Antimicrobial resistance 2010: global attention on carbapenemase-producing bacteria

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A year ago in November 2009, a study in this journal highlighted the emergence of infections with totally or almost totally resistant bacteria in European intensive care units [1]. Most of them were Gram-negative bacilli that showed resistance to a class of antibiotics considered last-line therapy: the carbapenems. Already in 2008, Souli *et al*. had reviewed the emergence of extensively drug-resistant (XDR) bacteria in Europe [2] and pointed out the high proportion of isolates that were resistant to carbapenems, through production of a carbapenemase enzyme. Indeed, an increasing number of reports on carbapenemases and infections with carbapenemase-producing bacteria have been published in recent years indicating the rising importance of these bacteria. A PubMed search with the keyword 'carbapenemase' and excluding review articles, yielded 35 articles for the year 2007, 48 articles for 2008, 80 articles for 2009 and 109 articles for 2010 (as of 14 November).

The year 2010 will certainly be remembered as the year when carbapenemase-producing, XDR bacteria attracted global attention. Significant media attention and increasing awareness of these bacteria followed the publication by Kumarasamy *et al*. on 11 August on the spread to the United Kingdom (UK) of a new type of carbapenemase, the New Delhi metallo-beta-lactamase 1 (NDM-1), often associated with travel to India or Pakistan [3]. In this issue of *Eurosurveillance*, Struelens *et al*. review the spread of NDM-1 in the European Union (EU), Iceland and Norway and show that, in addition to the UK, 11 other EU countries plus Norway have identified patients infected or colonised with NDM-1-producing *Enterobacteriaceae* [4]. Similar to the cases described in the UK, the majority of these NDM-1 cases had previously travelled or been admitted to a hospital in India or Pakistan. In addition, a few cases had been hospitalised in the Balkan region [4].

Several other types of carbapenemases have been described since the 1990s such as *Klebsiella pneumoniae* carbapenemase (KPC), Verona integron-encoded metallo-beta-lactamase (VIM) and the oxacillinase-type beta-lactamase OXA-48 [5]. All these have in common that they are able to rapidly hydrolyse most of the beta-lactams including the carbapenems, thus conferring resistance to these antibiotics. In addition, they are in most cases encoded by a gene located on transferable elements which allows transfer of the gene among species of Enterobacteriaceae. This issue of *Eurosurveillance* highlights the challenges represented by carbapenemase-producing, XDR bacteria, but also offers examples from EU countries on how the spread of such bacteria can be contained.

Although NDM-1 has been the focus of media attention concerning antimicrobial resistance during the past months, it is neither the most frequently identified carbapenemase in Europe, nor the only carbapenemase associated with transfer of patients between countries. In this issue of the journal, a group of European experts report on carbapenemase-producing *Enterobacteriaceae* in Europe and show that carbapenemases other than NDM-1 are the dominant types in all European countries except the UK [5]. As an example, Decré *et al*. describe the likely importation from Morocco to France of an OXA-48-producing *K. pneumoniae* strain with subsequent cross-transmission to another patient [6], a pattern similar to that described for previous OXA-48 cases from other countries. As for NDM-1, the spread of KPC- and OXA-48-producing bacteria has been associated with transfer of patients from hospitals in countries where they are frequently found, to hospitals in other countries [7,8].

Accurate laboratory detection, control of patient-to-patient transmission and prudent use of antibiotics are cornerstones of containment

Identification of carbapenemase-producing bacteria remains a challenge. According to the survey by Grundmann *et al*. there is likely underreporting of such isolates in more than one third of European countries [5]. Struelens *et al*. found that less than half of the countries reported having national guidance on surveillance and detection methods for carbapenemase-producing bacteria and, with two exceptions, countries that reported NDM-1 cases also reported having such

national guidance [4]. Availability of guidance and sufficient capacity of laboratories to routinely detect and confirm carbapenemase-producing isolates throughout and beyond Europe, are of paramount importance for their containment. Active surveillance and isolation of patients who are infected or colonised are essential for controlling the spread of these bacteria. Struelens *et al*. indicate that 11 European countries have developed infection control guidelines which in some countries, e.g. France, recommend the pre-emptive isolation and screening of patients transferred from hospitals in other countries [4].

To address the issues above, the United States (US) Centers for Disease Control and Prevention (CDC) developed a guidance document for the detection of metallo-beta-lactamases such as NDM-1 [9] and produced guidance for control of these infections in acute care facilities [10]. In Europe, the European Centre for Disease Prevention and Control (ECDC) is preparing evidence-based guidance on screening and confirmation of carbapenemase-producing bacteria and conducts a systematic review of the published evidence on interventions to control carbapenemase-producing Enterobacteriaceae. A group of European experts convened by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) reviewed detection and surveillance issues [11]. Another expert group under the auspices of ESCMID, suggested implementation of different control measures for countries with sporadic occurrence of these bacteria and for countries where they are endemic [12].

Early warning and sharing information between countries facilitates prevention and control

In this issue, Kassis-Chikhani *et al*. [13] show that it is possible to contain outbreaks of carbapenemase-producing bacteria if rapid control measures are implemented. National and international early warning and response systems allow for the timely sharing of information that is necessary to investigate possible inter-hospital transmission. The EU Early Warning and Response System (EWRS) is a tool to rapidly share confidential information between countries, with the assistance of the European Commission, to improve prevention and control of communicable diseases. However, the EWRS has rarely been used for communication about resistant bacteria in the past. In addition to rapid exchange of information, discussion between risk assessment entities and experts in EU countries is crucial to prevent the spread of resistant bacteria including the ones discussed in this editorial. To support such discussions, ECDC is developing a specific module of its Epidemic Intelligence Information System (EPIS).

Antimicrobial resistance and consumption in EU Member States

Data on antimicrobial resistance are available from the European Antimicrobial Resistance Surveillance Network (EARS-Net, formerly EARSS) (http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx). They show increasing resistance to third-generation cephalosporins and multidrug resistance in invasive infections due to *K. pneumoniae* and *Escherichia coli* in many EU countries. For this reason, hospital physicians have increasingly used carbapenems, in particular to treat infections in the most severely ill patients, e.g. in intensive care units. In a point prevalence survey on antimicrobial consumption in a sample of 75 European hospitals, the European Surveillance of Antimicrobial Consumption (ESAC) project showed that on average 11%, and up to 50%, of patients in intensive care units were receiving a carbapenem [14]. Since the introduction of antibiotics into medical practice, prescribers have mostly relied on the constant availability of new antibiotics to effectively treat patients infected with resistant bacteria. However, this forward escape strategy now looks like a leap of faith since innovative antibiotics active against these bacteria are unlikely to be developed in the very near future [15], leaving therapeutic options for carbapenemase-producing, XDR bacteria limited. These consist mainly of the polymyxins and tigecycline, but experts agree that neither of them are ideal because of the toxicity of polymyxins and the variable clinical efficacy of tigecycline [8,12]. Avoiding unnecessary use of antibiotics and reserving them for appropriate indications, starting with carbapenems, is therefore essential to preserve options for therapy of infections in hospitalised patients.

Point prevalence surveys have been developed to ascertain the appropriateness of antibiotic prescription practices in hospitals and other healthcare facilities. In the ESAC point prevalence survey, 57% of antibiotic courses for surgical prophylaxis lasted more than one day, thus highlighting short duration of prophylaxis as an obvious target for improvement of antibiotic prescribing practices in hospitals [14]. Even in a country with a history of prudent use of antibiotics such as the Netherlands, Willemsen *et al*. showed that, in their prevalence survey in 19 hospitals, 16% patients were receiving antimicrobial therapy that they judged inappropriate [16]. The Eurobarometer survey on antimicrobial resistance performed in November-December 2009 showed that almost half of Europeans still believed that 'antibiotics are active against colds and flu' and these results point towards a challenge for prudent use of antibiotics outside of hospitals [17].

Meticillin-resistant *Staphylococcus aureus*

Recent data from EARS-Net show that six countries reported decreasing trends in the proportion of meticillin-resistant *Staphylococcus aureus* (MRSA) among *S. aureus* isolates from invasive infections for the period 2006 to 2009. This is likely due to sustained efforts to contain the spread of MRSA in hospitals and other healthcare facilities [18]. MRSA remains a public health threat with a proportion of MRSA above 25% in more than one third of countries participating in EARS-Net. In addition, new strains of MRSA are emerging

from other environments such as human infections in the community, food animals and foods [19]. In this issue, De Jonge *et al*. add to our knowledge about MRSA with a study suggesting that, although present in some meat samples in the Netherlands, the risk to humans of being colonised by MRSA through handling of contaminated meat is low [20].

MRSA emerged in hospitals in the 1960s and, with the exception of the Scandinavian countries and the Netherlands, other European countries did not seriously consider its prevention and control before the 1990s. In countries with a low MRSA prevalence, MRSA control relies heavily on the so-called 'search-and-destroy' strategy which includes the pre-emptive isolation and screening of patients who have been in contact with healthcare facilities in countries with high prevalence of MRSA [18].

International efforts to tackle antimicrobial resistance - joining forces is essential

Europe is reacting much faster to contain the spread of carbapenemase-producing, extensively drug-resistant bacteria when compared with MRSA. It follows the path of a few leading countries which are taking measures similar to those for MRSA prevention and control in low prevalence countries. Contemporary life-style, however, poses an additional challenge with ever increasing international travel and patients seeking healthcare abroad, which means that containment of carbapenemase-producing, XDR bacteria can only be addressed internationally.

The European Commission has reported this year that EU countries have made significant progress toward implementing the Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine. However, there are still several areas where improvement is needed, including education and awareness of healthcare personnel and the general public [21]. On 18 November 2010, 36 European countries will participate in the third European Antibiotic Awareness Day (http://antibiotic.ecdc.europa.eu). The focus of this year's European Antibiotic Awareness Day is to raise awareness about prudent use of antibiotics among hospital prescribers. Key messages have been developed to help hospitals and hospital prescribers in their efforts to reach this goal. Evidence suggests that multifaceted hospital strategies may improve antibiotic prescribing practices and decrease antibiotic resistance. In addition, specific strategies may help prescribers optimise antibiotic therapy and reduce unnecessary use.

Worldwide attention on antimicrobial resistance allows for many stakeholders and countries to be involved. In planning for next year, the World Health Organization has declared antimicrobial resistance and its global spread as the topic for the next World Health Day on 7 April 2011 [22]. Already this year, antibiotic awareness campaigns are taking place at the same time on both sides of the Atlantic. The United States' Get Smart About Antibiotics Week (http://www.cdc.gov/getsmart/) takes place on 15-21 November [23] and Canada's first Antibiotic Awareness Day (http://antibioticawareness.ca/) will take place on the same day as European Antibiotic Awareness Day, 18 November 2010. Joining forces is essential for tackling a global issue such as antimicrobial resistance.

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