Quantifying changes in incidences of nosocomial bacteraemia caused by antibiotic-susceptible and antibiotic-resistant pathogens

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Objectives: The aim of this study was to determine, over time, changes in annual trends of nosocomial bacteraemia (NB) and to quantify pathogen-specific changes and emergence of antibiotic resistance.

Methods: A retrospective cohort study in a 997 bed tertiary care centre in the Netherlands was performed. All adult patients (≥18 years old) admitted for >48 h between 1 January 1996 and 31 December 2005 were included.

Results: A total of 163525 patients, comprising 1826852 patient-days and 1785 episodes of NB, were analysed. The number of admissions per year and length of hospital stay decreased over time. Crude incidence of NB per year remained unchanged, but cumulative incidence (cases/10000 admissions) and incidence densities (cases/100000 patient-days at risk) increased, on average, by 2.0% and 4.0% per year, respectively, primarily because of infections caused by Enterococcus spp. and Pseudomonas aeruginosa. The incidence density of NB caused by highly resistant microorganisms increased, on average, by 26.1% [95% confidence interval (CI): 17–37] per year, when compared with an annual increase of 3% (95% CI: 1–5) for NB caused by susceptible pathogens. Ratios of increased incidence densities of resistant and susceptible bacteria were 8.7, 3.5, 2.6 and >37.9 for all pathogens, Enterococcus spp., P. aeruginosa and Enterobacteriaceae, respectively.

Conclusions: Due to changes in the patient population, increased incidences of NB over time are only evident when expressed as cumulative incidence or incidence densities. Despite overall low levels of antibiotic resistance, the incidence of NB caused by multiresistant pathogens rapidly increased, adding to the total burden of NB.

Keywords: trends, emergence, crude incidence, incidence density, cumulative incidence

Introduction

Nosocomial bacteraemia (NB) is an important complication of hospital treatment, associated with increased morbidity and mortality, especially when caused by antibiotic-resistant pathogens. It is widely believed that the problem of antibiotic resistance is increasing over time in hospitals worldwide. Yet, there is no uniformly used methodology to quantify longitudinal trends, taking changes in patient populations into account. Moreover, most studies investigate the epidemiology of a single pathogen, which precludes an analysis of changes in the total burden of disease caused by antibiotic-resistant bacteria. Incidence rates of NB have been expressed as crude numbers,2,3 cumulative incidence (i.e. incidence risk; number of events per number of hospital admissions, discharges or people in a population)4–16 or incidence density (i.e. incidence rate; number of events per number of patient-days).17–19 Naturally, changes in patient population characteristics over time (such as number of admissions and number of patient-days) affect these incidences of NB, thereby hampering the comparison of incidences between settings, if
Quantifying changes in bacteraemia incidence

Various definitions are used. Importantly, longitudinal studies should not focus on a single microorganism, as an increased incidence of pathogen A could be accompanied by a reduced incidence of pathogen B, and, in this way, the total burden of disease might remain unchanged. An unambiguous method to report temporal trends in incidences of NB of both antibiotic-susceptible and antibiotic-resistant pathogens would allow quantification of the total antibiotic resistance problem and comparison of trends between hospitals and countries.

We determined the temporal trends of NB in our hospital using the various described incidence definitions in order to quantify the temporal changes of episodes caused by antibiotic-susceptible and antibiotic-resistant pathogens and to determine which definition should be propagated in future surveillance studies.

Materials and methods

Design

This is a retrospective cohort study design with anonymized record linkage of databases from hospital information systems and the department of microbiology.

Setting

The study setting is the University Medical Centre Utrecht, a 997 bed tertiary care centre in the centre of the Netherlands, containing all medical specialties, including organ (except liver) and bone marrow transplantations, cardiothoracic surgery and neurosurgery.

Population

The cohort consists of all patients admitted between 1 January 1996 and 31 December 2005 at the University Medical Centre Utrecht, aged 18 years or more on the day of admission. Patients admitted to the day-care units and psychiatric units were excluded. We restricted our analyses to patients with a hospital stay of more than 48 h, as only these patients are at risk of acquiring NB. Only first episodes of NB per admission were included.

Data sources

The hospital’s microbiological database was linked to the patient-administrative system, thereby providing a database with all patient admissions, in the University Medical Centre Utrecht between 1 January 1996 and 31 December 2005. The database contained microbiological results of all blood cultures obtained, as well as data on gender, age, department of admission, length of stay (LOS) and mortality at hospital discharge for each admission. The different departments are aggregated into six divisions: internal medicine, cardiology, surgery, neurology, intensive care and one division of other departments (comprising the departments of gynaecology, otorhinolaryngology, oral and maxillofacial surgery, and ophthalmology; accounting for 27.6% of admissions, 16.5% of patient-days and 3.9% of episodes of NB).

Ethics

Since this was an observational retrospective study with anonymized patient data, ethics approval was not required.

Microbiological methods

Bacteraemia was detected in blood culture bottles from 1996 until 2001 using the BacT/Alert Microbial Detection System (Organon Teknika, Scarborough, Ontario, Canada) and from 2002 until 2005 using BACTEC 9240 (Becton Dickinson, Canada Inc., Mississauga, Ontario, Canada). Species determination and susceptibility testing were performed using standard microbiological procedures.

Definitions

Bacteraemia. Isolation of bacteria from at least one blood culture set. Organisms typically belonging to the flora of the skin [coagulase-negative staphylococci, Micrococcus species, Bacillus species, diphteroids (corynebacteria) or propionibacteria] are considered as contaminants and were excluded in this study.

NB. Bacteraemia occurring >48 h after hospital admission and without a documented bacteraemia with a similar pathogen in the first 48 h of admission.

Polymicrobial bacteraemia. Bacteraemia with more than one organism in a single set of blood cultures or in different sets within 48 h.

Highly resistant microorganisms (HRMO). Antibiotic-resistant pathogens; definitions of HRMO are based on Dutch guidelines (Table 1). Since amoxicillin is considered to be the first choice therapy for enterococcal infections, we added amoxicillin resistance (which also encodes resistance to piperacillin and carbapenems) to the list of HRMO.

Non-HRMO. Antibiotic-susceptible pathogens; all microorganisms cultured that do not fulfil the definition of HRMO (total number of NB – total number of HRMO).

Crude incidence. Number of events per year.

Cumulative incidence. Incidence risk, number of events per 10000 hospital admissions.

Incidence density. Incidence rate, number of events per 100000 patient-days at risk.

Statistical analysis

We used χ² tests for dichotomous variables (gender, mortality), logistic regression for the categorical variable department of admission and Mann–Whitney U-tests for continuous, non-normally distributed variables (age, total LOS) to analyse relations between patients with and without NB. Risk ratios (RRs) were calculated for proportions of NB caused by multiresistant bacteria during the first and second 5 year period. Secular trends in cumulative incidence and incidence density of NB (with and without stratification by causal pathogen) were plotted in steps of 1 year. To determine temporal trends in incidences, we used univariate and multivariate Poisson regression, a method to model rates, and thereby related these variables to year of admission. We used the Akaike information criterion to find the model that best explains the data with a minimum of free parameters. To examine changes in continuous variables over time, we used linear regression to relate the variables age and LOS to year of admission in a univariate manner. The results are shown with RRs [RR_C (cumulative incidence), RR_C (crude incidence)] or rate ratios [RR_ID (incidence density)] and the corresponding 95% confidence intervals (95% CIs) for each included variable. To quantify the contribution of emergence of antibiotic resistance to trends in NB incidences, we calculated a ratio by dividing RR_ID of HRMO by RR_ID of non-HRMO. The data
were analysed using SPSS version 12.0 (SPSS, Chicago, IL, USA) and R version 2.4.0.

**Results**

**Study population and patient characteristics**

The study cohort contained 163525 patients and 1826852 patient-days. Annual numbers of admissions gradually decreased from 18478 in 1996 to 15153 in 2005 [average decrease of 2.4% per year, RR 0.98 (0.97–0.98), P<0.001], as did the number of patient-days per year [from 220288 in 1996 to 151613 in 2005; average decrease of 4.2% per year, RR 0.96 (0.96–0.96), P<0.001]. The median LOS decreased from 7 days [interquartile range (IQR) 4–14] in 1996 to 6 days (IQR 4–11) in 2005 (P=0.006). This trend was observed for patients on all wards, except for those admitted to intensive care and surgery whose LOS remained similar. The median age increased from 53 years (IQR 37–67) in 1996 to 56 years (IQR 39–68) in 2005 (P<0.001), and this was most prominent for patients admitted to surgery, neurology and internal medicine (data not shown).

       The crude mortality during admission did not change in the 10 year period [RR 1.01 (0.98–1.05), P=0.19]. On average, 495 [standard deviation (SD) 38] patients died during admission per year. The cumulative mortality incidence, though, increased from 249 in 1996 to 283 in 2005 per 10000 admissions [on average, 1.8% per year, RR 1.02 (1.01–1.03), P=0.001], as did the incidence density from 209 in 1996 to 283 in 2005 per 100000 patient-days [on average, 3.6% per year, RR 1.04 (1.03–1.05), P<0.001] (data not shown).

**Cumulative incidence and incidence density of NB**

There were 1785 cases of NB (first episodes) [Figure S1, available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/)]. Of these, 538 (30.1%) were caused by Enterobacteriaceae, 381 (21.3%) by *Staphylococcus aureus*, 183 (10.3%) by *Enterococcus* species, 164 (9.2%) by *Streptococcus* species, 32 (1.8%) by other Gram-positive species, 85 (4.8%) by *Pseudomonas aeruginosa*, 26 (1.5%) by *Acinetobacter* species, 52 (2.9%) by other Gram-negative species, 73 by fungi (4.1%), 52 (2.9%) by anaerobes and 199 (11.1%) episodes were polymicrobial. Patients developing NB were older [60 years (IQR 47–71) versus 54 years (IQR 38–68)] (P<0.001), more frequently male (60.2% versus 48.3%) (P<0.001) and more often admitted to intensive care (20.3% versus 2.4%) (P<0.001) or internal medicine (33.7% versus 19.1%) (P<0.001) when compared with patients not developing NB. Moreover, patients with NB had a longer LOS [35 days (IQR 20–62) versus 7 days (IQR 4–12)] (P<0.001) and a higher mortality (26.6% versus 2.8%) (P<0.001).

       The crude incidence of NB did not change from 1996 to 2005 [mean of 179 (SD 13) NB per year], whereas cumulative incidence and incidence density increased on average by 2.0% and 4.0% per year from 90 to 118 per 10000 admissions and from 77 to 103 per 10000 patient-days, respectively (Table 2). After adjustment for changes in the distribution of patients with regard to age, gender and admission departments during the study period, the crude incidence remained unchanged, but the cumulative incidence and incidence density increased by, on average, 7.6% and 9.1% per year (Table 2), demonstrating that the changed incidences over time did not result from these changes in patient characteristics. The higher incidences of NB resulted, to a large extent, from increased infection rates with *Enterococcus* spp. and *P. aeruginosa* (Table 3). Exclusion of both pathogens would reduce the 2.0% and 4.0% annual increases in cumulative incidence and incidence density towards an increase of 0.3% in cumulative incidence [RR<sub>CI</sub> 1.003 (0.99–1.02)] and an increase of 2.3% in incidence density [RR<sub>ID</sub> 1.02 (1.005–1.04)]. The change of the blood culture detection system in 2002 was not discernable in the trend lines of NB.

**Antimicrobial resistance**

The proportion of HRMO of all pathogens causing NB increased from 3.0% (28/947) in the first 5 years to 8.0% (67/838) in the
second 5 years [RR = 1.02 (1.00–1.03), P = 0.03]. Largest increases were observed for amoxicillin-resistant Enterococcus faecium (ARE) [from 12.0% (9/75) in the first 5 years to 31.5% (34/108) in the second half of the study] [RR = 1.28 (1.10–1.50), P = 0.002] and for multiresistant Enterobacteriaceae [from 0.7% (2/302) to 4.7% (11/236)] [RR = 1.04 (1.01–1.07), P = 0.003] (Table 4).

Over time, crude incidence, cumulative incidence and incidence density of HRMO increased, on average, by 20.5% [RR = 1.21 (1.11–1.31)], 23.4% [RR = 1.23 (1.14–1.34)] and 26.1% [RR = 1.26 (1.17–1.37)] per year, respectively. For a detailed analysis of the temporal trends of individual bacteria, we only present the incidence density data (Table 5). Similar findings were obtained when using cumulative incidences (data not shown). When distinguishing trends for HRMO and non-HRMO, the annual increases were 26.1% and 3.0%, respectively, which implies that the incidence of HRMO increases 8.7 times as rapidly as that of non-HRMO. For Enterococcus spp. and P. aeruginosa, the total burden of NB increased by 14.2% and 15.0%, respectively. For both species, the relative increase was larger for HRMO strains (33.2% and 35.4% for Enterococcus spp. and P. aeruginosa, respectively) than for non-HRMO ones (9.4% and 13.5%, respectively). The ratios of incidences of HRMO versus non-HRMO were 3.5 for Enterococcus spp. and 2.6 for P. aeruginosa, indicating that the increase in the burden of NB due to these species resulted from a larger increase in HRMO than non-HRMO. For Enterobacteriaceae, though, there was no increase in the overall burden of NB. Yet, there was a 37.9% increase in the incidence density of HRMO strains, reflecting a HRMO/non-HRMO ratio of >37.9. For S. aureus, trends did not change significantly for both HRMO and non-HRMO.

Discussion

We have quantified changes in incidences of NB over time and found that: (i) because of changes in the patient population, increases over time are only evident when expressed as cumulative incidences or incidence densities; (ii) these incidences increased per year and this increase could not be explained by observed changes in patient population characteristics; (iii) the incidence ofNB due to HRMO increased 8.7 times as fast as that of non-HRMO; and (iv) this increase was caused by
multiresistant *Enterococcus* spp. (HRMO/non-HRMO ratio of 3.5), *P. aeruginosa* (HRMO/non-HRMO ratio of 2.6) and Enterobacteriaceae (HRMO/non-HRMO ratio $>37.9$). Despite overall low levels of antibiotic resistance in our hospital, these longitudinal trends demonstrate that the increase in NB caused by multiresistant pathogens rapidly increases. Moreover, the increase in resistance does not replace infections with susceptible pathogens, but adds to the total burden of NB. No increase in multiresistant pathogens is shown when analysing the community-acquired bacteraemias due to *Enterococcus* spp., *P. aeruginosa* and Enterobacteriaceae (data not shown), which confirms that the increased incidences of HRMO-related NBs are truly hospital-associated. Furthermore, the observed trends also remain when including successive episodes of NB of individual patients during admission, instead of including only the first episode of NB (data not shown).

Table 4. Prevalence of HRMO causing NB

<table>
<thead>
<tr>
<th>Pathogen/period</th>
<th>OXA</th>
<th>GLY</th>
<th>PEN</th>
<th>ESBL&lt;sup&gt;a&lt;/sup&gt;</th>
<th>SXT&lt;sup&gt;b&lt;/sup&gt;</th>
<th>AMG</th>
<th>QUI</th>
<th>CPM</th>
<th>PIP</th>
<th>CAZ</th>
<th>HRMO</th>
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<tbody>
<tr>
<td><strong>Summary of all pathogens</strong></td>
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<td>1996–2000</td>
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<td>28/947</td>
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<td>2001–05</td>
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<td></td>
<td></td>
<td></td>
<td>67/838&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td><em>S. aureus</em></td>
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<td>2001–05</td>
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<td>1/179</td>
<td>0/179</td>
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<td>1/179</td>
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<tr>
<td><em>Enterococcus</em> spp.</td>
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<td></td>
<td>0/75</td>
<td>9/75</td>
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<td></td>
<td>9/75</td>
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<tr>
<td>1996–2000</td>
<td></td>
<td></td>
<td></td>
<td>0/108</td>
<td>34/108</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>34/108&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td></td>
<td></td>
<td></td>
<td>4/207</td>
<td>7/95</td>
<td>16/302</td>
<td>14/302</td>
<td>0/297</td>
<td>5/302</td>
<td></td>
<td></td>
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<tr>
<td><em>P. aeruginosa</em></td>
<td></td>
<td></td>
<td></td>
<td>3/51</td>
<td>4/51</td>
<td>6/51</td>
<td>7/51</td>
<td>7/51</td>
<td>5/51</td>
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</table>

OXA, (flucl)oxacillin; GLY, glycopeptides (vancomycin, teicoplanin); PEN, penicillins (benzylpenicillin, ampicillin); ESBL, extended-spectrum β-lactamases; SXT, trimethoprim/sulfamethoxazole; AMG, aminoglycosides (tobramycin, amikacin, gentamycin); QUI, quinolones (ciprofloxacin, levofloxacin, moxifloxacin); CPM, carbapenems (meropenem, imipenem); PIP, piperacillin; CAZ, ceftazidime.

<sup>a</sup>ESBL: only including *E. coli* and *Klebsiella* spp., based on resistance to cefuroxime, ceftazidime and ceftriaxone, only in the second half of the study confirmed by an Etest.

<sup>b</sup>Not applicable for *E. coli* and *Klebsiella* spp.

<sup>c</sup>$P=0.03$, RR = 1.02 (1.00–1.03) (including ARE).

<sup>d</sup>$P=0.002$, RR = 1.28 (1.10–1.50).

<sup>e</sup>$P=0.004$, RR = 1.06 (1.02–1.10).

Table 5. Annual changes in incidence densities of total NB, HRMO and non-HRMO during the study period, 1996–2005

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>RR&lt;sub&gt;ID&lt;/sub&gt; HRMO (95% CI)</th>
<th>RR&lt;sub&gt;ID&lt;/sub&gt; non-HRMO (95% CI)</th>
<th>RR&lt;sub&gt;ID&lt;/sub&gt; total NB (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Summary of all pathogens</strong></td>
<td>1.26 (1.17–1.37)</td>
<td>1.03 (1.01–1.05)</td>
<td>1.04 (1.02–1.06)</td>
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<tr>
<td><em>S. aureus</em>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.12 (0.67–1.94)</td>
<td>1.03 (0.99–1.06)</td>
<td>1.03 (0.99–1.06)</td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.33 (1.19–1.51)</td>
<td>1.09 (1.03–1.16)</td>
<td>1.13 (1.08–1.19)</td>
</tr>
<tr>
<td>Enterobacteriaceae&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.38 (1.12–1.76)</td>
<td>1.02 (0.99–1.05)</td>
<td>1.03 (0.998–1.06)</td>
</tr>
<tr>
<td><em>P. aeruginosa</em>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.35 (1.03–1.90)</td>
<td>1.13 (1.05–1.23)</td>
<td>1.16 (1.08–1.26)</td>
</tr>
</tbody>
</table>

RR<sub>ID</sub>, trend in incidence densities from 1996 to 2005; NB, nosocomial bacteraemia; HRMO, highly resistant microorganisms (including ARE); non-HRMO, non-highly resistant microorganisms, 95% CI, 95% confidence interval.

<sup>a</sup>RR non-HRMO<sub>ID</sub>/HRMO: the trend for HRMO is larger than the trend for non-HRMO, indicating that the increase in burden of HRMO is larger than that of non-HRMO.

<sup>b</sup>RR non-HRMO<sub>ID</sub>/HRMO: both the trend for HRMO and non-HRMO did not change significantly during the study period.
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increased the annual incidence densities and by our finding that the likelihood of mortality per hospital day increased by 3.6% per year. This is in agreement with other publications.\textsuperscript{5,22–25} Although longitudinal changes in incidences and proportions of pathogens causing nosocomial infections have been reported before, results have varied from unchanged distributions of microorganisms to significant shifts in pathogens with varying proportions of Gram-positive and Gram-negative bacteria.\textsuperscript{2–19} Multiple study designs and outcome measures have been reported, and a critical assessment of the quantified trends in NB (and their interpretation) has never been performed. Most surveillance studies used cumulative incidences to compare risks over time and between hospitals.\textsuperscript{4–16} Few studies used number of bacteraemias per number of patient-days as a proxy for the incidence density.\textsuperscript{17–19} This measure does not fully describe the actual incidence density, as it does not provide information on the number and proportion of patients actually at risk of acquiring NB. In only one study was the analysis restricted to those patients truly at risk of NB, i.e. those who stayed in the hospital for at least 2 days.\textsuperscript{16} Both the cumulative incidence and incidence density are sensitive to changes in number of hospital admissions and number of patient-days over time. Incidence density most accurately reflects the risk per day in hospital. Previously, incidence densities have been propagated for quantifying antibiotic use.\textsuperscript{26} In this study, we used the actual incidence density, determined by number of NB per number of patient-days at risk (before acquiring NB) in patients who were admitted for at least 2 days.

The quantified trends in NB provide a convenient tool for comparison between different settings, regions and countries. In our hospital, patients have become increasingly at risk of developing NB, while being admitted for shorter periods of time. In most studies, a reported higher burden of disease due to HRMO reflects the epidemiology of a single pathogen, which precludes interpretation of changes in the total burden of disease. For instance, Wyllie et al.\textsuperscript{16} convincingly demonstrated that the longitudinal increase in NB due to methicillin-resistant \textit{S. aureus} (MRSA) occurred in addition to a rather stable incidence of methicillin-susceptible \textit{S. aureus}. However, patients at risk of nosocomial infections with MRSA are also at risk of nosocomial infections with other, frequently multiresistant, nosocomial pathogens. An increased incidence of NB with MRSA could result in a reduced incidence of other nosocomial pathogens. To the best of our knowledge, integrated trend analysis of all relevant nosocomial pathogens has not been performed previously.

In our population, the all-cause incidence density of NB increased, on average, by 4.0% per year. However, the annual increases of NB due to HRMO and non-HRMO were 26.1% and 3.0%, respectively. We, therefore, conclude that the increase in the total burden of NB results from a small increase in non-HRMO and a relatively large increase in HRMO. For three pathogens (\textit{Enterococcus} spp., \textit{P. aeruginosa} and Enterobacteriaceae), large increases were observed, which were, in all cases, additive to NB caused by non-HRMO and not associated with any reductions in incidences of other pathogens. Hence, we conclude that, in our setting, antibiotic resistance does not replace episodes of NB caused by other or less resistant pathogens. This is important when quantifying the impact of antibiotic resistance on patient care.

Our study has several limitations. As this is a single tertiary care centre study in the Netherlands, our findings may not be generalizable to other non-tertiary care centres in the Netherlands or to centres in other countries, where the baseline incidences of antibiotic-resistant organisms may be different from those in the Netherlands. Misclassification might have occurred for patients who had been discharged recently and were readmitted with bacteraemia, though this would only represent a limited number. Episodes of NB caused by skin contaminants were excluded (1635 patients with at least one positive blood culture). Although some of these might have been true episodes of NB, these could not be identified as information on clinical signs and symptoms was not available.\textsuperscript{27} Finally, we could not determine whether changes in co-morbidity or the severity of illness of our population explains the increasing incidences of NB, as these data were not available.

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Transparency declarations

H. S. M. A., A. T. and C. L. J. J. K. have no potential conflict of interest. J. A. J. W. K. has received consulting fees from 3M, NovaBay and Wyeth, has received honoraria from 3M and Becton Dickenson for lectures, is a member of the speakers’ bureau for bioMérieux and is a member of the advisory board of Destiny Pharma. M. J. M. B. has received research funding from Novartis and 3M, is a member of the speakers’ bureau for Pfizer and is a member of the advisory boards of 3M and Novartis.

H. S. M. A. designed the study and obtained, analysed and linked the data and wrote the paper. M. J. M. B. contributed to the design of the study. All authors contributed to the analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

Supplementary data

Figure S1 is available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

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