‘CRE, CRO, CPE and CPO’: terminology past its ‘sell-by-date’ in an era of new antibiotics and regional carbapenemase epidemiology.

David M Livermore[1], David P Nicolau[2], Katie L Hopkins[3], Danièle Meunier[3]

[1]*Norwich Medical School, University of East Anglia, Norwich NR4 7TJ, United Kingdom*

[2]*Center for Anti-Infective Research & Development, Hartford Hospital, Hartford, CT 06102, United States*

[3]*Antimicrobial Resistance & Healthcare Associated Infections Reference Unit, National Infection Service, Public Health England, 61 Colindale Avenue, London NW9 5EQ, United Kingdom*

Terminology of carbapenem resistance

40-Word summary

The term ‘CRE’ has become inadequate with the advent of new therapies. These make it essential for authors and licensing agencies to specify the particular carbapenemase(s) meant. The future may demand greater precision, for mutations modulate activity, within carbapenemase families.

Abstract. Carbapenem resistance in Gram-negative bacteria is a public health concern. Numerous government and agency reports consequently discuss 'CRE' and 'CROs', meaning 'Carbapenem-Resistant Enterobacterales' or 'Carbapenem-resistant organisms'. Unfortunately these terms are fuzzy. Do they include (i) Proteeae with inherent imipenem resistance, (ii) porin-deficient Enterobacterales resistant to ertapenem but not other carbapenems, (iii) Enterobacterales with OXA-48-like enzymes that remain 'carbapenem susceptible' at breakpoint, and (iv) *Pseudomonas aeruginosa* that merely lack OprD? Counting carbapenemase-producing Enterobacterales/organisms ('CPE' or 'CPOs') is better but still insufficient, because different carbapenemases have differing treatment implications, particularly for new β-lactam/β-lactamase inhibitor combinations. At the least it is essential for authors, journals, and regulatory agencies to specify the carbapenemases meant. The future may demand even greater precision, for mutations can alter activity, and the ability to confer resistance, *within* carbapenemase families.

For 25 years after imipenem's launch in 1985, carbapenems were the 'go to' antibiotics for infections involving multiresistant Gram-negative bacteria. The recent accumulation of carbapenem resistance among Enterobacterales consequently is concerning, and these organisms top the WHO's priority list of resistant pathogens, along with 'carbapenem-resistant *Acinetobacter baumannii*' and 'carbapenem-resistant '*Pseudomonas aeruginosa'*[1] Carbapenem-resistant Enterobacterales also achieve the top tier of the CDC's 'Urgent Resistance Threats' [2] and are prioritised in the UK's 5-Year antimicrobial resistance national action plan [3].

'Carbapenem-resistant': What is included?

If we are to prioritise carbapenem resistance we need a clear definition. Unfortunately the moniker is elastic, meaning that prevalence rates of 'carbapenem resistance' can be misleading.

It is easy to miss this lack of clarity, especially once 'Carbapenem-Resistant Enterobacterales' and 'Carbapenem-Resistant Organisms' are shortened to acronyms – CREs and CROs. In reality, these encompass multiple species and mechanisms, differing greatly in significance. This is unlike, say, 'MRSA', which denotes a single species almost always with one mechanism, or even 'ESBL producers' where – although ESBLs belong to multiple families – they almost all are Class A β-lactamases attacking oxyimino-aminothiazolyl cephalosporins, not cephamycins nor carbapenems, and inhibited by clavulanate and penicillanic acid sulfones [4].

Examples illustrate the problem. First, consider a *Proteus mirabilis, Morganella morganii or Providencia* spp. with an imipenem MIC of 8 mg/L. Is this a 'CRE', despite meropenem and ertapenem, of (say) MICs 0.03 mg/L? Imipenem MIC_{90}s of 8 mg/L were reported for Proteeae when imipenem was launched [5], but there is no evidence that such Proteeae have since proliferated, or are a source of failures with imipenem. Secondly, what about a *Klebsiella* or *Enterobacter* spp. with (resistant) ertapenem MICs of 2 or 4 mg/L but retained – albeit reduced – susceptibility to imipenem and

meropenem (MICs, 0.25-0.5 mg/L)? This profile commonly arises via combinations of AmpC or ESBL activity together with porin loss [6]. Does resistance to ertapenem qualify the isolate as a 'CRE'? On the other hand, how about a *Klebsiella* with weakly-expressed OXA-48 enzyme, susceptible to all carbapenems at clinical breakpoints, but meeting EUCAST's 'screening threshold' of a meropenem MIC >0.12 mg/L? It fails the literal definition of 'CRE' but has a carbapenemase. Lastly, most 'carbapenem-resistant *Pseudomonas aeruginosa*' have simply lost OprD and this, of itself, compromises only carbapenems. Such isolates are 'CROs', but present little problem unless they have other resistances. In the UK twice as many *P. aeruginosa* are 'CROs' as are ceftazidime resistant [7].

These points are more than pedantic. A rate of 20% carbapenem resistance in *P. aeruginosa* is undesirable, but not catastrophic if most are OprD mutants. The situation is more troubling if 40% of carbapenem-resistant *P. aeruginosa* have carbapenemases, as in parts of the Middle East [8]. The WHO's generic inclusion of 'carbapenem-resistant *P. aeruginosa*' among its priorities is unhelpful. And, whilst ertapenem-resistant Enterobacterales with ESBLs and impermeability cause problems in individual patients, and can be selected during carbapenem therapy, their resistance is often unstable, limiting impact. They rarely cause outbreaks. OXA-48-like enzymes, by contrast, are plasmid-mediated, allowing horizontal transfer; moreover, producers with low MICs are easily overlooked, permitting 'stealth spread' [9].

The fact that specialist readers know these nuances does not alter the fact that the loosely used 'CRE' and 'CRO' confuse as they percolate wider clinical and public health communities.

'Carbapenemase-producing'... Better than 'carbapenem-resistant'

'Carbapenemase-Producing Enterobacterales' (CPE) and 'Carbapenemase-Producing Organism' (CPO) are more precise than 'carbapenem-resistant'. The only medically-important bacteria with strongly-expressed, endogenous carbapenemases are *Stenotrophomonas maltophilia* and some

Chryseobacterium and *Aeromonas* spp. [10]. Consequently *all* CPEs and *almost all* CPOs are exceptional, meriting concern. The counterpoint applies too: if a 'CRE' is resistant to only ertapenem and is not a CPE then imipenem and meropenem remain valid treatments at high dose. Moreover, given the rarity of outbreaks involving such strains, infection control need not be enhanced above normal good practice.

Asides from treatment issues, CPE/CPOs are important because (excepting SME and some IMI/NMC types) their enzymes typically are plasmid-mediated, facilitating horizontal spread. Some, notably *K. pneumoniae* ST258 with KPC enzymes, belong to globally successful strains (11-13) that, unlike porin mutants, unequivocally are biologically fit and able to cause outbreaks.

Carbapenemase type is crucial

A further step is needed, though, for it is unhelpful to lump different carbapenemases together. The predominant KPC, OXA-48-like, *Acinetobacter* OXA (i.e. OXA-23, 24, 51 and -58) and metallo (i.e. IMP, VIM and NDM) enzymes differ greatly, leading to differing treatment implications [14]. Occasional isolates with FRI, GES, IMI and SME types add complexity, but are rare.

If all carbapenemase types were evenly distributed authors would craft their language to specify the enzyme(s) meant. But, in reality, carbapenemase distributions are regional or national, and the common CPE of an author may differ radically from those troubling his reader elsewhere. KPC enzymes dominate in the Americas (except maybe Canada), Italy, Israel, Greece and Portugal, NDM in South Asia, and OXA-48-like in the Middle East (except Israel), North Africa, and much of Europe except for Italy, Greece and Portugal [15]. IMP and VIM MBLs dominate in carbapenemase-producing *P. aeruginosa* [16] except that SPM enzymes are prevalent in Brazil and that KPC types have spread in Colombia [11]. OXA-23 and -40 dominate everywhere in *A. baumannii*, with MBLs occasionally seen [17].

Again, examples illustrate how confusion spreads. Lecturing internationally on carbapenem resistance one regularly took questions along the lines of "What do you think of double carbapenem combinations?" Such combinations work on the principle that a high-affinity carbapenem acts as a competitive substrate/inhibitor, allowing the second carbapenem to exert its antibacterial activity. There is evidence of their efficacy against Enterobacterales with KPC enzymes [18] and the approach originated in the US [19] where these dominate [11]. Elsewhere in the world it is easy – reading (predominantly) US publications that used 'carbapenemase' and 'KPC enzyme' interchangeably – to miss the point that such combinations have little logic (or synergy) in countries where other carbapenemase types dominate.

Knowing the carbapenemase family supports treatment choices. Among older agents, (i) temocillin may be active against CPE with KPC enzymes, though MICs are often around a tentative 8 mg/L breakpoint and clinical data are scanty [20], whilst (ii) ceftazidime typically retains activity against CPE with OXA-48-like enzymes if these lack ESBL or AmpC activity [21] and (iii) aztreonam remains active against those with either OXA-48 or MBLs if they lack ESBL or AmpC activity [22].

More critically, knowledge of the carbapenemase type is vital to predicting the utility of recently licensed β-lactamase inhibitor combinations (Table 1). Ceftazidime/avibactam, meropenem/vaborbactam and imipenem/relebactam cover Enterobacterales with KPC carbapenemases *in vitro*. For meropenem/vaborbactam and ceftazidime/avibactam, there is trial or case-series evidence of superiority over colistin combinations [23,24]. Ceftazidime/avibactam additionally covers CPE with OXA-48-like carbapenemases (primarily because avibactam inhibits co-produced ESBLs; OXA-48 lacks activity against ceftazidime) and, again, case series point to better outcomes than for colistin or carbapenem-based regimens [25]. Aztreonam/avibactam should additionally cover Enterobacterales with MBLs, again because avibactam should inactivate co-produced ESBLs [22].

None of these combinations has reliable activity against carbapenemase-producing *P. aeruginosa*, which mostly have MBLs and sufficient efflux to compromise aztreonam, or against OXA-carbapenemase-producing *A. baumannii*. Cefiderocol, (assuming a 4 mg/L breakpoint), potentially achieves wider activity, encompassing carbapenemase-producing *P. aeruginosa* and *A. baumannii* as well as most CPE. Caveats are that its MICs show wide scatter, probably reflecting factors besides carbapenemase type and that, irrespective of species, MICs for isolates with NDM carbapenemases exceed those for isolates possessing other carbapenemase types. (Public Health England, in preparation).

Knowing the carbapenemase type is also pertinent for plazomicin. Most Enterobacterales with NDM enzymes co-produce ArmA or Rmt methyltransferases [26], altering the rRNA to prevent the binding of 3-ring aminoglycosides, including plazomicin. Co-carriage of methyltransferases with other carbapenemases is rarer, but may be emerging for OXA-48-like enzymes [27]. *K. pneumoniae* ST258 typically has an AAC(6')-Ib acetyltransferase along with its KPC carbapenemase, thus compromising tobramycin and amikacin but not plazomicin or gentamicin [11].

Carbapenems against carbapenemase producers: again, type matters

If newer agents are unavailable or inappropriate carbapenems are often added to regimens against CPE, particularly if their MICs remain low. Justification comes e.g. from Vatopoulos *et al*., who found that carbapenems remained useful against bloodstream *Klebsiella* with VIM carbapenemases up to an MIC of 4 mg/L [28], whilst Tumbarello *et al.* found colistin combination regimens also including carbapenems were more efficacious than colistin monotherapy for bacteraemias due to *K. pneumoniae* with KPC carbapenemases [29], although a later trial suggest that this is the case only for severe infections [30].

However, a growing body of evidence, from animal models, small trials and case series suggests that the *type* of carbapenemase may be as important as the carbapenem MIC. Fig. 1 depicts meropenem MICs for 906 CPE submitted to Public Health England (PHE) in 2015/16 [using data from ref 21], showing that values typically were lowest for isolates with OXA-48-like enzymes and highest for those with NDM types: 72.5% of isolates with OXA-48-like enzymes counted as 'meropenem susceptible' at EUCAST's 2 mg/L clinical breakpoint and 56.7% at CLSI's 1 mg/L value whereas 94.6% with NDM enzymes were resistant at EUCAST's high breakpoint, with MICs >8 mg/L. Pharmacodynamics would therefore predict that carbapenems might remain widely useful against bacteria with OXA-48-like carbapenemases but not against those with NDM carbapenemases. Experience however suggests the opposite. Wiskirchen et al. [31] found that acquisition of a $bla_{\text{OXA-48}}$ plasmid, conferring a doripenem MIC of 0.38 mg/L (versus 0.03 mg/L for the recipient and CLSI/EUCAST breakpoints of $\leq$1/>4 mg/L), dramatically reduced the efficacy of doripenem in a mouse thigh infection treated with a human-simulated regimen. There was no such reduction of efficacy for ceftazidime, which had MICs of 0.25 mg/L irrespective of the plasmid. Moreover, clinical outcomes with carbapenems against pathogens with OXA-48 enzymes are poor, even when MICs remain low: Cuzon *et al.* [32] recorded 3 deaths among 5 such cases, all with MICs of the therapeutically-used carbapenem within the EUCAST susceptible or (one case) intermediate/'susceptible increased dosage' range. Four patients, including two fatalities, also received colistin, to which all the bacteria were susceptible. Larger studies reported 1-month mortality rates around 50% in bacteraemias due to CPE with OXA-48 carbapenemases, with many patients receiving carbapenems as well as colistin [33,34]. Much better outcomes, with low mortality were reported when ceftazidime/avibactam was used in severely-ill patients infected by pathogens with OXA-48 enzymes [25]. In contrast to these poor outcomes against bacteria with the 'weak' OXA-48-like carbapenemases, Chibabhai *et al.* [35] noted good outcomes for carbapenems, alone or combined, in 18/26 cases infected by Enterobacterales with NDM enzymes, despite MICs mostly >8 mg/L. This observation agrees with Wiskirchen *et al*. [36] who found humanised regimens of doripenem and ertapenem as effective against transconjugant *K.*

pneumoniae with NDM-1 carbapenemase (MICs 4 and 16 mg/L, respectively) as against the plasmid-free recipient (MICs 0.03 and 0.12 mg/L). Neither carbapenem was effective against the corresponding transconjugant with a KPC carbapenemase despite a 'doripenem-susceptible' MIC of 1 mg/L.

Clearly the clinical studies are small and one cannot be certain that the animal studies will predict behaviour in humans; nonetheless, and taking these data collectively, there is a growing body of evidence to suggest that OXA-48 enzymes cause more-problematic resistance *in vivo* than *in vitro*, whilst NDM types are less problematic *in vivo* than *in vitro*. Reasons remain uncertain, but a plausible contributory factor is that, *in vivo*, NDM-1 MBLs may struggle to acquire the zinc essential for their catalytic activity.

Variation within carbapenemase families

Identification of the carbapenemase family is as much as can be reasonably expected of diagnostic laboratories at present, given the PCR and immunochromatography methods available (see below). But the future may demand identification *within* families.

Over 53 IMP, 46 VIM, 24 KPC 14 NDM, and 12 OXA-48-like carbapenemases are described. Much of the variation within families matters only insofar as it complicates the design of comprehensive PCR and immunochromatographic detection methods, necessitating repeated 'tweaking' as new variants are added to the detection repertoire. In a few cases, however, there is consequential variation. The clearest example is that changes to KPC carbapenemase – most often an Asp179Tyr substitution in the omega loop – increase ceftazidimase activity, thereby conferring ceftazidime/avibactam resistance whilst impairing activity against carbapenems [37] Such changes – which do not compromise meropenem/vaborbactam or imipenem/relebactam – may be selected during ceftazidime/avibactam therapy, perhaps particularly when the dosage has been reduced to

(over)-compensate for renal insufficiency [38]. Another possible example concerns the NDM family, where higher-numbered variants, which perhaps evolved more recently, have higher affinity for zinc than NDM-1, and a greater ability to confer resistance on zinc-deficient media [39]. If, as speculated above, NDM-1 is less effective *in vivo* because it struggles to acquire zinc, then this variation may be significant, though the necessary animal studies with different NDM variants remain to be done.

In the near future it may become necessary to split 'carbapenemase' families into sub-groups, in the same way as we do e.g. for TEM β-lactamases. Asides from adding another layer of complexity for microbiologists and infectious disease physicians this will present a challenge to rapid detection methods – a clinician will reasonably wish to know if the bla_{KPC} gene (say) found by diagnostic PCR encodes a classical variant or one that evades ceftazidime/avibactam.

Clarity needed in Prescribing Information

Throughout this article we had underscored the need for clarity in writing of carbapenem resistance and carbapenemases. Unfortunately this is not evident in package inserts. For meropenem-vaborbactam the FDA insert (accurately) states '… not active against bacteria that produce metallo-β-lactamases or oxacillinases with carbapenemase activity' [40] but then indicates general breakpoints of S $\leq$4, R >8 mg/L. These will lead to many isolates with OXA-48-like enzymes being categorised as susceptible (see fig. 1) despite the lack of clinical evidence and even though vaborbactam does not inhibit OXA-48-like enzymes. For ceftazidime-avibactam the insert reads: "In a subset of Gram-negative pathogens … genotypic testing identified certain ESBL groups (e.g., TEM-1, SHV-12, CTX-M-15, OXA-48) and AmpC that were expected to be inhibited by avibactam …."[41]. This is unfortunate wording, to say the least: neither OXA-48 nor TEM-1 is an 'ESBL,' and the activity of ceftazidime/avibactam against isolates with OXA-48 is due to ceftazidime being stable to this enzyme rather than to its inhibition by avibactam. The EMA is clearer than the FDA on carbapenemase types but, for meropenem/vaborbactam, its Specification of Product Characteristics reads "Vaborbactam's

inhibitory spectrum includes class A carbapenemases (such as KPC) and Class C carbapenemases… not class D carbapenemases … or class B metallo-β-lactamases….”[42]. To the best of our knowledge no Class C carbapenemase has been described, and there is no evidence that vaborbactam potentiates meropenem against AmpC hyperproducers in general.

Prescribing information sheets for new drugs need to be clearer regarding the carbapenemase types covered, for example by incorporating a simple standard table of (i) which β-lactamases compromise the β-lactam partner, (ii) which of these are inactivated by the inhibitor, (iii) whether particular species with the particular enzyme are likely to be susceptible, and (iv) whether clinical trials support efficacy against producers of the particular enzyme.

Practical aspects for diagnostic laboratories

There remains the practical issue of identifying carbapenemases in routine practice, both to manage cross-infection risk – greater for CPE than other CRE – and to inform use of new-β-lactamase inhibitor combinations.

For Enterobacterales, insight can be gleaned from relative resistance to ertapenem versus imipenem and meropenem, with single ertapenem resistance often pointing to AmpC or ESBL activity combined with impermeability, rather than to carbapenemases, particularly if cephalosporin/clavulanate or cephalosporin/cloxacillin synergy is also seen. Hydrolytic tests (e.g. acidimetric/Carba-NP tests or carbapenem inactivation methods) distinguish CPE from other CRE [43] but do not sufficiently discern the particular carbapenemase type to support precision medicine; moreover OXA-48-like enzymes can be hard to detect by these methods which must either (i) be supplemented with additional phenotypic data (e.g. imipenem/EDTA synergy tests, which predict MBLs and tests for high-level temocillin resistance, which predicts OXA-48-like) (Table 2) or (ii) be supplanted with PCR or immunochromatographic methods, which are reviewed separately [44].

P. aeruginosa resistant only to carbapenems can be assumed to have lost OprD and not to have a carbapenemase. When *P. aeruginosa* isolates are broadly resistant, including to carbapenems, it is necessary to discriminate whether they have carbapenemases or – as is more frequent – combinations of OprD loss and upregulation of efflux and/or AmpC β-lactamase. MBLs are the commonest carbapenemases here and can be sought by carbapenem/EDTA or carbapenem/dipicolinic acid tests, though the former are prone to give false positive results, probably because EDTA-extractable divalent cations ordinarily stabilise the *P. aeruginosa* outer membrane [45]. A simpler approach is to test ceftolozane/tazobactam, where high-level resistance (MIC >16 mg/L or growth up to a 30 μg disc) is a good predictor that an isolate has either a carbapenemase or an ESBL [46]; the one caveat is that the few *P. aeruginosa* with OXA-48 or GES carbapenemases will be missed, being susceptible to ceftolozane/tazobactam. In the case of *A. baumannii*, most carbapenem-resistant isolates have OXA carbapenemases or (rarely) MBLs: these can be distinguished by imipenem/EDTA synergy tests, though these often give weak false positive results (4- to 8-fold MIC reduction) for isolates with OXA enzymes; strong positives, with >16-fold synergy, are the preserve of MBL producers (PHE Data on file).

Conclusions

For as long as carbapenem resistance was exceptionally rare it was acceptable to term 'carbapenem resistant' and 'carbapenemase-producing' bacteria as single entities. The proliferation of diverse carbapenemases and the advent of new therapies mean that this is no longer adequate. New drugs or combinations may be an answer to CPE in one country where (say) KPC carbapenemases dominate, but not in another, where OXA-48 or MBL types are the 'typical' CPE. Authors, referees and editors all have roles in ensuring clarity, as do licensing agencies and international agencies.

Not only in the literature, but also in routine practice it is increasingly important to detect carbapenemase production rather than 'carbapenem resistance' and – wherever possible - to identify

the enzyme family present. And, last, in the common vernacular 'carbapenemase-producing' or 'non-carbapenemase-producing' should be encouraged. 'Carbapenem resistance' is no longer sufficiently precise to aid therapeutic optimisation or to correctly alert infection control teams.

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Table 1 Spectra of new and anticipated β-lactams and β-lactamase inhibitor combinations, in relation to bacterial group and carbapenemase type.

Drug and status[a]	Enterobacterales			*P. aeruginosa*	*A. baumannii*	
	KPC	OXA-48-like	MBL	MBL	MBL	OXA
Diazabicyclooctane-based inhibitor combinations						
Ceftazidime/avibactam (L)	++	++	-	-	-	-
Imipenem/relebactam (L)	++	-	-	-	-	-
Aztreonam/avibactam (PIII)	++	++	++	+[b]	-	-
Boronate-based inhibitor combinations						
Meropenem/vaborbactam (L)	++	-	-	-	-	-
Single agents						
Cefiderocol (L)	++	++	+(+)[c]	++	+(+)[c]	++

++, broadly active; +, weak activity; - not generally active

[a] L, licensed by either or both FDA and EMA; R, under review by FDA and/or EMA; PIII, in phase III trials. Earlier-stage agents are excluded

[b] Aztreonam only has weak activity in general *vs. P. aeruginosa*.

[c] MIC are raised for isolates with NDM MBLs, which are the commonest MBLs in Enterobacterales and *A. baumannii*, (though not in *P. aeruginosa*)

452 **Table 2**. Predicting carbapenemase types from interpretive reading of phenotypes

Group and mechanism	**Useful pointers from routine testing**
Enterobacterales	
Non-carbapenemase-mediated type resistance	Resistant only to ertapenem among carbapenems, with strong cephalosporin/cloxacillin or cephalosporin/clavulanate synergy, predicting AmpC or ESBL activity respectively
KPC	• Strong potentiation of meropenem by vaborbactam • Meropenem resistance combined with susceptibility to temocillin
OXA-48-like	• High-level resistance to temocillin and piperacillin/tazobactam, coupled with carbapenem resistance or reduced susceptibility
Metallo types (IMP, VIM, NDM)	• Synergy between carbapenems and EDTA or dipicolinic acid combined with a lack of cephalosporin/clavulanate synergy and clear resistance to ceftazidime avibactam
P. aeruginosa	
OprD loss, alone	Resistance to carbapenems combined with susceptibility to all other β-lactams
OprD loss, combined with efflux or derepressed AmpC	• Resistance that includes carbapenems and some or all penicillins and cephalosporins but with ceftolozane/tazobactam susceptibility retained (Can also arise with OXA-48, but extremely rare in species)
Metallo types (IMP, VIM, NDM)	• Strong carbapenem/EDTA synergy (≥8-fold reduction in MIC), combined with clear resistance (MIC 16 mg/L) to ceftolozane/tazobactam and if ceftazidime MIC > aztreonam MIC. (NB weak carbapenem/EDTA synergy does not reliably indicate MBL production)
***Acinetobacter* spp.**	
OXA carbapenemase	Carbapenem resistance with weak <8-fold carbapenem/EDTA synergy coupled to broad resistance to all other β-lactams
Metallo types (IMP, VIM, NDM)	Carbapenem resistance with strong ≥8-fold carbapenem/EDTA synergy coupled to broad resistance to all other β-lactams

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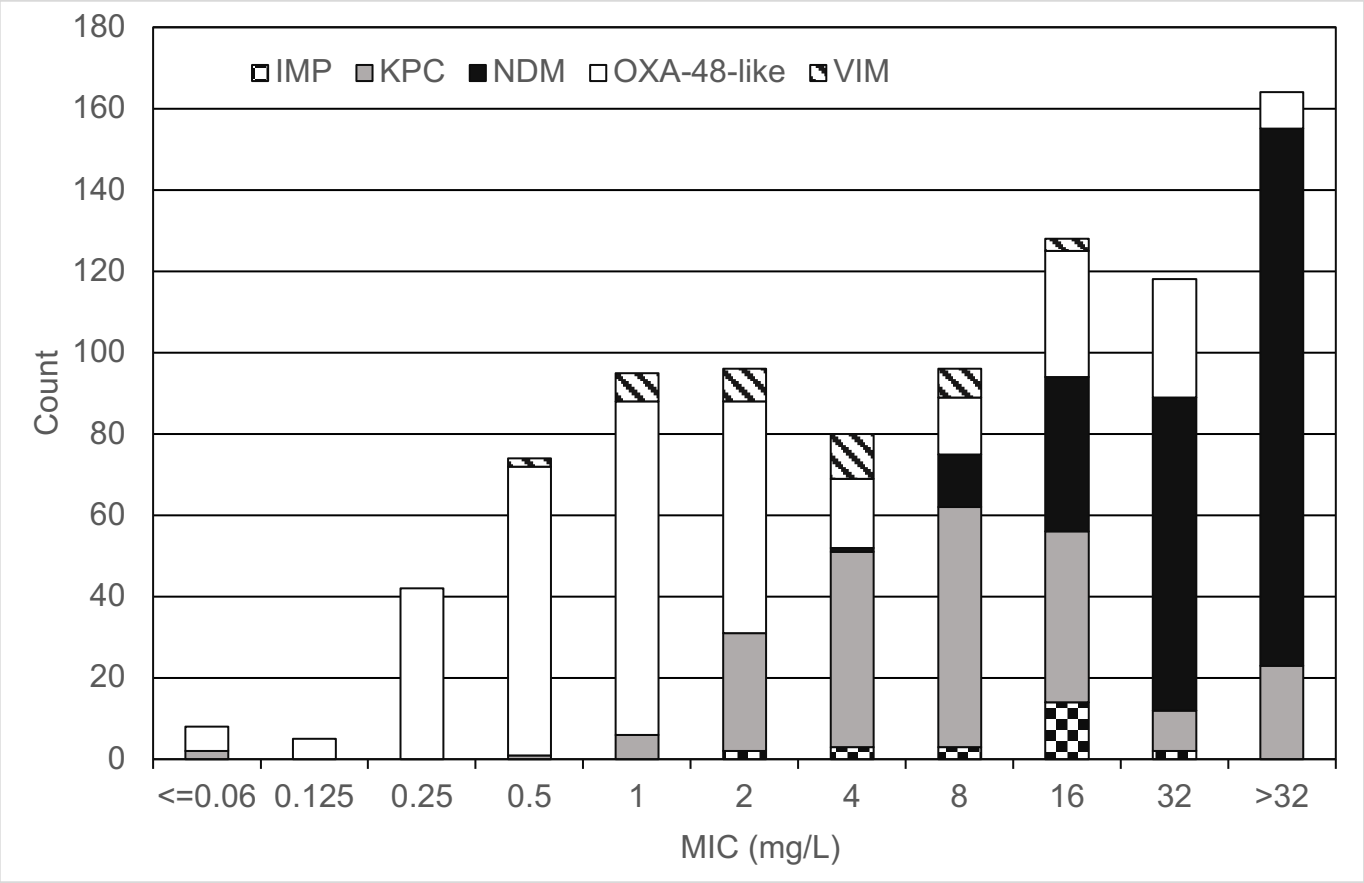
Note to Table 2. None of these behaviors is definitive, and interpretive reading should always be based on review of all susceptibility results. For example the combination of resistance to meropenem, ceftazidime and cefepime together with clear susceptibility to aztreonam strongly suggests presence of an MBL in Enterobacterales, however most MBL-producing Enterobacterales fail to show this phenotype because they co-produce aztreonam-hydrolysing ESBLs.

The table omits combinations of organism and enzyme that are extremely rare (*P. aeruginosa* with OXA-48-like carbapenemase) or localized (*P. aeruginosa* with KPC enzymes).

Unequivocal confirmation of carbapenemase type is best achieved by PCR or immunochromatographic methods.

464 Fig 1



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467 Fig 1 legend.

468 MIC distributions of meropenem for Enterobacterales submitted to PHE's Antimicrobial Resistance
469 and Healthcare Associated Infection Reference Unit from July 2015 to July 2016. Methodology and
470 collection as in references [21].

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