Healthcare Improvement Scotland

evidence note

In response to an inquiry from Health Protection Scotland

Number 62 November 2016

What is the published evidence on the accuracy, turnaround time and cost/ cost effectiveness of tests to identify carbapenemase-producing *Enterobacteriaceae* (CPE) in hospital screening samples obtained from patients identified as at risk of CPE colonisation during clinical risk assessment?

What is an evidence note

Evidence notes are rapid reviews of published secondary clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions. Information is available to the topic referrer within a 6 month period and the process of peer review and final publication of the associated advice is usually complete within 6–12 months. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The reports are subject to peer review. Evidence notes do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produces an Advice Statement to accompany all evidence reviews.

Key points

- Reduced susceptibility or resistance to carbapenem antibiotics, mediated through production of carbapenemases, is a critical public health issue.
- Implementation of screening for carbapenemase-producing *Enterobacteriaceae* (CPE) is recommended in Scotland.
- There is no gold standard method for screening for CPE.
- Evidence on screening methods for CPE is limited in quantity and also in its applicability to NHSScotland.
- No cost-effectiveness evidence was identified. Diagnostic test accuracy, turnaround time and cost will influence the overall cost effectiveness of any infection control programme.
- Based on current evidence of diagnostic accuracy, it is not possible to identify the most effective rectal-swab based screening test to identify patients colonised with CPE.

Definitions

Carbapenemases: enzymes that inactivate carbapenem antibiotics[1].

Carbapenems: a class of broad spectrum antibiotics which includes meropenem, ertapenem and imipenem[1].

Diagnositic test accuracy parameters[2]

Sensitivity	Ability of the test to detect all those with disease in the screened population. This is expressed as the proportion of those with disease correctly identified by a positive screening test result.
Specificity	Ability of the test to identify correctly those free of disease in the screened population. This is expressed as the proportion of those without disease correctly identified by a negative screening test result.
Positive predictive value	The probability of having the disease given a positive screening test result in the screened population. This is expressed as the proportion of those with disease among all screening test positives
Negative predictive value	The probability of not having the disease given a negative screening test result in the screened population. This is expressed as the proportion of those without disease among all screening test negatives.

***Enterobacteriaceae*:** a family of bacteria which are part of the gastrointestinal flora of humans; some are readily transmitted particularly in the healthcare setting[1].

Gram-positive/Gram-negative bacteria: groups of bacteria differentiated on the basis of the chemical and structural make-up of their cell walls as identified by a microbiological staining procedure[3].

Literature search

A systematic search of the secondary literature was carried out between 11–14 April 2016 to identify systematic reviews, health technology assessments and other evidence-based reports. Medline, Medline in process, Embase, Cinahl and Web of Science databases were also searched for systematic reviews and meta-analyses.

The primary literature was systematically searched between 25 May–13 June 2016 using the following databases: Medline, Medline in process, Embase, Cinahl, Web of Science and Cochrane CENTRAL. Results were limited to English language and 2011 onwards.

Key websites were searched for guidelines, policy documents, clinical summaries and economic studies.

Concepts used in all searches included: carbapenemase, *Klebsiella pneumoniae, Enterobacteriaceae*. A full list of resources searched and terms used are available on request.

Introduction

Carbapenems are a class of broad spectrum antibiotics important as last line treatment of healthcare associated infections. They include ertapenem, imipenem, doripenem and meropenem[4]. Carbapenemase-producing organisms (CPO) are Gram-negative bacteria that are resistant to carbapenem antibiotics through acquisition of the genes coding for carbapenemases. CPOs include *Enterobacteriaceae* (CPE). *Klebsiella* species and *Escherichia coli* (*E. coli)* are examples of *Enterobacteriaceae*, normal human gut bacteria, which can become carbapenem-resistant (CRE). Reduced susceptibility or resistance to carbapenems mediated through production of carbapenem-hydrolysing enzymes, carbapenemases, is a critical clinical and public health issue[5].

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) identifies epidemiological susceptibility breakpoints and screening cut-offs for identifying carbapenem resistance *in vitro*[6]. A World Health Organization (WHO) report describes how resistance to this treatment of last resort for life-threatening infections caused by common intestinal bacteria has spread to all regions of the world[7]. In a 2015 European survey examining the threat to patient safety in hospitals in Europe around the occurrence of CPE, 13 out of 38 countries reported inter-regional spread of CPE or described an endemic situation (Greece, Italy, Malta and Turkey). Only three countries had not identified a case of CPE. For the United Kingdom (UK), the report notes that the number of CPE isolates received by the national reference laboratory has increased continuously since 2008[8].

The major carbapenemases of interest for this evidence note are grouped into three classes based on their molecular structure as outlined in Table 1. Although outside the scope of this evidence note, other enzymes such as extended spectrum beta lactamases (ESBL) and AmpC beta lactamases are associated with reduced susceptibility to carbapenems as a result of altered bacterial cell membrane permeability.

Table 1 Major carbapenemase enzymes

Molecular class	Enzyme group
A	KPCs (*Klebsiella pneumoniae* carbapenemases)
B (metallo-beta-lactamases MBL)	NDMs (New Delhi metallo-beta-lactamases) VIMs (Verona integron-encoded metallo-beta-lactamases) IMPs (IMP-type metallo-beta-lactamases)
D	OXA-48-like (Carbapenem-hydrolysing oxacillinase-48 like enzymes)

In August 2013, a letter from the Chief Medical Officer, Chief Nursing Officer and Chief Pharmaceutical Officer to NHS boards in Scotland set out the threat posed by this issue, the increasing instances of CPE detection in Scotland and the principles for combating the threat. In addition to early detection and prudent prescribing, the requirement for the

implementation of screening and infection control measures was detailed (www.sehd.scot.nhs.uk/cmo/CMO(2013)14.pdf). To date, the use of screening to identify asymptomatic carriers is thought to be variable across Scotland with many of the NHS boards screening only on an *ad hoc* basis. It is estimated that compliance with Scottish screening recommendations would result in 24,000 patients being screened each year[9]. Patient and staff acceptability associated with collecting rectal swab samples is considered to be a significant barrier to the screening programme[9]. Work is ongoing through the Scottish Infection Research Network to examine staff and patient acceptability around CPE screening and to investigate the barriers and drivers at management and ward level (www.gcu.ac.uk/newsroom/news article/?id=116940).

Public Health England (PHE) has established an enhanced surveillance system for carbapenemase-producing Gram-negative bacteria, which collects a core and enhanced data set via a web-based electronic reporting system (https://cro.phe.nhs.uk/). A similar system is under development in Scotland using an informatics/data linkage based approach with supplementary enhanced data collection via the local teams.

This evidence note examines laboratory methods for screening for CPE in rectal swabs or faecal specimens obtained from patients at risk of colonisation with CPE. It focuses on resistance mechanisms linked to the five major target enzyme groups described in Table 1. Outcomes are diagnostic test accuracy (sensitivity, specificity, positive predictive value, negative predictive value), cost/cost effectiveness and laboratory process outcomes (turnaround time and hands on time).

Technologies examined are restricted to those which claim to identify each of the 'big 5' carbapenemases (KPC, NDM, VIM, IMP and OXA-48 like enzymes).

Epidemiology

It is not possible to determine the prevalence of CPE colonisation in Scotland given the very limited screening activity currently ongoing. Although total numbers remain low, there has been a growing trend in Scottish CPO reports since surveillance began, which may be partly the result of improved awareness of CPOs and the introduction of CPE screening in Scotland[10]. In 2014, there were 41 CPEs confirmed in samples submitted from Scotland to Public Health England's Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit at Colindale. The enzymes were IMP (2), KPC (4), NDM (12), OXA-48 (10) and VIM (13). Six species were involved: *Citrobacter freundii, Enterobacter cloacae complex, Escherichia coli, Klebsiella pneumoniae, Providencia rettgeri* and *Proteus mirabilis*. Of 63 CPOs identified in 2015, 56 were CPE[10].

Health technology description

Three strategies for identifying the presence of CPE in screening samples or bacterial isolates derived from screening samples are addressed in this evidence note.

1. Phenotypic culture methods.
   These methods identify CPE through observation of patterns of bacterial growth on or in selective media which incorporate various combinations of carbapenems, specific enzyme inhibitors and colorimetric indicators[11].

   Chromogenic media may be used directly with rectal swab samples and aim to provide presumptive species identification of CPE through colorimetric identification of the most frequently isolated CPE. Agents are included which inhibit the growth of Gram-positive bacteria and non-carbapenemase producers and antibiotics are included to favour the growth of CPE. The growth of CRE that are not CPE may be supported so further testing is warranted to confirm CPE. It is likely that some media are optimised for KPC producers and may have decreased sensitivity for mechanisms based on other enzymes, particularly OXA-48 like which have weaker hydrolysis activity[12,13].

   Combination disc tests identify carbapenemase type(s) present through assessment of growth response/zone of inhibition around discs impregnated with specific enzyme inhibitors[13]. These tests are generally applied to bacterial isolates and so require a culture step. However, there is at least one study in the literature where the test has been applied directly to a suspension from a rectal swab sample[14].

2. Phenotypic biochemical methods.
   These assays identify the presence of CPE through colorimetric identification of the products of the hydrolytic action of carbapenemases on a substrate. The focus on generic carbapenemase activity means that these tests encompass both known and unknown carbapenemases but, as they require an isolation or enrichment step, are not used directly on rectal swab samples[12].
3. Genotypic methods.
   The presence of the genes coding for the beta-lactamase (bla) enzymes can be ascertained by genotypic methods such as polymerase chain reaction (PCR) assays. Some methods can be applied to rectal swab samples without a culture step. The major limitation of genotypic methods is that they can only identify genes already known and characterised, and covered by the assay chosen. Novel genes, or newly emergent variants of previously characterised genes, may not be reliably detected[12]. Also, if undertaken on a rectal swab sample, such methods give no microbiological information on the species of CPE.

Technologies may be combined to provide one, two or three step processes for screening and confirmation of CPE presence. Table 2 outlines the step testing flow in line with current practice. Although there are examples which differ from these pathways, for example use of combined disc testing directly on rectal swab screening samples, these would require further careful assessment by medical microbiology departments (M Lockhart, Consultant Microbiologist, Health Protection Scotland. Personal Communication, 1 September 2016). The number of steps undertaken will determine the reporting time and the overall costs. The health technologies selected for inclusion in this evidence note by representatives of Health Protection Scotland in collaboration with the Scottish Microbiology and Virology Network (SMVN) are listed in Table 3. Table 4 summarises information on turnaround time and costs of consumables. Information is extrapolated from a previous report by the SMVN[9].

Table 2 Combining technologies for detection of CPE in rectal swab samples

Step	Option 1	Option 2	Option 3	Option 4	Option 5
1	Genetic identification of carbapenemase genes present direct from sample using PCR*	Culture of samples on MacConkey agar + carbapenem disc or commercial chromogenic medium to presumptively identify CPE			
2	Not required	Confirmation of CPE in bacterial culture obtained from Step 1 by genetic identification of carbapenemase genes present using PCR method	Combination disc testing to confirm presence of a CPE	If compatible chromogenic medium used in Step 1, specific biochemical hydrolysis test to confirm generic carbapenemase activity	Sub culture onto non-selective agar
3	Not required	Not required	Not required	Not required	Biochemical hydrolysis tests to confirm generic carbapenemase activity

*Culture also necessary if further information on isolates required[12].

Table 3 Health technologies included in evidence note

Phenotypic	
MacConkey agar + carbapenem disc	Non commercial European Committee on Antimicrobial Susceptibility Testing (EUCAST) screening cut offs recommended[6].
Chromogenic media	
chromID™ CARBA SMART	www.biomerieux-diagnostics.com/chromid-carba-smart CE marked product
Colorex™ mSuperCARBA™	www.eolabs.com/colorex-msuper-carba-pp3095.html CE marked product
Brilliance™ CRE Agar	www.oxoid.com/UK/blue/prod_detail/prod_detail.asp?pr=PO1226 CE marked product
Brilliance™ CRE /ESBL biplate	www.oxoid.com/UK/blue/prod_detail/prod_detail.asp?pr=PO1226 CE marked product
Combined disc tests	
MASTDISCS™ID D70C + TEM30C	www.mastgrp.com CE marked product
Confirm kit™ 98015	www.rosco.dk/gfx/pdf/KITS(1).pdf CE marked product
Biochemical	
RAPIDEC® CARBA NP	www.biomerieux-diagnostics.com/rapidec-carba-np CE marked product
Rosco Rapid CARB Screen Kit 98024	www.rosco.dk/?id=14&c=Detection-of-resistance-mechanisms CE marked product
Genotypic	
In-house PCR	Non commercial (Colindale validated method)
Xpert® Carba-R	www.cepheid.com/en/cepheid-solutions-uk/clinical-ivd-tests/healthcare-associated-infections/xpert-carbar CE marked product
Check-MDR CT103XL	www.check-points.eu/products/check-direct-cpe.html CE marked product
Check-MDR Carba	www.check-points.eu/products/check-mdr-carba.html CE marked product

Table 4 Time and cost estimates (consumables) for the technologies included in evidence note

	Approximate time to confirmed result	Estimated cost per sample
Phenotypic		
Agar-based methods	48-72 hours	£2.00-£3.00
Biochemical methods	Minimum ~25 hours	£11.00-£13.00
Genotypic		
Commercial PCR-based methods	1-4 hours	£20.00-£30.00

Clinical effectiveness

Study selection

No systematic reviews were identified.

Studies evaluating the performance of the technologies as applied to rectal swab or stool specimens in a routine microbiology laboratory setting are the most relevant to this evidence note. Validation studies which evaluate the technologies using collections of pre-characterised bacterial isolates either originating directly from clinical specimens or having been modified in the laboratory to express certain characteristics have been excluded[12].

There is no gold standard for diagnostic test accuracy studies for identification of patients colonised with CPE using hospital admission screening samples. Studies were excluded if they did not describe both the test method and the reference standard employed.

Where a range of outcomes are available, test performance data relating to identification of patients colonised with CPE is reported.

PHENOTYPIC (culture) METHODS

MacConkey agar plus carbapenem disc

Table 5 describes three studies which provided screening test accuracy data for MacConkey selective agar plus carbapenem disc(s) as applied to rectal swab samples. All were at risk of incorporation bias since the result of the index test formed part of the reference standard. One study from Israel reported sensitivity of 75.8% and specificity of 89.6% for detection of KPC producing *Enterobacteriaceae* with MacConkey agar plates with imipenem, meropenem and ertapenem 10 microgram discs[15]. The authors noted that, in their hospital, the bla $_{KPC}$ - expressing *Klebsiella pneumoniae* strain dominant at the time of their study had a high level of resistance to carbapenems. A second study, conducted in Greece, reported sensitivity of 96.9% and specificity of 98.9% for MacConkey agar plate with two 10 microgram ertapenem discs in identifying CPE expressing any of the main five carbapenemases[14]. KPC producers predominated and there were no IMP producers identified. Another study from Greece, identified at peer review, assessed the performance of MacConkey plates with ertapenem discs or imipenem discs in identifying carbapenemase-producing *Klebsiella pneumonia*[16]. For both tests, sensitivity was low (81.8% for ertapenem and 67.2% for imipenem).

Chromogenic media

No studies were identified which assessed the accuracy of Colorex™ mSuperCARBA™ or *Brilliance*™ CRE ESBL biplate for identification of CPE in rectal swab screening samples.

Seven studies were identified as outlined in Table 6. All were at risk of incorporation bias since the result of the index test formed part of the reference standard. Two studies compared chromID™CARBA and *Brilliance*™ CRE. In a Belgian study, with predominance of OXA-48 producers, the sensitivity of both media for identification of patients colonised with a CPE was low (33.3% and 66.7% respectively). The study authors note that OXA 48-like carbapenemases weakly hydrolyse carbapenems and may, therefore, be difficult to detect in screening cultures[17]. A Pakistani study focusing on detection of NDM-1 found that chromID™CARBA had sensitivity of 100% and specificity of 98%, whilst for *Brilliance*™ CRE both measures were poor at 59% and 34% respectively[18]. The study authors suggest that this could be due to storage conditions during transit. A study conducted in the context of Belgian long term care reported that, in this low CPE prevalence clinical context (0.39%), sensitivity of chromID™CARBA could not be defined since only one CPE strain was isolated. Specificity was 99.2% at 24 hours[19]. A study of chromID™CARBA conducted in Greece reported sensitivity of 96.5% and specificity of 91.2% for detection of CPE harbouring bla $_{KPC}$ or bla $_{VIM}$[11]. An evaluation from Turkey found chromID™CARBA delivered sensitivity of 57.6% and specificity of 99.3% for detection of patients with CPE colonisation with OXA-48 producers[20]. Where data were combined with chromID™OXA-48 as would be achieved by the biplate - chromID™CARBA SMART - sensitivity was increased in this clinical setting to 90.9% with specificity slightly reduced at 98.5%. An evaluation from Morocco reported the sensitivity and specificity of *Brilliance*™ CRE for the detection of bla $_{KPC}$, bla $_{OXA-48}$, bla $_{VIM/NDM}$ to be 80.0% and 86.6%[21]. In the study, 10 CPE were identified, all of which produced OXA-48. A study from Greece identified at peer review assessed the performance of *Brilliance*™ CRE in identifying

carbapenemase-producing *Klebsiella pneumonia*[16].Focusing on this particular species the sensitivity was 96.8% and specificity was 90.9%.

Combined disc tests

No studies were identified which examined the sensitivity and specificity of the MASTDISCS™ID D70C + TEM30C or the ROSCO Confirm kit™ 98015 for CPE detection in isolates originating from rectal swab screening samples.

One study evaluated the Mast discs combi-70C using 140 isolates from clinical samples, including urine, blood and sputum reported as 'potential carbapenemase producers'[22]. Previously characterised non-carbapenemase producing isolates (n=45) were included as controls. When compared with results from the Xpert CARBA-R molecular assay, sensitivity and specificity were both 100%. The applicability of this study to screening of rectal swab samples is uncertain. A study from Greece used a combined disc assay applied directly to rectal swabs within a screening context and reported sensitivity of 94.8% and specificity of 100% - see Table 7[14].

BIOCHEMICAL METHODS

No studies were identified which examined the sensitivity and specificity of the RAPIDEC® CARBA NP test for CPE detection from rectal swab screening samples. Table 8 outlines studies examining the Rapid CARB Screen Kit.

A Belgian study evaluated the performance of the Rapid CARB Screen Kit applied to 135 consecutive *Enterobacteriaceae* clinical isolates referred to the national reference laboratory for suspected carbapenemase production[23]. In the setting of OXA-48 predominance, the PPV was 81% and the NPV 95%. In 16 cases (9%), the result was uninterpretable. When combined with 100 pre-characterised isolates, the sensitivity was 98% and specificity was 83%. The version of the test used was not specified in the study report.

Another study from Belgium evaluated the Rapid CARB Screen Kit on 92 suspected CPE strains collected from a University Hospital between 2009 and 2014. The sensitivity and specificity was 73.3% and 100%[24]. Sensitivity increased to 86.7% when colour changes from red to orange (as opposed to yellow) were considered positive.

A narrative review noted issues around uninterpretable results and the potential for growth media to affect the performance of colorimetric assays to identify carbapenemase activity[12]. This has implications for the selection of appropriate growth media when combining methods.

GENOTYPIC METHODS

No studies were identified which assessed the accuracy of Check-MDR Carba or Check-MDR CT103XL in relation to CPE in screening samples.

A National Institute for Health and Care Excellence (NICE) medtech innovation briefing[25] identified two studies on the current version of the Xpert® Carba-R for identification of people carrying carbapenemase-producing organisms[26,27]. One of the studies was conducted using a collection of pre-characterised isolates with defined resistance mechanisms[27]. The other study screened 26 faecal specimens but was very poorly reported, and sensitivity and specificity for these tests was not provided[26]. A multi-site evaluation of the Xpert® Carba-R for use with rectal swab samples published since the NICE briefing is outlined in Table 9[28]. Although this was a well-conducted study, importantly for the present analysis, it did not separate out data for *Enterobacteriaceae* but provided data for all CPO. Results were not provided separately for the screening samples and the contrived specimens. Overall sensitivity and specificity for detection of the five carbapenemase genes directly from rectal swabs was 96.6% and 98.6% respectively. Data for each of the bla genes is in Table 9.

One study was identified which assessed the accuracy of an in-house multiplex PCR-based assay for the surveillance of hospitalised patients at risk of colonisation with CPE[29]. Sensitivity and specificity were high (100% and 89.9% respectively). Negative predictive value was 100% but given the low prevalence of patients colonised with CPE (1.99%) PPV was only 16.6%- see Table 9.

Safety

No safety outcomes related to the use of the technologies examined were identified.

Cost effectiveness

No cost-effectiveness studies were identified. An understanding of the difference in consumables and labour costs for the various screening and confirmation tests and the cost implications of positive and negative results is essential to selecting the most appropriate technologies[30]. The overall costs of an infection control programme will be influenced by both test accuracy and turnaround time. The rapid availability of results from genotypic methods may limit unnecessary prolonged isolation of newly admitted patients[12].

Discussion

For phenotypic methods, the test performance in individual studies was related to the prevalence of each carbapenemase in the clinical context investigated. This varied widely with a predominance of either OXA-48, KPC or NDM. This, in turn, influenced the reference standards selected making it difficult to compare diagnostic test accuracy data between studies. The relevance of the population group in one study (long term care) is unclear. One study focused only on a single species. Only two relevant studies on biochemical methods were identified. Both highlighted issues around interpretation of test results. The larger of the two genotypic method studies was multi-centre, with the UK being one of three locations. The authors used contrived specimens to ensure balance of enzyme groups. Although sensitivity (93.5% to 100%) and specificity (99.3% to 100%) were high, the results for CPE were not presented separately from CPO overall. Although no cost-effectiveness evidence was identified, turnaround times are shorter for the more expensive genotypic methods when compared to less expensive phenotypic methods where a greater number of processing steps are generally required.

Conclusion

There is insufficient evidence to compare the accuracy of screening tests performed on rectal swabs. For more than half of the technologies examined in this evidence note, there were no studies identified. For each of the other technologies, there were only a few studies and, although many reported good sensitivity and specificity results, the applicability of the findings was limited by the very specific clinical contexts in which they were undertaken.

A narrative review on the current status of surveillance methods lists considerations for implementing a screening programme[12]. These include epidemiology of CPO in the community in terms of the prevalence of each carbapenemase, the current clinical microbiology laboratory capabilities, the ability to identify high risk patient groups and the availability and cost of isolation beds. The review notes that, whatever modality is chosen for screening, local validation will be required.

Identified research gaps

There is a need for large scale prospective multi-centre studies comparing the diagnostic accuracy, clinical utility and cost-effectiveness of technologies used to screen people for CPE carriage.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence notes has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

About evidence notes

This evidence note will be considered for review 2 years post-publication, and at 2-yearly intervals thereafter. For further information about the evidence note process see http://www.healthcareimprovementscotland.org/our_work/clinical__cost_effectiveness/shtg/standard_operating_procedures.aspx

To propose a topic for an evidence note, email evidencenotes.HCIS@nhs.net

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network http://www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

Table 5 Diagnostic accuracy studies – MacConkey agar plus carbapenem disc

Study	Samples/Population/ Clinical context	Test(s)	Reference standard	Results
Adler (2011)[15] Israel 2008-2009	139 rectal swabs from known CRE carriers and their contacts at tertiary hospital 33/139 (24%) samples bla $_{KPC}$ Main organisms: *Klebsiella pneumoniae* *Klebsiella oxytoca* *Enterobacter aerogenes*	MacConkey agar plates with imipenem, meropenem and ertapenem 10 microgram discs	PCR for bla $_{KPC}$ True positive defined as growth with phenotypic features compatible with CRE diagnosed as CPE by confirmatory testing	For detection of CRE harbouring bla $_{KPC}$ Sensitivity 75.8% Specificity 89.6% PPV 69.5% NPV 92.2%
Pournaras (2013)[14] Greece 2010	189 rectal swabs from 165 patients included in CPE screening programme for patients at high risk at tertiary hospital 97/189 (51.3%) swabs CPE positive 60 KPC 9 VIM 25 KPC and VIM 3 OXA-48 Main organisms: *Klebsiella pneumoniae* *Escherichia coli*	MacConkey plate with two 10 microgram ertapenem disks (MacERT)	PCR for carbapenemase genes (bla $_{KPC, OXA-48}$ $_{VIM, NDM}$ and $_{IMP}$) on presumptive positive screening	For detection of CPE positive swabs harbouring bla $_{KPC, OXA-48,}$ $_{VIM, NDM}$ and $_{IMP}$) Sensitivity 96.9% 95% CI (90.5-99.1) Specificity 98.9% 95% CI (93.2-99.9) PPV 98.9% 95% CI (93.4-99.9) NPV 96.8% 95% CI (90.2-99.1)
Papadimitriou-Olivgeris[16] (2016) Greece 2009-2011	912 rectal swabs from university hospital intensive care unit (swabs taken on admission and weekly during hospitalisation) 329 carbapenemase producing *Klebsiella* pneumonia were present in the 912 swabs (prevalence within study population not provided)	MacConkey plate with two 10 microgram ertapenem discs (MC-Er) Or two 10 microgram imipenem discs (MC-Im)	PCR for identification of bla $_{KPC}$ or bla $_{VIM}$ True positive samples were *Klebsiella pneumoniae* isolated from one of four culture methods then confirmed as carrying a carbapenemase encoding gene by PCR	For detection of carbapenemase-producing *Klebsiella pneumonia* MC-Er Sensitivity 81.8% Specificity 97.9% PPV 95.7% NPV 90.5% MC-Im Sensitivity 67.2% Specificity 98.1% PPV 95.3% NPV 84.1%

Table 6 Diagnostic accuracy studies – Chromogenic media

Study	Samples/Population/ Clinical context	Test(s)	Reference standard	Results/ Notes from study authors
Heinrichs (2016)[17] Belgium 2012-2013	730 rectal swabs from 480 patients in tertiary hospital Intensive care Haematology High risk admissions Low prevalence of CPE (<2%) Predominance of OXA-48-like producers 17 OXA-48-like (12 samples/8 patients) 2 VIM (2 samples, 1 patient) Main organisms: *Citrobacter freundii* *Escherichia coli* *Klebsiella pneumoniae*	chromID™CARBA *Brilliance*™ CRE	Multiplex PCR for bla $_{KPC, OXA-48 VIM, NDM}$ and $_{IMP)}$ and RAPIDEC® CARBA NP True positive defined as typical colonies confirmed as CPE by PCR and RAPIDEC® CARBA NP	chromID™CARBA Identification of patients with CPE 24 hours Sensitivity 33.3% Specificity 99.8% 48 hours Sensitivity 33.3% Specificity 98.9% After overnight enrichment Sensitivity 55.6% Specificity 97.9% *Brilliance* ™ CRE Identification of patients with CPE 24 hours Sensitivity 66.7% Specificity 96.4% 48 hours Sensitivity 66.7% Specificity 94.7% After overnight enrichment Sensitivity 100% Specificity 92.6%
				chromID™CARBA and *Brilliance*™ CRE do not show enough sensitivity to detect OXA-48-like CPE in rectal swabs. Combining with media specific to detection of OXA-48-like CPE should be considered. In the study overnight enrichment increased systematically (but not statistically significantly) the sensitivity of both media but extended final reporting time by an additional 24 hours.

Study	Samples/Population/ Clinical context	Test(s)	Reference standard	Results/ Notes from study authors
Day (2013)[18] Pakistan 2011	175 stools samples from distinct patients (143 randomly selected inpatients and 32 outpatients – military hospital) 32/175 (18.3%) patients colonised with CPE 37 NDM-1 producers Main organisms *Klebsiella pneumoniae* *Escherichia coli* *Enterobacter cloacae*	chromID™CARBA *Brilliance*™ CRE	PCR for bla $_{NDM-1}$ applied to all isolates showing phenotypic evidence of carbapenemase production	Where only coloured colonies considered presumptive: chromID™CARBA For identification of CPE expressing bla $_{NDM-1}$ Sensitivity 100% Specificity 98% PPV 91% *Brilliance*™ CRE For identification of CPE expressing bla $_{NDM-1}$ Sensitivity 59% Specificity 34% PPV 16%
				Poor performance of *Brilliance*™ CRE could have been due to suboptimal storage conditions during transport to Pakistan. Alternatively the high frequency of *Enterobacteriaceae* with other enzyme activity may have proved too strong a challenge for the selective ability of the test.
Saegeman (2015)[19] Belgium 2013-2014	261 rectal swabs from residents at three nursing homes and one rehabilitation centre CPE prevalence 0.39% Main organism: *Klebsiella pneumoniae*	chromID™CARBA	Check-Direct CPE (bla $_{KPC, OXA-48, VIM, NDM}$) True positive samples were those yielding presumptive colonies on any six culture methods then confirmed by Check-Direct CPE	Sensitivity could not be calculated since only one CPE strain isolated For detection of CPE harbouring bla $_{KPC, OXA 48, VIM, NDM}$ Specificity 24 h 99.2%, 95% CI (98.1 to 100) 48 h 98.0% 95% CI (96.3 to 99.7) n= 257 (four samples had no growth on agar – presumed due to incorrect swab procedure)
				The one asymptomatic CPE carrier was not identified by chromID™CARBA. Colour codes mentioned in the commercial insert were not always concordant.

Study	Samples/Population/ Clinical context	Test(s)	Reference standard	Results/ Notes from study authors
Papadimitriou-Olivgeris (2014)[11] Greece 2011-2012	177 rectal swabs from university hospital intensive care unit (swabs taken on admission and every 5-7 days during hospitalisation) 86/177 (48.6%) of swab samples were CPE positive (prevalence within study population not provided) 88 KPC 1 VIM Main organisms: *Klebsiella pneumoniae* *Escherichia coli*	chromID™CARBA	Real time PCR for identification of bla $_{KPC}$ or bla $_{VIM}$ True positive samples were those isolated from one of three culture methods then confirmed as carrying a carbapenemase encoding gene by PCR	For detection of CPE harbouring bla $_{KPC}$ or bla $_{VIM}$ Sensitivity 96.5% Specificity 91.2% PPV 91.2% NPV 96.8%
				A considerable number of *Acinetobacter* species and *Pseudomonas* species were identified. Also 20 Gram positive bacterial isolates were identified on chromID™CARBA.
Zarakolu (2015)[20] Turkey 2013	302 rectal swabs from hospitalised patients 11% prevalence of CPE colonisation 33 OXA-48 Main organism: *Klebsiella pneumoniae*	chromID™CARBA chromID™CARBA plus chromID™ OXA-48 (equivalent to chromID™CARBA SMART)	Rosco confirm kit (KPC, MBL and OXA- 48) PCR for bla $_{KPC, OXA-48 VIM, NDM}$ and $_{IMP}$) applied to presumptive colonies	For detection of patients with CPE colonisation chromID™CARBA Sensitivity 57.6% Specificity 99.3% PPV 86.4 NPV 95% chromID™CARBA plus chromID™ OXA-48 Sensitivity 90.9% Specificity 98.5% PPV 88.2% NPV 98.9%
				chromID™CARBA SMART is commercial product combining chromID™CARBA plus chromID™ OXA-48.

Study	Samples/Population/ Clinical context	Test(s)	Reference standard	Results/ Notes from study authors
Girlich (2014)[21] Morocco 2012	77 rectal swabs from distinct hospitalised patients Prevalence with carbapenemase producing organisms in rectal swabs(13%) 10/77 10 OXA-48 Main organisms: *Klebsiella pneumoniae* *Escherichia coli*	*Brilliance*™ CRE	PCR assay and sequencing for carbapenemase genes (bla $_{KPC, OXA-48 VIM, NDM}$ and $_{IMP}$) applied to presumptive colonies	*Brilliance*™ CRE For detection of CPE harbouring bla $_{KPC}$, bla $_{OXA-48}$, bla $_{VIM/NDM}$ Sensitivity 80.0% Specificity 86.6% Sensitivity following enrichment 100% Specificity when non-fermenting bacteria included 71.6% Although enrichment step is time consuming it could be recommended for detection of carbapenemase producers in hospitals where OXA-48 may be endemic.
Papadimitriou-Olivgeris[16] (2016) Greece 2009-2011	513 rectal swabs from university hospital intensive care unit (swabs taken on admission and weekly during hospitalisation) 95 carbapenemase producing *Klebsiella* pneumonia were present in the 513 swabs (prevalence within study population not provided)	*Brilliance*™ CRE	PCR for identification of bla $_{KPC}$ or bla $_{VIM}$ True positive samples were *Klebsiella pneumoniae* isolated from one of four culture methods then confirmed as carrying a carbapenemase encoding gene by PCR	For detection of carbapenemase-producing *Klebsiella pneumonia* Sensitivity 96.8% Specificity 90.9% PPV 70.8% NPV 99.2%

Table 7 Diagnostic accuracy studies – Combined disc tests

Study	Samples/Population/ Clinical context	Test(s)	Reference standard	Results/ Notes from study authors
Pournaras (2013)[14] Greece 2010	189 rectal swabs from 165 patients included in CPE screening programme for patients at high risk at tertiary hospital 97/189 (51.3%) swabs CPE positive 60 KPC 9 VIM 25 KPC and VIM 3 OXA-48 Main organisms: *Klebsiella pneumoniae* *Escherichia coli*	MacConkey plate with 4 discs 10 microgram meropenem 10 microgram meropenem plus PBA 10 microgram meropenem plus EDTA 10 microgram meropenem plus PBA and EDTA	PCR for carbapenemase genes (bla $_{KPC, OXA-48}$ $_{VIM, NDM}$ and $_{IMP}$) on presumptive positive screening	For detection of CPE positive swabs harbouring bla $_{KPC, OXA-48, VIM, NDM}$ and $_{IMP}$) Sensitivity 94.8% 95% CI (87.8 to 98.0) Specificity 100% 95% CI (95 to 100) PPV 100% 95% CI (95 to 100) NPV 94.8% 95% CI (87.8 to 98.0)
				Only lactose fermenting colonies were followed up.

Table 8 Diagnostic accuracy studies – Biochemical methods

Study	Samples/Population/ Clinical context	Test(s)	Reference standard	Results
Huang (2014)[23] Belgium 2013	135 consecutive clinical isolates referred to the Belgian reference centre for suspected carbapenemase production CPE prevalence 53% across clinical isolates (72/135) OXA-48 predominant carbapenemase (59/72)	Rapid CARB Screen Kit (version information not provided)	In-house multiplex PCR for carbapenemase genes (bla $_{KPC, OXA-48}$ $_{VIM, NDM}$ and $_{IMP}$)	Excluding uninterpretable results Based on 135 consecutive clinical isolates PPV 81% NPV 95% Based on 135 consecutive clinical isolates plus 100 pre-characterised isolates For detection of carbapenemase production Sensitivity 98% Specificity 83% 9% (16/135) uninterpretable results
Yusuf (2014)[24] Belgium 2009-2014	92 suspected CPE collected at University Hospital CPE prevalence 49% (45/92) KPC predominated Main organism: *Klebsiella pneumoniae*	Rapid CARB Screen Kit 98021 on strains recovered from Mueller-Hinton agar plates	Multiplex PCR for PCR for carbapenemase genes (bla $_{KPC, OXA-48}$ $_{VIM, NDM}$ and $_{IMP}$)	Rapid CARB Screen Kit based on colour change from red to yellow Sensitivity 73.3% Specificity 100% PPV 84.6% NPV 88.7% Rapid CARB Screen Kit based on colour change from red to orange Sensitivity 86.7%

Table 9 Diagnostic accuracy studies – Genotypic methods

Study	Samples/Population/ Clinical context	Test(s)	Reference standard	Results/ Notes from study authors
Tato (2016)[28] USA UK Spain 2013-2014	383 prospectively recovered double rectal swab sets plus 250 contrived specimens 23.5% of the samples (n=633) were PCR positive for CPO	Xpert® Carba-R for detection of CPO	Culture plus bidirectional DNA sequence analysis for identification of bla $_{KPC,}$ $_{OXA-48}$ $_{VIM,}$ $_{NDM}$ and $_{IMP}$ conducted at blinded independent laboratory using primers which were different from Xpert® Carba-R	For combined clinical and contrived specimens Target gene **IMP-1** Sensitivity 96.3% 95% CI (81.0 to 99.9) Specificity 100% 95% CI (99.4 to 100) PPV 100% NPV 99.8% **VIM** Sensitivity 93.5% 95% CI (78.6 to 99.2) Specificity 99.8% 95% CI (99.1 to 100) PPV 96.7% NPV 99.7% **NDM** Sensitivity 100% 95% CI (86.8 to 100) Specificity 99.8% 95% CI (99.1 to 100) PPV 96.3% NPV 100% **KPC** Sensitivity 96.7% 95% CI (82.8 to 99.9) Specificity 99.3% 95% CI (98.3 to 99.8) PPV 87.9% NPV 99.8% **OXA-48** Sensitivity 95.0% 95% CI (83.1 to 99.4) Specificity 99.8% 95% CI (99.1 to 100) PPV 97.4% NPV 99.7%
				Assay has ability to detect multiple resistance genes in organisms which may not be detected by culture methods.

Study	Samples/Population/ Clinical context	Test(s)	Reference standard	Results/ Notes from study authors
Lowman (2014)[29] South Africa 2013	251 consecutive rectal swabs from hospital patients at risk of CPE colonisation VIM predominant (no KPC gene in any sample) Screening positivity rate (CPE and/or CPO) 12%	In house multiplex PCR for bla $_{KPC, OXA-48, VIM, NDM}$ and $_{IMP}$ Nuclisens Easymag instrument to isolate nucleic acid then PCR on LightCycler instrument	Modified Centres for Disease Control (CDC) protocol for detection of carbapenemase producing *Kelbsiella* and *Escherichia coli*	For detection of CPE Sensitivity 100% Specificity 89.8% PPV 16.6% NPV 100%
				PCR does not provide information on bacterial load or species and has potential to identify low levels of colonisation with CPE which may not be clinically relevant in terms of potential for horizontal transmission. High proportion of carbapenemase-producing non-fermenters in sample. In this study population,low PPV most likely linked to screening criteria which are too broad.

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