National multidrug-resistant bacteria (MDRB) surveillance in France through the RAISIN network: a 9 year experience

Anne Carbonne1*, Isabelle Arnaud1, Sylvie Maugat2, Nicole Marty3, Catherine Dumartin4, Xavier Bertrand5, Odile Bajolet6, Anne Savey7, Thierry Fosse8, Mathieu Eveillard9, Hélène Sénéchal10, Bruno Coignard2, Pascal Astagneau1 and Vincent Jarlier11,12 on behalf of the MDRB Surveillance National Steering Group (BMR-Raisin)†

1CCLIN Paris Nord, rue Didot, 75014 Paris, France; 2INVS, rue du val d’Osne, 94415 Saint-Maurice, France; 3University Hospital, rue Vuguerie, 31059 Toulouse cedex 9, France; 4CCLIN Sud Ouest, GH Pellegrin, 33076 Bordeaux, France; 5University Hospital, place Saint Jacques, 25000 Besançon, France; 6University Hospital, 51092 Reims cedex, France; 7CCLIN Sud-Est, hospital Henry Gabrielle, route de Voules, 69230 Saint Genis Laval, France; 8University Hospital, Ave Reine Victoria, 06003 Nice cedex 1, France; 9University Hospital, rue Larrey, 49933 Angers cedex 9, France; 10CCLIN Ouest, University Hospital Hôtel Dieu, rue de l’Hôtel Dieu, 35000 Rennes, France; 11Bactériologie-Hygiène, UPMC University Paris 6, EA1541, 75634 Paris cedex 13, France; 12Bactériologie-Hygiène, Groupe Hospitalier Pitié-Salpêtrière Charles Foix (Assistance Publique-Hôpitaux de Paris), 75651 Paris cedex 13, France

*Corresponding author. Hygiène Hospitalière, Groupe Hospitalier Corentin Celton/HEGP/Vaugirard Gabriel-Pallez, 20-40 rue Leblanc, 75908 Paris cedex 15, France. Tel: +33-1-56-09-29-73; Fax: +33-1-56-09-39-19; E-mail: anne.carbonne@egp.aphp.fr
†The other members are listed in the Acknowledgements section.

Received 2 August 2012; returned 11 September 2012; revised 5 October 2012; accepted 23 October 2012

Background: In the mid-1990s, the prevalence rate of multidrug-resistant bacteria (MDRB) in French hospitals was high and control of MDRB spread then became a major priority in the national infection control programme (ICP).

Methods: To evaluate the impact of the ICP, a national coordination of MDRB surveillance was set up in 2002. Data were collected 3 months a year in healthcare facilities (HCFs) on a voluntary basis. All clinical specimens of methicillin-resistant Staphylococcus aureus (MRSA) and extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBLE) were prospectively included. Incidences per 1000 patient days (PDs) were calculated and trends in incidence from 2003 to 2010 were assessed.

Results: Participation in the surveillance increased from 478 HCFs in 2002 to 933 in 2010. In 2010, MRSA incidence was 0.40/1000 PDs: 1.14 in intensive care units (ICUs), 0.48 in acute care facilities (ACFs) and 0.27 in rehabilitation and long-term care facilities (RLTCFs). ESBLE incidence was 0.39/1000 PDs: 1.63 in ICUs, 0.46 in ACFs and 0.23 in RLTCFs. MRSA incidence significantly decreased from 0.72/1000 PDs in 2003 to 0.41/1000 PDs in 2010 (P<10−3); in contrast, ESBLE incidence significantly increased from 0.17/1000 PDs to 0.48/1000 PDs (P<10−3). The most prevalent ESBLE were Enterobacter aerogenes (34%) and Escherichia coli (25%) in 2003 and E. coli (60%) and Klebsiella pneumoniae (18%) in 2010.

Conclusion: These results demonstrate the positive impact of the national ICP on MRSA rates. In contrast, ESBLE incidence, especially ESBL-producing E. coli, is increasing dramatically and represents a serious threat for hospitals and for the community that deserves specific control actions.

Keywords: MRSA, ESBLE, prevention, programme, healthcare setting

Introduction

Over recent decades, multidrug-resistant bacteria (MDRB) have had a significant clinical impact, have been linked with higher mortality and have led to additional financial burden. Among MDRB, methicillin-resistant Staphylococcus aureus (MRSA) and extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBLE) are of immediate concern, given their pathogenicity and the risk of their spread in healthcare settings. In addition, the carriage of MRSA and ESBLE can last for several months, even after hospital discharge, enhancing the risk of dissemination in the community. The incidence of MRSA and ESBLE is primarily the consequence of patient-to-patient transmission in healthcare settings and, in part, in the community, and is...
MDRB surveillance in France 2002–10

Table 1. Control measures against MDRB epidemic recommended by the French Ministry of Health (1999)

<table>
<thead>
<tr>
<th>Aim and action</th>
</tr>
</thead>
</table>
| Identify reservoirs | detection of MDRB (MRSA and ESBLE) in laboratory
| early notification of the MDRB by the laboratory to the care unit
| signalling MDRB carriers in the care unit (room door, medical chart…)
| notification of MDRB carriage when patient is transferred to another unit or hospital
| Stop transmission among patients | barrier precautions for colonized and infected patients (antiseptic hand-washing or alcohol-based hand-disinfecting, wearing gloves and gown for most patient care)
| patient placement in private room or cohorting when possible
| Systematic detection of carriers | indicated in units with high risk of cross-transmission (ICU…)
| decontamination of human reservoirs: selected indications
| Control antibiotic use | 

favoured by antibiotic pressure.\(^1\)\(^2\) Therefore the rate of these MDRB represents an indirect indicator of effectiveness hygiene precautions as well as antibiotic stewardship.

In France, the prevalence of MRSA was one of the highest among European countries in the mid-1990s and that of ESBLE is today higher than in northern European countries.\(^3\)\(^4\) Surveillance and prevention of these MDRB became national priorities in 1999 as part of the hospital-acquired infection control programme in France.\(^5\) This programme contains bundle measures aimed at decreasing cross-transmission (Table 1). A national network called BMR-RAISIN was set up in 2002 by the RAISIN (the French national healthcare-associated infection early warning, investigation and surveillance network), federating (i) the pre-existing networks created and coordinated by the five interregional centres for infection control (CCLINs) and (ii) the National Public Health Surveillance Institute (Institut de veille sanitaire, InVS).\(^6\)

Incidence data produced by the BMR-RAISIN network have been available for analysis since 2003. Based on these data, the present study describes (i) the endemic level of MRSA and ESBLE in 2010 and (ii) the temporal trends during the years 2003–10 in order to evaluate the impact of the MDRB control programme.

Methods

Setting and data collection

All French healthcare facilities (HCFs) were invited to participate in the survey on a voluntary basis under the interregional coordination of the five CCLINs. Since 2002, the volunteer HCFs have participated in the survey over a period of 3 months every year. During this period, all strains of MRSA and ESBLE isolated from clinical specimens in patients hospitalized for more than 24 h were included. This definition excludes most community-acquired MRSA or ESBLE infections. Strains isolated through systematic survey of MRSA or ESBLE colonization (e.g. nasal or rectal swabs) were not included. When multiple strains of the same species were isolated from the same patient, in order to avoid duplicates of cases, only the first strain was included. For each strain, information on the type of hospital unit where the patient was hospitalized, the date of admission to the hospital, the unit, the date of a positive specimen and the site of sampling were recorded.

Laboratory methods

Antibiotic susceptibility tests were performed according to the guidelines of the Committee for Antimicrobial Testing of the French Society of Microbiology. Enterobacteriaceae were considered as producing ESBLs in the case of synergy between third-generation cephalosporins and clavulanic acid, as recommended.\(^7\)

Data analysis

The incidence of MRSA and ESBLE cases per 1000 patient days (PDs) has been calculated using a centralized database. For that purpose, data were recorded using Epilinfo software (Epilinfo, CDC, Atlanta, GA, USA) in each HCF. At the end of the study period, data files were returned to the manager of the central database and were concatenated to be validated and analysed. Temporal trends (2003–10) were estimated using Poisson regression. All tests were considered significant at P<0.05. SAS software version 9.2 (SAS, Cary, NC, USA) was used for data analysis.

Results

Coverage of the survey

In 2010, 933 HCFs, totalling 242 128 beds, i.e. 55.2% of all French hospital beds, participated in the survey. In 2002, the corresponding figures were 478 HCFs, totalling 160 000 beds, i.e. one-third of all French hospital beds.\(^8\) During the 3 month period of the survey, the number of patients admitted to acute care facilities (ACFs) was 1278524 in 2003 and 2022066 in 2010 and the total number of PDs during the 3 month period of the survey was 12 282 593 in 2003 and 17 853 669 in 2010.

Main results for 2010

In 2010, a total of 7214 cases of MRSA and 6992 cases of ESBLE, including 4177 (59.7%) Escherichia coli, 1225 (17.5%) Klebsiella pneumoniae, 252 (3.6%) Enterobacter aerogenes and 789 (11.3%) Enterobacter cloacae were identified during the 3 month survey.

Overall, the incidence of MRSA was 0.40/1000 PDs, ranging from 0.15 to 0.73 depending on the region (Table 2 and Figure 1a). The highest MRSA incidences were observed in the north and the south-west regions of France (Figure 1a). Overall, the incidence of ESBLE, all species together, was 0.39/1000 PDs (range 0.16–1.34 depending on the region) (Table 2 and Figure 1b). More specifically, the incidence of ESBL-producing E. coli, the most prevalent species of ESBLE, was 0.24/1000 PDs. The highest incidence of ESBLE was observed in the north, east and south-east of France, as well as in Corsica and the French Antilles (Figure 1b).

The incidence of MRSA was highest in intensive care units (ICUs; 1.14/1000 PDs) and lowest in rehabilitation and long-term care facilities (RLTCFs; 0.27/1000 PDs). The incidence of ESBLE was also the highest in ICUs (1.63/1000 PDs). See Table 2.

The proportions of strains isolated from blood cultures and urines were, respectively, 9.5% and 19.5% for MRSA and 7.9% and 67.0% for ESBLE. The incidence rate of bacteraemia was 0.04/1000 PDs for MRSA and 0.03/1000 PDs for ESBLE.

Temporal trends

One hundred and seventy-five HCFs participated continuously in the survey from 2003 to 2010. For this subset of HCFs, the
Incidence of MRSA per 1000 PDs decreased significantly and steadily, by 43% (range 40%–60% depending on the type of hospital activity; Table 3). In contrast, the incidence of ESBLE increased significantly during the same period of time, by 182% (range 80%–210% depending on the type of hospital activity; Table 4). The increase was particularly sharp between 2006 and 2010.

Interestingly, the evolution of MRSA and ESBLE incidences observed for all HCFs participating in the survey, although their number varied over time, was very similar to those observed for all laboratories in 2010 by French region.
observed for the subset of 175 continuously participating HCFs (Figure 2).

Between 2003 and 2010, the overall incidence of MRSA bacteremia decreased from 0.044/1000 PDs to 0.038/1000 PDs ($P=0.08$), whereas that of ESBLE bacteremia increased from 0.006/1000 PDs to 0.031/1000 PDs ($P<10^{-3}$). The proportion of bacteremia among MDRB cases was, respectively, in 2003 and 2010, 8.0% and 9.5% for MRSA and 4.7% and 8.0% for ESBLE.

Finally, for all participating HCFs, the distribution of the main species among the ESBLE markedly changed during the period of the survey: the proportion of *E. aerogenes* decreased, whereas the proportion of *E. cloacae* and *E. coli* increased (Figure 3).

**Discussion**

The main result of this study is the opposite evolution of the incidence of MRSA, a decrease of 43%, and of ESBLE, an increase of 182%, during the 9 years of the survey in French hospitals. During the 1990s, the prevalence of MRSA in France was among the highest in Europe, but that of ESBLE was low. Moreover, a previous study showed that the incidence of MRSA increased during the 1990s in the north of France, reaching rates as high as 1/1000 PDs. A 15 year experience at the level of a multi-hospital institution in the Paris area demonstrated the positive impact of a bundle programme for controlling cross-transmission of MRSA that led to a significant reduction of MRSA rates. This programme was close to that recommended by the Healthcare Hospital Infection Control Practices Advisory Committee. It has been widely disseminated in healthcare settings, and control of MRSA was considered to be a national public health priority.

The decrease in MRSA incidence was particularly marked in ICUs (63%), as previously observed in the Paris area, but was also significant for ACFs taken as a whole (42%) and in RLTCFs (42%). Interestingly, the incidence of MRSA bacteremia has also decreased since 2003, although the decrease did not reach statistical significance ($P=0.08$), a fact that could be explained by the relatively low proportion of blood cultures (around 8%) among all positive specimens. Efforts for prevention of intravascular device-associated bacteremia should be made.
The results of this longitudinal national survey focused on MDRB are consistent with those of the three national cross-situational studies that showed a decrease in the proportion of MRSA among S. aureus strains in hospital-acquired infections (57% in 1996, 64% in 2001 and 52% in 2006). These results are also consistent with those of the French networks participating in the European Antimicrobial Resistance Surveillance Network (EARS-Net), which showed a decrease in the prevalence of MRSA, expressed as the proportion of methicillin resistance among the strains of S. aureus isolated from blood cultures, from 33% in 2001 to 22% in 2010. A dramatic decrease in MRSA rates has also been obtained during the 2000s after implementation of control measures in the UK, a country where MRSA rates were particularly high at the end of the 1990s. In contrast, the prevalence of MRSA remained unchanged, or even increased, over the last 9 years in several European countries. Despite the decrease in the MRSA rate demonstrated in this study, the rate observed in 2010 (0.40/1000 PDs) remains far higher than that prevailing in northern European countries, which should stimulate French HCFs to pursue their efforts to control cross-transmission and to implement antibiotic stewardship.

In contrast, ESBL incidence increased dramatically, almost 3-fold between 2003 and 2010. The increase was particularly marked for ESBL-producing E. coli. Figure 2 shows that the incidences of MRSA and ESBL have clear opposite trends and that, for the first time in 2010, the slope of the incidence of ESBL crossed that of MRSA in France. This increase in ESBL is consistent with the data from the French facilities participating in EARS-Net, which showed an increase in the proportion of strains resistant to third-generation cephalosporins, taken as a surrogate for ESBLs, among the two main species of Enterobacteriaceae isolated from blood cultures: from <1% in 2001 to 7% in 2010 for E. coli and from 4% in 2005 to 18% in 2010 for K. pneumoniae. EARS-Net data showed the same trend of increase in many European countries. In response to this worrying situation, in 2010 the French Ministry of Health released specific recommendations for controlling the spread of ESBL, particularly focusing on ESBL-producing E. coli.

These recommendations focus on the importance of the management of excreta and control of faecal matter. Indeed, the main reservoir of Enterobacteriaceae is the digestive tract, and a majority of ESBL-positive specimens are from the urinary tract. However, the emergence of ESBL-producing E. coli is very complex, with several studies showing that a large number of carriers come from the community, but several cases of ESBL-producing E. coli have been also well documented in healthcare settings, whether associated or not with cross-transmission. ESBL-producing E. coli bacteraemias are often nosocomial in French HCFs. Today, surveillance, therapeutic impact and control of ESBL-producing E. coli spread are of great concern, both directly considering the number of ESBL cases that can be extrapolated from the data obtained in the present study (~40000 cases in 2010 in France, including ~20000 cases of ESBL-producing E. coli) and indirectly by triggering the use of carbapenems that, in turn, increase the selective pressure on carbapenemase-producing Enterobacteriaceae.

Another interesting result of the present study is the differences observed throughout France in 2010 in the rates of MRSA, which are higher in the north and south-west, as well as in the rates of ESBL, which are higher in the north, east and south-east. The reasons for these differences remain unclear and might be due to the type of patients hospitalized in HCFs, the extent of MDRB programme implementation or antibiotic policy. However, the rates of MRSA and ESBL were significant in all areas of France, demonstrating that these MDRB are widely disseminated and that the programme aiming to control them should be pursued for MRSA and intensified for ESBL over the entire country.

**Acknowledgements**
The MDRB Surveillance National Steering Group also includes Emmanuelle Caillet-Vallet, Nadine Garreau, Olivier Hoff, Loïc Simon, Sandrine Mariani, Pierre Parneix, Emmanuelle Reyreau, Elisabeth Sousa, David Trystram and Karin Lebascle.
MDRB surveillance in France 2002–10

Funding
This study was conducted under the auspices of the National Nosocomial Infection Alert, Investigation and Surveillance Network (RAISIN) and was funded by a specific grant from the National Public Health Surveillance Institute (Institut de veille sanitaire, Saint-Maurice, France).

Transparency declarations
None to declare.

References