

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

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14 Terminology of carbapenem resistance

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#### 16 **40-Word summary**

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

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24 **Abstract.** Carbapenem resistance in Gram-negative bacteria is a public health concern. Numerous  
25 government and agency reports consequently discuss ‘CRE’ and ‘CROs’, meaning ‘Carbapenem-  
26 Resistant Enterobacterales’ or ‘Carbapenem-resistant organisms’. Unfortunately these terms are  
27 fuzzy. Do they include (i) Proteeae with inherent imipenem resistance, (ii) porin-deficient  
28 Enterobacterales resistant to ertapenem but not other carbapenems, (iii) Enterobacterales with OXA-  
29 48-like enzymes that remain ‘carbapenem susceptible’ at breakpoint, and (iv) *Pseudomonas*  
30 *aeruginosa* that merely lack OprD? Counting carbapenemase-producing Enterobacterales/organisms  
31 (‘CPE’ or ‘CPOs’) is better but still insufficient, because different carbapenemases have differing  
32 treatment implications, particularly for new  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations. At the  
33 least it is essential for authors, journals, and regulatory agencies to specify the carbapenemases  
34 meant. The future may demand even greater precision, for mutations can alter activity, and the ability  
35 to confer resistance, *within* carbapenemase families.

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

48

#### 49 **'Carbapenem-resistant': What is included?**

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

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

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

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

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

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

84

#### 85 **'Carbapenemase-producing'... Better than 'carbapenem-resistant'**

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

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

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

98

#### 99 ***Carbapenemase type is crucial***

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

104 If all carbapenemase types were evenly distributed authors would craft their language to  
105 specify the enzyme(s) meant. But, in reality, carbapenemase distributions are regional or national,  
106 and the common CPE of an author may differ radically from those troubling his reader elsewhere. KPC  
107 enzymes dominate in the Americas (except maybe Canada), Italy, Israel, Greece and Portugal, NDM in  
108 South Asia, and OXA-48-like in the Middle East (except Israel), North Africa, and much of Europe except  
109 for Italy, Greece and Portugal [15]. IMP and VIM MBLs dominate in carbapenemase-producing *P.*  
110 *aeruginosa* [16] except that SPM enzymes are prevalent in Brazil and that KPC types have spread in  
111 Colombia [11]. OXA-23 and -40 dominate everywhere in *A. baumannii*, with MBLs occasionally seen  
112 [17].

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

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

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

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

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

151

#### 152 ***Carbapenems against carbapenemase producers: again, type matters***

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

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



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

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

196

#### 197 ***Variation within carbapenemase families***

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

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

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

215 In the near future it may become necessary to split ‘carbapenemase’ families into sub-groups,  
216 in the same way as we do e.g. for TEM  $\beta$ -lactamases. Besides from adding another layer of complexity  
217 for microbiologists and infectious disease physicians this will present a challenge to rapid detection  
218 methods – a clinician will reasonably wish to know if the *bla<sub>KPC</sub>* gene (say) found by diagnostic PCR  
219 encodes a classical variant or one that evades ceftazidime/avibactam.

220

### 221 ***Clarity needed in Prescribing Information***

222 Throughout this article we had underscored the need for clarity in writing of carbapenem resistance  
223 and carbapenemases. Unfortunately this is not evident in package inserts. For meropenem-  
224 vaborbactam the FDA insert (accurately) states ‘... not active against bacteria that produce metallo- $\beta$ -  
225 lactamases or oxacillinases with carbapenemase activity’ [40] but then indicates general breakpoints  
226 of S  $\leq$ 4, R  $>$ 8 mg/L. These will lead to many isolates with OXA-48-like enzymes being categorised as  
227 susceptible (see fig. 1) despite the lack of clinical evidence and even though vaborbactam does not  
228 inhibit OXA-48-like enzymes. For ceftazidime-avibactam the insert reads: “In a subset of Gram-  
229 negative pathogens ... genotypic testing identified certain ESBL groups (e.g., TEM-1, SHV-12, CTX-M-  
230 15, OXA-48) and AmpC that were expected to be inhibited by avibactam ....”[41]. This is unfortunate  
231 wording, to say the least: neither OXA-48 nor TEM-1 is an ‘ESBL,’ and the activity of  
232 ceftazidime/avibactam against isolates with OXA-48 is due to ceftazidime being stable to this enzyme  
233 rather than to its inhibition by avibactam. The EMA is clearer than the FDA on carbapenemase types  
234 but, for meropenem/vaborbactam, its Specification of Product Characteristics reads “Vaborbactam’s

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

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

244

#### 245 ***Practical aspects for diagnostic laboratories***

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

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

259 *P. aeruginosa* resistant only to carbapenems can be assumed to have lost OprD and not to  
260 have a carbapenemase. When *P. aeruginosa* isolates are broadly resistant, including to carbapenems,  
261 it is necessary to discriminate whether they have carbapenemases or – as is more frequent –  
262 combinations of OprD loss and upregulation of efflux and/or AmpC  $\beta$ -lactamase. MBLs are the  
263 commonest carbapenemases here and can be sought by carbapenem/EDTA or  
264 carbapenem/dipicolinic acid tests, though the former are prone to give false positive results, probably  
265 because EDTA-extractable divalent cations ordinarily stabilise the *P. aeruginosa* outer membrane [45].  
266 A simpler approach is to test ceftolozane/tazobactam, where high-level resistance (MIC >16 mg/L or  
267 growth up to a 30  $\mu$ g disc) is a good predictor that an isolate has either a carbapenemase or an ESBL  
268 [46]; the one caveat is that the few *P. aeruginosa* with OXA-48 or GES carbapenemases will be missed,  
269 being susceptible to ceftolozane/tazobactam. In the case of *A. baumannii*, most carbapenem-resistant  
270 isolates have OXA carbapenemases or (rarely) MBLs: these can be distinguished by imipenem/EDTA  
271 synergy tests, though these often give weak false positive results (4- to 8-fold MIC reduction) for  
272 isolates with OXA enzymes; strong positives, with >16-fold synergy, are the preserve of MBL producers  
273 (PHE Data on file).

274

## 275 **Conclusions**

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

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

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

287

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- 440

441 **Table 1** Spectra of new and anticipated  $\beta$ -lactams and  $\beta$ -lactamase inhibitor combinations, in relation  
 442 to bacterial group and carbapenemase type.

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

443

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

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

447 <sup>b</sup> Aztreonam only has weak activity in general vs. *P. aeruginosa*.

448 <sup>c</sup> MIC are raised for isolates with NDM MBLs, which are the commonest MBLs in Enterobacterales and  
 449 *A. baumannii*, (though not in *P. aeruginosa*)

450

451

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

Group and mechanism	Useful pointers from routine testing
<b>Enterobacterales</b>	
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	<ul style="list-style-type: none"> <li>• Strong potentiation of meropenem by vaborbactam</li> <li>• Meropenem resistance combined with susceptibility to temocillin</li> </ul>
OXA-48-like	<ul style="list-style-type: none"> <li>• High-level resistance to temocillin and piperacillin/tazobactam, coupled with carbapenem resistance or reduced susceptibility</li> </ul>
Metallo types (IMP, VIM, NDM)	<ul style="list-style-type: none"> <li>• Synergy between carbapenems and EDTA or dipicolinic acid combined with a lack of cephalosporin/clavulanate synergy and clear resistance to ceftazidime avibactam</li> </ul>
<b><i>P. aeruginosa</i></b>	
OprD loss, alone	Resistance to carbapenems combined with susceptibility to all other $\beta$ -lactams
OprD loss, combined with efflux or derepressed AmpC	<ul style="list-style-type: none"> <li>• 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)</li> </ul>
Metallo types (IMP, VIM, NDM)	<ul style="list-style-type: none"> <li>• Strong carbapenem/EDTA synergy (<math>\geq 8</math>-fold reduction in MIC), combined with clear resistance (MIC 16 mg/L) to ceftolozane/tazobactam and if ceftazidime MIC &gt; aztreonam MIC. (NB weak carbapenem/EDTA synergy does not reliably indicate MBL production)</li> </ul>
<b><i>Acinetobacter</i> spp.</b>	
OXA carbapenemase	Carbapenem resistance with weak <8-fold carbapenem/EDTA synergy coupled to broad resistance to all other $\beta$ -lactams
Metallo types (IMP, VIM, NDM)	Carbapenem resistance with strong $\geq 8$ -fold carbapenem/EDTA synergy coupled to broad resistance to all other $\beta$ -lactams

453

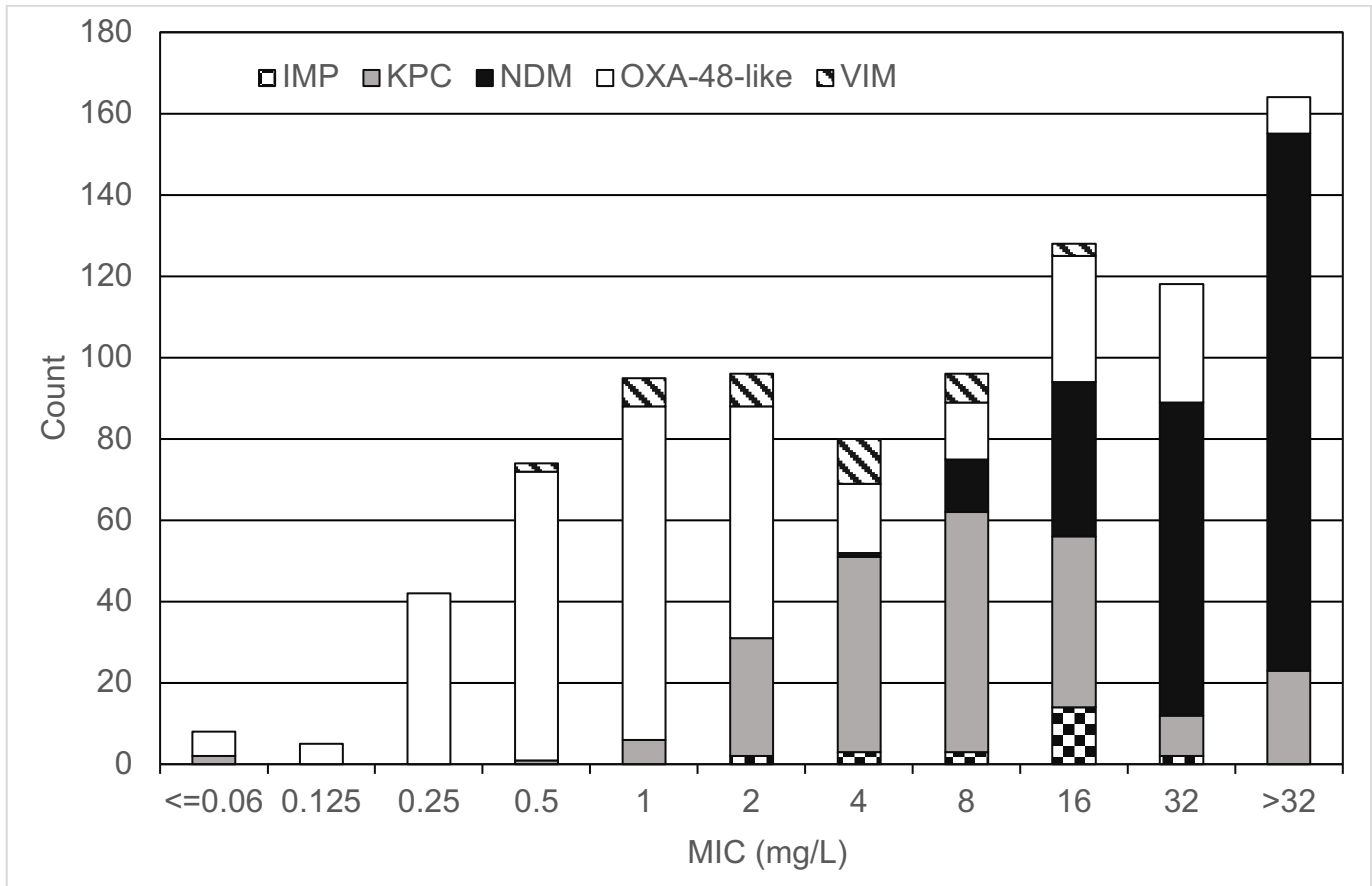
454

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

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

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

464 Fig 1



465

466

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].

471