Exploring the epidemiology of carbapenem-resistant Gram-negative bacteria in west London and the utility of routinely collected hospital microbiology data

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Objectives: The objective of this study was to identify carbapenem-resistant organisms using routinely collected local microbiology data and describe the epidemiology of carbapenem resistance in two London teaching hospitals.

Methods: Data on inpatients infected or colonized with Gram-negative organisms between March 2009 and February 2012 were extracted. A computer algorithm was developed incorporating internationally recognized criteria to distinguish carbapenem-resistant organisms. Multivariable analysis was conducted to identify factors associated with infection or colonization with carbapenem-resistant organisms. Binomial regression was performed to detect changes in resistance trends over time.

Results: Yearly incidence of carbapenem resistance was observed to be increasing, with significant increasing trends in Acinetobacter baumannii (47.1% in 2009–10 to 77.2% in 2011–12; P < 0.001) and Enterobacter spp. (2.2% in 2009–10 to 11.5% in 2011–12; P < 0.001). Single-variable and multivariable analysis demonstrated differences in the proportion of carbapenem-resistant isolates across all variables investigated, including age, sex and clinical specialty; in the latter organism-specific niches were identified. Patients in the youngest age group (16–24 years old) had the highest odds of being infected or colonized with carbapenem-resistant organisms. Binomial regression was performed to detect changes in resistance trends over time.

Conclusions: Carbapenem resistance is an emerging problem within the UK inpatient healthcare setting. This is not an issue confined to the Enterobacteriaceae and fine-resolution surveillance is needed to identify at-risk groups. Regular analysis of routinely collected data can provide insight into the evolving carbapenem-resistance threat, with the ability to inform efforts to prevent the spread of resistance.

Keywords: surveillance, resistance, microbiology

Introduction

The WHO deems antimicrobial resistance in commonly isolated bacteria to have reached ‘alarming levels’ in many parts of the world.1 Perhaps of most concern is resistance to carbapenems, which results from one or more of several different mechanisms: (hyper)production of ESBL or Ambler class C β-lactamases (including chromosomal AmpC β-lactamases) with concomitant loss of outer membrane porins; augmented drug efflux; alteration in penicillin-binding proteins; and carbapenemase production.2 Among these mechanisms the expression of carbapenemases by Gram-negative organisms is of particular concern. Klebsiella pneumoniae carbapenemase is one of the most frequently isolated carbapenemases globally and has been responsible for a number of outbreaks in the healthcare setting.3–6 Another carbapenemase, New Delhi metallo-β-lactamase, was first identified in 2008 and is already regarded as being one of the biggest antimicrobial resistance threats because it can be expressed by numerous pathogens, including Escherichia coli ST131, the strain associated with the global spread of CTX-M-15 ESBLs.6 Antimicrobial resistance, and specifically carbapenem resistance, has been highlighted as a key threat to health in the UK,7 the USA8 and internationally.1 Among the areas identified to combat antimicrobial resistance, surveillance for infections occurring in the healthcare setting should be expanded; specifically there

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is a need for the surveillance of carbapenem resistance in Gram-negative bacteria.7 Furthermore, these surveillance systems must be able to rapidly identify new threats and changing patterns in resistance.9 It is likely that national strategies will be needed to achieve this. A centrally coordinated approach has been taken in Israel,10 and national toolkits have been published in the UK11 and the USA.12 Although the toolkits are focused on Enterobacteriaceae, it is recognized that carbapenem resistance is also of concern in other Gram-negative organisms, including Pseudomonas spp. and Acinetobacter spp.

How such surveillance should be conducted is, as yet, unclear. However, the wealth of routinely collected electronically stored data concerning infections occurring within healthcare settings may be useful for antimicrobial resistance surveillance.13 The development of systems to identify, process, and analyse this high-volume data will improve understanding of carbapenem resistance in the healthcare sector and will be critical in implementing effective strategies for prevention and control. This study presents an approach that utilizes routinely collected local microbiology data to investigate carbapenem resistance epidemiology in a range of Gram-negative organisms in the context of inpatients from two London teaching hospitals.

Materials and methods

Data processing

Microbiology data for analysis were extracted from a laboratory information management system (LIMS) containing routine data electronically captured from the two hospitals included in the study (which form part of a large Academic Health Sciences Centre in west London). Hospital 1 includes general medicine, general surgery, trauma and orthopaedics wards, and tertiary referral centres for oncology and neurosurgery. Hospital 2 includes general medicine and cardiology wards, as well as tertiary referral haematology, cardiothoracic surgery and hepatobiliary surgery units. These services are divided into overarching clinical specialties across both hospital sites (Table 1). Furthermore, both hospitals employ the same antimicrobial and infection control policies.

Organisms isolated from all specimen types (i.e. clinical and screening specimens) taken during the 3 years between March 2009 and February 2012 were included in the study. A single laboratory serves both hospitals, and standard operating protocols follow national guidelines,14 with susceptibility testing conforming to BSAC guidelines.15 Isolate identification was by API® (bioMérieux) from 2009 to 2011 and by MALDI-TOF MS (Biotyper®; Bruker) from 2011 to 2012. Prior to analysis, data were anonymized in line with an agreed ethical protocol using a secure hash algorithm.

The routine nature of the data meant that some re-shaping was necessary. Each row in the dataset represented an individual susceptibility result for an organism; to create antibiograms, the data were re-shaped so that all susceptibility results for an isolate were stored in one row. Complications in the data processing resulting from data re-shaping arose on several occasions and are discussed below. Several new variables were created to facilitate analysis. Age was categorized as follows: 16–24, 25–39, 40–54, 55–64, 65–74, 75–84 and ≥85 years old. Patients with a reported age of <16 years old (n=24) were removed prior to analysis as the hospitals included in the analysis specialized in adult care. Patient location (ward) at the time of specimen collection was assigned to the corresponding clinical specialty (Table 1).

Criteria used to identify carbapenem-resistant organisms

An initial literature review identified organisms for inclusion in the study: E. coli, Klebsiella spp., Enterobacter spp., Pseudomonas aeruginosa and Acinetobacter baumannii. A computer algorithm was developed to identify carbapenem-resistant organisms from the data extract. The algorithm was informed by guidelines for the detection of resistance mechanisms prepared by EUCAST.16 Additionally, cases of MDR A. baumannii (MRAB) were defined based on criteria described in the ‘Working Party Guidance on the Control of Multi-Resistant Acinetobacter Outbreaks’.17 Figure 1 summarizes the antimicrobial susceptibility results used to identify carbapenem-resistant organisms; results used to indicate ESBL/AmpC phenotypes have also been included. For A. baumannii, isolates exhibiting a MRAB profile plus carbapenem resistance (MRAB-C) were included in the analysis. An isolate was classed as carbapenem resistant if a resistant result was recorded against at least one carbapenem.

Data de-duplication

To avoid multiple isolates from individual patients being included in the epidemiological analysis and potentially skewing results, only the first report of distinct strains from a patient was retained, where a strain was determined by the antimicrobial resistance phenotype. If more than one organism was isolated from the same specimen, each was included in the analysis. To avoid artificially reducing the number of cases of particular strains in the later years of the time period studied, a report would be

Table 1. Clinical specialty groups across the two London hospitals

<table>
<thead>
<tr>
<th>Clinical specialty</th>
<th>Sub-specialties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicine</td>
<td>emergency medicine, clinical pharmacology, endocrinology, gastroenterology, hepatology, genito-urinary medicine, infectious diseases, medicine for the elderly, respiratory medicine, stroke medicine</td>
</tr>
<tr>
<td>Surgery and Cancer</td>
<td>general surgery, breast surgery, endocrine surgery, hepatobiliary surgery, urology, oncology critical care, anaesthesia, neurology and neurosurgery, orthopaedic and reconstructive surgery cardiology, cardiothoracic surgery, renal transplant, renal dialysis, vascular surgery, rheumatology haematology (including bone marrow transplant)</td>
</tr>
<tr>
<td>Specialist Services</td>
<td></td>
</tr>
<tr>
<td>Circulation Sciences and Renal Medicine</td>
<td></td>
</tr>
<tr>
<td>Clinical and Investigative Sciences</td>
<td></td>
</tr>
<tr>
<td>Private patients</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

NA, not applicable.

The two hospitals included in this study are NHS (public) hospitals, with small private wards (42 beds in Hospital 1 and 107 beds in Hospital 2).

Clinical specialty group classed as ‘Unknown’ if patient location not recorded.
counted again if the same strain was isolated from the same patient more than one year after the initial report.

Methods for epidemiological analysis

The analysis was performed after the data had been re-shaped and de-duplicated. At the organism level, \( \chi^2 \) tests of association were employed to assess whether there were differences in the proportions of carbapenem resistance between age groups, sex, clinical specialties, hospital sites or full-year time periods (March–February). The total number of reports for each organism has been used as the denominator data to produce proportions of resistance. For example, the reported percentage of MRAB-C represents the proportion of isolates that were identified as MRAB-C within all reports of \( A. \) baumannii. To quantify any observed changes in the proportion of resistance over time, binomial regression analysis was performed if the results from the \( \chi^2 \) analysis were significant (at the 5% significance level). A multivariable logistic regression model was used to allow the inclusion of all explanatory variables (as listed above) in the analysis and thus determine whether any factor was associated with a significantly higher proportion of carbapenem resistance when all other variables had been adjusted for. Finally, tests of interaction were performed to determine whether the observed time trend was consistent across both hospital sites; interactions were assessed if results from the binomial regression analysis indicated a significant change in the proportion of carbapenem-resistant organisms isolated across any of the three time periods investigated.

The data processing, application of criteria to distinguish carbapenem-resistant isolates and epidemiological analysis were performed using Stata/SE Version 11.

Results

There were 9748 microbiology reports made across all bacterial species included in the analysis. The distribution of organisms is summarized in Table 2. The rate of positive microbiology reports for all organisms included in the study was similar over the three time periods investigated (12.2 reports per 1000 occupied bed days (OBDs) in 2009–10; 11.8 reports per 1000 OBDs in 2010–11; and 12.4 reports per 1000 OBDs in 2011–12). The most frequently recorded specimen types were urine cultures (44.5%), wound cultures (23.7%) and sputum cultures (14.5%). Isolates from blood cultures represented 8.8% of specimen types, with screening specimens representing 3.1% of all specimen types. Organism-specific analyses are presented for all organisms included in the study to investigate the epidemiology of each in the healthcare setting.

**E. coli**

Of the 4683 isolates of \( E. \) coli, 43 (0.9%) demonstrated carbapenem resistance (all but one of these carbapenem-resistant isolates also displayed an ESBL/AmpC phenotype). Significant differences in the proportion of carbapenem-resistant \( E. \) coli were observed between hospital sites (Hospital 1 = 0.5%, Hospital 2 = 1.4%; \( P=0.002 \), clinical specialties (\( P<0.001 \); Table 3), sex (males = 1.4%, females = 0.7%; \( P=0.01 \)) and age groups (\( P=0.01 \); Table 4). There was no evidence of a change in the
The proportion of carbapenem-resistant E. coli isolates identified over time (2009–10 = 1.1%, 2010–11 = 1.0%, 2011–12 = 0.6%; P = 0.3).

Results from the multivariable logistic regression analysis indicated that the odds of isolating carbapenem-resistant E. coli were significantly different across the clinical specialties when other factors had been adjusted for (P < 0.001), with higher-risk specialties observed to be Specialist Services, Clinical and Investigative Sciences and Private Patients, compared with Medicine. The odds of isolating carbapenem-resistant E. coli from patients located at Hospital 2 were also significantly greater than those for patients at Hospital 1 (OR = 3.1, 95% CI = 1.4–7.2, P = 0.007). As initially indicated by the results of the χ² analysis, the proportion of isolates identified as being carbapenem resistant was highest in patients aged 16–24 years. This was supported by results from the logistic regression, with the odds of isolating carbapenem-resistant E. coli from patients in all other age groups significantly lower than those for patients aged 16–24 years (Table 4).

Klebsiella spp.

Of the 865 isolates of Klebsiella spp., 49 (5.7%) carbapenem-resistant isolates were identified (47 of the carbapenem-resistant isolates also exhibited an ESBL/AmpC phenotype). There were no significant differences in the proportion of carbapenem-resistant Klebsiella spp. isolated by hospital site (Hospital 1 = 5.1%, Hospital 2 = 6.3%; P = 0.7), sex (males = 6.3%, females = 4.8%; P = 0.3) or across the three time periods (2009–10 = 4.4%, 2010–11 = 5.8%, 2011–12 = 6.8%; P = 0.4). Differences in proportions across clinical specialties was observed (P = 0.05; Table 3), and strong evidence of differences by age group was also seen (P < 0.001; Table 4).

The multivariable logistic regression analysis revealed that the odds of isolating carbapenem-resistant Klebsiella spp. from patients on wards associated with different clinical specialty groups were still significant (P = 0.02), with Circulation Sciences and Renal Medicine found to have the highest proportion of resistance. Similar to the results for carbapenem-resistant E. coli, the highest proportion of carbapenem resistance in Klebsiella spp. was observed in patients aged 16–24 years old. The results from the regression analysis can be found in Table 4, which shows that the ORs in all other age groups are significantly lower when compared with patients in the 16–24 year-old age category.

Enterobacter spp.

There were 885 cases of Enterobacter spp. in the 3 year study period. Carbapenem-resistant Enterobacter spp. represented only a small proportion (69 cases, 7.8%); of note, 65 out of the 69 carbapenem-resistant isolates (94.2%) also displayed a resistance profile indicative of ESBL/AmpC production. A difference in the proportion of carbapenem-resistant strains isolated at the different hospital sites was observed: 6.8% (n = 32) at Hospital 1; 9.9% (n = 37) at Hospital 2 (P = 0.05). No strong evidence of differences in proportions was observed across clinical specialties (P = 0.08), patient sex (males = 8.9%, females = 6.1%; P = 0.1) or age groups (P = 0.5).

A year-on-year increase in the proportion of carbapenem-resistant Enterobacter spp. was observed over the three time periods, which was found to be significant from the χ² analysis (P < 0.001). In 2009–10 the proportion of carbapenem resistance was 2.2% (n = 7), which increased to 10.2% (n = 27) in 2010–11, rising again to 11.5% (n = 35) in the final year of analysis. Results from the binomial regression analysis indicated that there had been a significant increase in the proportion of carbapenem resistance from 2009–10 to 2010–11 (4.6-fold increase, 95% CI = 2.0–10.4, P < 0.001). Although there was a small increase from 2010–11 to 2011–12, this was not found to be significant (relative increase of 12.2%, P = 0.6). After including all variables in the logistic regression model to provide adjusted ORs, the increase in carbapenem resistance from the baseline year (2009–10) to 2010–11 and 2011–12 was still found to be significant (P < 0.001 in both cases). There was no evidence of interactions between time period and hospital site for carbapenem-resistant Enterobacter spp. (P = 0.7).

P. aeruginosa

There were 3119 cases of P. aeruginosa in the study period, with 591 (19.0%) identified as being carbapenem-resistant isolates; of these, 138 (23.4%) also exhibited third-generation cephalosporin resistance. Significant differences in the levels of carbapenem resistance were observed in all variables analysed; the proportion of resistance was higher at Hospital 2 (21.2%) compared with Hospital 1 (17.3%) (P = 0.01); it was higher in males (21.3%)
than females (16.2%) (P<0.001); and the proportion of carbapenem-resistant organisms decreased over the analysis period (2009–10 = 22.6%, 2010–11 = 18.3%, 2011–12 = 15.7%; P<0.001). Differences in proportions observed across clinical specialties and age groups were also found to be significantly different (P<0.001 in both instances) and are displayed in Tables 3 and 4, respectively.

The results from the multivariable logistic regression model showed that differences in the proportions of carbapenem resistance observed with different patient sex were still significant (P=0.02), as were the differences observed across clinical specialty groups (P<0.001), hospital sites (P<0.001) and time periods (P=0.003). Similar to the findings from the analysis performed on E. coli and Klebsiella spp., carbapenem resistance was highest in patients in the youngest age group (Table 3). The odds of isolating carbapenem-resistant P. aeruginosa in the older age groups were lower compared with that in patients in the youngest age group, as can be seen in Table 4.

**A. baumannii**

There were 196 cases of A. baumannii in the 3 year study period, with MRAB-C isolates being the most commonly identified form (n=129, 65.8%). According to the results of the χ² analysis, there was no significant difference in the proportion of isolates identified as MRAB-C between the hospital sites (Hospital 1 = 68.9%, Hospital 2 = 59.4%; P=0.2). Additionally, there was no difference in the proportion of MRAB-C across the clinical specialties (P=0.2). The proportion of isolates identified as MRAB-C between male and female patients was also similar (68.4% and 62.0%, respectively, P=0.4) and there was no strong evidence of differences in proportions across age groups (P=0.8).

Results from the χ² analysis indicated that there was a significant difference in the proportion of MRAB-C isolates identified over the three full-year time periods: in 2009–10 the proportion of MRAB-C isolates was 47.1%, which increased to 74.7% in 2010–11, increasing again in 2011–12 to reach a level of 77.2% (P<0.001). Binomial regression analysis demonstrated a significant relative increase in the isolation of MRAB-C of 58.6% (95% CI = 19.1%–111.2%, P=0.002) between 2009–10 and 2010–11. Although there was a small relative increase from 2010–11 to 2011–12, this was not found to be significant (P=0.7). After performing multivariable logistic regression including all variables individually investigated, significant increases in MRAB-C from the baseline year (2009–10) were still observed (2009–10 to 2010–11: OR = 3.6, 95% CI = 1.6–8.3, P=0.002; 2009–10 to 2011–12: OR = 3.9, 95% CI = 1.6–9.4, P=0.002).

Investigation into the presence of interactions revealed that the trends over time were different at the two main hospital sites (P=0.01). At Hospital 1 the odds of isolating MRAB-C increased significantly from 2009–10 to 2010–11 (OR = 6.1, 95% CI = 2.5–15.0, P<0.001) and from 2009–10 to 2011–12 (OR = 7.8, 95% CI = 2.5–24.6, P<0.001). During the same time period, the odds of isolating MRAB-C from patients at Hospital 2 did not appear to change.

**Discussion**

Results from the epidemiological analysis identified significant increases in carbapenem resistance over time in two organisms investigated: A. baumannii and Enterobacter spp. The proportion of MRAB-C isolates identified was alarming, with 77.2% of A. baumannii isolates found to be resistant to imipenem or meropenem in addition to aminoglycosides and third-generation cephalosporins in 2011–12. There was also a year-on-year increase in the number of cases of carbapenem-resistant Klebsiella spp., although these increases were not found to be statistically significant. The results from this analysis indicate that carbapenem resistance appears to be an increasing problem within the healthcare setting investigated.

Differences in the proportions of carbapenem resistance were observed across all variables analysed. Evidence of differences in the proportion of carbapenem-resistant isolates across clinical specialties was observed in E. coli, Klebsiella spp. and P. aeruginosa. Patients in the Circulation Sciences and Renal Medicine wards appeared to be disproportionately affected by carbapenem-resistant Klebsiella spp., whereas patients in the Specialist Services, Clinical and Investigative Sciences (see Table 1) and Private Patient settings were more affected by carbapenem-resistant E. coli. This information can be used to identify areas that may require increased infection prevention and control efforts to prevent further dissemination of these resistant pathogens. Furthermore, the high rates observed among private patients may be driven by the high proportion of overseas visitors obtaining private healthcare at these hospitals; travel is known to be associated with an increased risk for carbapenem-resistant organisms. It is therefore essential that information on travel history is captured on admission to healthcare facilities to ensure that appropriate infection control measures are implemented rapidly.11,12

Patients aged 16–24 years old were found to have the highest odds of being infected or colonized with isolates of E. coli, Klebsiella spp. or P. aeruginosa resistant to carbapenems. A recent study by Mammina et al.18 found that colonization of patients with carbapenem-resistant K. pneumoniae and A. baumannii disproportionately affected young trauma patients with prolonged stay in ICU. This may also explain the higher proportions of carbapenem-resistant organisms in younger patients observed in this study, although patient admission, discharge and transfer data were not available to confirm this.

Differences in proportions of resistance between the hospital sites were observed for the majority of organisms. Investigation into the presence of interactions revealed evidence of increased odds of isolating MRAB-C from patients in Hospital 1, which had not been initially identified from the χ² analysis. In contrast, there was evidence of higher levels of carbapenem-resistant Enterobacter spp., E. coli and P. aeruginosa at Hospital 2 compared with Hospital 1. This is despite overarching antimicrobial prescribing policies and a consolidated laboratory across both institutions.

Although differences in the proportions of resistance were observed between the hospital sites, a difference in trend was only identified in A. baumannii. Therefore, it does not appear that differences in microbiological screening strategies between the two hospitals were likely to have impacted on our findings. Hospital 1 screened for resistant Gram-negative bacteria using cepodoxime and meropenem whereas Hospital 2 screened using meropenem alone. In the case where evidence of differing trends did exist (MRAB-C), both screening methods used are equally sensitive in the detection of carbapenem resistance. Clinical samples from both hospitals are processed in an identical...
manner and the screening method for carbapenem resistance among Enterobacteriaceae in both hospitals has been revised to include ertapenem subsequent to the time periods included in this study. Ertapenem appears to have an improved sensitivity (but a poorer specificity) for carbapenemase producers compared with either meropenem or imipenem. This method does not differentiate between ESBL/AmpC production and porin loss or carbapenemase production as the mechanism of carbapenem resistance.

This study has demonstrated how routinely collected microbiology data can be used to develop a greater understanding of the epidemiology of carbapenem resistance in the healthcare setting. However, as mentioned, there were complications encountered when data processing necessary to produce antibiograms was attempted. The LIMS used in this data analysis is an example of a hierarchical data model and is not an ideal system for use in data processing and epidemiological analysis. To overcome these issues manual data manipulation had to be performed prior to data re-shaping and the creation of antibiograms, which was required to identify carbapenem-resistant organisms. This presents limitations in the implementation of a fully automated system for the identification of carbapenem-resistant isolates, and therefore more flexible LIMS should be employed to ensure that electronic data can be used to its full potential.

A large number of reports were not speciated beyond ‘coliforms’. This may affect the findings (in terms of proportions of resistance) presented in this study as the epidemiological analysis was only performed on organisms identified to at least the genus level. It was not possible to determine whether observed increases in carbapenem resistance were due to the increasing speciation of carbapenemase-producing organisms, although it is worth noting that there were no significant changes across the hospital network in non-speciated coliforms following the transition from API to MALDI-TOF MS in 2011 (2009–10 19.9%, 2010–11 19.8%, 2011–12 20.3%, 2012–13 17.0%). The introduction of rapid, inexpensive, bacterial identification platforms such as MALDI-TOF MS may in the future resolve the issue of organism identification as speciation becomes near ubiquitous. Further to this, molecular studies are required to quantify how much resistance is due to the presence of carbapenemase-producing organisms, and determine whether particular risk factors are associated with specific resistance mechanisms.

It is important to perform regular, fine-resolution, epidemiological analysis of antimicrobial resistance to help understand local resistance patterns and identify potential risk factors, particularly those associated with carbapenem-resistant organisms. Further work including the incorporation of information on antimicrobial consumption, compliance with prescribing policies and detailed information on patient characteristics should be considered to allow more comprehensive analysis. Antimicrobial use at both hospital sites investigated has been described previously; however, the incorporation of these data for further analysis was not within the scope of our study.

Results from the analysis presented in this study have provided an initial insight into the epidemiology of carbapenem resistance in the healthcare setting investigated. In support of the published literature, patients on wards associated with Specialist Services (see Table 1), which includes intensive care wards, were found to have the highest level of carbapenem-resistant E. coli and carbapenem-resistant P. aeruginosa. This information can be used to target infection control and antimicrobial stewardship interventions. However, with the isolation of carbapenem-resistant organisms from patients in the non-ICU setting (as demonstrated here), and from the community, the evolving epidemiology of carbapenem resistance must also be considered when developing infection prevention and control strategies within the wider healthcare setting.

Analysis of routinely collected local microbiology data provides an opportunity to improve our knowledge and understanding of antimicrobial resistance. Better epidemiological analysis of readily accessible, electronically stored data identified that there is an increasing issue with carbapenem resistance within inpatient healthcare settings in London. The results of the study presented here revealed that carbapenem resistance is not an issue limited to Enterobacteriaceae. Regular analysis of antimicrobial resistance data is crucial to ensure that policy, infection control measures and surveillance strategies are effective in addressing the increasing threat of carbapenem resistance in Gram-negative bacteria.

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**Transparency declarations**

L. S. P. M. and A. H. H. have consulted for bioMérieux. H. D. has received a speaker’s honorarium from Astellas. R. F. and A. C.: none to declare.

**Disclaimer**

The views expressed are those of the authors and are not necessarily those of the NHS, the NIHR, the Department of Health or PHE.

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