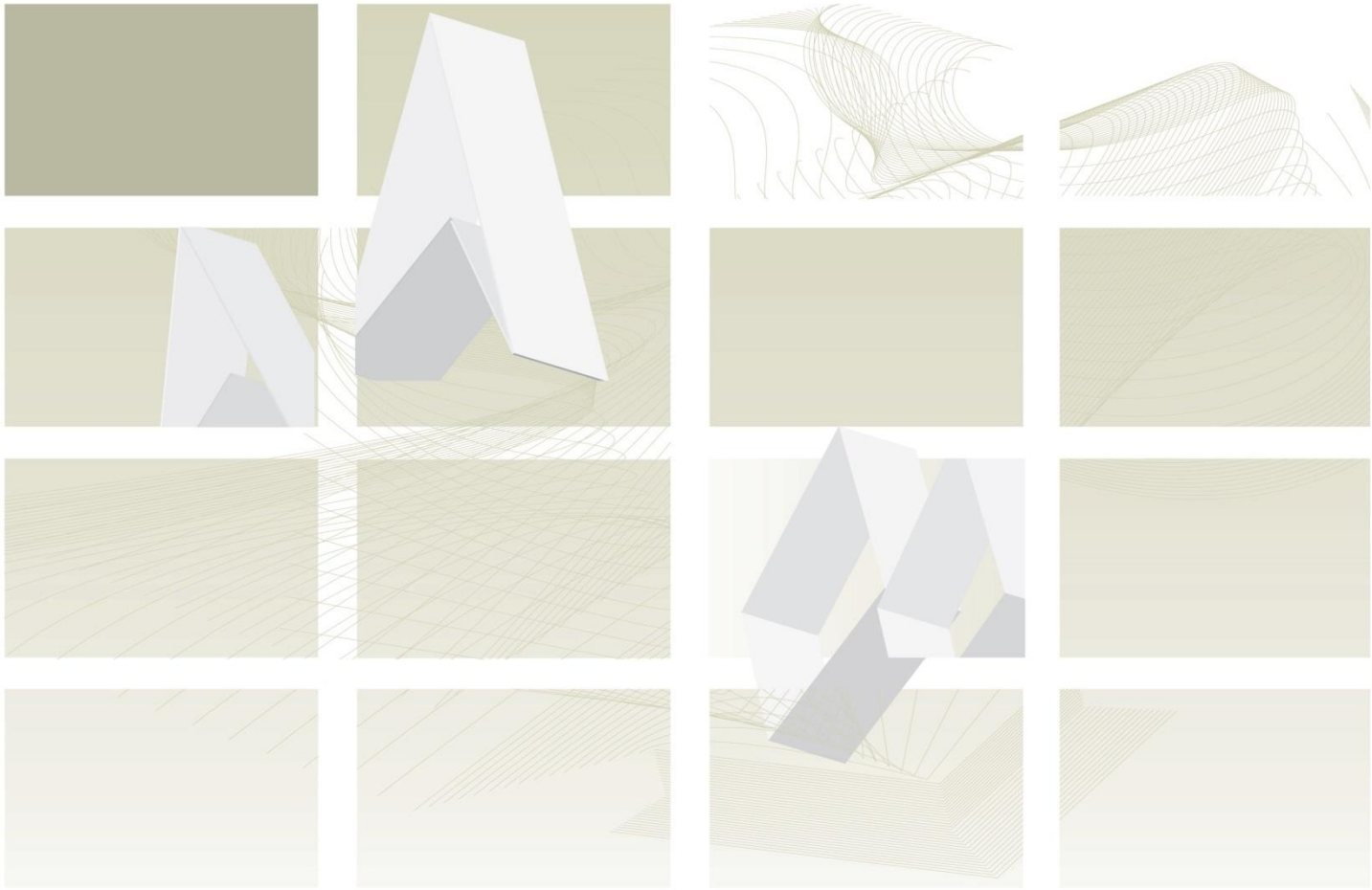
UK Standards for Microbiology Investigations

Review of users' comments received by
Working group for microbiology standards in clinical bacteriology

B 60 detection of bacteria with carbapenem hydrolysing β-lactamases (carbapenemases)



"NICE has renewed accreditation of the process used by **Public Health England (PHE)** to produce **UK Standards for Microbiology Investigations**. The renewed accreditation is valid until **30 June 2021** and applies to guidance produced using the processes described in **UK standards for microbiology investigations (UKSMIs) Development process, S9365', 2016**. The original accreditation term began in **July 2011.**"

This publication was created by Public Health England (PHE) in partnership with the NHS.

Issued by the Standards Unit, National Infection Service, PHE

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Consultation: 12/08/2020 to 26/08/2020

Version of document consulted on: dx+

Proposal for changes

Comment number	1		
Date received	19/08/2020	**Lab name**	Freeman Hospital
Section	See below		
Comment			

Section for comments

Thank you for the opportunity to comment on this important document. I offer the following comments/suggestions for consideration:

a) Page 5: “carbepenemases producers” (typo)
b) Page 9, paragraph 1: “reduced carbapenem susceptibility of resistance”. Do you mean “reduced carbapenem susceptibility OR resistance”? Suggest breaking this paragraph into 2 sentences to make it easier to read.
c) Section 4.3 appears to be exclusively about culture of specimens for carbapenemase producers. I suggest that the title of this section should reflect this.
d) Page 10 paragraph 4: I suggest replacing “may appear” with “appearing”
e) Page 11. 4.3.1. “clinically-significant”
f) Page 12: paragraph 3. Meropenem resistance isolates (typo)
g) Page 12. Section 4.4. What is the difference between the two subtitles in section 4.4?
h) Page 12. Paragraph 5 states that: “For those laboratories screening clinical samples on MacConkey or CLED agar with ertapenem disc, this UK SMI recommends reducing the zone size of 27mm to 25mm for increased sensitivity”. There are a couple of issues with this statement. Notwithstanding the citation of Lolans et al, there are no formal recommendations that I am aware of for using a zone diameter of 27 mm for CPE screening with ertapenem. More importantly, reducing the zone diameter cut-off to 25 mm will reduce sensitivity rather than increase it (for example a low inoculum of E. coli with OXA-48 on MacConkey with a zone diameter of 26 mm to ertapenem would now be missed). Reducing the zone diameter to 25 mm will increase specificity rather than sensitivity. (Note: this also has relevance to paragraph 1 of section 4.4. where it is also erroneously states that reduction of zone diameter cut-offs are recommended to improve sensitivity).It is noteworthy that Lolans et al. (cited in this section) advocated a zone diameter cut-off of 27 mm for ertapenem to adequately detect KPC. It is therefore extremely optimistic in my view to expect that you will detect OXA-48 using a zone diameter cut-off of 25 mm (especially when inocula are light). If the authors of the SMI insist on allowing laboratories to use disc testing for direct detection from rectal swabs (where the inoculum of CPE is completely uncontrolled and often very light), I would suggest something like the following…….. “For those laboratories screening clinical samples on MacConkey or CLED agar with an ertapenem disc, this UK SMI recommends using the

EUCAST screening cut-off of 25 mm. However, this is only valid for isolates that are recovered as a confluent growth. If the growth appears lighter than that stipulated for disc testing by EUCAST, colonies will require formal susceptibility testing.

i) Page 13: Paragraph on MALDI-TOF. The words “mass spectrometry” are missing from the title.

j) Section 6.1.1. infers that a rectal swab is preferable to a stool sample for screening (with respect to sensitivity). It would be of interest to know whether there is any evidence for this. Our (anecdotal) experience suggests the opposite is true – but I can offer no proof either way. Unless there is evidence to the contrary, I would suggest recommending that rectal swabs or stool samples are appropriate samples. This would also ensure consistency with the text in 6.1.3.

k) Table 3: footnote g “All co-amoxiclav resistant isolates should be screened for resistance to carbapenems”. Would it be worth adding “(if meropenem has not been already tested)?

l) Table 4 footnote states that “Escherichia coli NCTC 10418 (equivalent to ATCC 25922) should be used as a negative control in confirmation tests”. Although both of these strains are indeed suitable, the direct equivalent to ATCC 25922 is NCTC 12241.

Evidence

Financial barriers

No.

Health benefits

Yes. Likelihood of improved surveillance.

Are you aware of any interested parties we should consider consulting with on the development of this document?

Not in addition to those already listed.

Recommended action	**a) NONE** Wording “carbapenemases producers” has been removed from section 3. **b) ACCEPT** This has been updated in the document **c) ACCEPT** This has been updated in the document **d) ACCEPT** This has been updated in the document **e) ACCEPT**

	This has been updated in the document **f) ACCEPT** This has been updated in the document **g) ACCEPT** This has been updated in the document **h) ACCEPT** This has been updated in the document **i) ACCEPT** This has been updated in the document **j) ACCEPT** This has been updated in the document **k) ACCEPT** This has been updated in the document **l) ACCEPT** This has been updated in the document

Comment number	2		
Date received	21/08/2020	**Professional body**	Northern Health and Social Care Trust
Section	See below		
Comment			

Section for comments 1: Scope of document
Comments/evidence 1

a) Note the use of the three stages in this section. The stages are not directly referred to in the SMI again. Feels like the three stages are mixed up in the main body of the SMI rather than separated out and in sequence.

Section for comments 2: Background
Comments/evidence 2

b) Page 7: Should Title 4.2. be changed to Complexities of detection of carbapenemases production?
c) Page 9: line 3: change to reduced carbapenem susceptibility or resistance
d) Page 9: Should Title 4.3. be changed to Complexities of screening of clinical samples as it talks about chromogenic agars etc?
e) Page 11: Should Title 4.3.1 be changed to Complexities of detection of carbapenemase production in non-fermentors and some of the recommendations in this section moved to 4.4 Summary of UK SMI recommendations.
f) Page 12: Summary of UK SMI recommendations Should first paragraph get the title Recommendations for Screening of Clinical Samples
g) Page 12: Change Recommendation of cultured isolates of Enterobacterales to Recommendation for cultured isolates of Enterobacterales.

h) Page 12: Also, should section 7.1 Cultured isolates of Enterobacterales be merged with this section rather than being another section talking about the same thing?
i) Page 12: Change to Any suspect isolates with co-amoxiclav resistance or resistance or reduced susceptibility to meropenem must be subjected
j) Page 12: Add Recommendations for cultured isolates of Pseudomonas: Pseudomonas resistant to all relevant carbapenems (that is, imipenem, meropenem and doripenem), ceftazidime, ceftolozane/tazobactam and piperacillin/tazobactam may be tested for strong (>=8 fold) imipenem-EDTA or meropenem/DPA synergy37,38. Positives require further investigation using a molecular or an immunochromatographic assay.
k) Page 12: Add Recommendations for cultured isolates of Acinetobacter: Meropenem/imipenem resistant Acinetobacter if affected patient has been hospitalised overseas recently (for example, in the Middle-East or Indian subcontinent) in which case imipenem-EDTA or meropenem/dipicolinic acid (DPA) synergy37,38 (>=8-fold) may be of value and could be sought to rule out the presence of a metallo-carbapenemase.
l) Page 12: Should Title 4.5 be changed to Difficulties around reporting carbapenem susceptibility for Carbapemase Producing Enterobacterales
m) Page 13 4.6: Should section 7.2.1 Confirmatory tests for carbapenemases: inhibitor-based methods be moved here from page 18 and 19 be moved here as it talks about inhibitor-based methods?

Section for comments 3: Investigation

Comments/evidence 3

n) Page 14: 6.1.1 Specimen type change to and any Enterobacterales isolates found grossly resistant to co-amoxiclav.
o) Page 15: Table 3 Change foot note a: Following screening of clinical sample by any of the above methodologies; relevant isolates must have susceptibility testing in accordance with EUCAST recommendations. Does the sentence mean: Detection of Acinetobacter using this method may be reduced?
p) Table 3: g All co-amoxiclav resistant isolates should be screened for resistance or reduced susceptibility to carbapenems according to EUCAST recommendations

Section for comments 4: General comments

Comments/evidence 4

q) Appreciate that SMI groups are busy and it takes time to put together. Feels like it needs some editing as there is repetition in the document and could be structured better. Would it be better indicating more clearly that the carbapenem screening cut-offs from EUCAST resistance mechanism documents are be followed?

Evidence

Financial barriers

No.

Health benefits

r) Some concern that using meropenem as the screening carbapenem instead of ertapenem might lead to OXA-48 carbapenemase producers going undetected. Hopkins KL, Meunier D, Mustafa N et al. Evaluation of temocillin and meropenem MICs as diagnostic markers for OXA-48-like carbapenemases. J Antimicrob

Chemother. 2019; 74: 3641â€• 3643. Meropenem MIC screening cut-off 0.125 mg/L missed 12% of E. coli OXA-48 producers. However, changing this would go against EUCAST guidance and increase laboratory workload due to reduced specificity.	
Are you aware of any interested parties we should consider consulting with on the development of this document?	
No	
Recommended action	**a) ACCEPT** This has been updated in the document **b) ACCEPT** This has been updated in the document **c) ACCEPT** This has been updated in the document **d) NONE** It was decided to use the following wording for the title “Detection of carbapenem resistance in screening samples” **e) PARTIAL ACCEPT** Some text for the section title has been accepted and updated in the document **f) ACCEPT** This has been updated in the document **g) NONE** It was decided to use the following wording for the title “Recommendation for preliminary detection of carbapenem resistance in cultured isolates from clinical samples” **h) NONE** It was decided to leave section as it is. **i) ACCEPT** This has been updated in the document **j) NONE** It was decided to leave section as it is. **k) NONE** It was decided to leave section as it is. **l) ACCEPT** This has been updated in the document

	m) PARTIAL ACCEPT Information was moved to relevant section **n) ACCEPT** This has been updated in the document **o) PARTIAL ACCEPT** Footnote ‘a’ reworded to make it clearer. **p) ACCEPT** This has been updated in the document **q) PARTIAL ACCEPT** Edits has been made to the document and repetition reduced. EUCAST resistance mechanism document is already referenced in the document. **r) NONE** This UK SMI is following EUCAST guidance for using meropenem as the indicator carbapenem.

Comment number	3		
Date received	21/08/2020	**Lab name**	UK Anaerobe Reference Unit (UKARU)
Section	See below		
Comment			
Section for comments 1: Scope of document **Comments/evidence 1** a) Whilst I realise that the primary focus of this document is on the aerobic pathogens with aquired carbapenem resistance, there is no mention of the important anaerobic pathogen Bacteroides fragilis. B.fragilis harbours a chromosomally mediated metallo beta lactamase gene called cfiA (ccrA) and I believe it should be mentioned if only to raise awareness as it could have clinical implications. I can provide more information if required and am happy to also remind colleagues that any anaerobes with unusual resistance patterns can be referred to us at the UKARU for further advice and clinical guidance.			
Evidence			
Financial barriers			
Health benefits			

Are you aware of any interested parties we should consider consulting with on the development of this document?	
Recommended action	**a) ACCEPT** This has been updated in the document

Comment number	4		
Date received		**Professional body**	Southern Health and Social Care Trust
Section	See below		

Comment

a) Why is ertapenem recommended for carbapenemase screening and not meropenem (as per EUCAST recommendations)? This is especially confusing in light of the subsequent paragraph: *'This UK SMI supports the EUCAST recommendation to use meropenem as the indicator carbapenem as it offers the best compromise between sensitivity and specificity.'*

b) 'For those laboratories screening clinical samples on MacConkey or CLED agar with ertapenem disc, this UK SMI recommends reducing the zone size of 27mm to 25mm for increased sensitivity' Surely reducing the zone size would reduce the sensitivity, not increase it?

c) *'6.1.1 Specimen type'* states: *'Minimum testing should include isolates from 'high-risk' patients and settings in accordance with current national guidance and any isolates found grossly resistant to co-amoxiclav or Pseudomonas piperacillin-tazobactam'.* There is no explanation as to what is meant by 'grossly resistant'. From conversations with AMRHAI we previously took this to mean growth up to the disk, but it would be useful if this was clarified, or a specific zone size given. In addition, does 'grossly resistant' also apply to Pseudomonas and piperacillin-tazobactam?

d) '*7.1 Cultured isolates of Enterobacterales'* again states the minimum testing requirements, but these appear to differ to those stated above. There is very little information given on confirmatory testing – are we to simply follow EUCAST guidelines?

Evidence
Financial barriers
Health benefits

Are you aware of any interested parties we should consider consulting with on the development of this document?	
Recommended action	**a) NONE** This UK SMI supports the EUCAST recommendation to use meropenem as the indicator carbapenem however ertapenem is recommended for those laboratories with low throughput who may not stock chromogenic agar and may wish to use MacConkey and CLED agar with an ertapenem disc. **b) ACCEPT** This has been updated in the document **c) ACCEPT** This has been updated in the document **d) ACCEPT** Section rephrased to make it clearer.

Respondents indicating they were happy with the contents of the document

Overall number of comments: 0			
Date received		**Lab name/Professional body (delete as applicable)**	
Health benefits			