Selective decontamination of the oropharynx and the digestive tract, and antimicrobial resistance: a 4 year ecological study in 38 intensive care units in the Netherlands

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Received 16 July 2013; returned 9 August 2013; revised 23 September 2013; accepted 26 September 2013

Objectives: Selective oropharyngeal decontamination (SOD) and selective decontamination of the digestive tract (SDD) are associated with improved outcomes among patients in intensive care units (ICUs), but uncertainty remains about their long-term effects on resistance levels. We determined trends in antibiotic resistance among Gram-negative bacteria in 38 Dutch ICUs using and not using SOD/SDD.

Methods: The Infectious Disease Surveillance Information System–Antibiotic Resistance (ISIS–AR) was used to identify all Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter spp. isolates from blood and respiratory tract specimens from ICUs between January 2008 and April 2012. Per patient, the last isolate per species per specimen per month was selected to determine cumulative resistance rates (per 100 beds/month) for colistin, tobramycin, ciprofloxacin, ceftazidime and cefotaxime/ceftriaxone in ICUs that continuously used or did not use SOD/SDD, and ICUs that introduced SOD/SDD. Time trends were analysed by multilevel Poisson regression.

Results: Seventeen ICUs continuously used SOD/SDD (859 months), 13 did not use SOD/SDD (663 months) and 8 introduced SOD/SDD (223 and 117 months before and after introduction). There were no discernible trends in antibiotic resistance among 637 blood isolates. For the 8353 respiratory isolates, resistance to cefotaxime/ceftriaxone increased in ICUs that did not use SOD/SDD (P = 0.001) and decreased in those that continuously used SOD/SDD (P = 0.04), as did resistance to ciprofloxacin (P < 0.001). The introduction of SOD/SDD was followed by statistically significant reductions in resistance rates for all antimicrobial agents.

Conclusions: Continuous use of SOD/SDD was associated with decreasing trends for resistance to cefotaxime/ceftriaxone and ciprofloxacin. The introduction of SOD/SDD was associated with reductions in resistance rates for all antimicrobial agents included.

Keywords: bacterial drug resistance, selective oropharyngeal decontamination, selective decontamination of the digestive tract, surveillance

Introduction

Nosocomial infections, in particular respiratory tract infections, are common in patients treated in intensive care units (ICUs) and are associated with considerable mortality and morbidity.1,2 Infections in ICU patients are most frequently caused by potentially pathogenic microorganisms carried in the throat and gut, present either on ICU admission or acquired during the ICU stay. Selective oropharyngeal decontamination (SOD) and selective decontamination of the digestive tract (SDD) are antibiotic...
pharynx prophylaxis strategies used to prevent infections by these microorganisms in ICU patients.

SOD and SDD both consist of the topical application of non-absorbable antimicrobial agents in the oropharynx. SDD also includes the administration of the same topical agents in the gastrointestinal tract, and systemic prophylaxis, usually consisting of a third-generation cephalosporin, during the first 3 or 4 days of ICU admission. SOD and SDD both result in a lower incidence of ventilator-associated pneumonia, and in ICUs with low levels of antibiotic resistance they also lead to better patient outcomes.

Nevertheless, the acceptance of SOD and SDD has remained low, partly because of uncertainties about the long-term effects of both regimens on antibiotic resistance. In theory, SOD and SDD may select for microorganisms that are intrinsically resistant or for acquired resistance to the antibiotics used. However, in most randomized studies, patients receiving SOD or SDD had lower carriage rates of antibiotic-resistant bacteria than those not receiving any of these interventions. In an ecological study, SOD and SDD were both associated with lower unit-wide prevalence of antimicrobial resistance among Gram-negative bacteria during the interventions, but there was an increased prevalence of resistance to ceftazidime among Gram-negative bacteria isolated from rectal swabs after discontinuation of SDD.

In the Netherlands, SOD and SDD are used in many but not all ICUs. Using data from the Dutch Infectious Disease Surveillance Information System–Antibiotic Resistance (ISIS–AR), with 32 participating laboratories serving 45 ICUs, we evaluated trends in antimicrobial resistance among Gram-negative bacteria in Dutch ICUs that did not use SOD or SDD and in ICUs that used or introduced SOD or SDD.

Methods

Setting and interventions

Antimicrobial susceptibility test results [i.e. susceptible (S), intermediate resistant (I) and resistant (R)], the underlying MICs obtained from Etests or automated susceptibility testing systems, and patient data (i.e. age, gender, specimen site, patient location) for all routinely cultured bacterial species are collected on a monthly basis in the Dutch ISIS–AR system. Data collection started in January 2008 and currently includes 32 laboratories serving 45 hospitals with at least one ICU, dispersed over the Netherlands. With ~65% of Dutch laboratories and hospitals participating, ISIS–AR is considered representative of clinical antimicrobial susceptibility testing data in the Netherlands.

Information on SOD/SDD use and policy was collected from all ICUs by a structured online questionnaire completed by a clinical microbiologist (Table S1, available as Supplementary data at JAC Online). For this study, SOD was defined as the application of topical non-absorbable antimicrobials to the oropharynx only; SDD was defined as the application of topical non-absorbable antimicrobials to the oropharynx and/or the gastrointestinal tract in combination with intravenous antibiotics. In the Netherlands, the most frequently used topical antibiotic mixture consists of tobramycin, colistin and amphotericin B applied four times daily until ICU discharge (Table S1, available as Supplementary data at JAC Online).

Isolate selection and antimicrobial susceptibility

From January 2008 until April 2012, we included all isolates of Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter spp. from blood and lower respiratory tract specimens taken for either clinical or surveillance purposes. The main reasons for choosing these sample sites were that (i) blood specimens are collected when infection is anticipated and bias due to differences in sampling policy between ICUs is unlikely; (ii) both SOD and SDD exert effects in the oropharynx, with similar effects on respiratory tract colonization, and the inclusion of specimens from other sites was therefore considered less relevant; (iii) other surveillance cultures, such as from rectal swabs, is not routine practice in ICUs not using SDD.

Only isolates from laboratories that submitted complete data to the ISIS–AR database for the whole study period were included (i.e. consistently reporting laboratories). To avoid bias by patients admitted to an ICU for only a short period of time, we excluded all patients who only had isolates available for two consecutive days, as these patients probably reflect short-term ICU admissions. When studying the effect of SOD or SDD on resistance, the effects are anticipated to be most pronounced in the last isolates from individual patients found during ICU admission, due to selective antibiotic pressure. Additionally, in order to avoid the inclusion of multiple isolates from the same patient, we included the last isolate (i.e. cumulative resistance) per species per specimen per patient per month for statistical analysis.

As breakpoint guidelines for antimicrobial susceptibility testing changed over time, we calculated non-susceptibility to colistin, tobramycin, ciprofloxacin, ceftazidime and cefotaxime/ceftriaxone (i.e. if an isolate was non-susceptible to either cefotaxime or ceftriaxone it was considered to be non-susceptible) by reinterpreting available MIC values according to the EUCAST January 2012 guidelines (v2.0, www.eucast.org). If MIC values for an antimicrobial agent were available for <80% of all isolates, antimicrobial susceptibility interpretations as reported by the laboratories were used. Since ISIS–AR only collects data on isolates (i.e. positive cultures), the total number of cultures obtained could not be determined.

Analysis

Resistance rates were calculated per 100 patient beds per month. We assumed bed occupancy to be 100% and the total number of beds to be constant over time. Analyses were performed for ICUs that continuously used or did not use SOD/SDD from January 2008 to April 2012, using all data. For ICUs that introduced SOD or SDD during the period of study, the first month after introduction was excluded from the analyses and resistance rates were calculated before and after the introduction of SOD/SDD, with the month of switch fixed at t = 0 for all ICUs. Trends over time were analysed by multilevel Poisson regression, taking into consideration the variation between and within ICUs by including them as a level in the model. The number of beds, log-transformed, was used as an offset. All Poisson regression analyses were performed separately for Enterobacteriaceae and P. aeruginosa isolates. Additionally for colistin, stratified analyses were performed for Enterobacteriaceae intrinsically resistant to colistin, and Enterobacteriaceae intrinsically susceptible to colistin, according to the EUCAST expert rules. Statistical significance was defined as P < 0.05. All data were analysed using SPSS statistical software 19.0 (IBM, Armonk, NY, USA).

Ethics

This study was considered exempt from review by the Institutional Review Board.

Results

Of the 45 ICUs included in ISIS–AR, complete data for the whole study period were available for 38 ICUs, which offer different levels of care representing all three levels of ICU care available in the Netherlands (Table S2, available as Supplementary data at JAC Online). Among the included ICUs, 13 of the 38 did not use SOD/SDD during the study period (accounting for 663 months).
Effects of SOD and SDD on antimicrobial resistance in Dutch ICUs

Table 1. Average number of ICUs and beds per month for ICUs with and without SOD or SDD per quarter from January 2008 to April 2012

<table>
<thead>
<tr>
<th>Time period</th>
<th>No SOD/SDD</th>
<th>SOD&lt;sup&gt;b&lt;/sup&gt;</th>
<th>SDD&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of ICUs</td>
<td>beds/month</td>
<td>number of ICUs</td>
</tr>
<tr>
<td>Q1 2008</td>
<td>21</td>
<td>224</td>
<td>2</td>
</tr>
<tr>
<td>Q2 2008</td>
<td>21</td>
<td>224</td>
<td>2</td>
</tr>
<tr>
<td>Q3 2008</td>
<td>21</td>
<td>224</td>
<td>2</td>
</tr>
<tr>
<td>Q4 2008&lt;sup&gt;c&lt;/sup&gt;</td>
<td>21</td>
<td>219</td>
<td>2</td>
</tr>
<tr>
<td>Q1 2009</td>
<td>20</td>
<td>210</td>
<td>2</td>
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<td>Q2 2009</td>
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<td>Q3 2009</td>
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<td>Q4 2009&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>177</td>
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<tr>
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<td>13</td>
<td>136</td>
<td>12</td>
</tr>
<tr>
<td>Q1 2012</td>
<td>13</td>
<td>136</td>
<td>13</td>
</tr>
</tbody>
</table>

<sup>a</sup>Q1, January–March; Q2, April–June; Q3, July–September; Q4, October–December.
<sup>b</sup>Nine ICUs switched from SOD to SDD or vice versa during the period of study; see Table S2, available as Supplementary data at JAC Online for detailed information.
<sup>c</sup>Eight ICUs introduced SOD or SDD during the period of study. The times of introduction were December 2008 (n = 1), December 2009 (n = 1), January 2010 (n = 2), October 2010 (n = 1) and January 2011 (n = 3).

while 17 continuously used SOD/SDD (accounting for 859 months) (Table 1 and Table S2, available as Supplementary data at JAC Online). There were 637 unique blood culture isolates (Enterobacteriaceae n = 519; P. aeruginosa n = 107 and Acinetobacter spp. n = 11) and 8353 unique respiratory isolates (Enterobacteriaceae n = 6353; P. aeruginosa n = 1672 and Acinetobacter spp. n = 342). For ciprofloxacin, ceftazidime, cefotaxime/ceftriaxone and tobramycin, MIC values were available for 91%, 88%, 100% and 94% of isolates, respectively. For colistin, MIC values were available for 73% of isolates. We included only isolates with an MIC value for the agent studied, or in the case of colistin with an available antimicrobial susceptibility test result. For ciprofloxacin, cefotaxime/ceftriaxone and tobramycin, there were no changes over time in the percentage of MIC values available. The percentage of isolates with an MIC or antimicrobial susceptibility test result increased over time for ceftazidime (from 75% in 2008 to 85% in 2012) and colistin (from 34% in 2008 to 84% in 2012).

Figure S1 (available as Supplementary data at JAC Online) shows the rate of resistant respiratory isolates per month per analysis group; for ICUs that did not use SOD/SDD during the period of study the average rate of resistant isolates per month was 7.3/100 beds for ciprofloxacin (range 2.1–13.2/100 beds/month), 6.2/100 beds for ceftazidime (1.5–10.3/100 beds/month), 5.0/100 beds for cefotaxime/ceftriaxone (0.7–11.3/100 beds/month), 3.2/100 beds for tobramycin (0–6.2/100 beds/month) and 6.3/100 beds for colistin (3.0–11.0/100 beds/month). For ICUs that used SOD/SDD continuously during the period of study, these numbers were 3.5/100 beds for ciprofloxacin (0.9–6.7/100 beds/month), 3.4/100 beds for ceftazidime (0.6–7.0/100 beds/month), 3.0/100 beds for cefotaxime/ceftriaxone (0.6–5.8/100 beds/month), 3.5/100 beds for tobramycin (1.2–6.1/100 beds/month) and 5.3/100 beds for colistin (2.1–10.1/100 beds/month) (Figure S1, available as Supplementary data at JAC Online). Since the number of Acinetobacter spp. isolates was low, these isolates were excluded from further analysis.

Considering resistance over time, for isolates obtained from blood specimens, no discernible trends were observed for all antibiotics studied in ICUs with and without SOD/SDD (data not shown). For Enterobacteriaceae from respiratory specimens, the rate of isolates resistant to cefotaxime/ceftriaxone increased by 2% per month (95% CI 0.009 to 0.028) and to tobramycin by nearly 1% per month (95% CI 0.000 to 0.019) in ICUs that did not use SOD/SDD during the period of study (Table 2). In the ICUs that continuously used SOD/SDD there was a trend towards a decrease in the rate of resistance for all antimicrobial agents among Enterobacteriaceae isolates from respiratory specimens, with statistical significance reached for ciprofloxacin (β = −0.009, 95% CI −0.015 to −0.002) and cefotaxime/ceftriaxone (β = −0.006, 95% CI −0.012 to −0.000) for P. aeruginosa from respiratory specimens, there was a decreasing trend in the rate of isolates resistant to ceftazidime in ICUs without SOD/SDD (β = −0.015, 95% CI −0.028 to −0.002; Table 2). In ICUs with SOD/SDD there was a decreasing trend in the rate of resistance for most antimicrobial agents, which reached statistical significance for ciprofloxacin only (β = −0.016, 95% CI −0.027 to −0.004).

Eight ICUs introduced SOD (n = 6) or SDD (n = 2) during the period of study. The duration of data available for analysis before and after
the introduction of SOD/SDD ranged from 11 to 36 months and from 14 to 39 months, respectively (Table 1 and Table S2, available as Supplementary data at JAC Online). We included in the analyses only those months for which data were available from at least four ICUs (≥50% of the ICUs), resulting in periods of 33 and 26 months before and after SOD/SDD introduction, respectively. The number of resistant blood isolates was too small to perform time-trends analysis (n ≤ 20). Before the introduction of SOD/SDD, the rate of colistin resistance among Enterobacteriaceae from respiratory specimens gradually increased (β = 0.025, 95% CI 0.005–0.045; Table 3), which was followed by statistically significant decreasing trends in resistance rates for all antimicrobial agents after the introduction of SOD/SDD (Table 3 and Figure 1). No significant time trends were found for P. aeruginosa isolates (Table 3).

For colistin, stratified analyses were performed for Enterobacteriaceae that are intrinsically resistant (e.g. Proteus spp. and Serratia marcescens) and those that are intrinsically susceptible (e.g. Escherichia coli, Klebsiella spp., Citrobacter spp. and Enterobacter...
spp.). For blood and respiratory isolates, 89 (14%) and 1578 (18%) isolates belonged to the group of intrinsically resistant Enterobacteriaceae, and there were no time trends in the rate of resistance discernible for ICUs with and without SOD/SDD (Table 2). In ICUs that introduced SOD/SDD during the study period, there was an increasing trend before introduction in the rate of Enterobacteriaceae intrinsically resistant to colistin \( (b = 0.022, 95\% \text{ CI } 0.001 \text{ to } 0.042) \), which was followed by a decreasing trend after introduction \( (b = -0.049, 95\% \text{ CI } -0.078 \text{ to } -0.02; \text{ Table 3}) \). Among species that are considered intrinsically susceptible to colistin, only 246 (3%) of all respiratory isolates and 13 (2%) blood isolates were resistant to colistin, and these numbers did not allow trend analyses.

Discussion

This ecological study on the antimicrobial resistance rates of Gram-negative bacteria in 38 Dutch ICUs using national surveillance data demonstrated a decreasing trend in the rate of resistance to all marker antibiotics in respiratory isolates from ICUs that continuously used SOD/SDD during the 4 years of study, and significant decreases in resistance rates of respiratory isolates for all marker antibiotics in ICUs that introduced SOD/SDD. In ICUs that did not use SOD/SDD, the rates of resistance to cefotaxime/ceftriaxone increased over time. The prevalence of resistance to colistin among Enterobacteriaceae that are intrinsically susceptible was only 3% in respiratory isolates, precluding meaningful time trend analyses. The rate of Enterobacteriaceae intrinsically resistant to colistin decreased after the introduction of SOD/SDD. These results are in line with those from previous studies and a meta-analysis determining resistance among respiratory isolates from individual patients receiving SOD or SDD.6,7,11

Most studies of SOD or SDD, like this study, originate from the Netherlands, which is considered a low-prevalence country for antimicrobial resistance.17 Results of these studies might therefore not be generalizable to countries with a higher level of resistance. However, a recent meta-analysis that showed no association between selective decontamination and resistance included studies from various parts of the world, including countries in southern Europe with a higher baseline prevalence of resistance.11 Declining rates of antibiotic resistance during daily prophylactic administration of non-absorbable antibiotics in ICU patients seems counterintuitive, but might result from lower nosocomial infection rates6,18–20 yielding reductions in the use of systemic antibiotics.5,11,21 However, associations between lower infection rates and less antibiotic prescription have not been reported consistently from SDD studies. Therefore, this issue cannot be answered adequately with the available evidence. Another explanation might be the fact that SDD creates a unique environment that prevents the overgrowth of resistant mutants because of the combination

Figure 1. Rate of resistant respiratory isolates per 100 beds per month for the eight ICUs that introduced SOD or SDD from January 2008 to April 2012. The time of SOD or SDD introduction has been fixed for all ICUs at \( t = 0 \). The rate of resistance before the introduction of SOD or SDD is presented before \( t = 0 \). The rate after the introduction of SOD or SDD is presented after \( t = 0 \). The table represents the number of beds and number of ICUs included at the indicated times.
of very high topical bactericidal antibiotic levels in saliva and faeces, the use of synergistic antibiotic mixtures and the maintenance of colonization resistance.²²

Colistin resistance remained rare in Gram-negative bacteria intrinsically susceptible to colistin, even though most ICUs with SOD or SDD have used colistin as part of the prophylactic regimen since the early 2000s. Some reports have suggested the development of resistance after treatment with colistin;¹³,²⁴ colistin resistance was found in a patient receiving colistin both orally as well as intravenously,²³ and was also found among newborns receiving oral colistin as a single agent in the prophylaxis of neonatal necrotizing enterocolitis during an outbreak of resistant E. coli.²⁴ In both studies the setting in which colistin was used is not comparable to the use of colistin during SOD or SDD in ICUs in the Netherlands. During SOD or SDD, oral colistin is always given in combination with an aminoglycoside, which reduces the likelihood of resistance development. Previous Dutch studies of SOD and/or SDD have reported only low acquisition rates for colistin-resistant Gram-negative bacteria, which were comparable in patients with and without topical use of colistin.²² Yet, these studies have also demonstrated that colistin resistance can develop, albeit at a low rate, and that the use of SOD or SDD can facilitate the clonal spread of Gram-negative bacteria resistant to colistin and tobramycin.²⁶

Most studies evaluating the effects of SOD or SDD on antibiotic resistance have used individual patient data from randomized trials with a median duration of intervention of 16 months.¹¹ In such studies, patient groups are usually comparable due to randomization, with similar surveillance and culture methods within studies. However, the analyses have included only those patients that are enrolled, precluding assessment of the effects of SOD or SDD on the ecology of antimicrobial resistance in ICUs is unknown. To our knowledge, only two longitudinal ecological studies have been published, neither of which detected increases in the incidence of resistant bacteria during 5 years of SDD.²⁷,²⁸ However, both studies were single-centre studies that included only one ICU. A post hoc ecological analysis of the results of a Dutch cluster-randomized study in 13 centres demonstrated reduced rates of antibiotic resistance among Gram-negative bacteria during SOD or SDD, yet with an abrupt increase of resistance after discontinuation of SDD, suggesting a rebound effect on resistance in the intestinal tract, probably due to the recolonization of the patient by the surrounding microbiological flora.¹²

The present ecological study shows resistance patterns over time at the ICU level, not the patient level, and has a relatively long-term follow-up period for a large number of ICUs. However, the study has some limitations. First, ISIS–AR only collects data on positive cultures, and information on the total number of cultures taken or the total number of patients admitted was consequently unavailable. We therefore calculated rates using the number of beds per month as the denominator. Patient-days at risk would have been a better denominator, as incidence densities most accurately reflect the true resistance burden. In our study, the number of beds was assumed to remain stable throughout the period of study. Rates presented might therefore represent either an under- or over-estimation if the number of hospitalized patients changed over time (e.g. fewer hospitalized patients will result in fewer isolates cultured and consequently an underestimation of the rate). In our study, there was a significant decrease in the number of isolates available in the ISIS–AR database per bed per month over time (β = −0.004, 95% CI –0.005 to –0.002; Table S3, available as Supplementary data at JAC Online). However, the decrease in the number of isolates was only visible in ICUs that used SOD or SDD, or ICUs that introduced SOD or SDD, reflecting the effects of SOD/SDD on the total number of isolates cultured rather than a decrease in the number of patients.

Second, individual patient data were not available and adjustments for differences between ICUs – such as on infection control measures and patient characteristics, such as severity of illness and antibiotic therapy – therefore could not be made and consequently no causality between SOD and SDD and antimicrobial resistance could be studied. We therefore analysed data on an ICU level and only compared trends over time within the same ICU group, minimizing bias by confounding.

Third, due to the low number of ICUs that continuously used SOD or SDD during the period of study, we combined these two interventions. When considering blood isolates, the combination of SOD and SDD does not seem clear-cut, since SDD consists of intravenous cefotaxime/ceftriaxone, i.e. systemic treatment. However, combining SOD and SDD for respiratory tract isolates is justifiable, since both regimens exert effects in the oropharynx, with similar effects on respiratory tract colonization, both with susceptible and resistant bacteria.²²

Fourth, as we studied the combined effects of SOD and SDD in order to minimize bias by different SOD/SDD surveillance practices between ICUs, we only included data on respiratory tract specimens. Inclusion of other sample sites might have yielded different results.

Fifth, details on microbiological culture procedures, antibiotic susceptibility testing and surveillance policies were not available, and for the ICUs that introduced SOD or SDD during the study period, detection bias might have occurred through a higher frequency of sampling and the use of selective media for detection of microorganisms resistant to the prophylactic antibiotics. However, this detection bias would have resulted in an increased detection of resistant isolates, which would imply that the observed decrease in resistance rate would have underestimated the true decrease in resistance.

Sixth, MIC values or antimicrobial test results were not available for all isolates, possibly introducing bias for agents with a change over time in the percentage of available susceptibility test results (such as ceftazidime and colistin). For both agents, the increase in the percentage of available susceptibility test results would have resulted in bias towards an increase in resistance over time, which was not observed, except for isolates intrinsically resistant to colistin. We therefore feel that this limitation did not bias the results of our study.

Finally, although the follow-up of the present study was relatively long, individual patient follow-up was restricted to the period of the ICU stay, and the effects of SOD or SDD on resistance after their discontinuation were not evaluated.

Due to these limitations, we did not compare resistance rates and trends between ICUs with and without SOD/SDD. However, this study provides unique information on the trends in antibiotic resistance in ICUs with and without SOD or SDD. In conclusion, these results provide evidence that in ICUs with a low endemicity of antibiotic resistance, the use of SOD and SDD is not associated with an increase in resistance rates over time but rather with a
reduction in resistant isolates. Studies evaluating the clinical benefits and ecological safety of these measures in settings with different bacterial ecology are warranted, as well as studies on the impact of SOD and SDD on resistance after their discontinuation.

Acknowledgements

Results of this study have been presented as an oral presentation at the Twenty-third European Congress of Clinical Microbiology and Infectious Diseases, Berlin, Germany, 2013 and as a poster presentation (P120) at the Scientific Spring Meeting KNVM and NVMM, Papendal, The Netherlands, 2013.

We are grateful for the support of all the clinical microbiologists of the ISIS–AR Study Group and of our colleagues of the ISIS–AR Project Group, RIVM, for their contribution to the data collection. We thank J. van de Kassteele and A. Wong, RIVM, for their statistical support.

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Funding

This study was carried out as part of our routine work. ISIS–AR is supported by the Dutch Ministry of Health.

Transparency declarations

None to declare.

Supplementary data

Tables S1, S2 and S3, and Figure S1 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

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