**Organisation name: Shionogi B.V**

**Disclosure:** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry:

**Name of person completing form: Warren Cowell**

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| **Comment no.** | **Pag**  **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. |
|  |  |  | **Overview of Shionogi response** |
| 1 | NA | General | Introduction  This consultation response provides feedback on the Assessment Report (AR), and associated modelling. The sections below provide a comprehensive set of comments describing a range of concerns with specific elements of the analysis performed by EEPRU. Each of the main sections also include a summary of the key points. The contents of this form cover feedback on the AR, whilst more technical ‘QC’ feedback on the model is covered in our separate response.  Several of our comments have been raised previously (e.g. in response to the draft scope, evaluation protocol, etc.), but they remain relevant at this stage.  Many of our comments are also relevant in response to the AR on ceftazidime with avibactam, for which we are a commentator. |
| 2 | NA | General | Summary  A range of significant challenges associated with the assessment of antibiotics have previously been identified, as described in the EEPRU 2018 ‘Framework’ report and in the NICE ‘HTA Process’ document (Annex 7) for this project. These documents also outlined some commendable proposals for how to address these issues. These key principles and features of a novel evaluation approach include:   * The need to encompass all potentially beneficial uses of the technology * The need to generate estimates of immediate individual patient benefit and then multiply by estimates of eligible patient numbers * The need to estimate a wider set of ‘population’ benefits (e.g. the ‘STEDI’ values), including forecasts of how differing antibiotic utilisation patterns could impact on prevailing trends for increasing antibiotic resistance in the future * The need to consider a wide range of evidence, in particular in-vitro susceptibility data and expert opinion   These two NICE assessments are intended to ‘test’ whether/how a comprehensive evaluation can be achieved in practice, by implementing an HTA system that successfully includes the features described above. Based on the two ARs, we do *not* consider these key features to have been satisfactorily demonstrated, for the following reasons:   1. Not all potentially beneficial uses of cefiderocol have been assessed. The HVCSs and areas of expected usage entirely miss several populations/scenarios where cefiderocol use – either immediately, or in the future - is suitable. For example, **all** MBL infections occurring at **any** site in the body and with **any** pathogen species, are potentially suitable for treatment with cefiderocol. This EEPRU analysis only covers a few of the most typical infection site/species combinations, and this represents a clear under-estimation of value. See section 8.2.6.1. 2. The analysis of individual patient benefit within HVCSs – and extrapolation to the population level - is flawed and in general underestimates cefiderocol’s benefit, and/or overestimates the comparators’ benefit. This is due to a combination of factors, including numerous model assumptions and inputs that are questionable, and various other aspects of modelling/analysis that are sub-optimal. Particular issues relate to: - Inappropriate interpretation of the susceptibility data, especially for colistin and fosfomycin, which results in an over-estimation of the comparators’ in vitro efficacy. In particular, the exclusive use of historic EUCAST breakpoints, without consideration of other recognised systems or recent/ongoing changes to breakpoints is unsatisfactory. Furthermore, the EEPRU logic for assessing in vitro data of comparator combination regimens is flawed and over-estimates their efficacy.  - Lack of consideration of how PK/PD factors affect efficacy, which results in an over-estimation of the comparators’ clinical effectiveness against some infection types. - Exclusion of trial data on cefiderocol effectiveness against MBL infections, which represents the single most relevant item of evidence providing a direct estimate of comparative clinical effectiveness in the population of interest. This was not even used to validate the results of the model in terms of patient benefit estimation. - Underestimation of the costs associated with renal toxicity and no inclusion in the model of other adverse events commonly reported for comparators. - Lack of clarity regarding drug-acquisition costing of combination therapies. - Incomplete modelling of treatment pathways in the ES, with no consideration of false-negatives, omission of the option to de-escalate, and omission of the impact of delays to effective therapy on outcomes. This results in considerable uncertainty over robustness of the consequent benefit estimates, and very likely underestimation of the value. See sections 5 & 8. 3. A thorough consideration of the broader and more ‘dynamic’ population-level benefits (including STEDI values) has clearly proved difficult for the assessment group, in part due to resource constraints (leading to the inability to develop and utilise a mechanistic model of resistance), but also due to analytic omissions and questionable assumptions. Notable findings that are consequently counter-intuitive and open to challenge include: - Resistance levels for some pathogens (e.g. *Pseudomonas*) will not increase in the future - Resistance levels to existing antibiotics will not increase in the future - Development of resistance to existing antibiotics will not be reduced by decreased use - No transmission, diversity or spectrum value associated with the availability of these new antibiotics - Only marginal insurance and enablement value associated with the availability of these new antibiotics All of these conclusions lack face validity and overall, this reflects a failure to properly account for these wider aspects of benefit, which was the primary objective of this project. See section 9.3. Furthermore, some conclusions from EEPRU appear to be inconsistent with certain basic tenets of AMR, including the underlying problem of increasing resistance to existing antibiotics and the principle of antibiotic conservation. 4. Whilst expert opinion was sought to supplement other evidence, this was not done extensively or thoroughly enough. Consequently, the opportunity to demonstrate how this type of evidence can address gaps in the standard empiric evidence base has been missed.   In general, this analysis is incomplete and flawed – with many assumptions/inputs that disadvantage cefiderocol, thus under-estimating its value. Cefiderocol performs highly in the NHSE selection test, scoring 36750 (96%) out of a maximum possible of 38250 points, indicating that it is almost as good an antibiotic as it is possible to be. If such a product is nevertheless found to have low levels of immediate/direct benefit – and negligible value from any of the STEDI values - this will have significant implications for the validity of the evaluation based on this assessment.  Therefore, the ‘test’ has *not* - so far - shown that a comprehensive and credible evaluation can be achieved in practice. An area of further work that should be considered, is the development/agreement of a mechanistic model that can properly reflect the dynamic population-level benefits of additional new antibiotics. It seems unlikely that NICE will be able to quantify these benefits accurately until such a model is utilised in the analysis.  It is critical for these evaluations to demonstrate that the full value of AMs can be satisfactorily captured by this novel methodology, and for any NICE outputs to be relevant for subsequent subscription payment level discussions. This proof of concept is relevant for the broader AMR policy ‘learnings’ from this NICE pilot evaluation – and the future implementation of HTA for antibiotic assessments both in the UK and abroad. |
|  |  |  | **1. Report summary** |
| 3 | 19 | 1 | Is there an error in Figure 1? The bullet point ‘Baseline number of...’ under the ‘Modelling population-level INHEs in HVCSs’ column, is duplicated under the ‘Extrapolation from HVCSs’ column, which seems odd. |
|  |  |  | **5. Clinical evidence** |
| 4 | 39 - 98 | 5 | Overall, this section has severe limitations regarding selection and interpretation/use of data for cefiderocol and comparators that reduces the reliability of the overall results in the model. Whilst in vitro data is a key source of evidence for antimicrobials, it should not be considered in isolation, and PK/PD, tissue penetration and available clinical data should have also been incorporated alongside the in vitro data, to better estimate clinical effectiveness.  The AR does not address some key data points available for cefiderocol (namely, the existing clinical data on MBL effectiveness, from the CREDIBLE-CR study). EEPRU has not given sufficient consideration to the importance of PK/PD data, particularly when thinking about tissue penetration and pathogen coverage.  The literature search conducted by EEPRU regarding fosfomycin is not robust for this type of analysis, and presumed usage patterns for fosfomycin do not reflect actual practice. Furthermore, EEPRU did not consistently implement the EUCAST breakpoints regarding fosfomycin in *Pseudomonas*.  There have been important changes made by both EUCAST and CSLI regarding colistin breakpoints, which NICE must consider. Both organisations have concluded that polymyxins, including colistin, are inadequate antimicrobial agents with poor tissue penetration, and have announced changes to their susceptibility definitions for colistin. CLSI revised their clinical breakpoints and have removed the category of ‘susceptible’ for the polymyxin class and EUCAST have publicised that these drugs should not be used in monotherapy for systemic infections. This has implications for EEPRU’s assumptions on the effectiveness of mono- and multi-agent regimens.  Finally, there were significant deviations from standard literature searches that may have introduced bias, and reduced the overall reliability of the results in this AR. |
| 5 | 41 | 5.1.1.1 | For the analysis of comparative in vitro susceptibility, EEPRU use EUCAST clinical breakpoints, with CLSI breakpoints only used for a secondary sensitivity analysis. We believe that both should be incorporated together, and given equivalent weight, based on the following explanation.  It is worth highlighting the fact that CLSI is not the only other independent breakpoint setting body and breakpoints for cefiderocol have also been approved by the FDA and by USCAST (an affiliated sister organisation to EUCAST based in the USA but which employs a similar approach to breakpoint setting). All four organisations recommend the same international reference standard *in vitro* testing methodology to determine MICs (ISO 2776-1:2019), but have different approaches on setting interpretative breakpoints. As can be seen from the table below there is considerable disagreement on the appropriate susceptibility breakpoint for cefiderocol, particularly with respect to *Enterobacterales* for which EUCAST has the most conservative breakpoint at 2 mg/L while the other organisations have accepted a susceptibility breakpoint of 4 mg/L as appropriate (USCAST reserves a breakpoint of 2 mg/L only for respiratory tract infections).    It is also worth highlighting that since 2019, EUCAST removed the ‘intermediate’ categorisation, which explains why definition of ‘resistant’ to cefiderocol (*Enterobacterales* with MIC of 4 mg/L or above) is considerably lower than would be defined by other organisations which only consider isolates with MIC of 16 mg/L and above to be resistant to cefiderocol (USCAST define *Enterobacterales* with MIC of 8 mg/L to be resistant in the pneumonia setting).    Highlighting this variation is relevant to EEPRU’s analysis as it relates directly to the limitations of *in vitro* susceptibility alone in predicting clinical outcomes. For example, while *Enterobacterales* isolates labelled as ‘susceptible’ by EUCAST will always be ‘susceptible’ by alternative breakpoints and would be expected to have a high probability of therapeutic success, the same is not true for isolates with MIC of 4 mg/L which would be categorized as resistant by EUCAST (predicted to have low probability of clinical success), but classed as fully susceptible or intermediate by CLSI, FDA and USCAST and predicted to have a good probability of clinical success in sites with adequate exposure. This paradox should be considered by reviewers when comparing the reported *in vitro* susceptibility of cefiderocol in the *Enterobacterales* group by EUCAST breakpoints versus comparators such as colistin. |
| 6 | 40 - 41 | 5.1.1.1 | In November 2020, an article was published in the journal Clinical Infectious Diseases (Satlin M. *et al*., 2020) written jointly by the Clinical Laboratory Services Institute (CLSI) in the USA and the European Committee for Antimicrobial Susceptibility Testing (EUCAST) which set out their respective positions on the pharmacokinetic profile and clinical effectiveness of the polymyxin class of antibiotics (including colistin). Therefore, this analysis should now be conducted, incorporating the new EUCAST and CLSI conclusions on colistin.  The two organisations agreed that polymyxins are poor antimicrobial agents which fail to achieve adequate exposures in tissue sites (especially the lung) required to inhibit growth of *in vitro* ‘susceptible’ bacteria. This is the case in more than 50% of patients with normal renal function and in addition to the significant nephrotoxicity associated with the class has been associated with increased mortality when used as monotherapy compared to alternative agents.    Subsequently, the CLSI revised their clinical breakpoints and have removed the category of ‘susceptible’ for the polymyxin class, meaning all bacterial isolates are now considered either ‘intermediate’ or ‘resistant’ and so intrinsically non-susceptible to colistin monotherapy.    In October 2021, EUCAST also announced a public consultation and proposed to introduce caveats on the reporting of susceptibility to colistin, similar to those already applied to breakpoints for aminoglycosides, emphasizing that colistin should not be used in monotherapy for systemic infections outside the urinary tract and should only be used in combination with other active therapy, and even when MICs are below the resistance breakpoint they should not be reported as susceptible [EUCAST Breakpoint Committee consultation on Colistin, December 2021].    These recent changes are important considerations for the EEPRU analysis for three reasons:    Firstly, the consensus of expert opinion from the two major clinical breakpoint setting bodies in USA and Europe that polymyxins, including colistin, do not reliably reach adequate concentrations in the tissues outside of the urinary tract to achieve inhibition of bacterial growth, and therefore cannot be depended upon as a monotherapy, calls into question the clinical relevance of any direct comparisons of percentage susceptibility from historical in vitro surveillance studies between colistin and cefiderocol.  Secondly, by assuming the higher susceptibility value for the components of a multi-drug regimen, particularly for colistin which has the higher susceptibility rates, EEPRU is assuming that the patients that fall between the difference in susceptibility rates only have colistin as an active agent, and that is no longer recommended for systemic infections and largely overestimates the effectiveness of the colistin containing multi-agent regimen. This is further detailed in section 8.2.2.1    Thirdly, the sensitivity analysis carried out by EEPRU reporting susceptibility data interpreted by historical CLSI breakpoints should be reconsidered to take into account that all isolates defined as susceptible to colistin should now be considered as ‘intermediate’ and so by EEPRU’s own requirements (as mentioned on page 54 of the report) grouped with resistant isolates as ‘non-susceptible.’    Ref: EUCAST Breakpoint Committee consultation on Colistin, Oct 2021; EUCAST Colistin Breakpoints – guidance document 2021 |
| 7 | 44 | 5.2.3 | The EEPRU report states: *Review question: “What is the comparative effectiveness of the treatment and comparators based on in-vitro susceptibility studies?*  *Because of their in vitro nature, and since clinical experts to EEPRU indicated that the site of the infection the isolate was obtained from was unlikely to affect the susceptibility profile of the infecting pathogen, isolates could be collected from any site*”  The highlighted text does not make sense, and indicates that EEPRU do not understand the relationship between in vitro susceptibility data and in vivo effectiveness.  Different sites of infection will result in different antibiotic efficacies due to different tissue penetration. Once the isolate is moved from the patient and into a test tube, the pathogen’s resistance in AST is the same if it comes from a lung or bone sample; as detailed above, penetrating the different tissues may require different dosing regimens for the same drug to make sure sufficient drug reaches the target infection site to be effective (i.e. tissue concentration above the MIC). Without these considerations, EEPRU have overestimated colistin and fosfomycin’s effectiveness.    Cefiderocol does not have a site-specific licence partly based on its published PK/PD data, clinical trial data and acknowledgement that it will be used in patients with limited treatment options. This licence has been further supported by the efficacy seen in the compassionate use program, early access program and recent real-world publications, demonstrating activity across many body sites and in different disease states. |
| 8 | 48 | 5.3.2 | The AR states that “*Study selection: At this point a decision was made not to review the PK/PD data, since this data is reviewed when setting breakpoints, and since clinical advisors to EEPRU stated that since the treatment and comparators penetrate to the sites of interest it was therefore reasonable to link directly between susceptibility and clinical outcomes"*  Breakpoints are meant to account for average PK/PD, and therefore tissue penetration in general, but they don’t reflect PK/PD differences between different body sites. Likewise, patients in ICU have different responses to treatment because their bodily systems are disrupted which may affect PK/PD further. Lack of inclusion of PK/PD is overestimating comparators’ effectiveness in specific infection sites, where there is documented poor tissue penetration and efficacy. |
| 9 | 51 | 5.3.2 (Table 5) | The AR states that “*Expert advice indicated that CLSI and EUCAST breakpoints differ and cannot be assumed to be interchangeable (see Section 5.1.1.1). It is unclear whether studies using EUCAST laboratory methods and breakpoints would return the same % susceptible as studies using CLSI laboratory methods and breakpoints. It cannot be assumed that breakpoints from one guideline can be applied where laboratory methods from the other guideline have been used.*  EUCAST and CLSI both use the same methodology (harmonised with ISO 20776-1 reference standard for broth microdilution; reference <https://www.iso.org/obp/ui/#iso:std:iso:20776:-1:ed-2:v2:en>). Therefore, even though breakpoints are different the methods are comparable which means EUCAST breakpoints can be applied to data generated by CLSI method and vice versa. |
| 10 | 54 | 5.4.2 | This analysis does not incorporate evidence from the CREDIBLE-CR subgroup of MBL producing pathogens, as it was considered ‘too small’ and liable to introduce bias due to baseline imbalances.  Shionogi has already determined the baseline characteristics for this subgroup of 21 patients (16 for cefiderocol and 7 for BAT arm), and can provide these baseline data upon request, as was done for SIDERO studies.  EEPRU appear to apply these criteria inconsistently, since the NMA includes at least 4 in vitro studies for fosfomycin that have a sample of 21 or less (see Table 6). |
| 11 | 55 | 5.4.3.1 | The AR has concluded that PK/PD studies should be excluded: *Furthermore, neither the Shionogi company submission nor discussion with the clinical advisors to EEPRU identified a quantitative approach to linking PK/PD evidence to clinical outcomes. Consequently, as part of the mapping exercise, PK/PD studies were excluded*.  The absence of a clear and established quantitative approach does not excuse this failure to account for it somehow, given its relevance has been established. If not quantitatively, at least efforts towards a qualitative integration of this evidence should have been explored. |
| 12 | 57 - 58 | 5.4.3.3 | With regards to the supplementary search of fosfomycin, there are several data points and references which do not warrant inclusion in the NMA, rendering the NMA inadequate for use in its current format. A more robust analysis should be conducted, but questions still remain about fosfomycin being an appropriate comparator, for the reasons stated in this section. As justified below we recommend that:  1) the limitations of the studies reporting fosfomycin susceptibility are highlighted with greater transparency  2) serious consideration be given as to whether these studies can robustly be included within the NMA  3) Findings of the NMA relating to the susceptibility of fosfomycin be at most considered exploratory in nature  4) The NMA be re-run with the exclusion of the fosfomycin studies which are arguably incomparable  5) The economic analyses be re-run with the results of the revised NMA that does not include the limited fosfomycin studies  - Several studies use varying methods of susceptibility testing such as E-test, agar plates and BMD, meaning there is no standardisation across the susceptibility testing.  - Some publications do not report any MICs and others define the susceptibility by different MICs.  - Two of the studies (ref 52,55) did not use EUCAST or CLSI laboratory methods, but instead used a commercial assay (E-test). This is not a recommended method, because it over-estimates susceptibility.  - Table 5 defines a preference for consecutive sampling, which does not occur in some of the selected fosfomycin articles.  - 3 of the studies considered had a very small sample (16 or below isolates), which was deemed not sufficient to consider clinical subgroups, but considered sufficient for in vitro data.  Criteria used to select isolates for inclusion in the study, and for β-lactamase testing, were often not well described, meaning it is unclear to what extent the studies reflect the true distribution of susceptibility for the population they drew from. In addition to this, the isolates tested were not collected from infection sites and were predominately rectal swabs/screening samples, which may be non-pathogenic and therefore likely to over-estimate susceptibility.  Neither EUCAST nor CLSI have set breakpoints for fosfomycin in *Pseudomonas* and its inclusion on the NMA is therefore inconsistent with the criteria applied to other drugs. The studies that are referenced 54 and 55 reported susceptibilities of fosfomycin in *Pseudomonas* isolates using epidemiological breakpoints (breakpoints that distinguish between wild type pathogens, and those with acquired resistance) that do not, according to EUCAST, predict clinical susceptibility. Therefore, these studies should not be considered for the base case scenario, as only EUCAST breakpoints are considered.  Despite these limitations, these studies were considered by EEPRU to have similar/lower risk of bias (table 7) compared to large surveillance studies and sufficiently robust to be introduced in the NMA without further considerations, which we believe is not appropriate and introduces bias and uncertainty to the overall results of this report.  The use of fosfomycin outside of cUTI is not recommended due to resistance development. Furthermore, *Pseudomonas* is often described as intrinsically resistant to fosfomycin because it develops rapid resistance to this pathogen, even in the presence of polymyxins. Therefore, as described for colistin based regimen above, the assumption that a patient that is susceptible to fosfomycin alone has the same outcomes as a patient susceptible to both fosfomycin and 2nd component of the regimen does not apply in this case. Effectiveness for fosfomycin in *Pseudomonas*, particularly in HAP/VAP should consider only patients that are susceptible to both fosfomycin AND the second component of the regimen, otherwise the effectiveness of the regimen is likely to be overestimated and an increment in the resistance rate for fosfomycin should be considered in the model, which is not considered at the moment.  The SmPC for IV fosfomycin also recommends that it should only be used to treat the listed indications when it is inappropriate to use antibacterial agents that are commonly recommended for their initial treatment. This highlights the fact that fosfomycin should only be considered as a comparator for last line salvage use in combination with colistin. For the purpose of modelling therefore, this combination should also consider the increased risk of AKI.  All the limitations detailed above should have been thoroughly assessed in sensitivity analyses and properly noted when interpreting the results of the meta-analyses, especially with respect to the estimates for fosfomycin in *Pseudomonas*, which was not the case. |
| 13 | 63 | 5.4.3.4 (Table 7) | The analysis provided in this table with reference to the SIDERO studies is flawed.  SIDERO is a longitudinal and standardised *in vitro* study over 5 years, using recognised methodologies of testing. This is being compared against small, random studies for fosfomycin that are not surveillance studies (and some of which do not even use sequential sample selection), and may have been subject to publication bias. The AR shows a lack of understanding as to the relevance and reliability of these different pieces of data, and demonstrates that the analysis is not being conducted with the understanding required to include or decline key pieces of data throughout. Both subsets of SIDERO studies (WT and CR) were carried out using the same methodology with the difference that SIDERO-CR isolates were from a pre-selected resistant subset. That this risk of bias assessment was only performed by 1 reviewer alone (as opposed of 2 in normal circumstances), introduces bias in the assessment and overall interpretation of the evidence, particularly in such a complex area where new tools have to be developed. |
| 14 | 67 | 5.5.1 | EEPRU have made note of use of PHE data in the AR: *“Therefore, EEPRU planned analyses to test the impact of the inclusion of data not meeting the inclusion criteria in the economic model. Since PHE data was of high relevance, this data alone would be used wherever possible to inform the susceptibility for the comparators in a scenario analysis. The relative effect estimates for cefiderocol and fosfomycin (which are missing from the PHE data) could then come from one of two sources: a network including all three sources of data; or a network including only cefiderocol or only fosfomycin studies respectively. Therefore, an analysis of studies reporting cefiderocol susceptibility and a separate analysis of studies reporting fosfomycin data were planned to provide the relative effects to apply to the PHE data”*  The quality of the PHE data is limited by heterogeneity of methods used by different hospitals in the initial collection and analysis of samples.  Due to the fragility of this data set, any conclusions should be interpreted with caution, and ideally used alongside other sources of data. Overall conclusions drawn from this data-set warrants validation and face-validity checking, and any conclusions drawn will require greater adjustment to ensure this is appropriately taken into account. |
| 15 | 70-72 | 5.5.3 | Considering the limitations for colistin and fosfomycin sources and data described above, the in vitro and susceptibility values in these tables to be included in the NMA should be completely reviewed and updated. |
| 16 | 77,  81 | 5.5.4.1  (Fig.2), 5.5.4.2 (Fig.4) | The comparators listed in these network diagrams are not appropriate for MBL use.   * Meropenem is not appropriate for MBL producers as they are carbapenem resistant * Tigecycline is only licensed for skin and IAI and not for UTI, HAP/VAP or BSI for which mortality is higher * Aminoglycosides (gentamicin, amikacin and tobramycin) are not active against NDM producing *Enterobacterales* due to co-expression of the rmt (ribosomal methyltransferase) resistance gene on NDM plasmid. * Aztreonam is stable to MBL but most CRE are positive for ESBLs which degrade aztreonam unless protected by an inhibitor such as avibactam * Fosfomycin IV should only be used in combination * Colistin should only be used in combination according to new EUCAST guidance   While we realise comparators are required for an analysis, it must be acknowledged and accounted for, that cefiderocol is unique to the field of antimicrobial agents in its profile. |
| 17 | 84 | 5.6 | Approach A was chosen, even though it ignores a very important point when considering antibiotics, because the data does not exist. Therefore, the acknowledgement that on-treatment failure is disregarded, which is a significant issue for colistin, and likewise fosfomycin.  Also, and most importantly a third option could have been explored by EEPRU: validation of in vitro data with available clinical data (even if this was scarce); this had already been suggested in the manufacturer submission (to use clinical evidence as confirmatory of the in vitro data) and would have provided a more tangible and relevant link between in vitro results that come out of AST tests, and biological in-patient performance of the different drugs. Even if clinical data available in the target population is scarce, it is not non-existent and could have provided a face validity check of the extrapolation between in vitro data and clinical outcomes.  Shionogi advise that the main assumptions should be:  A. for patient with severe systemic infections, adequate treatment leads to positive clinical outcomes and inadequate treatment leads to poor clinical outcome and increased risk of mortality (this is well documented in the literature) and is why we include active comparators in RCTs rather than compare against placebo.  B. in vitro activity is a correlate for in vivo activity and susceptibility is a predictor of probability of clinical success (by definition) assuming adequate exposure at the site of infection, and available clinical data should be used to validate this correlation |
|  | 85 | 5.6 | Review question 5 asks ‘What is the long-term risk of mortality (and other outcomes) for patients with CR cUTI or HAP/VAP?’.  Instead, it would be more reasonable to assess the risk of mortality for patients with CR-infections if left 'untreated' or treated with inappropriate antibiotic therapy, hence causing delay in appropriate therapy. The answer can probably be estimated from historical mortality rates for cUTI and HAP/VAP in patients prior to effective antibiotics.  Also, as detailed in our submission, long-term risk of mortality is confounded by multiple variables that are not correlated at all with the infection, and is a poor predictor of effectiveness of a drug. E.g. in the early stages of the recent COVID-19 pandemic, there were multiple patients with a bacterial superinfection. In some cases, no matter how effective the antibacterial was to treat the infection, the patient would die, due to COVID. Long-term mortality should therefore not be the main endpoint in the assessment, but rather the risk of mortality within antibiotic therapy by lack of effectiveness of the antibiotic drug/regimen, and the impact of initial inappropriate therapy on the mortality risk of the patient. |
| 18 | 93 | 5.7 | SENTRY data was not available at the time of the submission or at the time of the additional data request, but the first year of data including cefiderocol is now available and could be provided to NICE upon request (either in a report or raw data). A full manuscript is in preparation and will be submitted for publication in December. |
| 19 | 94 | 5.8 | The justification for inclusion of fosfomycin as a comparator for in vitro efficacy is flawed since there are no breakpoints for *Pseudomonas,* so it should not be included in theEUCAST or CLSI *Pseudomonas* network.  Other alternatives for estimation of effectiveness could have been considered in the model. |
|  |  |  | **6 & 7. Expert elicitation and existing economic evidence** |
| 20 | 98 – 1-4 | 6 | Expert elicitation should have been employed much more extensively in areas of limited data, such as:   * Correlation between in vitro susceptibility and clinical effectiveness, according to particular infection sites and antibiotics * Effect of AKI on need for long-term care * Probability of false-negatives in the ES * Epidemiology * STEDI values   Also, the manner in which evidence from expert elicitation was gathered and utilised could have been improved:   * In several instances (as highlighted by various comments on the AR), EEPRU appear to have received expert feedback that does not make sense (presumably, either because the question had been misinterpreted or was incomplete, or because EEPRU misinterpreted what the experts said). These instances should have been detected and addressed, rather than incorporated at face value. * For some enquiries, some experts did not respond or had their responses discounted, reducing the sample considerably. Importantly, this sample reduction may have also resulted in a less informed panel (e.g. microbiologists only, rather than clinicians, advising on clinical matters) |
| 21 | 105 | 7.1.1 | Review 1 for existing cost-effectiveness evidence for cefiderocol states that no basis is provided for relevant references due to US focused information.  However recent publications at ISPOR Europe show cost effectiveness for cefiderocol in both the empiric setting and the microbiology directed setting using European isolate data for susceptibility. These are now available on ISPOR website and can be provided upon request. |
|  |  |  | **8. EEPRU assessment methods** |
| 22 | 107 - 168 | 8 | There are multiple issues we have noted in this section which are unclear, do not provide sufficient evidence and greatly underestimate the value of cefiderocol. In addition to this, we have identified several issues with implementation (contained in the proforma for the executable model) which have led to many aspects of the treatment pathway not being captured accurately and concerns with the resulting EEPRU analysis.  For example:  -There is no consideration given to de-escalation, which saves money and supports stewardship.  - There is no adjustment for delayed time to effective therapy, despite the published evidence showing its effect on length of stay and even patient outcomes. - Ototoxicity and *C.difficile* infection are not included.  - It is well documented that colistin is associated with renal dysfunction and cefiderocol has a better safety profile. Despite our initial submission noting the high long-term care cost associated with acute kidney injury (AKI), EEPRU have not considered these costs in their base case analysis. - The contraindications of colistin have not been accounted for, particularly when it comes to the subset of patients where colistin is not the appropriate choice of treatment (such as in ICU).  - Infections that are not initially in the ES identified as e.g., MBL but are subsequently treated as such (i.e. false negative) in the MDS are omitted from ES and MDS scenarios. - We have also noted areas of implausibility within this section. EEPRU have noted the comparative efficacy of cefiderocol versus colistin in MBLs which appears clinically doubtful since it states that colistin is more clinically effective in MBL infections than cefiderocol. This highlights the implausibility of the assumption that susceptibility of a pathogen to a substance is the same as the probability that a patient will be clinically cured. The CREDIBLE CR results offer a clear demonstration of this point (see comments in section 5). - There is also lack of clarity regarding costing as it appears that combination costs are estimated as equivalent to monotherapy costs, which is unlikely. Thus, whilst the incremental efficacy of combining antibiotics is taken into account, it does not appear that the incremental costs are.  Overall, several causes for concern on the face validity and reliability of the results have been raised, and we hope that these can be resolved as the process continues. |
| 23 | 109 - 110 | 8.2.2 | We note that ototoxicity & *C.difficile* are not modelled. Although infrequent, these effects do exist and their absence from the analysis therefore represents an under-estimation of value.  *C.difficile* has been modelled before in the context of cost-effectiveness for other drugs (such as fidaxomicin), showing it to be feasible for inclusion. |
| 24 | 110 | 8.2.2 | Lack of inclusion of the impact of delayed time to effective therapy is an important omission from the ES model, and results in an under-estimate of value for cefiderocol.  EEPRU’s statement in Section 8.2.2. suggests a lack of clarity in the manufacturer submission about patients who never receive appropriate therapy and how they should be reflected. This could be accounted for by an increase in the time to effective therapy for the overall population with that treatment pathway, which has been published (Chest. 2020 Sep;158(3):929-938. doi: 10.1016/j.chest.2020.03.087. Epub 2020 May 22. PMID: 32446623).  Time to appropriate therapy is a metric which may be causally associated with and therefore predictive of patient outcomes. There are well established econometric analysis methods available (e.g. zero-inflated negative binomial, double-hurdle models, others) which can model both a binary outcome (in this case whether the patient ever receives appropriate therapy or not) and a count outcome (i.e. days to appropriate therapy received, given that one is received) simultaneously. Both of these are covered in detail in Andrew Jones’ book “Applied Econometrics for Health Economists” from the York stable of economists. Separately from this, a statistical link between time to appropriate therapy and patient outcomes can be established alongside clinical outcomes for those patients that do not receive a first-line appropriate therapy and only go onto receive it in the MDS. These could have been integrated within a patient level simulation model.  The issue of patients never receiving appropriate therapy is present in the current EEPRU model also, because it is indeed possible that patients can have infections to which no current medicines are effective. Scenarios placing e.g. salvage susceptibility to much lower values or even 0, alongside those reducing susceptibility to colistin over time would test the importance of such a factor.  Time to appropriate therapy is most relevant in the ES, in which it takes time to identify the exact pathogen and therefore there is a chance of receiving inappropriate therapy. In the MDS it is more a case of whether such a therapy exists, rather than its appropriateness for that patient under diagnostic uncertainty.  In essence, a model using time to effective therapy data would aspire to be a statistical construct using time to appropriate therapy to predict clinical outcomes rather than susceptibility, which does not correlate 100% with clinical outcomes. This model, and the uncertainties surrounding it could be used in a patient level simulation to estimate the distribution of clinical outcomes, which could then be validated against the available clinical evidence, or even future clinical evidence which could be collected within a data gathering arrangement. The model and hypotheses therein can then be updated to refine the predictive model. |
| 25 | 110 | 8.2.2 | There is a chance of both type I (false positive) and type II (false negative) error in treatment strategy selection within the ES.  Patients who are suspected of having a particular pathogen/resistance permutation are given a treatment under uncertainty, so there is a chance that they do not have the permutation, but also a chance that patients with that permutation are given another treatment entirely as they have been misidentified. The current EEPRU model does not take the latter into account as only those initiated on 1L treatment are followed through the model. This leads to an underestimate of INHE in the cefiderocol-first state of the world because such patients would subsequently be treated with cefiderocol, meaning it would have 1L and 2L use, even in the state of the world where it is used first. Therefore, patient numbers are underestimated in this (and all) scenarios.  This underestimate is still present in the cefiderocol 2nd state of the world as patients misidentified as not having e.g. an MBL *Enterobacterales* infection who actually do have that infection upon entering the MDS would subsequently be treated in the MDS with cefiderocol, yet are not in the colistin baseline treatment pool as they were never treated as if they did have an MBL *Enterobacterales* infection in the first line ES.  As the impact of this omission on INHE is dependent on the accuracy and precision with which doctors can hypothesise an infection in the HVCS, and this value is uncertain, we are unable to estimate the magnitude of the bias introduced. This point is discussed in detail in our submission in section “3.2.1.2 Diagnostic precision and accuracy” of our submission, where we recommended that both type I and type II treatment/diagnostic errors should be taken into account. |
| 26 | 110 | 8.2.2.1 | The AR states that clinical advice in the MDS for cefiderocol described either no other treatment options or increased risk of nephrotoxicity yet this link is not well explored and could underestimate the number of patients treated with cefiderocol and its overall benefits. |
| 27 | 111 | 8.2.2.1 | A proportion of patients modelled as receiving colistin will in clinical practice not receive colistin due to renal concerns or contraindications. Colistin cannot be used alongside many other drugs (especially nephrotoxic drugs) due to interactions, and is unlikely to be used in frail patients on ICU. |
| 28 | 111 | 8.2.2.1 | EEPRU, under the advice of the clinical experts, has assumed “*that in MDS, a patient susceptible to a single AM within a multi-agent regimen perform as well as those susceptible to all components of that regimen*” (i.e patients only need to be susceptible to drug A or B in that regimen, but do not need to be susceptible to both drugs in order for the regimen to be considered effective). As a consequence, effectiveness rates on the model for multi-agent regimen consider the higher of the individual drugs’ susceptibility rate in that regimen.  However, this assumption is only true for multi-agent regimens where one or more of the agents are considered to be highly effective as monotherapy. EUCAST’s recent recommendations for colistin detailed already in this document, reflect the increasing scientific consensus that colistin is a poor drug when given as monotherapy as it does not achieve adequate inhibitory concentrations in all tissue sites and so is associated with suboptimal clinical outcomes and high mortality, even when the target pathogen is ‘susceptible’ by in vitro AST. This baseline assumption by EEPRU therefore is not applicable or recommended in this situation, and has the effect of overestimating the clinical effectiveness of colistin.  Breakpoints are set for individual drugs considering both the *in vitro* potency*,* the tissue distribution, and clinical trial outcome data, and predict the maximum MIC at which infecting pathogens might be expect to be successfully eradicated when treated with the drug as monotherapy within its regulatory licenced indications. Breakpoints intended to define susceptibility as monotherapy cannot be used to predict clinical response for drugs that are recommend to be used only in combination.  EUCAST’s new guidance recommends that colistin should only be used as a combination for systemic infections and not as a monotherapy, i.e. colistin on its own is not an effective treatment alternative (and this fact is widely understood by physicians who rarely use colistin alone).  Therefore, this contradicts EEPRU’s assumptions where it does not matter if the patient is susceptible to drug A or Drug B, or Drug A and B, the regimen is effective as long as 1 drug is effective.  Instead EUCASTs recommendations suggest that colistin based regimens are only effective if the target pathogen is susceptible to Drug B (non-colistin) ***or*** both Drug A (colistin) AND also Drug B (the other component of the regimen), but not Drug A alone (colistin). As a consequence, the lowest (and not the highest) value of each drug’s susceptibility rate should be considered in the NMA and model.  Such combinations are also only valid if both agents are judged to be appropriate therapies for the target infection eg. a combination of colistin and fosfomycin may be considered inadequate for *Pseudomonas* HAP/VAP as detailed in section 5 comments.  By selecting the highest susceptibility value between the 2 drugs (which is usually colistin) EEPRU is assuming in the model that there will be patients that are only susceptible to colistin in that regimen, and colistin is deemed no longer an effective monotherapy treatment option by EUCAST or CLSI.  REF: EUCAST Colistin Breakpoints – guidance document 2021 |
| 29 | 111 | 8.2.2.1 & model code | EEPRU have assumed that combinations have the same efficacy as the main regimen for that context (evident from the code). Yet, it does not follow that they have the same cost. Only the cost of the main agents is taken into account in the model code and input files.  The consequence of this is that the cost of both cefiderocol and the comparators are underestimated. However, as EEPRU themselves state, cefiderocol is most often used as a monotherapy, meaning that a larger proportion of comparator patients receive combinations than cefiderocol patients. Consequently, excluding the full cost of combinations will under-estimate INHE. |
| 30 | 111 | 8.2.2.1 | For the model structure in the MDS, we note that there is a lack of clarity in Table 16 regarding which regimen is used. More specifically, the row labelled ‘Susceptible to one or more non-colistin/aminoglycosides option’ is inconsistent with the comparators defined in the PICO for MBL *Enterobacterales*, which **all** contain either colistin and/or aminoglycosides, i.e:   * Tigecycline + colistin * Fosfomycin + colistin * Aztreonam + colistin * Aminoglycosides (gentamicin, amikacin, tobramycin)   It is unclear what the regimen(s) considered under non-colistin/aminoglycoside group is, and what the effectiveness and safety profile considered as model inputs for these comparator regimens was estimated to be. However, by not including colistin/aminoglycosides in the regimen as the table 16 is suggesting, in effect these regimens would be monotherapy only, which is not consistent with the PICO defined comparators, or indeed with overall recommendations for the treatment of these patients with MBL *Enterobacterales* infections. This would be a gross oversight and inappropriate definition of comparators in the model, overestimating their effectiveness, when in fact they should not be considered as an alternative at all.  A similar consideration is also applicable for MBL *Pseudomonas*. The only 2 regimens considered for this model in the PICO are: fosfomycin + colistin and fosfomycin + meropenem. In theory, when considering non-colistin/aminoglycosides containing regimens, for MBL *Pseudomonas* fosfomycin + meropenem would still be a valid treatment option for these patients. However, considering that these patients are carbapenem resistant, meropenem would not be effective, and fosfomycin in *Pseudomonas* in monotherapy has been proven to be clinically ineffective (see previous section 5 discussion) particularly in HAP/VAP. Therefore, this regimen is not suitable for these patients either.  Given these considerations, and the lack of effective treatment options in this setting, there is no reason why cefiderocol should not be considered as an alternative treatment option for these patients, and as such it should be included in table 16 and modelled accordingly. |
| 31 | 113 | 8.2.2.2 | We have noted that there is no consideration given to de-escalation, i.e where the pathogen and resistance mechanism has been identified and there are other alternative therapies with no compromise in efficacy. As a part of antimicrobial stewardship to reduce the usage of new agents (and save costs), a treatment like cefiderocol would be discontinued early and an equally efficacious product would substitute for it in the MDS. |
| 31 | 119 | 8.2.3.2 | The model assumes that in the ES if a patient does not have what is referred to as “the bug” then susceptibility is no different between comparators. This is demonstrably not the case, as there is susceptibility data available showing the susceptibility of patients across all infection types and sites is higher with cefiderocol than with colistin. Therefore, differential efficacy outside of MBL infections (i.e. in those given cefiderocol in the ES that do not have ‘the bug’) should be taken into account in the model.  In the model code, this is done here:  # assume that if bug isn't present all patients receive the susceptibility of colistin-based therapy  if (bug\_pres == "hasbug") {  sus\_Emptx <- sus\_Emptx  } else {  sus\_Emptx <- sus\_drug\_rdm[j, 4]  }  This assumption is made around 250 lines into the definition of function simulate\_outcome. As susceptibility of cefiderocol outside of MBL infections is still superior to colistin and this is not being taken into account in the model, the current base case is biased against cefiderocol.  We would like to clarify with EEPRU whether susceptibility is being assumed to be a perfect surrogate for clinical cure, and whether apparently very high susceptibility (and therefore clinical cure) rates (95%+) in first line treatment are realistic. |
| 33 | 121 | 8.2.3.2 (Table 18) | The susceptibility value for isolates for non-colistin regimens is reported as 91%. We disagree with this susceptibility number because only aminoglycosides and fosfomycin + meropenem are relevant here, but as discussed above in section 5 this susceptibility number is incorrect with regards to the effectiveness for MBL *Enterobacterales* and *Pseudomonas.* |
| 34 | 123 | 8.2.3.2 | The inclusion of aztreonam as a singular treatment for MBL *Enterobacterales* is not appropriate because the almost ubiquitous co-carriage of an ESBL (extended spectrum beta-lactamase) or other SBL in MBL *Enterobacterales* means aztreonam has to be co-prescribed alongside an inhibitor, most commonly in the form of aztreonam/avibactam for this type of pathogen. (Shields https://DOI: 10.1093/cid/ciz1159.)  However, recent data suggests emergence of growing resistance to this combination; Nordmann <https://doi.org/10.1128/AAC.01090-21>  Alternatively, prescribing colistin in combination as highlighted in the PICO remains a relatively ineffective option, again due to the highly likely presence of ESBLs or another SBL. This would therefore equate to prescribing colistin alone, which we have previously highlighted is not recommended by either EUCAST or CLSI. |
| 35 | 130 - 136 | 8.2.3.5 & 8.2.3.6 | According to the below line of code, it appears that patient longer-term outcomes are assumed the same for BSI and HAP/VAP.  surv\_vap\_cpembl\_det <- surv\_bsi\_cpembl\_det<-read.csv(file="data\_nhe/Cat2\_1\_Empcombined.csv", row.names = 1, header=TRUE)["Death\_all","E1"]  We question the clinical plausibility of this, given the evidence we presented in Figure 15 of our submission, which indicated poorer long-term outcomes for sepsis patients compared to pneumonia patients. This challenges the simplifying assumption that all patients follow the same mortality trajectory, irrespective of infection site.  Also, as outlined in our submission we could not identify any data suggesting elevated mortality for cUTI patients that recover from their infection; we therefore suggest that these patients are likely to have survival closer to that of the general population. Thus, incremental survival in cUTI is likely to generate more QALYs than the others, illustrating the biases introduced when assuming them to be the same. |
| 36 | 134 | 8.2.3.6 (Table 23) | The visual fit of all standard survival extrapolations in the base-case model is very poor. Standard survival models do not appear to be sufficient to model the long-term outcomes from CARBAR. These fits are not presented visually in the AR.  When running these models, it would seem that perhaps more flexible models such as those proposed in TSD21 would be more appropriate, as the ability of “standard” models to capture mortality appears to be limited. |
| 37 | 137 | 8.2.3.7 | The AR mentions that “*The HRQoL implications of the infection are not modelled as these are expected to be short-lived and, therefore, are not expected to impact substantively on the model results*”  This assertion is unfounded. Several other cost-effectiveness publications have reflected the impact of infection on HRQoL and have shown this to have significant impact on the results, particularly when infection is not appropriately treated.  Utility values differ depending on the infection site (cUTI vs pneumonia, vs BSI infections) as these infections have various degrees of severity and impact on the overall QoL for the patient. This was not accounted in the model.  EEPRUs assumption was not further validated externally or in literature, nor explored in the model, which could underestimate the overall value of cefiderocol in the model. |
| 38 | 138 -142 | 8.2.3.8 | The impact of AKI on long-term care and AKI has not been investigated thoroughly.    An important benefit of cefiderocol is its improved safety profile compared to colistin. This manifests in this analysis as the incremental number of patients with AKI at the end of their course of therapy. According to data on US patients presented by Zheng et al., there is a considerable difference in the proportion of patients that are subsequently discharged into long-term care depending on AKI status (37% vs 12.3% P<0.001). Despite the data presented by Zheng et al. and our suggestion that this difference is likely to exist (exact magnitude notwithstanding) in the UK (see Sections 1.1.3. and 3.3.2. of our submission dossier), EEPRU assumed there to be no difference in the UK in their base case (stated in Section 8.2.3.8. (Page 142) of the document).    It is stated on page 142 that a scenario is included in combination with long-term care costs. We assume that the scenarios relevant to this issue are in fact separated, i.e. “lt.care” or “all.aki.lt” in tables 35 and 37. In Table 35, base case INHE is 0.136, which becomes 0.177 per patient in “all.aki.lt” (a 30% increase) and 0.157 in “lt.care” (another 15% increase). The impact of these scenarios is similar in Table 37, with both increasing INHE considerably compared to base-case. We argue that the base-case should be a combination of “all.aki.lt” and “lt.care” scenarios for the reasons we stated in our submission dossier (Sections 1.1.3., 3.3.2.), and not a set of separate scenarios which do not represent their combined impact on INHE.    Several other important inputs were elicited using SEE or were derived using expert input. Yet it appears from section 6 of the AR that experts were not consulted on this matter. Instead EEPRU simply state that there is no UK evidence and adopt a base-case ignoring a large proportion of the benefit that cefiderocol brings.  As can be seen from EEPRU’s scenario analyses, INHE is highly sensitive to parameters related to AKI and long-term care, particularly AKI affecting the probability of going into care. We therefore argue that SEE should be used to determine the relative probabilities of discharge to long-term care with and without AKI as a result of treatment. |
| 39 | 138 | 8.2.3.8 | EEPRU have considered resource costs and use for the model, however there is no differentiation with regards to length of stay for patients presenting with AKI and patients not presenting with AKI. As noted, increased exposure to treating with colistin will increase the risk of renal impairment and patients will therefore have an increased length of stay; which needs to be reflected in the modelling. Given the strong safety profile of cefiderocol, patients who are treated with cefiderocol will have shorter length of stay relative to colistin. |
| 40 | 140 | 8.2.3.8 (Table 26 footnote) | The report states that ‘The uncertainty surrounding the proportion of time spent in ITU/ICU is not elicited to reduce participant burden.’  This parameter is a strong cost driver. It is not clear whether uncertainty is assumed around these point estimates, and there are no scenarios included relating to this. We would request clarification on these points, and the inclusion of scenarios to explore higher proportion of ITU times than base-case. |
|  |  |  | **8.2.5 Population estimates** |
| 41 | 144 - 152 | 8.2.5 | There are a number of estimates and conclusions in this section that we do not agree with.  The use of retrospective time series data to predict future rates of resistance has conceptual flaws. Reliance on this suboptimal data highlights the problem of not developing the more ‘dynamic’ model (due to resource constraints) that was originally envisaged for this evaluation.  In addition, the time series data itself is limited and this report involves a number of debateable assumptions about how to use it.  Consequently, we believe that:   * The conclusion that there will be no increase in the number of MBL *Pseudomonas* infections is wrong * The estimated increase in number of MBL *Enterobacterales* infections may be an underestimate * The conclusion that there will be no increase in resistance to comparator antibiotics is wrong * The estimated increase in resistance to cefiderocol may be an overestimate * The conclusion that reduced use of antibiotics will not lead to reduced resistance is wrong   Some of these conclusions from EEPRU appear to be inconsistent with certain basic tenets of AMR, including the underlying problem of increasing resistance to existing antibiotics and the principle of antibiotic conservation.  The delayed availability of EEPRU’s population modelling details has resulted in a lack of visibility of these details. This area of the analysis is thus subject to potential further critique when the details become known. |
| 42 | 145 - 148 | 8.2.5.1 | The AR concludes that the number of MBL *Enterobacterales* will increase in the future, but that the number of MBL *Pseudomonas* will not.  This conclusion, which is based on the limited time series data, does not have face validity, and expert clinical advice confirms this.   * The PHE ‘Fingertips’ data shows an increase in AM consumption over recent years, which will have an inevitable ‘knock-on’ effect on levels of resistant infections. * Resistance mechanisms are evolving, both for *Enterobacterales* and *Pseudomonas*. In terms of MBL, IMP & NDM (including in *Pseudomonas)* is emerging as an increasingly significant concern for the UK. This pattern can be seen in the AMRHAI data on an increasing range of isolates reported over the past ten years. Whilst the dataset may indicate that the number of (carbapenem) resistant cases may not have increased substantially, this masks the more granular pattern of increasing levels of MDR cases with increasing cases of NDM, VIM and IMP. These resistance patterns are likely to continue, with an increasing proportion of cases being XDR (including MBL) in the future. * The data used for this analysis does not account for the past two years of COVID and the permanent impact this has had on antibiotic prescribing (particularly for VAP) and resistance. It is well recognised that antibiotic prescribing in hospitals has increased, and that resistance has thus increased too. This will include an increase in MBL *Pseudomonas*. Clinical advisers have described a permanent attitudinal change regarding use of AMs, with increased use of broad-spectrum AMs to tackle infections caused by an increasing breadth of organisms (e.g. in elderly non-CF patients with *Pseudomonas*) as a result of COVID. |
| 43 | 145 - 148 | 8.2.5.1 | The AR concludes that a ‘damped’ trend for future increase in MBL *Enterobacterales* should be considered in the base-case analysis.  Whilst this may merit consideration, Shionogi suggest that the non-damped trend should be the (single) base-case.   * The data is out of date as data after March 2018 is not included. This more recent period would have reflected COVID impacts, which are likely to have increased AM use (and thus resistance) - a trend which is likely to continue in the future. * A non-damped trend is a better fit to the available time series data. * The report states that it is ‘...unclear if any genuine increases would persist into the future’ but does not provide any rationale for why they would *not* persist. * The concept of ‘damping’ was not supported as an intuitively accurate model by clinical experts. * In fact, an alternative ‘accelerated’ growth model was considered more plausible. Once a resistance gene becomes established, this ‘step change’ event can lead to exponential growth in resistance if there is selective pressure for it. COVID-related changes (i.e. an increase in overall use of antibiotics in hospital setting, driving increased selection pressure). |
| 44 | 145 -148 | 8.2.5.1 | This section does not present any estimated trend for future numbers of *Stenotrophomonas* infections.  Clarification on whether this issue has been addressed would be helpful. |
| 45 | 148 - 149 | 8.2.5.2 | The report concludes that resistance to comparator antibiotics will not increase in the future.  This conclusion (which EEPRU state is caused by the inability to construct a model due to limited time series data) does not have face validity, and expert clinical advice confirms this.   * Expert advisors have concurred that it is unreasonable to expect resistance levels to existing AMs not to change, especially the comparator products (colistin, fosfomycin) which are used broadly. * COVID pressures are likely to further exacerbate resistance. * This conclusion is inconsistent or incompatible with other conclusions in the report (i.e. that overall resistance rates will increase, and that resistance to cefiderocol will increase). Nor is it consistent with a trend for increased resistance to ceftazidime/avibactam, which is observable from the published literature, and noted in the NICE assessment report for that product. * Given the importance of this central tenet of AMR and stewardship - the principle of avoiding over-use in order to minimise resistance – the absence of any form of estimation in this report is surprising and shocking. |
| 46 | 149 - 152 | 8.2.5.3 | The AR describes alternative methods for estimating future resistance to cefiderocol, and reports a range of findings (e.g. 20- year rates of between 1% and 30%), but it is unclear what the overall conclusion is, i.e. for the base-case analysis.  To date, surveillance data indicates a low level/rate of resistance against cefiderocol. This can be explained by limited exposure and a reduced correlation between exposure and resistance (compared to other antibiotics). This evidence therefore supports the rationale for expecting low levels of resistance to cefiderocol in the future, because these resistance determinants (limited exposure, and correlation between exposure and resistance) will remain.  Shionogi would like to highlight the following points that explain why resistance to cefiderocol may be less than other antibiotic analogues, which would mean that the report has overestimated future resistance to cefiderocol:   * Exposure levels will be less than for most other antibiotics. Cefiderocol use will be restricted to certain clinical scenarios and managed carefully, unlike that of many of the antibiotics used prior to cefiderocol, thus avoiding widespread and intense use. This is *despite* its broad coverage of Gram-negative pathogens; broad coverage does not, per se, increase resistance (as inferred on pg.149). * Resistance development per unit of exposure may be less. Cefiderocol resistance is seen primarily to its iron-uptake mechanism. Since this is unique to cefiderocol, cross resistance from (or to) other ABs that do not share this feature is not possible. Also, pathogens with this resistance are ‘unstable’ (i.e. unlikely to survive) since iron uptake is necessary for normal bacteria metabolism, and so this form of resistance is unlikely to persist or spread. Furthermore, this iron-uptake method of cell entry can effectively bypass the porin/efflux removal mechanisms, thus providing ‘insurance’ against that type of resistance.   We believe that only the lower estimates are realistic.  Gentamycin is a suitable analogue; having been over-used in a similar patient cohort over a long timeframe, gentamycin’s ‘terminal resistance’ rate only reached approximately 9%. Cefiderocol resistance rates should be anticipated to be well below this this level if it is used appropriately.  In contrast, resistance to more widely used comparator agents can be expected to increase more significantly (see previous comment). |
| 47 | 152 | 8.2.5.4 | The AR concludes that decreased use of comparator antibiotics will not result in reduced resistance to them.  This conclusion is counter-intuitive and does not have face validity.   * This contradicts the statement and evidence (references 128-130 cited on pg.149) outlining the link between exposure and resistance. * The AR highlights other factors that can contribute to resistance. Nevertheless, these factors should be viewed as ‘confounders’ and that all other thigs equal, increased exposure increases resistance. * Managing exposure is the basis of antibiotic stewardship (and the ‘diversity’ value of having more antibiotic options), so to dismiss it is nonsensical. |
| 48 | 152 - 167 | 8.2.6 | There are a number of estimates and conclusions in this section that we do not agree with.  In summary:   * The range of ex-HVCS patient populations that the report had identified as suitable for treatment with cefiderocol is incomplete. A more comprehensive list of populations suitable for treatment with cefiderocol (with clear rationales for each) was outlined in our response to the Evaluation Protocol and a full list of eligible patient types is provided in the comment on section 8.2.6.3 below. This is critical, as it is clear that *all* relevant patients must be accounted for in the estimated PNHB. * The analysis under-estimates current patient numbers for the identified HVCSs and ex-HVCSs. * Estimates for patient numbers for non-identified clinical scenarios are absent (because these clinical scenarios are missing). |
| 49 | 155-156 | 8.2.6.2 | The manufacturer model is criticised (and dismissed) as being uncertain. However, it should be acknowledged that the AG model is also uncertain (for similar reasons, including the incorporation of assumptions). We therefore suggest that the AG (or NICE Committee) should consider population estimates based on the manufacturer sources and modelling approach, alongside those from the AG model, rather than dismiss one model and set of evidence sources altogether.  The AR criticises assumptions based on qualitative arguments, which are implied to necessarily lead to ‘highly uncertain’ estimates. We caution against a viewpoint that seems to automatically dismiss qualitative rationale and subjective opinion, in favour of quantitative evidence. This mindset is dangerous; reliance on quantitative data can lead to false precision, and qualitative/subjective evidence can often have greater face validity.  The AR argues that 750 infections is an overestimate of patient numbers in the ES, because not all MBL infections would be identified as high risk of MBL. This statement ignores the fact that the 750 estimate does already account for this (i.e. the 50% estimate in Table 30).  The AR also states that it is unknown what proportion of MBL infections are likely to be confirmed as MBL and treated accordingly, and thereby dismisses the manufacturer estimates. We agree that this is unknown, but propose that it is the responsibility of the ERG/NICE to estimate this proportion (rather than simply say it is unknown). |
| 50 | 156 - 157 | 8.2.6.3 | The list of ex-HVCS populations is incomplete, and must be extended to include estimates for the full range of infection types which are currently suitable for treatment with cefiderocol, as listed below. This needs to be done comprehensively in order to meet objective iv. of this evaluation, as outlined on pg.29. This is important, to avoid a systematic under-estimate of patient numbers, and therefore of value.   1. Infections caused by ***any*** MBL pathogen, in addition to *Enterobacterales*, *Pseudomonas*, and *Stenotrophomonas*. Other relevant species include *Acinetobacter, Serratia, Burkholderia, Proteus, Providencia, Morganella*, *Achromobacter*, etc. (as highlighted on pg.28). Individually, these additional numbers may be small in comparison to other species, but they are nevertheless significant at the cumulative level. This is relevant for both ES and MDS. 2. *Stenotrophomonas* in the ES, not just in the MDS. There is no logic to support exclusion of MBL *Stenotrophomonas* from the ES, in patients with clinically urgent disease (as the ES PICO describes). 3. BSI & HAP/VAP in the MDS, not just in ES. As the AR highlights (pg.156), the ‘majority’ of use will be in the MDS, which indicates there will also be some use in the ES. Not all MBL pneumonias are necessarily urgent, or predictable and these cases therefore qualify for the MDS, if not the ES. Similarly, even if all BSIs are urgent, they are not all predictable. 4. **All** other infection sites which are relevant must be accounted for. These include bone & joint, and skin infections (e.g. from burns), at least in the MDS and ES setting for burns. 15% of the early use of cefiderocol has been in bone & joint infections (see Shionogi submission). 5. In the MDS, MDR pathogens with multiple resistance mechanisms (not necessarily just MBL), i.e. ‘difficult to treat resistance’ (DTR) infections should be included (as suggested on pg.154). These will typically (but not exclusively) be *Pseudomonas*, which is often complex, due to its inherent porin channel loss, efflux pump over-expression, and ability to acquire various carbapenamases. Clinical advisors have confirmed that non-MBL *Pseudomonas* is a growing problem, since resistance to ceftolozane/tazobactam and ceftazidime/avibactam is growing, and will require greater antibiotic usage in response. 6. A broader definition of ‘MDS’ should be considered and incorporated, including treatment of infections known to be caused by MBLs on the basis of panel testing, not just gene testing. Gene testing facilities are not available in many hospitals, and in practice are not required to make an informed judgement about the likely presence of MBLs. It would not be appropriate for cefiderocol use to be restricted to NHS hospitals that have gene testing facilities. 7. An additional risk-factor for MBL suspicion should be recent return from an MBL ‘hot spot’ abroad. 8. A broader definition of ES should be considered and incorporated, including suspicion of MDR, not just MBLs. As highlighted in the manufacturer submission, these patients are suitable for treatment with cefiderocol when they are ‘urgent’, because there is no other agent (with the possible exception of colistin) that this wider range of possible pathogens are susceptible to. In practice, these scenarios are not as ‘exceptional’ as advisors may have considered, since a large proportion of all MDR (or even of all MBLs) will exhibit CR risks without MBL-specific risks. In addition, the ES use should not be defined/limited according to any particular species (see point 1 above) - both conceptually (suspicion of MBL/MDR in any species is relevant) and practically (the species may not be known in the ES). Clinical experts have concurred that cefiderocol use in the ES should extend beyond suspected MBLs only, with de-escalation to an alternative AM if/when a non-MBL pathogen is confirmed in the MDS.   Also, the list of ‘future’ populations potentially suitable for treatment with cefiderocol should be extended to cover an even broader spectrum of infection types (e.g. Including SBLs). In these groups, cefiderocol treatment could be appropriate because current treatments have become ineffective, whilst cefiderocol remains effective. |
| 51 | 157 | 8.2.6.3 | The SGSS data is incomplete. Whilst not exactly ‘sampled’ data, the overall real capture rate of SGSS is not good despite being mandatory in theory:   1. Not all hospitals have microbiology laboratories (e.g. only 2 out of the 4 hospitals within University Birmingham Hospitals trust have labs). 2. Only 98% of laboratories provided data at some time (as stated on pg.157). Furthermore, the previous ERS system – which SGSS replaced - achieved reporting rates of only 70% (on initiation) to 45% (when it was replaced), and it would therefore be surprising if SGSS – which is not dissimilar to ERS – has truly achieved a 98% reporting rate. 3. The data that is provided may be incomplete (as highlighted on pg.161). Some labs are better than others, having greater capacity to identify pathogens at the gene level than others. Therefore, it is possible that cases have been missed, even from the 98% referred to previously. 4. Under-reporting will have been further exacerbated by COVID pressures, as highlighted by clinical experts engaged   The AR therefore underestimates the total number of infections. The AR describes this incompleteness as resulting in ‘uncertainty’. This is true, but it could perhaps be better described as systematic ‘bias’ since all these uncertainties are unidirectional (i.e. all the individual limitations listed above will result in *under*-estimates). |
| 52 | 157 | 8.2.6.3 | The challenge of categorising infection sites (in the SGSS data) is highlighted. Shionogi suggest that for much of this analysis – and at least for all estimates of MDS infections – this categorisation is unnecessary, because all/any MBL infections, regardless of site of infection, are suitable for treatment with cefiderocol (see comments on section 8.2.6.1 above). |
| 53 | 160 | 8.2.6.3 | The division of *Enterobacterales* and *Pseudomonas* MBL samples tested (by 3 and 4 respectively) does not make sense, unless there is a high level of coincidence (e.g. MBL infections typically involving IMP, VIM and NDM together) – which is not the case. Instead, these cases should all be counted individually, to avoid a significant under-estimation based on flawed logic. Expert clinical advisors concur with this. |
| 54 | 160 | 8.2.6.3 | The assumption that 85% of *Stenotrophomonas* are not eligible for cefiderocol because they either do not need treatment or may be effectively treated with other AMs is not justified.   * According to clinical advice, the majority of *Stenotrophomonas* infections *are* treated. * The main agent used to treat *Stenotrophomonas* is co-trimaxazole, for which there are ongoing global supply restrictions. This means that the product may have to be imported, leading either to a decision not to use it, or increased costs if it is used.. |
| 55 | 160 | 8.2.6.3 | The second paragraph on pg.160 suggests that the MDS population size was estimated based on confirmed MBL isolates, which are themselves a subset of the specimens tested for MBL in the ES.  If so, this underestimates the MDS population, because only a subset of the actual cases (which will in practice be identified in the MDS) are identified as suspicious and tested for at the previous ES stage. |
| 56 | 161 | 8.2.6.3 | The advisors/AG verdict on the clinician survey results warrants further attention, before this evidence is dismissed altogether. For example, their rationale that the weighted average estimates are implausibly high and likely to be reflective of only ‘high intensity’ clinicians, seems inconsistent with the range of estimates (i.e. some responses including zero).  Furthermore, this evidence does not seem to be available for either stakeholder or Appraisal Committee scrutiny. We request that the results from these nine clinical experts are shared, so that an informed comparison versus the alternative estimates from the assessment group and manufacturer modelling can be performed. |
| 57 | 167 | 8.2.6.3 | On page 167 it is stated that weightings were calculated for INHE in *Stenotrophomonas* patients based on the values in Table 32. However, the weightings used are not reported or derived from first principals.  Our understanding in the code is that the absolute population of *Stenotrophomonas* patients is initially taken from the overall MDS population in the following lines within the 1\_pop\_level\_benefit.R script:  mat\_abs\_pop\_stenos\_vap[,1] <- pop\_size\_mds[4,"HAP/VAP"]  mat\_abs\_pop\_stenos\_bsi[,1] <- pop\_size\_mds[4,"BSI"]  mat\_abs\_pop\_stenos\_uti[,1] <- pop\_size\_mds[4,"cUTI"]  mat\_abs\_pop\_stenos\_iai[,1] <- pop\_size\_mds[4,"IAI"]  Then, the following lines are used to estimate population growth (where i is the index for year):  temp1<-mat\_abs\_pop\_stenos\_vap[,i-1]\* pop\_change\_cpembl[,i]  temp2<-mat\_abs\_pop\_stenos\_vap[,i-1]\* pop\_change\_psambl[,i]  mat\_abs\_pop\_stenos\_vap[,i]<-(temp1\*pop\_size\_mds[2,"HAP/VAP"]+temp2\*pop\_size\_mds[3,"HAP/VAP"])/sum(pop\_size\_mds[2:3,"HAP/VAP"])    temp1<-mat\_abs\_pop\_stenos\_uti[,i-1]\* pop\_change\_cpembl[,i]  temp2<-mat\_abs\_pop\_stenos\_uti[,i-1]\* pop\_change\_psambl[,i]  mat\_abs\_pop\_stenos\_uti[,i]<-(temp1\*pop\_size\_mds[2,"cUTI"]+temp2\*pop\_size\_mds[3,"cUTI"])/sum(pop\_size\_mds[2:3,"cUTI"])    temp1<-mat\_abs\_pop\_stenos\_bsi[,i-1]\* pop\_change\_cpembl[,i]  temp2<-mat\_abs\_pop\_stenos\_bsi[,i-1]\* pop\_change\_psambl[,i]  mat\_abs\_pop\_stenos\_bsi[,i]<-(temp1\*pop\_size\_mds[2,"BSI"]+temp2\*pop\_size\_mds[3,"BSI"])/sum(pop\_size\_mds[2:3,"BSI"])    temp1<-mat\_abs\_pop\_stenos\_iai[,i-1]\* pop\_change\_cpembl[,i]  temp2<-mat\_abs\_pop\_stenos\_iai[,i-1]\* pop\_change\_psambl[,i]  mat\_abs\_pop\_stenos\_iai[,i]<-(temp1\*pop\_size\_mds[2,"IAI"]+temp2\*pop\_size\_mds[3,"IAI"])/sum(pop\_size\_mds[2:3,"IAI"])  In other words, the absolute population is taken from the MDS population in that infection site and the two different growth rates applied to it (one for *Enterobacterales*, one for *Pseudomonas*) to generate 2 population sizes. The population is then calculated as a weighted average of those populations based on the MDS population sizes. We are unsure of the reasoning behind not simply calculating a weighted average growth rate and applying that to the previous year *Stenotrophomonas* population. However, aside from this, this seems reasonable. Yet, we request that EEPRU provide the final weightings used for all infection sites in *Stenotrophomonas* infections so that these can be clinically validated. |
|  |  |  | **9. EEPRU results** |
| 58 | 170 | 9.1.1 (Table 34) | Given the approximately 60% survival rate, baseline age of 63 years old, and the CARBAR survival extrapolations, 2.7 years seems implausibly low. For table 36, this is more pronounced, as cUTI patients that survive their infection would not be expected to have significantly elevated mortality compared to the general population (aside from any renal issues). Therefore, those that survive cUTI may be expected to have survival of around 20 years (per area under general population survival curve starting at age 63, with some adjustment for initial and changing sex distribution through the years per standard NICE methods).  Furthermore, the survival extrapolation selected in the base case has a long tail and does not reach median until around 3 years, so the mean survival for those patients that survive their infection without AKI (the majority of patients on cefiderocol) would be expected to survive longer in the mean compared to median.  Could EEPRU provide a more detailed explanation why the mean life expectancy for these patients is being estimated to be so low? |
| 59 | 170 | 9.1.1 (Table 34) | Lifetime long-term care costs of less than £650 in E1, E2ca, and E3ca seem implausibly low considering the evidence we presented in our submission of almost 40% of US patients with AKI going into long-term care (which may last several years), which costs £1,049 per week (reported in section 8.2.3.8.). Even if the proportion of patients with AKI is lower than the clinical evidence that we presented in section 3.2.2. of our submission would suggest, it seems implausible that expected time in care is less than 1 week. This may be a result of the above issue regarding EEPRU assuming no differential probability of going into long-term care following AKI as a result of antibiotic treatment. We expect there to be a more substantial cost differential, given the prevention of long-term care that cefiderocol is likely to have in the HVCSs considered in this decision problem. |
| 60 | 173 -174 | 9.1.1 (Table 35) | According to these results, colistin is more effective than cefiderocol in MBL infections, and cefiderocol is more effective than colistin in non-MBL infections. This seems to be clinically implausible.  Could EEPRU please clarify? |
| 61 | 173 - 174 | 9.1.1 (Table 35) | It is unclear to us why doubling the risk of CKD would reduce INHB when less patients being treated in the empiric setting would ultimately have CKD in a world with cefiderocol being used more and colistin being used less. Given that CKD is associated with elevated mortality and an increased need for long-term care, we are having difficulty reconciling why reducing it more would worsen the value of cefiderocol. In absence of further explanation or clarification, therefore, we consider this to lack face validity. |
| 62 | 173 - 174 | 9.1.1 (Table 35) | Table 35 seems to indicate that no costs of long-term care are incorporated in the base-case model (scenario lt.care, which in the base-case column states “No costs of long-term care”). When incorporating those costs, the INHE moves to 0.157 from 0.136. The same impact is true in table 37.  This is confirmed in the following line in Markovmodelling\_PSA.R from the EEPRU modelling folder:  state.costs <- c(0, 0, c.CKD.rdm[j], 0)  Which states that only CKD has any cost attached in terms of health care resource use.  In the “lt.care” scenario, this is amended to  state.costs <- c(0, 0.089 \* 52 \* 1049, c.CKD.rdm[j] + 0.178 \* 52 \* 1049, 0)  This lacks face validity as long-term care is a major component of the cost associated with treating patients for serious infections. Therefore, it should be included in the base-case and not as a scenario.  On page 142 of the AR the following is stated: *“Liangos 2006 found that 8.9% of patients without AKI will be discharged to long-term care, and this is elevated to 17.8% in those with an AKI (reflecting an adjusted odds ratio of 2.2 (95% CI 2.1, 2.2))”*  Yet in the above scenario analysis, 8.9% is being applied to those patients that *do* have an AKI (the second element in the vector state costs) rather than those that don’t. Instead, the assignment should be 8.9% of those without AKI are discharged to LT care, whilst 17.8% of those with AKI and those with CKD are discharged to LT care. This may therefore be underestimating the impact which AKI has on the true cost of caring for serious infection patients. |
| 63 | 188 | 9.2 | The AR provides results for the amount of value accruing in the first ten years, “...as this is the period of the contract for the delinked payment”. This might be intended to imply that the contract value should be based on the value accrued over 10 years only (rather than the full value accrued over the 20-year time horizon for this evaluation).  If so, we argue that the full 20-year value should be used for contract negotiation purposes, because:   * This evaluation was designed and intended to capture the ‘full’ value of a new antimicrobials, which includes the complete time horizon within which benefits will be accrued if that antimicrobial is developed, approved and adopted within the UK. * After 10 years, a new antimicrobial will typically go ‘off patent’ (in the case of cefiderocol this will be in 2031) and so the originator manufacturer will not receive much value after this stage. |
|  |  |  | **9.3 Additional value elements** |
| 64 | 199 - 204 | 9.3 | Overall, this portion of EEPRU’s assessment has inadequately answered the brief and therefore does not seem to have delivered on the required scope.  The AR concludes that there is unlikely to be any significant benefit from either diversity, transmission or spectrum value. Furthermore, it concludes that there is no insurance or enablement value, beyond that already captured by the standard analysis. Certain aspects of enablement value – in particular the benefit of increasing number of viable procedures – are acknowledged, but not captured. All of this is highly concerning, as it appears counter-intuitive that an antibiotic with cefiderocol’s profile (i.e. better coverage of WHO priority pathogens than existing agents) has no extra value assigned for these STEDI values – which were the main component of this ‘novel’ NICE evaluation methodology.  It is noteworthy that there are only six pages (3%) of this 220-page report on the STEDI values, and this indicates a serious lack of attention to these central considerations.  It is possible that the decision not to develop a dynamic mechanistic model (and rely on a static forecast model, with fixed resistance development rate parameters) has prevented the STEDI values from being analysed satisfactorily.  Again, some of these conclusions from EEPRU appear to be inconsistent with certain basic tenets of AMR, including the underlying problem of increasing resistance to existing antibiotics and the principle of antibiotic conservation.  These shortcomings must be addressed – or at least acknowledged – by the NICE appraisal committee. |
| 65 | 200 - 201 | 9.3.2.1 | Enablement:  The AR states that there is uncertainty whether these benefits are reflected fully. In fact, it is hard to see that *any* additional enablement value (in particular from improved treatment of pre-operative infections, and consequent improved likelihood of receiving procedures and/or of receiving them without delay) is estimated*.* The AR highlights at the outset (pg.25) how important the benefit of enabling procedures to be performed is, but it appears that this has not been included in the analysis. The AR describes these as ‘areas of uncertainty’, but they are better described as ‘missing’ areas of analysis and sources of under-estimates of value.    This key threat of AMR on broader functioning of the health system, particularly in future scenarios where overall AMR levels may be higher – must be accounted for by NICE. |
| 66 | 201 - 202 | 9.3.2.2 | Diversity:  The AR explanation (citing expert opinion) of why use of cefiderocol within a ‘cycling’ approach is not possible, does not make sense. A clear example of a clinical scenario where cefiderocol could expand the available armamentarium would be in treatment of CRE infections harbouring serine B-lactamases like (e.g. KPC or OXA-48), where (contrary to the stated clinical advisor view) there clearly *are* multiple alternative agents available (e.g. ceftazidime/avibactam, meropenem-vaborbactam, Imipenem-relebactam, eravacycline and now cefiderocol) which could be ‘cycled’ or ‘mixed’ to reduce selection pressure on any one of them.  Furthermore, while the scientific rationale for diversified prescribing is widely accepted, even more so is the negative impact of the alternative, narrow formulary prescribing of a limited number of antibiotics which increases selective pressure on those antibiotics, increasing the rate of resistance emergence and driving evolution of compensatory mutations which counteract any fitness cost and allow resistance phenotypes to persist even when the selective pressure is removed.  Therefore, CFDC use in these other pathogens – either now, or in the future – is clearly possible and justifiable. Some potential value - whether described as ‘diversity’ or simply ‘ex-HVCS’ value – must therefore be acknowledged.  The AR also appears to argue that diversity will always probably result in ‘net zero’ benefit due to countervailing effects. This seems counter-intuitive and contradictory to EEPRU’s original recommendation of this additional value element.  There is also some immediate ‘diversity’ value in adopting any use of cefiderocol, since this will result in the level of use of some other (displaced) therapy decreasing, thus lowering the ‘resistance pressure’ on that agent. This is relevant for estimating future resistance against existing AMs (section 8.2.5). It is contrary to accepted stewardship principles to conclude that reduced use of alternative AMs through adoption of cefiderocol, will not decrease selection pressure and thus slow the emergence of resistance to them.  A dynamic mechanistic model of resistance would facilitate the capture this STEDI value. |
| 67 | 202 | 9.3.2.3 | Insurance:  No additional value was modelled, and the AR acknowledges uncertainty about whether the (basic) modelling (i.e. estimates of future use/value based on general resistance trends) capture the potential ‘insurance’ value against more high consequence (but arguably low probability) scenarios. We suggest that these ‘high consequence’ scenarios may be akin to the 4th type of ‘enablement’ described (i.e. ability to keep wards open during MDR outbreaks). Without some reflection of this additional insurance value for managing ‘catastrophic’ outbreaks of resistant infections, the value has been under-estimated.  The COVID pandemic has clearly demonstrated the widespread burden and cost of infectious disease, and the ‘insurance’ value of having suitable medical interventions available. |
| 68 | 202 – 203 | 9.3.2.4 | Transmission:  Similar to diversity, this value element has not been captured at all, partly due to limitations of the model (which cannot capture the impact of reduced time in hospital) plus conceptual objections (*w*hich seem to amount to a conclusion that the best way to reduce transmission is for patients to die quickly).  Again, this is counter-intuitive – and contradictory to the fundamental ethos of the STEDI values – that an antibiotic which will improve infection management will *not* have some transmission value. |
| 69 | 203 | 9.3.2.5 | Spectrum:  The AR does not address the manufacturer evidence submitted regarding minimal/reduced impact on gut microbiota (including on *C.difficile*), so we must assume this was not included in the analysis, and thus represents a gap/under-estimate of value. |
|  |  |  | **9. EEPRU Discussion & Conclusion** |
| 70 | 205 - 208 | 10 | The results not only indicate high uncertainty, but exhibit a lack of face-validity (e.g. The QALY gains in MDS *Enterobacterales* being an order of magnitude less than ES *Enterobacterales* and MDS *Pseudomonas*, which is inexplicable in reality).  The AR narrative admits various shortcomings of this analysis, highlighting the degree of uncertainty, incompleteness and thus likely under-estimation of value in this analysis. The AR and the analysis/model that it is based upon, as it stands, is therefore not wholly fit-for-purpose as a demonstration of how to capture and quantify the full value of a new antibiotic. |
|  |  |  |  |

**Insert extra rows as needed**

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