**EEPRU’s responses to important consultee comments**

**Context**

Given the time available, here EEPRU responds to what we consider the most important issues raised in the consultees’ comments. The criteria we have used to select these issues are: (i) that they may imply substantial modifications to the quantitative estimates of population incremental health effects in our reports; and (ii) the issues have not already been covered in our reports.

EEPRU would also like to make the following points to contextualise these responses:

* As indicated in our protocol, EEPRU was committed to the view that estimating the population health effects of CAZ-AVI and cefiderocol needed to be grounded in specific clinical scenarios (defined in terms of pathogen, resistance mechanism, site and setting). Given the nature of the project, focussing on high value clinical scenarios (HVCSs) guided by EEPRU’s clinical advisors and based on current usage was considered the only practical approach to modelling these patient-level scenarios. An important area of reflection for a formal NICE assessment programme of new antibiotics would be the most appropriate means of agreeing these HVCSs.
* These HVCSs reflect EEPRU’s clinical advisors’ assessment of appropriate stewardship of CAZ-AVI and cefiderocol. As such, estimates of the short-term usage of the products were defined to reflect these types of stewardship. Given the specification of the project, it was not possible to assess the cost-effectiveness of these stewardship arrangements. Nor was it possible to model the optimal forms of stewardship taking into consideration the long-term implications for patients’ health benefits of preserving these products for future use.
* We have received various comments suggesting additional sensitivity/scenario analysis. We are grateful for these suggestions and hope they will inform future research and help shape a future formal NICE assessment programme for antibiotics. However, not all these areas of uncertainty could be fully addressed given the specification of the project.

| **Key issue number** | **Key issue raised** | **Commentator** | **Response** |
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| 1 | Susceptibility data may not reflect current definitions of susceptibility to colistin. Susceptibilities used in the evaluations based on earlier data may not translate to therapeutic benefit due to inadequate tissue penetration. (Shionogi comment #6) | Shionogi | Shionogi notes that EUCAST and CLSI have recently stated that polymixins (including colistin) do not reach adequate exposure levels in some tissues. They further note that EUCAST now indicates that polymixins should not be applied as monotherapies, and that CLSI has removed the susceptible category, and report all isolates as intermediate.  EEPRU believes that EUCAST recommendations have the highest applicability in the UK. In our assessment, colistin is always used as a combination treatment in the empiric setting. However, our method for calculating the susceptibility of combination treatments does assume that isolates susceptible to colistin are susceptible independently. Currently we assume that, for example, if 60% are susceptible to colistin and 50% susceptible to tigecycline, we calculate the overall susceptibility as 60% plus 50% of the remaining 40% = 80%. In the MDS, colistin is evaluated as a monotherapy, but since drug costs have a minimal impact on incremental net health effects (INHEs), and since clinicians always use colistin in combination with other treatments, this is likely to underestimate the effectiveness of any colistin-based comparator.  We have discussed these issues with our clinical advisors. They believe the estimates linking susceptibility to clinical outcomes for colistin should remain the same as for other antimicrobials, and that EUCAST has taken these issues into consideration when setting the breakpoints. They also note that the evidence to inform any assumptions around whether using colistin in combination with other treatments improves outcomes is extremely limited, subject to issues of confounding (observational studies), and limited treatment combinations having been tested. Since combinations are used in practice, they felt it was, therefore, reasonable to assume an additive effect from combination therapy. We note that CREDIBLE-CR, for which cefiderocol was compared to best-available therapy (which was mainly colistin-based), demonstrated similar clinical outcomes between the two arms.  With respect to older studies of colistin which use different colistin breakpoints, EEPRU took the approach throughout both assessments, and for all treatments, to apply the breakpoints that were reported in the publications, which largely equated to the breakpoints that were current at the time the analysis was conducted, and/or the time the isolates were collected. This was on the advice of PHE, and because to try to retrospectively apply 2021 breakpoints would have been excessively time-consuming, and in many cases not possible as only data for a given breakpoint was reported.  For the EUCAST networks, the EUCAST breakpoint has been 2mg/L since at least 2010. In the CAZ-AVI assessment, all three data sources (Vazquez-Ucha 2021; Matarachi 2020; PHE data) used 2mg/L as a breakpoint for colistin. In the cefiderocol assessment, all the older fosfomycin studies were published subsequent to 2010, so are unlikely to have been affected by a historical change in the breakpoint.  In addition, we conducted several sensitivity analyses around which studies should be included in the meta-analysis. In one of these, for *Enterobacterales* in our base case EUCAST analysis, we included only Shionogi’s analysis of SIDERO studies (which applied current (2021) breakpoints) and excluded the older fosfomycin studies that used historic colistin breakpoints, and the PHE data. This showed that the OR for cefiderocol versus colistin was largely unaffected (0.32, 95% CrI: 0.04 to 2.47 in the base case, versus 0.33, 95% CrI: 0.06 to 1.65 when using the SIDERO studies only). Similar was true in the EUCAST *Pseudomonas* analysis (0.44 95% CrI: 0.03, 3.94 versus 0.49, 95% CrI: 0.03 to 5.29 respectively). A similar analysis was not done for the CLSI networks as these were not our base case.  Shionogi notes that there is now no “susceptible” breakpoint for colistin according to CLSI, and EEPRU agrees that this is the case. Other than this change, it is unclear when or whether CLSI breakpoints changed historically, since CLSI holds breakpoints behind a paywall. In the cefiderocol assessment, the data used in the CLSI network was supplied by Shionogi; Shionogi applied a breakpoint of 1mg/L for colistin in these analyses. |
| 2 | Robustness of fosfomycin susceptibility evidence and translation of fosfomycin susceptibility to therapeutic benefit (Shionogi comment #12) | Shionogi | Shionogi had several criticisms relating to fosfomycin.  Of these, we have addressed the issue of historical breakpoints in our response to Shionogi comment #6, and the sensitivity analysis reported there applies here too, since this effectively excluded fosfomycin from the analysis.  Addressing issues to do with heterogeneity in testing methods was beyond the scope of this assessment, but this is a valid limitation to note. Clinical advisors explained that the only recommended method for fosfomycin susceptibility testing currently is by Agar dilution, but that this method is cumbersome to implement and expertise in doing so is not widely available. In the cefiderocol assessment, three out of five studies in the EUCAST *Enterobacterales* network conducted testing using Agar methods. It is unclear what effect excluding studies using inappropriate methods would have on the NMA results. *N.B*. The PHE data did not contribute to estimates of fosfomycin susceptibility in our networks. In the CAZ-AVI EUCAST network, only one study reported fosfomycin data, and the Agar dilution method was used in that study (Vazquez-Ucha 2021).  The problems with using the epidemiological cut off point for *Pseudomonas* were stated clearly in EEPRU’s report, including in the executive summary, and should be taken note of. The link between susceptibility and clinical outcomes when treating *Pseudomonas* with fosfomycin is uncertain. However, fosfomycin is used in clinical practice in combination with other treatments.  The review methods used to identify fosfomycin data were necessarily rapid, since at this point in the assessment time was extremely short. However, the impact of this is likely to be that studies were missed at random, not that systematic bias was introduced.  Should the committee decide to disregard fosfomycin data, scenario 3 in the CAZ-AVI analysis and scenario 4 in the cefiderocol analysis only include PHE data (*Enterobacterales*), which did not report data for fosfomycin. An equivalent analysis for *Pseudomonas* was not conducted, but note that in the base-case the susceptibility to fosfomycin is 3.7%. |
| 3 | Method for estimating susceptibility to combination therapies including colistin, and susceptibilities in the MDS | Shionogi | Combination treatment is currently only modelled in the ES. For the MDS it is assumed that an antimicrobial for which susceptibility is known would be used as monotherapy (with preference given to non-colistin/aminoglycoside options).  When modelling combination treatment in the ES, it was assumed that susceptibility to the overall combination was a combination of susceptibilities to the individual treatments (see response to key issue one above for an illustrative example using colistin and tigecycline). This approach was supported by analysis of PHE susceptibility data.  Our clinical advice has been that, whilst our approach was a simplification of a complex issue, it was acceptable and better than the alternative proposed by Shionogi (which was for overall susceptibility to be the lowest of the two individual susceptibilities). |
| 4 | Meropenem may remain effective in some patients | BSAC and RCPath | Within the economic modelling, the effectiveness of AMs is based upon their susceptibility profile. As noted in the submitted reports, a limitation is the lack of inclusion of meropenem:  “Of note, whilst evidence on susceptibility to meropenem was available, this was not used in the economic modelling. This is because clinical advice was that, for meropenem, susceptibility amongst carbapenem-producing pathogens was not a good surrogate predictor of clinical outcomes. This reflects advice in the literature.64,121 Hence, whilst meropenem is included as a comparator in the PICOS, it is assumed to have zero efficacy in the economic modelling (and so not actively modelled).”  This limitation will under-estimate the effectiveness of comparators (and so over-estimate the incremental benefits of CAZ-AVI and cefiderocol). However, the magnitude of this bias is unknown. |
| 5 | There is no adjustment for delayed time to effective therapy within the economic model | Shionogi | This effect is accounted for in the economic model. Patients who receive ineffective therapy in the empiric setting (i.e. an antimicrobial to which they are not susceptible) have a delay of five days until they receive a therapy to which they are (typically) susceptible in the microbiology-directed setting.  This delay is associated with increased mortality and length of stay compared to patients who receive a treatment to which they are susceptible in the empiric setting. |
| 6 | The value of the drug in patients with contraindications to colistin has not been reflected in the quantitative analysis | Shionogi | The clinical advisors to this project indicated that, in the context of multi-drug resistant infections where patients are at high risk of mortality from their infection, adverse events will be tolerated by clinicians and only a small proportion of patients would be considered completely contraindicated to colistin. |
| 7 | False negatives (infections that are not identified as e.g., MBL in the empiric setting but are subsequently treated as such in the microbiology-directed setting) are omitted from the modelling completely. | Shionogi | Shionogi raised the concern that MBL infections that have not been identified as suspected MBL in the empiric setting were omitted from our modelling.  These patients are indeed not reflected in the empiric setting modelling as their treatment pathway is not influenced by the availability of cefiderocol until they enter the microbiology-directed setting where they are identified as MBL. Benefits to these patients are, however, reflected in the microbiology-directed setting model.  In principle, we could therefore estimate overall INHEs in a given population by combining (1) information on the number of patients receiving treatment in the empiric setting due to a suspicion of MBL with evidence on INHEs from the empiric setting model, and (2) information on the number of patients receiving treatment in the microbiology-directed setting with evidence on INHEs from the microbiology-directed setting model.  However, in practice, this is challenging as we only know the total number of tests carried out for MBL and not the setting in which these tests were conducted. Based on expert advice we therefore assumed that:   * All MBL tests in HAP/VAP or BSI patients related to a suspicion in the empiric setting * All tests in cUTI or cIAI were only acted on when patients reached the MDS.   If we had instead (for example) assumed that some of the tests for MBL in HAP/VAP patients were conducted outside of our empiric setting (e.g. following poor response to empiric treatment) then we note that this would be expected to reduce our estimates of population INHE. This is because only patients with confirmed MBL would receive cefiderocol and typically INHE estimates for the microbiology-directed setting are lower than for the empiric setting. |
| 8 | cUTI patients that recover from their infection are likely to have survival closer to that of the general population  Why is the mean life expectancy for these patients so low? | Shionogi | Survival in recovered patients was informed by the CARBAR study to reflect the highly comorbid nature of patients who acquire these infections. We explored using different survival models for different sites of infection; however, we did not find data to support this. CARBAR survival conditional on site of infection, provided by Shinogi via a data request, indicates that survival in cUTIs is comparable to that in pneumonia and bloodstream infections in this patient population.  On the more general question about the face validity of the life expectancy estimates, the CARBAR study found a median overall survival of approximately 1.5 years. The mean survival of patients without AKI who survive to 30 days estimated from our modelling based on CARBAR is 4.5 years. This reflects the “long-tail” of the parametric survival model used. Life expectancy of those in the model is shorter than 4.5 years as many (~30-50% depending on population and comparator) die within the first 30 days of treatment. |
| 9 | Model doesn’t account for impact of AKI on length of stay | Shionogi | An overall cost of AKI is included in the model. This reflects impacts on length of stay. |
| 10 | Resistance emergence was modelled for the new drugs but not comparators | Shionogi, Pfizer | Within the economic modelling it is important to distinguish between two types of resistance:   1. Resistance to carbapenems (typically viewed as last-resort antimicrobials), and 2. Resistance to non-carbapenem antimicrobials amongst carbapenem-resistant pathogens.   Changes over time in both types of resistance were considered. For the first, there was evidence to suggest an increase in resistance to carbapenems (due to the resistance mechanisms included in the high value clinical scenarios), and this was modelled.  Evidence on resistance to non-carbapenem antimicrobials for the high value clinical scenarios was obtained from Public Health England. There was insufficient evidence to suggest that there was a trend in these, hence no trend was modelled for the comparators.  EEPRU will be running additional scenario analyses to help quantify the longer-term health effects of the new antimicrobials. This will include increased levels of resistance to comparator antimicrobials. |
| 11 | Expected usage is underestimated | Shionogi, Pfizer | Shionogi raises concerns that patient numbers in the EEPRU analysis are underestimated due to exclusion of MBL pathogens other than *Enterobacterales/Pseudomonas/ Stenotrophomonas*, exclusion of empiric use in *Stenotrophomonas*, exclusion of bone/joint/skin sites of infection, exclusion of non-MBL multiple resistance mechanism patients, and exclusion of patients with only panel testing for MBL.  Pfizer raises concerns that expected usage forecast by EEPRU is lower than current usage of CAZ-AVI.  Our work aimed to quantify the benefits of expected usage under appropriate stewardship arrangements. The areas of expected usage were characterised based on feedback from clinical experts. There is no reason to expect this to align with current usage.  Nonetheless, given the challenges of the project, it is feasible that there are areas of expected usage not reflected in our current estimates. Based on our discussions with clinical advisors and as discussed in the reports, the main areas of potential additional usage are in immunocompromised patients, patients with cystic fibrosis, burns patients and patients with renal compromise. Infections in these patient groups will be reflected within our analysis to the extent that they are caused by the bugs modelled (so OXA-48 *Enterobacterales* for CAZ-AVI and MBL *Enterobacterales, Pseudomonas or Stenotrophomonas* for cefiderocol) and the site of infections fall within those modelled (HAP/VAP, cUTI, IAI and BSI). The question is, therefore, whether there are infections within these patient groups caused by different pathogens and/or presenting at different sites where the new drugs offer health benefits over existing therapies. We think it is appropriate for the committee to reflect on this.  In their deliberations, the committee may wish to consider whether any additional areas of usage fall within the product licenses, how any expansion of expected usage would influence the INHEs delivered by the new products (e.g. some uses may offer more marginal incremental health benefits than estimated within the HVCS); and how expected usage might influence the most plausible scenario with respect to emergence of resistance to the new drugs. |
| 12 | Selection of modelling approach was inconsistent with EEPRU’s previous recommendations | Pfizer | It is unclear how Pfizer concluded from our [2018 report](http://www.eepru.org.uk/article/framework-for-value-assessment-of-new-antimicrobials-implications-of-alternative-funding-arrangements-for-nice-appraisal/) that EEPRU recommends dynamic disease transmission modelling. EEPRU was very clear about the challenges of developing reliable mechanistic dynamic modelling (e.g. pages 72-73). For example, “Thus, mechanistic models require knowledge of the parameters that drive the mechanisms of resistance, many of which are non-measurable and not well understood” (p72).  A key recommendation of that report was “Given the difficulties associated with developing credible mechanistic dynamic models and concerns relating to the simplicity of statistical models for the prediction of resistance to different AM prescribing strategies, consideration should be given to the development of both statistical and mechanistic models. Differences in outcomes between these two modelling approaches should be clearly described, explained and justified.” (p86).  The specification of the project made this latter joint modelling approach unfeasible, and this should be a reflection for a formal assessment programme for antibiotics. |
| 13 | Incremental QALY gains reported by EEPRU lack face validity | Pfizer | The incremental QALY gains make sense in the context of the underpinning efficacy and safety evidence for each drug/pathogen/mechanism considered.  For example, for CAZ-AVI, the INHE in the empiric setting is 0.16 compared to the best available alternative (non-colistin/aminoglycoside-based therapy). This reflects the weighted average of a large gain in QALYs of 0.81 in patients who do indeed have the suspected pathogen/mechanism and where CAZ-AVI offers higher susceptibility, and no difference in outcomes in patients with other pathogens/mechanisms. |
| 14 | Limitations in quantification of additional elements of value relevant to new antimicrobials (sometimes called the STEDI values) | Pfizer, MSD, Shionogi, NHSEI, Andrew Seaton, BSAC and RCPath | The [earlier EEPRU work](http://www.eepru.org.uk/article/framework-for-value-assessment-of-new-antimicrobials-implications-of-alternative-funding-arrangements-for-nice-appraisal/) outlined the alternative pathways through which new antimicrobials can, *in principle,* improve outcomes. It referred to literature on these additional sources of value (sometimes called STEDI values). EEPRU’s earlier work highlighted that these sources of value are predominantly related to population health gains. It discussed how these could, *in principle,* be captured in economic evaluation using modelling, although the evidential burden was likely to be significant. It should be noted that, as sometimes described, these sources of value are not mutually exclusive and may not apply to all products.  In the current evaluations, EEPRU used available evidence to estimate population health effects over a 20-year time horizon of CAZ-AVI and cefiderocol compared to alternative treatments, focussing on HVCSs. It is not conceptually or practically appropriate to separate out the ‘STEDI values’ and to aggregate across them. Therefore, based on available evidence and clinical advice, EEPRU assessed whether (a) there are clinically relevant pathways through which CAZ-AVI and cefiderocol could generate these sources of value; (b) where this was the case, whether these were wholly or partially captured in EEPRU’s modeling; and (c) where not captured in EEPRU’s modelling, to provide a qualitative assessment of the consequent uncertainty.  The results of this part of EEPRU’s work are set out in Section 8.3 of the CAZ-AVI report and Section 9.3 of the cefiderocol report. The conclusion is that the main areas of uncertainty are enablement value and transmission value, with the magnitude of the former likely to be greater than the latter, but both are highly uncertain.  As set out in the introduction to these responses, EEPRU’s evaluations were not able to evaluate optimal stewardship policies for CAZ-AVI and cefiderocol. Instead, we modelled HVCSs which reflect our clinical advisors’ views on how these products would be used currently. Relatively low usage in the short term would, in principle, preserve the effectiveness of the products to the emergence of greater numbers of patients with challenging pathogens and resistance mechanisms in the future. This could be considered the insurance value of the product as discussed in some literature. EEPRU has tried to capture this by estimating the growth of patient numbers over time in the HVCSs.  It is recognised that there may be new (perhaps currently unknown) pathogens or resistance mechanisms emerging over time for which CAZ-AVI and cefiderocol would be valuable treatments. This aspect of insurance value is not captured in the modelling given the profound uncertainty regarding these future developments. To inform the NICE Committee’s deliberations, however, EEPRU is undertaking additional scenario analyses. |
| 15 | Use of oral fosfomycin cost in the model, instead of IV | NHSEI | In each setting (bug, site of infection, empiric vs MDS), there are several available comparators. We based drug costs on the most expensive option available to reflect that often combination or higher doses of therapy may be used.  NHSEI have highlighted that the cost of fosfomycin was based on oral, rather than IV formulations, and that IV fosfomycin is up to 100 times more expensive than oral.  We have explored the impact of increasing the drug cost for HAP/VAP suspected to be caused by MBL *Enterobacterales* in the empiric setting. Increasing the treatment cost 100 times, increased INHE from 0.12 to 0.78.  However, we highlight the uncertainty in the relevance of this scenario, as our clinical advisors have highlighted that the drug costs in the model (based on oral fosfomycin) were already quite high. |
| 16 | Comments on executable model | Shionogi | We have identified comments that indicate potential errors in the model:   1. Issue 1 regarding line “l2choice <- select(outcome, c(1:4, 6))”. 2. Issue 2 regarding the code for sampling uncertainty in the probability of having the bug of interest in the empiric setting (parameter p\_bug in the model). 3. Issues 6 and 16, regarding the choice of seeds and convergence of the patient level model. 4. Issue 9 regarding the naming of rows and columns for “outAll”. 5. Issue 62 (included in general comments from Shinogi on the submission rather than the comments on the executable model), highlighting that the cost of patients being discharged to long term care in one of the scenario analyses was entered incorrectly.   Points 1 and 4 above did not impact the results because the code in question was not called in the final version of the model.  For points 2 and 5, we have identified and rectified the errors. Point 2 impacted uncertainty in the probability of having the bug of interest in empiric setting. Rectifying the error had no impact on expected outcomes in the model, and negligible impact on uncertainty in patient-level INHE in empiric setting.  Point 5 led to lower INHE associated with cefiderocol and CAZ-AVI for all bugs and sites of infection for this particular scenario analysis. This is because it increased costs associated with survival, and survival was higher with the new drugs than with comparators. The impact on cefiderocol INHE is shown in the table below. The impact of correcting the error is shown comparing the third and fourth lines of the table.   |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | |  | CPE HAP/VAP ES | CPE HAP/VAP MDS | CPE cUTI | PsA HAP/VAP ES | PsA HAP/VAP MDS | PsA cUTI | | Base case table | 0.136 | 0.021 | 0.019 | 0.145 | 0.150 | 0.125 | | Lt cost (report) | 0.157 | Change <10% | 0.022 | Change <10% | 0.167 | 0.174 | | Lt cost (update) | 0.109 | 0.017 | 0.017 | 0.121 | 0.130 | 0.141 |   Point 3 was explored by re-running the probabilistic model for CPE-OXA48 in the empiric setting with a different seed (set.seed(456)) and a larger number of simulations (5000). The new results were nearly identical to our original results, indicating model convergence.  We have also identified an additional error in the modelling. This relates to how survival was incorporated into the model. The effects of this error look small although this needs to be assessed in all sub-groups. |
| 17 | Comparators used in the assessment (Shionogi comment #16) | Shionogi | The comparators selected were based on extensive consultation with clinical advisors. EEPRU would like to point out the following:   * The comparators listed in the PICOS are all combination therapies, except for aminoglycosides. * In the ES, combination therapies were modelled. In the MDS, monotherapies were modelled, but in clinical practice combinations would be used, and since drug acquisition costs do not impact significantly on INHBs, this is likely to underestimate the efficacy of comparators and overestimate the INHB of the interventions. * Meropenem was not used in the modelling * Inactivity of an antimicrobial to NDMs, or ESBLs will be reflected in the susceptibility reported in studies |