UK Health Security Agency

Commercial assays for the detection of acquired carbapenemases

Contents

Executive summary

Almost all NHS hospitals in England have detected carbapenemase-producing Gram-negatives bacteria within their patient populations, either as colonisations or causing clinical infections. The purpose of this report is to provide evidence-based guidance to enable diagnostic laboratories to make an informed choice in their selection of one or more commercially available methods for the detection of carbapenemase-producing Gram-negatives bacteria when considering local business needs. The report strongly recommends the implementation of an assay for the detection of the ‘big 4’ carbapenemases in frontline diagnostic laboratories. Local testing with rapid turnaround will have maximal impact on individual patient management to prevent onward transmission and effective clinical treatment. Since October 2020, acquired carbapenemase-producing Gram-negative bacteria isolated from human samples are included in the Health Protection (Notification) Regulations 2020.

1. Introduction

1.1. What are acquired carbapenemases?

Resistance to carbapenem antibiotics is one of the major threats faced in antimicrobial treatment of Gram-negative infections. Acquired carbapenem resistance, predominantly mediated by transferable genes, is of particular importance as these genes (usually located on mobile genetic elements such as transposons or plasmids) can move vertically (within a strain) and horizontally (between strains, species and genera), causing multi-species outbreaks that can be difficult to recognise and control unless the resistance mechanism is tracked in relative real-time.

This document focusses on acquired carbapenemases, which are detected in a growing number of Enterobacterales and are currently the most important mechanisms of resistance to carbapenems from a public health perspective. Different families of carbapenemases have been reported globally and nationally within the UK, of which the KPC, OXA-48-like, NDM and VIM families (often referred to as the 'big 4') are the most commonly identified (1, 2). KPC, OXA-48-like, NDM and VIM carbapenemases (and combinations thereof) accounted for 95.4% of the 3587 carbapenemase-producing Enterobacterales (CPE) referred to the UK Health Security Agency (UKHSA)'s Second Generation Surveillance System (SGSS) from October 2020 to June 2022, with coverage increasing to 99.6% if IMP carbapenemases are included (3). However, carbapenemases belonging to the DIM, FRI, GES, GIM, IMI, OXA-23-like, SME, SPM, and families have also been detected in low numbers of UK isolates (see Appendix, Table 2).

1.2 Why is it important to detect carbapenemase-producing Enterobacterales?

Although still responsible for a low number of invasive infections within the UK (5.6% of CPE reported to UKHSA between October 2020 and June 2022 (3), CPE are widely scattered in the UK population. However, the rates reported vary by region and are increasingly associated with hospital- and community-acquired infections. Infections caused by CPE are challenging to treat, and are associated with an increase in morbidity, attributable mortality, and increased healthcare costs resulting from prolonged hospital stays and the care of infected and colonised patients.

Acquired carbapenemase genes are frequently located on mobile genetic elements, which can potentially transfer resistance between different bacterial strains, species and genera. Thus, early detection of CPE and distinction from bacteria with other carbapenem resistance

mechanisms is important to minimise their spread by the rapid implementation of effective infection prevention and control procedures.

Differentiation between the various carbapenemase families is also essential, not only to inform epidemiology, but also to guide patient treatment. Whilst β-lactam/β-lactamase inhibitor combinations such as ceftazidime/avibactam, meropenem/vaborbactam and imipenem/relebactam offer potential treatment options for infections caused by CPE, it is important to note that they do not cover all carbapenemase families. For example, ceftazidime/avibactam is effective for the treatment of CPE producing a KPC or OXA-48-like non-metallo-carbapenemase, whilst meropenem/vaborbactam and imipenem/relebactam are only effective against CPE producing a KPC enzyme (4). None of these β-lactam/β-lactamase inhibitor combinations, when used alone, are effective against metallo-carbapenemase producers. A report from the British Society for Antimicrobial Chemotherapy, Healthcare Infection Society and British Infection Association Joint Working Party strongly recommended that laboratories should determine the responsible family of carbapenemase in all meropenem- or imipenem-resistant Enterobacterales (5). This is best achieved via the application of rapid and accurate molecular or immunochromatographic assays.

1.3 What is the current guidance for the detection of CPE?

As a means to strengthen antimicrobial resistance surveillance, legislation amendments came into force on 1 October 2020. Carbapenamase-producing bacteria are now included in the Health Protection (Notification) Regulations 2020 meaning diagnostic laboratories now have the duty as part of Regulation 4 to report the following to UKHSA :

- acquired carbapenemase-producing Gram-negative bacteria isolated from human samples
- the results of any antimicrobial susceptibility test and any resistance mechanism identified in any of the causative agents listed in Schedule 2 of the Regulations where this is known to the operator

Alongside the updated Regulations, UKHSA published the 'Framework of actions to contain carbapenemase-producing Enterobacterales' in October 2020, which sets out a range of measures to prevent and control CPE in healthcare settings; this was updated in September 2022 (6). One of the key recommendations of the Framework centred on laboratory methods, namely that acute healthcare providers should:

- implement molecular or immunochromatographic assays in frontline diagnostic laboratories for at least the detection of KPC, OXA-48-like, NDM and VIM

carbapenemase families in Gram-negatives that meet screening criteria outlined in the UK Standards for Microbiology Investigations (SMI) to complement culture-based testing (7)
- refer carbapenem-resistant isolates negative in local carbapenemase detection tests to UKHSA's AMRHAI Reference Unit to seek IMP and other rarer carbapenemase families

In support of these recommendations, the UK SMI 'Detection of bacteria with carbapenem-hydrolysing β-lactamases (carbapenemases)' published in October 2020 and recently reviewed in June 2022, endorses the implementation of an assay to detect at least the 'big 4' carbapenemase families (7).

1.4 Who is this report for and what is its purpose?

In May 2019, UKHSA's predecessor organisation (Public Health England) published guidance to provide the evidence base to support diagnostic laboratories in making an informed choice on the implementation of commercially-available carbapenemase detection assays when considering local business needs; this report is a further update of that guidance.

This report focusses on molecular and immunochromatographic assays that detect specific carbapenemase families; phenotypic assays are outside the scope of this report. It strongly recommends the implementation of an assay for at least the detection of the 'big 4' carbapenemases in frontline diagnostic laboratories to inform appropriate individual patient management at a much earlier stage and accelerate infection prevention and control decisions.

2. Commercial assays available for detection of the 'big 4' carbapenemase families

We established a list of commercial assays available in the UK for detection of acquired carbapenemases by searching the published literature and the websites of commercial companies marketing assays for the detection of the 'big 4' carbapenemase families. The literature search was carried out between January 2021 and October 2022 using Google Scholar and PubMed and the following search terms: [carbapenemase], [diagnostic], [assay], [‘name of the assay’]. The assays listed are limited to those that claim to identify as a minimum the ‘big 4’ carbapenemases (KPC, OXA-48-like, NDM and VIM). Publications referring to the assay, but not including data for detection of the ‘big 4’ carbapenemases were excluded. To our knowledge and at the time of publication, this list should be as exhaustive as possible and no bias is intended if any assay has been excluded from this report.

The list of assays has been divided into 3 categories: nucleic acid amplification technologies (NAATs), immunochromatographic assays and syndromic assays. Details of assay performance (as presented in the published literature and on company websites) can be found in the sections that follow to assist diagnostic laboratories in making a choice regarding which assay(s) to implement. However, performance characteristics are not readily comparable as the evaluations were performed by multiple groups using different sample panels with variation in the size of panel and carbapenemase family coverage.

Images provided in the tables are for information only and diagnostic laboratories should consider that the platform footprints will vary. List price as provided to UKHSA on request during preparation of this document is reported as per test, although laboratories should be aware that costs are likely to vary depending on sample throughput and local arrangements made between companies and distributors.

2.1 Nucleic acid amplification technologies (NAATs)

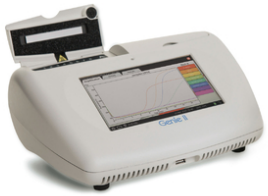
Nucleic acid amplification technologies (NAATs) generate results within 15 minutes to 7 hours. The technology principle relies mostly on the detection of carbapenemase genes by real-time PCR (RT-PCR), although some tests use isothermal amplification. The required platform may be a generic RT-PCR thermocycler already available in the diagnostic laboratory or a proprietary platform requiring capital expenditure. Sample throughput depends on the platform and can be increased if using modular systems.

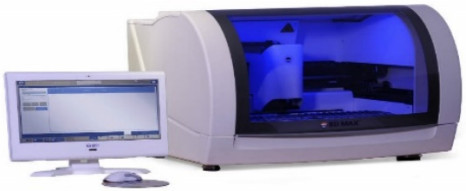
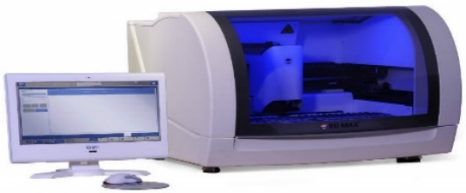
In the following tables the £ symbols relate to the costs as outlined below:

**Cost per isolate under £10 = £; £10 to £49 = ££; £50 to £100 = £££; more than £100 = ££££; x = price not available at time of publication.

***Equipment cost less than £1000 = £; £1,000 up to £10,000 = ££; £10,000 to up to £50,000 = £££; more than £50,000 = ££££; x = price not available at time of publication.

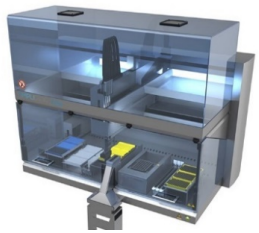
Table 1. NAATs integrated workflow - proprietary platform required

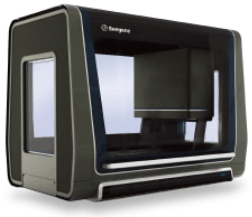
Assay	Assay coverage*	Additional equipment required	Workflow	Cost per isolate**	Equipment cost***
eazyplex® Superbug complete A/complete B/complete C/CRE Amplex 	KPC, OXA-48-like, NDM, VIM	Heating block, centrifuge (for processing blood cultures)	Sample in buffer, heating 2 minutes at 99°C, processing in the GENIE®	£££	£££
ESBL 16-well CRE 16-well CRE EU 16-well AusDiagnostics 	KPC, OXA-48-like, NDM, VIM, IMP	Plate spinner	Sample in sample buffer, processing in the MT processor and RT-PCR in the MT analyser (automated extraction method provided upon demand)	££	Equipment provided and installed for free

Assay	Assay coverage*	Additional equipment required	Workflow	Cost per isolate**	Equipment cost***
BD MAX™ Check-Points CPO BD/Check-Points 	KPC, OXA-48-like, NDM, VIM/IMP (VIM/IMP not differentiated by the assay)	None	Add 50 µl Amies tube to Sample Buffer Tube, processing in the BD MAX™ system	x	x
Check-Direct CPE for BD Max™ BD/CheckPoints 	KPC, OXA-48-like, NDM, VIM, IMP	None	Add 10 µl bacterial cell suspension from colonies to Sample Buffer Tube, processing in the BD MAX™ system	x	x

Assay	Assay coverage*	Additional equipment required	Workflow	Cost per isolate**	Equipment cost***
Check-MDR CT103 XL Array Check-Points 	KPC, OXA-48-like, NDM, VIM, IMP	Thermocycler, heating block, centrifuge	DNA extraction from pure culture, block-based PCR, hybridisation of PCR products to the array	£££	x
XPERT® CARBA-R Cepheid 	KPC, OXA-48-like, NDM, VIM, IMP-1-like	None	Swab/colonies in sample reagent, transfer of sample reagent to cartridge, processing of cartridge in GeneXpert®	££	£££-££££

Assay	Assay coverage*	Additional equipment required	Workflow	Cost per isolate**	Equipment cost***
CRE ELITe MGB® kit ELITechGroup 	KPC, OXA-48-like, NDM/VIM/IMP (NDM/VIM/IMP not differentiated by the assay)	None	DNA extraction process in cartridge and RT-PCR in cartridge	££	££££
Revogene® Carba C meridianBIOSCIENCE 	KPC, OXA-48-like, NDM, VIM, IMP	None	Colonies in saline solution, 15 µl of 0.5 Mc Farland suspension in Sample Buffer Tube. Suspension loaded in sample loading chamber of the microfluidic PIE cartridge	££	£££

Assay	Assay coverage*	Additional equipment required	Workflow	Cost per isolate**	Equipment cost***
Amplidiag® CarbaR+VRE CarbaR+MCR Mobidiag 	KPC, OXA-48-like, NDM, VIM, IMP	Cycler BioRad CFX 96	Sample in buffer, processing in Amplidiag® Easy, RT-PCR, automated result analysis and reporting with Amplidiag Analyzer software	££	££££
Novodiag® CarbaR+ Mobidiag 	KPC, OXA-48-like, NDM, VIM, IMP	None	Rectal swab or colony into 2 ml eNAT tube, 600 µl in the cartridge, cartridge inserted in the Novodiag® platform	££	£££

Assay	Assay coverage*	Additional equipment required	Workflow	Cost per isolate**	Equipment cost***
AllPlex™ Entero-DR assay Seegene 	KPC, OXA-48-like, NDM, VIM, IMP	Different platforms for automated extraction and set-up, cycler BioRad CFX 96	DNA extraction, set-up, RT-PCR	x	x
EntericBio® CPE Screen Serosep 	KPC, OXA-48-like, NDM, VIM, IMP	EntericBio® heatstation, Lightcycler	Swab into Sample Preparation Solution, heating for 30 minutes at 103°C, processing in the EntericBio workstation, load onto Lightcycler for amplification or detection	££	££££

*Coverage within carbapenemase families may vary between each assay.

Table 2. NAATs – PCR kits required and compatible PCR platforms

Assay	Assay coverage*	Compatible platforms	Workflow	Cost per isolate**	Equipment cost***
AID carbapenemase AIDGmbH	KPC, OXA-48-like, NDM, VIM, IMP	Any cycler platforms	DNA extraction from sample, PCR, reverse hybridisation	££	N/A
CARBAPLEX® Bruker	KPC, OXA-48-like, NDM, VIM, IMP	ABI 7500, BioRad CFX96, RotorGene Q, ABI QuantStudio 5, Bruker Hain Fluorocycler XT	DNA extraction from rectal swab, crude extract from pure culture, PCR using 2 mastermixes	££	N/A
Check-Direct CPE Check-Points	KPC, OXA-48-like, VIM/NDM (VIM/NDM are not differentiated by the assay)	ABI 7500, BioRad CFX96, RotorGene Q, LightCycler® 480 system I&II,	DNA extraction from rectal swab using NucliSENS® easyMAG®, crude extract from pure culture	£	N/A
EasyScreen™ ESBL/CPO Detection Kit Genetic Signatures	KPC, OXA-48-like, NDM, VIM-2, IMP	AB QuantStudio 7 Flex (96 well system), BioRad CFX96, BioRad CFX384, MIC qPCR (48 well system),	DNA conversion with the EasyScreen™ Sample Processing kit, converted DNA used for PCR (5 mastermixes)	££	N/A

Assay	Assay coverage*	Compatible platforms	Workflow	Cost per isolate**	Equipment cost***
		Roche Lightcycler 480 (96 well block)			
MAST ISOPLEX® CRE-ART MAST Group	KPC, OXA-48-like, NDM, VIM, IMP	ABI 7500, ABI 7500 FAST	Colonies in reconstitution buffer, 10 µl of the reaction mix added to individual tube of the CRE strip containing specific target LAMP assay	£££	N/A
Amplidiag® CarbaR + VRE or CarbaR+MCR Mobidiag	KPC, OXA-48-like, NDM, VIM, IMP	ABI 7500, BioRad CFX96, RotorGene Q	DNA extraction from stool samples, rectal swabs or pure culture, crude extract from pure culture, automated result analysis and reporting with Amplidiag Analyzer software	££	N/A

Assay	Assay coverage*	Compatible platforms	Workflow	Cost per isolate**	Equipment cost***
PANA RealTyper™ CRE Kit Panagene	KPC, OXA-48-like, NDM, VIM, IMP	BioRad CFX96, QuantStudio 5	DNA extraction from pure culture	x	N/A
STRECK ARM-D® kit Streck	KPC, OXA-48-like, NDM, VIM, IMP	ABI 7500 Fast, BioRad CFX96, RotorGene Q, ABI QuantStudio 7 Flex, Streck Zulu RT™	DNA extraction from pure culture, PCR using 3 mastermixes	££	N/A
AllPlex™ Entero-DR assay Seegene	KPC, OXA-48-like, NDM, VIM, IMP	BioRad CFX96	DNA extraction from rectal swabs, pure culture	x	N/A

*Coverage within carbapenemase families may vary between each assay.

Table 3. Performance of NAATs integrated workflow – proprietary platform required

Assay	Assay coverage*	Throughput per run	Hands on time per sample	Sample to results#	Sample types validated by manufacturer	Performance characteristics (sample types tested)
eazyplex® Superbug complete A/complete B/CRE Amplex	KPC, OXA-48-like, NDM, VIM	8 to 12 samples	2 minutes	15 to 20 minutes	c, liquid swab, u, bc	From manufacturer: Sens 100% Spec 99.4% (c)[a*]
						From published data: (8) Sens 95.7% Spec 100% (c) (9) Sens 100% Spec 100% (c) (10) Sens 100% Spec 100% (c) (10) Sens 100% Spec 59% (cs)
ESBL 16-well CRE 16-well CRE EU 16-well AusDiagnostics	KPC, OXA-48-like, NDM, VIM, IMP	24 samples	5 minutes	Less than 4 hours	c	From manufacturer: Sens 98 to 100% Spec 99.5 to 100% (c)[a*]
						From published data: (11) Sens 100% Spec 100% (c) (12) Sens 100% Spec 99.4% (rs - requires prior DNA extraction)

Assay	Assay coverage*	Throughput per run	Hands on time per sample	Sample to results#	Sample types validated by manufacturer	Performance characteristics (sample types tested)
BD MAX™ Check-Points CPO BD/Check-Points	KPC, OXA-48-like, NDM, VIM/IMP (VIM/IMP not differentiated by the assay)	Up to 24 tests	Less than 5 minutes	Less than 3 hours	rs	From published data: (13) Sens 97.1% Spec 98.8% (**rs**), (13) Sens 95.1% Spec 96.1% (c) (13) Sens 92.8% Spec 97.8% (rs) (14) Sens 90.3% Spec 100% (c) (15) Sens 95.7% Spec 96.5% (rs)
Check-Direct CPE for BD Max™ BD/Check-Points	KPC, OXA-48-like, NDM, VIM, IMP	Up to 24 tests	Less than 5 minutes	Less than 3 hours	c	From manufacturer: Sens 100% Spec 100% (c)[a*] From published data: (8) Sens 100% Spec 100% (c)
XPERT® CARBA-R Cepheid	KPC, OXA-48-like, NDM, VIM, IMP	1 to 80 samples depending on the number of modular systems	Less than 1 minute	48 minutes	c, rs, prs	From manufacturer: Sens 99.4 to 100% Spec 100% (rs, prs)[b*] Sens 100% Spec 99.7 to 100% (c)[b*] From published data: (15) Sens 97.9% Spec 99.8% (rs) (16) Sens 100% Spec 100% (u, bc) (8) Sens 94.4% Spec 100% (c) (17) Sens 100% Spec 97.1 to 98.1% (c) (18) Sens 84 to 100% Spec 84 to 100% (**br**)

Assay	Assay coverage*	Throughput per run	Hands on time per sample	Sample to results#	Sample types validated by manufacturer	Performance characteristics (sample types tested)
						(19) Sens 96.6% Spec 98.6% (rs) (20) Sens 97.7% Spec 97.2% (rs) (21) Sens 96.4 % Spec 100% (c) (22) Sens 100% Spec 100% (bc) (23) Sens 100% Spec 100% (bal) (24) Sens 99.1% Spec 98% (c) (24) Sens 96% Spec 94% (rs) (14) Sens 95.7% Spec 98.5% (c)
Check-MDR CT103 XL Array Check-Points	KPC, OXA-48-like, NDM, VIM, IMP	1 to 24 samples	1 hours	6 hours 30 minutes	c	From manufacturer: Sens 90 to 100% Spec 100% (c)[b*]
						From published data: (25) Sens 100% Spec 100% (c) (26) Sens 95 to 100% Spec 100% (c) (27) Sens 98.7% Spec 100% (c) (28) Sens 97% Spec 100% (c) (29) Sens 100% Spec 95.7% (c)
CRE ELITe MGB® kit ELITechGroup	KPC, OXA-48-like, NDM/VIM/IMP (NDM/VIM/IMP not	1 to 12 samples	Less than 2 minutes	Less than 3 hours	rs, bc	From manufacturer: Sens 99.3% Spec 100% (rs)[b*]
						From published data: (30) Sens 100% Spec 100% (c, rs, bc)

Assay	Assay coverage*	Throughput per run	Hands on time per sample	Sample to results#	Sample types validated by manufacturer	Performance characteristics (sample types tested)
	differentiated by the assay)					
Revogene® Carba C meridianBIOSCIENCE	KPC, OXA-48-like, NDM, VIM, IMP	1 to 8 samples	2 minutes	1 hour 10 minutes	c	From manufacturer: Sens 98.9 to 100 % Spec 95.9 to 99.8% (c)
						From published data: (31) Sens 100% Spec 100% (c) (32) Sens 100% Spec 100% (c) (21) Sens 100% Spec 100% (c) (33) Sens 100% Spec 100% (c) (34) Sens 98.9% Spec 97.2% (c) (35) Sens 100% Spec 99.5 (c)
Novodiag® CarbaR+ Mobidiag	KPC, OXA-48-like, NDM, VIM, IMP	4 to 16 samples per run	35 minutes	1 hour 20 minutes	rs, c	From manufacturer: Sens 100% Spec 100% (c) Sens 85.7 to 100% Spec 84.6 to 100% (rs)
						From published data: (10) Sens 100% Spec 100% (c) (10) Sens 100% Spec 63% (cs) (36) Sens 98.2% Spec 99.7% (c) (36) Sens 97.6% Spec 98.7% (rs)

Assay	Assay coverage*	Throughput per run	Hands on time per sample	Sample to results#	Sample types validated by manufacturer	Performance characteristics (sample types tested)
EntericBio® CPE Screen Serosep	KPC, OXA-48-like, NDM, VIM, IMP	1 to 46 samples per run	Less than 2 minutes	3 hours	c, st, liquid rs	From manufacturer: Sens 100% Spec 99.8% (rs)[a*] Sens 100% Spec 100% (c)[a*]
						From published data: (37) Sens 100% Spec 100% (c)

Table 4. Performance of NAATs – PCR kits and compatible PCR platforms

Assay	Assay coverage*	Throughput per run	Hands on time per sample	Sample to results#	Sample types validated by manufacturer	Performance characteristics (sample types tested)
AID carbapenemase AIDGmbH	KPC, OXA-48-like, NDM, VIM, IMP	Depending on the platform	3 hours	4 hours	bc, u	From published data: (38) Sens 100% Spec 100% (c)
CARBAPLEX® Bruker	KPC, OXA-48-like, NDM, VIM, IMP	Depending on the platform	5 minutes	Less than 3 hours	c, rs	From published data: (39) Sens 96.2% Spec 90% (rs)
Check-Direct CPE Check-Points	KPC, OXA-48-like, VIM/NDM (VIM and NDM are not differentiated by the assay)	Up to 96 tests	5 minutes	2 hours	c, rs, prs	From manufacturer: Sens 100% Spec 100% (c)[b*]
						From published data: (8) Sens 100% Spec 100% (c) (40) Sens 100% Spec 94% (rs) (41) Sens 100% Spec 100% (c, rs) (42) Sens 100% Spec 88% (rs) (43) Sens 100% Spec 100% (c)

Assay	Assay coverage*	Throughput per run	Hands on time per sample	Sample to results#	Sample types validated by manufacturer	Performance characteristics (sample types tested)
EasyScreen™ ESBL/CPO Detection Kit Genetic Signatures	KPC, OXA-48-like, NDM, VIM-2, IMP	Depending on the platform	Less than 1 minute (Depending on the platform)	Less than 5 hours (Depending on platform and sample number)	c, lfs, cfs (diluted in PBS and extracted)	From manufacturer: Sens 100% Spec 100% (c, lfs, cfs) From published data: (12) Sens 100% Spec 99.3% (rs - requires prior DNA conversion) (44) Sens 100% Spec 96.3% (c)
MAST ISOPLEX® CRE -ART MAST Group	KPC, OXA-48-like, NDM, VIM, IMP	Depending on the platform	15 minutes	45 minutes	c	From manufacturer: Sens 100% Spec 97% (c) From published data: (45) Sens 98.2% Spec 100% (c)
Amplidiag® CarbaR+VRE or CarbaR+MCR Mobidiag	KPC, OXA-48-like, NDM, VIM, IMP	Up to 29 samples 48 samples with Amplidiag® Easy	5 minutes	Less than 2 hours	c (CarbaR+VRE and CarbaR+MCR) c, rs, st (CarbaR+MCR)	From manufacturer: Sens 91.7 to 100% Spec 99.4 to 100% (c)[a*] Sens 95.5 to 100% Spec 98.5 to 100% (st, rs)[a*] From published data: (46) Sens 100% Spec 88.9 to 100% (c)

Assay	Assay coverage*	Throughput per run	Hands on time per sample	Sample to results#	Sample types validated by manufacturer	Performance characteristics (sample types tested)
						(47) Sens 92.5 to100% Spec 86 to100% (c, rs) (12) Sens 83.3% Spec 98.85% (rs) (10) Sens 100% Spec 100% (c) (10) Sens 100% Spec 63% (cs) (48) Sens 100% Spec 98.6% (rs) AMRHAI (unpublished): Sens 99% Spec 97.6% (c)
PANA RealTyper™ CRE Kit Panagene	KPC, OXA-48-like, NDM, VIM, IMP	Up to 48 tests	x	x	x	From published data: (49) Sens 99.5% Spec 99.7% (c)
STRECK ARM-D® kit Streck	KPC, OXA-48-like, NDM, VIM, IMP	Depending on the platform	5 minutes	22 minutes to 1 hour	c	From manufacturer: Sens 100% Spec 97 to100% (c)[b*]
AllPlex™ Entero-DR assay Seegene	KPC, OXA-48-like, NDM, VIM, IMP	40 samples per run	5 minutes	3 hours	c, rs, u	From published data: (12) Sens 100% Spec 98.2% (rs)

Assay	Assay coverage*	Throughput per run	Hands on time per sample	Sample to results#	Sample types validated by manufacturer	Performance characteristics (sample types tested)
						(50) Sens 100% Spec 100% (bc) (51) Sens 100% Spec 92-100% (c)

#: time to result excludes the incubation time required for bacterial growth. x = information not available at time of publication.

sample type: c = bacterial colonies; u = urine; bc = blood culture; rs = rectal swab, prs = peri-rectal swabs, br = bronchial specimens, st = stool samples, cs = clinical samples, bal = bronchoalveolar lavage, lfs = liquid faecal screen, cfs = charcoal faecal screen, bold: spiked sample.

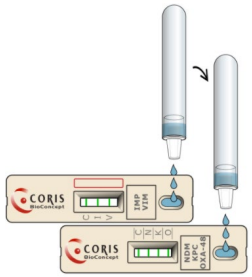
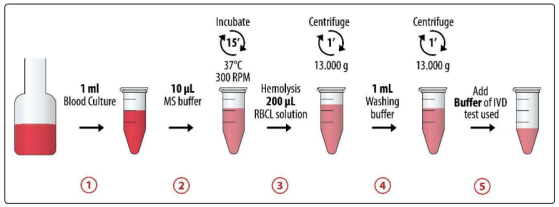
a*: assay performance determined from multi-centre evaluations.

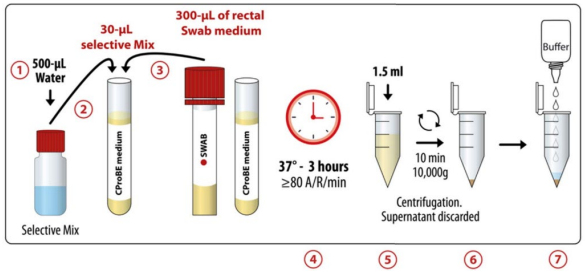
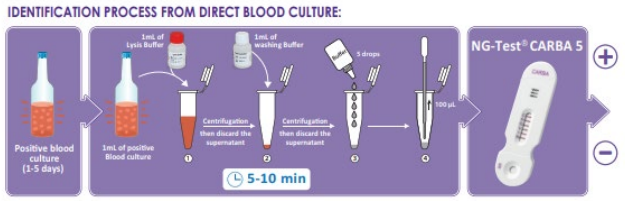
b*: assay performance without evidence of multi-centre evaluations.

2.2 Immunochromatographic assays

Immunochromatographic assays (or lateral flow assays) are based on immunological detection of epitopes of the targeted carbapenemase enzyme (rather than gene detection). These are typically formatted as cassettes with a 10 to 15 minute running time and allow screening of one sample per cartridge.

Table 5. List of immunochromatographic assays

Assay	Assay coverage*	Additional equipment required	Workflow	Cost per test**	Equipment cost***
O.K.N.V.I. RESIST-5 Coris BioConcept 	KPC, OXA-48-like, NDM, VIM, IMP	Vortex	Colonies in lysis buffer, suspensions added in the strips, 2 strips required (KPC/OXA-48-like/NDM and VIM/IMP).	£	N/A
O.K.N.V.I. RESIST-5 RESIST-BC Coris BioConcept	KPC, OXA-48-like, NDM, VIM, IMP	Shaker, centrifuge	To be used with O.K.N.V.I. RESIST-5, haemolysis of 1 ml positive blood culture, centrifugation, centrifugation, buffer added to the bacterial pellet, suspension added to the strip. 	££	N/A
O.K.N.V.I. RESIST-5 RESIST-ReSCape Coris BioConcept	KPC, OXA-48-like, NDM, VIM, IMP	Waterbath, centrifuge, vortex	To be used with O.K.N.V.I. RESIST-5, 300 µl of rectal swab transport medium added to CProBE broth, incubaction in waterbath, centrifugation, buffer added to the bacterial pellet, suspension added to the strip.	££	N/A

Assay	Assay coverage*	Additional equipment required	Workflow	Cost per test**	Equipment cost***
					
NG-test® Carba-5 NG-Biotech 	KPC, OXA-48-like, NDM, VIM, IMP	Vortex	Colonies in lysis buffer, suspensions added in the strips.	££	N/A
NG-test® Carba-5 NG-Test® Blood Culture Prep NG-Biotech	KPC, OXA-48-like, NDM, VIM, IMP	Vortex, centrifuge	To be used with the NG-test® Carba-5, haemolysis of 1 ml positive blood culture, centrifugation, washing of pellet, extraction buffer added to the bacterial pellet, suspension added to the strip. 	££	N/A

*Coverage within carbapenemase families may vary between each assay.

Table 6. Performance of immunochromatographic assays

Assay	Assay coverage*	Throughput per cartridge	Hands on time per sample	Sample to results#	Sample types validated by manufacturer	Performance characteristics (sample types tested)
O.K.N.V.I. RESIST-5 Coris BioConcept	KPC, OXA-48-like, NDM, VIM, IMP	1 sample	Less than 5 minutes to 30 minutes depending of sample types to be tested	20 minutes to less than 4 hours depending of sample types to be tested	c, bc, rs	From the manufacturer: Sens 100% Spec 100% (c)[a*] From published data: (52) Sens 98.4% Spec 100% (c) (53) Sens 94.9% Spec 93.3% (c) (53) Sens 93.8% Spec 98.1% (c)
NG-test® Carba-5 NG-Biotech	KPC, OXA-48-like, NDM, VIM, IMP	1 sample	Less than 5 minutes to 20 minutes depending of sample types to be tested	20 minutes to 30 minutes depending of sample types to be tested	c, bc	From the manufacturer: Sens 100% Spec 100% (c)[a*] Sens 100% Spec 100% (bc) From published data: (53) Sens 100% Spec 86.7% (c) (53) Sens 99.3% Spec 94.6% (c)

Assay	Assay coverage*	Throughput per cartridge	Hands on time per sample	Sample to results#	Sample types validated by manufacturer	Performance characteristics (sample types tested)
						(54) Sens 100% Spec 95.3 to 100% (c) (55) Sens 97.3% Spec 99.7% (c) (56) Sens 100% Spec 100% (c) (4) Sens 97.9% Spec 100% (c) (57) Sens 96.3% Spec 100% (c) (58) Sens 100% Spec 100% (c) (59) Sens 100% Spec 100% (c) (60) Sens 90% Spec 100% (**bc**) (61) Sens 100% Spec 100% (bc, **bc**) (61) Sens 94.1% Spec 100% (uri, **uri**) (61) Sens 92.3% Spec 100% (rs after overnight enrichment culture)

*Coverage within carbapenemase families may vary between each assay.

#: time to result excludes the incubation time required for bacterial growth.

sample type: c = bacterial colonies; u = urine; bc = blood culture; rs = rectal swab; bold: spiked sample

ND = not determined.

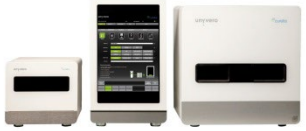
a*: assay performance determined from multi-centre evaluations.

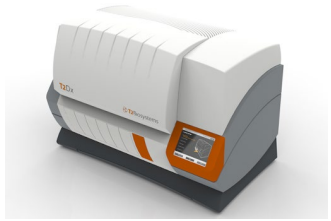
b*: assay performance without evidence of multi-centre evaluations.

2.3 Syndromic assays

Syndromic assays combine approaches for the detection and identification of bacterial species associated with clinical syndromes (such as bloodstream, respiratory or urinary tract infections) and selected antimicrobial resistance genes. The technology principle relies on a combination of PCR and DNA hybridization.

Table 7. List of syndromic assays

Assay	Assay coverage*	Additional equipment required	Workflow	Cost per isolate**	Equipment cost***
BIOFIRE® Blood Culture Identification 2/BIOFIRE® FILMARRAY® Pneumonia plus Panel Biomérieux 	KPC, OXA-48-like, NDM, VIM, IMP	BIOFIRE® FILMARRAY® Multiplex Real-Time PCR systems	Sample in FILMARRAY sample buffer then injected in FILMARRAY pouch	x	x
Unyvero® Curetis AG 	KPC, OXA-48-like, NDM, VIM, IMP	None	Sample in Unyvero Sample tube, sample tube inserted in the Unyvero Lysator, sample tube and mastermix in the Unyvero cartridge, cartridge in the Unyvero Analyzer	x	x

Assay	Assay coverage*	Additional equipment required	Workflow	Cost per isolate**	Equipment cost***
ePlex® BCID-GN panel GenMarkDx 	KPC, OXA-48-like, NDM, VIM, IMP	None	Blood culture sample loaded in cartridge	££££	£££
Verigene® Gram-negative blood culture test (BC-GN) Nanosphere Luminex 	KPC, OXA-48-like, NDM, VIM	none	Blood culture sample loaded in cartridge	££	£££
T2Resistance™ Panel T2Biosystems® 	KPC,OXA-48-like, NDM/VIM/IMP	None	Blood culture loaded in sample tube and reagent tray and snapped onto cartridge, inserted in the T2Dx® Instrument	Depending on number of tests	Depending on number of tests

*Coverage within carbapenemase families may vary between each assay.

Table 8. Performance of syndromic assays

Assay	Assay coverage*	Throughput per run	Hands on time per sample	Sample to results#	Samples types validated by manufacturer	Performance characteristics (sample types tested)
BIOFIRE® Blood Culture Identification 2 / BIOFIRE® FILMARRAY® Pneumonia plus Panel Biomérieux	KPC, OXA-48-like, NDM, VIM, IMP	44 to 264 samples	2 minute	1 hour	Positive bc, sputum-like, BAL-like	From published data: (62) Sens 100% Spec 100% (bc) (63) Sens 100% Spec ND (bc)
Unyvero® Curetis AG	KPC, OXA-48-like, NDM, VIM, IMP	1 to 8 samples	2 minutes	5 hours	bc, u	From published data: (64) Sens 100% Spec 100% (IAI)
ePlex® BCID-GN panel GenMarkDx	KPC, OXA-48-like, NDM, VIM, IMP	3 to 24 samples depending on the number of platforms	Less than 2 minutes	1.5 hours	bc	No data
Verigene® Gram-negative blood culture test	KPC, OXA-48-like, NDM, VIM	Depending on the number of platforms	Less than 5 minutes	Less than 2 hours	bc	From manufacturer: Sens 77.8 to 100% Spec 100% (bc)[b*]

Assay	Assay coverage*	Throughput per run	Hands on time per sample	Sample to results#	Samples types validated by manufacturer	Performance characteristics (sample types tested)
Nanosphere - Luminex						From published data: (65) Sens 92.3% Spec 100% (bc) (66) Sens 100% Spec ND (bc) (67) Sens 100% Spec ND (bc, **bc**) (68) Sens 100% Spec ND (bc)
T2Resistance™ Panel T2Biosystems®	KPC,OXA-48-like, NDM/VIM/IMP	1 to 7 samples	About 10 minutes	3 to 5 hours	bc	(69) Positive percent agreement 85.7%

#: time to result excludes the incubation time required for bacterial growth.

sample type: u = urine; bc = blood culture; IAI = fluid samples from intra-abdominal infections; bold: spiked sample

ND = not determined.

a*: assay performance determined from multi-centre evaluations.

b*: assay performance without evidence of multi-centre evaluations.

3. Points to consider for implementation

Diagnostic laboratories should consider whether carbapenemase detection is to be performed from isolated bacterial colonies or directly from clinical specimens such as rectal swabs or faeces. The latter will be more appropriate for rapidly identifying patients colonised with CPE.

UKHSA recommends that diagnostic laboratories should have methods in place for both and at least for testing from bacterial colonies.

There are few studies assessing the role of molecular assays in direct testing of rectal swabs; however, a meta-analysis focussing on evaluating the performance of molecular assays when applied in this context identified that they exhibited good sensitivity (0.95) and specificity (0.994) when used for direct detection of CPE from rectal swabs although there was considerable heterogeneity in the sensitivity and specificity between studies (70). However, as previously highlighted by Health Improvement Scotland, a lack of evidence of diagnostic accuracy means that it is not currently possible to identify the most effective assay for screening using rectal swabs (71).

Published evaluations (including head-to-head and multi-centre evaluations) are still lacking for some assays, with syndromic assays being particularly under-represented in the literature. In several studies referenced in this report, ability of the assay to detect the ‘big 4’ carbapenemases was evaluated on spiked blood culture, urine or bronchial samples as the prevalence of bacteria containing these carbapenemases in such clinical samples is likely to be low in most hospital settings. Diagnostic laboratories wishing to test direct from clinical specimens (and bacterial cultures) must therefore perform their own assay validation locally to conform to United Kingdom Accreditation Service (UKAS) requirements.

Overall, the assays presented in this report vary considerably in the amount of user input and molecular expertise required to set up each test, ranging from assays that require minimal staff training (for example, eazyplex® Superbug complete A/complete B/complete C CRE (Amplex), CRE 16-well/ EU 16-well (AusDiagnostics), XPERT® CARBA-R (Cepheid), BD MAX™ Check-Points CPO assay, Revogene® Carba C (Meridian BioSciences), immuno-chromatographic tests or syndromic assays) to assays that require prior extraction of DNA from clinical specimens/bacterial isolates and/or preparation of several reagent master mixes or hybridisation of PCR products. Diagnostic laboratories should also note that testing of sample types different from those initially validated by the manufacturer might require additional DNA extraction steps. Choice of an assay will therefore depend on staff

expertise and ability of an assay to fit into local workflows. Bench space required for the installation of the platform should also be assessed prior to implementation.

The ASSURED (Affordable, Sensitive, Specific, User-friendly, Rapid and robust Equipment-free and Deliverable to end-users) criteria can be used to help in the decision for identifying an appropriate diagnostic test (72). These criteria cover 6 steps required to select an in vitro diagnostic test.

1. Define the test's purpose.
2. Review the market and check product's specification (for example, sample type required, time to results, additional equipment required).
3. Review the test's regulatory approval (for example, determine if the test is CE marked).
4. Obtain data on the diagnostic accuracy of the test under ideal conditions (that is, in laboratory-based evaluations).
5. Obtain data on the diagnostic accuracy of the test in clinical practice.
6. Monitor the test's performance in routine use (quality control and proficiency testing undertaken, supervison and training of the end-users).

(Adapted from 'A guide to aid the selection of diagnostic tests' by Kosack CS and others, (72).)

When comparing performance characteristics, readers should be aware that calculations of sensitivity and specificity will be based on the assumption that all isolates of CPE will be detected by either the assay under evaluation or the comparator test. Analytical performance of an assay may be exaggerated if it is compared against a poorly performing alternative and will also depend on the diversity and size of the test panel. Laboratories should therefore ensure that representatives of each carbapenemase family circulating in their patient population, and preferably representatives of at least each of the 'big 4' carbapenemase families, are included in local validation exercises. To assist with local validation a panel of CPE isolates representing common variants of KPC, OXA-48-like, NDM, VIM and IMP carbapenemases known to be circulating in the UK can be obtained from the National Collection of Type Cultures NCTC.

All the assays listed in this report claim to detect the 'big 4' carbapenemases, with some assays having coverage extended to include detection of IMP metallo-β-lactamases (MBLs) and the detection of rarer class A carbapenemase families (GES, IMI, FRI) (Amplidiag® CarbaR+MCR, CRE 16-well/ EU 16-well (AusDiagnostics), EntericBio® CPE screen, CT103 XL Array (Check-Points), PANA RealTyper™ CRE Kit (Panagene)). Laboratories should consider implementing an assay covering as broad a spectrum of carbapenemases as possible or at least include detection of IMP carbapenemase as its identification has been

reported in all regions of the UK with incidence rates variable between regions (3). However, some assays included here (Check-Direct CPE (Check-Points), BD MAX™ Check-Points CPO (Check-Points), CRE ELITe MGB® kits (ELITech)) will detect but not distinguish between all carbapenemases (see Tables 1 and 2). Whilst a 'yes/no' answer regarding presence of an MBL is sufficient to implement infection prevention and control procedures and enable appropriate patient management, the knowledge of which MBL family is present will inform local epidemiology.

All assays in this report will be limited in that they will only detect known carbapenemases (or closely related variants) within the families covered; newly emerged variants may not be reliably detected and, obviously, carbapenemases belonging to families outside of an assay's scope will not be detected. Coverage within a carbapenemase family may also vary from assay to assay, for example, the Superbug complete A (Amplex) does not detect 2 variants of OXA-48 (OXA-181 and OXA-232), whilst the Xpert® Carba-R (Cepheid) focusses on detection of IMP-1-like carbapenemases rather than the entire IMP family (8).

In April 2018, AMRHAI introduced charging for detection of the 'big 4' carbapenemase families. Extended molecular screening for IMP, GES and other rarer carbapenemase families remains free-of-charge for any carbapenem-resistant isolates that meet EUCAST criteria for further investigation but are negative for the 'big 4' families in local tests.

The CE-marked real-time PCR assay that we use screens for class A (KPC, IMI, GES, FRI and SME), class B (DIM, GIM, IMP, NDM, SIM, SPM and VIM) and class D (OXA-48-like) carbapenemases, which covers all carbapenemase families identified amongst more than 18,000 CPE submitted to AMRHAI from UK laboratories since 2000 (2). AMRHAI will monitor for the emergence of novel carbapenemases not covered by our PCR assay by more detailed investigation of PCR-negative isolates from clinical specimens.

To ensure locally-confirmed isolates continue to contribute to national CPE surveillance UKHSA has developed methods to collect results of local carbapenemase detection testing via UKHSA's Second Generation Surveillance System (SGSS; see Appendix).

Appendix: Changes to referral and reporting of carbapenemase-producing Gram-negative bacteria in England

Rationale for change

Following the decommissioning of the Electronic Reporting System (ERS) for enhanced surveillance of carbapenemase-producing Gram-negative bacteria on 30 April 2019, UKHSA has modified its surveillance approach. A number of changes have been made to allow more efficient capture of data on carbapenemase producers identified in England and streamline the referral of isolates that continue to be submitted to the national reference laboratory.

Summary of changes:

From 1 October 2020 all diagnostic laboratories in England have a duty to notify the following to the UKHSA notifications of infectious diseases (NOIDs) via UKHSA's Second Generation Surveillance System (SGSS):

- acquired carbapenemase-producing Gram-negative bacteria identified in human samples
- the results of any antimicrobial susceptibility test and any resistance mechanism for any of the causative agents listed in Schedule 2 of the Health Protection (Notifications) Regulations 2010

Specimens sent to the reference laboratory need to include patient identifiers (particularly NHS number and date of birth) and specimen identifiers (specimen type and laboratory number). UKHSA will then link the reference laboratory specimens to the SGSS reports in order to allow NHS laboratories to review and download their own data.

- SGSS can be accessed online

As of 1 January 2019 only locally-confirmed carbapenemase producers from sterile sites (for example, blood, CSF, joint fluid) should be sent to the AMRHAI Reference Unit for inclusion in the national strain archive.

The AMRHAI Reference Unit is regularly asked to define criteria for referring carbapenem-resistant bacteria for investigation. These criteria are subjective and under regular review.

For the current referral criteria, please refer to the latest Bacteriology Reference Department user manual, which can be accessed online.

Submission of enhanced surveillance data is no longer required on identification of carbapenemase presence.

Reporting of locally-confirmed carbapenemase-producing Gram-negative bacteria

Laboratories using one of the molecular or immunochromatographic methods described in the main body of this report are requested to record their findings on their Laboratory Information Management System (LIMS) and make use of 'dummy' antibiotic codes to report results via SGSS.

This new approach of reporting locally confirmed carbapenemase producers to SGSS for surveillance will avoid the requirement of manual reporting to UKHSA. To ensure its success and allow comprehensive national capture of data on CPE, diagnostic laboratories should have now established processes that allow confirmatory testing of suspected acquired carbapenemase producers locally and ensure that these results are captured by their LIMS.

SGSS reporting support

Guidance on how to set up systems to report results via SGSS is briefly explained here. For further information and support please contact your local UKHSA Field Service Information Manager (see below for contact details).

For each carbapenemase gene you can identify, create a 'dummy' antibiotic code in your LIMS. Suggested codes to use are listed in Table 1. Please inform us of alternative dummy codes being used so that we are able to translate and interpret these in SGSS.
The results (detected or not detected) need to be reported as a single character, preferably '+' for detected and '-' for not detected.

Systems that are only able to store alphanumeric characters should preferably use 'P' for detected and 'N' for not detected. However, if the system only allows 'R' and 'S' then please use 'R' for detected and 'S' for not detected.

For specimens that have not undergone culture, report organism as 'NO ORGANISM ISOLATED'.

These results may need to be suppressed for your reports. However, the SGSS AMR feed should be configured to include all test results (including those suppressed for the purpose of local reporting).

Table 1. Suggested codes and descriptions for reporting local carbapenemase results

Code	Description
IMP	Imipenemase
KPC	Klebsiella pneumoniae carbapenemase
NDM	New Delhi metallo-β-lactamase
OXA48	Oxacillinase 48
VIM	Verona integron metallo-β-lactamase

Referral of suspected carbapenemase producers

Local laboratories that are yet to implement methods for the identification of the 'big 4' carbapenemase genes (KPC, OXA-48-like, NDM and VIM) should continue to refer isolates to the national reference laboratory until local methods for detection are in place. Some UKHSA Specialist Laboratories offer referral services at a regional level, and then refer selected isolates onwards to the AMRHAI Reference Unit. Laboratories using this regional service should not submit isolates to AMRHAI directly. Isolates that are negative for the 'big 4' on local testing but meet EUCAST criteria (74) for further investigation should be referred to the national reference laboratory to rule out presence of uncommon carbapenemases.

Any local laboratory requiring identification or confirmation of carbapenemase presence should refer isolates in line with the UK Standards for Microbiology Investigations: Laboratory Detection and Reporting of Bacteria with Carbapenem-Hydrolysing β-lactamases (Carbapenemases). Referrals should be made using the relevant 'Healthcare Pathogens: Characterisation and resistance' form (H1 and H2).

Table 2 summarises carbapenemase gene families that are targeted using our reference service PCR. Where an 'exceptional' carbapenemase and species combination result (cells without a ¥ symbol in Table 2) has been identified, or where an unusual organism has been identified with an acquired carbapenemase (that is, any bacterial genera other than a member of the Enterobacterales, *Pseudomonas* spp. or *Acinetobacter* spp.), isolates should

be sent to the AMRHAI Reference Unit for confirmation after ruling out a mixed culture and confirmation of local results.

Table 2: Distribution of carbapenemase genes covered by AMRHAI Reference Unit PCR (based on AMRHAI data)

Carbapenemase gene family	Associated with common 'host' organism		
	Enterobacterales	*Pseudomonas* spp.	*Acinetobacter* spp.
KPC	¥	<10[D]	<10[D]
OXA-48-like	¥	<10[D]	0
NDM	¥	¥	¥
VIM	¥	¥	<10[D]
IMP	¥	¥	¥
IMI/NMC-A	¥[B]	0	0
GES	¥	¥	<10[D]
FRI	<10	0	0
SME	¥[C] <10[D]	0	0
DIM	0	<10[D]	0
GIM	<10[D]	0	0
SIM	0	<10[D]	0
SPM	0	<10[D]	0
OXA-23-like	<10[D]	0	¥
OXA-40-like	0	0	¥
OXA-51-like[A]	0	0	¥
OXA-58-like	0	0	¥

Note to Table 2
Note 1. Table 2 uses the following symbols:
¥ = combinations of mechanism and species would not be considered as exceptional.
A = intrinsic to *A. baumannii* and only expressed when associated with an insertion element.
B = almost exclusively reported in *Enterobacter* spp. with less than a handful of reports in other genera of Enterobacterales.
C = reported only in *Serratia marcescens*.
D = fewer than 10 in total ever identified by the AMRHAI Reference Unit.

UKHSA Field Service Information Manager or SGSS support contact details

Region	Contact details
Central	FES.central@ukhsa.gov.uk
East of England	EFEU@ukhsa.gov.uk
Midlands	FSMidlands@ukhsa.gov.uk
National	FES.National@ukhsa.gov.uk
North East	FES.NorthEast@ukhsa.gov.uk
North West	FES.NorthWest@ukhsa.gov.uk
South East and London (SEaL)	FES.SEaL@ukhsa.gov.uk
South West	FES.southwest@ukhsa.gov.uk
Yorkshire and the Humber	YHFES@ukhsa.gov.uk

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