NICE advice

# Xpert Carba-R to identify people carrying carbapenemase-producing organisms

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## Summary

Xpert Carba-R is a qualitative in vitro diagnostic test that detects organisms that have carbapenemase genes and differentiates between the 5 most prevalent carbapenemase gene families. Three diagnostic accuracy studies were identified involving a total of 990 clinical bacterial isolates and faecal samples. One study reported an overall test sensitivity of 94%. Reported test results for individual carbapenemase genes ranged from 71% to 100% for sensitivity, 77% to 99% for specificity and 81% to 93% for positive predictive values. Negative predictive values were only reported in 2 studies, but both reported a value of 100%. The Xpert Carba-R test must be run on the GeneXpert molecular diagnostic system, which costs between £18,077 and £121,308 depending on the module configuration, excluding VAT. Each single-test Xpert Carba-R cartridge costs £30, excluding VAT.

| Product summary and likely place in therapy | Accuracy and effectiveness |
| --- | --- |
| • The Xpert Carba-R test is a qualitative in vitro diagnostic test used to detect colonisation with carbapenemase-producing organisms. It detects and differentiates the 5 most prevalent carbapenemase gene families: KPC, NDM, VIM, IMP-1 and OXA-48 (including the OXA-181 and OXA-232 variants of OXA-48).<br>• The Xpert Carba-R test would be used in place of standard culture-based tests and as an adjunct to supplementary and confirmatory tests such as antimicrobial resistance testing. This would guide local infection control protocols for preventing transmission to other susceptible people. | • The published evidence summarised in this briefing comes from 3 studies including a total of 990 clinical bacterial isolates and faecal samples.<br>• One diagnostic accuracy study used a panel of 450 clinical bacterial isolates to compare the sensitivities of 3 commercial assays. The sensitivity of Xpert Carba-R for each carbapenemase gene ranged from 71% to 100%. The overall test sensitivity was reported as 94%.<br>• One diagnostic accuracy study used 394 rectal, peri-rectal and stool samples to determine the performance characteristics of Xpert MDRO, an earlier version of Xpert Carba-R. The negative predictive values and sensitivities for Verona integron-encoded metallo-beta-lactamase (VIM) and *Klebsiella pneumoniae* carbapenemase (KPC) genes were 100%.<br>• One diagnostic accuracy study used 120 clinical bacterial isolates and 26 faecal samples and reported the negative predictive value and sensitivity of Xpert Carba-R as 100%. |

| Technical and patient factors | Cost and resource use |
| --- | --- |
| • The Xpert Carba-R test detects bacterial DNA from a rectal swab specimen.<br>• Results are available in about 50 minutes.<br>• The test can be done in any healthcare setting with access to the GeneXpert system. | • Each single-test Xpert Carba-R cartridge costs £30, excluding VAT. The GeneXpert system, needed to run the test, costs between £18,077 and £121,308 depending on configuration, excluding VAT.<br>• One conference abstract with limited evidence on resource consequences for Xpert Carba-R reported that the cost of reagents plus technical time was approximately £35 per test, compared with £75 for the standard culture with PCR test. |

## Introduction

Carbapenemase-producing organisms (CPOs) are Gram-negative bacteria that are usually resistant to carbapenem antibiotics, the 'drug of last resort' for many bacterial infections (Papp-Wallace et al. 2011) because they are often used when other courses of antibiotic treatment have failed.

Normal gut bacteria can acquire the characteristics of CPOs (Walsh 2007). People who are identified as carriers of CPOs are said to be 'colonised', but do not need to be treated. However, if these CPOs spread outside of the gut causing infection, treatment is necessary but difficult because they have high levels of antibiotic resistance.

CPOs include enterobacteriaceae and non-fermenting bacteria that have become resistant to carbapenems by acquiring genes that make carbapenemases, which are powerful types of beta-lactamases. These are enzymes that break down the beta-lactam antibiotics, meaning they are no longer effective (Queenan and Bush 2007). Carbapenemases include the following gene families:

- *K. pneumoniae* carbapenemase (KPC)
- New Delhi metallo-beta-lactamase (NDM)
- Verona integron-encoded metallo-beta-lactamase (VIM)
- imipenemase metallo-beta-lactamase (IMP)

- oxacillinase (OXA).

These bacteria usually also possess genes encoding for resistance to other classes of antibiotics, including the aminoglycosides and fluoroquinolones (Ageevets et al. 2013).

People who are particularly at risk of CPO colonisation are typically tested when admitted to hospital. These include people who in the last 12 months have been:

- an inpatient in a hospital abroad
- an inpatient in a UK hospital which has problems with the spread of CPOs
- previously colonised with CPOs.

The NICE accredited joint working party guidance on multidrug-resistant Gram-negative bacteria describes the following risk factors for CPO: prior antimicrobial use, length of stay, severity of illness, mechanical ventilation, admission to ICU, high procedure score, presence of wounds, positive culture from a blood isolate, transfer between hospital units within the same hospital, prior surgery, prior hospital stay, proximity to other colonised/infected patients, presence of a biliary catheter and recent transplantation. For NDM, prior hospitalisation on the Indian subcontinent and, for OXA-48, prior hospitalisation in the Middle East, are additional risk factors (Wilson et al. 2016).

People who carry these bacteria harmlessly in their gut can transmit them to other people in hospitals through faecal contamination of hands, shared equipment and the hospital environment. These people may then become infected with the bacteria, or become colonised without symptoms, contributing to further transmission. Without being able to identify people who are colonised, and implementing appropriate infection prevention and control measures, these bacteria can quickly become established in a hospital.

Few treatment options are currently available for infections caused by CPOs. Polymyxins, some aminoglycosides and tigecycline generally retain activity against CPOs, and are the most commonly used treatments (van Duin et al. 2013). However, infections with CPOs are associated with increased hospital length of stay, mortality and healthcare costs. Specifically, patients colonised with these bacteria have on average a 1.79-times greater risk of dying in intensive care than non-colonised patients, primarily linked to an increased length of hospital stay (Dautzenburg et al. 2015).

# Technology overview

This briefing describes the regulated use of the technology for the indication specified, in the setting described, and with any other specific equipment referred to. It is the responsibility of healthcare professionals to check the regulatory status of any intended use of the technology in other indications and settings.

## *About the technology*

### CE marking

The Xpert Carba-R test is classed as an in vitro diagnostic device. The manufacturer, Cepheid, received the first CE mark for the device in June 2014. The current certification is dated July 2015 and covers the updated version of the test currently supplied in the UK, which detects an increased number of carbapenemase genes.

### Description

Xpert Carba-R is an on-demand, qualitative in vitro diagnostic test to identify people carrying CPOs, including at least 91 genes within the 5 most prevalent carbapenemase gene families (KPC, NDM, VIM, IMP-1 and OXA-48, updated to include the OXA-181 and OXA-232 variants).

The test identifies bacterial DNA from a rectal swab specimen, using fully automated real-time polymerase chain reaction (PCR) with fluorogenic detection of the amplified DNA. Results are available in about 50 minutes.

Each test kit is designed to process 10 samples and contains 10 individual test cartridges, sample reagent vials and disposable transfer pipettes. A separate specimen collection container (not part of the kit) has a pair of swabs attached to its lid. Rectal swab samples are collected from approximately 1 cm beyond the anal sphincter using the paired swabs. The swabs are then returned to the container for transport to the laboratory. Only 1 swab is needed for Xpert Carba-R testing. The second swab can be stored for repeat testing if necessary. Swabs in the transport container can be stored at room temperature for up to 6 hours and refrigerated for up to 7 days.

The Xpert Carba-R test is run using the Cepheid clinical in vitro diagnostic system, which consists of 3 main components:

- The GeneXpert molecular diagnostic system – available in 4 configurations (I, II, IV or XVI) consisting of 1, 2, 4 or 16 modules respectively, and a larger Infinity version with 16 to

80 modules. Point-of-care testing is more suited to the smaller 1 or 2 module versions; the larger 4 to 80 module configurations are more suitable for clinical laboratory use. Each module is loaded with 1 Xpert Carba-R test cartridge per person. Multi-module versions can run several on-demand and independent tests using different test cartridges at any time.

- A computer which runs the GeneXpert DX software and stores the results – the software is used to input the patient and test information, to monitor the automated test process, and to view, print and export the results as well as to generate reports. A barcode scanner is included to automate data entry. The computer and barcode scanner are supplied with the GeneXpert system.

- The single-use Xpert Carba-R cartridge – the DNA extraction and PCR reaction is carried out within the cartridge. There are 2 automated internal quality controls in each cartridge: a probe check control and a sample processing control.

One of the Xpert Carba-R test swabs is inserted into the sample reagent vial and mixed at high speed for 10 seconds using a standard laboratory vortex mixer. A pipette is then used to transfer approximately 1.7 ml of the liquid sample to the cartridge sample chamber. The cartridge is loaded into a GeneXpert system module, and test processing and analysis starts automatically by closing the module door.

Results are analysed by the GeneXpert DX software from measured fluorescent signals, using calculation algorithms. Results for each of the 5 gene families (detection or no detection) are reported in tabular and graphical formats in about 50 minutes.

The manufacturer also supplies a range of Xpert cartridges for 22 other in vitro diagnostic tests including additional infection control tests for *Clostridium difficile* (Xpert *C. difficile*), methicillin-resistant *Staphylococcus aureus* (Xpert MRSA), vancomycin-resistant enterococci (Xpert vanA/van B), Xpert Flu/RSV and Norovirus (Xpert Norovirus). These tests also run on the GeneXpert platform but are beyond the scope of this briefing.

## Setting and intended use

The Xpert Carba-R can be used in any suitable healthcare setting with access to the GeneXpert system. In secondary or tertiary care clinical laboratories, the Xpert Carba-R test and GeneXpert systems would be operated by qualified laboratory staff with appropriate training on the test and system.

Xpert Carba-R could also be used in secondary care during pre-admission patient assessment procedures, where it would be used to provide point-of-care testing by appropriately trained healthcare professionals.

## Current NHS options

Screening is currently not recommended in the UK for people with no known risk of CPOs, but people known to be previously colonised or who are at risk of colonisation are tested for CPOs during routine hospital admission. This includes people who have been hospital inpatients within the previous 12 months, either abroad or at a UK hospital which has problems with the spread of CPOs (Public Health England – Acute trust toolkit). The standard method for detecting CPOs in high-risk people is by testing 3 stool samples or rectal swabs collected on days 0, 2 and 4 after admission. The samples are initially tested for CPO colonisation by microbiological culturing, typically with chromogenic agar. This process typically takes 24 hours for positive samples and 48 hours for negative samples. The person is kept in isolation until all 3 culture results are available. If all 3 culture tests are negative the person can be considered for removal from isolation. If any CPO colonies are detected following culture and incubation, additional tests are needed to determine carbapenem resistance (Public Health England 2013). This would involve antimicrobial susceptibility testing using microbiological agar plates and an indicator carbapenem such as meropenem, doripenem or imipenem. If a sample is considered resistant to the carbapenem, further supplementary tests are done to distinguish carbapenemase producers from those that have other carbapenem resistance mechanisms. Confirmatory tests can be inhibitor-based where synergy can be demonstrated between the indicator carbapenem and various carbapenemase inhibitors. Other methods include the modified Hodge test, matrix assisted laser desorption/ ionisation time-of-flight mass spectrometer (MALDI-ToF), the Carba-NP test (Biomerieux, USA) or PCR-based assays (Public Health England 2014).

The following samples should also be sent to the Reference Laboratory at Public Health England for further testing, to assess outbreaks and identify transmission pathways:

- all enterobacteriaceae suspected of producing a carbapenemase
- all *Pseudomonas* sp. suspected of producing a carbapenemase
- all *Acinetobacter* sp. suspected of producing a metallo-carbapenemase.

NICE is aware of the following CE-marked devices that appear to fulfil a similar function to the Xpert Carba-R:

- eazyplex SuperBug CRE/SuperBug complete A/SuperBug Complete B – Amplex Biosystems
- Check-Direct CPE – Check-Points.

## *Costs and use of the technology*

The Xpert Carba-R system consists of several essential components and optional accessories. List prices (excluding VAT) for the essential components are as follows:

- Xpert Carba-R cartridge: £30 per single test
- sample collection device (transport container with dual swab): £37 per pack of 50
- GeneXpert molecular diagnostic system (1–16 modules) including computer system and barcode scanner costs from £18,077 for a single-module system to £121,308 for a 16-module system.

List prices for optional accessories (excluding VAT) are:

- uninterruptible power supply for the GeneXpert system: £1522
- laser printer with USB cable: £110
- GeneXpert 16-cartridge tray: £8
- GeneXpert 32-cartridge tray: £12.

The GeneXpert system has an anticipated lifespan of at least 10 years. The manufacturer offers annual maintenance contracts from £2103 to £7107 depending on the number of modules in the system. The annual service includes preventative maintenance and module calibration. On-site and telephone technical support are available.

Training covers sample collection, preparing the cartridge and analysing the results. Standardised training material and training guides are also provided. Training takes about 30 minutes and is offered during the initial installation and on request. Experienced staff already familiar with the process may train new staff members.

## *Likely place in therapy*

The Xpert Carba-R would be used to detect the presence of CPOs in people who are suspected of colonisation or infection. It would deliver results faster than the standard culture technique used to

identify colonisation and would be used in placed of standard culture-based tests and an adjunct to the supplementary and confirmatory tests such as antimicrobial resistance testing. This could therefore result in a quicker diagnosis of CPO colonisation and allow healthcare providers to implement local infection control protocols to prevent transmission to other susceptible people.

## *Specialist commentator comments*

One specialist commentator indicated that, because most people tested would not be colonised with CPOs, the main purpose and value of using Xpert Carba-R in a screening programme is likely to be in excluding (rather than diagnosing) colonisation. The group of people to be tested would be determined locally and may include patients with risk factors (for example people transferred from certain hospitals or previous CPO colonisation); patients having a high-risk type of care (for example ICU); or regular screening of patients during an outbreak. This specialist commentator was aware that in some parts of the country, all new admissions to hospital are tested. However another specialist commentator highlighted that the Xpert Carba-R test would be too expensive for universal screening of all admissions.

One specialist commentator suggested other instances when the Xpert Carba-R test result could be useful, such as when a patient identified as being at increased risk of CPO colonisation becomes septic. In this case CPO colonisation could be determined at the onset of sepsis and a different antibiotic therapy could be provided much sooner. Additionally, the rapid availability of results could also help when a patient who is not in isolation is identified as carrying CPOs, allowing infection control teams to screen contacts for evidence of spread. This could potentially bring any outbreak under control faster, allowing a closed ward to be re-opened and could help in the identification of people who might need a different antibiotic treatment if they become unwell.

One specialist commentator highlighted that there are many other diagnostic tests that can be run on the GeneXpert System and a fair number of hospitals will already be using this platform.

One specialist commentator indicated that because the Xpert Carba-R uses bespoke rectal swabs, there may be implications in the supply of swabs to wards. They also indicated that standard practice is to take rectal samples at 48-hour intervals until 3 negative screens are obtained, so the culture screening process will always take approximately 96 hours from admission. They suggested that a quick turnaround time for any test would be beneficial and will speed up the process with possible transfer out of isolation. Another specialist commentator advised that repeated sampling (3 times) to prove a negative result is not commonly practicable and in most cases, clinicians rely on the first result.

One specialist commentator highlighted that the main evidence supporting the Xpert Carba-R test is dominated by enterobacteriaceae, with few non-fermenting bacteria. They considered that there is scant evidence on the utility of the Xpert Carba-R test for the detection of carbapenemase genes in bacteria other than enterobacteriaceae, for example important genera such as *Acinetobacter* which produces OXA-23. The specialist commentator also noted that the performance characteristics of the Xpert Carba-R for individual genes reported in the evidence could be misleading. The sensitivity figure of 71% related solely to the detection of the IMP carbapenemase gene from a single study and in the UK, this carbapenemase gene is present in no more than 1% of CPOs.

### *Equality considerations*

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to:

- promote race and disability equality and equality of opportunity between men and women
- eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

## Evidence review

### *Clinical and technical evidence*

#### Regulatory bodies

A search of the Medicines and Healthcare Products Regulatory Agency (MHRA) website revealed no manufacturer Field Safety Notices or Medical Device Alerts for this device.

#### Clinical evidence

A literature search identified 2 published studies that used the Xpert Carba-R test: 1 comparative diagnostic accuracy study (Findlay et al. 2015) and 1 non-comparative diagnostic accuracy study (Anandan et al. 2015). Another non-comparative diagnostic accuracy study using Xpert MDRO, an earlier version of the test (Tenover et al. 2013), is also included in this briefing. The Xpert MDRO was designed to detect only 3 of the 5 major carbapenemase gene families (KPC, NDM and VIM)

and so this study is only considered relevant to the technical performance of the test in identifying these gene families. Detection capabilities for the IMP and OXA gene families were added to the later generation Carba-R test.

The comparative diagnostic accuracy study by Findlay et al. (2015) aimed to assess the performance of 3 commercial molecular assays for detecting carbapenemase genes (including the 5 major carbapenemase families: KPC, NDM, VIM, IMP, and OXA) in pure bacterial isolates. A panel of 450 carbapenem resistant isolates were tested using the Check-Direct CPE kit (on 2 different platforms), the eazyplex SuperBug complete A kit and the Xpert Carba-R kit. The carbapenemase genes had been previously detected and identified using in-house PCR assays, a commercial microarray (Check-MDR CT102) or a combination of both tests. These data were regarded as the gold standard against which the commercial assays were compared. The panel of 450 isolates comprised 100 samples each of KPC, NDM, VIM and OXA-48 variants, 2 isolates co-producing NDM and OXA-48 variants, 24 IMP producers and 24 isolates that were carbapenem-resistant, but did not contain a known carbapenemase gene. The overall test sensitivity was reported as 94.3% (402/426). The Xpert Carba-R test successfully detected the correct carbapenemase gene in all 302 isolates with a KPC, NDM or VIM enzyme and so achieved 100% sensitivity for these targets. In those isolates with an OXA-48 variant carbapenemase gene (n=102), 18 of them (17 with the OXA-48 variant alone and 1 with an OXA-48-variant co-produced with NDM) were not detected by Xpert Carba-R. PCR and sequencing identified an OXA-181 gene in each of the 18 false-negative isolates. A modified Xpert Carba-R version 2 kit was subsequently provided and correctly identified the 18 OXA-181 producers. The Xpert Carba-R test detected 71% (17/24) IMP producers; however, PCR confirmed the presence of a IMP gene in the 7 false negative isolates that were closely matching IMP-4, IMP-7, IMP-8, IMP-13 and IMP-14, which Xpert Carba-R does not cover. The authors concluded that the commercial tests offer a reliable means of detecting bacteria with clinically significant carbapenemases. A summary of the study and results can be found in tables 1 and 2 of the appendix.

The diagnostic accuracy study by Tenover et al. (2013) aimed to determine the sensitivity and specificity of Xpert MDRO, an earlier version of the Xpert Carba-R test, by comparing it with a culture method with and without a broth enrichment step. The authors collected 328 clinical specimens from human rectal, perirectal and stool samples. The presence of carbapenemase genes was confirmed using culture on a MacConkey agar plate followed by Check-Points microarray detection. For a control test, 41 bacterial isolates containing a variety of carbapenemases were tested with the Xpert MDRO cartridge, which gave positive results for the KPC, NDM and VIM genes and no false positives. For the 328 clinical samples, the sensitivity, specificity, positive predictive value and negative predictive value for the VIM gene were reported as 100%, 99.4%, 81.8% and 100% respectively. The sensitivity, specificity, positive predictive value and negative

predictive value for the KPC gene were reported as 100%, 99.0%, 93.0% and 100% respectively. False-positives were observed in 2 and 3 cases for VIM and KPC genes respectively. None of the 328 specimens contained the NDM gene. Therefore, 66 contrived stool samples were prepared using various dilutions of 3 *Klebsiella pneumoniae* isolates containing NDM. The experiments were done in 5 replicates for the 2 lowest dilutions of 150 and 300 colony forming unit/ml (CFU/ml) and 4 replicates for the 3 highest dilutions of 600, 1200 and 1800 CFU/ml. Xpert MDRO showed 100% positivity at dilutions from 300 CFU/ml to 1800 CFU/ml and 93.3% at 150 CFU/ml. The authors concluded that the Xpert MDRO test can detect the KPC, NDM and VIM carbapenemase genes directly from rectal swab samples. They considered that Xpert MDRO could provide valuable information for infection control programs designed to limit the spread of multi-drug resistant organisms in healthcare settings (tables 3 and 4).

The diagnostic accuracy study by Anandan et al. (2015) evaluated the performance of Xpert Carba-R using clinical isolates and faecal specimens when compared with conventional multiplex PCR. One hundred and twenty clinical isolates of carbapenem resistant *E. coli* (n=32) and *K. pneumoniae* (n=88) were collected from people with bloodstream infections. These isolates were concurrently investigated for the 5 clinically relevant carbapenemase coding genes KPC, NDM, IMP, VIM and OXA-48, using conventional multiplex PCR. Additionally, 26 of the faecal specimens were tested for the presence of carbapenemase genes using the Xpert Carba-R test. Conventional PCR identified NDM in 40% (48/120) of isolates, OXA-48 variants in 39.2% (47/120) of isolates and co-producers of NDM and OXA-48 variants in 12.5% (15/120) of isolates. Notably, 8.3% (10/120) of isolates were negative for all 5 tested genes, and all tested isolates were negative for IMP, VIM and KPC genes. The Xpert Carba-R test identified NDM in 55% (66/120) isolates, but like the Findlay et al. study (2015) it did not identify either OXA-48 variants or co-producers of OXA-48 variants and NDM in the isolates. The identified OXA-48 variant was found to be OXA-181 by sequencing. The authors reported the sensitivity, specificity, positive predictive value and negative predictive value of the Xpert Carba-R test to be 100%, 77%, 96% and 100% respectively (the OXA-48 variant results were excluded from these figures, owing to the missed OXA-181 target). Of the tested faecal samples, 46% (12/26) contained carbapenem-resistance genes, 9 had NDM, 2 had both NDM and VIM and 1 had both NDM and KPC. The authors concluded that the Xpert Carba-R test would be useful for the prompt detection of people infected or colonised with strains of bacteria that may harbour carbapenemase-encoded genes. However, they highlighted that incorporating additional OXA-48 variant specific sequences in the panel may help to improve its sensitivity and maximise the coverage of the assay (tables 5 and 6).

## Recent and ongoing studies

No ongoing or in-development trials on Xpert Carba-R for detecting CPOs were identified.

## *Costs and resource consequences*

Individual Xpert Carba-R tests and the GeneXpert system are considerably more expensive than current microbiological culture techniques and would therefore represent an additional acquisition cost to the NHS. However, the faster turnaround time could lead to quicker detection, faster infection control implementation and faster optimal treatment. This may in turn lower the risk of spread and reduce overall costs such as unnecessary bed days in isolation. Xpert Carba-R would be used in place of standard culture-based tests and as an adjunct to supplementary and confirmatory tests such as antimicrobial resistance testing.

One conference abstract with limited evidence on resource consequences for Xpert Carba-R was identified. Delbarre et al. (2014) reported in a French study that the cost of reagent plus technical time was $54.60 (about £35) per test, compared with $116.10 (about £75) for the culture plus PCR. The results were available in 48 minutes compared with at least 30 hours for the culture plus PCR. No specialised staff were needed. No further detail is available and these figures should therefore be interpreted with caution.

## *Strengths and limitations of the evidence*

The available evidence on the use of Xpert Carba-R to detect CPOs is currently limited in quantity and quality. Three diagnostic accuracy studies, 1 of which compared Xpert Carba-R to alternative rapid identification methods, were identified. No studies were identified that reported clinical or healthcare-related outcomes.

The comparative diagnostic accuracy study by Findlay et al. (2015) compared the performance of 3 commercial assays for detecting carbapenemases in bacterial isolates. One of the main strengths of this study was the large panel of bacterial isolates used (n=450), with carbapenemase resistance mechanisms defined through appropriate methods. The 24 samples which were carbapenem-resistant through other mechanisms and were therefore negative for CPO genes could have allowed for a calculation of specificity. This was not reported and the published results were limited to sensitivities and false negatives. The Xpert Carba-R test was able to identify carbapenemase genes in 402 of 426 isolates (overall sensitivity of 94.3%). The isolates were selected for geographical, temporal and carbapenemase diversity; however, because of the nature of diagnostic accuracy studies, there is no risk of selection bias. The study was done in the UK at the Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit and so results would be generalisable to the NHS. Due to the selection of isolates for carbapenemase diversity, the distribution of the carbapenemases observed in this study would not mimic the

natural distribution of carbapenemases. The original Xpert Carba-R assay did not detect OXA-48 variant genes but the authors later acquired a modified version to detect OXA-181 genes.

The diagnostic accuracy study by Tenover et al. (2013) evaluated the Xpert MDRO test, an earlier version of Xpert Carba-R, and therefore could only report on the performance characteristics for 3 of the 5 major carbapenemase gene families (KPC, NDM and VIM). The authors stated that they chose a broth enrichment culture and sequencing of the target genes as the reference standard. However, 2 of the 3 samples that tested positive for the KPC gene using Xpert MDRO had been classified as negative by broth culture but positive by sequencing, and the other sample had not been sequenced at all. As the authors stated there were only 40 true positives, it is evident that the status of these 3 samples had only been based on broth culture alone, which is not a suitable reference standard. In addition, the reported specificities and negative predictive values for both VIM and KPC genes could not be independently replicated from the results presented in the published paper, raising concerns of reporting bias in this study. The authors highlighted that the number of organisms they used to establish the sensitivity and specificity of the Xpert MDRO assay did not cover the entire range of genes that could be detected in each of the 3 carbapenemase families. However, they observed that by using computer modelling, there were no mismatches between the primers chosen for the assay and any mutations associated within the individual target genes. Additionally, the culture media they used in the evaluation were limited to MacConkey agar and did not include a broad range of agar plates that may have supported the growth of other organisms for the 3 Xpert MDRO-positive, culture-negative samples. It is also possible that some organisms lost viability during transport to the central testing laboratory.

The diagnostic accuracy study by Anandan et al. (2015) aimed to evaluate the performance of Xpert Carba-R using clinical isolates and faecal specimens directly. The authors used conventional multiplex PCR as the reference standard for the diagnostic accuracy study, but did not specify which technology was used. It was also apparent that the Xpert Carba-R test identified more isolates containing NDM than the reference standard, although the authors made no attempt to explain this discrepancy. It is also not clear whether the 26 faecal samples tested by Xpert Carba-R were confirmed by a reference standard. The performance characteristics that were reported by the authors could not be independently replicated and it is unclear which raw data were used to calculate these. The authors noted that among the 10 OXA-48 variants, the Xpert Carba-R test is designed to only identify 4 variants. They highlighted that this provides an explanation for why the Xpert Carba-R failed to identify the OXA-48 variants within the clinical isolates. Overall, the study was very poorly reported and results should be interpreted with caution.

## Relevance to NICE guidance programmes

NICE has issued the following guidance:

- Healthcare-associated infections: prevention and control (2011) NICE guideline PH36
- Xpert GBS test for the intrapartum detection of group B streptococcus (2015) NICE medtech innovation briefing 28
- Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) NICE guideline NG15

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# Appendix

## *Contents*

### Data tables

## Table 1 Summary of the Findlay et al. (2015) study

| Study component | Description |
|---|---|
| Objectives/ hypotheses | To compare the performance of 3 commercial assays in detecting carbapenemases:<br>• Xpert Carba-R<br>• Check-Direct CPE (on 2 different platforms)<br>• eazyplex SuperBug complete A kit. |
| Study design | Comparative diagnostic accuracy study.<br>The carbapenemase genes had been previously detected using in-house PCR assays or a commercial microarray (Check-MDR CT102). These data were regarded as the gold standard against which the commercial assays were compared. A modified Xpert Carba-R version 2 kit was subsequently used to test any isolates with an OXA-48 variant carbapenemase gene that were not detected by the original Xpert Carba-R assay. |
| Setting | Non-consecutive isolates submitted to Public Health England's AMRHAI Reference Unit from laboratories across the UK between July 2009 and April 2014. |
| Inclusion/ exclusion criteria | No inclusion/exclusion criteria were reported.<br>Isolates were not consecutive referrals, but were selected for geographical, temporal (within the above timeframes) and carbapenemase diversity. |
| Primary outcomes | Performance characteristics – sensitivity. |
| Statistical methods | Not reported. |

| | |
|---|---|
| Results | The overall test sensitivity was 94.3% (402/426).<br>The Xpert Carba-R test successfully detected the correct carbapenemase gene in all 302 isolates with a KPC, NDM or VIM variant gene.<br>A modified Xpert Carba-R version 2 assay correctly identified the OXA-181 variants not detected by Xpert Carba-R. |
| Conclusions | The authors concluded that the commercial assays offer a reliable means of detecting bacteria with clinically significant carbapenemases. |
| Abbreviations: AMRHAI, Antimicrobial Resistance and Healthcare Associated Infections; PCR, polymerase chain reaction. | |

## Table 2 Summary of results from the Findlay et al. (2015) study

| | | | | |
|---|---|---|---|---|
| Isolates included | 450 isolates comprising of 100 samples each with KPC, NDM, VIM and OXA-48 variant genes, 2 isolates containing both NDM and OXA-48 genes, 24 isolates containing IMP genes and 24 isolates that were carbapenem resistant, but did not contain a known carbapenemase gene. | | | |
| Primary outcome results:<br>Assay performance (sensitivity) | | | | |
| | Xpert Carba-R | Check-Direct CPE with ABI 7500 platform | Check-Direct CPE with BD MAX platform | eazyplex SuperBug complete A |
| KPC | 100% | 100% | 100% | 100% |
| OXA-48 variant | 83%[a,b] | 100% | 100% | 83%[a,b] |
| NDM | 100% | 100%[c] | 100%[c] | 100% |
| VIM | 100% | 100%[c] | 100%[c] | 100% |
| IMP | 71%[d] | N/A | N/A | N/A |
| NDM + OXA-48 variant | 2 × NDM;<br>1 × OXA-48 | 2 × NDM;<br>2 × OXA-48 | 2 × NDM;<br>2 × OXA-48 | 2 × NDM;<br>1 × OXA-48 |
| Non-carbapenemase | 0% | 0% | 0% | 0% |

| |
|---|
| The overall test sensitivity was 94.3% (402/426).<br>The Xpert Carba-R test successfully detected the correct carbapenemase gene in all 302 isolates with a KPC, NDM or VIM enzyme.<br>17.6%[e] (18/102) of the isolates with an OXA-48 variant carbapenemase gene were not detected by Xpert Carba-R. A modified Xpert Carba-R version 2 kit was subsequently provided and correctly identified these as OXA-181 variants. |
| Abbreviations: IMP, imipenemase metallo-beta-lactamase; KPC, *Klebsiella pneumoniae* carbapenemases; NDM, New Delhi metallo-beta-lactamase; OXA, oxacillinases; VIM, Verona integron-encoded metallo-beta-lactamase.<br>[a]Sequencing identified OXA-181 in 18 isolates where the OXA-48 variant gene was not detected.<br>[b]Calculated to be 82.4% by the authors of this briefing.<br>[c]The Check-Direct CPE kit does not distinguish between NDM and VIM producers on the ABI 7500 platform, but does on the BD Max platform.<br>[d]Sequencing identified close matches with IMP-4, IMP-7, IMP-8, IMP-13 and IMP-14 in 7 isolates where an IMP-1 variant gene was not detected.<br>[e]Calculated by the authors of this briefing, not explicitly reported in the study. |

## Table 3 Summary of the Tenover et al. (2013) study

| Study component | Description |
|---|---|
| Objectives/ hypotheses | To determine the sensitivity and specificity of the Xpert MDRO for detecting carbapenem resistance genes (KPC, NDM, VIM) when compared to the results of culture with and without a broth enrichment step followed by Check-Points microarray detection. |
| Study design | Diagnostic accuracy study. |
| Setting | Swab samples were obtained from 2 hospitals in the United States and 1 hospital in Spain. Stool samples were obtained from another US hospital. |
| Inclusion/ exclusion criteria | None reported. |

| | |
|---|---|
| Primary outcomes | Performance characteristics: sensitivity, specificity, PPV, NPV. |
| Statistical methods | 95% confidence intervals were calculated using the Clopper-Pearson/Fisher exact. |
| Conclusions | The authors concluded that the Xpert MDRO assay can detect the KPC, NDM and VIM carbapenemase genes directly from rectal swab samples. |
| Abbreviations: CI, confidence intervals; IMP, imipenemase metallo-beta-lactamase; KPC, Klebsiella pneumoniae carbapenemases; MDRO, multi-drug resistant organisms; NDM, New Delhi metallo-beta-lactamase; NPV, negative predictive value; PPV, positive predictive value; US, United States; VIM, Verona integron-encoded metallo-beta-lactamase. | |

## Table 4 Summary of results from the Tenover et al. (2013) study

| | | |
|---|---|---|
| Samples included | 328 swab samples were included; 121 single rectal swabs in Amies medium, 74 single rectal swabs in Stuart's medium, 35 single peri-rectal swabs in Stuart's medium, and 98 double swabs that were dipped in discarded stool specimens and placed in Stuart's medium.<br>66 contrived stool samples were prepared and confirmed to have various dilutions using 3 *Klebsiella pneumoniae* isolates containing the NDM gene. | |
| Primary outcome results: | | |
| Reported Xpert Carba-R performance characteristics from swab samples (95% CI): | | |
| | VIM | KPC |
| Sensitivity | 100% (71.7–100%) | 100% (92.8–100%) |
| Specificity | 99.4% (97.7–99.9%) | 99.0% (97.0–99.8%) |
| PPV | 81.8% (48.2–97.7%) | 93% (80.9–98.5%) |
| NPV | 100% (99.1–100%) | 100% (98.9–100%) |
| Positivity of the Xpert Carba-R on contrived stool samples with NDM-containing organisms (%) (95% CI): | | |

| Dilution of Klebsiella pneumoniae isolates | Positivity |
|---|---|
| 150 CFU/ml (n=15) | 93.3% (68.1–99.8%) |
| 300 CFU/ml (n=15) | 100% (81.9–100%) |
| 600 CFU/ml (n=12) | 100% (77.9–100%) |
| 1200 CFU/ml (n=12) | 100% (77.9–100%) |
| 1800 CFU/ml (n=12) | 100% (77.9–100%) |
| Abbreviations: CI, confidence intervals; CFU, colony-forming unit; IMP, imipenemase metallo-beta-lactamase; KPC, *Klebsiella* pneumoniae carbapenemases; MDRO, multi-drug resistant organisms; NDM, New Delhi metallo-beta-lactamase; NPV, negative predictive value; PPV, positive predictive value; VIM, Verona integron-encoded metallo-beta-lactamase. | |

## Table 5 Overview of the Anandan et al. (2015) study/trial

| Study component | Description |
|---|---|
| Objectives/ hypotheses | To evaluate the performance of the Xpert Carba-R assay using clinical isolates and faecal specimens directly when compared to conventional multiplex PCR. |
| Study design | Diagnostic accuracy. |
| Setting | Clinical isolates of carbapenem resistant *E. coli* and *K. pneumoniae* were collected from bloodstream infections between January and December 2013.<br>Faecal specimens were also directly tested for the presence of carbapenemase genes using the Xpert Carba-R test. |
| Inclusion/ exclusion criteria | Not reported. |
| Primary outcomes | Performance characteristics: sensitivity, specificity, PPV and NPV. |
| Statistical methods | Not reported. |

| | |
|---|---|
| Conclusions | The authors concluded that the Xpert Carba-R would be useful for the prompt detection and isolation of patients infected or colonised with strains that may harbour carbapenemase genes. However, they highlight that the incorporation of OXA-48 variant specific sequences in the panel may help improve its sensitivity and maximise the coverage of the assay. |
| Abbreviations: *E. coli*, *Escherichia coli*; *K. pneumoniae*, *Klebsiella pneumoniae*; NPV, negative predictive value; OXA, oxacillinases; PPV, positive predictive value. | |

## Table 6 Summary of results from the Anandan et al. (2015) study

| | | | |
|---|---|---|---|
| Samples included | 120 clinical isolates: *E. coli* (n=32), *K. pneumoniae* (n=88)<br>26 faecal specimens. | | |
| Primary outcome results: | | | |
| Prevalence of each carbapenemase gene | | Conventional multiplex PCR | Xpert Carba-R |
| | NDM | 40% (48/120) | 55% (66/120) |
| | OXA-48 variant | 39.2% (47/120) | 0% (0/120) |
| | Co-producers of NDM and OXA-48 variant | 12.5% (15/120) | 0% (0/120) |
| Reported performance characteristics of Xpert Carba-R test (as reported, excluding the OXA-48 variant results): | Sensitivity: 100%,<br>Specificity: 77%,<br>PPV: 96%<br>NPV: 100%<br>Of the tested faecal samples, 46% (12/26) were identified as carbapenemase producers, 9 with NDM, 2 with the co-production of NDM and VIM and one with the co-production of NDM and KPC. | | |
| Abbreviations: *E. coli*, *Escherichia coli*; IMP, imipenemase metallo-beta-lactamase; *K. pneumoniae*, *Klebsiella pneumoniae*; KPC, *Klebsiella pneumoniae* carbapenemases; NDM, New Delhi metallo-beta-lactamase; NPV, negative predictive value; OXA, oxacillinases; PPV, positive predictive value; VIM, Verona integron-encoded metallo-beta-lactamase. | | | |

## Search strategy and evidence selection

### *Search strategy*

The search strategy was designed to identify evidence on the clinical and cost effectiveness of the Xpert Carba-R to identify patients carrying CPOs, specifically KPC, NDM, VIM, IMP-1, OXA-48, OXA-181 and OXA-232.

The strategy was developed for MEDLINE (Ovid interface). The strategy was devised using a combination of subject indexing terms and free text search terms in the title, abstract and keyword heading word fields. The search terms were identified through discussion within the research team, scanning background literature, browsing database thesauri and use of the PubMed PubReMiner tool (http://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi). The strategy reflected the nature of the MIB assessments as rapid evidence reviews, with a pragmatic, focused search approach being used.

The main structure of the search strategy comprised 2 concepts:

- CPO (KPC, NDM, VIM, IMP-1, OXA-48, OXA-181 and OXA-232);
- Polymerase chain reaction (PCR) assay.

The search concepts were combined as follows: CPO AND PCR.

The strategy also included an additional focused approach which combined CPO terms with screening / diagnosis terms in the title field, 2 stand-alone search lines which co-ordinated CPO terms and non-specific diagnosis / screening terms in close proximity, and 4 standalone lines which searched on the manufacturer and device names. These lines were designed to retrieve studies which might be missed by the 2 concept approach.

The strategy excluded animal studies using a standard algorithm. Non-English language publications were also excluded from the search results. The strategy was limited to studies published from 2013 to date; this reflected the date when the device was first developed.

The MEDLINE strategy was translated appropriately for the other databases searched. The PubMed search was limited to all records not fully indexed for MEDLINE apart from In-Process records and PubMed-not-MEDLINE records, which were also excluded.

The following databases were searched:

- Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley);
- Cochrane Database of Systematic Reviews (Cochrane Library, Wiley);
- Database of Abstracts of Reviews of Effects (Cochrane Library, Wiley);
- Embase (Ovid SP);
- Health Technology Assessment Database (Cochrane Library, Wiley);
- MEDLINE and MEDLINE in Process (Ovid SP);
- NHS Economic Evaluation Database (Cochrane Library, Wiley);
- PubMed (http://www.ncbi.nlm.nih.gov/pubmed).

### *Evidence selection*

A total of 1705 records were retrieved from the literature search. After de-duplication, 1036 records remained. Records were grouped into 2 batches, 1 batch with search results from a focussed search strategy (n=452) and a second batch which included the remainder of the search results.

Records from batch 1 were sifted independently by 2 researchers against the inclusion criteria at title and abstract level. Any disagreements were discussed and agreement was reached in all cases, so a third independent arbiter was not required. The first sift removed 432 records based on the following exclusion criteria:

- articles of poor relevance against search terms
- publication types that were out of scope
- non-English language studies
- conference abstracts
- review articles.

Full articles were retrieved for 20 of the remaining studies. Full text assessment was done independently by 2 researchers to identify relevant primary research addressing the key outcomes of interest. At this stage, 17 papers were excluded:

- Incorrect technology (n=10)

- Not peer-reviewed studies (n=7).

Three studies remained from batch 1, which included 1 comparative diagnostic accuracy study and 2 diagnostic accuracy studies. These studies became the focus of the evidence review.

The second batch of studies was reviewed by 1 researcher to ensure that no additional relevant studies had been overlooked. No additional studies were identified from this review.

## About this briefing

Medtech innovation briefings summarise the published evidence and information available for individual medical technologies. The briefings provide information to aid local decision-making by clinicians, managers and procurement professionals.

Medtech innovation briefings aim to present information and critically review the strengths and weaknesses of the relevant evidence, but contain no recommendations and **are not formal NICE guidance**.

### *Development of this briefing*

This briefing was developed for NICE by Newcastle and York External Assessment Centre. The interim process & methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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## Specialist commentators

The following specialist commentators provided comments on a draft of this briefing:

- Dr Jim Gray Consultant Microbiologist, Birmingham Children's Hospital NHS Foundation Trust
- Ms Louise Hall, Matron in Infection Prevention and Control, Newcastle upon Tyne Hospitals NHS Foundation Trust
- Professor John Perry, Clinical Scientist, Newcastle upon Tyne Hospitals NHS Foundation Trust
- Professor Peter Wilson, Consultant Microbiologist, University College London Hospitals NHS Foundation Trust
- Professor Neil Woodford, Head of Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit, Public Health England.

## Declarations of interest

- Professor John Perry has received funding for research or royalty payments from diagnostics companies, including bioMérieux and Lab M, which market competing products to Xpert Carba-R
- Professor Peter Wilson has acted as a consultant in rapid diagnostics to Momentum BioScience.
- Professor Neil Woodford, as Head of Public Health England's AMHRAI Reference Unit, is actively engaged in assessing commercial systems for confirming carbapenemase production. He has been involved in commercially-funded independent scientific evaluations including the Findlay et al. 2015 study. He is also involved in contract research for pharmaceutical and diagnostic companies, including Cepheid. He is in discussions with several companies, including Cepheid, about diagnostics for CPE.

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