**Expert name: xxxxxxxxxxxxx (representing BSAC and RCPath)**

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| **Comment no.** | **Page** **no.** | **Section no.** | **Comment** Insert each comment in a new row.Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
| 1 | 1 | 1 | As a general point, the assessment report is comprehensive and the rationale for decisions is explained clearly and logically. The input of the clinical advisors is noted. The members of this panel include colleagues who are senior members of BSAC and RCPath, even if they were not formally representing these organisations. |
| 1 | 24 | 3.2.3.1 | The uncertainty around the projected use of Caz-Avi is well explained. Use is unlikely to reflect the licenced indications and will probably be restricted to select groups of vulnerable patients with proven resistant Gram-negative infections, most likely with carbapenemases. Of the HVCS, microbiology directed treatment reflects current practice more than risk-based empiric treatment. |
| 2 | 31 | 4.1.2 | In the discussion on setting breakpoints it could be acknowledged that considerable work has been done to standardise breakpoints within European countries and more recently between EUCAST and CLSI. Therefore, the variation and lack of standardisation is much less than historically. Also, in light of the variation described, it is most important that any review of surveillance data takes account of the actual breakpoints used within each publication at the time. That is, not simply report the number of ‘sensitive’ or ‘resistant’ isolates. Ideally, consider actual MICs. The MIC is the baseline upon which all susceptibility testing methods are standardised. |
| 4 | 31 | 4.1.2 | It may be the professional view of BSAC that EUCAST breakpoints should be used, but laboratories are free to choose what method they want. CLSI breakpoints are very widely used worldwide and are an acceptable alternative. It is more important the laboratories using a EUCAST test methodology interpret results using EUCAST breakpoints and that laboratories using a CLSI test methodology interpret results using CLSI breakpoints. This is because breakpoints are calibrated for the method used. |
| 3 | 31 | 4.1.2 | There are major methodological issues with susceptibility testing of colistin. Laboratory practice has changed in the last 5 years. Results using surveillance data may be unreliable. |
| 3 | 102 | 6.1.5.6 | While appreciating that licencing studies have focussed on UTI and HAP/VAP, these infections are notorious for having issues with diagnosis and specifically differentiating between colonisation and infection. This is a major weakness of assessment of these indications, which are unlikely to reflect most common use of Caz-Avi. |
| 4 | 119 | 7.2.3.2 | In the summary, it is acknowledged that carbapenems have variable activity against carbapenemase-producing isolates. However, this is not considered further in the modelling. Meropenem is a common component of treatment regimens for OXA-48 CPE if the meropenem MIC has been shown to be low (e.g. 1-2 mg/L). It is accepted that published data may be lacking, but in reality, use of meropenem in these infections will often mean that treatment is not escalated to Caz-Avi.  |
|  | 150 | 7.5.2.6 | The discussion on expected areas of empiric use notes differences between views of the clinical advisors and the manufacturer. I consider that the narrower use suggested by the clinical advisors is probably more accurate in the short term (~5 years). Broader use is possible in the longer term if Caz-Avi ceases to be used as a restricted agent and becomes a part of the standard hospital formulary. This might be influenced by a variety of factors, for example, drug costs to the Trust and pressure to avoid carbapenems to meet prescribing targets, among others. |
| 5 | 152 | 7.5.2.7 | Note that estimates based on lower respiratory tract sample surveillance data will significantly overestimate incidence, since the diagnosis of HAP/VAP is made on clinical and radiological grounds, as well as from culture results.  |
| 6 | 163 | 8.1.2 | It is an interesting finding that the benefit of microbiology directed treatment is less than empirical treatment, given that this would be where Caz-Avi is more likely to be used. The explanation given is that the advantages of Caz-Avi are less once susceptibilities are known as a wider number of non-toxic options are available. This implies that a lot of the modelled empiric use would be unnecessary, because susceptibility information would later demonstrate that an alternative could be used instead. |
| 7 | 176 | 8.3.2.2 | An uncertainty under Diversity value is the use of Caz-Avi as a carbapenem sparing agent. NHS Trusts are put under pressure to avoid prescribing carbapenems and this may drive use of Caz-Avi outside the clinical scenarios modelled.  |
| 8 | 177 | 8.3.2.3 | Insurance value is very important, although clearly difficult to model as a ‘on the shelf in case we need it’ scenario. As a result insurance value maybe under-appreciated. The experience in the US is quite telling. Initially a reserve agent, use quickly became very widespread as KPC carbapenemases became prevalent.  |
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**Insert extra rows as needed**

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