# The changing epidemiology of bacteraemias in Europe: trends from the European Antimicrobial Resistance Surveillance System

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## Abstract

We investigated bacteraemia trends for five major bacterial pathogens, *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus pneumoniae*, *Enterococcus faecalis* and *Enterococcus faecium*, and determined how expanding antimicrobial resistance influenced the total burden of bacteraemias in Europe. Aetiological fractions of species and antibiotic phenotypes were extracted from the European Antimicrobial Resistance Surveillance System (EARSS) database for laboratories, which consistently reported between 2002 and 2008. Trend analyses used generalized linear models. Robustness of results was assessed by iterative analysis for different geographic regions. From 2002 to 2008, the overall number of reports increased annually by 6.4% (95% confidence interval (CI) 6.2–6.5%), from 46 095 to 67 876. In the subset of laboratories providing denominator information, the overall incidence increased from 0.58/1000 patient-days to 0.90/1000 patient-days (7.2% per year; 95% CI 6.9–7.5%). The frequency of reported bacteraemia isolates of *S. aureus* and *Streptococcus pneumoniae* increased moderately, while increase in *E. coli* and *Enterococcus faecium* was more pronounced. Bacteraemias caused by methicillin-resistant *S. aureus* increased until 2005 (7.6% per year; 95% CI 6.1–9.1%), and then decreased (−4.8% per year; 95% CI −6.1 to −3.5%), whereas the number attributable to methicillin-sensitive *S. aureus* increased continuously (3.4% per year; 95% CI 3.0–3.7). Increasing rates of *E. coli* were mainly caused by antibiotic-resistant phenotypes. Our data suggest that the burden of bacterial bloodstream infection has been increasing for all species during EARSS surveillance. Trends were mainly driven by resistant strains and clearly dissociated between resistant and susceptible isolates. It appears that infections with resistant clones add to rather than replace infections caused by susceptible bacteria. As a consequence, expansion of antibiotic resistance creates an additional strain on healthcare systems.

**Keywords:** Antimicrobial resistance, bacteraemia, *Enterococcus faecalis*, *Enterococcus faecium*, epidemiology, *Escherichia coli*, Europe, *Staphylococcus aureus*, *Streptococcus pneumoniae*, trend
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## Introduction

It has been suggested that, more than 23 000 people died of *Staphylococcus aureus* and *Escherichia coli* bacteraemias in Europe in 2007 alone [1]. At the same time, bacteraemias seem to be rising in numbers [2–4], although most of the recent investigations have focused on *S. aureus* at national level. It remains unclear whether these trends can be generalized across species and across Europe. It is also unknown what may cause this dynamic; (i) changes in pathogen-specific transmissibility, virulence or resistance, (ii) new ecological opportunities linked to an aging population or increasingly complex medical care, or (iii) a combination of these. Alternatively, we could be merely seeing some random fluctuation at regional levels or an increase in detection rates caused by better diagnostic practices.

One of the possible, adaptive responses of bacteria under antibiotic selection includes the emergence of antimicrobial resistance. A number of observational studies have suggested that resistant strains cause additional infections rather than replacing those caused by susceptible bacteria [5–8]. This hypothesis was first put forward by Boyce *et al.* [9]. and was based on data for *S. aureus* from single centres or countries.

The European Antimicrobial Resistance Surveillance System (EARSS, renamed EARS-Net in 2010), maintains the largest database of routinely collected antibiotic susceptibility data for bacteraemia isolates worldwide [10]. Since its launch in 1999, the initiative has grown in scope and size. Over the last 10 years, antibiotic susceptibility test (AST) results for seven major pathogens from more than 900 000 bacteraemic episodes have been reported by over 900 laboratories from 33 countries in Europe [11]. The EARSS participants have been using consistent protocols and frequently provide denominator data so this dataset provides a useful tool to describe the changing epidemiology of bacteraemias for different species and different species-specific resistance traits. On the basis of surveillance data, we here describe the temporal dynamics of five major pathogens (*S. aureus*, *E. coli*, *Streptococcus pneumoniae*, *Enterococcus faecalis* and *Enterococcus faecium*) causing bacteraemias between 2002 and 2008, and explore how antimicrobial resistance impinges on the total burden of bacteraemias in Europe.

## Material and Methods

Data consisted of routine AST results reported to EARSS for primary isolates (first isolate per species per patient per year) of five bacterial species causing bloodstream infections; *S. aureus*, *Streptococcus pneumoniae* (since 1999), *E. coli*, *Enterococcus faecalis* and *Enterococcus faecium* (since 2001). Participating laboratories routinely include all diagnostic blood cultures that become positive for the above-mentioned species and report results through their laboratory information system using a standardized digital communication tool. Data for the first year of reporting were excluded to correct for potential inconsistencies introduced at the start of the surveillance initiative. Data collected after the transfer of the network to the European Centre for Disease Prevention and Control in 2009 were excluded to rule out possible artefacts caused by changes in hospital and laboratory coding. Analyses are therefore based on data reported to EARSS between 2002 and 2008. The AST results were ascertained according to agreed protocols [12] and the general quality and comparability of these data were evaluated by annual external quality assessment exercises [11]. For detailed trend analyses, reports for *S. aureus* and *E. coli* were stratified by class-specific susceptibility patterns: *S. aureus*, $\beta$-lactams (J01C and D); *E. coli*, aminopenicillins (J01CA: ampicillin or amoxicillin), aminoglycosides (J01GB: gentamicin, tobramycin or amikacin), fluoroquinolones (J01MA: ciprofloxacin, ofloxacin or levofloxacin) and third generation cephalosporins (J01DD: ceftriaxone, ceftazidime or cefotaxime). Class resistance was defined as resistance to at least one antimicrobial compound within each ATC category. Information concerning denominator data including type of hospital, number of patient-days, number of hospital beds, occupancy and total number of blood culture isolates, was available for 5 years (2002, 2004, 2006, 2007 and 2008) [11,13].

### Selected datasets

We included data from laboratories that consistently reported AST results between 2002 and 2008 (Subset A). Consistency was regarded as quarterly reporting of bacteraemias by the laboratory identifiable by laboratory identification code in the surveillance database. Subset A consisted of 438 laboratories (71% of laboratories participating in 2002) from 27 countries (96% of countries participating in 2002) reporting 410 333 bacteraemias (66% of the total number of cases). Incidence densities were calculated for institutions, which reported both AST and denominator data between 2002 and 2008 (Subset AD). Subset AD consisted of 136 (22%) laboratories from 12 (43%) countries, reporting 149 933 (24%) bacteraemias. For a more inclusive analysis of all countries participating in EARSS in 2008, all data reported for 2008 were used for subset 2008A. Incidence densities for 2008 were obtained for laboratories that reported both AST and denominator data (Subset 2008AD, 62% of 2008 laboratories, 61% of 2008 bacteraemias) (Table 1).

### Statistical analysis

Incidence densities were based on the number of reported bacteraemia isolates per 1000 patient-days. The number of patient-days was approximated by multiplying the number of reported beds per hospital with 365.25 days assuming an 80% bed occupancy (mean European bed occupancy) [11]. The average annual increase in bacteraemias was calculated using generalized linear models with Poisson distribution and loglink function with year as the independent variable. Species-specific trends were compared with the overall trend by including the overall number of bacteraemia isolates as a baseline (offset). Trends in resistance phenotypes were modelled by including each phenotype as a dependent variable in a separate generalized linear model. The significance of trends was determined at the conventional probability threshold of $p < 0.05$ using the Wald test.