surveill 2010; 15:pii:19734.
12. Vaux S, Carbonne A, Thiolet JM, et al. Emergence of carbapenemase-producing *Enterobacteriaceae* in France, 2004 to 2011. Euro Surveill 2011; 16:pii:19880.
13. Lucet JC, Armand-Lefrevre Laurichesse JJ, et al. Rapid control of an outbreak of vancomycin-resistant enterococci in a French university hospital. J Hosp Infect 2007; 67:42–48.
14. Aumeran C, Baud O, Lesens O, et al. Successful control of a hospital-wide vancomycin-resistant *Enterococcus faecium* outbreak in France. Eur J Clin Microbiol Infect Dis 2008; 27:1061–1064.
15. Naas T, Coignard B, Carbonne A, et al. VEB-1 extended-spectrum ß-lactamase-producing *Acinetobacter baumannii*, France. Emerg Infect Dis 2006; 12:1214–1222.
16. Haut Conseil de la Santé publique. Commission spécialisée Sécurité des patients : infections nosocomiales et autres évènements indésirables liés aux soins et aux pratiques. Recommandations pour le dépistage du portage digestif des bactéries commensales multi-résistantes aux antibiotiques importées en France à l'occasion du rapatriement de patients en provenance de l'étranger et maîtrise de leur diffusion. 2010. Available at: http://www.hcsp.fr/docspdf/avisrapports/hcspr20100518_bmrimportees.pdf. (Accessed 2011 May).
17. Nordmann P, Cuzon G, Naas T. The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria. Lancet Infect Dis 2009; 9:228–236.
18. Oteo J, Perez-Vasquez M, Campos J. Extended-spectrum [beta]-lactamase producing *Escherichia coli*: changing epidemiology and clinical impact. Curr Opin Infect Dis 2010; 23:320–326.
19. Livermore DM, Woodford N. The β-lactamase threat in *Enterobacteriaceae*, *Pseudomonas* and *Acinetobacter*. Trends Microbiol 2006; 14:413–420.

20. Cornaglia G, Akova M, Amicosante G, et al. Metallo-β-lactamases as emerging resistance determinants in Gram-negative pathogens: open issues. Int J Antimicrob Agents 2007; 29:380–388.
21. Yong D, Toleman MA, Giske CG, et al. Characterization of a new metallo-β-lactamase gene, *bla*(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence type 14 from India. Antimicrob Agents Chemother 2009; 53:5046–5054.
22. Yigit H, Queenan AM, Anderson GJ, et al. Novel carbapenem-hydrolyzing β-lactamase KPC-1 from a carbapenem-resistant strain of *Klebsiella pneumoniae*. Antimicrob Agents Chemother 2001; 45:1151–1161.
23. Kitchel B, Rasheed JK, Patel JB, et al. Molecular epidemiology of KPC-producing *Klebsiella pneumoniae* isolates in the United States: clonal expansion of multilocus sequence type 258 Antimicrob Agents Chemother. 2009; 53: 3365–3370.
24. Leavitt A, Navon-Venezia S, Chmelnitsky I, et al. Emergence of KPC-2 and KPC-3 in carbapenem-resistant *Klebsiella pneumoniae* strains in an Israeli hospital. Antimicrob Agents Chemother 2007; 51:3026–3029.
25. Woodford N, Zhang J, Warner M, et al. Arrival of *Klebsiella pneumoniae* producing KPC carbapenemase in the United Kingdom. J Antimicrob Chemother 2008; 62:1261–1264.
26. Giakoupi P, Maltezou H, Polemis M, et al. KPC-2-producing *Klebsiella pneumonia* infections in Greek hospitals are mainly a hyperepidemic clone. Euro Surveill 2009; 14:pii:19218.
27. Dortet L, Radu I, Gautier V, et al. Intercontinental travel of patients and dissemination of plasmid-mediated carbapenemase KPC-3 associated with OXA-9 and TEM-1. J Antimicrob Chemother 2008; 61:455–457.
28. Cuzon G, Naas T, Demachy MC, Nordmann P. Plasmid-mediated carbapenem-hydrolyzing β-lactamase KPC in *Klebsiella pneumoniae* isolate from Greece. Antimicrob Agents Chemother 2008; 52:796–797.
29. Decre D, Birgand G, Geneste D, et al. Possible importation and subsequent cross-transmission of OXA-48-producing *Klebsiella pneumoniae*, France, 2010. Euro Surveill 2010; 15:pii:19718.
30. European Antimicrobial Resistance Surveillance Network (EARS-Net). Antimicrobial Resistance Surveillance in Europe. Available at: http://www.ecdc.europa.eu/. (Accessed 2011 Feb).
31. Kamarasamy K, Toleman MA, Walsh TR, et al. Emergence of a new antibiotic resistance in India, Pakistan, and the UK: a prospective survey. Lancet Infect Dis 2010; 10: 597–602.
32. Livermore DM, Walsh TR, Toleman MA, Woodford N. Balkan NDM-1: escape or transplant? Lancet Infect Dis 2011; 11:164.
33. Walsh TR, Livermore DM, Toleman MA. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human: an environmental point prevalence study. Lancet Infect Dis 2011; 11: 355–362.
34. Werner G, Coque TM, Hammerum AM, et al. Emergence and spread of vancomycin resistance among enterococci in Europe. Euro Surveill 2008; 13:pii:19046.
35. Sievert DM, Rudrik JT, Patel JB, et al. Vancomycin-resistant *Staphylococcus aureus* in the United States, 2002-2006. Clin Infect Dis 2008; 46:668–674.
36. Deshpande LM, Fritsche TR, Moet GJ, et al. Antimicrobial resistance and molecular epidemiology of vancomycin-resistant enterococci from North America and Europe: a report from the SENTRY antimicrobial surveillance program. Diagn Microbial Infect Dis 2007; 58:163–170.
37. McGowan JE. Debate-guidelines for control of glycopeptide-resistant enterococci (GRE) have not yet worked. J Hosp Infect 2004; 57:281–284.
38. Bourdon N, Fines-Guyon M, et al. Changing trends in vancomycin-resistant enterococci in French hospitals, 2001-08. J Antimicrob Chemother 2011; 66:713–721.
39. Lucet JC, Andremont A, Coignard B. Les entérocoques résistants aux glycopeptides (ERG): Glycopeptide-resistant enterococci (GRE): epidemiological situation, current control measures and future challenge. Bull Epidemiol Hebd 2008; 41–42:386–390.
40. Haut Conseil de la Santé Publique. Rapport relatif à la maîtrise de l'émergence et de la diffusion des ERG dans les établissements de santé. 2010. Available at: http://www.hcsp.fr/docspdf/avisrapports/hcspr20090219_ERG.pdf. (Accessed 2011 Jan).
41. Peleg AY, Seifert H, Paterson DL. *Acinetobacter baumannii*: emergence of a successful pathogen. Clin Microbial Rev 2008; 21:538–582.
42. Towner KJ. *Acinetobacter*: an old friend, but a new enemy. J Hosp Infect 2009; 73:355–363.
43. Uçkay I, Sax H, Harbarth S, et al. Multi-resistant infections in repatriated patients after natural disasters: lessons learned from the 2004 tsunami for hospital infection control. J Hosp Infect 2008; 68:1–8.
44. Calhoun JH, Murray CK, Manring MM. Multidrug-resistant organisms in military wounds from Iraq and Afghanistan. Clin Orthop Relat Res 2008; 466: 1356–1362.
45. Tien HC, Battad A, Bryce EA, et al. Multi-drug resistant *Acinetobacter* infections in critically injured Canadian forces soldiers. BMC Infect Dis 2007; 7:95.
46. Davis KA, Moran KA, McAllister CK, Gray PJ. Multidrug-resistant *Acinetobacter* extremely infections in soldiers. Emerg Infect Dis 2005; 11:1218–1224.
47. Griffith ME, Lazarus DR, Mann PB, et al. *Acinetobacter* skin carriage among US army soldiers deployed in Iraq. Infect Control Hosp Epidemiol 2007; 28:720–722.
48. Cross-contamination prevention: additional contact precautions. National guidelines 2009. French Society for Hospital Hygiene. 2009. Available at: http://www.sf2h.net/SF2H_english/SF2H_contact-precautions-guidelines-2009.pdf.
49. Circulaire N°DGS/RI/DGOS/PF/2010/413 du 6 décembre 2010: relative à la mise en œuvre de mesures de contrôles des cas importés d'entérobactéries productrices de carbapénèmases (EPC).
50. Soto SM. Human migration and infectious diseases. Clin Microbial Infect 2009; 15(Suppl 1):26–28.
51. Arguin PM, Marano N, Freedman DO. Globally mobile populations and the spread of emerging pathogens. Emerg Infect Dis 2009; 15:1713–1714.
52. Gushulak B, Funk M, Steffen R. Global changes related to travelers' health. J Travel Med 2007; 14:205–208.
53. Steffen R, Amitirigala I, Mutsch M. Health risks among travelers—need for regular updates. J Travel Med 2008; 15:145–146.

54. Hawkey PM, Jones AM. The changing epidemiology of resistance. J Antimicrob Chemother 2009; 64(Suppl 1): i3–i10.
55. MacPherson DW, Gushulak BD, Bala S, et al. Population mobility, globalization, and antimicrobial drug resistance. Emerg Infect Dis 2009; 15:1727–1732.
56. Fisher D, Vedman A, Diefenbach M, Shäfer V. Bacterial colonization of patients undergoing international air transport: a propsective epidemiologic study. J Travel Med 2004; 11:44–48.
57. Kaiser AM, Schultsz C, Kruithof GJ, et al. Carriage of resistant microorganisms in repatriates from foreign hospitals to the Netherlands. Clin Microbiol Infect 2004; 10:972–979.
58. Steffen R, Rickenbach M, Wilhelm U, et al. Health problems after travel to developing countries. J Infect Dis 1987; 156:84–91.
59. Hill DR. Health problems in a large cohort of Americans travelling to developing countries. J Travel Med 2000; 7:259–266.
60. CDC. Detection of *Enterobacteriaceae* isolates carrying metallo-betalactamase—United States, 2010. MMWR Morb Mortal Wkly Rep 2010; 59:750.
61. Leverstein-Van Hall MA, Stuart JC, Voets GM, et al. Global spread of New Delhi metallo-β-lactamase 1. Lancet Infect Dis 2010; 10:830–831.
62. Pitout JD. The latest threat in the war on antimicrobial resistance. Lancet Infect Dis 2010; 10:578–579.
63. Wise R, Piddock L. The need for new antibiotics. Lancet 2010; 375:638.
64. Grundmann H, Livermore DM, Giske CG, et al. Carbapenem-non-susceptible *Enterobacteriaceae* in Europe: conclusions from a meeting of national experts. Euro Surveill 2010; 15:pii:19711.
65. Comité sur les infections nosocomiales du Québec. Institut National de Santé Publique du Québec. Avis et recommandations : Prévention et contrôle de la transmission des entérobactéries productrices de carbapénèmases dans les milieux de soins aigus du Québec. Octobre 2010. Available at: http://www.inspq.qc.ca/pdf/publications/1168_PreventionTransmissionEnterobactCarbapenemases.pdf. (Accessed 2011 May).
66. Kluytmans-Vanderbergh MF, Kluytmans JA, Voss A. Dutch guideline for preventing nosocomial transmission of highly resistant microorganisms (HRMO). Infection 2005; 33:309–313.
67. Wernli D, Haustein T, Conly J, et al. A call for action: the application of the international health regulations to the global threat of antimicrobial resistance. PLoS Med 2011; 8:e1001022.

Appendix

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