White Rose Research Online

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk
Universities of Leeds, Sheffield and York

Deposited via The University of Leeds.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/id/eprint/134048/

Version: Accepted Version

Article:
Berry, C, Davies, K, Woodford, N et al. (2019) Survey of screening methods, rates and policies for the detection of carbapenemase producing Enterobacteriaceae in English hospitals. Journal of Hospital Infection, 101 (2). pp. 158-162. ISSN: 0195-6701

https://doi.org/10.1016/j.jhin.2018.08.005

© 2018 The Healthcare Infection Society. Published by Elsevier Ltd. This manuscript version is made available under the CC-BY-NC-ND 4.0 license http://creativecommons.org/licenses/by-nc-nd/4.0/.

Reuse
This article is distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND) licence. This licence only allows you to download this work and share it with others as long as you credit the authors, but you can't change the article in any way or use it commercially. More information and the full terms of the licence here: https://creativecommons.org/licenses/

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

UNIVERSITY OF LEEDS
University of Sheffield
UNIVERSITY of York

Essential title page

Claire Berry
Healthcare Associated Infection Research Group
Leeds Institute for Biomedical and Clinical Sciences, University of Leeds and Leeds Teaching Hospitals NHS Trust
Old Medical School
Leeds General Infirmary
Leeds, LS1 3EX
W. Yorkshire

Kerrie Davies
Healthcare Associated Infection Research Group
Leeds Institute for Biomedical and Clinical Sciences, University of Leeds and Leeds Teaching Hospitals NHS Trust

Neil Woodford
NIS Laboratories,
National Infection Service, Public Health England

Mark Wilcox
Healthcare Associated Infection Research Group
Leeds Institute for Biomedical and Clinical Sciences, University of Leeds

Caroline Chilton
Healthcare Associated Infection Research Group
Leeds Institute for Biomedical and Clinical Sciences, University of Leeds

UK survey of screening methods, rates and policies for the detection of carbapenemase producing Enterobacteriaceae.

Summary

Multi-drug resistant Gram negative bacteria are of major clinical concern. The increasing prevalence of carbapenemase-producing Enterobacteriaceae (CPE), resistant to all beta-lactams including carbapenems, and able to colonise the large intestine represent a key threat. Rapid, accurate detection of intestinal CPE colonisation is critical to minimise transmission, and hence reduce costly, difficult to treat CPE infections. There is currently no 'gold standard' CPE detection method. Following a survey of diagnostic laboratories in England, we report considerable heterogeneity in diagnostic CPE testing methods and procedures.

Keywords
Carbapenemase, Enterobacteriaceae, screening, laboratory detection

Introduction

Antibiotic resistance in bacteria is of increasing concern. In particular, the prevalence of carbapenemase-producing Enterobacteriaceae (CPE) has increased in recent years, and CPE have become an important threat to public health [1, 2]. Rapid, accurate detection of these organisms in patients is paramount to ensure appropriate patient management, infection prevention and infection control procedures are put in place to minimise spread [3]. This is complicated, however, by a number of factors, not least which patients to screen for CPE carriage. It is unrealistic and too expensive to test all patients in most hospitals, and so detection is usually targeted at particular 'at risk' patient subgroups [3, 4].

There is no 'gold standard' method for detection of CPE in stool samples or rectal swabs; UK Standards for Microbiology Investigations (SMI) guidelines recommend only that methods used should 'have demonstrated performance at least equivalent to plating on to a commercially-prepared agar specifically recommended for this purpose' [5]. Molecular methods allow rapid screening for selected carbapenemase genes and real-time PCR assays offer laboratories the ability to reduce turnaround times. It has been reported that these tests may have lower limits of detection than conventional agar-based methodologies [6, 7].

Finally, cost is an important factor in CPE detection, and assay cost is often a major concern to hospitals when devising their CPE detection policy, especially given the potentially large volume of testing. However, CPE can contribute to a large burden on healthcare facilities in many different ways; infections are often difficult and expensive to treat, and can lead to a prolonged hospital stay, with the associated increase in costs and colonised patients require isolation. As such, minimisation of CPE transmission is key.

Generation of evidence to support adoption of a preferred CPE detection method would thus be greatly beneficial to healthcare systems in the UK. However, for the reasons described above, no single method is likely to meet these requirements. Testing algorithms, combining screening and confirmatory/validation tests, can offer improved sensitivity and specificity compared with single assays [8]. We have used a survey to determine current testing practices across laboratories in England.

Methods

Two surveys were sent to all (n=153) acute NHS trusts in England and their associated laboratories. One survey (laboratory, 8 questions) gathered information on the testing protocols used to detect CPEs in the laboratory while the other (trust, 10 questions) gathered data on CPE testing rates and policies. Each site was assigned a unique study number so that results could not be linked back to an individual trust. Data were input directly, by each site, into the web based database

Bristol Online Survey Tool (https://www.onlinesurveys.ac.uk/) before being downloaded for basic statistical analysis in Excel (Microsoft® Office 2010).

Data were analysed to identify commonly used detection methods and compare methods and policies across different NHS Trusts. Both, rates of testing and CPE positivity were calculated per 10 000 patient bed days (pbds) to allow comparison between hospitals of differing size. Data were gathered for the period 1st January 2016 to 31st December 2016.

Results

Laboratory and trust surveys were completed by 50/153 (32.7%) and 36/153 (23.5%) participants respectively; 34 trusts/laboratories completed both surveys. A wide variety of screening protocols were reported (Figure A.1).

Laboratory results

Phenotypic tests made up 25/45 (55.6%) of local confirmatory tests, but there was considerable heterogeneity and one phenotypic test was not clearly preferred. Twelve laboratories used a molecular test, with Cepheid Gene Xpert Carba-R the most popular molecular assay (11/12 (91.7%)).

When testing clinical isolates for CPEs, 10 (20%) laboratories used alternative tests to those employed for screening. All laboratories using alternative laboratory methods used chromogenic agar as the first stage in their screening protocol; however, for clinical isolates (that had already been isolated from a sample), this step was omitted and the laboratories proceeded straight to phenotypic and molecular tests.

Trust results

The most common reason for screening patients for CPEs was patients with a history of hospitalisation abroad in the last 12 months (34/36 (94.4%)). The second most common reason was patients hospitalised in the last 12 months in a UK hospital with a recent CPE outbreak (28/36 (77.8%)). Admissions to a particular unit accounted for 6/36 (16.7%). When laboratories tested patients due to an admission to a particular location, it was predominantly admission to an intensive care unit. Other reasons given for testing included transfer from a UK hospital out of the region, contacts and positives from a previous outbreak and dialysis patients that had travelled abroad or had treatment away from their base hospital.

All trusts that responded had a written CPE screening policy detailing where, when and how often patients should be screened. Most Trusts (30/36 (83.3%)) reported screening up to three times during an admission if each screen is negative. Patients with a known previous positive screen are rescreened in 31/36 of Trusts. In addition, 24/31 (77.4%) hospitals rescreen patients with a previous CPE positive result, if the patient is readmitted to hospital.

Although there were 36 respondents to the Trust questionnaire, six gave total number of beds instead of patient bed day data; rate data could therefore only be calculated for 30 trusts. To preserve anonymity, data from trusts were combined into English regions (Figure B. 1.) Nationally, 60 samples were screened per 10 000 pbds, with 0.33/10 000 of these positive for CPE, which equates to a positivity rate of 0.85%.

The response rate by region can be broken down as follows; 9/22 (40.9%) NE, Yorkshire and Humber, 4/28 (14.3%) responded from NW, 6/25 (24%) responded from Midlands, 6/17 (35.3%) responded from SW and 11/61 (18%) responded from SE (including London). There was a marked difference in the number of screening samples tested per 10 000 pbds (Figure B.1.). The highest level of testing was seen in the North West with 121 samples screened/10 000 pbds, followed by the South East (98/10 000 pbds) and the North East (39/10 000 pbds). The highest number of positive screens/10 000 pbds was also seen in the region that had the highest testing rate, the North West. In contrast however, the second highest positive screen/10 000 pbds rate was seen in the North East, even though the South East had a higher screening rate.

Discussion

There was no consensus between trusts on which patients should be screened or how often to test them. However, trusts were mostly in agreement that patients that had been hospitalised aboard in the last 12 months should be screened for CPE carriage. Trusts were reasonably consistent in their reasons for rescreening, with those patients with a previous CPE positive readmitted to hospital meeting the local criteria for rescreening. In addition, patients with a negative screen were screened up to a maximum of three times per admission.

All laboratories reported that they screened faecal and/or rectal samples, as recommended by UK Standards for Microbiology Investigations (SMI) guidelines [5]. Culture using chromogenic agar (76%) was by far the most popular first-step in trusts' screening policies, although the media type varied. Laboratories were confident that a negative result by this method was a genuine negative and so reported as such. Confirmatory testing was performed for all samples with a positive result by the first-step test, but this confirmatory testing is where most of the heterogeneity in the testing methods was introduced. Although over 50% of laboratories used phenotypic methods there was no consensus on which phenotypic

method to use; possibly due to the variable sensitivity and specificity and difficulty in result interpretation [5].

There were a considerable number of trusts that referred samples/isolates, in particular positive samples, to external laboratories. The ideal algorithm would enable each laboratory to be confident with their in-house testing method and reduce the requirement, not to mention cost and time delays introduced, in referring samples for confirmatory testing. Local testing also increases the impact that results can have on patient management to prevent onwards transmission. Timely reporting of CPE screening enables patients that have been isolated or cohort nursed to be returned to the wards, if they are CPE-negative, as they are not a transmission risk. Conversely, patients with a sample that was positive on screening and that needed to be isolated could have this process expedited due to reduced turnaround times. Collecting data regarding isolation policies was beyond the remit of this work but accurate CPE detection would obviously impact on this area.

There were some limitations to our project. There was a disappointing response rate to the survey with only 34/153 (22%) trusts/laboratories completing both questionnaires. Nevertheless, the data clearly demonstrate the considerable heterogeneity of testing within trusts. The majority of respondents were from the South East but there was representation across England. The surveys should perhaps have included a definition of patient bed days to ensure we received the required data. It is unclear whether respondents were confused about what we were asking for, or if they could not easily access the data

Unbeknown to us at the time, a similar survey was sent to the same hospitals, gathering data on the awareness, uptake and implementation of the Public Health England toolkit for CPE detection, management and control [9]. The authors found CPE prevention and control was influenced by a complex set of factors, which lead to variable implementation of the toolkit across England.

Our study confirms our suspicion that there is marked heterogeneity in CPE screening/testing across England. This highlights the requirement for the development of a diagnostic testing algorithm to ensure uniformity of optimised testing across the UK. In addition, the rate of testing varied widely; which suggest that there is considerable scope for missing cases, in some centres.

Acknowledgements

We thank all the NHS Trusts that completed the surveys.

Conflicts of interest statement

None

Funding source

This work was funded by a major research grant awarded in 2016 by the Healthcare Infection Society

References

[1] Johnson AP, Woodford N. Global spread of antibiotic resistance: the example of New Delhi metallo-beta-lactamase (NDM)-mediated carbapenem resistance. *Journal of Medical Microbiology* 2013; **62**: 499-513.
[2] Lee CR, Lee JH, Park KS, Kim YB, Jeong BC, Lee SH. Global Dissemination of Carbapenemase-Producing Klebsiella pneumoniae: Epidemiology, Genetic Context, Treatment Options, and Detection Methods. *Frontiers In Microbiology* 2016; **7**: 895
[3] PHE. Acute trust toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae. 2014. https://www.gov.uk/government/publications/carbapenemase-producing-enterobacteriaceae-early-detection-management-and-control-toolkit-for-acute-trusts
[4] Vella V, Moore LS, Robotham JV, Davies F, Birgand GJ, Otter JA et al. Isolation demand from carbapenemase-producing Enterobacteriaceae screening strategies based on a West London hospital network. *The Journal of Hospital Infection* 2016.
[5] UK Standards for Microbiology Investigations. Laboratory Detection and Reporting of Bacteria with Carbapenem-Hydrolysing β-lactamases (Carbapenemases). 2014. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/344071/P_8i1.1.pdf
[6] Antonelli A, Arena F, Giani T, Colavecchio OL, Valeva SV, Paule S et al. Performance of the BD MAX instrument with Check-Direct CPE real-time PCR for the detection of carbapenemase genes from rectal swabs, in a setting with endemic dissemination of carbapenemase-producing Enterobacteriaceae. *Diagnostic Microbiology and Infectious Disease* 2016.
[7] Ellington MJ, Findlay J, Hopkins KL, Meunier D, Alavrez-Buylla A, Horner C et al. Multicentre evaluation of a real-time PCR assay to detect genes encoding clinically relevant carbapenemases in cultured bacteria. *International Journal of Antimicrobial Agents* 2016; **47**: 151-4.
[8] Department of Health. Updated guidance on the diagnosis and reporting of *Clostridium difficile*. 2012
[9] Coope CM, Verlander NQ, Schneider A, Hopkins S, Welfare W, Johnson AP et al. An evaluation of a toolkit for the early detection, management and control of carbapenmase-producing Enterobacteriaceae: a cross sectional survey of NHS acute trusts in England. *Journal of Hospital Infection*. 2018, doi: 10.1016/j.jhin.2018.03.007

Figure A. 1.

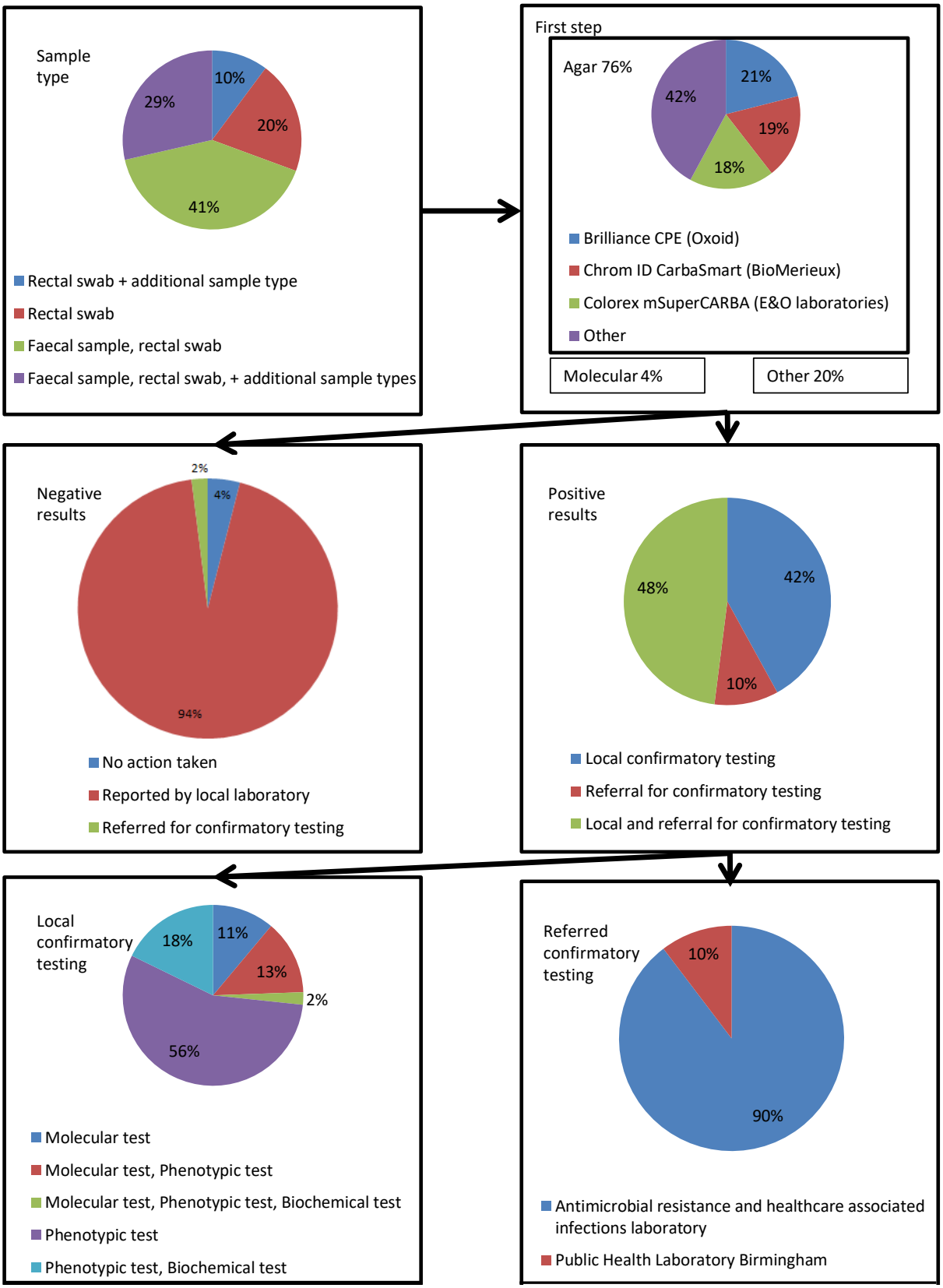
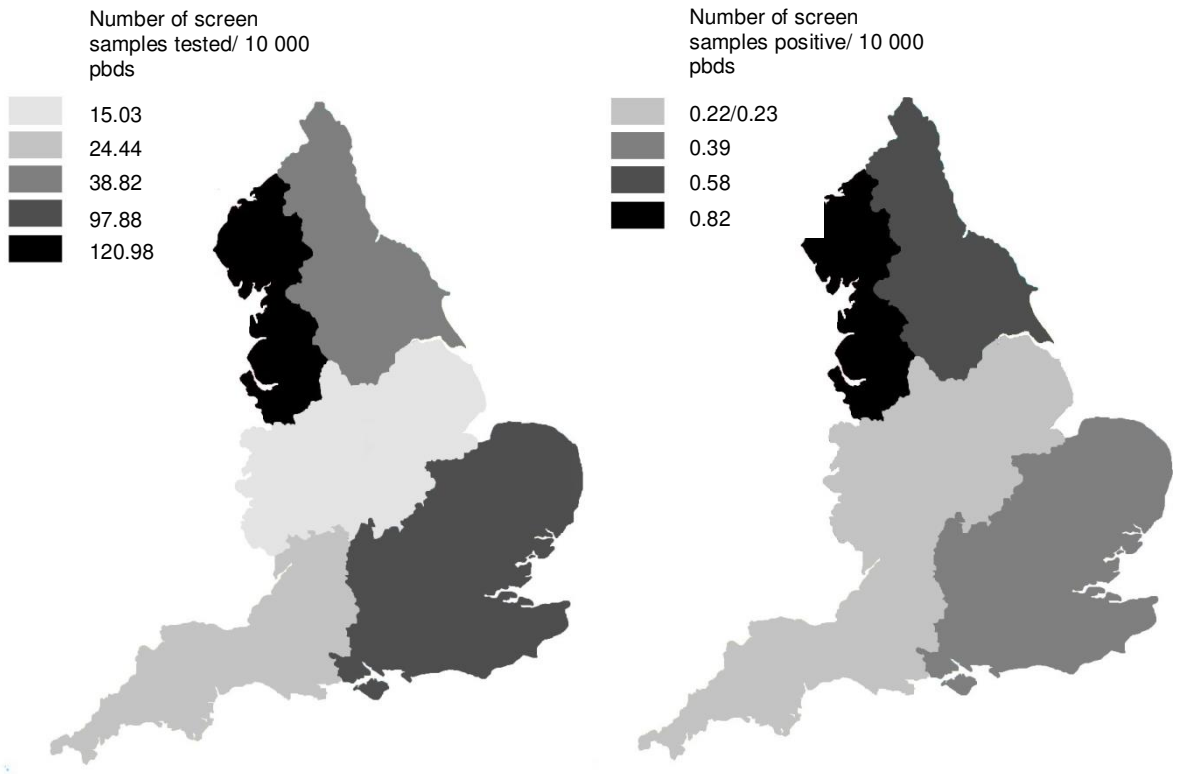

Sample type
10%
20%
41%
29%
Rectal swab + additional sample type
Rectal swab
Faecal sample, rectal swab
Faecal sample, rectal swab, + additional sample types
First step
Agar 76%
21%
19%
18%
42%
Brilliance CPE (Oxoid)
Chrom ID CarbaSmart (BioMerieux)
Colorex mSuperCARBA (E&O laboratories)
Other
Molecular 4%
Other 20%
Negative results
4%
2%
94%
No action taken
Reported by local laboratory
Referred for confirmatory testing
Positive results
42%
10%
48%
Local confirmatory testing
Referral for confirmatory testing
Local and referral for confirmatory testing
Local confirmatory testing
11%
13%
2%
56%
18%
Molecular test
Molecular test, Phenotypic test
Molecular test, Phenotypic test, Biochemical test
Phenotypic test
Phenotypic test, Biochemical test
Referred confirmatory testing
10%
90%
Antimicrobial resistance and healthcare associated infections laboratory
Public Health Laboratory Birmingham

Figure B.1.



Legends

Figure A. 1. Flowchart detailing the wide variety of screening protocols across the UK.

Figure B. 1. Maps showing the number of screen samples tested/10 000 pdbs and number of screen sample positive/10 000 pbds by region