Escherichia coli and *Staphylococcus aureus*: bad news and good news from the European Antimicrobial Resistance Surveillance Network (EARS-Net, formerly EARSS), 2002 to 2009

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Based on data collected by the European Antimicrobial Resistance Surveillance Network (EARS-Net) and the former EARSS, the present study describes the trends in antimicrobial susceptibility patterns and occurrence of invasive infections caused by *Escherichia coli* and *Staphylococcus aureus* in the period from 2002 to 2009. Antimicrobial susceptibility results from 198 laboratories in 22 European countries reporting continuously on these two microorganisms during the entire study period were included in the analysis. The number of bloodstream infections caused by *E. coli* increased remarkably by 71% during the study period, while bloodstream infections caused by *S. aureus* increased by 34%. At the same time, an alarming increase of antimicrobial resistance in *E. coli* was observed, whereas for *S. aureus* the proportion of meticillin resistant isolates decreased. The observed trend suggests an increasing burden of disease caused by *E. coli*. The reduction in the proportion of meticillin-resistant *S. aureus* and the lesser increase in *S. aureus* infections, compared with *E. coli*, may reflect the success of infection control measures at hospital level in several European countries.

Introduction

Escherichia coli and *Staphylococcus aureus* are the main causes of bloodstream infections (BSIs) in humans. The antimicrobial resistance of *E. coli* causing BSI is increasing alarmingly across Europe, while meticillin-resistant *S. aureus* (MRSA) is decreasing in several countries [1]. The antimicrobial susceptibility of these microorganisms and other selected bacterial pathogens causing invasive infections has been monitored for a decade by the European Antimicrobial Resistance Surveillance System (EARSS) [1]. Coordination and administration of the EARSS project, previously conducted by the Dutch National Institute of Public Health and the Environment (RIVM), was transferred to the European Centre for Disease Prevention and Control (ECDC) on 1 January 2010, and the network was renamed European Antimicrobial Resistance Surveillance Network (EARS-Net). The first data collection by EARS-Net (antimicrobial susceptibility data referring to 2009) took place during June and July 2010.

Whereas detailed analysis and trends at the national level are available in the EARSS and EARS-Net reports [1,2], the present study describes the trends in susceptibility patterns and number of invasive infections caused by *E. coli* and *S. aureus* in Europe from 2002 to 2009, based on data from laboratories reporting continuously during this period.

Methods

Data for *E. coli* and *S. aureus* BSIs were extracted from the EARSS/EARS-Net database for a convenience sample of laboratories reporting susceptibility results continuously during the period from 2002 to 2009 for aminopenicillin, fluoroquinolones, third generation cephalosporins and aminoglycosides in *E. coli* and for oxacillin in *S. aureus* [3]. Countries in which no laboratory participated for the entire period or that had only a small data set (less than 20 isolates per microorganism per year) were not included in the analysis. Only

the first isolate per patient, microorganism and year was included as a representative sample. Sampling and processing of isolates was done in agreement with the EARSS manual 2005 [3]. Resistance (R category of S, I, R) was defined by the guidelines in use in the reporting countries.

The number of BSIs caused by *E. coli* and *S. aureus* and the proportions of third-generation cephalosporin-resistant *E. coli* and of MRSA were recorded for each year from 2002 to 2009. To assess the patterns of combined resistance of *E. coli*, the following antimicrobial classes were analysed: aminopenicillins (ampicillin and amoxicillin), aminoglycosides (gentamicin, tobramycin and amikacin), third-generation cephalosporins (ceftriaxone, cefotaxime and ceftazidime) and fluoroquinolones (ciprofloxacin, ofloxacin and levofloxacin). Resistance to a class was defined as resistance (R category) to at least one agent in the class. The significance of the temporal linear trends for resistance proportions was evaluated by the Cochran–Armitage test for trend.

Results

A total of 198 laboratories in 22 countries continuously reported data from 2002 to 2009. The number of laboratories per country ranged between one (Iceland and Malta) and 33 (Czech Republic), while the mean number of *E. coli* and *S. aureus* isolates reported yearly per country ranged from 96 to 1,973 and from 56 to 1,290, respectively (Table).

Considering the whole group of selected laboratories, the reported number of *E. coli* BSIs increased by 71% from 10,688 in 2002 to 18,240 in 2009 (Figure 1); most of the rise (38% of 71%) in *E. coli* BSIs was due to isolates resistant to two or more antimicrobials. During the same period, *S. aureus* BSIs showed a 34% increase from 7,855 to 10,503 (Figure 1). In the period from 2002 to 2009, if only *E.coli* susceptible to aminopenicillins, third-generation cephalosporins, fluoroquinolones and aminoglycosides are considered, the number of BSIs increased by 39%. Similarly, the BSIs caused by meticillin-susceptible *S. aureus* showed an increase of 37%.

In the period from 2002 to 2009, the proportion among all *E. coli* of *E. coli* resistant to third-generation cephalosporins increased significantly from 1.7% to 8% ($p<0.001$) and the proportion of MRSA decreased from 21.5% to 19.7% ($p<0.001$) (Figure 2). Similar trends of resistance proportions as observed for aggregated data of all 198 laboratories were also observed at country level in 18 of 22 countries for *E. coli*, and in seven of 22 countries for *S. aureus*.

Table

Mean annual number of *Escherichia coli* and *Staphylococcus aureus* isolates per country reported by laboratories (n=198) reporting continuously to EARSS/EARS-Net, 2002–09

Country	Number of laboratories	Number of *Escherichia coli* isolates	Number of *Staphylococcus aureus* isolates
		Mean per year (2002–09)	Mean per year (2002–09)
Austria	10	802	630
Belgium	9	646	343
Bulgaria	7	96	82
Czech Republic	33	1,837	1,290
Estonia	5	142	125
Finland	5	849	381
France	12	1,583	1,018
Germany	2	156	121
Greece	22	829	472
Hungary	14	446	526
Iceland	1	97	56
Ireland	15	1,086	961
Italy	3	237	166
Luxembourg	4	176	80
Malta	1	104	96
Netherlands	4	291	238
Norway	7	975	467
Portugal	8	559	574
Slovenia	9	572	321
Spain	19	1,973	835
Sweden	3	578	331
United Kingdom	5	641	373

EARSS: European Antimicrobial Resistance Surveillance System; EARS-Net: European Antimicrobial Resistance Surveillance Network.

Combined resistance in *E. coli* (defined as resistance to two, three or four antimicrobial classes reported to EARS-Net) showed a significant increase (p<0.001) (Figure 3) whereas single resistance diminished from 37.1% in 2002 to 35.8% in 2009 (p<0.001). The proportion of *E. coli* isolates susceptible to all four antimicrobial classes decreased from 51.4% in 2002 to 41.7% in 2009 (p<0.001).

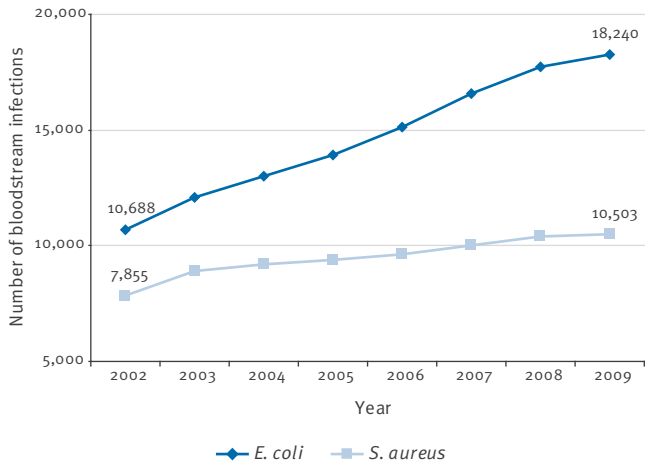
Discussion

The increase in antimicrobial resistance in *E. coli* between 2002 and 2009 was evident both in the observed increase of combined resistance and in the reduction of full susceptibility to the antimicrobials included in the analysis. In the same time period and considering the same data source, a significant decrease of meticillin resistance was observed for *S. aureus*. For this species, the number of BSIs increased less (+34%) than for *E. coli* BSI (+71%). Consistently, increasing resistance in *E. coli* and combined resistance of invasive and non-invasive isolates was reported by several European countries [4-8]. At the same time, the proportion of MRSA showed a significant decrease in many European countries [1,2]. The numbers of BSIs caused by MRSA, as reported by the mandatory surveillance system in England, decreased by 56% between 2004 and 2008 [9], and in France a significant decrease in the occurrence of MRSA was reported in 2008 [10]. A similar reduction in the rate of healthcare-associated invasive MRSA infections was observed in the general population in the United States [11].

The sampling approach selected for this study is likely to eliminate a large part of the possible temporal variation in the size of the catchment population behind the numbers. Based on the available surveillance data, it provides the best possible evidence of the increasing burden of disease caused by *E. coli* and *S. aureus* bacteraemia in the European Union. Nevertheless, if the population covered by the participating laboratories became larger during the study period, this may have contributed to the observed increase. Likewise, the sample approach includes laboratories without taking into account the size of the country, and therefore does not allow detailed analysis at national level. The disparity in the BSI trends for *E. coli* and *S. aureus* could partly be explained by ascertainment bias leading to higher reporting of *E. coli* infections. This could be caused by an increase of empirical treatment failures triggering delayed diagnostic procedures (blood culture). A similar upward trend in the number of reported cases of *E. coli* BSIs has been observed by

Figure 1

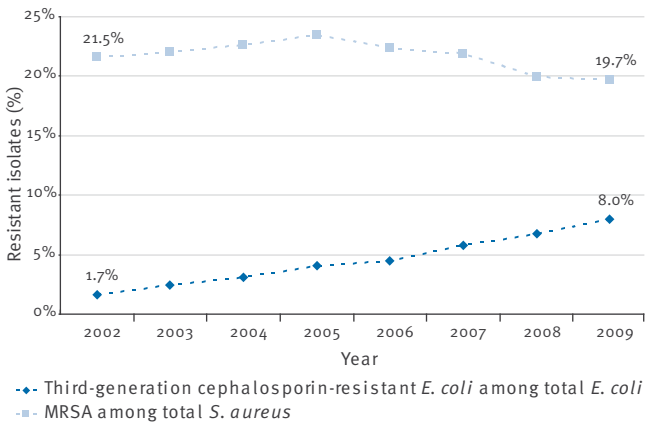
Annual number of bloodstream infections caused by *Escherichia coli* and *Staphylococcus aureus*, EARSS/EARS-Net, 2002-09 (22 countries/198 laboratories)



EARSS: European Antimicrobial Resistance Surveillance System; EARS-Net: European Antimicrobial Resistance Surveillance Network.

Figure 2

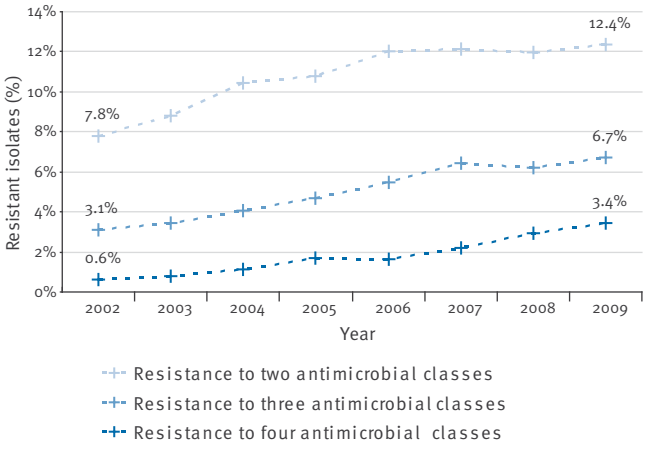
Proportion of third-generation cephalosporin-resistant *Escherichia coli* and of meticillin-resistant *Staphylococcus aureus*, EARSS/EARS-Net, 2002-09 (22 countries/198 laboratories)



EARS-Net: European Antimicrobial Resistance Surveillance Network; EARSS: European Antimicrobial Resistance Surveillance System.

Figure 3

Combined resistance of *Escherichia coli* to aminopenicillins, third-generation cephalosporins, fluoroquinolones and aminoglycosides, EARSS/EARS-Net, 2002-09 (22 countries/198 laboratories)



EARSS/EARS-Net: European Antimicrobial Resistance Surveillance Network; EARSS: European Antimicrobial Resistance Surveillance System.

the national voluntary surveillance scheme in England, Wales, and Northern Ireland between 2005 and 2009. The increase (37%) in BSIs caused by *E. coli* observed by this surveillance system is larger than the increase in all BSIs reported during that time period [12].

Despite the study limitations, the observed trends regarding resistance to third-generation cephalosporins and combined resistance in *E. coli* deserve further consideration. According to the results, it appears that the emergence and spread of combined resistance during the study period was the main factor that influences the decline in antimicrobial susceptibility in *E. coli*. From 2002 to 2009, a relative increase of combined resistance with a concurrent reduction of the proportion of single resistance was observed. The resistance pattern with the largest relative growth in the period from 2002 to 2009 was resistance to all four antimicrobial classes under surveillance: the frequency of this pattern increased more than fivefold from 0.6% to 3.4%. This trend suggests that within the subpopulation of resistant isolates, there was a continuous relative growth of combined resistance, possibly caused by the addition of resistance traits to strains that were already resistant to at least one of the considered antimicrobial classes. This trend may be explained by the spread of multidrug-resistant plasmids which also contain genes for the extended-spectrum beta-lactamase (ESBL) production [13-16].

Resistance trends were monitored using interpretations: susceptible, intermediate or resistant (SIR) [3], since the actual minimum inhibitory concentrations (MIC) were not systematically available from participating laboratories. Reporting MICs rather than SIR interpretations based on clinical breakpoints would improve the dynamic monitoring of subtle, incremental changes in antimicrobial susceptibility. Moreover, the interpretation using SIR categories reported to EARS-Net is based on breakpoints defined in the participating countries' guidelines over time. Nevertheless, for the combinations of microorganisms and antimicrobials included in this study, the variation in the proportion of resistance caused by using different guidelines is very limited (unpublished data).

Conclusion

This is a serious concern since, if the increasing trend of antimicrobial resistance and the spread of ESBL are not contained, the use of carbapenems will increase favouring the emergence of carbapenemase producing enterobacteria. This has been already observed for *Klebsiealla pneumoniae* in Greece, Israel and Cyprus [1,2].

At the same time, *S. aureus* showed a relatively smaller increase in the number of reported BSIs, but a significant decrease in the proportion of MRSA overall in the countries participating in EARSS/EARS-Net. This could be the result of public health efforts targeted at the containment of MRSA in several European countries.* Although an overall decreasing trend for MRSA is evident in Europe, not all countries contribute to this result. Efforts to reduce the occurrence of MRSA should remain a priority irrespective of decreasing trends.

In this context, coordinated international surveillance is particularly important in order to obtain accurate knowledge of the occurrence and spread of antimicrobial resistance and to plan public health interventions.

*** Authors' correction:**
At the request of the authors, the following correction was made on 18 March 2011: The sentence 'This could be the result of public health efforts targeted at the containment of MRSA in several European countries.' was changed to 'This could be the result of public health efforts targeted at the containment of MRSA in several European countries.'

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