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Antibiotic Resistance and the Risk of Recurrent Bacteremia

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Background. Direct health effects of antibiotic resistance are difficult to assess. We quantified the risk of recurrent bacteremia associated with resistance.

Methods. We extracted antimicrobial susceptibility testing data on blood isolates from the Dutch surveillance system for antimicrobial resistance between 2008 and 2017. First and first recurrent (4–30 days) bacteremia episodes were categorized as susceptible, single nonsusceptible, or co-nonsusceptible to third-generation cephalosporins without or with carbapenems (Enterobacteriaceae), ceftazidime without or with carbapenems (*Pseudomonas* species), aminopenicillins without or with vancomycin (*Enterococcus* species), or as methicillin-sensitive/-resistant S. aureus (MSSA/MRSA). We calculated risks of recurrent bacteremia after nonsusceptible vs susceptible first bacteremia, estimated the crude population attributable effect of resistance for the Netherlands, and calculated risks of nonsusceptible recurrent bacteremia after a susceptible first episode.

Results. Risk ratios for recurrent bacteremia after a single- and co-nonsusceptible first episode, respectively, vs susceptible first episode, were 1.7 (95% confidence interval [CI], 1.5–2.0) and 5.2 (95% CI, 2.1–12.4) for Enterobacteriaceae, 1.3 (95% CI, 0.5–3.1) and 5.0 (95% CI, 2.9–8.5) for *Pseudomonas* species, 1.4 (95% CI, 1.2–1.7) and 1.6 (95% CI, 0.6–4.2) for *Enterococcus* species, and 1.6 (95% CI, 1.1–2.4) for MRSA vs MSSA. The estimated population annual number of recurrent bacteremias associated with nonsusceptibility was 40. The risk of nonsusceptible recurrent bacteremia after a susceptible first episode was at most 0.4% (*Pseudomonas* species).

Conclusions. Although antibiotic nonsusceptibility was consistently associated with higher risks of recurrent bacteremia, the estimated annual number of additional recurrent episodes in the Netherlands (40) was rather limited.

Keywords. antibiotic resistance; recurrent bacteremia; population attributable effect; acquired antibiotic resistance.

Antibiotic resistance is considered a major threat for human health. Although infections caused by antibiotic-resistant bacteria have frequently been associated with increased morbidity, higher mortality, and enhanced healthcare costs, the direct and attributable effects of antibiotic resistance have been less accurately quantified. Detrimental health effects of antibiotic resistance may result from inappropriate empiric therapy, from reduced effectiveness of definite therapy with last-resort antibiotics, or a higher frequency of adverse events created by such antibiotics. Several studies have quantified the effects of antibiotic resistance, usually in patients with bacteremia, and mostly on survival (either 30 days after bacteremia or during hospitalization) and length of hospital stay [1–3]. Yet, associations between antibiotic resistance and patient outcome can be confounded

and can be affected by competing events [4, 5]. Adjustment for patient-related and disease-associated factors typically reduces the observed crude associations between antibiotic resistance and patient outcome. As a result, the consequences of antibiotic resistance for patient health are not accurately quantified.

An important sequela of antibiotic resistance could be the occurrence of recurrent infection, either because of delays in providing appropriate antibiotic therapy or because of suboptimal definite antibiotic therapy. Furthermore, the risk of resistance development during antibiotic therapy and the subsequent risk of developing recurrent infections have never been quantified. In the current study, we quantified the association between antibiotic susceptibility and the occurrence of recurrent bacteremia, and to what extent antibiotic susceptibility had changed between first and recurrent infections.

METHODS

Setting

Since 1 January 2008, results of antimicrobial susceptibility testing, including underlying minimum inhibitory concentration (MIC) values and inhibition zone diameters, of isolates routinely tested in Dutch medical microbiology laboratories are collected in the Infectious Diseases Surveillance Information System–Antimicrobial Resistance (ISIS-AR) [6]. This surveillance system is a combined initiative of the Dutch Ministry

of Health, Welfare and Sport and the Netherlands Society for Medical Microbiology, and is coordinated by the Centre for Infectious Disease Control at the National Institute for Public Health and the Environment. Data on blood cultures from 41 of 57 Dutch medical microbiology laboratories (72%) were available in ISIS-AR in May 2017 and were included in the current study. Four of these laboratories exclusively serve a university hospital, 1 exclusively serves general practices and long-term care facilities, and 36 serve both general hospitals and general practices. As both partners of ISIS-AR agreed that no identifiable personal data are collected, individual patient consent was not required for the current study.

Data Extraction and Preparation

On 17 May 2017, data on all blood isolates of Enterobacteriaceae, *Pseudomonas* species, *Enterococcus* species, and *Staphylococcus aureus* present in the database were extracted. After excluding polymicrobial episodes (defined as ≥2 isolates of different microorganisms in samples taken ≤1 day apart from the same patient, 12.6% of all isolates), first and recurrent episodes of bacteremia were identified. A first episode of bacteremia was defined as the first isolate from a blood culture per patient or an isolate not preceded by an isolate of the same species from the same patient in the previous 30 days. A recurrent episode was defined as an isolate of the same bacteria (at species level) from a blood culture taken between 4 and 30 days after the first episode. In patients with multiple recurrent episodes, only the first recurrent isolate was included. Isolates were categorized as either susceptible, single nonsusceptible, or co-nonsusceptible bacteremias based on their antibiotic susceptibility test results for the most frequently used antibiotics for the specific species. Categorization for susceptibility was based on reinterpretation of MIC values according to clinical breakpoints set by the European Committee on Antimicrobial Susceptibility Testing (version 7.0; 2017, EUCAST), using results from gradient tests above automated MIC determinations. Zone diameter values were excluded, as methods for disk diffusion are not harmonized across laboratories and exact inhibition zone diameters are often not reported to ISIS-AR. Enterobacteriaceae were categorized as single nonsusceptible if they were intermediate (I) or resistant (R) to third-generation cephalosporins (ceftriaxone/cefotaxime or ceftazidime), and as co-nonsusceptible when I/R to carbapenems (imipenem or meropenem) as well. *Pseudomonas* species were categorized as single nonsusceptible if I/R to ceftazidime, and as co-nonsusceptible when I/R to carbapenems (imipenem or meropenem) additionally. *Enterococcus* species were categorized as single nonsusceptible (ampicillin-resistant Entercocci [ARE]) when I/R to aminopenicillins (amoxicillin or ampicillin). When ARE were I/R to vancomycin as well, they were categorized as co-nonsusceptible. *Staphylococcus aureus* was categorized as methicillin-resistant *S. aureus* (MRSA) or methicillin-sensitive *S. aureus* (MSSA), based on (in hierarchical order) results from *mec*A or pbp2 confirmation tests, cefoxitin susceptibility (I/R), or flucloxacillin or oxacillin susceptibility (I/R to at least one), as reported by the laboratory.

Statistical Analysis

We calculated absolute and relative risks (including 95% confidence intervals [CIs]) of recurrent bacteremia in patients with single nonsusceptible and co-nonsusceptible vs susceptible first bacteremias for each of the 4 causative pathogen groups, using Poisson regression models in SAS software (version 9.4; SAS Institute, Cary, North Carolina). Furthermore, we estimated the crude attributable effect of antibiotic resistance per pathogen group, defined as the difference in absolute risk of recurrent episodes after a first episode caused by nonsusceptible strains (single and co-nonsusceptible episodes combined) minus the absolute risk after a first episode caused by susceptible strains, multiplied by the number of first episodes caused by nonsusceptible strains ($[AR_{I/R} - AR_S] \times$ number of first episodes$_{I/R}$). We extrapolated these results to estimate the total number of recurrent episodes attributable to antibiotic resistance in the Netherlands. For that, we assumed inclusion of 60% of all blood culture results in ISIS-AR during the study period of 9.4 years (based on the average estimated hospital coverage in the Netherlands throughout the study period). Last, we calculated absolute risks of a recurrent bacteremia caused by a nonsusceptible pathogen after a first episode caused by a susceptible strain. To evaluate the impact of the arbitrarily chosen follow-up time of 30 days for recurrent bacteremia, we performed 2 sensitivity analyses using a maximum of 15 and 60 days of follow-up.

RESULTS

On 17 May 2017, the ISIS-AR database contained 170 677 isolates of Enterobacteriaceae, *Pseudomonas* species, *Enterococcus* species, and *S. aureus* from monomicrobial blood cultures. A total number of 116 720 (68.4%) fulfilled the criteria of first episode or first recurrent episode of bacteremia and were included in this study. Of a total of 75 963 Enterobacteriaceae, results for ceftriaxone/cefotaxime/ceftazidime and imipenem/ meropenem could not be interpreted according to EUCAST clinical breakpoints in 4450 (5.9%) and 4585 (6.0%) isolates, respectively, and original susceptibility as reported by the local laboratory was used instead. This also applied to 536 (11.7%) and 498 (10.3%) among 4844 *Pseudomonas* species isolates for ceftazidime and imipenem/meropenem, respectively, and to 3307 (28.0%) and 2416 (20.4%) among 11 824 *Enterococcus* species isolates for amoxicillin/ampicillin and vancomycin, respectively.

Enterobacteriaceae

A number of 75 963 Enterobacteriaceae bacteremia episodes were included, of which 73 912 were classified as first episodes (97.3%) and 2051 (2.7%) as first recurrent episodes (Figure 1A). Overall, 5873 (7.7%) bacteremia episodes were caused by nonsusceptible Enterobacteriaceae.

Co-nonsusceptibility to carbapenem antibiotics among nonsusceptible Enterobacteriaceae was observed in 37 of 5573 (0.7%) first episode isolates and in 8 of 300 (2.7%) isolates from recurrent episodes.

The absolute risk of recurrent bacteremia was 2.6% (1769/67 608 episodes), 4.5% (251/5536 episodes), and 13.5% (5/37 episodes) for subjects with a first episode caused by either susceptible, single nonsusceptible, or co-nonsusceptible Enterobacteriaceae, respectively. Compared to susceptible first episodes, risk ratios for single and co-nonsusceptible first bacteremias were 1.7 (95% CI, 1.5–2.0) and 5.2 (95% CI, 2.1–12.4), respectively (Table 1). The absolute risk of a recurrent infection caused by nonsusceptible Enterobacteriaceae after a first episode caused by a susceptible isolate was 0.1% (74/67 608 episodes; Figure 1A). The likelihood that recurrent bacteremia was caused by a nonsusceptible isolate was 87.9% (225/256 episodes) when the first episode was caused by a nonsusceptible isolate.
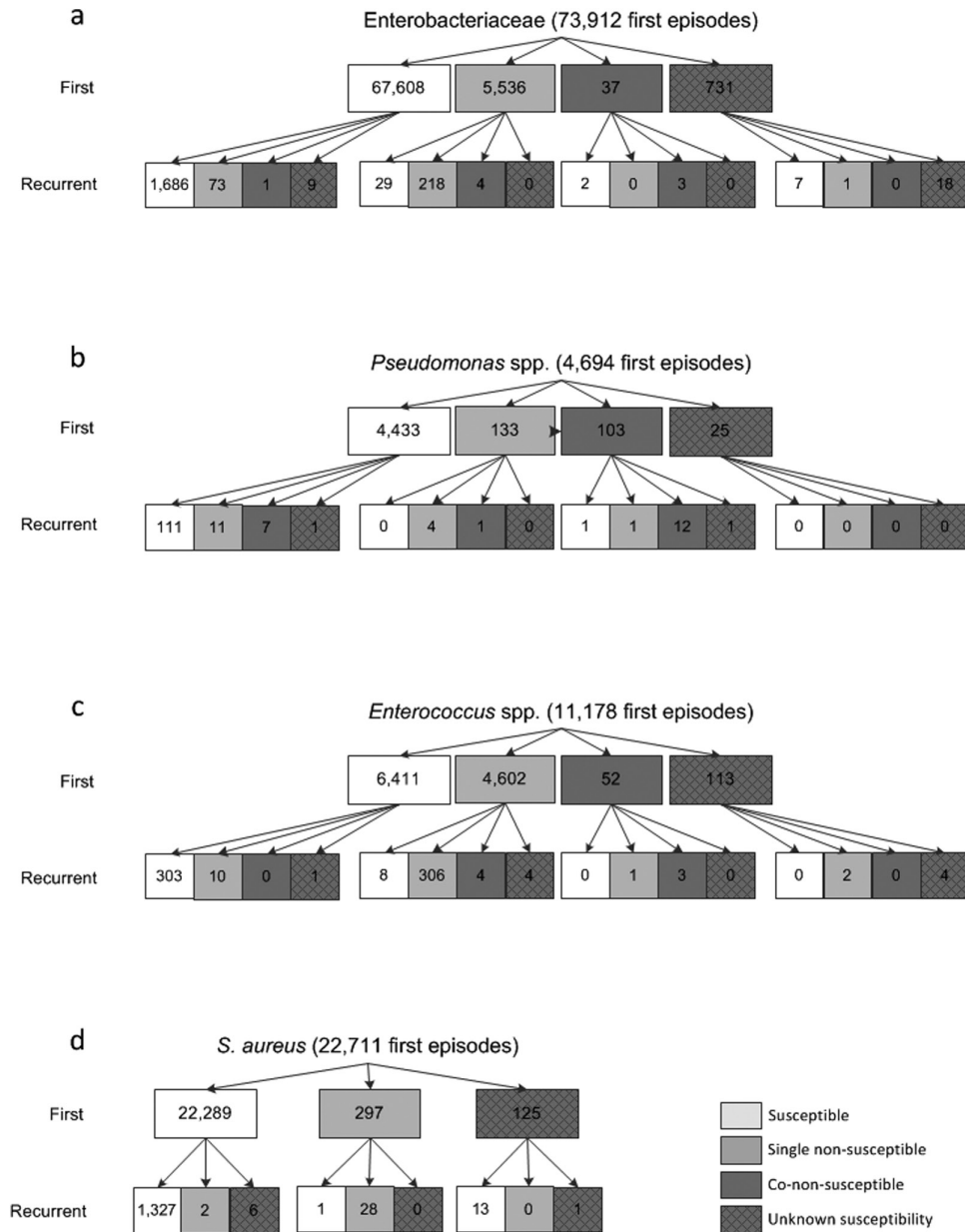
Figure 1. Absolute number of first and recurrent bacteremia episodes between 1 January 2008 and 17 May 2017, by pathogen group and susceptibility category. *A*, Susceptible: susceptible to third-generation cephalosporins and carbapenems. Single nonsusceptible: (intermediate) resistant to third-generation cephalosporins, susceptible to carbapenems. Co-nonsusceptible: (intermediate) resistant to third-generation cephalosporins and carbapenems. *B*, Susceptible: susceptible to ceftazidime and carbapenems. Single nonsusceptible: (intermediate) resistant to ceftazidime, susceptible to carbapenems. Co-nonsusceptible: (intermediate) resistant to ceftazidime and carbapenems. *C*, Susceptible: susceptible to aminopenicillins and vancomycin. Single nonsusceptible: (intermediate) resistant to aminopenicillins, susceptible to vancomycin. Co-nonsusceptible: (intermediate) resistant to aminopenicillins and vancomycin. *D*, Susceptible: methicillin-sensitive *Staphylococcus aureus*. Single nonsusceptible: methicillin-resistant *Staphylococcus aureus*.

Table 1. Susceptibility Distribution of First Bacteremias and Absolute and Relative Risk of Recurrent Bacteremia Following Single or Co-nonsusceptible First Bacteremia, Compared With Susceptible First Bacteremia

| Pathogen (Group) | First Episodes, No. (%) | | | Risk of Recurrent Episode by Susceptibility Status of First Episode (95% CI) | | | |
	Susceptible	Single Nonsusceptible	Co-nonsusceptible	Risk	Susceptible	Single Nonsusceptible	Co-nonsusceptible
Enterobacteriaceae	67 608 (91.5)	5536 (7.5)	37 (0.1)	Absolute, %	2.6 (2.5–2.7)	4.5 (4.0–5.1)	13.5 (5.6–32.5)
				Relative		1.7 (1.5–2.0)	5.2 (2.1–12.4)
Pseudomonas species	4433 (94.4)	133 (2.8)	103 (2.2)	Absolute, %	2.9 (2.5–3.5)	3.8 (1.6–9.0)	14.6 (8.8–24.2)
				Relative		1.3 (.5–3.1)	5.0 (2.9–8.5)
Enterococcus species	6411 (57.4)	4602 (41.2)	52 (0.5)	Absolute, %	4.9 (4.4–5.5)	7.0 (6.3–7.8)	7.7 (2.9–20.5)
				Relative		1.4 (1.2–1.7)	1.6 (.6–4.2)
Staphylococcus aureus	22 289 (98.1)	297 (1.3)		Absolute, %	6.0 (5.7–6.3)	9.8 (6.8–14.1)	
				Relative		1.6 (1.1–2.4)	

Abbreviation: CI, confidence interval.

Pseudomonas Species

A number of 4844 *Pseudomonas* species bacteremia episodes were identified; 4694 (96.9%) were classified as first episodes and 150 (3.1%) as first recurrent episodes (Figure 1B). Of all *Pseudomonas* species bacteremia episodes, 272 (5.7%) were caused by nonsusceptible *Pseudomonas* species. Among first episode isolates, 103 of 236 (43.6%) nonsusceptible *Pseudomonas* species were co-nonsusceptible to carbapenem antibiotics, as were 20 of 36 (55.6%) in recurrent episodes.

The absolute risk of recurrent bacteremia was 2.9% (130/4433 episodes), 3.8% (5/133 episodes), and 14.6% (15/103 episodes) for subjects with a first episode caused by susceptible, single nonsusceptible, or co-nonsusceptible *Pseudomonas* species, respectively. Risk ratios for single and co-nonsusceptible first bacteremias were 1.3 (95% CI, .5–3.1) and 5.0 (95% CI, 2.9–8.5), respectively, compared to susceptible first episodes (Table 1). The absolute risk of a recurrent infection caused by a nonsusceptible *Pseudomonas* species after a first episode caused by a susceptible strain was 0.4% (18/4433 episodes; Figure 1B). The likelihood that recurrent bacteremia was caused by a nonsusceptible strain was 90.0% (18/20 episodes) when the first episode was caused by a susceptible strain.

Enterococcus Species

In total, 11 824 *Enterococcus* species bacteremia episodes were included, of which 11 178 (94.5%) were classified as first episodes and 646 (5.5%) as first recurrent episodes (Figure 1C). Of all *Enterococcus* species bacteremia episodes, 4980 (42.1%) were caused by nonsusceptible *Enterococcus* species (ARE). Among first episode isolates 52 of 4654 (1.1%) ARE were co-nonsusceptible to vancomycin, as were 7 of 326 (2.1%) in recurrent episodes.

The absolute risk of recurrent bacteremia was 4.9% (314/6411 episodes), 7.0% (322/4602 episodes), and 7.7% (4/52 episodes) for subjects with a first episode caused by susceptible, single nonsusceptible, or co-nonsusceptible *Enterococcus* species, respectively. Compared to susceptible first episodes, risk ratios for single and co-nonsusceptible first bacteremias were 1.4 (95% CI, 1.2–1.7) and 2.6 (95% CI, .6–4.2), respectively (Table 1).

The absolute risk of a recurrent infection caused by a nonsusceptible strain after a first episode caused by a susceptible strain was 0.2% (10/6411 episodes; Figure 1C). The likelihood that recurrent bacteremia was caused by a nonsusceptible strain was 96.3% (314/326 episodes) when the first episode was caused by a nonsusceptible strain.

Staphylococcus aureus

A total of 24 089 *S. aureus* bacteremia episodes were included, of which 22 711 (94.3%) were classified as first episodes and 1378 (5.7%) as first recurrent episodes (Figure 1D). Overall, 327 (1.4%) bacteremia episodes were caused by MRSA.

The absolute risk of recurrent bacteremia was 6.0% (1335/22 289 episodes) and 9.8% (29/297 episodes) for subjects with a first episode caused by MSSA or MRSA, respectively, yielding a risk ratio of 1.6 (95% CI, 1.1–2.4; Table 1). The absolute risk of a recurrent infection caused by MRSA after a first episode caused by MSSA was 0.01% (2/22 289 episodes; Figure 1D). The likelihood that recurrent bacteremia was caused by MRSA was 96.6% (28/29 episodes) when the first episode was caused by MRSA.

Relative risks of recurrent bacteremia in each pathogen group were similar in sensitivity analyses using a maximum of 15 and 60 days of follow-up (Supplementary Table 1).

Population Attributable Effects

The absolute risk difference in the occurrence of recurrent bacteremia between first bacteremia episodes with susceptible and total nonsusceptible Enterobacteriaceae was 2.0% (Table 2). As the total number of nonsusceptible first episodes was 5536, this implies that the number of recurrent episodes attributable to nonsusceptibility was 110. Extrapolated to the total population, the estimated number of recurrent Enterobacteriaceae bacteremia episodes attributable to nonsusceptibility in the Netherlands was 183 between 1 January 2008 and 17 May 2017, or 19 per year. For *Pseudomonas* species, *Enterococcus* species, and *S. aureus*, the absolute risk difference was 5.5%, 2.1%, and 3.8%, respectively, yielding 22 (2 per year), 163 (17 per year), and 18 (2 per year) episodes attributable to antibiotic

Table 2. Population Attributable Effect of Nonsusceptibility of First Bacteremia Episode on Recurrent Bacteremia

Pathogen (Group)	Risk Difference for Recurrent Bacteremia Between Susceptible and Intermediate/Resistant First Episodes[a]	Additional No. of Recurrent Episodes Associated With Nonsusceptibility in Study Population[b]	Population Attributable Effect (per Year)[c]
Enterobacteriaceae	2.0%	110	183 (19)
Pseudomonas species	5.5%	13	22 (2)
Enterococcus species	2.1%	98	163 (17)
Staphylococcus aureus	3.8%	11	18 (2)

Abbreviations: I/R, single or co-nonsusceptible; S, susceptible.

[a]Absolute risk$_{I/R}$ − absolute risk$_S$.

[b](Absolute risk$_{I/R}$ − absolute risk$_S$) × number of first episodes$_{I/R}$.

[c](Absolute risk$_{I/R}$ − absolute risk$_S$) × number of first episodes$_{I/R}$ / national coverage proportion of 0.60.

nonsusceptibility on the population level for the respective pathogens. For all species combined, the estimated number of recurrent bacteremia episodes attributable to nonsusceptibility in the period under study was 386 (40 per year).

DISCUSSION

In this study, the absolute risk of recurrent episodes of bacteremia was consistently higher among patients with bacteremia caused by nonsusceptible bacteria, compared with episodes caused by susceptible strains, with relative risks ranging from 1.4 for ARE to 5.2 for Enterobacteriaceae nonsusceptible to third-generation cephalosporins and carbapenems. The absolute risk of developing a recurrent episode of bacteremia ranged from 2.6% for susceptible Enterobacteriaceae, to 14.6% for *Pseudomonas* species nonsusceptible to ceftazidime and carbapenems. The estimated crude population attributable effect of nonsusceptibility among Enterobacteriaceae, *Pseudomonas* species, *Enterococcus* species, and *S. aureus* to first-line antibiotic treatment in the Netherlands was 40 recurrent episodes of bacteremia per year.

These findings add to those of a number of other recent studies quantifying the health effects of antibiotic resistance for individual patients. Several studies have demonstrated that bacteremia caused by third-generation cephalosporin-resistant Enterobacteriaceae is associated with a higher risk of hospital mortality or 30-day mortality and a longer hospital stay, compared with infections caused by susceptible bacteria [2, 3]. Likewise, bacteremia caused by MRSA has been associated with considerable higher risks of mortality compared with that caused by MSSA [7, 8]. Yet, more recent studies using methods to control for confounders and competing events reported lower attributable effects of methicillin resistance on patient outcome [2, 9–11]. The overarching conclusion of all these studies is that antibiotic resistance negatively affects patient outcome, but that application of more sophisticated techniques to adjust for confounding and competing events consistently leads to lower negative impacts than previously assumed. Increased

mortality and prolonged hospital stay attributed to antibiotic nonsusceptibility may be partially explained by higher risks of recurrent bacteremia. This outcome has not been studied extensively. A population-based study in Denmark found a 25% higher risk of recurrent bacteremia within 2–365 days in patients who had received inappropriate antibiotic therapy, compared with appropriate therapy [12]. However, differences in definitions and methodology hamper a direct comparison of the results of that study and the current study.

In our study, the estimated crude population attributable effect of nonsusceptibility to first-line antibiotic treatment among all species combined is 40 recurrent episodes of bacteremia per year, of which almost half are caused by the widely considered low-grade enterococcal pathogens. This finding emphasizes that antibiotic resistance currently has—at most—a very minor impact on the population health in the Netherlands. This most likely results from effective infection control in Dutch hospitals and the continuing efforts made to reduce unnecessary and inappropriate antibiotic use [13, 14]. Naturally, numbers of recurrent bacteremia in general, and bacteremia attributable to antibiotic nonsusceptibility in particular, will be higher in countries with less effective infection control and more liberal antibiotic use. Yet, our analysis quantifies the risk of recurrent infection in individual patients, and we consider this risk to be mostly independent from the level of antibiotic resistance in other patients.

In our study, the absolute risk of developing recurrent infections with an antibiotic nonsusceptible variant, after a first bacteremia episode caused by a susceptible strain, was low. The highest risk (0.4%) was observed for bacteremia caused by *Pseudomonas* species, in which resistance to ceftazidime in *Pseudomonas* species may develop during treatment due to selection of mutants with changed porins and/or expressing efflux pumps. The transition from susceptibility to resistance to third-generation cephalosporins in Enterobacteriaceae requires the acquisition of either a plasmid with an extended-spectrum β-lactamase (ESBL) gene or overexpression of ampC mutations, which may largely depend on the presence of such genes in other bacteria of the microbiome. Yet, with current estimates of the prevalence of intestinal carriage with ESBL-producing bacteria of 5%–10% among Dutch inhabitants [15, 16], the observed absolute risk of 0.1% suggests that such within-host horizontal gene transfer events do not occur with high frequency. This also holds for *S. aureus* where a phenotype switch (from MSSA to MRSA) would require acquisition of the *mec*A gene. In the setting of Dutch hospitals, with low prevalence of MRSA, such a change in susceptibility would be more indicative of an infection caused by a different bacterial species, rather than a relapse of the initial infection. This is different for enterococci, where the prevalence of carriage with ARE in hospitalized patients is high (up to 35% in high-risk wards such as hematology and the intensive care unit [17]). Antibiotic treatment for susceptible enterococci may select for acquisition through cross-transmission of

ARE carriage and subsequent infection, which occurred in 0.2% of all first bacteremia episodes in our study.

Strengths of our study include the large and complete data collection in ISIS-AR, allowing population-based estimates for rare but clinically relevant outcomes. Study limitations are those linked to population-based studies. First, as data were collected from different hospitals that all use their own patient identification system, recurrent bacteremias diagnosed in another hospital than the first episode may have been misclassified as first episodes. Second, misclassification may have occurred as a result of our choice for the definition of a recurrent episode (a positive culture within 4–30 days after the first positive culture). However, sensitivity analyses using 15 and 60 days as the maximum follow-up period did not change the results. Third, as we did not have information on the genome of the strains causing first and recurrent bacteremias, we could not differentiate whether recurrent episodes were due to relapse or reinfection. Therefore, our estimated proportions of recurrent bacteremias with a phenotype switch may also include episodes in which resistance was not acquired during treatment, but resulted from infection with a new genotype. Reinfection is also the most likely scenario in cases where the opposite occurred. For example, among first episodes caused by single-resistant Enterobacteriaceae, 29 of 251 (11.6%) of the recurrent episodes were caused by a susceptible strain. Last, absence of patient-related data precludes inferences on the causal nature of observations. Our findings confirm our hypothesis that antibiotic resistance is associated with a higher crude risk of recurrent bacteremia. Yet, in the absence of patient-related data (eg, comorbidities, source and severity of infection, treatment regimen) it is not possible to quantify the proportion of this increased risk that can be attributed to antibiotic resistance. On the one hand, patients with a primary episode caused by a nonsusceptible bacterium may have had more frequent and more prolonged hospital exposure and comorbidities, which could also increase risks of recurrent episodes. On the other hand, patients with nonsusceptible bacteremia might have had a higher risk of dying before developing a recurrent infection. More detailed studies are needed to quantify the attributable effects of antibiotic resistance on the occurrence of recurrent bacteremia.

The occurrence of recurrent bacteremia is a simple measure to quantify the consequences of antibiotic resistance. The next step should be to quantify the attribution of antibiotic resistance to the increased risk of recurrent bacteremia. Our study provides further evidence that Dutch patients are currently well protected against the detrimental consequences of antibiotic resistance, and exemplifies the power of large-scale data collection for quantifying the effects of antibiotic resistance.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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APPENDIX