**Organisation name: Pfizer Ltd.**

**Disclosure:** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry: None

**Name of person completing form: Jack Charles Kowalik**

# Executive Summary

To address the significant ongoing concerns of future healthcare, both for individual patients and the population, the UK Government has prioritised efforts to address antimicrobial resistance (AMR) for our G7 presidency this year. G7 Finance and Health Ministers in June committed to tackle the AMR pipeline challenge through exploring proposals for strengthening market incentives for antibiotic drug development, underpinned by a set of shared valuation principles. The world eagerly awaits the outcomes of the UK project, to develop and test innovative models for the evaluation and purchase of antimicrobials (AMs) and to apply the finding principles that would comply with international health and care landscapes, as means to resolving the broken market for antibiotics and ensure patients can access a critical lifesaving antibiotic.

EEPRU’s assessment report, to which we are responding to through this consultation, is fundamental for informing the next stage of this project. However, we are deeply concerned that this assessment fails to quantify the wider value of antimicrobial innovation and service offerings. This sends a detrimental signal to industry and investors that antimicrobial innovation continues to be undervalued and consequently both the immediate and future population health will suffer if we are unable to combat the continued rise of AMR.

The final scope1 and paragraph 4.5 of the NHS’s Annex 72 clearly set out the objective for this assessment to capture the broader value of antibiotics, both direct health costs and effects and indirect value via the inclusion of a number of additional value elements (e.g., Spectrum, Transmission, Enablement, Diversity, Insurance). The final scope1 was developed in line with the 2018 EEPRU framework3. However, the EEPRU model deviates significantly from the EEPRU framework1 and the NICE reference case (see Table 1 for further information). As per the NICE evaluation framework2,4, values were to be measured quantitatively where feasible, and qualitatively where not, with uncertainty recognised as leading to a likely under-valuation, and not being penalised.

Areas of value not quantified should be clearly highlighted to the NICE Committee to ensure that the full potential value can at least be qualitatively considered by the Committee, and recommendations for further research can be clearly identified. The clear undervaluation of the individual and population health benefit puts at risk the ability to meet the UK Government’s vision of addressing AMR by 2040, and as stands would not pave the way forward that would set a precedent of a new valuation framework for AMs, either in the UK or globally.

No separate report has been provided for the Cefiderocol response given most / all key concerns within this report are directly relatable to the EEPRU assessment report for Cefiderocol.

Our key concerns, provided in more detail in the body of this response document, may be summarised as follows, each concern outlines clear calls to action to be addressed by the Committee:

1. **Defining treatment, and success (see section Modelling approach and Issue 2)**: There are several high-quality pivotal Phase II/III studies for CAZ-AVI, and a plethora of real-world evidence linked to the full licensed indication for CAZ-AVI. Despite this, EEPRU focused on very specific niche ‘high value clinical scenarios’ (HVCSs), where there is a lack of clinical effectiveness data, forcing a reliance on *in vitro* susceptibility. EEPRU’s clinical experts stated in vitro susceptibility does not equate to treatment success and is likely to undervalue the effectiveness of an antibiotic.

The EEPRU approach unnecessarily deviates from the NICE methods and process guide.4 The focus on HVCSs has led to minimal clinical benefit being identified. The Committee need to consider; the relevancy of the narrow approach taken in using the HVCSs (a result of time and resource constraints), the subsequent reliance on *in vitro* susceptibility data (despite Phase II/III studies and real-world evidence) and how this approach has impacted on the recognition of patient health benefit.

1. **Importance of additional value elements (Issue 1)**: the EEPRU framework3 cites six additional elements of value for new antibiotics, but the EEPRU assessment report doesn’t fully recognise a single one of these value elements, with diversity and transmission value being completely disregarded, despite evidence to suggest its significance3,5, and insurance and enablement value only being captured to a very limited extent.

We request that the value elements which have been quantified and those that have not, along with the limitations are clearly laid out for the Committee. We request that the Committee consider the likely undervaluation of CAZ-AVI as a result of not quantifying all value elements and make clear recommendations for future research.

1. **Modelling of resistance (Issue 2):** Only emergence of resistance for the new antibiotic (CAZ-AVI) was considered in the EEPRU model, critically resistance to existing antibiotics was not captured.

Reducing development of resistance is a key objective for development and reimbursement of novel antibiotics. The absence of modelling resistance of the use of existing antibiotics does not allow for successful evaluation of the introduction of a new AM in the treatment pathway. Resistance development should be modelled and assessed for all therapies.

1. **Treatment efficacy is the key driver of model benefits (Issue 2)**: Unsuccessful treatment of infection would most likely result in death (with exception of those which naturally resolve infection), a patient level QALY gain of 0.1-0.2 (per the EEPRU model) lacks face validity where the most probable outcome of unsuccessful treatment of complicated infections leads to death.

The stated QALY gain represents that of comparable treatment efficacy to the current standard of care, indicating the EEPRU model fails to recognise the additional clinical benefit of CAZ-AVI. Considering death as a primary outcome of unsuccessful treatment the QALY gains estimated via a more holistic, dynamic modelling approach validated by at least 14 KOLs estimates patient QALY gain of 0.67. The Committee must address the face validity of both modelled QALY gains and the appropriateness with respects to this critical lifesaving medicine.

1. **Model validation (Issue 3)**: The validation undertaken by EEPRU is not in alignment with the EEPRU framework3 as the scope of the decision model, model structure and some model inputs were not able to undergo the robustness of expert peer-review or be externally validated. The validation techniques used were limited by both the availability of resource and time. EEPRU outline that the approaches conducted were not as robust or thorough as a Delphi Panel and not validated against historical data.

We request that the Committee seek to contextualise the EEPRU model and outputs against historical data and the Pfizer model. The robustness of external validation each model has undergone to solidify clinical relevance of the assumptions and comparison to historical data should be considered by the Committee.

1. **Estimation of the potential patient population (Issue 4)**: EEPRU focuses on two HVCSs, underestimating the potential patient population (70–575 patients per year) compared to current UK usage (currently estimated at 1,400 patients).6 Equally, this approach significantly underestimates the total number of multidrug resistance (MDR) Gram-negative infections. It is estimated there is 50,000 new cases per annum of patients with MDR Gram-negative infections7, and therefore the estimated eligible population of CAZ-AVI if the optimal antimicrobial stewardship approach was applied in clinical practice (\*\*\*\*\*\*\*\*\*\*\* patients per year). These numbers were shared and discussed during the scoping and dialogue stages of the project.

The publication of these numbers significantly underestimates the health threat of MDR infections and could result in further restricting patient access to a critical lifesaving medicine. We urgently request EEPRU to re-run their analysis using updated patient numbers and provide a subsequent scenario to the Committee ahead of the committee meeting. We request that the Committee should consider current real-world usage and increasing resistance trends both domestically and globally when considering future lifetime usage patterns.

1. **Antimicrobial stewardship and the diversity value of novel antibiotics (Issue 5)**: Antimicrobial stewardship (AMS) strategies have been developed with the aim of limiting the rise of antimicrobial resistance. There is significant clinical need and societal benefit associated with obtaining a diverse set of novel antibiotics, reducing selection pressure and minimising resistance development.

In complete contrast to the EEPRU framework3 and protocol, the current EEPRU model has not attempted to assess the diversity value of novel antibiotics. We request EEPRU to present an alternative scenario for Committee consideration that attempts to model different AMS strategies and their impact on the emergence of resistance. If it is not possible to provide some quantification of diversity value, we request that the Committee qualitatively consider the impact and appropriate usage of new antibiotics as a critical factor in attempting to tackle the clear trend of increasing resistance.

Whilst we recognise the complexity and challenges inherent to the valuation of antibiotics and the work of all stakeholders to improve the assessment framework, we remain concerned about this report, and its potential impact on this project, the future valuation of antibiotics and global efforts to reinvigorate antimicrobial R&D. We therefore ask for our recommendations and the limitations of the EEPRU assessment report to be considered by the NICE Committee, with clear identification of the areas where future ongoing collaboration and research is required. This will ensure a comprehensive review is undertaken that we hope will enable the committee, and NICE, to reach a well-informed and evidence-based decision for the next stages of the project process ensuring the UK Government goals are met, and together we can change the course of antibiotic value assessments.

# Modelling approach

|  |
| --- |
| ***Key messages***  |
| * The EEPRU model deviates significantly from the EEPRU framework3 and the NICE reference case.4 Considerations as to why deviations were made, and to what extent must be identified and the impact on patient / population outcomes explored.
* The proposed model should, where feasible, adhere to the NICE reference case,4 with adaptations to align to the EEPRU protocol8, the EEPRU framework for AMs3, and the final NICE scope.1
 |

Cost-effectiveness modelling of infectious diseases is set apart from other diseases by the communicable nature of infections and the association between the individual and the population. At the individual level, the clinical efficacy of an antibiotic and the time to effective treatment are key drivers of benefits, impacting on mortality as the main patient outcome. However, at the population level, the clinical efficacy of an antibiotic is a determinant of resistance rates (i.e., the proportion of the infections that are susceptible to anti-infectives or resistant to treatment), which in turn is a determinant of patient outcomes, health service and societal costs. Therefore, evidence strongly suggests that mathematical models incorporating the variables discussed above can predict future rates of antibiotic resistance based on antibiotic usage.

Economic evaluation using dynamic transmission models is important for capturing the direct and indirect effects that may arise from a communicable disease. Recent research has evaluated the role of dynamic transmission economic evaluation defined as a modelling analysis i) where the force of infection (risk of infection) is dependent on the model state in a previous time step and ii) that makes a comparison of the costs and effects of one or more interventions or events.

Due to time and resourcing constraints, EEPRU developed a *de novo* decision analytic model to predict the cost and health consequences of CAZ-AVI treatment within HVCSs. Pfizer appreciate the feedback on the company submitted model which followed the advice of experts. Pfizer’s objective was to build an AMR transmission model which was in line with the technical recommendations provided in the EEPRU framework3; an open-cohort disease transmission and cost-effectiveness model where externally validated simplifying assumptions were made, due to model complexity, during model conceptualisation, implementation and validation. This validation also included a Delphi panel.

Both the EEPRU and the company’s model aim to quantify the costs and health consequences of CAZ-AVI treatment. The EEPRU approach is closely aligned to the standard HTA approach, assessing patient-level outcomes before scaling these to a population-level, with no assessment of transmission, limited to no exploration of resistance development and no evaluation of the benefits of a diverse portfolio of AMs. Antimicrobial transmission and resistance do not occur for each patient in isolation and being fundamental aspects of identifying the broader population value of new AMs, Pfizer has directly assessed population outcomes to capture the value of CAZ-AVI at a UK population level in the company submission.

To illustrate the differences of the two models the objectives were compared as well as the model facets and rationales which are presented alongside the EEPRU framework (Table 1). Of particular note is that the EEPRU framework3 was published in 2018, authored by members of the team involved in the development of the EEPRU assessment report.

Table 1. Model facets and rationales - Pfizer vs EEPRU model

| **Facets** | **EEPRU framework3** | **Model facets Pfizer model** | **Model facets EEPRU model** |
| --- | --- | --- | --- |
| Objectives  | Specific objectives of this framework were:* + - * To develop a framework that captures the expected value of a new AM. This involves defining and characterising all relevant costs and health benefits to be considered as part of NICE assessment;
			* Consistent with this framework, to assess the implications of an insurance-based approach to reimbursement for the evidence and evaluation methods used as part of NICE assessment;
			* To illustrate the framework using one or more case studies to highlight methods and evidence issues and alternative ways of addressing these;
			* To suggest any changes that might be required to the methods used in the NICE technology appraisal programme;
			* To provide brief consideration of remaining issues and to make recommendations for further research.
 | * Estimate the value of CAZ-AVI under stewardship scenarios, likely to be applied in clinical practice, that are expected to generate the greatest value to the NHS while maximising population health.
* Reflect real-word practice, focusing on a treatment pathway and assuming a steady state, that accounts for time to effective therapy via a risk factor approach in order to identify and treat those with multi-drug resistant gram-negative infections, in line with the standards of Public Health England.
* Capture population level QALY gains
 | * Identify two high value clinical scenarios for which CAZ-AVI is expected to have a significant impact on patients’ outcomes.
* Establish an appropriate decision-analytic model to quantify the costs and health benefits of the use of CAZ-AVI under various usage scenarios compared with alternative treatments and management strategies in the high value clinical scenarios. Costs and health effects were estimated at individual and aggregated population level and provided as population incremental net health effects (INHEs).
* Use structured expert elicitation to supplement the available evidence to populate the decision-analytic model.
 |
| Model type | For antimicrobials (AMs) the models generally and ideally need to be transmission models that reflect between-host dynamics in order to account for indirect population benefits. These models can capture how susceptible and resistant strains of pathogens spread through population over time.” (p. 32)“The conceptual framework for value assessment of new AMs focuses on population-level models since the aim is to predict the evolution of resistance in the population over time and the associated outcomes for the alternative treatment protocols. […] (p.65) | Dynamic disease transmission and cost-effectiveness model. The economic analysis outputs are expressed as population net health benefits as measured in quality-adjusted life years (QALYs).Rationale: Based on systematic literature review, recommendations from ISPOR and the Society for Medical Decision Making. | Decision-analytic model to estimate costs and health effects at both the individual level and the population aggregated level, providing incremental net health effects (INHEs)Rationale: The objective is to use appropriate analyses of the available evidence at every level, but the detail in those analyses is inevitably constrained by the time and resources available for the project.”**“[t]he use of a transmission model was considered but not pursued […]. […] [A] mechanistic transmission model […] was not considered feasible within the time and resources available …] (p. 104)** |
| Model structure | Population-level models typically consist of mutually exclusive compartments and reflect the dynamic changes in the uninfected population and those infected with susceptible and resistant strains.” (p.65) | The model combines a compartmental multi-state disease transmission module (colonised, infected, susceptible, death) and a decision-tree treatment pathway component. | Decision tree for microbiology-directed setting for acute kidney injury. Markov model used to calculate post-30-day outcomes in patients with recovered renal function and irreversible renal failure.Empiric setting used a three-component decision tree. |
| Indication/ Population | “In most cases, the licensed indications will describe the specific types of clinical infections to be treated by the new AM (e.g., complicated intra-abdominal infection, hospital-acquired pneumonia), but it may also include a pathogen-specific indication […].” (p.39)Represent “the different ways that the AM may be used in clinical practice.” (p.22) | Aligned with the therapeutic indication and current UK usage. Patients with the following infections: cIAI, cUTI, HAP/VAP caused by the following pathogens: *E. coli, Klebsiella spp., P. aeruginosa*To note: as outlined in the submission; this approach was not fully comprehensive in capturing the full licenced indication. | Subgroup of licensed indication and population currently receiving CAZ-AVI in UK clinical practice. HVCSs which include: HAP/VAP and cUTI patients infected with OXA-48 *Enterobacterales.*To note: that although extrapolation occurred to reach beyond the HVCSs, the limited data on the HVCSs and data sources used impacted significantly on the estimates of the wider eligible population.  |
| Comparators | "One important alternative to the new AM will be ‘existing care’ for a particular indication, which represents what would be done in the absence of the new AM.”“The comparators should reflect the treatment protocols typically seen in practice and ones that can reflect the diversity value of AMs […].” (p. 40) | The most appropriate comparators determined during expert elicitation were as follows: piperacillin/tazobactam (cIAI and cUTI) or colistin (HAP/VAP) and meropenem (all modelled indications – simplifications were required).The economic model does include a no comparator alternative – a world without CAZ-AVI. | The following comparators were included: colistin, meropenem, tigecycline, azetreonam, fosfomycin, levofloxacin, ciprofloxacin, gentamicin, amikacin, tobramycin, ceftriaxone, cefepime, ceftazidime (p.6)It is to note that EEPRU mainly used non-inferiority trials and did not consider evolving resistance of the comparator drugs to the pathogens included. |
| Time horizon | “There are three potentially relevant time horizons for the value assessment of AMs: i) the analytic or model time horizon […]; ii) the technology time horizon […]; and iii) the contractual time horizon […].” (p.41) | 10-year transmission horizon; lifetime perspective for LYs/QALYs for evaluated patients | Lifetime horizon (based on predicted number of CAZ-AVI patients over 20 years) |
| Discount applied | 3.5% | 3.5% (1.5% included as scenario) | 3.5% (1.5% included as scenario as requested by NICE) |
| Resistance | “The first step in the development of a model should be an understanding of the mechanisms of resistance […] for a new AM and its comparator strategies […] “Estimating the population health effect […] involves adequately reflecting the expected rate of growth in resistance and associated outcomes over time […] (p.61) | Baseline pathogen resistance was included using ESPAUR 2018/2019 report and ATLAS surveillance data as resources. The ESPAUR 2019/20 report was not used for reasons stated in Issue 5 such as change in reporting of carbapenem resistance.The dynamic disease transmission component was capable of estimating changes to future resistance. Scenarios were run to reflect increasing resistance to CAZ-AVI (see Issue 3). | Changes in resistance to existing AMs over time was not included since evidence was deemed to be sparse. (p.11). For the estimates of AM use employed in the model, the 2019/20 ESPAUR report was used (p. 148) - of note the report was impacted by both COVID and reporting changes as stated in Issue 5. |
| Treatment efficacy and duration | “New AMs are usually evaluated using non-inferiority clinical trials in usual drug resistant pathogens.” (p.48)“Alongside the clinical phase II studies, microbiological in-vitro data are often collected. […] this involves susceptibility testing.” (p.51)“In general, a positive correlation between [clinical and microbiological response] outcomes would be expected […]. However, results of prospective studies that have assessed both clinical responses and microbiological eradication rates have shown that it is not always possible to presume that what happens in-vitro can be extrapolated to therapeutic outcomes of clinical success or failure.” (p.56) | Treatment efficacy was based on several high-quality pivotal Phase II/III studies of CAZ-AVI and supplemented by published literature.Baseline pathogen resistance levels were sources primarily from the 2019 ESPAUR report, where required data was not appropriate or available, the 2018 report was used as supplementary evidence. | Treatment efficacy did rely on *in vitro* susceptibility data due to lack of *in vivo* data. A link was then made between susceptibility and clinical outcomes using published data and expert elicitation.The focus was put on nephrotoxicity and the occurrence of acute kidney injury. |
| Costs  | Standard sources for cost of AMs and administration and monitoring costs (p.76) | The costs were taken from public UK sources. | The costs were taken from published UK literature adjusted to 2019/2020 prices. |
| Validation | “There is a strong requirement for validation of model outcomes against historical data.” (p.81) | Model outputs have been validated against historical data. Further, the economic model has been subjected to extensive, peer-reviewed, published validation. Clinical experts were involved in model conceptualisation, implementation, and validation. Additionally, any assumptions included in the submitted model were addressed by Delphi panel, for which full documentation has been provided. | Scope of decision model, model structure and evidence used was validated by clinical and microbiologist experts using techniques limited by resource and time constraints.  |
| Additional value elements | “Specific values that need to be captured for AMs: transmission, diversity, enablement, insurance, and spectrum” | The focus was on transmission and diversity: enablement and insurance were captured partially.Separate modelling of insurance value is soon to be published, with an outline provided in Section 2.4. | Enablement and insurance value was assessed; however, full value enablement value may not be captured (as outlined in Table 2). Further, transmission and diversity value were deemed to be insignificant as drivers of benefit.To note: the exploration of the enablement and insurance value is to be heavily caveated |
| Expert elicitation | “[…] some areas of the NICE methods guide for technology appraisal may need to be extended to deal with the complexities of assessing new AMs. These include […] the more extensive and systematic use of expert elicitation methods and model calibration for inferring values for unobservable parameters.” (p.7)“In the absence of data for a particular model parameter, expert elicitation may be used where relevant experts are asked to provide their judgement regarding the magnitude of a given parameter and its uncertainty” p. 37“The elicitation of scientific and technical judgements from experts can be a valuable addition to other forms of evidence to support effects on key parameters” (p.85) | Robust and thorough expert elicitation was used at different stages of the model development:* During model conceptualisation through extensive expert consultation to ensure and demonstrate the rigour, relevance and value of the model
* To determine the most appropriate comparators (including clinical experts and microbiologists)
* To verify model assumptions by Delphi panel with 11 experts (including modeller and health economists)
* To verify model parameters by Delphi panel with 11 experts (including clinicians and health economists)

For further information please see Gordon et al.5 and the Delphi panel report (appendix K of company submission). | “In absence of empiric evidence, outcomes were informed by eliciting judgments of individuals who have expertise on the subject matter” (p.81) – of note according to the EEPRU framework expert opinions are to be considered supportive alongside other empiric evidence.“A structured elicitation process was used to improve accountability and transparency.” (p.82)An expert elicitation task was conducted with 9 experts, with seven experts completing the task using the Chips and Bins method as it was deemed to be less complex and easier to complete. It is a new method that may not be suitable for digital elicitation and is not as robust and thorough as a Delphi panel.9 |

### Key questions

The Pfizer model was developed to align with the recommendations made in the EEPRU framework.3 The company are not clear on the basis for some of the concerns and critique from the EEPRU assessment, which appears to deviate significantly from the previous EEPRU framework.3 The company request further clarification on the following questions:

* Why was the proposed model type changed from the previously suggested dynamic disease transmission model?
* Why was the approach to define the eligible population a significant deviation from the traditional NICE approach, and not a reflection of how CAZ-AVI is currently used in clinical practice?
* Why was resistance over time not applied to the comparator AMs but a scenario analysis for CAZ-AVI conducted with varying resistance rates (1%, 5%, 10%, and 30% in 20 years)?
* Why was susceptibility testing used as a proxy for clinical effectiveness although it is known that a correlation is afflicted with high uncertainty?

Pfizer raised concerns of the revised approach to the above questions at the protocol development stage and how time and resource constraints consistently mentioned as a driver for proposed revisions of approach may lead to suboptimal outcomes.

# Elements of value

|  |
| --- |
| ***Key messages***  |
| * Defined in the EEPRU framework3 there are specific value elements that need to be captured for AMs: transmission, diversity, enablement, insurance, and spectrum.
* The EEPRU model partly discuss partly assessing enablement and insurance value, however state other values elements, diversity and transmission have significant impact on health benefit. Although no attempt was made to quantify these values as outlined in the NICE scope.1
* The Pfizer model attempted to capture both transmission and diversity value as the focus was to determine the value of CAZ-AVI when it is available as an additional option to existing AMs. Assessing the impact of avoiding infections/spreading infections when used in the approved indications. Additionally, the enablement and insurance values were assessed partly.
* Additional work has been undertaken by Pfizer to capture the insurance and enablement value of CAZ-AVI (Section 2.4 and 2.5, respectively).
 |

# Overview of value elements in the two models

According to the EEPRU framework, it is a prerequisite to characterise the expected value of a new product over an appropriate time horizon to propose alternative funding arrangements of new AMs.3 In addition to value typically assessed within HTAs for other new technologies, additional elements of value for AMs need to be reflected (Issue 2). The additional elements assessed in the Pfizer model were the transmission and diversity value for novel AMs. The EEPRU model did not focus on exploring, in part, or in full, all of these additional value elements.

According to the EEPRU framework, the “population health effects can be estimated through appropriate modelling, ideally using dynamic transmission models that are capable of reproducing both the direct and indirect effects.”3 This was not the approach the EEPRU model used in its assessment. Instead, a decision-analytic model was used due to time constraints and resources available (p. 104 of EEPRU assessment report). Reducing the development of resistance is a key objective of the UK Government and the UK project. This model format fundamentally falls short in the ability to capture the importance of avoiding the spread of an infection (transmission) and limiting the development of resistance (diversity). Alternative models which aim to capture the emergence of resistance and assess optimal treatment strategies must be considered in line with the EEPRU framework,3 as highlighted in Table 2.

Table 2. Value elements in the two models

|  |  |  |  |
| --- | --- | --- | --- |
| **Value element** | **EEPRU framework** | **Pfizer model** | **EEPRU model** |
| Transmission | “In the case of AMs, both direct and wider health effects and costs by avoiding the spread of infection to the population should be considered.” (p.30) | **Assessed:** The model demonstrates this value element within the disease transmission component which was validated by several experts and agreed upon with EEPRU earlier.According to the EEPRU framework it is important to include a model component that can estimate the infection transmission dynamics and associated resistance.  | **Not assessed:** According to clinical advisor the effect of including CAZ-AVI on transmission was uncertain. Key drivers of OXA-48 *Enterobacterales* are broad and challenging to model, so no attempt was made to quantify that value in the model. (p. 177/178) |
| Diversity | “Diversity value can be reflected in the range of alternative strategies or treatment protocols being compared, representing the different ways that the new and existing AMs may be used.” (p.35) | **Assessed:** The base-case analysis uses an all-lines diversity stewardship strategy which considers a multiple line treatment approach (empiric and suspected usage) to represent real life practice usage scenarios. It also provides an optimal balance between maximizing population health gains and minimizing resistance development. | **Not assessed:** This was not included in the model since clinical advisors indicated that a diverse prescribing strategy is very unlikely with in the HVCSs (p. 176).To note: comment on use of diverse prescribing. Used to reflect that CAZ-AVI may not only be used as a last option, when there is suspected resistance. As validated by clinicians.  |
| Enablement | “[The] indirect benefits to individuals associated with enabling other treatments or procedures to take place.” (p.35) | **Not assessed:** This was not captured in this economic model, but a separate model has been developed that looks at exploring the enablement value (see Section 2.5). | **Partly assessed:** Improved treatment of pre- and post-operative MDR infections is included but there is some uncertainty as to whether the full benefits are reflected within the analysis. […] There is uncertainty with respect to number of patients who would be affected as this would depend on both the number of patients whose treatment would be impacted by an outbreak and the frequency of outbreaks in key units […] There is also uncertainty about the consequences for patients not receiving planned therapy. […] These effects are not captured within the EEPRU modelling.” (p.175/176) |
| Spectrum | Nearly impossible to model “since it requires estimation of impact of the alternative AM treatment strategies on health outcomes and costs of future resistant infections.” (p.36) | **Not assessed:** Not reflected in the model. | **Not assessed:** It was not considered in the assessment. (p. 178) |
| Insurance | Two components: i) conservation value of holding back new AM for future need – can be reflected by including full range of alternative strategies about usage; ii) value associated with avoiding major catastrophic health consequences – may be partly modelled through its impact on population health effects. (p.36/37) | **Partly assessed:** The economic model can explore scenarios associated with withholding an AM for the treatment of resistant infections but is unable to explore in full the concept of insurance value.Further work is being undertaken by Pfizer that looks to model insurance value to a more comprehensive extent (described in Section 2.4). Measuring the value which an antibiotic has in mitigating several clinically relevant future probabilistic scenarios where an antibiotic may not be available.  | **Partly assessed:** The scenarios modelled were considered to reflect insurance value as they involved heavy restricted usage but a scenario where CAZ-AVI was hold back completely was not modelled (p. 177); therefore, results are uncertain. |

# Impact of CAZ-AVI on transmission

|  |
| --- |
| ***Key messages***  |
| * **Transmission Value** –an important value element to capture in the model as continuous use of current AMs can see an increase in the spread of infections resistant to these AMs. Avoiding the spread of resistant infections can see a reduction in life years lost due to infection within the population.
* The Pfizer model demonstrates this value element within the disease transmission component of the model. This was excluded from the EEPRU model as clinical advisors indicated that the effect of CAZ-AVI was uncertain and the magnitude of the effect expected to be small***.***
 |

The EEPRU framework clearly states that the economic model should include a component that can estimate not only the infection transmission dynamics but the associated resistance.3 The Pfizer model was built according to these principles, with disease transmission and resistance development modelled for all AMs, in line with clinical expert advice; a full description the Pfizer economic model is provided in the company submission.

As an example, when a new antimicrobial with an efficacy of 70% and with no resistance at baseline is considered as a first-line treatment compared with no new antimicrobial, resistance to the initial first-line treatment (piperacillin/tazobactam for cUTI and cIAI, colistin for HAP/VAP) and second-line treatment (meropenem) is reduced by 12.7% and 9.1%, respectively, after a 10-year period. A reduction in resistant infections can have a positive influence on the number of patients clearing infection.

# Impact of CAZ-AVI on diversity

|  |
| --- |
| ***Key messages***  |
| * ***Diversity Value***-. The incorporation of diversification prolongs the efficacy of existing AMs, introducing a new AM increases the effectiveness of diversification. In the modelled base case analysis, the use of diversification saw resistance to the initial existing first-line treatment (piperacillin/tazobactam for cUTI and cIAI, colistin for HAP/VAP) reduce by 9.2%. Further, this scenario was associated with a gain of up to 20,487 QALYs (15,169 QALYs lost due to infection compared with 35,657 QALYs lost in a scenario without CAZ-AVI) over 10 years (approximately 1,381 patient lives saved). In contrast, the EEPRU model calculated 587-2,211 INHEs over a 20-year period within their scenarios.
 |

The Pfizer base case analysis uses an all-line diversity stewardship strategy. This “diversity” approach provides a pragmatic modelling proxy whereby CAZ-AVI may be given to patients meeting risk factors for early empiric therapy such as previous ICU admission, critical illness, use of invasive devices, or prior antibiotic therapy as first treatment option. Those patients would be treated with CAZ-AVI more promptly resulting in improved outcomes associated with appropriate early effective treatment. Therefore, this approach serves as a metric of both empiric and suspected usage scenarios.

# Impact of CAZ-AVI on insurance

|  |
| --- |
| ***Key messages***  |
| * **Insurance Value** –COVID-19 has highlighted theimportance of having therapeutics available to mitigate the impact of future probabilistic events. This is particularly relevant to the availability of new antibiotics to mitigate the impact of an increase in incidence of infections.
* EEPRU have defined this with restrictions to consider; 1) the impact of holding CAZ-AVI back in reserve and or 2) ameliorate a potentially catastrophic situation, i.e., where multidrug resistance becomes so widespread. Considerations must be made to what is both probable and relevant in the context of this medicine.
* Despite clinical advisors highlighting the substantial impact that MDR infections have in terms of disrupting healthcare provision and the significant increase in ongoing costs caused by the disruption. EEPRU has failed to account for this cost saving within their model.
* It must also be recognised that both the company’s submission also does not capture the full essence of insurance value.
* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*
 |

Despite the concerns voiced by clinicians of the troublesome impact of MDR outbreaks, which result in large one time and ongoing costs to the healthcare system, this was not assessed or quantified in the EEPRU assessment report. Pfizer has conducted an extensive research project, soon to be published, \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*
* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*
* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*
* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

* \*\*\*\*\*\*\*\*\*\*\*\*\*\*
* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*
* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*
* \*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

It must be recognised that both the company’s (Pfizer) submission and the EEPRU Assessment Report do not capture the full concept of insurance value. However, we would implore the committee to recognise that well established insurance modelling techniques can be used to capture the value of new antibiotics in mitigating future probabilistic events, and that although this value would likely need to be considered collectively across the antibiotic spectrum, the value is significant and not currently captured under any of the documentation provided as evidence for the committee meeting.

# Impact of CAZ-AVI on enablement

|  |
| --- |
| ***Key messages***  |
| * **Enablement value** – New AMs provide additional value enable a wide range of surgical and medical procedures, such as chemotherapy, to take place with reduced risk of post-procedure infection.
* The enablement value captured in the EEPRU assessment does not consider the holistic value associated with a new AM, and therefore, underestimates the true enablement value of CAZ-AVI.
 |

The ability to effectively treat and prevent infection is an essential element of modern healthcare, without effective AMs many hospital services would not be able to operate.12 Enablement value is the value associated with surgical and medical procedures are enabled by effective AMs preventing or treating post-procedure infections. The submitted Pfizer model did not assess this value element; however, Pfizer do have concerns with the approach taken in the EEPRU assessment. Enablement value has only been considered in terms of treating pre- or post-operative infections, and the reduced use of hospital resources that are associated with the HVCS assessed. Enablement value has much broader implications that are not recognised in this assessment including:

* Implications of enabled procedures (due to avoiding pre-procedure infection, ward closure from outbreak, or additional resource utilisation for MDR infection)
* Avoidance of post-procedural infection (i.e., improved prophylaxis efficacy)
* Effective treatment of post-procedural infection

The definition of enablement value of CAZ-AVI goes beyond the direct use, as considered by EEPRU, but is linked to its impact on AMR. Pfizer have a developed a model that aims to incorporate elements of the enablement value associated with a new AM. This approach estimates the improvement in AM prophylaxis in surgical and chemotherapy procedures, that occurs due to reduced projected AMR. This association is based on the research conducted by Teillant *et al*.13 Analyses based on US healthcare system shows that enablement value accounts for around 40% of the overall value (the remaining 60% being diversity value).

# Key drivers of CAZ-AVI model benefits – treatment efficacy and resistance

|  |
| --- |
| ***Key messages***  |
| * The key driver of QALY gains is driven by treatment efficacy, namely, preventing loss of life years as a consequence of unsuccessful treatment.
* Time to appropriate therapy is critical to ensuring the optimal outcomes for patients in terms of preventing unnecessary death.
* Reducing projected resistance levels to current AMs promotes the insurance value element as there is less chance of an outbreak of resistant infections. Additionally, if an outbreak of infections resistant to a particular antimicrobial were to occur, more options would be available by preserving susceptibility to current AMs.
* Reducing projected resistance levels for current AMs is a smaller driver of QALY accrual in the Pfizer model. However, preventing resistance development supports fewer unsuccessful treatments (and hence fewer deaths). Further, this objective has broader societal value.
* Given that introduction of a new antimicrobial (in this case CAZ-AVI) would have value in terms of fewer unsuccessful treatments, the estimated QALY gains predicted by the EEPRU approach (approx.0.1–0.2 per patient) lack face validity where the most probable outcome of unsuccessful treatment leads to death. The EEPRU approach cannot be considered to identify the value of novel AMs and hence would defeat the whole objective of the value assessment of CAZ-AVI.
 |

### Differences in key drivers: EEPRU approach vs Pfizer approach

As outlined previously, there are numerous differences between the EEPRU approach and the Pfizer approach. However, the following differences impact on key cost-effectiveness drivers.

* **Model approach**: The EEPRU approach is more aligned with a standard HTA perspective, assessing patient-level outcomes before scaling these to a population-level. However, as antimicrobial transmission and resistance does not occur for each patient in isolation, Pfizer has directly assessed population outcomes. This has direct implications for several key cost-effectiveness drivers.
* **Population and source of evidence**: as outlined under Issue 4 and in the Modelling approach section, EEPRU is modelling HVCSs, which is a small subgroup of the patient numbers currently receiving CAZ-AVI. As a result, EEPRU is reliant on *in vitro* susceptibility evidence and an uncertain surrogate relationship with clinical outcomes, resulting in a lack of clarity as to actual efficacy for CAZ-AVI and comparators. By contrast, the Pfizer approach models the population currently receiving CAZ-AVI in the UK, which is aligned with the marketing authorisation and the clinical trial evidence. As effectiveness data is a key driver for outcomes in both modelling approaches, this difference in approach has a large impact on outcomes.
* **Onwards transmission**: as previously discussed in Section 2.2, the Pfizer model reflects the transmission value for new AMs, in line with the EEPRU framework; the Pfizer approach to transmission has been peer-reviewed, published and subject to considerable external validation. By contrast, transmission was not considered within the EEPRU approach, as this was not thought feasible within the time and resources available for this project and would be uncertain. However, this transmission value has a considerable impact on modelled outcomes, so that differences in approach lead to a large variation in outcomes.
* **Antimicrobial resistance**: as outlined in the Resistance development section, EEPRU modelled only resistance to CAZ-AVI while the Pfizer approach included resistance to both CAZ-AVI and existing AMs. However, one of the aspects of novel AMs is the reduction in resistance to existing AMs (as outlined in Figure 1). A reduction in population resistance levels corresponds with a reduction in patient resistance to infections and hence fewer instances of unsuccessful treatments. As a result, reduced resistance rates have a substantial impact on QALY gains predicted at a patient level in comparison to current antimicrobial use. This difference in approach between Pfizer and EEPRU causes a significant difference in cost-effectiveness outcomes. Considering this comparison, the Pfizer approach attempts to identify the additional value associated with minimising long-term resistance to the included AMs.
* **Placement of CAZ-AVI in treatment pathway**: the EEPRU approach takes a traditional HTA approach and considers the outcomes for CAZ-AVI treatment versus those for comparators. However, this misses a significant aspect of value for novel AMs. As resistance to current AMs is predicted to increase over time, the introduction of a novel AM has the potential to reduce this trend, with the reduction dependent on the stewardship strategy used.5 A diversity strategy (i.e. concurrent use of existing AMs with the novel AM at a population level) was included to ensure that the proposed treatment pathway matched to those discussions at earlier stages of the project (one which there is early empiric usage and suspected resistance). This strategy was seen to be representative of suspected usage of CAZ-AVI and, as per the Gordon et. al publication,5 has the most improved outcomes in terms of minimising resistance development (for existing AMs and the novel AM) and results in the largest number of QALYs.



Figure 1. Proportion of infections resistant to at least one of the existing antimicrobials over time for different stewardship strategies (derived from Gordon et al 2020)5

### Treatment efficacy

Given time and resourcing constraints EEPRU narrowed the focus of the modelling approach to very specific niche HVCSs. Despite there being several high-quality pivotal Phase II/III studies for CAZ-AVI, and a plethora of real-world evidence linked to the full licensed indication for CAZ-AVI. This strong clinical effectiveness data was unable to be used by EEPRU in their model due to this very targeted (narrow) approach. This forced a reliance on *in vitro* susceptibility studies which according to EEPRU’s clinicians in the assessment report and the original EEPRU framework3, it is not always possible to presume that it is not always possible to presume that what happens *in vitro* can be extrapolated to therapeutic outcomes of clinical success or failure (see Table 1). This may lead to an underestimation of the clinical benefit of CAZ-AVI to patients. A QALY gain of 0.1–0.2 represents that of a comparable treatment efficacy to the current standard of care, indicating that the EEPRU approach fails to recognise the clinical benefit of CAZ-AVI.

The above contrasts to the Pfizer approach which focuses on the full licensed indication as per the NICE scope1 and enables the use of clinical trial data and real-world evidence to inform treatment efficacy in the model.

Furthermore, the Pfizer model assesses lifetime outcomes for patients who become infected over a ten-year period. Successful treatment of the infection allows the accrual of QALYs in line with the quality-adjusted life expectancy of the general population. By contrast, unsuccessful treatment frequently results in death, resulting in loss of the QALYs that would have been accrued for that patient. Hence, treatment efficacy is the key driver of QALY gains in the Pfizer model (as shown in Figure 2).

As death is the most probable outcome of unsuccessful treatment, a QALY gain of 0.1–0.2 per patient (per the EEPRU model) appears to lack face validity where the likelihood of successful treatment is increased. CAZ-AVI is indicated in HAP/VAP, which has an estimated mortality rate of 30-70% and is estimated to increase hospital stays by 8 days.14 In the Pfizer model, introduction of CAZ-AVI as an additional AM (i.e. in addition to existing AMs) avoided 1,095 deaths over a 10-year period in an estimated population of 28,317 HAP/VAP patients. In this context, 20,487 QALY gains across the patient population can be considered more plausible.

### Resistance development

The EEPRU framework states that the economic model should reflect associated resistance development.3 The Pfizer model reflects resistance development in all modelled AMs and demonstrates that preventing resistance development in existing AMs is a significant aspect of value for novel AMs (as outlined in Section 2.2); preventing resistance development supports improved outcomes for all AMs, resulting in reduced unsuccessful treatment. However, the EEPRU approach captures development of resistance to CAZ-AVI but has not assessed resistance development for existing AMs; this significantly underestimates the value of novel AMs and overestimates the value of current AMs.

Of particular note, scenarios conducted by EEPRU assessing resistance development for CAZ-AVI (1%, 5%, 10% and 30%) are highly likely to be overestimates. CAZ-AVI has been increasingly used in UK clinical practice with very strong AMS safeguards and has had negligible reporting of true resistance in the UK. Resistance rates for commonly used AMs do not exceed 20% even for AMs that have been on the market for over 30 years, with the exception of co‑amoxiclav, which is characterised by poor stewardship and indiscriminate use across healthcare. Further, these AMs are frequently used empirically, sometimes without sensitivity data which may or may not become available during treatment. In this context, the estimates for CAZ-AVI. To complete this picture, Pfizer must consider carbapenem usage which still sits 63.4/100,000 DDDs and a carbapenem resistance rate estimated at 1% of all Gram-negative infections.15

Pfizer would highlight that mean consideration of these baseline resistance scenarios significantly lacks face validity, especially when viewed in parallel with the proposed patient numbers. That said, for openness, Pfizer did run a scenario analysis where treatment efficacy and baseline resistance was varied using the resistant rates that EEPRU used in its assessment (Figure 2). As previously noted, treatment efficacy is the key driver, regardless of baseline resistance rates. 

Figure 2. Heatmap of treatment efficacy and baseline resistance of CAZ-AVI

# Model validation

|  |
| --- |
| ***Key messages***  |
| * EEPRU conducted elicitation exercises and did not validate inputs against historical data. Exercises were limited to the time and resource constraints available. Using processes deemed to be “less complex and easier […] and not as robust and thorough as a Delphi Panel” 9.
* The company submission underwent significant validation; based on the recent Gordon et al.5 publication and subjected to extensive external validation exercises to demonstrate the scientific rigour, relevance and the generalisability to the real-world setting. Importantly, any assumptions were verified by a diverse range of external experts via a Delphi panel, with full documentation provided to EEPRU within the company submission.
 |

The EEPRU model was not able to undergo the robustness of expert peer-review or be externally validated. With techniques used limited by both the availability of resources and time. EEPRU outline that the approaches conducted were not as robust or thorough as a Delphi Panel.

The Pfizer modelling approach was based on published, peer-reviewed cost-effectiveness model and has been extensively validated during the publication process. In particular, thorough external validation was conducted using the Public Health England Report 2018 and 2019 to validate observed resistance trajectories.16 The Pfizer model was run over a five-year period, utilizing default settings (i.e. availability of piperacillin/tazobactam and meropenem only), and resistance trajectories predicted by the model compared with those observed in the PHE report.

Further, robust and thorough expert elicitation was during model conceptualisation, implementation and validation to ensure and demonstrate the rigour, relevance and value of the model. Further, economic modelling assumptions and parameters were verified prior to submission using the Delphi process with 11 experts (including clinicians and health economists); full documentation is provided in the company submission.

Finally, the Pfizer approach to expert elicitation contrasts with the EEPRU approach, where the scope of the decision model and model structure were validated through unspecified consultation with experts and some model inputs were derived through the SHELF process.

We request that the Committee seek to contextualise the EEPRU model and outputs against historical data and also the Pfizer model, which has undergone extensive peer review and external validation, including comparison to historical data as per the agreed framework.

# Population and patient numbers

|  |
| --- |
| ***Key messages***  |
| * The EEPRU approach depicts substantially lower patient numbers than expected to be clinically relevant, likely due to limiting the indication to two HVCSs with the extrapolation being based on susceptibility data which is associated with considerable uncertainty.
* EEPRU estimated the AM use on the 2019/2020 ESPAUR report, which was previously discussed as deemed to be inappropriate given i) the recording of reporting carbapenem resistance changed, and ii) the COVID-19 pandemic potentially results in this data being an outlier. This can be clearly seen in the graphic data cuts.
* Current market data show that about currently 1,400 patients6 receive CAZ-AVI. This does not align with the 70-575 patients per year that EEPRU calculated. Real world usage is expected to increase (in line with good AMS principles) over the life-time horizon demonstrating a significant underestimation of the patient population at present.
* Pfizer based the population used in the submission on the licensed indication and the uptake in clinical practice, which is in line with the EEPRU framework.
* No reference to, or explanation of, this discrepancy in predicted versus actual usage is provided in the EEPRU report. An urgent request to the re-run of their analysis is required using updated patient numbers.
 |

The EEPRU framework recommends the population size and the initial distribution of the population across health states should be based on routine, surveillance, or observational data.3 The company based the population used in the original submission on the licensed indication and the uptake in clinical practice. The number of patients currently receiving CAZ-AVI is considerably higher than the EEPRU patient numbers estimated for the HVCSs, which focuses on a narrow scope of use; carbapenemase-producing *Enterobacterales* with an OXA-48 mechanism only. EEPRU’s extrapolation to the population expected to use CAZ-AVI was based on a dataset that relies on susceptibility testing. As mentioned in Issue 3, correlation between susceptibility and clinical outcome, namely resistance, is associated with uncertainty.

Alternatively, EEPRU conducted a survey to estimate the patient numbers, but the results were inconclusive. A face-validity check of the estimates of AM use was conducted by EEPRU using the 2019/2020 ESPAUR report.17 The data from the ESPAUR 2019/2020 report17 was not used in the company submission due to the following reasons: i) the change of rules for reporting carbapenem resistance, and ii) the COVID-19 pandemic which means that 2020 data is likely to be an outlier, both due to limited healthcare capacity potentially affecting the reporting to Public Health England, and due to social distancing measures instituted at NHS hospitals potentially reducing the spread of bacterial, as well as viral infections. This issue was discussed with all stakeholders during prior engagement steps and generally understood to be of key consideration when utilising this surveillance report, however, omitted from the current EEPRU assessment report.

Pfizer conducted an internal assessment about the patient population eligible for CAZ-AVI treatment, looking at UK Gram-negative epidemiology, and by filtering the population down to adjust to CAZ-AVI indication and pathogen coverage. Data source for epidemiology was extracted from the Decision Resources Group (now Clarivate) reports on Gram-negative bacteria and treatment. To identify the proportion of resistant mechanisms, Pfizer used figures reported in table 2.1 of the latest ESPAUR report (published November 2021) (Table 3).18

Table 3. Trends in resistance in key drug/bug combinations in bacteraemia, 2016 to 2020, England



In the UK there are over 650,000 diagnosed Gram-negative hospitalisation events per year whereas 67% of total cases per year are caused by three pathogens: *E. coli (63%), Pseudomonas (25%) and Klebsiella* (12%).7

Treatment options become limited when resistance to antibacterial arise. To quantify the burden, Pfizer looked at the resistance in key drug/bug combinations published in the latest ESPAUR report, either to a 3rd generation cephalosporin or a carbapenem, and applied to the total patient population with a MDR Gram-negative cIAI, cUTI or HAP/VAP infection. This results in an estimation of 50,000 new cases per year.7,17 This epidemiology patient funnel was discussed with all stakeholders during the open dialogue stage and largely met consensus in being a reasonable approach to estimating the total eligible population.

The Pfizer model considered a constant infectious environment of 1,000 patients of a single UK hospital. Model outcomes were scaled up to reflect the population level in England, assuming that approx. 93,000 beds are constantly occupied in the general and acute wards. In total, the model calculated that 30,689 patients would be exposed to CAZ-AVI over a 10-year period (Table 4). The aggregated number of patients was validated against the number of patients currently receiving CAZ-AVI. The numbers EEPRU presented in its assessment are considerably lower, stretched over a 20-year period and do not reflect current clinical practice.

Table 4. Total number of patients exposed to CAZ-AVI

|  |  |  |
| --- | --- | --- |
| **Indication** | **Pfizer model(10-year period)** | **EEPRU model (20-year period)** |
| cUTI | 11,417 (incl. LTO) | 588-2,095 |
| cIAI | 5,086 (incl. LTO) | 257-571 |
| HAP/VAP | 14,185 (incl. LTO) | 576-8,860 |
| LTO | Included in above | Not included |
| Total | 30,689 (incl. LTO) | 1,421-11,526 |

### Patient population treated with CAZ-AVI

Current patients treated per year with CAZ-AVI, based on internal calculation using average duration of treatment of 11 days was estimated at 1,400 patients6 in 2021 which is approximately 3%19 of all treatment options currently available.

During the company’s analysis, and prior conversations during the open dialogue series with the AMR project team it was estimated that the maximum number of patients per year, keeping in line with principle of antimicrobial stewardship and use of all available options, would not exceed \*% to \*\*% of the MDR population, which equates to about \*\*\*\*\* to \*\*\*\*\* patients per year.

Therefore, Pfizer feels it is essential that as much effort goes into estimating the population at risk. Given the rising proportion of carbapenem-resistant infections from blood stream infections in the 2021 ESPAUR report Pfizer has a strong signal that the problem is still very much here to stay. Pfizer considers that phase 3 trial data is permissive in providing efficacy and tolerability information but that the focus of evaluation must remain strongly on prevalence (and future extrapolation) of AMR and specific mechanisms, namely here OXA-48.

Real world use of CAZ-AVI already suggests that there is a strong base of eligible patients. Without granular registry data tethered to each antimicrobial it is challenging to know what mechanism this use is directed at. The spectra of activity of CAZ-AVI (and Cefiderocol) can allow the clinical community to make pathogen-directed decisions for OXA-48 activity beyond the clinical syndrome alone. To reflect this, we feel it is vital to assess the value of CAZ-AVI including emergency urgent situations such as bacteraemia and where there are limited treatment options.

The approach of escalating (from comparators to other treatments) is outmoded and not consistent with good stewardship practice. It is very challenging to understand how this can best be approached in modelling with the current status quo of surveillance data.

We readdress the urgent call above, for EEPRU to re-run their analysis using updated patient numbers. In addition, we request that the Committee should consider current real world usage data and increasing resistance trends both domestically and globally when considering future lifetime usage patterns.

# Antimicrobial Stewardship

|  |
| --- |
| ***Key messages***  |
| * Antimicrobial stewardship (AMS) strategies have been developed with the aim of limiting the rise of antimicrobial resistance.
* Carbapenems are considered the last line of therapy for severe infection management in critically ill patients. While still relatively rare, detection of carbapenem-resistant bacteria has increased by over 1,000-fold in England. The rise in carbapenem resistance limits the available treatment options for some patients.
* There is significant clinical need and societal benefit associated with obtaining a diverse set of novel antibiotics.
* The Pfizer model is capable of reflecting a range of antimicrobial stewardship. An all-lines diversity stewardship strategy (i.e., use of CAZ-AVI alongside existing AMs) was chosen to provide an optimal balance between maximising population health gains and minimising resistance development. The different treatment lines allow for a simplified pathway to be modelled, capturing key aspects of CAZ-AVI value in an imperfect healthcare setting.
* Comparators should be considered in an adapted way to those in other clinical areas outside of infection. With pathogen-directed approaches for OXA-48 there are very few putative options available and therefore the term comparator must be used with awareness and caveat. Indeed, modelling against a placebo/limited treatment option situation is likely to reflect the value of having a novel option available more accurately.
 |

Antimicrobial stewardship (AMS) strategies aim to limit the rise of AMR and, at the same time, promote effective treatment of serious infections, which is generally separated into two phases (the “Start Smart – Then Focus” approach). This consists of an empirical phase (based on prompt risk factor-directed antibiotic prescribing) and a targeted phase (using mechanism / pathogen-directed treatment). CAZ-AVI can be used both as part of risk-based empirical therapy, to accelerate effective treatment and improve patient outcomes, where considered appropriate, and in the setting of pathogen- or resistance mechanism-directed approach, where antimicrobial susceptibility is known when therapy commences. According to EEPRU in its assessment CAZ-AVI is expected to be used in a more restricted way does not align properly with the principle of good stewardship.

### 5.1 Comparators

Comparators should be considered in a very different manner to those in clinical areas outside of infection. Therefore, comparators should be considered as other treatment options which are most commonly investigated in non-inferiority trials which include patients infected with the pathogen treatable with both the new AM and a comparator of best available therapy. Since there is a need for new AMs superiority trials would not be a good solution, it would give evidence to us reaching an antimicrobial resistance scenario we are working to prevent. New AMs with similar efficacy compared to current AMs are needed on the market in case of increased resistance of pathogens to the existing ones.

For OXA-48, as focused on in EEPRU assessment, there are very few putative options available and therefore the term comparator must be used with awareness and caveat. Indeed, modelling against a placebo/limited treatment option situation is more likely to reflect the value of having a novel option available. In that case instead of multi-drug salvage, CAZ-AVI could be given. Clinical practice often relies on changing the antibacterial option due to poor response and therefore, real world management is not consistent with using one comparator regimen at a given time.

EEPRU stated that evidence is lacking for the HVCSs. Concerns were raised by Pfizer at the protocol stage already. The EEPRU assessment included colistin and aminoglycosides as options when no other treatment option exists although they carry an elevated risk of neurotoxicity, as carbapenems are not a valid option for OXA-48 by virtue of the primary resistance issue. Aminoglycosides may variably have a role to play, however, they are not a preferred treatment for pneumonia (HAP/VAP) due to poor lung penetration.20 In general use, higher aminoglycoside doses have been recommended by ESPAUR but even they sometimes fall short of complete coverage.21

In contrast, Pfizer developed non-inferiority-trials which were based on expert advice such as REPROVE, RECAPTURE and REPRISE (see Document A of company submission, section 3) using the best available therapies for the pathogen to be treated.

As a note, comparator information on projected resistance was not included in the EEPRU model citing lack of data, however resistance rates of CAZ-AVI were modelled at 1%, 5%, 10% and 30% over 20 years. The proposed patient numbers in these scenarios significantly lack face-validity in terms of the number of patients treated with CAZ-AVI in clinical practice.

# Response comments

|  |  |  |  |
| --- | --- | --- | --- |
| **Comment no.** | **Page** **no.** | **Section no.** | **Comment** Insert each comment in a new row.Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|  |  |  | **Key issues identified in the assessment** |
| 1 |  |  | As the EEPRU approach is focused on very specific niche HVCSs, there is a lack of clinical effectiveness data in a relevant population as stated by EEPRU itself, resulting in a reliance on *in vitro* susceptibility, which as validated by their own clinical experts may not reflect treatment success. Why was the no attempt to capture more fully the full licenced indication as per normal NICE process and the final scope, and why was susceptibility testing used as a proxy for clinical effectiveness although it is known that a correlation is afflicted with high uncertainty?  |
| 2 |  |  | The EEPRU model deviates significantly from the EEPRU framework3 and the NICE reference case. Why was the proposed model type changed from the previously suggested dynamic disease transmission model? An analysis should be conducted as to whether the deviation from the original framework has now led to a lack of recognition of population health benefit? |
| 3 |  |  | Only emergence of resistance for the new antibiotic (CAZ-AVI) was considered in the EEPRU model however, resistance to existing antibiotics was not captured in their approach. Why was resistance over time was not applied to the comparator AMs but a scenario analysis for CAZ-AVI conducted with varying resistance rates? |
| 4 |  |  | Unsuccessful treatment of infection would most likely result in death (with exception of those which naturally resolve infection), therefore, a QALY gain of 0.1-0.2 (per the EEPRU model) lacks face validity in the recognition of the health benefit where the most probable outcome of unsuccessful treatment of complicated infections leads to death. The stated QALY gain represents that of comparable treatment efficacy to the current standard of care, indicating the EEPRU model fails to recognise the additional clinical benefit of CAZ-AVI. Considering death as a primary outcome of unsuccessful treatment the QALY gains estimated via a more holistic, dynamic modelling approach validated by at least 14 KOLs estimates patient QALY gain of 0.67. The Committee must address the face validity of both modelled QALY gains and the appropriateness with respects to this lifesaving. |
| 5 |  |  | The EEPRU framework3 cites six additional elements of value for new antibiotics, but the EEPRU assessment report does not recognise or explore a number of these important value elements. We request that the value elements which have been quantified and those that have not, along with the limitations are clearly laid out for the Committee. We request that the Committee consider the likely undervaluation of CAZ/AVI as a result of not quantifying all value elements and make clear recommendations for future research. |
| 6 |  |  | The validation undertaken by EEPRU is not in alignment with the EEPRU framework3 as the scope of the decision model, model structure and some model inputs were validated only by expert opinion and not against historical data. We request that EEPRU provide commentary as to why this approach was taken. And propose the Committee seek to contextualise the EEPRU model and outputs against historical data and the Pfizer model. The robustness of external validation that each model has undergone to solidify clinical relevancy of the assumptions and comparison to historical data should be considered by the Committee. |
| 7 |  |  | EEPRU focuses on two HVCSs. This approach to extrapolate to the full licenced indication for CAZ-AVI has significantly underestimated the eligible patient population, and the overall health threat of MDR infections. Why was the approach to define the eligible population a significant deviation from the traditional NICE approach, and not a reflection of how CAZ-AVI is currently used in clinical practice? We urgently request EEPRU to re-run their analysis using updated patient numbers (as provided under Issue 4) and provide a subsequent scenario to the Committee ahead of the committee meeting. We request that the Committee should consider current real-world usage and increasing resistance trends both domestically and globally when considering future lifetime usage patterns. |
| 8 |  |  | In complete contrast to the EEPRU framework3 and protocol, the current EEPRU model has not attempted to assess the diversity value of novel antibiotics. We request EEPRU to present an alternative scenario for Committee consideration that attempts to model different AMS strategies and their impact on the emergence of resistance. If it is not possible to provide some quantification of diversity value, we request that the Committee qualitatively consider the impact and appropriate usage of new antibiotics as a critical factor in attempting to tackle the clear trend of increasing resistance. |
|  |  |  | **Addressing EEPRU’s comments** |
|  |  |  | **Defining treatment, and success (see Issue 2 for further clarification)** |
| 9 | 106 | 7.2.2 | “We have assumed that differences across treatments in *in vitro* susceptibility are predictive of *in vivo* clinical outcomes.”**Clinical advisors noted to EEPRU in the assessment that “*in vitro* susceptibility to meropenem in particular does not always indicate how well a patient will respond to this treatment in clinical practice.” In line with this advice, the difference in the treatment effectiveness for the Pfizer model was informed by clinical trial data and *in vivo* evidence from the published literature.** |
| 10 | 158 | 8.1.1 | “In the average ES patient suspected of having OXA-48 *Enterobacterales*, use of CAZ-AVI in the ES is associated with a per patient INHE gain of 0.19 QALYs […].” | **The Pfizer model looked at lifetime QALY gains as a result of successful versus unsuccessful treatment of infection over a 10-year transmission horizon. As unsuccessful treatment of infection would frequently result in death, a QALY gain of 0.1-0.2 may not fully reflect the benefits for scenarios where fewer people have unsuccessful treatment. Further information is provided as Issue 3.** |
| 11 | 163 | 8.1.2 | “Overall, the per patient INHE associated with using CAZ-AVI in the MDS are 0.06 QALYs for HAP/VAP and 0.05 QALYs for cUTI.” |
|  |  |  | **Key drivers of benefit – treatment efficacy and resistance (see Issue 2 for further clarification)** |
| 12 | 9 | As above | “In the model, CAZ-AVI is associated with similar efficacy to comparator AMs and Pfizer has not provided account of the processes driving the large health benefits estimated in the model.”**The key driver of the model outcomes is the treatment efficacy, as successful treatment directly impacts the loss of life years over a lifetime through the treatment decision tree component of the model. These drivers are shown in the deterministic scenario analysis presented in the company submission (see p.192 – 194 in Document A).**  |
| 13 | 89 | 6.1.5 | “[…] there was a lack of transparency on the processes that are driving the economic results.”**As stated above, the key driver of the model outcomes is the treatment efficacy. Further, it should be noted that this model has been peer-reviewed and published, including several validation exercises to verify the accuracy of projections for resistance development. The submission was kept concise, with the additional sharing of a technical report, and reference to the peer reviewed publication which provided further details.** |
|  |  |  | **Elements of value (see Issue 1 for further clarification)** |
| 14 | 177 | 8.3.2.4 | “Our clinical advisors indicated that the direct of effect of introduction CAZ-AVI on transmission was uncertain, but that overall, the magnitude effect was expected to be small.”**The Pfizer model was built on the EEPRU framework3, which clearly states that the economic model should include a component that can estimate the infection transmission dynamics and the associated resistance. Further, transmission value is a key objective in the development and introduction of novel antibiotics. Availability of these antibiotics increases the likelihood of successful treatment of infection, which inherently supports reductions in transmission, particularly in outbreak situations.** |
| 15 | 176 | 8.3.2.2 | “[Our clinical advisors] were not supportive of the use of CAZ-AVI in broader populations as part of a diverse prescribing strategy […] and concerns that the evidence for diverse prescribing was uncertain.”**The incorporation of diversification prolongs the efficacy of existing AMs by reducing selection pressure and minimising resistance development, and introducing a new AM increases the effectiveness of diversification. In the modelled base case analysis, the use of diversification saw resistance to the initial existing first-line treatment (piperacillin/tazobactam for cUTI and cIAI, colistin for HAP/VAP) reduce by 9.2%.** |
|  |  |  | **Population and patient numbers (see Issue 4 for further clarification)** |
| 16 | 21 | 3.1 | “[…] CAZ-AVI is expected to be used in a more restricted group of patients than permitted by its license.”**Real-world evidence and marketing data show that CAZ-AVI is used in a broader indication than outlined in the EEPRU assessment report, namely cIAI, cUTI (incl. pyelonephritis), HAP/VAP, and bacteraemia (adults only).** **CAZ-AVI can be used both as part of risk-based empirical therapy, to accelerate effective treatment and improve patient outcomes, where considered appropriate, and in the setting of pathogen- or resistance mechanism-directed approach, where antimicrobial susceptibility is known when therapy commences.** |
| 17 | 101 | 6.1.5.5 | “There is uncertainty in the appropriateness of the population size used in the NMB calculation.”**The population size used in the calculation is within the range of patients currently receiving CAZ-AVI for the treatment of cUTI, cIAI, and HAP/VAP. According to the model 3,069 were exposed to CAZ-AVI and in clinical practice around 1,400 patients are treated with CAZ-AVI each year (see section 5.1), where suboptimal outcomes are already being obtained due to restricted patient access issues.** |
| 18 | 148 | 7.5.2.3 | “As a face-validity check of the estimates of AM use employed in the model, these were compared to hospital inpatient drug use as reported in the 2019/20 ESPAUR report.”**The data from the ESPAUR 2019/2020 report was not used in the company submission due to the following reasons: i) the change of rules for reporting carbapenem resistance, and ii) the COVID-19 pandemic which means that 2020 data is likely to be an outlier, both due to limited healthcare capacity potentially affecting the reporting to Public Health England, and due to social distancing measures instituted at NHS hospitals potentially reducing the spread of bacterial, as well as viral infections. This issue was discussed during prior stages of this project with EEPRU and was generally understood that the prior ESPAUR report would be a better base.** |
|  |  |  | **Modelling approach (see Modelling approach for further clarification)** |
| 19 | 9 | Executive summary – economic evidence | “The model makes several strong assumptions relating to the impact of CAZ-AVI on transmission (namely, that treatment can eradicate patients of colonisation) which were not thought to be credible to the clinical advisors to EEPRU.”**Pfizer stated that only patients with cUTI would lose colonisation after successful treatment which was based on a publication from Tlaskalová-Hogenová22 Additionally, Pfizer conducted an expert elicitation and the medical experts did not reach consensus but stated that it would depend on whether a patients with cUTI have a device or not.** |
| 20 | 89 | 6.1.5 | “As shall be seen, there were high-level concerns about the relevance of the company’s submitted model and evaluation.”**The economic model adheres to the NICE reference case, with adaptations aligning to the EEPRU framework for antimicrobials, and the final NICE scope and was validated extensively by external experts including formal methods such as a Delphi panel. The EEPRU model presented in the EEPRU assessment does not align to either of the methodologies agreed on previously. The company does not understand why the relevancy of the Pfizer model was questioned although consensus on this approach was reached before (see Modelling approach section for further details).** |
| 21 | 90 | 6.1.5.1 | “The comparator line is CAZ-AVI, and the treatment line is a sequence of two antibiotics.”**In contrast to the EEPRU’s microbiology-directed setting where only one line of treatment was explicitly modelled the Pfizer model included up to three treatment lines. This simplification allowed for an easy-to-use economic model, which was validated by external experts, and reflects real-life practice.** |
| 22 | 98 | 6.1.5.5 | “During the treatment pathway, a patient with an infection and sensitive pathogen may develop resistance from treatment and become infected with a resistant pathogen. Such changes are not represented in the model.”**The Pfizer model used simplifications (validated by experts), including assumptions that apply to the general population but does not consider specific cases such as the development of reinfection due to resistance within one treatment cycle. In the Pfizer model, to capture resistance gain within the infectious environment, a patient may develop resistance due to treatment exposure, where it is assumed any resistance gain is applied to the resistance profiles of newly admitted patients.** **Infections are treated using the appropriate stewardship strategy which should include to avoid using an AM which can cause a sensitive pathogen to develop into a resistant pathogen. It will be complicated to assess how many patients would be re-infected with a now resistant pathogen and the impact on the value is potentially not that huge.** |
| 23 | 98 | 6.1.5.5 | “There is a transition from infected with a sensitive pathogen to colonised with a sensitive pathogen. The submission does not explain the mechanism of this transition.”**This transition is captured via the outcomes of patients infected with a sensitive pathogen going through the treatment pathway. Of these patients who are cured and do not gain resistance, the resistance profile is applied to those who are newly admitted to hospital. This is shown in the below diagram.**Diagram  Description automatically generated |
| 24 | 98 | 6.1.5.5 | “The model can allow treatment cycling to examine the impact of different stewardship strategies. The approach to treatment cycling adopted in the model is explained in detail in the submission. However, it appears that all results are presented without any form of treatment cycling because cycling is not mentioned in the company’s result section.”**The model has the capability to explore treatment cycling, however, this was not considered in the results. In the base case the model uses an all-line diversity antimicrobial stewardship strategy where infected patients are treated with piperacillin/tazobactam or colistin, meropenem, and CAZ-AVI in the following sequences:*** **piperacillin/tazobactam (or colistin) → meropenem → CAZ-AVI**
* **meropenem → piperacillin/tazobactam (or colistin) → CAZ-AVI**
* **CAZ-AVI → piperacillin/tazobactam (or colistin) → meropenem**

**The publication and technical report highlight the additional abilities of the model, however, these are not addressed in the company’s submission due to the need to focus on depicting a scenario of both suspected and empiric usage treatment pathway. The diversity scenario was the best scenario to depict both forms of usage.** |
| 25 | 98 | 6.1.5.5 | “The description of treatment success is ambiguous in places: “after a patient is successfully treated, they may return to the susceptible or colonised health states” is in contrast to a suggestion that the pathogen is always eliminated: “The proportion of infections cleared, denoted by the symbol φ, corresponds to the likelihood that a patient has been successfully treated, resulting in the patient no longer being infected or colonised by the pathogen.” (p.11, Appendix K)”.**As clearly stated in the technical model report (appendix K to original company submission) it should be noted that φ is only applied in indications where clearance of colonisation or infection is plausible (i.e. cUTI). φ is applied at the final step of the treatment pathway and is considered for the health state profiles of newly admitted patients.**  |
| 26 | 98 | 6.1.5.5 | “The model assumptions appear to be inconsistent regarding the transmission of resistant pathogens between colonised patients. The company submission states that “Patients may not move directly between different colonised health states” […] This appears to contradict the model schematic” **The model schematic correctly depicts possible patient movement between health states. The patients are able to move directly between different colonised health states which is reflected in the model. The “not” would need to be removed from the model assumption section.** |
| 27 | 99 | 6.1.5.5 | “The model assumes that on presentation, 20% of patients have known resistance […]. Further, no evidence is provided for the assumed 20% rate of directed testing.”**The 20% were verified by experts in Delphi panel and the statement is presented in the Delphi panel report (Appendix L of original company submission).****“[C]omments indicated that 15% of patients receiving targeted therapy is reasonable but still quite low, the exact proportion would be highly variable in practice depending on the indication. In consideration of these comments, using 20% targeted therapy was considered to be a more appropriate representation of UK clinical practice and was incorporated into the base case model.”** |
| 28 | 99 | 6.1.5.5 | “The clinical advisors to EEPRU believe that complete eradication is unlikely to happen as there will always be a reservoir of the pathogen remaining in the gut.”**Pfizer stated that only patients with cUTI would lose colonisation after successful treatment which was based on a publication from Tlaskalová-Hogenová *et al*.22 Additionally, Pfizer conducted an expert elicitation, and the medical experts did not reach consensus but stated that it would depend on whether a patient s with cUTI have a device or not. In general, to build economic models pragmatic approaches are required and model simplification need to be made. The company determined that an incomplete eradication would not have a significant impact on the establishing the value of CAZ-AVI. This was also previously validated as part of the peer reviewed publication5 and the Delphi panel (see Appendix L of company submission).**  |
| 29 | 100 | 6.1.5.5 | “[...T]he company’s model applies a two-line sequence as the comparator (it is unclear if a treatment could be used twice). A clear justification for choice of comparators is not provided in the company’s submission.”**The model assumes that patients may receive up to three treatment lines, as a simplified assumption. In theory, more treatment lines could be added, however, this would increase the complexity of the disease transmission component and decrease the user-friendliness of the model. In scenarios without CAZ-AVI, only two-lines of treatment were considered where the same treatment cannot be used twice. As stated above when building an economic model, simplifications are necessary especially when the value of adding further complexity is potentially not adding to the value of, in this case, CAZ-AVI. Additionally, the EEPRU model did not use more than two treatment lines in their model. Additionally, Pfizer questions what impact an additional line would have. From a clinical perspective the addition of CAZ-AVI should provide an additional treatment option and not be considered as a potential third line agent.****All simplifications were validated by extensive expert elicitation, including the Delphi panel exercise where results in full were submitted as part of the company’s submission.**  |
| **Model validation (see Issue 3 for further clarification)** |
| 30 | 102 | 6.1.5.6 | “Model calibration is conducted with reference to national resistance and incidence data in all settings. Calibration to the subset of data available from hospital settings (acute trusts) is more appropriate given that the model simulates a hospital environment and the greater use of antibiotics in hospital environments means the rates of resistance are typically larger than in the community.”**Thorough external validation was conducted. The Pfizer model was run over a five-year period, utilizing default settings (i.e. availability of piperacillin/tazobactam and meropenem only), and resistance trajectories predicted by the model compared with those observed in the PHE report.** |
| 31 | 102 | 6.1.5.6 | “There do not appear to be any formal structured expert elicitation exercises to reduce this reliance on assumptions. This is a concern as there is no validation of the model outcomes to additional data sources.”**The Pfizer model was based off the recent Gordon *et al*.5 publication and subjected to extensive external validation exercises to demonstrate the scientific rigour, relevance and the generalisability to the real-world setting. These external validation exercises compared outputs from the model to publicly available data not specifically used to construct the disease transmission component and demonstrated a high degree of accuracy for projections for resistance. In addition, model inputs were taken from published sources. Importantly, any assumptions were verified by external experts via Delphi panel, with full documentation provided to EEPRU.** |
|  |  |  | **Antimicrobial stewardship (see Issue 5 for further clarification)** |
| 32 | 150 | 7.5.2.6 | “[T]he clinical advisors also expressed concerns that a broader definition could lead to stewardship challenges.”**The Pfizer model is capable of reflecting a range of antimicrobial stewardship. An all-lines diversity stewardship strategy was chosen to capture usage as part of an empirical and suspected usage setting. In addition, as depicted in the Gordon *et. al* publication, this provides the optimal balance between maximising population health gains and minimising resistance development.5 The different treatment lines allow for a simplified pathway to be modelled, capturing key aspects of CAZ-AVI value in an imperfect healthcare setting.** |
| 33 | 106 | 7.2.1.3 | “A wide range of drugs is considered relevant in the HVCS, and different drugs were considered relevant depending on the site, pathogen, mechanism and setting.”**Comparators should be considered in an adapted way to those in other clinical areas outside of infection. With pathogen-directed approaches for OXA-48 there are very few putative options available and therefore the term comparator must be used with awareness and caveat. Indeed, modelling against a placebo/limited treatment option situation is likely to reflect the value of having a novel option available more accurately.** |

# References

1. National Institute for Health and Care Excellence. Antimicrobial Health Technology Evaluation. Ceftazidime with avibactam for treating severe aerobic Gram-negative bacterial infections - Final scope 2021. Available from: <https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials/ceftazidime-with-avibactam> [accessed 2/2021].

2. NHS. AMR002 - Annex 7: health technology assessment process. . Available from: <https://www.nice.org.uk/Media/Default/About/what-we-do/Life-sciences/evaluation-framework.pdf> [accessed 12/2021].

3. EEPRU. Framework for value assessment of new antimicrobials - Implications of alternative funding arrangements for NICE appraisals. 2018. Available from: <http://www.eepru.org.uk/wp-content/uploads/2017/11/eepru-report-amr-oct-2018-059.pdf>.

4. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Available from: <https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781>.

5. Gordon J, Darlington O, McEwan P, et al. Estimating the Value of New Antimicrobials in the Context of Antimicrobial Resistance: Development and Application of a Dynamic Disease Transmission Model. Pharmacoeconomics. 2020;38(8):857-69.

6. Pfizer. Patient number calculation. data on file. 2021.

7. Clarivate DRG. Patient Populations Epidemiology - Number of Gram-negative hospitalisation events per year in the UK. 2021. Available from: <https://insights.decisionresourcesgroup.com/biopharma>.

8. EEPRU. Protocol for the technology evaluation of ceftazidime with avibactam for treating severe aerobic Gram-negative bacterial infections. 2021. Available from: <https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials/ceftazidime-with-avibactam>.

9. Zondervan-Zwijnenburg M, van de Schoot-Hubeek W, Lek K, et al. Application and Evaluation of an Expert Judgment Elicitation Procedure for Correlations. Front Psychol. 2017;8:90.

10. EEPRU. Ceftazidime with avibactam for treating severe aerobic Gram-negative bacterial infections: Assessment Report - Confidential - version for consultation. 2021.

11. O'Neill J. Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations. 2014.

12. World Health Organisation. Antimicrobial resistance - Global Report on Surveillance. 2014. Available from: <https://www.who.int/publications/i/item/9789241564748> [accessed 12/2021].

13. Teillant A, Gandra S, Barter D, et al. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. Lancet Infect Dis. 2015;15(12):1429-37.

14. National Institute for Health and Care Excellence. Pneumonia (hospital- acquired): antimicrobial prescribing guideline 2019. Available from: <https://www.nice.org.uk/guidance/ng139/> [accessed 12/2020].

15. Public Health England. AMR local indicators - Fingertips profile. Available from: <https://fingertips.phe.org.uk/profile/amr-local-indicators>.

16. Public Health England. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2018 to 2019. In: Department of Public Health., editor. UK: © Crown copyright [2019].

17. Public Health England. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2019 to 2020. In: Department of Public Health., editor. UK: © Crown copyright [2020].

18. Public Health England. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2020 to 2021. In: Department of Public Health., editor. UK: © Crown copyright [2021].

19. Pfizer. Based on Pfizer data on file (IQVIA data bought). 2021.

20. Najmeddin F, Shahrami B, Azadbakht S, et al. Evaluation of Epithelial Lining Fluid Concentration of Amikacin in Critically Ill Patients With Ventilator-Associated Pneumonia. J Intensive Care Med. 2020;35(4):400-4.

21. EUCAST. Guidance Document on Implementation and Use of the Revised Aminoglycoside Breakpoints. 2020. Available from: <https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Guidance_documents/Aminoglycoside_guidance_document_20200424.pdf>.

22. Tlaskalová-Hogenová H, Štěpánková R, Hudcovic T, et al. Commensal bacteria (normal microflora), mucosal immunity and chronic inflammatory and autoimmune diseases. Immunology Letters. 2004;93(2):97-108.

**Checklist for submitting comments**

* Use this comments form and submit it as a Word document (not a PDF).
* Complete the disclosure about links with, or funding from, the tobacco industry.
* Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
* Do not paste other tables into this table – type directly into the table.
* Please underline all confidential information, and separately highlight information that is submitted under ‘commercial in confidence’ in turquoise and all information submitted under ‘academic in confidence’ in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: ‘academic / commercial in confidence information removed’.
* Do not include medical information about yourself or another person from which you or the person could be identified.
* Do not use abbreviations
* Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must be sent by the deadline.

**Note:** We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.