Secular Trends in Nosocomial Bloodstream Infections: Antibiotic-Resistant Bacteria Increase the Total Burden of Infection

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Background. It is unknown whether rising incidence rates of nosocomial bloodstream infections (BSIs) caused by antibiotic-resistant bacteria (ARB) replace antibiotic-susceptible bacteria (ASB), leaving the total BSI rate unaffected.

Methods. We investigated temporal trends in annual incidence densities (events per 100 000 patient-days) of nosocomial BSIs caused by methicillin-resistant *Staphylococcus aureus* (MRSA), ARB other than MRSA, and ASB in 7 ARB-endemic and 7 ARB-nonendemic hospitals between 1998 and 2007.

Results. 33 130 nosocomial BSIs (14% caused by ARB) yielded 36 679 microorganisms. From 1998 to 2007, the MRSA incidence density increased from 0.2 to 0.7 (annual increase, 22%) in ARB-nonendemic hospitals, and from 3.1 to 11.7 (annual increase, 10%) in ARB-endemic hospitals ($P = .2$), increasing the incidence density difference between ARB-endemic and ARB-nonendemic hospitals from 2.9 to 11.0. The non-MRSA ARB incidence density increased from 2.8 to 4.1 (annual increase, 5%) in ARB-nonendemic hospitals, and from 1.5 to 17.4 (annual increase, 22%) in ARB-endemic hospitals ($P < .001$), changing the incidence density difference from −1.3 to 13.3. Trends in ASB incidence densities were similar in both groups ($P = .7$). With annual increases of 3.8% and 5.4% of all nosocomial BSIs in ARB-nonendemic and ARB-endemic hospitals, respectively ($P < .001$), the overall incidence density difference of 3.8 increased to 24.4.

Conclusions. Increased nosocomial BSI rates due to ARB occur in addition to infections caused by ASB, increasing the total burden of disease. Hospitals with high ARB infection rates in 2005 had an excess burden of BSI of 20.6 per 100 000 patient-days in a 10-year period, mainly caused by infections with ARB.

Keywords. Trends; nosocomial; bloodstream infections; antibiotic-resistant bacteria; antibiotic-susceptible bacteria.

Rates of nosocomial bloodstream infections (BSIs) caused by antibiotic-resistant bacteria (ARB) are increasing worldwide [1]. Yet, associated changes in total burden of disease and the dynamic interaction between ARB and antibiotic-susceptible bacteria (ASB) have not been accurately quantified [2]. For instance, one could hypothesize that the frequent use of antibiotics in hospitalized patients creates an ecological niche for ARB that replace ASB, without increasing the total burden of disease. Alternatively, ARB and ASB may not compete, and, thus, increasing infection rates caused by ARB incur an additive burden. Such information is critical for quantifying the health-economic effects of antimicrobial resistance and demonstrating the benefits of infection control [3]. Most longitudinal studies on the epidemiology of ARB addressed a single pathogen, frequently with comparison to its antibiotic-susceptible variant, but failed to include all other pathogens [2]. To assess whether incidences remain stable or increase, one should adjust for changes in duration of hospital stay over time. Hence, incidence density (ie, incidence rate; number of events per number of patient-days) will quantify the problem of antimicrobial resistance more accurately than crude numbers of events [4].

We quantified temporal trends in the microbiologic etiology of nosocomial BSIs due to ARB and ASB in 14 hospitals in Europe, North America, and South America over a 10-year period. We categorized hospitals as those with and without endemic ARB. We aimed to determine if ARB replace ASB, or if (and to what extent) they are additive to the total burden of nosocomial BSIs.

METHODS

Ethics Statement
Institutional review boards in most of the participating hospitals did not require a formal protocol review because this study was retrospective and thus did not affect patient care, and data were de-identified. Oxford data came from the Infection in Oxfordshire Research Database, approved by the Oxford Research Ethics Committee (09/H0606/85) and the United Kingdom National Information Governance Board (5–07(a)/2009).

Study Design, Study Setting, and Study Population
We performed a cohort study of patients with microbiologically confirmed nosocomial BSI by linking de-identified databases from the hospital information systems and the microbiology laboratories of the participating hospitals. Hospitals were eligible if they could provide (1) data on positive blood cultures, including susceptibility profiles, for at least 7 consecutive years, (2) numbers of hospital admissions and lengths of stay for the same period, and (3) the hospital day during which blood cultures were obtained. Patients admitted to ambulatory care and psychiatric units were excluded. Species identification and susceptibility testing were performed according to local guidelines and procedures.

We initially used the 2005 figures of methicillin-resistant *Staphylococcus aureus* (MRSA) reported by existing surveillance programs to categorize hospitals based on their countries' proportion of MRSA among *S. aureus* invasive infections, being more or less than 0.10, as having high or low infection rates of ARB [5–7]. After data collection we quantified the proportion of MRSA and ARB isolates and the incidence densities of nosocomial MRSA BSI and ARB BSI in 2005.

Data Collection and Variables of Interest
The hospitals' microbiological databases were linked to patient-administrative systems, thereby providing a database with all patient admissions. The database included microbiological results of all positive blood cultures obtained, and data on sex, age, department of admission, and length of stay before nosocomial BSI acquisition. Hospital departments were categorized as surgery, medicine, and mixed departments, and patient care units were categorized as intensive care units or regular wards.

Definitions
• *Bloodstream infection:* Isolation of bacteria or fungi from at least 1 blood culture set. Microorganisms typically belonging to the skin flora (coagulase-negative staphylococci, *Micrococcus* species, *Bacillus* species, or diphtheroids [corynebacteria or propionibacteria]) were considered to be probable contaminants and were excluded.

• *Nosocomial BSI:* BSIs occurring >48 hours after hospital admission and in patients who did not have documented BSI with the same microorganism during the first 48 hours after admission.

• *Polymicrobial BSI:* BSI with >1 microorganism in a single set of blood cultures or in different blood culture sets obtained within 48 hours of the first positive blood culture.

• *New episode of BSI:* BSI caused by a different microorganism >48 hours after the previous nosocomial BSI or by the same microorganism >30 days after the previous BSI.

• *Antibiotic-resistant bacteria:* Definitions of ARB were based on a Dutch guideline (resistance criteria for isolation of patients; Supplementary Table 1) [8]; these bacteria were subdivided in MRSA and non-MRSA ARB.

• *Antibiotic-susceptible bacteria:* Bacteria that did not meet the definition of ARB according to the Dutch guideline.

Statistical Analysis
Data were analyzed from each hospital independently, and from aggregate data from 2 groups, ARB-endemic and ARB-

nonendemic hospitals. Although the participating hospitals submitted data from somewhat different time periods, we assessed trends in the rates of nosocomial BSI by pooling results from the 10-year period 1998 to 2007. We did a sensitivity analysis by repeating calculations from the period 2000 to 2005, for which all participating hospitals submitted data (Supplementary Figure 1). In a second sensitivity analysis, we excluded hospitals with the most extreme nosocomial BSI incidence densities (Porto Alegre and Utrecht for the ARB-endemic and ARB-nonendemic hospitals, respectively).

We assessed changes in the incidence densities of nosocomial BSI to describe changes in the overall burden of disease over time, and we assessed changes in the incidence densities of cultured microorganisms (including each microorganism in polymicrobial nosocomial BSI) to describe changes in burden of nosocomial BSI infections caused by MRSA, ARB, and ASB. Incidence densities were calculated as the number of events per 100 000 patient-days. We modeled temporal trends of incidence densities using Poisson regression, presenting yearly change in incidence density as a rate ratio (RR) with a 95% confidence interval (CI). To determine whether differences between RRs from ARB-endemic and ARB-nonendemic hospitals were statistically significant, we calculated the P value for heterogeneity.

We repeated calculations with number of events per 10 000 admissions (cumulative incidence), to allow for the possibility of nonparametric changes in length of stay after the onset of nosocomial BSI compared to overall length of stay over the study period, leading to an overestimation of increased burden of disease when expressed as incidence densities (Supplementary Table 2).

We used the χ^2 test for dichotomous variables, univariable logistic regression for categorical variables, and Mann-Whitney U test for continuous, nonnormally distributed variables to analyze relations between patients and ARB endemicity. The data were analyzed using SPSS version 15.0 (SPSS, Chicago, Illinois) and R version 2.6.0.

RESULTS

Hospital Characteristics

Fourteen hospitals from 9 countries participated: 7 hospitals in countries with low proportions of MRSA among *S. aureus* BSIs in 2005 [5] (the Netherlands [2 university hospitals, 2 general hospitals], Norway [1 university hospital], and Sweden [1 university hospital, 1 general hospital]), and 7 in countries with high proportions of MRSA among *S. aureus* BSI in 2005 [5–7] (Germany [2 university hospitals], Switzerland [1 university hospital], United Kingdom [1 university hospital], Republic of Ireland [1 university hospital], United States [1 university hospital], and Brazil [1 university hospital]). The observed proportions of MRSA among *S. aureus* nosocomial BSIs in 2005 ranged from 0.00 to 0.05 among hospitals in countries with low prevalence of MRSA, and from 0.22 to 0.66 among hospitals in countries with high prevalence of MRSA. The observed incidence densities of nosocomial MRSA BSI in 2005 ranged from 0.0 to 1.1 per 100 000 patient-days among hospitals in countries with low MRSA rates and from 4.2 to 58 per 100 000 patient-days among hospitals in countries with high MRSA rates. The observed incidence densities of nosocomial ARB BSIs in 2005 ranged from 1.3 to 4.8 per 100 000 patient-days among hospitals in countries with low MRSA rates (ARB-nonendemic hospitals) and from 9.9 to 91 per 100 000 patient-days among hospitals in countries with high MRSA rates (ARB-endemic hospitals), which implies that the proportion of MRSA—in these hospitals—is a reliable proxy for ARB BSIs.

During the study period, 4 992 357 patients were admitted for a total of 36.391 175 patient-days. The annual number of patient-days increased by 0.3% among ARB-nonendemic hospitals and 0.5% among ARB-endemic hospitals (Supplementary Table 3).

Microbiology

Over the study period, 202 523 positive blood cultures were obtained (not including probable contaminants) during 64 417 BSI episodes (Figure 1), of which 33 130 (51.4%) were hospital-acquired, yielding 36 679 microorganisms: 9655 (25.9%) grew Enterobacteriaceae, 7367 (22.6%) *S. aureus*, 3673 (11.4%) *Enterococcus* species, 2824 (8.0%) *Streptococcus* species, 508 (1.5%) other gram-positive species, 1670 (5.3%) *Pseudomonas aeruginosa*, 640 (2.0%) *Acinetobacter* species, 1006 (3.3%) other gram-negative species, 1666 (4.9%) fungi, 1104 (3.3%) anaerobes, and 3017 (8.3%) polymicrobial episodes. Of the nosocomial BSIs, 30 178 (91.1%) were a patient's first nosocomial BSI following hospital admission, and the remaining 2962 were patients' second to fifth episodes during the same hospital stay. Nearly 14% (4484/33 130; 13.5%) of nosocomial BSIs were caused by ARB: 18.8% (4040/21 452) in ARB-endemic hospitals compared with 3.8% (444/11 688) in ARB-nonendemic hospitals ($P < .001$). Nineteen percent (574/3017) of polymicrobial nosocomial BSIs included at least 1 ARB.

Of nosocomial BSIs, 29 879 (90.1%) occurred between 1998 and 2007 (Table 1). Thus, data from this period were analyzed to assess differences in trends between ARB-endemic and ARB-nonendemic hospitals. The sensitivity analysis included 20 272 (61.2%) nosocomial BSIs that occurred from 2000 through 2005 (Supplementary Figure 1).

Patient Characteristics

Patients with nosocomial BSI had a median age of 61 years (interquartile range [IQR], 42–73), 59.1% were male, and
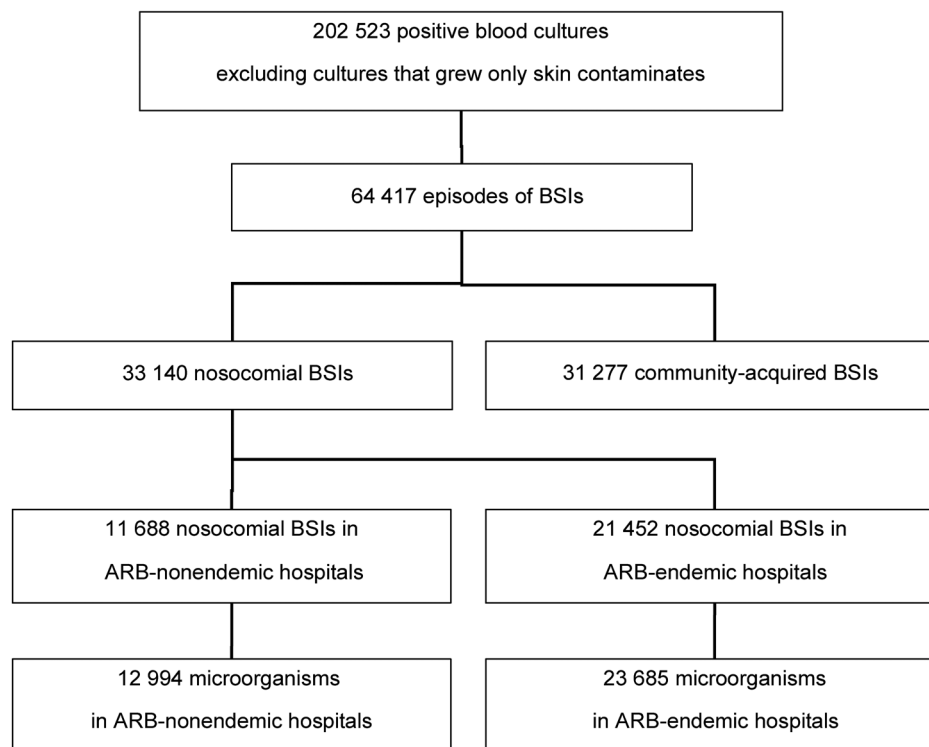
Figure 1. Flow diagram of the study. Abbreviations: ARB, antibiotic-resistant bacteria; BSI, bloodstream infection.

patients were hospitalized for a median of 13 days (IQR, 7–27) when their first positive blood culture was obtained. Thirty-six percent of nosocomial BSIs were acquired in a surgical ward, 49.3% in a medical ward, and 14.4% in a mixed surgical and medical ward. Twenty percent of nosocomial BSIs were acquired in an intensive care unit. Compared with bacteremic patients hospitalized in ARB-nonendemic hospitals, patients in ARB-endemic hospitals were younger (59 years [IQR, 40–72 years] vs 63 years [IQR, 47–74 years]), had longer lengths of stay before BSI acquisition (14 days [IQR, 7–28 days] vs 13 days [IQR, 7–25 days]), were more likely to be admitted to a medical ward (51.5% vs 45.0%), and were less likely to be admitted to an intensive care unit (18.1% vs 24.1%; all comparisons $P < .001$).

Incidence Rates of Nosocomial BSIs

Between 1998 and 2007, the average incidence density of nosocomial BSIs per hospital ranged from 62.3 to 185.5 per 100 000 patient-days. The 10-year trend of annual incidence densities increased in 12 hospitals, decreased by 1% in 1 hospital, and did not change significantly in another one. The increase in incidence densities was mainly due to increased rates of *Enterococcus* species, anaerobes, and *Candida* species in ARB-nonendemic hospitals and to *Enterococcus* species,

Enterobacteriaceae, *Acinetobacter* species, and *Candida* species in ARB-endemic hospitals (Table 1). The incidence density trends for nosocomial BSI caused by ASB, MRSA, and non-MRSA ARB in the participating hospitals are shown in Figure 2.

From 1998 to 2007, the incidence density of nosocomial BSI caused by MRSA increased from 0.2 to 0.7 per 100 000 patient-days in ARB-nonendemic hospitals, an annual increase of 22% (95% CI, 6%–40%). During the same period, the incidence density of MRSA increased from 3.1 to 11.7 per 100 000 patient-days in ARB-endemic hospitals, corresponding to an annual increase of 10% (95% CI, 9%–12%; Table 2). Although the relative rates of increase did not differ significantly between ARB-nonendemic and ARB-endemic hospitals ($P = .2$), the MRSA incidence density difference increased from 2.9 in 1998 to 11.0 per 100 000 patient-days in 2007. The incidence density of nosocomial BSIs caused by non-MRSA ARB increased from 2.8 to 4.1 per 100 000 patient-days in ARB-nonendemic hospitals, corresponding to an annual increase of 5% (95% CI, 1%–9%). In the same period, the incidence density of nosocomial BSIs caused by non-MRSA ARB increased from 1.5 to 17.4 per 100 000 patient-days in ARB-endemic hospitals, an annual increase of 22% (95% CI, 20%–25%; $P < .001$; Table 2; Supplementary Figure 2). As a result,

Table 1. Nosocomial Bloodstream Infections Caused by Specific Microorganisms During the Study Period (1998–2007) by Antibiotic-Resistant Bacteria (ARB)–Nonendemic and ARB-Endemic Hospitals

Microorganism	ARB-Nonendemic Hospitals			ARB-Endemic Hospitals			Heterogeneity[a] P Value
	Total	ID	Trend (ID) RR (95% CI)	Total	ID	Trend (ID) RR (95% CI)	
Staphylococcus aureus	2216	16.2	1.01 (.99–1.03)	5113	27.0	1.05 (1.04–1.06)	<.001
Enterococcus spp	1352	9.9	1.07 (1.05–1.09)	3037	16.0	1.06 (1.05–1.08)	.9
Streptococcus spp	1100	8.0	1.02 (1.00–1.04)	1417	7.5	1.01 (.99–1.03)	.4
Other gram-positives	198	1.4	1.08 (1.02–1.14)	281	1.5	1.15 (1.10–1.21)	.06
Enterobacteriaceae	4205	30.7	1.05 (1.04–1.06)	6036	31.9	1.07 (1.06–1.08)	.005
Acinetobacter spp	135	1.0	0.94 (.88–1.00)	626	3.3	1.10 (1.07–1.14)	<.001
Pseudomonas aeruginosa	643	4.7	1.05 (1.02–1.08)	1229	6.5	1.05 (1.02–1.07)	.9
Other gram-negatives	280	2.0	1.02 (.99–1.08)	646	3.4	1.05 (1.02–1.07)	.6
Anaerobes	413	3.0	1.06 (1.02–1.10)	573	3.0	0.99 (.96–1.03)	.008
Candida spp	522	3.8	1.06 (1.03–1.10)	1002	5.3	1.08 (1.05–1.10)	.5
Polymicrobial	997	7.3	1.05 (1.03–1.08)	1680	8.9	1.04 (1.03–1.06)	.6

Trend (ID) is secular changes in incidence density (on average, per year) of nosocomial bloodstream infections (number of infections per 100 000 patient-days) from 1998 to 2007, stratified by pathogen.

Abbreviations: ARB, antibiotic-resistant bacteria; CI, confidence interval; ID, incidence density; RR, rate ratio.

[a] The statistical significance of the difference between RRs from ARB-endemic and ARB-nonendemic hospitals was assessed by calculating the *P* value for the interaction term (calendar year–hospital type). *P* values <.05 indicate that the trends for ARB-endemic and nonendemic hospitals are significantly different.

the incidence density difference between ARB-endemic and ARB-nonendemic hospitals for nosocomial BSIs caused by non-MRSA ARB increased from −1.3 per 100 000 patient-days in 1998 to 13.3 per 100 000 patient-days in 2007.

Trends in incidence densities of nosocomial ASB BSIs were similar, with annual increases of 4.5% (95% CI, 4%–5%) and 4.2% (95% CI, 4%–5%) in ARB-nonendemic and ARB-endemic hospitals, respectively (*P* = .7). The overall incidence density difference between ARB-endemic and ARB-nonendemic hospitals increased from 3.8 per 100 000 patient days in 1998 (78.1 vs 74.3 per 100 000 patient-days, respectively) to 24.4 per 100 000 patient-days in 2007 (130.1 vs 105.7 per 100 000 patient-days, respectively), fully attributable to infections caused by ARB (*P* < .001).

Sensitivity analyses evaluating data from 2000 to 2005 and evaluating data that excluded data from the hospitals with the highest rates yielded similar results (data not shown). Moreover, trends in cumulative incidences were comparable to trends in incidence densities (Supplementary Table 2).

DISCUSSION

On the basis of detailed longitudinal data from 14 hospitals in 3 continent, we have demonstrated that an increasing incidence of nosocomial BSIs caused by ARB adds to the total burden of disease without replacing BSIs caused by more susceptible bacteria. While the total burden of nosocomial BSIs in both cohorts was similar in 1998, the excess increase in

incidence rates of nosocomial BSIs in ARB-endemic hospitals was 20.6 per 100 000 patient days in 2007 and almost fully attributable to increased rates of infections caused by ARB.

To the best of our knowledge, this study is the first to conduct integrated trend analyses of all relevant nosocomial pathogens on such a large multicenter dataset. This dataset allowed us to quantify the overall burden of nosocomial BSIs caused by ARB and ASB. Although longitudinal changes in incidences and proportions of pathogens causing nosocomial infections have been reported previously, in most studies reported changes in the burden of disease due to ARB reflected the epidemiology of a single pathogen [2, 9]. By comparing longitudinal data from hospitals with high and lower rates of nosocomial ARB BSIs, we took advantage of a natural experiment that allowed us to observe long-term effects of successful and less successful control of nosocomial spread of ARB. On a global level, this information is critical for assessing benefits of infection prevention and control strategies. In the past years, guidelines have focused specifically on prevention of ARB transmission in hospitals, in particular MRSA [10–13]. Our results stress the importance of successful prevention of all ARB.

Although our study was observational, we feel that the more pronounced increase of BSIs in the ARB-endemic hospitals reflects either differences in infection prevention practices or antibiotic prescription patterns, or both, of the hospitals and their home countries [14, 15]. Our findings suggest that hospitals (and their home countries) that effectively prevented
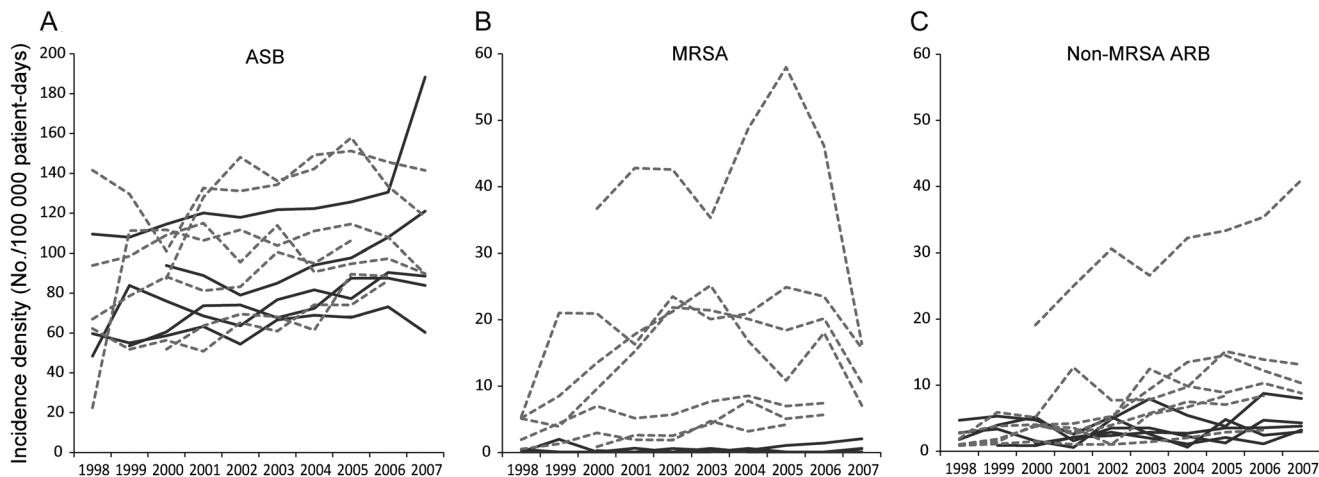
Figure 2. Trends in incidence densities of microorganisms. Lines show trends in incidence densities over the study period for each hospital (antibiotic-resistant bacteria [ARB]–endemic vs ARB-nonendemic hospitals) contributing data to the analysis. Light gray dashed line = ARB-endemic hospitals; dark gray solid line = ARB-nonendemic hospitals. Different y-axis scales are used in each panel. *A*, Incidence densities of bloodstream infection (BSI) caused by antibiotic-susceptible bacteria. *B*, Incidence densities of BSI caused by methicillin-resistant *Staphylococcus aureus* (MRSA). *C*, Incidence densities of BSI caused by non-MRSA ARB. Abbreviations: ARB, antibiotic-resistant bacteria; ASB, antibiotic-susceptible bacteria; MRSA, methicillin-resistant *Staphylococcus aureus*.

emergence of MRSA were also more successful in controlling the more recent emergence of resistance among gram-negative bacteria.

Three alternative explanations of our findings need to be addressed. The first is an imbalanced change in patient case mix that may have occurred during the study period. Such a change in case mix was not discernible from observed changes in age and length of stay. Moreover, annual changes in incidence rates of ASB BSIs were similar in both hospital groups. The second alternative explanation would be that ARB may be more virulent than their susceptible counterparts, but this would contradict the widely accepted view that resistance is associated with reduced fitness, and published studies do not convincingly prove that antimicrobial resistance confers increased virulence on pathogenic bacteria [16]. Finally, nonparametric changes in length of stay after nosocomial BSIs compared with overall length of stay could have caused us to overestimate the burden of disease when expressed as incidence density. However, the cumulative incidence, which is less sensitive to changes in the number of patient-days over time, revealed similar trends.

Our study has several potential limitations. Hospitals were included if they had the availability of an appropriate database, which could have selected hospitals with better surveillance systems and infection control policies. Naturally, results of the various participating hospitals were heterogeneous, which reflects differences in patient populations, local infection prevention measures, hospital organization, and antibiotic prescribing practices. Nevertheless, Figure 2 demonstrates broadly

similar results across our set of hospitals, and does not suggest important ecological biases.

In addition, incidence density analysis in general might be obscured when potential competing events (eg, in-hospital death and hospital discharge) are not taken into account [17]. However, the incidence density of nosocomial BSIs, as determined in our study, was conditional on patients being alive and hospitalized. Thus, the analysis of incidence densities corresponds to an analysis of the hazard for nosocomial BSIs before in-hospital death or hospital discharge.

In theory, hospitals that obtained more blood cultures than others might have higher rates of nosocomial BSIs. Because information on negative blood cultures was not part of this study, changes in blood culture practices over time could not be determined. However, we are unaware of such changes in the participating hospitals. Moreover, we think it is unlikely that such changes differed between hospitals with high and lower rates of nosocomial ARB BSIs.

Misclassification may have occurred for some positive blood cultures in patients who were discharged and then readmitted soon thereafter with a BSI, erroneously classified as community-acquired. Furthermore, we may have misclassified some nosocomial BSIs as noninfectious by excluding cultures that grew possible skin contaminants. Although some might have represented true episodes of nosocomial infection, we were unable to identify them, as information of clinical signs and symptoms was lacking [18]. However, misclassification would have affected rates of nosocomial BSI in a nondifferential manner.

Table 2. Incidence Densities of Microorganisms[a] at Baseline and End of Study

	ARB-Nonendemic Hospitals ID (Microorganisms per 100 000 Patient-Days)				ARB-Endemic Hospitals ID (Microorganisms per 100 000 Patient-Days)				Heterogeneity[b] P Value
	1998	2007	Increase 1998–2007	Trend RR (95% CI)	1998	2007	Increase 1998–2007	Trend RR (95% CI)	
Summary of all microorganisms	74.3	105.7	31.4	1.04 (1.03–1.04)	78.1	130.1	52.0	1.05 (1.05–1.06)	<.001
ARB	3.0	4.7	1.7	1.06 (1.02–1.10)	4.6	29.1	24.5	1.15 (1.13–1.16)	<.001
ASB	71.4	101.0	29.6	1.04 (1.03–1.04)	73.5	101.0	27.5	1.04 (1.03–1.04)	.7
Staphylococcus aureus	15.7	16.3	0.6	1.01 (.99–1.03)	14.9	26.6	11.7	1.05 (1.04–1.06)	<.001
MRSA	0.2	0.7	0.5	1.22 (1.06–1.40)	3.1	11.7	8.6	1.10 (1.09–1.12)	.2
MSSA	15.6	15.6	0.06	1.01 (.99–1.02)	11.8	14.9	3.1	1.00 (.99–1.02)	.8
Non–*S. aureus* microorganisms	58.6	89.4	30.8	1.05 (1.04–1.05)	63.2	103.5	40.3	1.06 (1.05–1.06)	.03
Non-MRSA ARB	2.8	4.1	1.3	1.05 (1.01–1.09)	1.5	17.4	15.9	1.22 (1.20–1.25)	<.001
Enterococcus spp	0.0	0.1	0.1	1.33 (1.02–1.84)	0.6	3.1	2.5	1.22 (1.17–1.27)	.6
Enterobacteriaceae	2.3	3.3	1.0	1.04 (1.00–1.09)	0.6	10.2	9.6	1.21 (1.18–1.25)	<.001
Acinetobacter spp	0.3	0.1	−0.2	0.81 (.67–.96)	0.1	1.9	1.8	1.29 (1.20–1.39)	<.001
P. aeruginosa	0.0	0.4	0.4	1.06 (.96–1.18)	0.1	1.3	1.2	1.19 (1.11–1.27)	.08
Non-MSSA ASB	55.8	85.4	29.6	1.05 (1.04–1.05)	61.7	86.1	24.4	1.04 (1.04–1.05)	.5
Enterococcus spp	8.4	14.2	5.8	1.07 (1.05–1.09)	8.8	11.5	2.7	1.05 (1.03–1.06)	.09
Enterobacteriaceae	23.4	37.4	14.0	1.05 (1.04–1.06)	22.0	35.7	13.7	1.05 (1.04–1.06)	.9
Acinetobacter spp	0.6	0.7	0.1	0.96 (.90–1.03)	1.3	4.0	2.7	1.07 (1.03–1.10)	.007
P. aeruginosa	3.3	5.2	1.9	1.05 (1.02–1.08)	5.4	6.7	1.3	1.03 (1.01–1.05)	.3

Trend is secular changes in incidence density (on average, per year) of nosocomial bloodstream infections (number of infections per 100 000 patient-days) from 1998 to 2007, stratified by pathogen.

Abbreviations: ARB, antibiotic-resistant bacteria; ASB, antibiotic-susceptible bacteria; CI, confidence interval; ID, incidence density; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; *P. aeruginosa*, *Pseudomonas aeruginosa*; RR, rate ratio.

[a] MRSA, MSSA, non-MRSA ARB, and non-MSSA ASB.

[b] The statistical significance between RRs from ARB-endemic and ARB-nonendemic hospitals was assessed by calculating the *P* value for the interaction term (calendar year–hospital type). *P* values <.05 indicate that the trends for ARB endemic and nonendemic hospitals are significantly different.

In conclusion, we demonstrated that nosocomial BSIs caused by ARB do not replace infections caused by more susceptible bacteria, but rather these infections increase the total burden of disease. This implies that successful control of antibiotic resistance improves patient outcome not only because of lower mortality from better treatable infections, but also because of a reduction, or at least a lower increase, in number of infections.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

References

1. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2009. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm, Sweden: ECDC, 2010.

2. Mostofsky E, Lipsitch M, Regev-Yochay G. Is methicillin-resistant *Staphylococcus aureus* replacing methicillin-susceptible *S. aureus*? J Antimicrob Chemother 2011; 66:2199–214.

3. Wassenberg MW, de Wit GA, van Hout BA, Bonten MJ. Quantifying cost-effectiveness of controlling nosocomial spread of antibiotic-resistant bacteria: the case of MRSA. PLoS One 2010; 5:e11562.

4. Ammerlaan HS, Troelstra A, Kruitwagen CL, Kluytmans JA, Bonten MJ. Quantifying changes in incidences of nosocomial bacteraemia caused by antibiotic-susceptible and antibiotic-resistant pathogens. J Antimicrob Chemother 2009; 63:1064–70.

5. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2005. Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC, 2005.

6. Styers D, Sheehan DJ, Hogan P, Sahm DF. Laboratory-based surveillance of current antimicrobial resistance patterns and trends among *Staphylococcus aureus*: 2005 status in the United States. Ann Clin Microbiol Antimicrob 2006; 5:2.

7. Gales AC, Sader HS, Ribeiro J, Zoccoli C, Barth A, Pignatari AC. Antimicrobial susceptibility of gram-positive bacteria isolated in Brazilian hospitals participating in the SENTRY Program (2005–2008). Braz J Infect Dis 2009; 13:90–8.

8. Kluytmans-Vandenbergh MF, Kluytmans JA, Voss A. Dutch guideline for preventing nosocomial transmission of highly resistant microorganisms (HRMO). Infection 2005; 33:309–13.

9. Boyce JM, White RL, Spruill EY. Impact of methicillin-resistant *Staphylococcus aureus* on the incidence of nosocomial staphylococcal infections. J Infect Dis 1983; 148:763.

10. Wertheim HF, Ammerlaan HS, Bonten MJ, et al. Optimisation of the antibiotic policy in the Netherlands. XII. The SWAB guideline for antimicrobial eradication of MRSA in carriers. Ned Tijdschr Geneeskd 2008; 152:2667–71.

11. Coia JE, Duckworth GJ, Edwards DI, et al. Guidelines for the control and prevention of meticillin-resistant *Staphylococcus aureus* (MRSA) in healthcare facilities. J Hosp Infect 2006; 63(suppl 1): S1–44.

12. Gemmell CG, Edwards DI, Fraise AP, Gould FK, Ridgway GL, Warren RE. Guidelines for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the UK. J Antimicrob Chemother 2006; 57:589–608.

13. Muto CA, Jernigan JA, Ostrowsky BE, et al. SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of *Staphylococcus aureus* and enterococcus. Infect Control Hosp Epidemiol 2003; 24:362–86.

14. Ostrowsky BE, Trick WE, Sohn AH, et al. Control of vancomycin-resistant enterococcus in health care facilities in a region. N Engl J Med 2001; 344:1427–33.

15. Lescure FX, Biendo M, Douadi Y, Schmit JL, Eveillard M. Changing epidemiology of methicillin-resistant *Staphylococcus aureus* and effects on cross-transmission in a teaching hospital. Eur J Clin Microbiol Infect Dis 2006; 25:205–7.

16. Andersson DI, Hughes D. Antibiotic resistance and its cost: is it possible to reverse resistance? Nat Rev Microbiol 2010; 8:260–71.

17. Grambauer N, Schumacher M, Dettenkofer M, Beyersmann J. Incidence densities in a competing events analysis. Am J Epidemiol 2010; 172:1077–84.

18. Weinstein MP. Blood culture contamination: persisting problems and partial progress. J Clin Microbiol 2003; 41:2275–8.