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Final report for the technology evaluation of cefiderocol for treating severe aerobic Gram-negative bacterial infections

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Abbreviations and definitions

AKI	Acute kidney injury
AM	Antimicrobial
AmpC	Ampicillinase C
AMR	Antimicrobial resistance
AMRHAI	Antimicrobial resistance and healthcare associated infections
AST	Antimicrobial susceptibility testing
ATLAS	Antimicrobial Testing Leadership And Surveillance
BAT	Best available therapy
BSAC	British Society for Antimicrobial Chemotherapy
BSIs	Bloodstream infections
CCI	Charlston comorbidity index
CEFIDEROCOL	Ceftazidime-avibactam
CKD	Chronic kidney disease
CLSI	Clinical Laboratory Standards Institute
CMY	Cephamecinases
CPE	Carbapenemases-producing <i>Enterobacterales</i>
CRD	Centre for Reviews and Dissemination
CRE	Carbapenem-resistant <i>Enterobacterales</i>
CrI	Credible intervals
cUTI	Complicated urinary tract infection
DIC	Deviance information criterion
DIM	Dutch imipenemase
EEPRU	Policy Research Unit in Economic Methods of Evaluation in Health and Social Care Interventions
EKHUFT	East Kent Hospitals University NHS Foundation Trust
ES	Empiric setting
ESBL	Extended-spectrum β -lactamase
ESPAUR	English Surveillance Programme for Antimicrobial Utilisation and Resistance
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GES	Guiana extended-spectrum β -lactamase
GIM	Germany imipenemase
GNB	Gram-negative bacteria
HAP	Hospital-acquired pneumonia
HDU	High dependency unit

HGT	Horizontal gene transfer
HRQoL	Health-related quality of life
HTA	Health technology assessment
HVCS	High value clinical scenario
IAIs	Intra-abdominal infections
ICU	Intensive care unit
IMI/NMC	Imipenemase/non-metallo-carbapenemase-A
IMP	Imipenemase
INHE	Incremental net health effect
IPD	Individual patient data
KPC	<i>Klebsiella pneumoniae</i> carbapenemase
LoS	Length of stay
MBL	Metallo-beta-lactamases
MCMC	Markov chain Monte Carlo
MDR	Multi-drug resistant
MDS	Microbiology-directed setting
MIC	Minimum inhibitory concentration
NDM	New Delhi MBL
NHE	Net health effects
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OR	Ddds ratios
OXA	Oxacillinase
PB	Probability of being the best treatment
PICOS	Population, intervention, comparison, outcomes, study designs
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PHE	Public Health England
PK	Pharmacokinetic
PrI	Prediction intervals
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-year

RCT	Randomised controlled trial
RE	Random effect
RIFLE	Risk, injury, failure, loss, and end-stage renal disease
SD	Standard deviation
SME	<i>Serratia marcescens</i> enzyme
SPM	Sao Paulo MBL
SGSS	Second Generation Surveillance System
TSD	Technical Support Document
UME	Unrelated mean effects
UTI	Urinary tract infections
VAP	Ventilator-associated pneumonia
VIM	Verona integrated-encoded MBL
WHO	World Health Organization
XDR	Extensively-drug resistant

1. Executive summary

1.1. Background

The National Institute for Health and Care Excellence (NICE), NHS England and NHS Improvement are currently undertaking a project to assess the feasibility of innovative models that pay for antimicrobials (AMs) based on an evaluation of their value to the National Health Service (NHS) as opposed to the volumes used. Following the selection of two products considered to be of high public health importance, this project involves evaluation of the selected products to inform commercial discussions regarding contract value for a period of up to 10 years. The selection process was a formal procurement exercise and aimed to identify one new AM and one existing but “nearly new” AM. The products selected by this process were, respectively, cefiderocol (Fetroja) which is manufactured by Shionogi; and ceftazidime with avibactam (Zavicefta), which is manufactured by Pfizer.

This report details the evaluation phase of this project for cefiderocol. Cefiderocol received a marketing authorisation in April 2020 for treating infections due to aerobic Gram-negative organisms in adults with limited treatment options.

1.2. Aim and objectives

The aim of this evaluation is to assess the value of cefiderocol to the NHS in England, for the treatment of severe aerobic Gram-negative bacterial (GNB) infections when used within its licensed indications.

Specific objectives are:

- i. To identify two high value clinical scenarios (HVCSs), within its broad licensed indications, for which cefiderocol is expected to have a significant impact on patients’ outcomes in terms of reducing mortality risks and improving health-related quality of life (HRQoL).
- ii. To undertake an ‘evidence mapping’ exercise and relevant systematic literature reviews to characterise the available clinical effectiveness evidence for the use of cefiderocol in the HVCSs.
- iii. To establish an appropriate decision-analytic model to quantify the costs and health benefits of the use of cefiderocol under various usage scenarios compared with alternative treatments and management strategies (usage scenarios of other available AMs) in the HVCSs. The decision-analytic model was required to estimate costs and health effects at both the individual level and the aggregate population level, providing population-level incremental net health effects (INHEs).

- iv. Drawing on the systematic reviews and evidence synthesis, national-level data on health-care associated infections, and other sources as needed, to identify evidence to populate the decision-analytic models.
- v. To use structured expert elicitation as necessary to supplement the available evidence to populate the decision-analytic models at the levels of both the individual patients and populations.
- vi. To use available evidence and, where necessary, expert opinion quantitatively to extrapolate estimated population-level INHEs associated with cefiderocol in the HVCSs to other expected uses for the product beyond the HVCSs and within the product's licensed indications.

1.3. Expected usage and high value clinical scenarios

The licensed indication for cefiderocol is broad. In practice, to control the spread of resistance to cefiderocol and to preserve its long-term viability as an effective treatment option against highly resistant pathogens, cefiderocol may be used in a more restricted group of patients than permitted by its license. Quantifying the health and cost implications of using cefiderocol across anticipated NHS usage, even within this restricted population, remains challenging, as use is expected in infections which differ in causative organism (pathogen, resistance mechanism), site of the infection, health care setting and other underlying features of the health status of the patient.

Using available evidence, this evaluation characterises the value of cefiderocol across its range of expected uses via a two-step approach. First, decision modelling is used quantitatively to assess the value of cefiderocol in a set of scenarios defined by features of the pathogen, site of infection, healthcare setting and other patient characteristics, considered to represent important uses of cefiderocol; referred to as the HVCSs. Secondly, rescaling is used to estimate how this evidence can be used to provide quantitative assessments of value in the overall population expected to receive cefiderocol, including patients who fall outside the HVCSs but whom are relevant to determining the overall value of cefiderocol to the English NHS.

The HVCSs were selected to reflect areas of clinical use where there is a current significant burden from resistant infections, and cefiderocol is expected to offer significant improvements over existing treatments in terms of efficacy and/or safety. The HVCSs were selected based on feedback from the manufacturer, clinical advisors to the Policy Research Unit in Economic Methods of Evaluation in Health and Social Care Interventions (EEPRU) and broader stakeholders involved in the NICE scoping process. The HVCSs focus on the following patient populations:

- 1) Empiric setting (ES): patients with an infection strongly suspected to be caused by metallo-beta-lactamase (MBL) producing *Enterobacterales* or MBL-producing *Pseudomonas aeruginosa* (PA) in patients with hospital acquired pneumonia or ventilator associated

pneumonia (HAP/VAP). In this patient group the pathogen, resistance mechanism and antibiotic susceptibility have not yet been established but treatment is initiated immediately due to the severity of the infection.

- 2) Microbiology-directed setting (MDS): patients with an infection confirmed to be caused by MBL *Enterobacterales* or MBL *Pseudomonas aeruginosa*, where antibiotic susceptibility testing results are available, and where the site of infection is HAP/VAP or complicated urinary tract infection (cUTI).

The resourcing for this project was equivalent to that of a diagnostic assessment review or multiple technology assessment for NICE, but the levels of analysis extend from the typical focus of those evaluations on a single type of patient for one indication and setting. In this evaluation, we also include population level health effects now and over time, and across several indications and settings. 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.

1.4. Clinical evidence

1.4.1. Methods

There are evidential challenges when evaluating the use of new or nearly new AMs to treat infections caused by multi-drug resistant (MDR) pathogens. Randomised controlled trials (RCTs) are of generally low relevance as they tend not to recruit patients with MDR pathogens. Therefore, relative treatment effects between the intervention and comparator cannot be generalised to MDR pathogens, as this may overestimate the efficacy of the comparator.

It was anticipated that RCTs were unlikely to be the primary source of evidence, and instead three approaches to estimating comparative efficacy between the intervention and comparators were considered. In approaches 1 and 2, RCTs and observational studies (Reviews 1 & 2, respectively), with data for patients with HAP/VAP or cUTI infections caused by MBL *Enterobacterales* or *Pseudomonas aeruginosa*, were considered. These could be used to construct a network meta-analysis (NMA) to compare the intervention and comparators. In Approach 3, *in vitro* susceptibility studies were considered. These studies provide evidence on the proportion of MBL *Enterobacterales* or *Pseudomonas aeruginosa* isolates that are susceptible to treatments and comparators as an indication of relative efficacy (Review 3). This approach would require additional evidence to link susceptibility to clinical outcomes in cUTI and HAP/VAP (Reviews 4 & 5, respectively). Susceptibility studies test isolates *in vitro* to ascertain the minimum concentration of any given treatment that is needed to inhibit growth of the microbe (the minimum inhibitory concentration (MIC)). If this is below the clinical

breakpoint published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (or by the Clinical Laboratory Standards Institute (CLSI) from the US), the isolate is considered susceptible, and likely to respond to treatment *in vivo*. In the UK, the British Society for Antimicrobial Chemotherapy (BSAC) recommends use of EUCAST guidelines.

A mapping review was conducted to identify relevant sources of evidence across the three reviews and ascertain which approach could inform an economic model. Systematic searches across relevant databases (Medline, Embase and Centre for Review and Dissemination (CRD) database) were conducted in March 2021. EEPRU also considered evidence submitted by Shionogi in their company submission, and made data requests to Shionogi and Public Health England (PHE). Records retrieved by the search were assessed for eligibility for inclusion in the mapping review by one reviewer, against pre-specified inclusion criteria. RCT and observational studies were eligible for mapping if they recruited patients with cUTI or HAP/VAP infections caused by MBL *Enterobacterales* or *Pseudomonas aeruginosa* (for the MDS) or suspected carbapenem-resistant *Enterobacterales* (CRE) or *Pseudomonas aeruginosa* (for the ES), and compared cefiderocol to any comparator (RCTs) or any comparator or no comparator (observational studies). Susceptibility studies were eligible for mapping if they reported susceptibility for MBL *Enterobacterales* or *Pseudomonas aeruginosa* isolates from any infection (clinical advisors indicated that infection site was not associated with susceptibility profile) to cefiderocol and at least one comparator as defined by the HVCSs (colistin, meropenem, tigecycline, aztreonam, fosfomycin, gentamicin, amikacin, tobramycin).

After mapping, only Review 3 was pursued, since there was insufficient evidence from Reviews 1 & 2 (see details in Results below). Susceptibility studies were further selected for inclusion based on susceptibility data format (proportion susceptible), avoidance of double counting and consideration of sources of heterogeneity, in consultation with clinical advisors. Risk of bias assessment was performed using a bespoke tool developed for this evaluation.

No studies of fosfomycin were identified in the mapping review, and the PHE data did not report this comparator either. An additional rapid review was conducted to identify studies reporting the susceptibility of fosfomycin and at least one other HVCS comparator.

A NMA of susceptibility studies was conducted to allow a comprehensive synthesis of evidence on all relevant treatments. The NMAs were performed using a Bayesian Markov chain Monte Carlo (MCMC) approach assuming a random effects (RE) model to allow for heterogeneity in treatment effects across studies. A different network was constructed for each subgroup of pathogens (MBL *Enterobacterales* and MBL *Pseudomonas aeruginosa*), since susceptibility profiles were expected to differ. For each of these, a network was constructed using EUCAST breakpoints and another using CLSI breakpoints, since EUCAST and CLSI breakpoints and laboratory methods differ, and it was unclear to what extent this might affect relative efficacy estimates between the intervention and comparator. In particular, the

EUCAST breakpoint for cefiderocol was 2mg/L, whilst the CLSI breakpoint was 4mg/L, and breakpoints for some comparators were also different, which could affect relative efficacy estimates. The EUCAST networks were considered the main analysis, whilst the CLSI networks were considered in sensitivity analyses. Sensitivity analyses were also conducted to test assumptions around the inclusion of comparators in the network, and to assess the impact of missed data on the analysis. Since data for cefiderocol and fosfomycin were identified via separate reviews, and since PHE data did not meet the inclusion criteria for the review, scenario analyses within the decision model were planned that would use the PHE data for the comparators (as PHE data is from English isolates and, therefore, has highest relevance), with a relative treatment effect for cefiderocol and fosfomycin obtained from a separate network of cefiderocol studies and fosfomycin studies, respectively. Therefore, analyses were run including the cefiderocol studies only and separately including the fosfomycin studies only.

Two additional reviews were conducted to provide evidence on the link between susceptibility and clinical outcomes (Review 4) and between susceptibility and long term outcomes (Review 5) in the sites of interest. Review 4 was widened to include any infections reporting outcomes for patients susceptible and non-susceptible to treatment regardless of the pathogen or resistance mechanism, since no evidence relating to MBL *Enterobacterales* or *Pseudomonas aeruginosa* was identified by Reviews 1 and 2. Review 5 was widened to include any resistant infection since no evidence relating to long term outcomes were found by Reviews 1, 2 or 4. A further review (Review 6) was conducted to identify any important safety implications of cefiderocol.

1.4.2. Results

Approaches 1 and 2 (RCT and observational studies, respectively) were not pursued since insufficient evidence from such studies was identified during the mapping review. One RCT did report subgroup data relating to MBLs, but the subgroup was small (n=16 in the cefiderocol arm, n=7 in the best available therapy arm) and was, therefore, not used due to the chance of baseline imbalances introducing bias. The key limitations of the observational studies that were identified included small numbers of MBL infections (range n=2-17 patients), high levels of heterogeneity with respect to prognostic factors, and data not being reported for the sites of interest.

In Approach 3 (susceptibility studies), relatively large samples of MBL *Enterobacterales* or *Pseudomonas aeruginosa* isolates obtained from a range of clinical sites of infection were available from *in vitro* susceptibility studies, and susceptibility (unlike clinical outcomes) was expected to generalise across sites. Three studies (SIDERO CR, SIDERO WT and Johnston *et al.*) reporting data for cefiderocol and at least one comparator met the inclusion criteria and were synthesised. The separate review of fosfomycin identified 10 studies.

In the MBL *Enterobacterales* EUCAST analysis, cefiderocol was associated with a lower susceptibility relative to colistin (odds ratio (OR) 0.32 95% credible intervals (CrI): 0.04 to 2.47), but the result was not statistically significant. Fosfomycin had a similar OR (OR 0.34, 95% CrI: 0.06 to 1.96) compared to colistin as cefiderocol. The remainder of the treatments were also associated with lower susceptibility than colistin, but the results were not statistically significant. In the MBL *Pseudomonas aeruginosa* EUCAST analysis, cefiderocol was associated with a lower susceptibility relative to colistin (OR 0.44 95% CrI: 0.03 to 3.94), but the result was not statistically significant. The remainder of the treatments were associated with no susceptibility. Heterogeneity was high in both networks.

In the sensitivity analyses using CLSI breakpoints, where the breakpoint for cefiderocol is higher, cefiderocol was associated with a higher susceptibility relative to colistin, rather than a lower susceptibility as seen in the EUCAST analysis. However, the results were very uncertain in some of the NMAs due to sparse data and a large number of treatment arms with either zero or 100% susceptibility.

Review 4 (link between susceptibility and clinical outcomes) identified two studies that reported mortality or hospital length of stay (LoS) conditional on susceptibility to empiric treatment and were selected for use in the model for the ES. No useful evidence relating to the MDS was identified. Review 5 (link between susceptibility and *long term* clinical outcomes) did not identify any relevant literature, but an unpublished study (CARBAR) was submitted by Shionogi that contained useful data. Review 6 indicated that cefiderocol does not appear to increase the risk of acute kidney injury (AKI), *C. difficile*, or any other serious adverse events, compared to non-toxic comparators (i.e. comparators other than colistin or an aminoglycoside). No study reported a comparison of cefiderocol exclusively to colistin or aminoglycosides. Event rates were generally very low or zero.

Discussion of clinical evidence: There were limitations to the approach selected and analyses done. Key limitations include: susceptibility could be considered, at best, a surrogate outcome, but no pre-specified criteria for judging the suitability of the surrogate or the linking evidence were applied; linking data were limited and not specific to the pathogen-mechanism combination, and expert elicitation had to be relied upon to evidence the link in the MDS; breakpoints are set by experts in a subjective process and may not predict clinical response equally in all treatments; for *Pseudomonas aeruginosa*, the breakpoint used for fosfomycin was not based on expected clinical outcomes; data in the EUCAST networks were based on studies that used CLSI laboratory methods, and it is unclear if this would affect absolute and relative values; it was not clear which breakpoints and laboratory methods contributed to the PHE data; the NMAs results were associated with high levels of heterogeneity.

1.5. Economic evidence

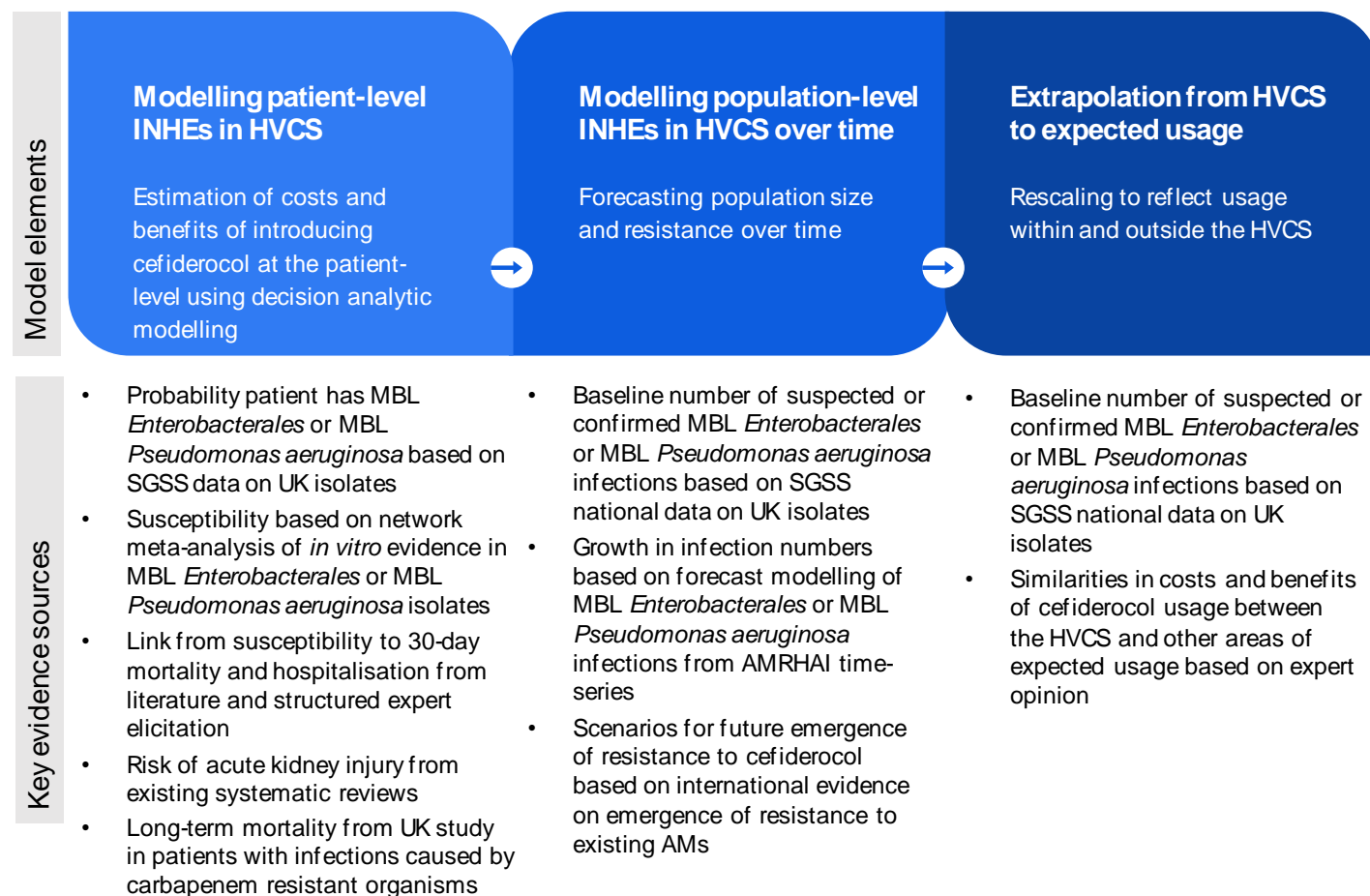
1.5.1. Methods

No published existing economic evaluations assessed the use of cefiderocol in the HVCSs or areas of expected usage. The manufacturer did not submit a cost-effectiveness model.

A *de novo* decision analytic model was developed to predict the cost and health consequences of introducing cefiderocol within the HVCSs. The costs and health consequences of introducing cefiderocol are summarised as incremental net health effects (INHEs). These are estimates of the quality-adjusted life-years (QALYs) associated with introducing cefiderocol if it was supplied free of charge to the NHS, taking in to account both its health benefits and the health benefits of freeing up NHS resources (e.g. via reduced time in hospital). The health benefits of freeing up NHS resources are calculated using an estimate of health opportunity cost to convert between cost savings and health benefits. In the base case analysis this estimate is £20,000/QALY. This means that for every £20,000 saved 1 QALY of health can be generated within the NHS. The estimates of INHE will be used in subsequent negotiations to determine an appropriate payment level for cefiderocol.

This quantitative analysis comprises three components: an assessment of the INHEs of introducing cefiderocol within the HVCSs at the patient level; an assessment of INHEs within the HVCSs at the population level; and an assessment of how population-level INHEs within the HVCSs might appropriately be rescaled to reflect expected usage across the English NHS. A schematic describing the modelling approach and key evidence sources is provided as Figure 1.

Figure 1: Schematic of modelling approach and key sources of evidence



AMRHAI, antimicrobial resistance and healthcare associated infections; HVCS, high value clinical scenario; INHEs, incremental net health effects; MBL, metallo-beta-lactamases; SGSS, Second Generation Surveillance System; UK, United Kingdom 5-7

The patient-level component is structured similarly to decision models developed as part of other NICE processes and characterises the cost, mortality and morbidity consequences of introducing cefiderocol over a patient's lifetime. Separate but related models are developed for the empiric and microbiology-directed settings. In the ES, empiric treatment with cefiderocol is compared to: empiric treatment with a non-colistin/aminoglycoside-based treatment (MBL *Pseudomonas aeruginosa* only); empiric treatment with colistin/aminoglycoside-based treatment (considered more toxic); and to use of existing treatments in the ES with cefiderocol restricted for use in the MDS. In the MDS we compare outcomes in the overall microbiology-directed cohort who receive tailored therapy with cefiderocol available as a treatment option, to outcomes in the overall microbiology-directed cohort who receive tailored therapy with existing AMs only.

In the ES patients are suspected to have an infection caused by MBL Enterobacterales or MBL *Pseudomonas aeruginosa*, so it is necessary to model outcomes for both patients in whom this suspicion is confirmed and for those in whom this suspicion turns out to be incorrect. The probability of having the suspected pathogen/resistance mechanism is informed by Second Generation Surveillance System (SGSS) national surveillance data supplied by PHE for this evaluation. The key driver of effectiveness is in vitro susceptibility as estimated via the evidence syntheses discussed above. Higher susceptibility reduces mortality and LoS in hospital. These relationships are based on a combination of evidence from the literature and structured expert elicitation. Colistin or aminoglycoside-based therapy is expected to be associated with higher rates of AKI than other agents (including cefiderocol), which has significant consequences for patients' short and long-term mortality, morbidity and costs. Safety differences between colistin or aminoglycoside-based therapy and other agents are, therefore, modelled using evidence from published systematic reviews. At 30 days patients were classified as dead or alive with those alive sub-classified according to their history of AKI. These outcomes were then used to predict patients' lifetime costs, quality of life and mortality accounting for the highly comorbid nature of the patient population with AM-resistant infections and the increased risk of chronic kidney disease (CKD) resulting from AKI.

The population-level component uses a forecast-based approach to aggregate the patient-level predictions to the population level accounting for the size of, and growth over time in, the eligible patient population in England within each HVCS. This component also reflects how resistance is likely to develop to cefiderocol and existing AMs over time. Current numbers of patients within the HVCSs were based on evidence from SGSS. Future growth in the number of patients in the HVCSs was based on statistical forecasting models fitted to time series data from the national reference laboratory dataset held by the antimicrobial resistance and healthcare associated infections (AMRHAI) and supplied by PHE for this evaluation. A series of scenarios reflects the potential emergence of resistance to cefiderocol with resistance emergence at 20 years of 1%, 5%, 10% and 30%. These scenarios were informed by international data on the emergence of resistance to existing AMs. Predictions of

population-level INHE are presented for patients initiated on treatment with cefiderocol over the next 20 years. This time horizon was chosen pragmatically to explore the long-term value of cefiderocol whilst avoiding additional uncertainties associated with very long-term population-level predictions. We did not model changes in resistance to existing AMs over time due to the sparsity of evidence available to inform these forecasts.

Predicted overall population-level INHEs corresponding to the expected use of cefiderocol in the English NHS were generated by rescaling the population-level INHEs from the HVCSSs to reflect additional areas of expected usage. These areas of expected usage were selected based on feedback from the manufacturer, clinical advisors to EEPRU and broader stakeholders involved in the NICE scoping process. These included patients with bloodstream and intra-abdominal infections (BSIs and IAIs) known or suspected to be caused by MBL *Enterobacterales* or MBL *Pseudomonas aeruginosa*, and patients with infections caused by *stentrophomonas* across a range of sites (HAP/VAP, cUTI, BSIs and IAIs). This rescaling was based on population size estimates from SGSS and the use of expert opinion to inform the similarity in patient-level INHEs between the patients falling within the HVCSSs and these additional sites and pathogens of interest.

The literature on the economic evaluation of AMs has described a range of elements of value associated with these products that are not relevant to evaluations of other health care interventions. We also, therefore, summarise the extent to which these elements of value are captured within the quantitative estimates and, where this has not been possible, whether they are likely to substantively modify the quantitative estimates of value presented.

1.5.2. Results

Table 1 summarises the patient-level INHEs for cefiderocol in the HVCSSs. Across subgroups, there is a high degree of uncertainty surrounding the benefits of cefiderocol.

For HAP/VAP patients treated empirically with cefiderocol due to suspected MBL *Enterobacterales*, cefiderocol is associated with lower susceptibility but improved safety compared to colistin/aminoglycoside-based treatment in those who are correctly suspected of having MBL *Enterobacterales* (patient-level INHE -0.22), and the same susceptibility but improved safety in those who have infections caused by other pathogens/mechanisms (patient-level INHE 0.18). As the proportion of patients who have MBL *Enterobacterales* increases, the patient-level INHEs therefore reduce dramatically. Conversely, if the CLSI breakpoints are used to determine susceptibility, the patient-level INHEs increase to 0.20 QALYs reflecting the higher susceptibility to cefiderocol in this scenario. Scenarios examining a larger effect of colistin/aminoglycoside-based treatment on AKI risk, that reduce the implications of AKI for short-term mortality and shorten long-term survival for this patient group, also markedly effect the results (patient-level INHE 0.08-0.19).

For HAP/VAP patients treated empirically with cefiderocol due to suspected MBL *Pseudomonas aeruginosa*, cefiderocol is associated with comparable susceptibility and improved safety compared to colistin/aminoglycoside-based therapy, and improved susceptibility compared to non-colistin/aminoglycoside-based therapy. The most significant source of uncertainty in this population is the effectiveness of non-colistin/aminoglycoside-based treatment. The synthesis of evidence using CLSI breakpoints indicated susceptibility to fosfomycin that was similar to cefiderocol and, therefore, there is limited advantage of using cefiderocol.

For patients treated in the MDS, the advantage of cefiderocol is much higher for MBL *Pseudomonas aeruginosa* than MBL *Enterobacterales* as the latter patient group has a higher probability of being susceptible to a non-colistin/aminoglycoside-based treatment, and hence not requiring treatment with cefiderocol. There is a large degree of uncertainty in the patient-level INHE in the MBL *Pseudomonas aeruginosa* population. This reflects the differences across scenarios in the susceptibility to non-colistin/aminoglycoside-based treatments. This is much higher when the CLSI breakpoint studies are synthesised, and much lower when the baseline colistin susceptibility is set at the value from SIDERO WT.

It should be noted that results in the MBL *Pseudomonas aeruginosa* populations are subject to particular uncertainty due to limitations in the evidence base for the comparators (fosfomycin plus meropenem and fosfomycin plus colistin), as fosfomycin does not have an established breakpoint for *Pseudomonas aeruginosa*, making links to clinical outcomes more tenuous. Furthermore, the available evidence to inform the relative susceptibility of fosfomycin was based on very small studies (n=7 in the EUCAST and n=20 in the CLSI networks).

Table 1: Summary of patient-level INHEs (QALYs) by HVCS subgroup, results presented as base case (scenario range)

	Empiric setting HAP/VAP	Microbiology-directed setting HAP/VAP	Microbiology- directed setting cUTI
MBL <i>Enterobacterales</i>	0.12 (0.00-0.20)	0.02 (0.01-0.05)	0.02 (0.01-0.05)
MBL <i>Pseudomonas aeruginosa</i>	0.15 (0.01-0.19)	0.13 (0.01-0.24)	0.10 (0.01-0.24)

cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia

EEPRU was unable to select a base case for the population-level results. Population-level results are, therefore, presented for two different approaches to estimating current MBL *Enterobacterales* and MBL *Pseudomonas aeruginosa* infection numbers (based on different methods to classify infections from clinical specimen sites); two alternative approaches to forecasting increases in infections over time (based on whether observed trends are assumed to persist indefinitely or not); and three different trajectories with respect to resistance emergence (1%, 5% and 10% at 20 years).

These results are summarised in Table 2. These indicate that assumptions about baseline population size and growth are strong drivers of population-level INHEs which vary from 839 to 2,994 QALYs depending on the scenario. The results are particularly sensitive to the assumption about which clinical specimen sites are indicative of HAP/VAP, with the more conservative definition provided by PHE indicating 131 HAP/VAP suspected MBL *Enterobacteriales* or MBL *Pseudomonas aeruginosa*, or confirmed *Stenotrophomonas* would be eligible to receive ceftazidime per annum; and the broader definition provided by our clinical advisors indicating that 791 patients with HAP/VAP infections would be eligible. Of note, a substantial part of the value of ceftazidime (21-40% depending on scenario) is generated amongst patients with *Stenotrophomonas* who were outside of the HVCSs considered by EEPRU. Departures from the base case assumptions in the patient level model also had substantial effects on population-level INHEs.

Table 2: Summary of population-level INHEs (QALYs)

Baseline population	Population growth rate	Predicted patients initiating ceftazidime over 20 years	Range of population-level INHEs across resistance scenarios 1%, 5%, and 10% at 20 years (base case assumptions used for patient level model)
PHE categorisation of infection sites	Model with damped trends	8,671	839-897
	Model with persistent trends	13,488	1,234-1,333
Clinical advisors' categorisation of infection sites	Model with damped trends	16,669	1,988-2,116
	Model with persistent trends	24,969	2,788-2,994

INHEs, incremental net health effects; PHE, Public Health England

The population size estimates used to generate the estimates of population-level INHEs are subject to considerable uncertainties relating to the completeness of the national data, how accurately specimen types represent the infection sites of interest, whether all tested patients would fall within the HVCS population for empiric treatment, the potential double counting of samples from the same infectious episode, and inherent uncertainties in forecasting population size over time.

In addition, estimates of population-level INHEs were generated using a number of strong assumptions about how evidence can be generalised between settings. Namely, that patient-level INHE of ceftazidime in patients with BSI can be approximated based on outcomes in HAP/VAP patients, and that the patient-level INHE of ceftazidime in patients with IAI can be proxied by that in patients with cUTI. These assumptions were based on discussions with clinical experts.

Table 3 summarises where EEPRU has been able to quantify the additional elements of value and, for those elements where this has not been feasible, provides an indication of their likely importance. Overall, EEPRU considers that the main areas of uncertainty are enablement value and transmission value. EEPRU considers it unlikely that transmission value is a significant driver of population-level INHE, though this remains an area of uncertainty. EEPRU considers that it is possible that, by treating pre-operative infections and offering the possibility of an effective low toxicity option for treating MDR infections, cefiderocol will facilitate additional or at least more prompt receipt of required treatments/procedures for certain groups. EEPRU considers that the magnitude of these population-level INHE remains highly uncertain.

Table 3: Additional elements of value

Element of value	Summary of importance in modifying quantitative estimates of population-level INHEs, * indicates areas of high uncertainty
Enablement value	Benefits of improved treatment of post-operative infections quantified Benefits of improved treatment of pre-operative infections partially quantified* Benefits of increasing number of procedures that can go ahead not quantified* Benefits of keeping wards open during MDR infection outbreaks unlikely to be a significant driver of population-level INHEs Benefits of reduced use of hospital resources quantified
Diversity value	Unlikely to be a significant driver of population-level INHEs
Insurance value	Quantified
Transmission value	Unlikely to be a significant driver of population-level INHEs *
Spectrum value	Unlikely to be a significant driver of population-level INHEs

INHEs, incremental net health effects

1.6. Conclusion

The quantitative assessment of value in this report indicates that cefiderocol is associated with a base case population-level INHE across its areas of expected usage of 839 to 2,994 QALYs over 20 years. These quantitative assessments of value were informed by a series of interlinked decision analytic models informed by evidence collated via systematic reviews of the literature and evidence synthesis, additional national data provided by PHE, structured expert elicitation and, where necessary, assumptions informed by clinical opinion.

This work has provided quantitative estimates of the value of cefiderocol within its areas of expected usage within the NHS. A broader and important question is “what would represent the “optimal” scope of usage for cefiderocol?” Further methodological and quantitative work is required to address this question.

2. Introduction

2.1. AM resistance

Antimicrobial resistance (AMR) develops when bacteria with mutations that prevent the activity of antimicrobials (AMs) emerge through selection pressure exerted by the use of AM agents. There are two major genetic processes involved: mutations in the genes native to the organism usually associated with the mechanism of action of the compound; and acquisition of foreign DNA coding for resistance determinants through horizontal gene transfer (HGT) of plasmids / genes (e.g., transposons).^{1,2} The majority of pathogenic microorganisms appear to have the capability to develop resistance to at least some AM agents. Mechanisms of resistance include limiting uptake of a drug by the microbe, modification of a drug target, inactivation of a drug and active efflux of a drug. Resistance to multiple agents can develop via successive mutations, through the dissemination of genes or through a combination of both processes.

The increased mobility of the global population has had the effect of promoting the evolution and movement of antibiotic resistance genes. For example, very high rates of extended-spectrum β -lactamase (ESBL) production among *Enterobacterales* strains in Asian countries has resulted in substantial use of carbapenem antibiotics worldwide, leading to the emergence of plasmid-mediated resistance to carbapenems.³ These have spread across the globe and between species. Multidrug-resistant bacteria can also spread rapidly within both hospitals and community settings, further contributing to increased AM use and heightened resistance,⁴ and narrowing the choices available for antibiotic treatment.

Gram-negative bacteria (GNB) pose a significant public health problem due to their increasing levels of resistance to antibiotics. This can lead to severe consequences where infections cannot be treated effectively, or where the increased risk of mortality and morbidity from infection can prevent life-saving procedures such as transplants or other invasive procedures. *Enterobacterales* account for many gram-negative infections in humans, including urinary tract infections (UTIs), pneumonia, diarrhoea, meningitis, and sepsis, whilst the non-fermenter gram-negative bacilli account for the largest share of infections caused by carbapenem-resistant GNB.⁵

Carbapenem resistance is a particular problem in GNB, since this constitutes the most reliable drug class for treating bacterial infections. There are two main types of carbapenem resistance, and these can be expressed in multiple pathogens:

- a) Carbapenemase-mediated carbapenem resistance occurs when the microorganism produces an enzyme (carbapenemase) that hydrolyses carbapenem antibiotics (such as penicillins, cephalosporins, monobactams, and carbapenems) and renders them ineffective. There are multiple carbapenemase enzymes, and these are grouped based upon the similarity of their

amino acid sequences according to the Ambler classification system as class A, B, C or D. Class A, C and D enzymes have a serine-based hydrolytic mechanism, while class B enzymes are metallo-beta-lactamases (MBL) that contain zinc in the active site. Each class comprises a number of variants, which include:

- Class A: *Klebsiella pneumoniae* carbapenemase (KPC), Guiana extended-spectrum β -lactamase (GES), Imipenemase/non-metallo carbapenemase-A (IMI/NMC), and *Serratia marcescens* enzyme (SME)
- Class B (MBLs): New Delhi MBL (NDM), Verona integrated-encoded MBL (VIM), Imipenemase (IMP), Sao Paulo MBL (SPM), and Germany imipenemase (GIM)
- Class C: Ampicillinase C (AmpC), cephamycinases (CMY)
- Class D: Oxacillinase (OXA)-23, OXA-24, OXA-48, OXA-58, and related enzymes

Carbapenemases are produced by a small but growing number of *Enterobacteriales* strains, especially *Escherichia coli* and *Klebsiella pneumoniae*, and some non-fermenter organisms such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (*A. baumannii*). Bacteria producing carbapenemases may cause serious drug-resistant infections, though the profile of resistance is different for each specific variant and is influenced by the pathogen expressing the resistance, and other resistance genes the organism may have. Of the Ambler Class A carbapenemases, the KPC carbapenemases are the most prevalent, found mostly on plasmids in *Klebsiella pneumoniae*. The class D carbapenemases are frequently detected in *A. baumannii*. The class B (MBLs) have been detected primarily in *Pseudomonas aeruginosa*; however, there are increasing numbers of reports worldwide of this group of β -lactamases in the *Enterobacteriales*. The main serine-carbapenemases among carbapenemases-producing *Enterobacteriales* (*Enterobacteriales*) in the UK are OXA-48 and KPC. The main MBLs in the UK are NDM, VIM and IMP.⁶ Specifically, 12.5% of *Enterobacteriales* are KPC, 36.5% are OXA-48-like, and 43.2% MBL (mostly NDM) in the UK.⁵

- b) **Non-carbapenemase carbapenem resistance** occurs through a variety of nonenzymatic mechanisms which include reduced cell membrane permeability to carbapenems through downregulation of porins (membrane proteins that allow carbapenems into the cell), or overexpression of efflux pumps which remove carbapenems from the peri-plasmic space. Such mechanisms are often considered to produce low-level resistance, and generally more treatment options are available that maintain activity against these mechanisms.

The World Health Organization (WHO) maintains a list of priority pathogens where, due to the development of resistance, new AMs are urgently needed. The pathogens that the WHO deems ‘critical’ priorities are: carbapenem-resistant *A. baumannii*; carbapenem-resistant *Pseudomonas aeruginosa*; carbapenem-resistant *Enterobacteriales* (CRE) (where *Klebsiella pneumonia* and *Escherichia coli*

account for the large majority of *Enterobacterales*). These pathogens are typically multidrug-resistant GNB that can cause severe infections in secondary care settings, such as pneumonia and BSIs (bacteraemia), that can often be fatal.^{7,8}

Early, targeted, effective and safe AM treatment is key for the management of patients infected with carbapenemase-producing carbapenem-resistant bacteria; however, reliable AM treatment options remain scarce. Therefore, individual treatment options tailored to susceptibilities of pathogens and severity of infection are the mainstay of clinical practice.⁶ Carbapenems are a class of β -lactams that are often reserved as a last-line treatment option for infections that are resistant to other β -lactams with a narrower spectrum of action.⁹ Carbapenems are considered one of the most reliable drugs for treating bacterial infections,¹ therefore the emergence and spread of resistance to these antibiotics is particularly concerning, especially resistance mediated via carbapenemase which renders other treatment options ineffective. This constitutes a major public health problem due to the morbidity and mortality associated with ineffectively treated infections by these bacteria.

2.2. New Antimicrobials

There is widespread recognition that the pipeline for new AMs is poor with few AM agents currently in clinical development. A range of policies have been implemented to address this lack of investment, however these have focused on “push incentives” that lower the costs of R&D. In 2015 a joint government and industry AMR working group was established that highlighted the need for the development of “pull mechanisms” and in particular a more appropriate payment model for new AMs. The payment model should align payment with value, support stewardship goals by delinking payment from drug sales volumes and provide smooth revenue from the point of approval even for AMs which are expected to be subject to strict stewardship and only used as drug-resistance increases.

National Institute for Health and Care Excellence (NICE), NHS England and NHS Improvement are currently undertaking a project to assess the feasibility of innovative models that pay for AMs based on an evaluation of their value to the National Health Service (NHS) as opposed to the volumes used. Following the selection of two products considered to be of high public health importance, this project involves evaluation of the selected products to inform commercial discussions regarding contract value for a period of up to 10 years. The selection process was a formal procurement exercise and aimed to identify one new AM and one existing but “nearly new” AM. The products selected by this process are cefiderocol (Fetcroja) which is manufactured by Shionogi and received its marketing authorisation in April 2020; and ceftazidime with avibactam (Zavicefta), which is manufactured by Pfizer and received its marketing authorisation in June 2016. This report details the evaluation phase of this project for cefiderocol.

Cefiderocol received a marketing authorisation in April 2020 for treating infections due to aerobic Gram-negative organisms in adults with limited treatment options. It is an injectable siderophore cephalosporin. It has a cephalosporin backbone with a catechol moiety at the 3- position side chain. The catechol moiety chelates ferric iron, which allows cefiderocol to cross the outer membrane via the bacteria's own active receptor-mediated iron transport system.^{10,11} The cephalosporin core then binds primarily to penicillin binding proteins, killing bacterial cells by inhibition of peptidoglycan cell wall biosynthesis.

Cefiderocol has been tested in three randomised controlled studies ¹²⁻¹⁴ (one described as a descriptive study) which recruited patients with complicated UTI (cUTI), bacteraemia, hospital-acquired pneumonia (HAP), ventilator associated pneumonia (VAP) and healthcare associated pneumonia; and in two in-vitro susceptibility studies ^{15,16} against carbapenem non-sensitive isolates from global sources. Cefiderocol is active against all four Ambler classes of carbapenemase in GNB, including the MBLs (class B) most prevalent in the UK (NDM VIM, IMP), and the serine carbapenemases most prevalent in the UK (KPC in class A and OXA-48 in class D) ^{16,17} as well as the non-mutational causes of carbapenem -resistance (Porin OprD, and efflux pump) in *Pseudomonas aeruginosa*. It is also active against other WHO priority pathogens on the critical list, including ESBL-producing *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter spp*, *Serratia spp.*, *Proteus spp.*, *Providencia spp*, and *Morganella spp* as well as carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.¹⁸

3. Aims and objectives

The aim of this evaluation is to assess the value of cefiderocol to the NHS in England for the treatment of severe aerobic GNB infections when used within its licensed indications.

Specific objectives are:

- i. To identify two high value clinical scenarios (HVCSs), within its broad licensed indications, for which cefiderocol is expected to have a significant impact on patients' outcomes in terms of reducing mortality risks and improving health-related quality of life (HRQoL).
- ii. To undertake an 'evidence mapping' exercise and relevant systematic literature reviews to characterise the available clinical effectiveness evidence for the use of cefiderocol in the HVCSs.
- iii. To establish an appropriate decision-analytic model to quantify the costs and health benefits of the use of cefiderocol under various usage scenarios compared with alternative treatments and management strategies (usage scenarios of other available AMs) in the HVCSs. The decision-analytic model was required to estimate costs and health effects at both the individual level and

also at the aggregate population level, providing population-level incremental net health effects (INHEs).

- iv. Drawing on the systematic reviews and evidence synthesis, national-level data on health-care associated infections, and other sources as needed, identify evidence to populate the decision-analytic models.
- v. To use structured expert elicitation as necessary to supplement the available evidence to populate the decision-analytic models at the levels of the individual patients and populations.
- vi. To use available evidence and where necessary expert opinion to quantitatively extrapolate estimated population-level INHEs associated with cefiderocol in the HVCSs to other expected uses for the product beyond the HVCSs and within the product's licensed indications.

4. Decision problem

4.1. Decision making context

The overarching purpose of the evaluation is to inform funding arrangements for cefiderocol in England. The drug's funding will differ from that of drugs evaluated under nice Technology Appraisals in two important ways. Firstly, the payment for cefiderocol will be delinked from usage volumes and, instead, represent a fixed annual payment over the term of the agreement (3 years in the first instance, followed by a potential extension to 10 years). Secondly, in a NICE Health Technology Assessment (HTA), the price is proposed by the manufacturer, whereas here the payment will be agreed via commercial discussions between the manufacturer (Shionogi) and NHS England, informed by the evaluation. The role of the evaluation and subsequent NICE Committee deliberations will be to provide guidance on the value of cefiderocol to the NHS in England to inform these commercial discussions. This will include providing advice on the preferred usage of cefiderocol including the role of stewardship strategies (i.e. policies to ensure appropriate prescribing).

In previous work, the Policy Research Unit in Economic Methods of Evaluation in Health and Social Care Interventions (EEPRU) set out principles for quantitatively evaluating the value of a new AM.¹⁹ The starting point for this is to identify the range of ways in which cefiderocol can be used and to compare these scenarios to the range of ways in which other comparator AMs can be used (usage scenarios).

Value is defined as the expected impact of each usage scenario on population-level INHEs. Value is defined at the population rather than individual-patient level as payments to the manufacturer will reflect overall value to the English NHS. Population-level INHEs reflect expected population-level health benefits to patients and the wider population, expected population-level costs borne by (or savings accruing to) the NHS, and a measure of the health opportunity cost of health-care funds which allows NHS costs to be converted to health foregone. As the purpose of the evaluation work is to inform

a value-based payment for cefiderocol, the drug acquisition cost for cefiderocol is excluded from the calculation of population-level INHE. The incremental value of cefiderocol is the difference between the population net health effects (NHE) associated with a given cefiderocol usage scenario and the highest population NHE for clinically relevant usage scenarios that include only comparator AMs. This is shown in Box 1.

Box 1: Assessing value in terms of population net health effects

Assume a number of strategies are being compared for a given indication. AM(N)i represent strategies using the new AM and AM(E)i are strategies for existing treatments. The table below provides illustrative estimates of the expected per patient treated costs (Column B) and health effects in terms of Quality-adjusted life-years (QALYs) per patient, Column C), over the relevant time horizon. The costs of the new AM strategies assume zero acquisition cost for the new product. Any indirect effects on others through changes in resistance are assumed to be reflected in the QALYs per patient treated.

A	B	C	D	E
Strategy	Expected costs, PPT	Expected QALYs, PPT	Expected net health benefit (QALYs) PPT	Expected population net health benefit (QALYs)
AM(N)1	6800	9.0	8.547	51280
AM(N)2	7000	9.3	8.833	53000
AM(N)3	7240	9.5	9.017	54104
AM(E)1	7500	8.9	8.400	50400
AM(E)2	7800	8.5	7.980	47880
AM(E)3	7600	8.4	7.893	47360

Column D shows the expected per patient NHEs in terms of QALYs. This is calculated as $QALYs - \frac{Cost}{K}$, where k is the estimate of health opportunity cost which in this illustration is £15,000 per QALY. Column E details the expected population NHEs in QALYs assuming the potential to benefit 6000 patients over the time horizon of the analysis. AM(N)3 represents the best of the strategies involving the new AM, with an expected population NHE of 54,104 QALYs for the new AM. To calculate the value of the new drug in NHEs the difference in population NHE between AM(N)3 and the best of the strategies using existing treatments is calculated ($54,104 - 50,400 = 3,704$ QALYs). This is the population INHE that is the focus of the current assessment as it will inform the value-based payment for the new treatment.

As the population-level INHEs will inform the value-based payment to the manufacturer, they should reflect the overall value resulting from expected NHS usage. Expected NHS usage, in principle, reflects both the preferred usage specified in NICE guidance and the implications of clinical decisions taken locally.

As documented in Section 2.2, the licensed indication for cefiderocol is fairly broad, being available to any patient with limited treatment options, regardless of the site of the infection. In practice, to control the spread of resistance to cefiderocol and to preserve its long-term viability as an effective treatment option, cefiderocol is expected to be used in a more restricted group of patients than permitted by its license. Quantifying the health and cost implications of using cefiderocol across anticipated NHS usage, even within this restricted population, remains challenging as use is expected across infections which differ in causative organism (pathogen, susceptibility and resistance mechanism), site of the infection, health care setting and other underlying features of the health status of the patient.

This evaluation will seek to characterise the value of cefiderocol across its range of expected uses using two approaches. Firstly, decision modelling will be used to evaluate quantitatively the value of cefiderocol in two scenarios defined by features of the pathogen, site of infection, healthcare setting and other patient characteristics, considered to represent important uses of cefiderocol (referred to as the HVCSs). Secondly, we will provide additional information and quantitative estimates to support the NICE Committee in assessing value in the overall population expected to receive cefiderocol in the English NHS including patients who fall outside the HVCSs.

The literature on the economic evaluation of AMs has described a range of elements of value associated with AMs that are not relevant to other interventions and previous work by EEPRU has sought to explain how these elements of value can be quantified in terms of population-level INHEs.¹⁹ As part of the current evaluation we assess the extent to which these additional elements of value are likely to apply in the context of cefiderocol and quantify them where this is feasible and they are expected to be quantitatively important.

The resourcing for this project was equivalent to that of a diagnostic assessment review or multiple technology assessment for NICE, but the levels of analysis extend from the typical focus of those evaluations on a single type of patient for one indication and setting. In this evaluation, we also include population level health effects now and over time, and across several indications and settings. 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.

4.2. High value clinical scenarios

4.2.1. Pathogen and resistance mechanisms

An important determinant of the efficacy of existing treatment and, therefore, to defining those patients most likely to benefit from cefiderocol, is the pathogen causing the infection and its mechanism of resistance.

Feedback during the NICE scoping consultation for cefiderocol, and subsequent consultation with clinical experts, has emphasised that cefiderocol should be prioritised for the treatment of patients with infections with confirmed or suspected carbapenem-resistant GNB in secondary/tertiary care. Carbapenem resistant pathogens can be categorised according to two main classes of resistance mechanisms as discussed in detail in Section 1: non-carbapenemase carbapenem resistance and carbapenemase-mediated carbapenem resistance. For infections caused by carbapenem-resistant organisms with non-carbapenemase resistance mechanisms, a range of treatment options remains available. Infections caused by carbapenemase-producing pathogens have fewer treatment options. There are two main classes of carbapenemase-producers: serine-carbapenemases and MBLs. The main serine-carbapenemases among CRE in the UK are OXA-48 and KPC. The main MBLs in the UK are NDM, VIM and IMP.

Cefiderocol is active against MBLs and serine-carbapenemases. It is also effective against a wide range of pathogens, including *Enterobacterales* and the non-fermenters *Pseudomonas aeruginosa* and *A. baumannii*. Based on the rates reported in the latest available data from the English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) (based on BSIs),⁵ the most common carbapenem resistant organisms are *Pseudomonas aeruginosa* and *Enterobacterales*. Infections by *A. baumannii* seem to represent a lower share of carbapenem resistant GNB infections, but where the pathogen has OXA mechanisms of resistance (OXA-40/24, OXA-51, OXA-58, OXA-143), there are very limited treatment options. For MBLs, there are often even more limited treatment options, and in some cases only cefiderocol is expected to be active. There may also be a use for cefiderocol in serine *Enterobacterales* which have more treatment options than MBLs; for example, in a stewardship/diversity treatment strategy. For this evaluation, the HVCSSs focus on the treatment of infections caused by MBL *Enterobacterales* and *Pseudomonas aeruginosa* based on the limited available treatment options for these patients. Clinicians and stakeholders to the project emphasised that cefiderocol may also be a relevant treatment option for patients with infections caused by *Stenotrophomonas* which is innately MBL, however this was only discussed subsequent to the development of the HVCSSs.

4.2.2. Availability of susceptibility data during the course of an infection

Infections in secondary/tertiary care are typically initially treated with empirically-chosen antibiotics. At this stage of treatment there is limited information available to inform treatment choice. Indicators of an elevated risk of carbapenem-resistance at this stage include a range of patient- and setting-specific risk factors. Patient-level factors include prior microbiology history, recent history of hospital or long-term care admissions or regular hospital-based treatments, epidemiological links to other carriers, international travel, immunosuppression and recent broad-spectrum antibiotic exposure. Setting-specific factors include being admitted to augmented care or high-risk units and local epidemiology (e.g. previous history of outbreaks).²⁰

In some hospitals and tertiary care centres, screening for carriage of carbapenem resistant pathogens is carried out. Routine screening for colonisation with *Enterobacterales* at the point of admission has recently been recommended by Public Health England (PHE) for specific high-risk patients and health care settings.²⁰ The objective of this screening is primarily to support enhanced infection control measures, surveillance and outbreak management efforts. However, information obtained via screening may also support treatment choice as colonisation with *Enterobacterales* is a risk factor for a *Enterobacterales* infection. Currently, implementation of screening for *Enterobacterales* is variable in the UK despite the PHE guideline,²⁰ and the level and timing of information provided via screening also varies.

At the point an invasive bacterial infection is suspected, where possible, specimens are obtained to support further diagnostic work. Various diagnostic technologies can be used to better understand the causative pathogen and how it may respond to treatment. There are broadly three layers to this:

- A **culture** is undertaken to understand the type of pathogen causing the infection.
- **AM-susceptibility testing** is conducted to assess the *in vitro* activity of a range of AMs against the pathogen in question.
- **Gene testing** may also be conducted to establish the presence of specific resistance mechanisms.

Cultures are typically available relatively quickly with AM-susceptibility testing and gene testing taking longer (typically more than 48 hours, although this depends on local availability of testing technology and laboratory capacity; e.g. centres with access to polymerase chain reaction (PCR) testing may have information much more quickly). The availability of gene testing also varies geographically. There may be an increase in the use of gene testing in the UK in the future as PHE has recently recommended routine use of molecular or immunochromatographic assays to detect the main carbapenemase producers.²¹

Overall, variability in local practice, laboratory capacity and availability of diagnostic technologies means that there is likely to be significant variation in the nature and timing of the information available to inform treatment decisions.

4.2.3. Overview of high value clinical scenarios

Based on feedback from stakeholders via the NICE scoping consultation and further discussion with clinical experts, EEPRU has identified two HVCSs for use of cefiderocol: microbiology-directed treatment and risk-based empiric treatment. We explain these separately here but, in practice, they are often linked in a single patient pathway.

Microbiology-directed treatment refers to the use of cefiderocol in individuals with infections caused by a pathogen confirmed to have a specific pathogen and resistance mechanism. This group of patients has undergone susceptibility testing and gene testing to understand specific resistance mechanisms. As this usage of cefiderocol will require susceptibility/gene testing to have been undertaken prior to receipt of cefiderocol, this clinical scenario will focus on individuals with non-critical infections. Section 4.2.4 describes in more detail the specific Population, Intervention, Comparison, Outcomes, Study designs (PICOS) considered for this scenario.

Risk-based empiric treatment refers to use of cefiderocol in the empiric setting (ES) for clinically urgent patients with high suspicion (i.e., a high risk) of specific carbapenem resistance based on patient phenotype but for whom information about the pathogen is currently very limited (susceptibility data and gene testing not yet available). Use within this HVCS should be restricted only to those patients in whom microbiology-directed treatment is likely to be considered inappropriate due to the potential delay in time to appropriate therapy. The risk-based empiric treatment HVCS is, therefore, focused on patients who meet two criteria: (i) the infection is considered clinically urgent based on a range of information including infection site and severity, and broader information relating to the health status of the patient; and (ii) the patient is considered at elevated risk of a specific type of carbapenem-resistant infection using the type of risk markers described in Section 4.2.2. Section 4.2.4 describes in more detail the PICOS for this scenario.

4.2.4. PICOS for high value clinical scenarios

Based on feedback from stakeholders via the NICE scoping consultation and further discussion with clinical experts, EEPRU has defined the PICOS for HVCS for the microbiology-directed and risk-based empiric treatment pathways (Table 1). The PICOS refine the NICE scope, which is broad and reflects the license of cefiderocol, to reflect the HVCS.

Microbiology-directed treatment: In the microbiology-directed usage scenario, feedback from stakeholders and clinical experts indicated that cUTIs have high-prevalence and a slower clinical course

than, for example, HAP and VAP. They are also responsible for a high proportion of BSI, the reduction of which is a key priority for the National Health Service England (NHSE). cUTI infections were therefore selected as the infection site for the microbiology-directed HVCS, with additional analysis also provided for HAP/VAP in the microbiology-directed setting (MDS).

Clinical and stakeholder advice also indicated that cefiderocol would be reserved for infections with limited treatment options, where susceptibility is demonstrated. This suggests cefiderocol should be reserved to treat infections caused by carbapenemase-producing pathogens. As discussed in Section 4.2, cefiderocol is active against MBL and serine mechanisms, and against a wide range of pathogens. Based on clinical feedback, the patient group for the HVCS will be limited to patients with infections caused by MBL *Enterobacterales* and *Pseudomonas aeruginosa*, since there are extremely limited treatment options for patients with these infections, and feedback from clinicians suggested that they would like to preserve cefiderocol's effectiveness by restricting its use.

Cefiderocol can be used as a monotherapy but may also be used in combination with other treatments, as indicated by microbiology and gene testing. In clinical practice, alternative treatment options (comparators) would be defined by the results of susceptibility and gene testing.

Risk-based empiric treatment: In the risk-based empiric usage scenario, feedback from stakeholders and clinicians indicated that the most frequent clinically urgent infections are HAP/VAP and BSI. cUTI infections were not considered relevant in this setting since they have a slower clinical course, giving time for susceptibility testing and genetic testing to be performed. Given the time and resources available for this project, the focus will be on the HAP/VAP sites as this was considered the most common indication for empirical antibiotics in high risk patients such as those in the Intensive Care Unit (ICU) or High Dependency Unit (HDU) (whereas patients with BSI are more likely to have had microbiology). Patients will be those who have a high risk of an MBL *Enterobacterales* or *Pseudomonas aeruginosa* infection. Focusing on this high-risk group was highlighted by the clinical advisors to this project as preferable to considering a broader group of patients with suspected carbapenem resistance, even if deteriorating rapidly on current therapy, as the latter group would be difficult to define and may lead to high levels of prescribing with associated risks of resistance emergence. Three patient characteristics were considered as relevant by our clinical advisors in identifying patients at high risk of an MBL *Enterobacterales* or *Pseudomonas aeruginosa* infection: a high rate of MBL *Enterobacterales* or *Pseudomonas aeruginosa* in a health care setting where the patient was previously admitted, an outbreak of MBL *Enterobacterales* or *Pseudomonas aeruginosa* in the ward where the patient is currently admitted, or previous cultures (taken during the current or previous hospital stays) showing the patient was colonised by an MBL *Enterobacterales* or *Pseudomonas aeruginosa*. Cefiderocol may be used as monotherapy in this usage scenario, or may be used in combination with other treatments to provide a broader spectrum of coverage. A range of

comparators are relevant in this setting. Once microbiology has confirmed the susceptibility profile and mechanisms of resistance of the pathogen, treatment may be continued or stopped, dosage may be altered, or different AMs may be initiated.

Table 1: PICOS for the HVCS

Element	Microbiology-directed setting (MDS)	Risk-based empiric setting (ES)
Population - Patients	Where microbiological susceptibility testing with gene testing has been performed	With clinically urgent disease with high risk of an infection caused by a resistant pathogen. Suspicion of infection may be based on knowledge of the local epidemiology where a patient was previously hospitalised, outbreak in the ward where the patient is currently admitted, or previous cultures (taken during the current or previous hospital stays) showing the patient was colonised by MBL-producing <i>Enterobacterales</i> or <i>Pseudomonas aeruginosa</i> .
Population - Pathogen-mechanism	Infections (<i>Enterobacterales</i> and <i>Pseudomonas aeruginosa</i>) confirmed to be caused by MBL of the following subtypes: <ul style="list-style-type: none"> • NDM, VIM, IMP 	Infections (<i>Enterobacterales</i> or <i>Pseudomonas aeruginosa</i>) suspected to be caused by MBLs of the following subtypes: <ul style="list-style-type: none"> • NDM, VIM, IMP
Population - Site of infection	<ul style="list-style-type: none"> • Complicated urinary tract infection (cUTI) • Hospital associated pneumonia (HAP)/ventilator associated pneumonia (VAP) 	HAP/ VAP
Intervention	Cefiderocol alone or in combination	Cefiderocol alone or in combination
Comparators Please note: These comparators reflect NHS practice based on clinical advice. The available evidence determines which of those listed (and possible additional products including combinations) can be formally incorporated into the modelling	Comparators used in clinical practice in England, as defined by susceptibility testing and/or gene testing and considering infection site and infiltration data. Potential comparators include: <i>Enterobacterales</i>: <ul style="list-style-type: none"> • Tigecycline + colistin • Fosfomycin + colistin • Aztreonam + colistin • Aminoglycosides (gentamicin, amikacin, tobramycin) <i>Pseudomonas aeruginosa</i>: <ul style="list-style-type: none"> • Fosfomycin + colistin • Fosfomycin+ meropenem 	Comparators used in clinical practice in England, based on high risk of an infection, which include: <i>Enterobacterales</i>: <ul style="list-style-type: none"> • Tigecycline + colistin • Fosfomycin + colistin • Aztreonam + colistin • Aminoglycosides (gentamicin, amikacin, tobramycin) <i>Pseudomonas aeruginosa</i>: <ul style="list-style-type: none"> • Fosfomycin + colistin • Fosfomycin+ meropenem
Outcomes	The outcome measures to be considered include: <ul style="list-style-type: none"> • All-cause mortality 	Same as microbiology-directed setting

	<ul style="list-style-type: none"> • Clinical cure (complete resolution of signs/symptoms of the index infection such that no further AM therapy is needed) • Microbiologic eradication • Emergence of resistance • Hospital days • Intensive care unit (ICU) days • Readmission rate within 90 days of treatment • Number of treatment days • Health-related quality of life (HRQoL) • Adverse events (including those associated with <i>Clostridium Difficile</i> infection and renal toxicity) 	
Study designs	<p>The types of studies and data to be considered include:</p> <ul style="list-style-type: none"> • Randomised controlled trial (RCTs) • Observational studies • In-vitro susceptibility data • National, regional or international datasets • Pharmacokinetic and pharmacodynamic (PK/PD) 	Same as microbiology-directed setting

cUTI, complicated urinary tract infection; ES, empiric setting; HAP, hospital-acquired pneumonia; HRQoL, health-related quality of life; ICU, intensive care unit; IMP, Imipenemase; MBL, metallo-beta-lactamases; MDS, microbiology-directed setting; NDM, New Delhi MBL; PD, pharmacodynamics; PK, pharmacokinetics; RCTs, randomised controlled trials; VAP, ventilator-associated pneumonia; VIM, Verona integrated-encoded MBL

5. Clinical evidence

The evidence reviews reported within this section focus on the clinical evidence required to inform the patient-level component of the decision-analytic modelling. This includes estimating the comparative effectiveness of treatments, including both efficacy and safety, and the consequences of treatments in terms of long-term clinical outcomes, for both efficacy and safety. Clinical evidence that informs the population-level components of the analysis is described in Section 8.2.5 and 8.2.6.

5.1. Approaches to estimating comparative effectiveness

5.1.1. Sources of evidence

In comparison to a standard HTA, the data available for evaluating new AMs are less straightforward. This has been discussed in detail in EEPRU's framework.¹⁹ This is largely because the randomised controlled trial (RCT) evidence is primarily generated for regulatory purposes, to demonstrate safety and efficacy against a range of pathogens. Trials are usually non-inferiority in design (usually with a -10% margin), and the comparators tend to be best available therapy (BAT). Patients with extensively drug resistant infections, such as those with MBL infections, are usually excluded from these trials because it would be unethical to randomise patients to an ineffective comparator treatment, and testing patients to find out which treatments they are susceptible to could introduce critical time delays in treatment of very ill patients. Therefore, trials tend to recruit patients who are expected to be susceptible to the intervention and the comparator, i.e. not extensively drug resistant. The relative treatment effect generated by such trials cannot be generalised to resistant populations, since this would overestimate the efficacy of the comparators, as resistant patients are unlikely to respond as well to BAT. In addition, BAT within the trials may not match clinical practice in England since best practice is highly variable due to local protocols reflecting testing capacities and the microbiological epidemiology in a given area. Regulatory trials also do not tend to address differences in treatment pathways, such as are found between the MDS and risk-based ES, or differences in stewardship protocols, such as rotation of AMs, mixing treatments, or combination therapies. For the evaluation within the MDS, RCTs and observational studies are required that report outcomes in patients with the confirmed pathogen-mechanism combination of interest, whilst in the ES, patients will only be suspected of having an infection with the pathogen-mechanism combination of interest.

As such, from the outset, EEPRU were aware that additional sources of evidence may be required to fulfil the comparative effectiveness component, since it was unlikely that the RCTs would have been performed in patients with infections caused by the specific pathogen-mechanisms of interest. The next levels of evidence in the evidence hierarchy are non-randomised studies and observational studies. EEPRU's earlier work¹⁹ also highlighted the potential for using susceptibility studies to supplement

clinical data. We therefore aimed to identify all these possible sources of evidence in our review (see Section 5.2). In the next section, a brief description of susceptibility studies is provided, since this study design is one not commonly encountered. Following this, a discussion of how the different study designs might be used to produce effectiveness estimates is provided (Section 5.1.2).

5.1.1.1. Susceptibility studies, PK/PD studies and breakpoints

Susceptibility studies are *in vitro* studies that report the results of AM susceptibility testing (AST). AST is a laboratory method where isolates taken from patients (from infections, or during screening) are grown *in vitro* (cultured), and tested for their susceptibility to various AM treatments. The AM being tested is applied at increasing concentrations to separate cultures of the sampled isolate, and the degree to which microbial growth is inhibited at each concentration is assessed. The lowest concentration at which microbial growth is inhibited is known as the minimum inhibitory concentration (MIC).

Clinical breakpoints distinguish between isolates where there is a likelihood of treatment success from those where treatment is more likely to fail.²² If the MIC of a given isolate is at or below the breakpoint, the isolate is judged to be “susceptible” (S). If it is above the breakpoint, the isolate is judged to be “resistant” (R). For some AMs, there is also an intermediate category (I), which more recently has become “susceptible – increased exposure” indicating that a higher dose of the drug should be used to elicit a response. They may also report the concentration at which 50% of isolates were inhibited (MIC 50), and the concentration at which 90% were inhibited (MIC 90).

The methods for setting breakpoints are not standardised. Currently, they are generally set by considering²²:

- The PK data: how the body affects the drug with respect to absorption, distribution, metabolism, and excretion, usually obtained from studies in healthy volunteers
- The PD data: how the drug affects the body (efficacy and toxicity) at its site(s) of action, usually obtained from *in vitro* studies, hollow fibre studies, animal studies, and human studies. This data is used to set pharmacodynamic (PD) targets e.g. for time above MIC
- Mathematical models (e.g. Monte Carlo simulation) to assess the likelihood of achieving the targets suggested by the PD data
- Any available clinical data linking treatment to clinical outcomes (e.g. from RCTs or observational studies).

PK/PD studies are conducted to estimate how much drug will be available at the site of interest, and for what period of time at a given dose. One of its primary uses is by manufacturers and regulatory bodies to decide on the appropriate dose and dose frequency of the drug, such that it is likely to be available at concentrations that are likely to have an effect at the sites of interest.

There are two main organisations that set breakpoints, the CLSI in the US, and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in Europe. These two organisations use different methodologies to set breakpoints, leading to differences in the breakpoints set both in absolute and relative terms, between treatments. They also describe different laboratory methods to assess MICs. In addition, many labs may use commercial assays, conducted according to manufacturer's instructions. Clinical advisors to EEPRU indicated that it was unclear to what extent CLSI, EUCAST and commercial methods would produce the same absolute values, and in the event that values were different, whether relative values between treatments would also be different (i.e. the difference in absolute values was not consistent across treatments). In the UK, the British Society for Antimicrobial Chemotherapy (BSAC) now recommends use of EUCAST methods and breakpoints.

Susceptibility studies tend to report the proportion S, I and R, or list the number of isolates at each MIC. An example is given in Table 2. Here, for cefepime, the breakpoint is 1mg/L, and since all isolates had MICs higher than the breakpoint, none were susceptible. For cefiderocol, with a breakpoint of 8mg/L, 90.9% were susceptible, since only one isolate had a MIC above this point.

Table 2: Example of a susceptibility study data table

Treatment; Breakpoint	Number susceptible Cumulative % susceptible											
	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	Susceptible
Drug concentration (mg/L)												
Cefepime (n=11) BP: 1mg/L								4 36	3 64	1 73	3 100	0%
Meropenem (n=11) BP: 2mg/L	4 36	3 64	0 64	1 73	3 100							100%
cefiderocol (n=11) BP: 8mg/L	1 9	0 9	0 9	1 18	0 18	3 45	5 91	0 91	0 91	0 91	1 100	90.9%

BP, breakpoint

5.1.2. Producing comparative efficacy estimates

Three main approaches, relating to the three main types of evidence available were developed:

- **Approach 1:** Review RCTs for any subgroup data relating to the pathogen-mechanisms-sites defined in the HVCSs and use these estimates to inform the model. A network meta-analysis (NMA) would likely be needed to provide estimates for the intervention and comparators, and all these studies would also need to be in the pathogen-mechanisms-sites defined in the HVCSs.
- **Approach 2:** Construct a network of observational studies relating to the pathogen-mechanism-sites defined in the HVCSs, treated with cefiderocol and comparators. Individual patient data (IPD) data would be required for at least one study to adjust for confounders.
- **Approach 3:** Use susceptibility studies (see Section 5.1.1.1 above), i.e. those that have tested relevant treatments in MBL *Enterobacterales* and *Pseudomonas aeruginosa* isolates *in vitro*, to provide estimates of relative treatment effects. Conduct an NMA of susceptibility evidence if necessary, to link the intervention and its comparators. Link *in vitro* susceptibility to clinical outcomes. Two approaches to linking susceptibility to clinical outcomes were considered:
 - a) Assume that, for patients who are susceptible to the treatment they are given, clinical outcomes would be similar regardless of the treatment received
 - b) Assume that different treatments may result in different outcomes even amongst those susceptible to their treatment. Use evidence from an NMA of RCTs (in any susceptible pathogen-mechanism, not just those considered within our HVCS) to estimate differences in treatment outcomes amongst susceptible patients. These relative treatment effects would then be applied to the proportion susceptible to the intervention and comparators, taken from the susceptibility NMA or epidemiological data.

Each of these approaches has its own merits and challenges.

In Approach 1, the difficulties with recruiting resistant patients means subgroup data from RCTs may be underpowered and under-representative of the full spectrum of MBL *Enterobacterales* and *Pseudomonas aeruginosa* infections. Where available, however, they could provide estimates with high internal validity (low risk of bias). Equivalent data for comparators from RCTs may be missing in the pathogen-mechanism-sites of interest.

In Approach 2, comparative observational studies are often at high risk of confounding due to imbalances between prognostic and/or predictive factors at baseline, whilst comparisons across single arm studies would require advanced synthesis techniques to mitigate against any apparent imbalances. Results from such analyses can be prone to a high degree of uncertainty and there may be residual confounding, e.g. from imbalances in unknown or unobserved confounders. However, such studies may be able to include higher numbers of patients, since the barriers to recruitment described for RCTs are reduced.

In Approach 3, susceptibility studies have the advantage of testing all the treatments in the same sample of isolates, thereby reducing the chance of heterogeneity in patient samples between arms introducing

confounding. They also tend to include higher numbers of patients/isolates. However, any given susceptibility study will have its own distribution of susceptibilities for each treatment, which give rise to the comparative treatment effects as expressed by % susceptibility, and this may not match the susceptibility profile of pathogens circulating in the UK, or that are likely to circulate in the future. In addition, susceptibility studies are *in vitro*, and no clinical outcomes are reported. In order to use this approach in the model, additional evidence requirements would be created since susceptibility can be considered a surrogate endpoint. It would be necessary to link susceptibility to clinical outcomes such as clinical cure, 30-day mortality, 90-day mortality, hospital length of stay (LoS), long term mortality and recurrence of infections (see questions 4-6 below). As noted above, this approach would assume that, conditional upon susceptibility, clinical outcomes are similar across different AMs. An extension to this approach would be to use evidence from a NMA of RCTs (in broader populations than those considered within our HVCS) to estimate differences in treatment outcomes amongst susceptible patients regardless of the pathogen-mechanism they are infected by, but dependent on the AM they were treated with. This would assume that relative treatment effects between AMs are generalisable across pathogen-mechanisms, so long as patients were susceptible to the treatment they were given. For both approaches, these assumptions would need to be supported by empirical evidence and/or expert opinion.

5.2. Review questions

For each approach, a corresponding review question was developed. This section briefly states each review question, whilst Sections 5.3 to 5.5 describe the PICOS, methods of evidence retrieval and results for each question. Subsequently, Section 5.6 describes three additional reviews (Reviews 4-6) relating to Approach 3.

5.2.1. Review 1

Review question: Based on RCT evidence, what is the comparative effectiveness of the intervention and comparators in patients with cUTI or HAP/VAP caused by a MBL *Enterobacterales* or *Pseudomonas aeruginosa* infection?

As well as recruiting patients infected with the relevant pathogen-mechanism combination, the ideal study would be based on treatment in the UK or a country with a similar demographic and healthcare system, to reduce the impact of other factors on patient outcomes. Only evidence relating to the sites of interest would be relevant, since the risk of mortality and morbidity from infections at other sites is likely to be different.

5.2.2. Review 2

Review question: Based on observational studies, what is the comparative effectiveness of the intervention and comparators in patients with cUTI or HAP/VAP caused by a MBL *Enterobacterales* or *Pseudomonas aeruginosa* infection?

Again, as well as recruiting patients infected with the relevant pathogen-mechanism combination, the ideal study would include patients in the UK or a country with a similar demographic and healthcare system, and would be in the sites of interest.

5.2.3. Review 3

Review question: What is the comparative effectiveness of the treatment and comparators based on in-vitro susceptibility studies?

Because of their *in vitro* nature, and since clinical experts to EEPRU indicated that the site of the infection the isolate was obtained from was unlikely to affect the susceptibility profile of the infecting pathogen, isolates could be collected from any site.

Table 3 provides a summary of the alternative approaches to estimating comparative efficacy and safety.

Table 3: Summary of the approaches to estimating comparative efficacy and safety

Approach number	Studies designs	Review question and number	Analytical approach	Taken forward (with reasons)?	Further detail
1	RCTs	1. Based on RCT evidence, what is the comparative effectiveness of the intervention and comparators in patients with cUTI or HAP/VAP caused by a MBL <i>Enterobacterales</i> or <i>Pseudomonas aeruginosa</i> infection?	NMA to estimate comparative efficacy	No, insufficient evidence in patients with MBL <i>Enterobacterales</i> or <i>Pseudomonas aeruginosa</i> infections	Section 5.4.2
2	Observational studies	2. Based on observational studies, what is the comparative effectiveness of the intervention and comparators in patients with cUTI or HAP/VAP caused by a MBL <i>Enterobacterales</i> or <i>Pseudomonas aeruginosa</i> infection?	Matched analysis	No, small studies, data not reported specific to the sites of interest; IPD not available	Section 5.4.2
3	Susceptibility studies	3. What is the comparative effectiveness of the treatment and comparators based on in-vitro susceptibility studies in isolates with MBL <i>Enterobacterales</i> or <i>Pseudomonas aeruginosa</i> ?	NMA to estimate comparative efficacy from susceptibility studies; link susceptibility to clinical outcomes	Yes	Sections 5.4.3
	Any clinical study	4. What is the link between <i>in vitro</i> susceptibility and clinical outcomes from the published literature?			Sections 5.6.1
	Any clinical study	5. What is the long-term risk of mortality (and other outcomes) for patients with carbapenem-resistant cUTI or HAP/VAP?	To supplement approaches 1-3		Sections 5.6.2
	RCTs	6. What are the important safety implications of cefiderocol?	To supplement approaches 1-3		Sections 5.6.3

cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; MBL, metallo-beta-lactamase; NMA, network meta-analysis; RCTs, randomised controlled trials; VAP, ventilator-associated pneumonia

5.3. Review methods

Since review questions 1-3 were of central importance to estimating the comparative efficacy of treatments, a *de novo* search from database inception was undertaken to address all three questions. The nature and suitability of the evidence base was unknown but as already discussed, there was a strong expectation that RCT evidence would not be of high relevance, that is to say, would not have recruited

patients MBL *Enterobacterales* or *Pseudomonas aeruginosa* infections. It was also unclear at this stage to what extent multiple HVCSs (e.g. including BSI) might be addressed in the evaluation (see Table 4 below). Therefore, a map of the available evidence was first constructed to maintain flexibility, and to aid an informed focusing of the inclusion criteria as the project proceeded (see Table 5 below). This methodology has been used elsewhere, and is especially suited to topics such as this where the initial scope is broad.^{23,24} The map comprised data extraction of key study characteristics. It was based on systematic literature searches of key bibliographic databases (see 5.3.1 below) supplemented by evidence submitted by experts and stakeholders, including the submission received from Shionogi and data requests to PHE, Shionogi and Pfizer (who were participating in a concurrent EEPRU evaluation of CAZ-AVI). Evidence was then selected for further consideration according to a balance of relevance with study quality, as recommended in the Decision Support Unit Technical Support Document (TSD) 13²⁵. Where preferred sources did not yield data, additional focused searches were employed to ensure studies had not been missed or to fill evidence gaps. Where additional searches still did not yield data, elicitation was performed to fulfil the evidence requirement (see Section 6).

5.3.1. Search strategy

The search strategy comprised terms relating to the treatment (cefiderocol). Terms relating to case-reports, letters and (animals NOT humans) were used to narrow the search, but no other study design filters were applied.

The following electronic databases were searched from database inception:

- MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions: Ovid, 1946 to Present
- EMBASE: Ovid, 1980 to present
- The University of York Centre for Reviews and Dissemination (CRD) platform
 - Database of Abstracts of Reviews of Effects (DARE): CRD, 1994 to 2015
 - Health Technology Assessment Database (HTA): CRD, 1989 to 2018
 - NHS Economic Evaluation Database (NHS EED): CRD, 1972 to 2015

The search strategies are provided in Appendix 1.

In addition to the database searches, the following unpublished data was requested:

- Public Health England

Evidence on susceptibility to MBL *Enterobacterales* and *Pseudomonas aeruginosa* for cefiderocol and the comparators defined by the HVCS were requested from PHE. This is detailed in Appendix 2.

- Data request to Shionogi (see Appendix 2):

- **Submitted to NICE on 11th August 2021:** Any MBL *Enterobacterales* or PA susceptibility data they had access to, for cefiderocol and the HVCS comparators, specifically relating to SIDERO studies and studies reported in two other publications, at both CLSI and EUCAST breakpoints (see Section 5.1.1.1 for description of breakpoints).

As will become apparent in Section 5.4.3.2 insufficient evidence was identified relating to fosfomycin, one of the comparators. An additional focussed search for fosfomycin studies was conducted. Due to time constraints, the search was conducted in Pubmed only (see Appendix A1.1.2 for the search strategy) on 26th August 2021.

Two surveillance databases were also identified and queried for data that could be included in the review (AM Testing Leadership And Surveillance (ATLAS)²⁶ and SENTRY)²⁷ but neither currently lists cefiderocol in the open access portal.

5.3.2. Keyword mapping, study selection, data extraction and quality assessment

Citations retrieved by the search were uploaded in Endnote (Clarivate Analytics), deduplicated, and considered for inclusion in the review.

Keyword mapping: Citations that met the inclusion criteria listed in Table 4 were tagged in Endnote (Clarivate Analytics) by one reviewer, according to key study characteristics: treatment (cefiderocol); study design (RCT, observational, susceptibility, PK/PD); mechanism (MBL, other); pathogen (*Enterobacterales*, *Pseudomonas aeruginosa*, other); and site (cUTI, HAP/VAP, BSI, other). All potential sources of evidence, including RCTs, observational studies, *in vitro* studies and national, local or international datasets identified in the grey literature were included in this stage of mapping.

Key characteristics mapping: A subset of studies that met the inclusion criteria listed in Table 4 were selected for key characteristics tabulation by one reviewer. The full text of RCT and observational studies identified as being potentially relevant based on their title and abstract were consulted in the first instance, and studies were tabulated and assessed for relevance against the key characteristics mapping criteria, and for relevance to the model. Since an assessment of this map concluded that insufficient relevant *in vivo* evidence was identified (see Section 4.2), the next level of evidence (susceptibility studies) was also tabulated.

Key study characteristics tailored to the study designs of interest (e.g., sample size, population, pathogen, mechanism, site, outcomes reported, susceptibility methodology, see Appendix 3) were tabulated by one reviewer. Data relating to numeric outcomes were not extracted and quality assessment was not performed at this stage.

Study selection: The inclusion criteria for the mapping are listed in Table 4. At the final stage of study selection, only susceptibility studies were considered since other sources did not meet the requirements of the project. The reasons for this decision are detailed in Section 5.4.1. Advice was sought from clinical advisors to aid the assessment of the relevance of susceptibility studies to the HVCSs, and to inform the final selection of evidence. Factors including location, date of recruitment, sampling strategy, screening and outbreak populations, and susceptibility testing methodologies were considered, and decisions made (see Table 5). At this point a decision was made not to review the PK/PD data, since this data is reviewed when setting breakpoints, and since clinical advisors to EEPRU stated that since the treatment and comparators penetrate to the sites of interest it was therefore reasonable to link directly between susceptibility and clinical outcomes (see Table 4).

Due to time restrictions on the project, only studies reporting susceptibility to both cefiderocol and also to any one of the comparators listed in Table 1 were included. This is a pragmatic approach to evidence retrieval, since ideally all susceptibility data relating to all comparators would have been included in the evidence synthesis, but searches to identify this evidence would have been large. No studies reported combinations of AMs, the process for estimating efficacy for combination treatments using the results of the evidence synthesis are described in Section 8.2.3.2. Consequently, studies reporting susceptibility to both cefiderocol and also to any one of the comparators listed in Table 2 were included.

As mentioned previously (Section 5.3.1), no susceptibility data for fosfomycin were identified in the initial search and data requests, necessitating a separate search for studies relating to fosfomycin. This means a different approach has been taken for this comparator which may introduce bias if studies reporting data for fosfomycin are systematically different to those reporting cefiderocol. Studies were included if they met the inclusion criteria in Table 4, but reported data for fosfomycin and at least one comparator within the HVCSs.

Data extraction: Data sources selected for inclusion in the review were data extracted by one reviewer and extractions were checked by a second. The initial key characteristics tabulation was expanded to include numerical outcome data for the susceptibility studies, and data were checked by a second reviewer. Data sources not selected for use in the model or clinical review were tabulated and reasons for their exclusion provided but were not assessed further.

Quality assessment: Since there is no published quality assessment tool for susceptibility studies, a bespoke set of questions were developed and applied, relating to internal bias and relevance. This tool was developed by consulting two tools developed for the assessment of prevalence studies^{28,29} (since studies report the prevalence of susceptibility), the ROBINS-1 checklist³⁰ for non-randomised studies (since the studies are comparative, but non-randomised), Cochrane's RoB2³¹ tool (since the NMA will assume the study arms are equivalent to randomised arms of an RCT), and the Newcastle-Ottawa Scale³² (since these are observational studies). Questions from all tools were considered for inclusion, and

adapted to the specifics of this review. The tool was reviewed by other members of the reviewing team, but no further validation work was undertaken. The final tool is reported in Appendix 4. Risk of bias was assessed using this tool by one reviewer.

Table 4: Inclusion criteria at each stage of the mapping review

Characteristic	Keyword mapping*	Key characteristics tabulation*	Selection for synthesis
Population			
Patients	Adults or children	Adults	Isolates from adults or children recruited consecutively, purposively, by convenience or as part of another study, e.g. RCT Screening or invasive samples
Pathogen-mechanism	MDS: <i>MBL Enterobacterales</i> or <i>Pseudomonas aeruginosa</i> ; KPC <i>Enterobacterales</i> ** ES: suspected carbapenem-resistant <i>Enterobacterales</i> or <i>Pseudomonas aeruginosa</i> treated empirically	MDS: <i>MBL Enterobacterales</i> or <i>Pseudomonas aeruginosa</i> ; KPC <i>Enterobacterales</i> ** ES: suspected carbapenem-resistant <i>Enterobacterales</i> or <i>Pseudomonas aeruginosa</i> treated empirically	<i>MBL Enterobacterales</i> or <i>Pseudomonas aeruginosa</i>
Site of infection	RCTs: any site Observational studies and case-series: cUTI, HAP/VAP or BSI** Susceptibility studies: any site	RCTs, observational studies and case-series: cUTI, HAP/VAP Susceptibility studies: any site	Susceptibility studies: any site
Setting	MDS or ES	MDS or ES	Any country; UK, Europe, USA, Canada, Australia, Asia and Middle East have highest relevance
Intervention			
	Cefiderocol	Cefiderocol	Cefiderocol
Comparators			
	Any	Any	At least one of: colistin, meropenem, tigecycline, aztreonam, fosfomycin, gentamicin, amikacin, tobramycin
Outcomes			
	As listed in Section 3.2.4	As listed in Section 3.2.4	<i>In vitro</i> susceptibility reported as proportion susceptible (not including intermediate) according to EUCAST or CLSI criteria Studies only reporting MIC50 and/or MIC90 with range were excluded
Study designs			
	RCT, observational studies, case series,	RCT, observational studies, case series, susceptibility, PK/PD	Susceptibility studies where isolates were collected and tested retrospectively or prospectively

	susceptibility, PK/PD		
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Abbreviations: BSI, bloodstream infection;; CLSI, Clinical Laboratory Standards Institute; cUTI, complicated urinary tract infection; ES, empiric setting; EUCAST, European Committee on Antimicrobial Susceptibility Testing; HAP, hospital-acquired pneumonia; KPC, klebsiella pneumoniae carbapenemase; PK, pharmacokinetic; PD, pharmacodynamic; MBL, metallo-beta-lactamase MDS, microbiology-directed setting; MIC50, minimum inhibitory concentration 50%; MIC90, minimum inhibitory concentration 90%; RCT, randomised controlled trial; VAP, ventilator-associated pneumonia

* where it was not possible to tell if a study met the inclusion criteria from the title or abstract, the study remained included at this stage.

**included in mapping review, when scope was kept intentionally wide. Ultimately, the scope was narrowed to exclude studies only relating to these criteria

Table 5: Additional study selection and prioritisation criteria for the review of susceptibility, developed through clinical advice

Topic	Summary of clinical response
Location	Europe, USA, Canada, Australia, the Middle East and Asia have the most relevance since pathogens tend to arrive in the UK from these countries. South America to a lesser extent.
Date of recruitment	Studies from 2012 onwards have highest relevance. Likely to observe increases in resistance over time.
Sampling strategy and outbreaks	Consecutive sampling (which is often associated with studies of outbreaks) not necessarily more generalisable, since outbreaks will reflect a narrow spectrum of pathogens and may therefore underestimate diversity of susceptibility; multi-centre studies should be more reflective of the diversity of isolates and should include outbreaks proportionate to their occurrence.
Isolates from screening	These are relevant since they will reflect the diversity of susceptibility found. Development of an infection is not dependent on the pathogen or mechanism <i>per se</i> , and so screening samples should be generalizable to infected patients.
AM susceptibility testing laboratory methodologies	There are differences between EUCAST and CLSI methodologies (see Section 5.1.1.1), and it is unclear whether the two methodologies result in the same distribution of MICs at the same values for a given set of isolates. If the distribution or absolute values differ, the methodologies cannot be considered interchangeable. EEPRU were unable to identify any literature directly comparing the two methodologies for the treatments in the HVCSs and concluded methodologies could not be assumed to be interchangeable.
Breakpoints	Expert advice indicated that CLSI and EUCAST breakpoints differ and cannot be assumed to be interchangeable (see Section 5.1.1.1). It is unclear whether studies using EUCAST laboratory methods and breakpoints would return the same % susceptible as studies using CLSI laboratory methods and breakpoints. It cannot be assumed that breakpoints from one guideline can be applied where laboratory methods from the other guideline have been used.
PK/PD data	Clinical advisors stated that the methodologies for conducting PK/PD data are not standardised and it is difficult to ascertain whether a study has been conducted well. Since the breakpoints set by EUCAST and CLSI are based on an assessment of the available PK/PD data, and as long as the treatment is known to infiltrate the appropriate site, it is reasonable to assume that susceptibility can be linked directly to clinical outcomes without further explicit consideration of PK/PD evidence. The advisors stated that cefiderocol and the comparators for each site penetrate to the sites of interest and it was therefore considered unnecessary to review this data.

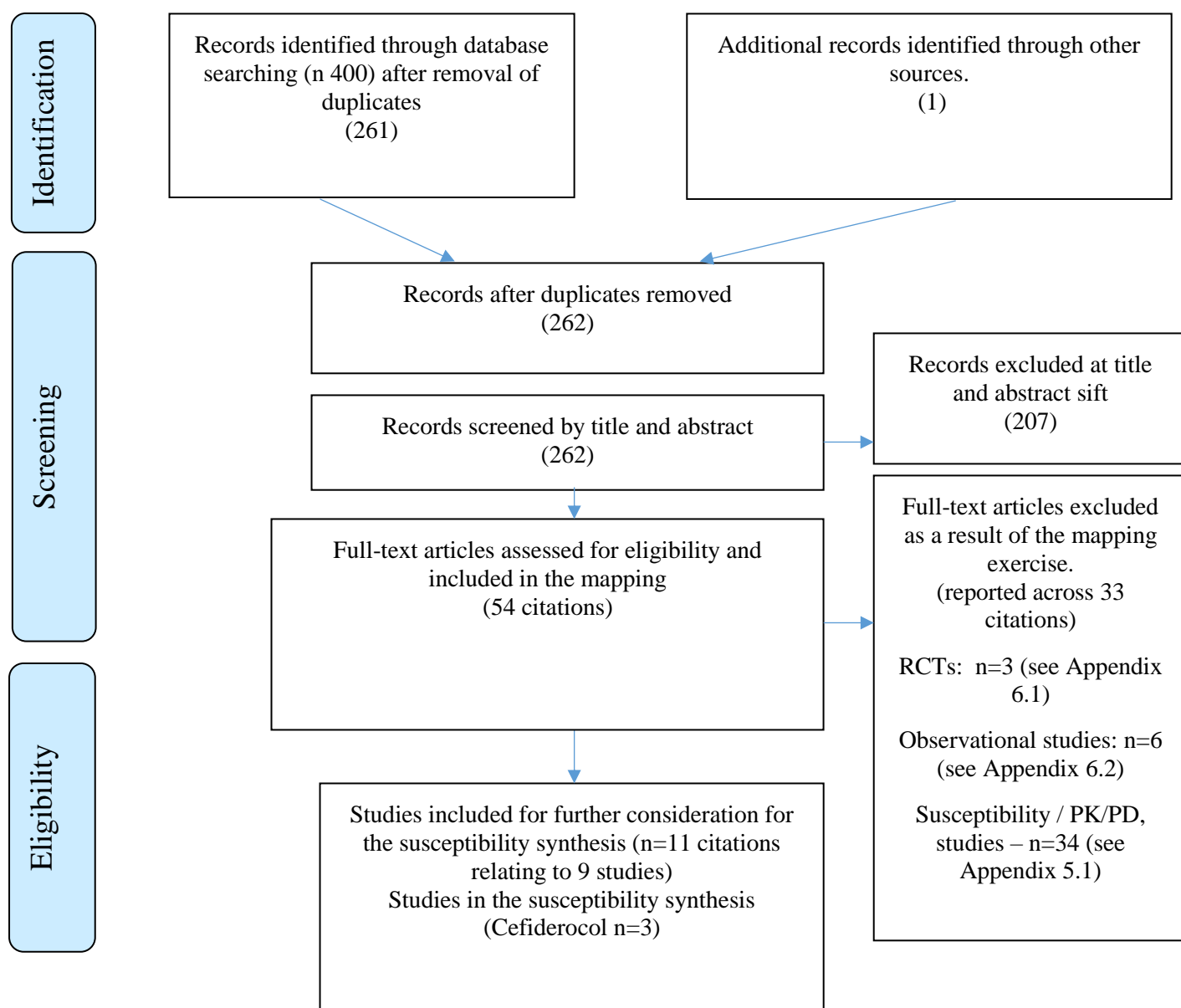
CLSI, Clinical Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibitory concentration; PK, pharmacokinetic; PD, pharmacodynamic

5.4. Review results

5.4.1. Study selection results (reviews 1-3)

The electronic database searches, following the removal of duplicates, identified 261 records relating to cefiderocol. One additional record was identified from the company submission. At this point, the decision was made to focus on *MBL Enterobacterales* or *Pseudomonas aeruginosa* infections in cUTI and HAP/VAP in the first instance and not to review PK/PD data (see Table 5). After examination of the title and abstracts, 207 records were excluded because they did not meet the inclusion criteria for the key characteristics mapping stage (see Table 4), whilst 54 records were included in the key characteristics map, and their full texts consulted. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram outlining the process of identifying relevant literature and the 9 included studies along with reasons for exclusion of full-text articles is provided in Figure 1.

Figure 1: PRISMA Flow diagram for the Cefiderocol Clinical Effectiveness Review



PD, pharmacodynamics; PK, pharmacokinetics; RCTs, randomised controlled trials

5.4.2. Reviews 1 and 2

The results of review questions 1 & 2 are reported in full in Appendix 6. A brief summary of the findings for each is provided here.

Review 1: Three RCTs in cUTI and HAP/VAP were identified (APEKS cUTI³³, APEKS NP¹³, CREDIBLE CR³⁴), but two excluded patients with carbapenem-resistant infections and therefore had low relevance to the HVCSs. No data was reported for patients with MBL infections in these two trials. CREDIBLE-CR³⁴ recruited patients with carbapenem-resistant infections, and reported subgroup data for patients with MBL infections. However, the subgroup was small, (n=16 in the cefiderocol arm, n=7 in the BAT arm) and was therefore not used due to the chance of baseline imbalances introducing bias. The RCTs indicated cefiderocol was an effective treatment in the sites of interest.

Review 2: Three³⁵⁻³⁷ observational studies reporting outcomes for patients with MBL infections treated with cefiderocol were identified. However, all reported infections across a range of sites, and in none of these was it possible to separate out patients with cUTI or HAP/VAP; there was insufficient time to obtain IPD. All studies were of a small sample size (range from n=2-17 patients) and were highly heterogeneous in terms of key characteristics that are prognostic and expected to modify treatment response (e.g. site, pathogen, treatment line), limiting the conclusions that could be drawn from them and increasing the likely uncertainty associated with any synthesis performed.

Approaches 1 and 2 could therefore not be pursued since there was a lack of evidence relating to cUTI and HAP/VAP infections caused by MBLs to inform an assessment of comparative effectiveness. Approach 3 was considered the most viable option, and reviews relating to this approach are described in the remainder of this chapter.

5.4.3. Review 3

5.4.3.1. Studies reporting the susceptibility of MBL *Enterobacterales* or *Pseudomonas aeruginosa* isolates to cefiderocol and at least one comparator

Since no RCTs or observational evidence was identified that met the requirements of the HVCSs, EEPRU considered the evidence relating to *in vitro* susceptibility. EEPRU's approach is supported by the company submission³⁸ which states that "*the in vitro data for cefiderocol should be considered the primary source of evidence to support the effectiveness and positioning of cefiderocol and is actually the only source of evidence for the risk-based empiric setting.*"

Of the 53 studies included as part of the mapping exercise, forty-four susceptibility or pharmacokinetic/pharmacodynamic (PK/PD) citations were considered. Of these, 33 citations were excluded (see

Appendix 5.1 for a list of excluded studies with reasons); the main reasons were no data reported by mechanism, only included PK/PD data, and did not include a relevant pathogen-mechanism). The three RCTs were also examined for relevant susceptibility data, but none were relevant to the susceptibility synthesis as they did not present data by mechanism. It is noted that the Shionogi company submission³⁸ recommends PK/PD evidence should be used alongside clinical and susceptibility data to extrapolate to other infection sites. However, the clinical advisors to EEPRU advised that as cefiderocol and comparators penetrate to the sites of interest, it was reasonable to link directly between susceptibility and clinical outcomes (see Table 5

Table). Furthermore, neither the Shionogi company submission nor discussion with the clinical advisors to EEPRU identified a quantitative approach to linking PK/PD evidence to clinical outcomes. Consequently, as part of the mapping exercise, PK/PD studies were excluded.

Nine susceptibility studies (reported over eleven publications, three³⁹⁻⁴¹ of which related to the same data as one other study and were therefore excluded)⁴² of cefiderocol were considered relevant for further appraisal against the factors for prioritisation for the susceptibility synthesis as described above. These studies are detailed in **Error! Reference source not found.**, with reasons for prioritisation or exclusion. Two^{43,44} were excluded since they reported less than 10 isolates, two^{45,46} were excluded as there was no data for relevant comparators, and one⁴⁷ was excluded since the only comparator was meropenem (see further discussion below). Ultimately, five studies met the inclusion criteria of the review.^{41,42,48-50} The characteristics of these studies are presented in Appendix 5.3.

EEPRU first considered whether any one of the studies met all the requirements of the evaluation (ideally consecutive English data from a multi-site study reporting outcomes for all relevant comparators, using BSAC/EUCAST breakpoints and laboratory methods), and could fulfil the evidence needs of the project without need of a meta-analysis. Since the PHE data did not report any evidence for cefiderocol this data was not able to fulfil the requirements of the project, and a meta-analysis of susceptibility studies was planned. There were also a number of other limitations to the PHE data. Isolates have not historically been routinely submitted by testing centres which may limit how representative this data is of the true distribution of MBL susceptibilities in England. In addition, there is inconsistency in the testing methodologies used by local laboratories (albeit the majority use EUCAST).⁵¹ Finally, not all isolates were tested for each comparator, and a compromise had to be made in conducting the analysis whereby to preserve internal validity only isolates tested amongst *all* comparators were included (see Appendix 2) which may have introduced selection bias. Given this approach we excluded PHE evidence for fosfomycin as this would have resulted in only 18 isolates being available for analysis across both MBL *Enterobacterales* and *Pseudomonas aeruginosa* populations.

There was some uncertainty during the development of the PICOS about whether meropenem should be considered a relevant comparator. This led to inconsistencies in the inclusion of evidence relating to

meropenem. Data from one study (Kohira *et al.* 2016⁴⁷) and the meropenem data from PHE was excluded erroneously from the synthesis. The sensitivity analyses performed to address this are described in Section 5.5.1.

5.4.3.2. Limitations of the data available from the published study reports

Two of the studies, Longshaw *et al.* (2020)⁴⁸ and Kazmierczak *et al.* (2019)⁴² drew isolates from SIDERO CR and SIDERO WT (wild type) respectively. These were surveillance studies conducted by Shionogi. The three further studies^{41,49,50} identified by the review were also funded by Shionogi.

EEPRU identified limitations with all five studies with respect to their relevance to the synthesis being conducted to inform estimates of relative effectiveness in the HVCS:

- Kazmierczak *et al.* (SIDERO WT)⁴² and Dobias *et al.*⁴⁹ only reported MIC50, MIC90 and range, not % susceptibility. Whilst these metrics could have been used to reconstruct the distribution curves and apply a breakpoint to generate an estimated % susceptibility, this was thought to introduce too much uncertainty to the estimates. In addition, not all three metrics were reported for all relevant subgroups in Kazmierczak *et al.* (SIDERO WT).⁴²
- Data from SIDERO CR (Longshaw *et al.* (2020))⁴⁸ covered only Europe, whereas the full data set used in Shionogi's response to a data request from EEPRU dated 14th June 2021 (see Appendix 2) used worldwide data. After consultation with our clinical advisers, it was decided that ideally we would include worldwide data in the synthesis since resistance mechanisms frequently arrive in the UK from elsewhere (see Table 5).
- Neither Johnston *et al.* (2020),⁵⁰ Kohira *et al.* (2016)⁴⁷, nor Dobias *et al.* (2017)⁴⁹ reported susceptibility using EUCAST breakpoints, only CLSI breakpoints.
- All four sources of data used CLSI laboratory methods, which may not be equivalent to EUCAST laboratory methods
- None of the studies included data for fosfomycin

Shionogi was approached to provide additional data to fulfil these requirements (Data request dated 11th August 2021, see Appendix 2) for all four studies. The request was for worldwide data, reporting % susceptibility using EUCAST and separately using CLSI breakpoints for cefiderocol and all relevant available comparators (in case data for fosfomycin was unpublished, but held by Shionogi). Shionogi supplied the requested analyses for SIDERO CR and SIDERO WT (see Table 6 below). The data were reported for *Enterobacterales* and *Pseudomonas aeruginosa* separately, and included isolates with carriage or co-carriage of MBLs. The data were not restricted by carbapenem sensitivity, or any other sensitivity or phenotype, and counted intermediate susceptibility as resistant, in accordance with

EEPRU's requirements. Data were reported using CLSI and EUCAST breakpoints, but using CLSI laboratory methods. No data for fosfomycin was available. The company were unable to provide additional data for Johnston et al. (2020)⁵⁰ or Dobias et al. (2017)⁴⁹ as they did not have access to the raw data. Therefore, Dobias et al (2017)⁴⁹ was excluded from the syntheses, whilst Johnston et al. (2020)⁵⁰ could only be included in a synthesis of data using CLSI breakpoints. Consequently, three studies (SIDERO CR, SIDERO WT and Johnston 2020)⁵⁰ of Cefiderocol were eligible for inclusion in the statistical synthesis. Due to the uncertainty around comparators, data for Kohira *et al.* (2016),⁴⁷ was not requested.

5.4.3.3. Characteristics of studies entering the NMA

Across the four cefiderocol studies, the sample size ranged from n=69⁴⁷ isolates to n=343⁵⁰ isolates. The cefiderocol studies collected isolates internationally, from multi-site locations. Expert advice indicated that resistant infections tend to arrive in the UK from around the world, and consequently isolates collected from any location were of relevance to the assessment. All studies were therefore retained in the analysis.

The isolates were collected since 2014 for the SIDERO studies, Johnston et al. (2020)⁵⁰ included isolates collected over the period 2002-2017 and Kohira *et al.* (2016)⁴⁷ included isolates from 2000-2011. Expert advice indicated that isolates collected since 2012 were of highest (but not exclusive) relevance, so all studies were retained in the analysis.

The PHE data did not meet the inclusion criteria for either the Cefiderocol or fosfomycin review since it did not report data for cefiderocol or fosfomycin. However, it was considered the best source of UK data for comparators, which were not well covered by the Cefiderocol review, so the PHE data were included for this reason.

Fosfomycin studies

The supplementary search for fosfomycin studies yielded 113 citations, 45 studies were considered at full text stage, and 10⁵²⁻⁶¹ studies were data extracted (see Table 6 below), and were eligible for inclusion in the statistical synthesis. The sample size ranged from n=7 to n=552 across the 10 fosfomycin studies. Studies were largely multi-site studies in a single country (Germany⁵⁶, Pakistan,⁵⁹ Brazil,⁵² Arabian Peninsula,⁶⁰ Singapore,⁶¹ USA⁵⁵), though one study drew from both Germany and Switzerland,⁵³ one was a single centre study from Poland,⁵⁸ and two were unclear.^{54,57} It should be noted that there are some limitations with these data, including:

- Neither EUCAST nor CLSI have set a breakpoint for fosfomycin in *Pseudomonas aeruginosa*. Both studies^{54,55} that reported susceptibility of fosfomycin in *Pseudomonas aeruginosa* isolates used epidemiological breakpoints (breakpoints that distinguish between wild type pathogens,

and those with acquired resistance)⁶² that do not, according to EUCAST, predict clinical susceptibility.

- Two of the studies^{52,55} did not use EUCAST or CLSI laboratory methods, but instead used a commercial assay (Etest).
- Criteria used to select isolates for inclusion in the study, and then for β -lactamase testing, were often not well described, meaning it is unclear to what extent the studies reflect the true distribution of susceptibility for the population they drew from.

Despite these limitations all studies were included since evidence was generally sparse across the network. These limitations should be noted when interpreting the results of the meta-analyses, especially with respect to the estimates for fosfomycin in PA.

Table 6: Study characteristics of the susceptibility studies entering the NMA

Study ID Funding	Country Multi-site? Year(s) of recruitment	N	Inclusion criteria/ β -lactamase testing selection criteria	% Mero non- susceptible	Laboratory methods Breakpoints	Included NMAs? in
Cefiderocol studies						
SIDERO CR (data request data)	Global Multi-site 2014-2016	305 (<i>Enterobacterales</i> 190; PA 115)	<i>Enterobacterales</i> and PA isolates from a surveillance collection with known AM susceptibility phenotypes and/or their species identification.	EUCAST: <i>Enterobacterales</i> 96.8%; PA 99.1% CLSI: <i>Enterobacterales</i> 100%; PA 100%	CLSI Data reported for both EUCAST and CLSI breakpoints	Y: CLSI <i>Enterobacterales</i> CLSI PA EUCAST <i>Enterobacterales</i> EUCAST PA
SIDERO WT (data request data)	Global Multi-site 2014	297 (<i>Enterobacterales</i> 131; PA 166)	Non-duplicate, non-consecutive isolates of Gram-negative bacilli	EUCAST: <i>Enterobacterales</i> 96.2%; PA 100% CLSI: <i>Enterobacterales</i> 99.3%; PA 100%	CLSI Data reported for both ECUAST and CLSI breakpoints	Y: CLSI <i>Enterobacterales</i> CLSI PA EUCAST <i>Enterobacterales</i> EUCAST PA
Johnston et al. (2020) ⁵⁰	Europe and North America 2002-2017	343 (all <i>Enterobacterales</i>)	Carbapenem-resistant (CR) clinical <i>E.</i> <i>coli</i> isolates	100%	CLSI CLSI; FDA for Cefiderocol	Y: CLSI <i>Enterobacterales</i>
Kohira 2016 ⁴⁷	International Multisite 2000-2011	NDM n=49 VIM n=12 IMP n=8	Unclear how selected for inclusion or for β -lactamase testing	17.4%	CLSI CLSI	Y, CLSI CPE
Fosfomycin studies						
EUCAST <i>Enterobacterales</i>						
Chakraborti et al. (2021) ⁵³	Switzerland and Germany Multisite 2018-2019	NDM n=30 (excluded n=3 from sewer, dog, river)	Unclear how selected from the surveillance study for inclusion in analysis	NR	NR EUCAST	Y: EUCAST <i>Enterobacterales</i>
Kaase et al 2015 ⁵⁶	Germany Multisite 2009-2014	VIM n=36	Voluntary submission of isolates from German laboratories, all tested for VIM, IMP and NDM by PCR	86.1%	EUCAST EUCAST	Y: EUCAST <i>Enterobacterales</i>

Study ID Funding	Country Multi-site? Year(s) of recruitment	N	Inclusion criteria/ β -lactamase testing selection criteria	% Mero non- susceptible	Laboratory methods Breakpoints	Included NMAs? in
Livermore et al. (2011) ⁵⁷	UK Unclear Unclear (pre 2011)	IMP n=13 NDM n=17 VIM n=5	Unclear how selected for inclusion, “diversity of carbapenem resistance types”	NR (but all CR)	CLSI EUCAST	Y: EUCAST <i>Enterobacterales</i>
Ojdana et al. 2019 ⁵⁸	Poland Single site 2009-2014	NDM n=10	Isolates selected for testing according to EUCAST carbapenemase screening protocol	NR (but all C non-susceptible)	EUCAST EUCAST	Y: EUCAST <i>Enterobacterales</i>
Perry et al. (2011) ⁵⁹	Pakistan Multisite 2010	NDM1 n=64	Unclear how all isolates selected, some by random selection. All Gram-negative tested for VIM, IMP and NDM	30%	EUCAST EUCAST, or if not available for a treatment, CLSI	Y: EUCAST <i>Enterobacterales</i>
EUCAST PA						
Cuba et al. (2020) ⁵⁴	Unclear Unclear Unclear	IMP n=4 VIM n=3	Unclear how selected for inclusion	100%	EUCAST EUCAST	Y: EUCAST PA
CLSI <i>Enterobacterales</i>						
Aires et al. (2017) ⁵²	Brazil Multisite 2013-2014	NDM n=16	Unclear how selected for inclusion, selected for β -lactamase testing using EDTA, phenyl boronic acid and <i>in vitro</i> analysis of imipenem hydrolysis	100%	eTest for mero, tig; agar dilution for others CLSI (except TIG-EUCAST)	Y: CLSI <i>Enterobacterales</i>
Sonnevend et al. (2020) ⁶⁰	Arabian Peninsula Multisite 2009-2017	MBL (NDM, VIM, IMP) n=552	All isolates received at laboratory were eligible, but unclear how selected for β -lactamase testing	100%	NR CLSI	Y: CLSI <i>Enterobacterales</i>
Vasso et al. (2015) ⁶¹	Singapore Multisite NR	<i>Enterobacterales</i> NDM n=32 IMP n=11	Unclear how selected for inclusion	90.7%	CLSI CLSI	Y: CLSI <i>Enterobacterales</i>
CLSI PA						
Jahan et al. (2021) ⁵⁵	USA Multisite 2016	PA n=20	20 genetically unique MBLs selected from CDC and FDA AM resistance bank, unclear how selected for inclusion in the bank	NR	Etest CLSI	Y: CLSI PA

Study ID Funding	Country Multi-site? Year(s) of recruitment	N	Inclusion criteria/ β -lactamase testing selection criteria	% Mero non- susceptible	Laboratory methods Breakpoints	Included NMAs? in
PHE data						
PHE data	UK, multi-site 2014-2021*	N=159	<i>Enterobacterales</i> isolates submitted to PHE AMRHAI with suspected carbapenem resistance and tested for all comparators	5.0%	Unclear Unclear	Y: EUCAST <i>Enterobacterales</i> EUCAST PA

CLSI, Clinical Laboratory Standards Institute; CPE, carbapenemases-producing *Enterobacterales*; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, Food and Drug Administration; IMP, Imipenemase; MBL, metallo-beta-lactamases; NDM, New Delhi MBL; NR, not reported; PA, *Pseudomonas aeruginosa*; UK, United Kingdom; VIM, Verona integrated-encoded MBL

5.4.3.4. Quality assessment of studies entering the meta-analysis

No study scored low risk for all items.

Amongst the cefiderocol studies, CLSI laboratory methods were used but EUCAST breakpoints applied in three of four studies, and CLSI methods and breakpoints were used in the fourth. These issues led to a high risk of bias in “Outcome measurement” compared to practice in England. All four scored unclear risk for “Target population” and “Sampling strategy”, largely due to a lack of clarity about how isolates were selected for inclusion in the data request response, or how they were selected for β -lactamase testing from the wider population. All scored low risk for missing data, since all isolates were tested for all comparators.

Amongst the fosfomycin studies, only one scored low risk for “Target population”, whilst the remainder scored unclear high risk, largely due to a lack of clarity around how isolates were selected for β -lactamase testing, and whether isolates collected before 2012 would impact on susceptibility estimates. All studies scored unclear risk for “sampling strategy”, usually because it was not stated how isolates were selected, or where it was reported, it was not clear whether the strategy was appropriate. Outcome measurement was either low or unclear risk, due to a lack of clarity around laboratory methods. All scored low risk for missing data, since all isolates were tested for all comparators.

The PHE data was unclear on all domains, since PHE were unable to ascertain how isolates were tested, it was unclear what criteria led to submission of isolates, and it was unclear whether isolates were selected for testing of some interventions on the basis of suspected resistance or susceptibility, which may introduce selection bias.

Table 7 Reviewer judgement of risk of bias in studies included in the meta-analysis, according to a bespoke tool

Study ID	1. Target population						2. Sampling strategy:		3. Outcome measurement				4. Missing data	
	Is the target population of the study broadly appropriate to the HVCS?	Were isolates selected based on resistance to comparators?	Were all isolates tested for the pathogen - mechanism of interest in a standard way, and does this match the HVCS?	Was the beta-lactamase test appropriate?	Were data collected over an appropriate time period?	Overall judgment	Were isolates sampled from the target population in an appropriate way?	Overall judgment	Was susceptibility measured in an appropriate, standard way?	Does the study demonstrate selective analysis reporting, with respect to S, I and R?	Were S, I and R reported consistently for all treatments?	Overall judgment	Is there a risk of bias from missing data?	Overall judgment
Cefiderocol studies														
SIDERO CR (data request data)	L	U	U	L	L	U	U	U	H	L	L	H	L	L
SIDERO WT (data request data)	L	U	U	L	L	U	U	U	H	L	L	H	L	L
Johnston et al. (2020) ⁵⁰	L	U	L	L	U	U	U	U	H	L	L	H	L	L
Kohira 2016 ⁴⁷	L	U	U	U	U	U	U	U	U	L	L	U	L	L
Fosfomycin studies														

EUCAST CPE														
Chakraborti et al. (2021) ⁵³	L	L	L	L	L	L	U	U	L	L	L	L	L	L
Kaase et al 2015 ⁵⁶	L	L	U	L	U	U	U	U	L	L	L	L	L	L
Livermore et al. (2011) ⁵⁷	U	L	L	L	U	U	U	U	U	L	L	U	L	L
Ojdana et al 2019 ⁵⁸	L	L	U	L	L	U	U	U	L	L	L	L	L	L
Perry et al. (2011) ⁵⁹	L	L	L	L	U	U	U	U	U	L	L	U	L	L
EUCAST PA														
Cuba et al. (2020) ⁵⁴	L	L	L	U	U	U	U	H	L	L	L	L	L	L
CLSI CPE														
Aires et al. (2017) ⁵²	L	L	U	L	L	L	U	U	U	L	L	U	L	L
Sonnevend et al. (2020) ⁶⁰	L	L	L	L	U	U	U	U	U	L	L	U	L	L
Vasso et al. (2015) ⁶¹	L	L	L	U	U	U	U	U	U	L	L	L	L	L
CLSI PA														
Jahan et al. (2021) ⁵⁵	L	L	L	L	U	U	U	U	U	L	L	L	L	L

PHE data														
PHE data	U	U	L	U	L	U	U	U	U	L	L	U	U	U

CLSI, Clinical Laboratory Standards Institute; CPE, carbapenemases-producing Enterobacterales; EUCAST, European Committee on Antimicrobial Susceptibility Testing; H, high risk of bias; HVCS, high value clinical scenario; I, intermediate or increased exposure; L, low risk of bias; PA, *Pseudomonas aeruginosa*; R, resistant; S, susceptible; U, unclear risk of bias

5.5. Statistical synthesis

5.5.1. Statistical synthesis plan

A NMA was planned to synthesise susceptibility studies identified by the review. Several sources of clinical heterogeneity were identified through the quality assessment and consideration of the study characteristics. As detailed in

Table , location, and whether the sample included screened isolates were not considered to be important sources of heterogeneity by clinical advisors. This section details the source of heterogeneity that was considered potentially important, the reasons why it was considered important, and the sensitivity analyses planned relating to these. A summary of the planned analyses is provided in bullet points at the end of this section. Section □ details the statistical methods used to conduct the NMA, whilst Sections 5.5.3-5.5.4 reports which studies entered each analysis, the results of these analyses, and which were used in the decision analytic model.

Susceptibility testing methodology: There were two main issues with respect to the susceptibility testing methodology used in the available evidence. The first relates to which breakpoints are used in England and the second relates to the breakpoint used for cefiderocol.

Breakpoints used in England: As detailed in Table 5, it cannot be assumed that all laboratory methods and breakpoints are interchangeable. In England, BSAC guidelines have recommend since 2016⁶³ that laboratories should use EUCAST laboratory methods and breakpoints. Therefore, currently in England, studies using EUCAST methods and breakpoints should have the highest clinical relevance. However, in their response to EEPRU's data request, PHE noted that not all English laboratories comply with BSAC guidelines, and it is unclear to what extent CLSI and potentially other methods, implemented by commercial assays, may have been included in the PHE data.

Breakpoint used for cefiderocol: Shionogi noted that the EUCAST breakpoint for cefiderocol is 2mg/L whilst the CLSI breakpoint is 4mg/L. The company also stated that negotiations were underway with EUCAST to change the breakpoint to 2mg/L. However, at the time of writing no change had been made. Since it was also unclear whether CLSI and EUCAST breakpoints are (and have been) the same for all comparators, it would have been inappropriate to mix CLSI breakpoints and EUCAST breakpoints within one data set as this may affect the relative efficacy reported, especially given the difference in the cefiderocol breakpoint between EUCAST and CLSI.

EEPRU therefore planned to conduct NMAs for EUCAST and CLSI breakpoints separately. Since PHE data was of high relevance and included data for comparators, and since guidelines in England

recommend EUCAST breakpoints, the base case analysis was to include EUCAST breakpoints, and data from PHE. A sensitivity analysis was planned including only studies using CLSI breakpoints, including the higher 4mg/L breakpoint for cefiderocol.

***Pseudomonas aeruginosa* and *Enterobacterales* isolates:** Since *Enterobacterales* and *Pseudomonas aeruginosa* have different resistance profiles due to innate resistance or acquired resistance other than that due to MBLs, EEPRU planned to conduct NMAs for each separately.

Sources of data: Three sources of data contributed to the networks: studies identified by the review of cefiderocol and related data requests; studies identified by the review of fosfomycin studies; and the PHE data. Since ideally the systematic review would have included systematic searches for all studies of all comparators in one network, there was some disparity in how the studies of fosfomycin had been identified compared to the other comparators, which may have introduced bias. Equally, the PHE data and fosfomycin studies did not, strictly speaking, meet the inclusion criteria for the review, since they did not report estimates for cefiderocol. Therefore, EEPRU planned analyses to test the impact of the inclusion of data not meeting the inclusion criteria in the economic model. Since PHE data was of high relevance, this data alone would be used wherever possible to inform the susceptibility for the comparators in a scenario analysis. The relative effect estimates for cefiderocol and fosfomycin (which are missing from the PHE data) could then come from one of two sources: a network including all three sources of data; or a network including only cefiderocol or only fosfomycin studies respectively. Therefore, an analysis of studies reporting cefiderocol susceptibility and a separate analysis of studies reporting fosfomycin data were planned to provide the relative effects to apply to the PHE data.

Comparators included in the network: Initially, when developing the HVCS PICOS it was anticipated that in the ES, it would be unclear which pathogen was responsible for the infection. EEPRU therefore conducted the NMA including all comparators indicated for either MBL *Enterobacterales* or *Pseudomonas aeruginosa*. However, during the course of the project the ES HVCS was focused on patients where there was a high suspicion of the causative pathogen-mechanism, leading to a change in the PICOS. This led to two analyses being conducted. One with all comparators included, and a sensitivity analysis with only the comparators relevant to the pathogen-mechanism included. For the *Enterobacterales* networks, this sensitivity analysis meant removing meropenem, and for the *Pseudomonas aeruginosa* networks this meant removing aztreonam, tigecycline and gentamicin (since data were not available for amikacin and tobramycin). However, due to inconsistencies in the application of this decision, data from one study (Kohira *et al.* 2016⁴⁷) and the meropenem data from PHE were excluded erroneously from analyses conducted including all comparators. This affected the CLSI and EUCAST *Enterobacterales* networks respectively (see bullet points below). Therefore, a sensitivity analysis was conducted to re-include the missing data.

In summary, the following analyses were planned:

Main analysis:

- *Enterobacterales* network including all studies using EUCAST breakpoints
 - *Additional analysis including the missing meropenem data from PHE*
 - *Additional analysis using only comparators specific to the pathogen*
- *Pseudomonas aeruginosa* network including all studies using EUCAST breakpoints
 - *Additional analysis using only comparators specific to the pathogen*

Sensitivity analyses

- *Enterobacterales* network including all studies using CLSI breakpoints
 - *Additional analysis including the missing data from Kohira et al. 2016⁴⁷*
 - *Additional analysis using only comparators specific to the pathogen*
- *Pseudomonas aeruginosa* network including all studies using CLSI breakpoints
 - *Additional analysis using only comparators specific to the pathogen*

Additional analyses for use in the economic model

- Cefiderocol studies using EUCAST breakpoints and separately using CLSI breakpoints
 - *Additional analysis using only comparators specific to the pathogen*
- Fosfomycin studies using EUCAST breakpoints and separately using CLSI breakpoints
 - *Additional analysis using only comparators specific to the pathogen*

5.5.2. Statistical synthesis methods for review question 3

An NMA was conducted to determine the relative susceptibility of cefiderocol and listed comparators. The data generation process was assumed to follow a Binomial likelihood with probabilities modelled using a logit link function. Random effect (RE) models were assumed to allow for expected between study heterogeneity in relative effects. Further details of the statistical model are given in Appendix 7.1.

All analyses were conducted in the freely available software package WinBUGS and R using the R2Winbugs interface package. Code was modified from NICE TSD 2 example 1c (RE models).⁶⁴

Convergence to the target posterior distributions was assessed using the Gelman-Rubin statistic, as modified by Brooks and Gelman, for two chains with different initial values. For all outcomes, a burn-in of 80,000 iterations of the Markov chain was used with a further 20,000 iterations retained to estimate parameters using one chain and thinning every 5 iterations.

The absolute goodness of fit was checked by comparing the total residual deviance to the total number of data points included in an analysis. The deviance information criterion (DIC) provides a relative measure of goodness-of-fit that penalises complexity and was used to compare different models for the same likelihood and data. Lower values of DIC are favourable, suggesting a more parsimonious model.

Inconsistency between direct and indirect evidence can arise because of an imbalance in treatment effect modifiers across studies comparing different pairs of treatments.^{65,66} Consistency between direct and indirect evidence can be assessed where there are “loops” of evidence in the network informed by separate, independent trials, so that both direct and indirect estimates are available.

Inconsistency was assessed by fitting unrelated mean effects (UME) models, based on code from NICE TSD4.⁶⁵ In the UME model the direct and indirect relative treatment effects are not constrained to be consistent with each other. This is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast and with a common variance parameter in RE models. To explore whether the direct and indirect evidence for particular treatment comparisons is inconsistent, the contribution to the posterior mean residual deviance was plotted for the UME model against the NMA model in a deviance contribution plot.^{65,66}

Results are presented using the posterior median treatment effects, 95% credible intervals (CrI) and 95% prediction intervals (PrI). The 95% PrI indicates the extent of between study heterogeneity by illustrating the range of odds ratios (ORs) that might be expected in a future study. Probabilities of treatment rankings were computed by counting the proportion of iterations of the Markov chain in which each intervention had each rank. Median treatment rankings and the probabilities of each treatment being the best treatment (i.e., ranks the first) are presented.

The estimated between study standard deviation (SD) for each analysis is also presented. Values below 0.05 is considered to indicate low heterogeneity. Values between 0.05 and 0.5 is considered to indicate moderate heterogeneity. Values between 0.5 and 1.0 is considered to indicate high heterogeneity. Values above 1.0 are considered to indicate extremely high heterogeneity.

In the case of zero events, a continuity correction was applied by adding 1 to the denominator and 0.5 to the numerator as suggested as a solution by NICE Decision Support Unit TSD2 to stabilise the results.⁶⁴

5.5.3. Susceptibility data entering the NMA

Table 8 (A-D) presents the susceptibility data from the four Cefiderocol studies (SIDERO CR, SIDERO WT, Johnston 2020, Kohira 2016⁴¹)⁵⁰ the 10⁵²⁻⁶¹ fosfomycin studies and the PHE data included in the NMA. Considering the absolute data, susceptibility to cefiderocol was highest in the *Pseudomonas aeruginosa* subgroups (96.9% to 99.1% in the *Pseudomonas aeruginosa* EUCAST network and 100% in both studies for the *Pseudomonas aeruginosa* CLSI subgroup). It was lowest in the *Enterobacterales* EUCAST subgroup (64.7% and 65.6%), but higher in the *Enterobacterales* CLSI subgroup (70.1% to 97.7%), where the breakpoint for cefiderocol is 4mg/L (compared to 2mg/L set by EUCAST).

The separate search for fosfomycin studies provided five data points for the *Enterobacterales* EUCAST network and three studies for the *Enterobacterales* CLSI network, but only one study for each of the *Pseudomonas aeruginosa* EUCAST and CLSI networks, with relatively small numbers (n=7 and n=20 respectively).

In the *Enterobacterales* subgroups, colistin generally had high susceptibility in both the EUCAST (80.9% in the SIDERO WT study to 100%)^{53,56} and CLSI (78.6% in the SIDERO WT study to 90.7%)⁶¹ subgroups. However, in comparison to cefiderocol colistin had lower susceptibility in the *Enterobacterales* CLSI subgroup whereas in the *Enterobacterales* EUCAST subgroup it had higher susceptibility. Fosfomycin also had generally good susceptibility in both subgroups (EUCAST 40.0%⁵⁸ to 100%^{53,56} (four out of five studies >74.3%);⁵⁷ CLSI 76.7%⁶¹ to 93.8%).⁵²

In the *Pseudomonas aeruginosa* subgroups, susceptibility estimates for colistin (98.1% in the SIDERO WT data to 100% in the PHE data and SIDERO CR data) were comparable to cefiderocol (96.9% in SIDERO WT to 99.1% in SIDERO CR) in the EUCAST subgroup but lower than cefiderocol in the CLSI subgroup (colistin 80.7% in the SIDERO WT study to 100%,⁵⁵ cefiderocol 100% in both studies). Fosfomycin had very different susceptibility in the EUCAST subgroup (14.3%) compared to the CLSI subgroup (80.0%), which may be due to chance since there was only one small study in each subgroup.

Table 8 Susceptibility data for studies of Cefiderocol and Fosfomycin, and PHE data included in the EUCAST NMA

A) Enterobacterales EUCAST Network

Study ID	N	% susceptible (number in analysis if different from N)								
		Cefi	Col	Mer	Tig	Az	Fos	Aminoglycosides		
								Gent	Ami	Tob
Cefiderocol Studies										
SIDERO CR (data request)	190	64.7	87.9	3.2						
SIDERO WT (data request)	131	65.6	80.9	3.8						
Fosfomycin studies										
Chakraborti et al. (2021) ⁵³	30		100		100		100			
Kaase et al 2015 ⁵⁶	36		100	13.9	94.4	55.6	100	77.8	100	52.8
Livermore et al. (2011) ⁵⁷	35		94.3		51.4		74.3			
Ojdana et al 2019 ⁵⁸	10				100		40.0			
Perry et al. (2011) ⁵⁹	64		96.9	29.7	89	6.25	93.8	21.9	20.3	
PHE data										
PHE data	159		86.2	5.0	73	25		16.4	36.5	6.3

Ami, amikacin; Az, aztreonam; Cefi, cefiderocol; col, colistin; Fos, fosfomycin; Gent, gentamicin; mer, meropenem; N, number; Tig, tigecycline; Tob, tobramycin

B) Pseudomonas aeruginosa EUCAST network

Study ID	N	% susceptible (number in analysis if different from N)								
		Cefi	Col	Mer	Tig	Az	Fos	Aminoglycosides		
Funding								Gent	Ami	Tob
Cefiderocol Studies										
SIDERO CR (data request)	115	99.1	100	0.87						
SIDERO WT (data request)	166	96.9	98.1	0						
Fosfomycin studies										
Cuba et al. (2020) ⁵⁴	7			0		0	14.3			
PHE data										
PHE data	86		100	0						

Ami, amikacin; Az, aztreonam; Cefi, cefiderocol; col, colistin; Fos, fosfomycin; Gent, gentamicin; mer, meropenem; N, number; Tig, tigecycline; Tob, tobramycin

NB: comparators not included in the HVCS for this subgroup are in grey

C) *Enterobacteriales* CLSI network

Study ID	N	% susceptible (number in analysis if different from N)								
		Cefi	Col	Mer	Tig	Az	Fos	Aminoglycosides		
Funding								Gent	Ami	Tob
Cefiderocol Studies										
SIDERO CR (data request)	190	91.1	85.3	0						
SIDERO WT (data request)	131	97.7	78.6	0.7						
Johnston et al. (2020) ⁵⁰	64	70.3	0	3.1						
Kohira 2016 ⁴¹	69	89.9		17.4						
Fosfomycin studies										
Aires et al. (2017) ⁵²	16			0	68.8	68.8	93.8	75	81.3	
Sonnevend et al. (2020) ⁶⁰	552		82	0	57.2	5.6	81.0	27.7	32.6	
Vasso et al. (2015) ⁶¹	43		90.7	9.3	65.1	11.6	76.7	11.6	51.2	9.3

Ami, amikacin; Az, aztreonam; Cefi, cefiderocol; col, colistin; Fos, fosfomycin; Gent, gentamicin; mer, meropenem; N, number; Tig, tigecycline; Tob, tobramycin

NB: PHE did not report data using CLSI breakpoints, and was therefore excluded from the CLSI analyses.

D) *Pseudomonas aeruginosa* CLSI Network

Study ID	N	% susceptible (number in analysis if different from N)								
		Cefi	Col	Mer	Tig	Az	Fos	Aminoglycosides		
Funding								Gent	Ami	Tob
Cefiderocol Studies										
SIDERO CR (data request)	115	100	94.8	0						
SIDERO WT (data request)	166	100	80.7	0						
Fosfomycin studies										
Jahan et al. (2021) ⁵⁵	20		100	0		45	80	5		

Ami, amikacin; Az, aztreonam; Cefi, cefiderocol; col, colistin; Fos, fosfomycin; Gent, gentamicin; mer, meropenem; N, number; Tig, tigecycline; Tob, tobramycin

NB: PHE did not report data using CLSI breakpoints, and was therefore excluded from the CLSI analyses.

5.5.4. Results of the NMA

Summaries of the results of the base case and sensitivity NMAs performed are presented in Table 9 and Table 10. Sections 5.5.4.1 to 5.5.4.3 provide more detail about these analyses.

Table 9 Summary of the base case and sensitivity NMAs performed to estimate the odds ratio for cefiderocol and comparators

Analysis	Scenario	Cefiderocol OR	Comparators	Section in report	Section in appendices
EUCAST <i>Enterobacterales</i>	All comparators, missing PHE meropenem data	0.32, 95% CrI: 0.04 to 2.47	See Figure 3	5.5.4.1	NA
	All comparators, including PHE meropenem data	0.31, CrI: 0.04 to 2.18	Similar OR for comparators as for “all comparators” analysis		
	Only comparators specific to the pathogen*	0.34, CrI: 0.05 to 1.97			
	<i>Using only studies that report cefiderocol data (SIDERO)</i>	<i>0.33, 95% CrI: 0.06 to 1.65</i>	NA – only cefiderocol OR used	5.5.4.3	Appendix 7.3.1.1, forest plot in Figure A7.2
	Using only studies that report cefiderocol data (SIDERO), and only including in the network comparators specific to the pathogen *	0.33 95% CrI 0.039 to 2.916	NA – only cefiderocol OR used	5.5.4.3	Appendix 7.3.1.1, no plot generated
EUCAST <i>Pseudomonas aeruginosa</i>	All comparators	0.44 95% CrI: 0.03, 3.94	See Figure 5	5.5.4.2	NA
	Only comparators specific to the pathogen*	0.44, CrI: 0.03 to 4.08	Similar OR for comparators as for “all comparators” analysis	Not presented	
	<i>Using only studies that report cefiderocol data (SIDERO)</i>	<i>0.49, 95% CrI: 0.03 to 5.29</i>	NA – only cefiderocol OR used	5.5.4.3	Appendix 7.3.1.2, forest plot in Figure A7.3
	Using only studies that report cefiderocol data (SIDERO), and only including in the network comparators specific to the pathogen	This network is the same as the “Using only SIDERO studies” network			
CLSI <i>Enterobacterales</i>	<i>All comparators, missing Kohira et al. data</i>	<i>1.38, 95% CrI: 0.16 to 12.05</i>	<i>See Figure A7.8a</i>	5.5.4.3	Appendix 7.3.3.1, forest plot in Figure A7.10a
	<i>All comparators, including Kohira et al. data</i>	<i>0.86, 95% CrI: 0.11 to 7.05</i>	<i>Small differences in comparator ORs</i>	5.5.4.3	Appendix 7.3.3.1, forest plot in Figure A7.10b
	<i>Only comparators specific to the pathogen*</i>	<i>1.30, 95% CrI: 0.16 to 10.40</i>	<i>Fosfomycin’s OR indicated susceptibility higher relative to colistin, rather than lower.</i>	5.5.4.3	Appendix 7.3.3.1, forest plot in Figure A7.10c
	<i>Using only studies that report cefiderocol data (SIDERO, Johnston et al., Kohira et al.)</i>	<i>15.70, 95% CrI: 0.83 to 320.72</i>	NA – only cefiderocol OR used	5.5.4.3	Appendix 7.3.4.1, forest plot in Figure A7.14a

	Using only studies that report cefiderocol data (SIDERO), and only including in the network comparators specific to the pathogen *	16.76, 95%CrI: 1.19 to 285.30	NA – only cefiderocol OR used	5.5.4.3	Appendix 7.3.4.1, forest plot in Figure A7.14b
CLSI <i>Pseudomonas aeruginosa</i>	<i>All comparators</i>	<i>71.34, 95% CrI: 4.33 to 5934.35</i>	<i>See Figure A7.12a</i>	5.5.4.3	Appendix 7.3.3.2, forest plot in Figure A7.12a
	<i>Only comparators specific to the pathogen*</i>	<i>64.19, CrI: 1.13 to 7672.55</i>	<i>Similar OR for comparators as for “all comparators” analysis</i>	5.5.4.3	Appendix 7.3.3.2, forest plot in Figure A7.12b
	<i>Using only studies that report cefiderocol data (SIDERO)</i>	<i>66.73, 95% CrI: 3.61 to 3284.37</i>	NA – only cefiderocol OR used	5.5.4.3	Appendix 7.3.4.2, forest plot in Figure A7.16
	Using only studies that report cefiderocol data (SIDERO), and only including in the network comparators specific to the pathogen *	This network is the same as the “Using only SIDERO studies” network			

CLSI, Clinical Laboratory Standards Institute; CrI, credible interval; EUCAST, European Committee on Antimicrobial Susceptibility Testing; NA, not applicable; OR, odds ratio

Bold indicates analyses that were used in the model base case.

Italics indicates analyses that were considered as scenarios in the model (see Section 8.2.3.2)

*For *Enterobacterales* networks, meropenem was excluded; for *Pseudomonas aeruginosa* networks aztreonam, tigecycline and gentamicin were excluded (no data for amikacin and tobramycin). Note that for the CLSI analyses, Kohira *et al.* could not be included in the network as it only reported data for cefiderocol and meropenem

Table 10 Summary of the NMAs scenario analysis performed to estimate the OR for fosfomycin, compared to the OR produced by the base case analysis

Analysis	Scenario	Fosfomycin OR	Section in report	Section in appendices
EUCAST <i>Enterobacterales</i>	All comparators, missing PHE meropenem data	0.34, 95% CrI: 0.06 to 1.96	5.5.4.1	NA
	<i>Using only fosfomycin studies</i>	0.24, 95% CrI: 0.02 to 3.09	5.5.4.3	Appendix 7.3.2, forest plot Figure A7.6a
	Using only fosfomycin studies and only including in the network comparators specific to the pathogen*	0.23, 95% CrI: 0.02 to 2.36	5.5.4.3	Appendix 7.3.2, forest plot Figure A7.6b
EUCAST <i>Pseudomonas aeruginosa</i>	All comparators	0.00 (0.00 to 0.19)	5.5.4.2	NA
	<i>Using only fosfomycin studies</i>	2.50 (0.04 to 52.37). Relative to aztreonam after applying a continuity correction.	5.5.4.3	Appendix 7.3.2, no forest plot
	Using only fosfomycin studies and only including in the network comparators specific to the pathogen*	2.50 (0.04 to 52.37). Relative to aztreonam after applying a continuity correction.	5.5.4.3	Appendix 7.3.2, no forest plot
CLSI <i>Enterobacterales</i>	All comparators, missing Kohira data	0.69 95% CrI: 0.07 to 6.70	5.5.4.3	Appendix 7.3.3, forest plot Figure A7.10
	<i>Using only fosfomycin studies</i>	0.52 95% CrI: 0.06, 4.01	5.5.4.3	Appendix 7.3.5, forest plot Figure A7.20a
	Using only fosfomycin studies and only including in the network comparators specific to the pathogen*	0.59, 95% CrI: 0.12 to 2.64	5.5.4.3	Appendix 7.3.5, forest plot Figure A7.20b
CLSI <i>Pseudomonas aeruginosa</i>	All comparators	0.06 95% CrI: 0.00 to 1.92	5.5.4.3	Appendix 7.3.3, forest plot Figure A7.12a
	<i>Using only fosfomycin studies</i>	0.10 (0.02 to 7.40). Relative to colistin after applying a continuity correction.	5.5.4.3	Appendix 7.3.5, no forest plot
	Using only fosfomycin studies and only including in the network comparators specific to the pathogen*	0.10 (0.02 to 7.40). Relative to colistin after applying a continuity correction.	5.5.4.3	Appendix 7.3.5, no forest plot

CrI, credible interval; EUCAST, European Committee on Antimicrobial Susceptibility Testing; NA, not applicable; OR, odds ratio

*For *Enterobacterales* networks, meropenem was excluded; for *Pseudomonas aeruginosa* networks aztreonam, tigecycline, amikacin, tobramycin and gentamicin were excluded where data was available for other comparators

5.5.4.1. Base case NMA: MBL *Enterobacterales* infections with EUCAST breakpoint

Eight studies contributed to the NMA of MBL *Enterobacterales* infections with EUCAST breakpoints, considering a total of 8 comparators, and the full network diagram is shown in Figure 2. Three studies^{53,56,58} contained 100% susceptibility counts for one or more of the included comparators and therefore had a continuity correction applied prior to synthesis.

The relative susceptibility for each comparator relative to colistin are shown in Figure 3a. The model fitted the data well, with a total residual deviance of 33.50, which was close to the number of data points included in the analysis of 35. The between-study SD was 1.45 (95% CrI: 0.93 to 2.35), which indicates extremely high heterogeneity. Cefiderocol was associated with a lower susceptibility relative to colistin (OR 0.32, 95% CrI: 0.04 to 2.47), but the result was not statistically significant. Cefiderocol was also associated with an 11% probability of being the most effective treatment; median rank 3. The remainder of the treatments were also associated with lower susceptibility than colistin, but the results were not statistically significant. For all comparators the high between-study SD results in wide 95% PrI. The updated analysis including the missing PHE meropenem data was very similar for cefiderocol (OR 0.31, CrI: 0.04 to 2.18) and comparators.

Inconsistency checking was performed using the UME model. The model fitted the data well and the DIC was similar to the base case NMA model (Appendix 7.2). The estimated between study SD is slightly smaller from the UME model compared to the base case NMA model, but it still indicates extremely high heterogeneity (1.08 (95% CrI 0.67 to 1.82)). The deviance plot (Appendix 7.4) indicates no obvious improvement in fit when using the UME model. As there is no evidence of inconsistency, no further steps were taken.

Enterobacterales network including missed PHE meropenem data, using EUCAST breakpoints

When the meropenem data that was missed was included in the network, the OR for cefiderocol was very similar (OR 0.31, 95% CrI: 0.04 to 2.18), and the same was true for the comparators.

Enterobacterales network restricted to comparators specific to the pathogen, using EUCAST breakpoints

When the network was restricted to comparators specific to the pathogen, the OR for cefiderocol was very similar (OR 0.34, CrI: 0.05 to 1.97), and the same was true for all other comparators.

Figure 2: Network diagram of all studies contributing to the NMA (MBL *Enterobacterales* with EUCAST breakpoint for SIDERO, fosfomycin and PHE studies)

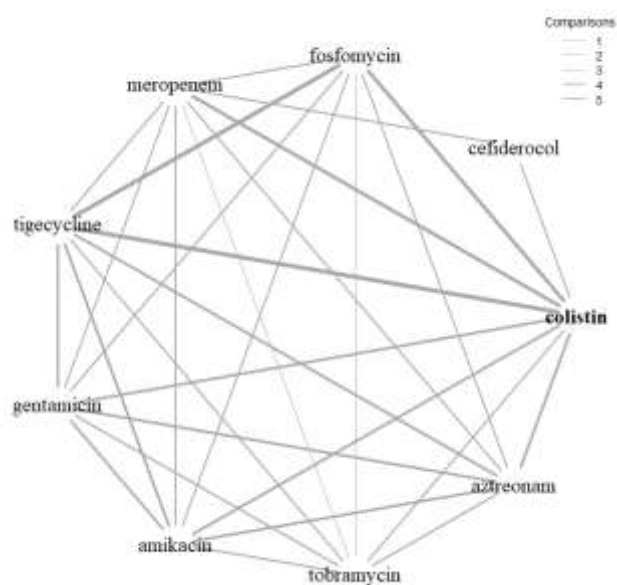
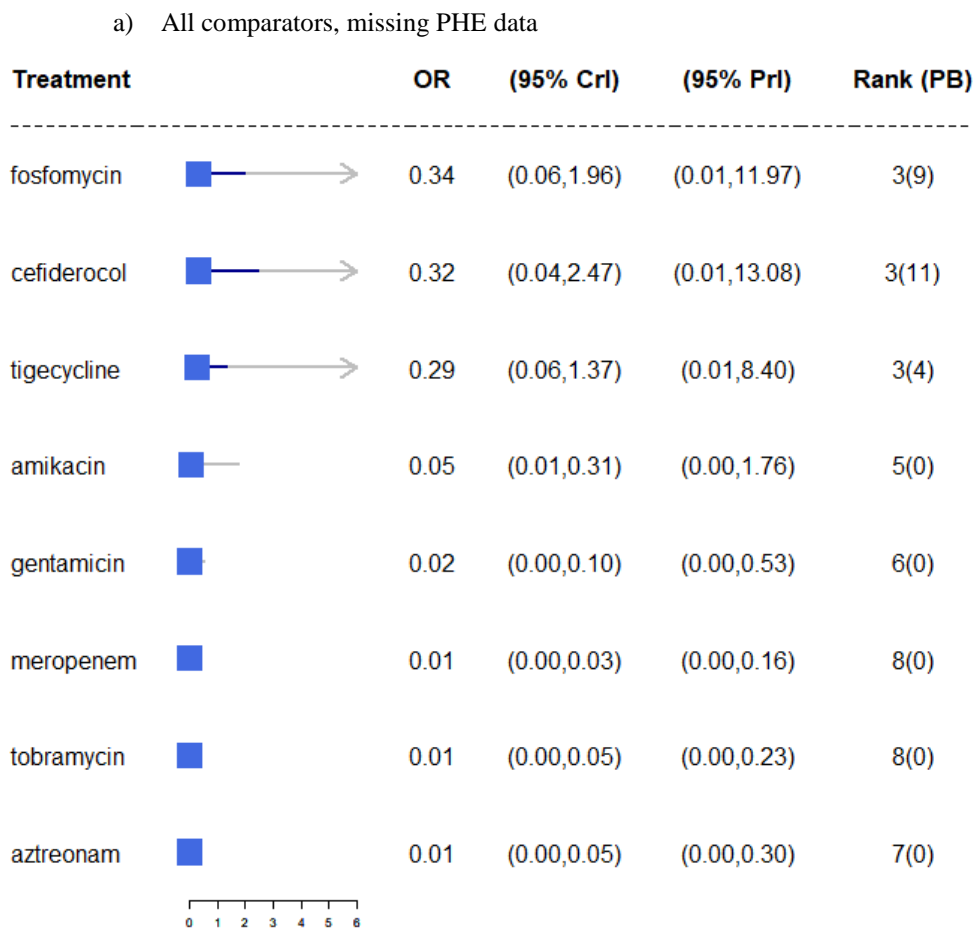
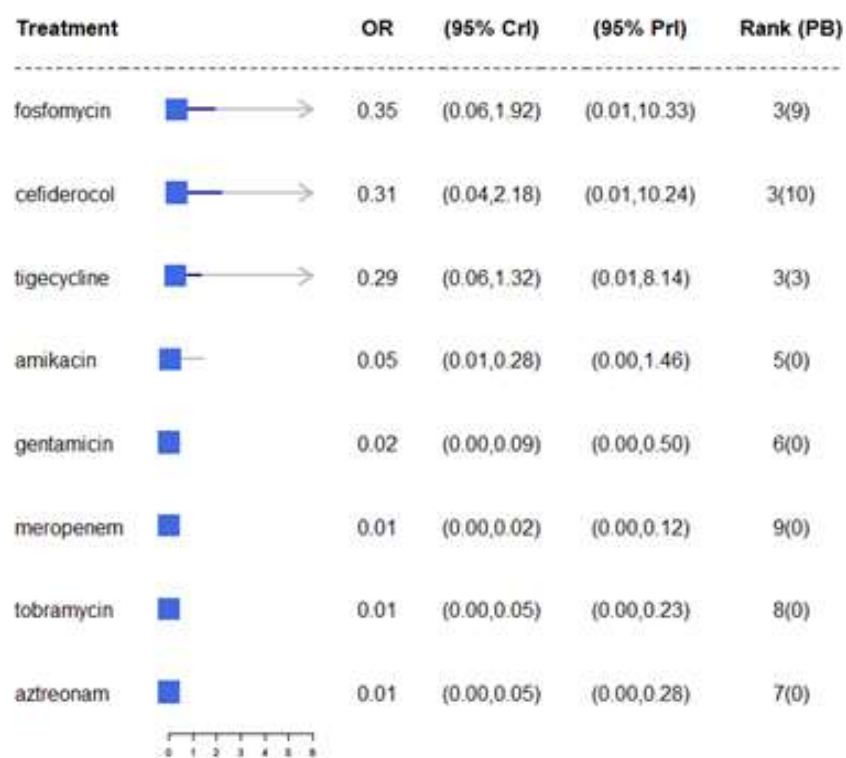


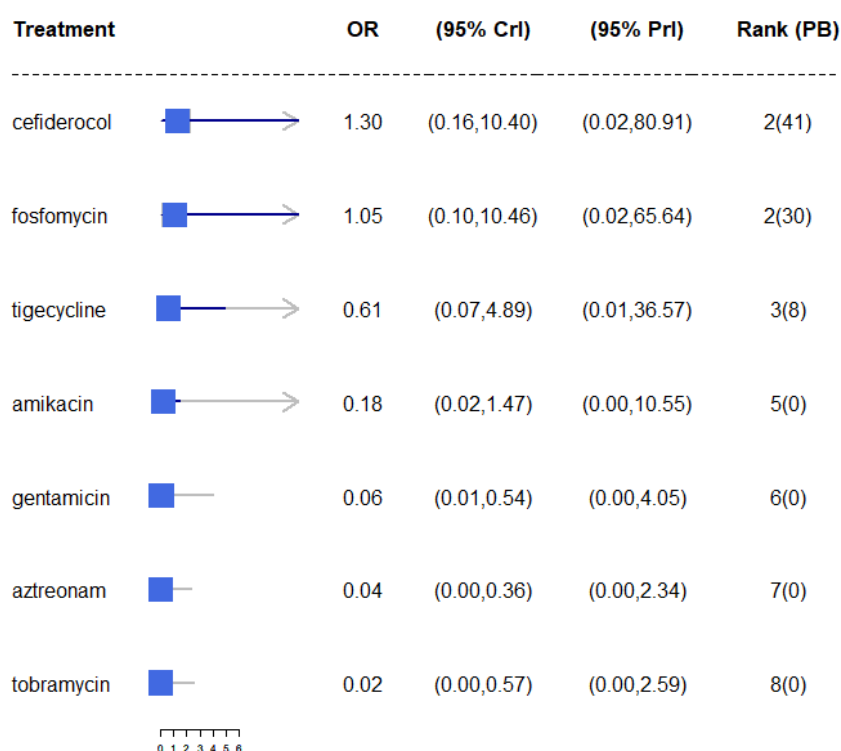
Figure 3: Forest plot of OR vs colistin for MBL *Enterobacterales* with EUCAST breakpoint (SIDERO, fosfomycin and PHE studies)



b) All comparators, including missing PHE data



c) Only comparators specific to the pathogen



Abbreviations: OR, odds ratio; CrI, credible interval, PrI, prediction interval; PB, probability of being the best treatment.

5.5.4.2. Base case NMA: MBL *Pseudomonas aeruginosa* infections with EUCAST breakpoint

Four studies contributed to the NMA of MBL *Pseudomonas aeruginosa* infections with EUCAST breakpoints for SIDERO, fosfomicin and PHE studies, considering a total of 4 comparators, and the full network diagram is shown in Figure 4. All four studies (SIDERO WT data request, SIDERO CR data request, PHE data request, and Cuba et al.)⁵⁴ contained either zero or 100% susceptibility counts for one or more of the included comparators and therefore a numerical adjustment was applied prior to synthesis.

The relative susceptibility for each comparator relative to colistin are shown in Figure 5. The model fitted the data well, with a total residual deviance of 9.3, which was considered close to the number of data points included in the analysis of 11. The between-study SD was 0.87 (95% CrI: 0.04 to 2.76), which indicates high heterogeneity. Cefiderocol was associated with a lower susceptibility relative to colistin (OR 0.44 95% CrI: 0.03, 3.94), but the result was not statistically significant. Cefiderocol was also associated with a 20% probability of being the most effective treatment; median rank 2. The

remainder of the treatments were associated with no susceptibility. For all comparators the high between-study SD results in wide 95% PrI. No inconsistency checking could be performed because the network does not include a feedback loop.

Pseudomonas aeruginosa network restricted to comparators specific to the pathogen, using EUCAST breakpoints

When the network was restricted to comparators specific to the pathogen, the OR for cefiderocol was very similar (OR 0.44, CrI: 0.03 to 4.08), and the same was true for all other comparators.

Figure 4: Network diagram of all studies contributing to the NMA (MBL *Pseudomonas aeruginosa* with EUCAST breakpoint for SIDERO, fosfomicin and PHE studies)

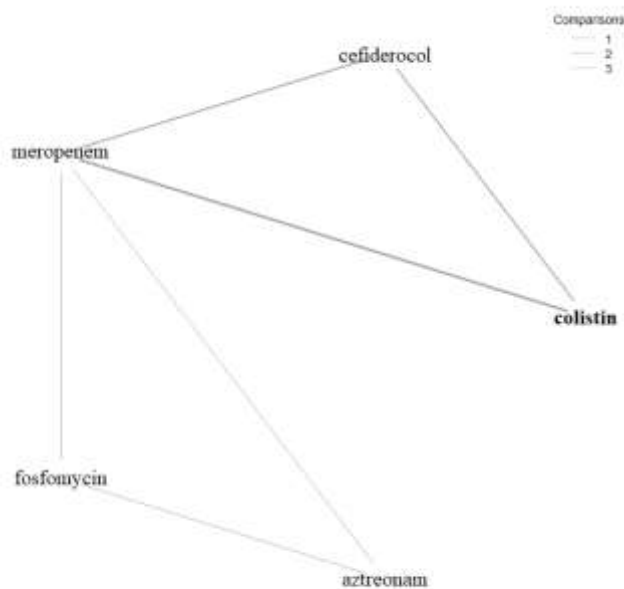
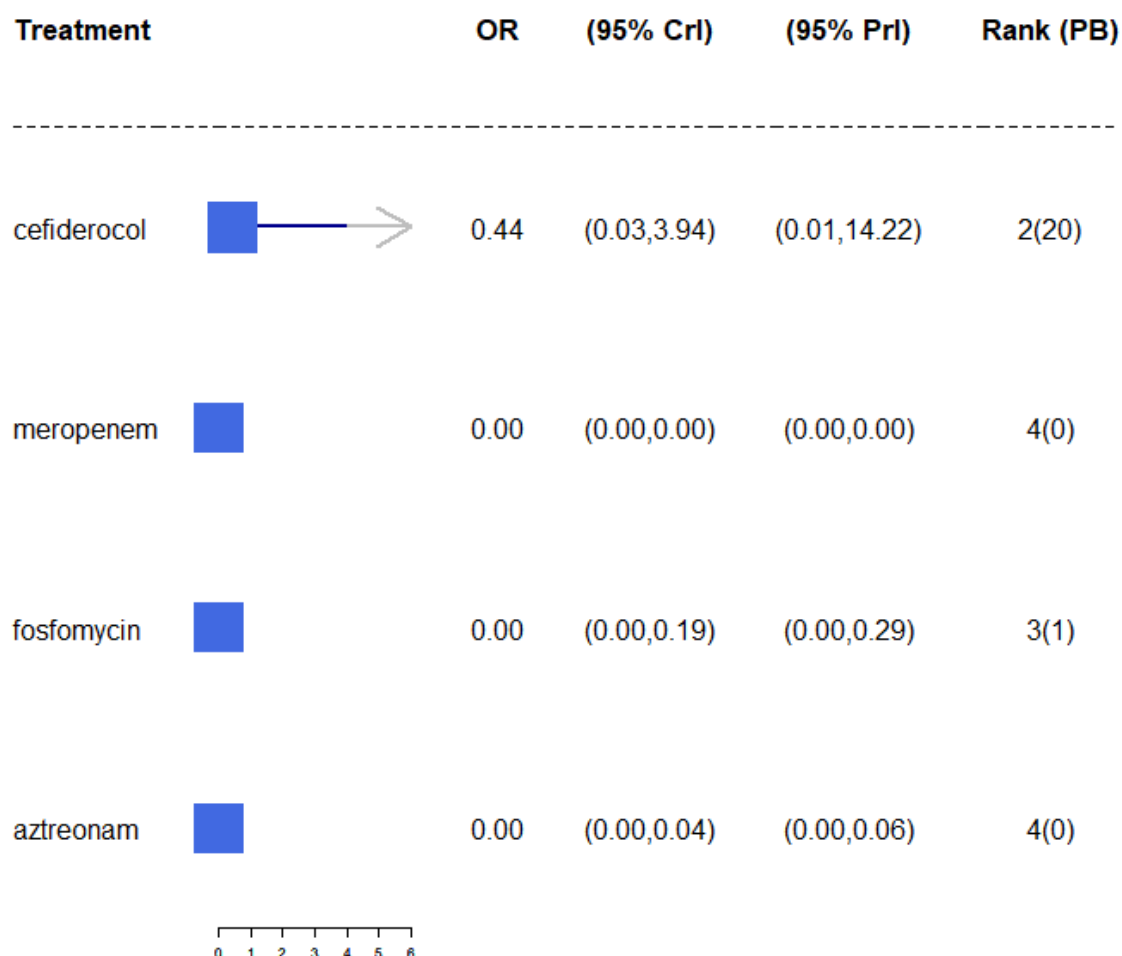


Figure 5: Forest plot of OR vs colistin for MBL *Pseudomonas aeruginosa* with EUCAST breakpoint (SIDERO, fosfomycin and PHE studies)



OR, odds ratio; CrI, credible interval, PrI, prediction interval; PB, probability of being the best treatment.

5.5.4.3. Sensitivity analyses

A summary of the results of the sensitivity analyses is presented in this section. Details of the results are presented in Appendix 7.3.

MBL Enterobacterales network including all studies using CLSI breakpoints

Further details can be found in Appendix 7.3.3.1 and Figure A7.10a. When using CLSI breakpoints, cefiderocol was associated with a higher susceptibility relative to colistin (OR 1.38, 95% CrI: 0.16 to 12.05), but the result was not statistically significant. The remainder of the treatments were associated with a lower susceptibility relative to colistin, and between-study SD was high.

When the missing study, Kohira 2016⁴¹ was included in the analysis, the OR for cefiderocol was 0.86 (0.11 to 7.05) (see Appendix 7.3.3.1, Figure A7.10b).

When the network was restricted to comparators specific to the pathogen, the OR for cefiderocol was very similar (OR 1.30, CrI: 0.16 to 10.40), but fosfomycin's OR indicated susceptibility higher relative to colistin, rather than lower) (see Appendix 7.3.3.1, Figure A7.10c).

MBL Pseudomonas aeruginosa network including all studies using CLSI breakpoints

When using CLSI breakpoints, cefiderocol was associated with a statistically significantly higher susceptibility relative to colistin (OR 71.34, 95% CrI: 4.33 to 5934.35), but the result was not statistically significant. All other treatments (fosfomycin, aztreonam, meropenem, gentamicin) were associated with OR at or near 0, and none were statistically significant (see Appendix 7.3.3.2, Figure A7.12a). Between-study SD was high.

When the network was restricted to comparators specific to the pathogen, the OR for cefiderocol was a little lower (OR 64.19, CrI: 1.13 to 7672.55). Other comparators (meropenem, fosfomycin) continued to be associated with OR at or near 0 (see Appendix 7.3.3.2, Figure A7.12b).

Networks using cefiderocol studies only

EUCAST breakpoints: When the NMAs were based on cefiderocol studies only (see Appendix 7.3.1), the results were similar to the base case NMAs for both MBL *Enterobacterales* and MBL *Pseudomonas aeruginosa* isolates. The OR for cefiderocol versus colistin was 0.33 (95% CrI: 0.06 to 1.65 compared to 0.32, 95% CrI: 0.04 to 2.47) for MBL *Enterobacterales* infections and 0.49 (95% CrI: 0.03 to 5.29) compared to 0.44 95% CrI: 0.03, 3.94 for MBL *Pseudomonas aeruginosa* infections. When the network also only included comparators specific to the pathogen, the *Enterobacterales* estimate was similar (0.33 95% CrI 0.039 to 2.916) and the *Pseudomonas aeruginosa* network did not change.

CLSI breakpoints: When the NMAs were based on cefiderocol studies only (see Appendix 7.3.1), the results for *Enterobacterales* were much higher (OR 15.70, 95% CrI: 0.83 to 320.72 compared to 1.38, 95% CrI: 0.16 to 12.05) and for *Pseudomonas aeruginosa* were similar (OR 66.73, 95% CrI: 3.61 to 3284.37 compared to 71.34, 95% CrI: 4.33 to 5934.35). When the network also only included comparators specific to the pathogen, the *Enterobacterales* estimate was similar (OR 16.76, 95%CrI: 1.19 to 285.30) and the *Pseudomonas aeruginosa* network did not change.

Networks using fosfomycin studies only

EUCAST breakpoints: When the NMAs were based on fosfomycin studies only (see Appendix 7.3.2), fosfomycin was again associated with a lower susceptibility relative to colistin (OR 0.24, 95% CrI: 0.02 to 3.09) for MBL *Enterobacterales* infection, but this effect was smaller compared to the base case NMA. When the network also only included comparators specific to the pathogen, the *Enterobacterales*

estimate was similar (OR 0.23, 95% CrI: 0.02 to 2.36). No NMA was performed for MBL *Pseudomonas aeruginosa* infection population using fosfomycin studies only because the network only consists of one study (see Table 8 for details).

CLSI breakpoints: When the NMAs were based on fosfomycin studies only (see Appendix 7.3.5), fosfomycin was again associated with a lower susceptibility relative to colistin (OR 0.52 95% CrI: 0.06, 4.01) for MBL *Enterobacterales* infection, but this effect was smaller compared to the base case NMA (OR 0.69 95% CrI: 0.07 to 6.70). When the network also only included comparators specific to the pathogen, the *Enterobacterales* estimate was similar (OR 0.59, 95% CrI: 0.12 to 2.64). No NMA was performed for MBL *Pseudomonas aeruginosa* infection population using fosfomycin studies only because the network only consists of one study (see Table 8 for details).

5.6. Additional review questions for Approach 3

Review questions 4-6 were defined in order to supply estimates to populate the decision-analytic model. Section 0 describes the rationale for and requirements of each additional question, whilst Sections 5.6.1-5.6.3 describe the methods and results for each question. The approach to evidence identification and selection differed for each of these three questions, due to their perceived importance to the model, time constraints, and the availability of existing reviews.

The additional review questions were:

Review question 4: What is the link between in vitro susceptibility and clinical outcomes from the published literature, in the sites of relevance, in patients according to their susceptibility to the treatment they were given?

As described above in Section 5.1.1.1, susceptibility studies do not report clinical outcomes, therefore it was necessary to establish the link between susceptibility *in vitro*, and clinical outcomes. Two approaches to evidencing this link were proposed:

- a) assume that clinical outcomes do not differ according to the specific antibiotic used or the specific pathogen-mechanism causing the infection, conditional upon susceptibility to that antibiotic. This assumption was validated by our clinical experts.
- b) assume that different treatments may result in different outcomes, conditional on susceptibility to the antibiotic given.

In both approaches, studies should have tested the susceptibility of a patient to the treatment they were given, and report clinical outcomes for those susceptible or not in cUTI and HAP/VAP separately. In approach b) data on effectiveness conditional upon susceptibility would be required for the intervention

and comparators, and would need to comprise a viable NMA. Initial scoping work based on a previous systematic review (reported as part of Shionogi's application to EUNETHTA (Project PTJA11))⁶⁷ indicated that the RCTs in the HVCS sites provided poor coverage of the comparators of interest. Clinical advisors were also supportive of approach a), and consequently approach b) was not pursued further.

Review question 5. What is the long-term risk of mortality (and other outcomes) for patients with carbapenem-resistant cUTI or HAP/VAP ?

This question became necessary since review question 4 did not identify any studies that reported long term clinical outcomes. The question was widened to include any carbapenem-resistant infections.

Review question 6. What are the important safety implications of cefiderocol?

This question was required to inform the modelling of important adverse events.

5.6.1. Review question 4

What is the link between *in vitro* susceptibility and clinical outcomes from the published literature, in the sites of relevance, in patients according to their susceptibility to the treatment they were given?

5.6.1.1. Methods

As detailed in Section 5.6, of the two proposed approaches, only approach a. was taken forward. In this approach, it is assumed that clinical outcomes would be similar regardless of the treatment received, conditional upon susceptibility. This review included studies of any design linking susceptibility (to any antibiotic) to clinical outcomes in cUTI or HAP/VAP caused by any pathogen-mechanism (Table 11). Three approaches were used to identify evidence relating to this question.

1. A systematic review update of Bassetti et al. 2020.⁶⁸
 2. Searching and screening of additional databases and review of studies included within Bassetti et al. 2020.⁶⁸
 3. Review of the RCTs identified in Review 1 for any subgroup data.
1. Bassetti et al 2020⁶⁸ systematically reviewed the impact of appropriate and inappropriate antibacterial therapy on clinical outcomes of patients with severe bacterial infections, where appropriate therapy was defined as treatment with an antibiotic the isolate was susceptible to. The review was assessed for quality and relevance (see Appendix 8.1) and was judged to be of good quality and suitable for updating. The original review covered the period from 2007 (to ensure clinical practices were contemporary) and the searches were performed in 2018. For the update,

given resource and time constraints the search strategy was restricted to terms relating to the UK (since clinical practice may differ in other countries), the sites of interest (cUTI, HAP/VAP), and to remove terms relating to treatment delay, which were included in Bassetti et al 2020⁶⁸ to address a separate review question (the effect of delayed appropriate antibiotic therapy) addressed in Zasowski et al 2020.⁶⁹ The adapted search strategy was run from 2007 to June 2021, to capture any new studies, as well as any studies the adapted strategy identified that were missed by the previous review (between 2007-2018). It was further noted that the original search strategy did not include search terms relating to susceptibility, and therefore an additional search, using this search term, was conducted to capture any additional studies from 2007 onwards. The search strategies are presented in Appendix 1.3.4 and were run in Ovid MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions: Ovid, 1946 to Present.

2. In addition to the update of Bassetti et al.,⁶⁸ a number of other approaches were taken to identify relevant studies (more detail is provided in Appendix 8.2):
 - A large database (3172 references) was created, based on search terms for the mechanisms of resistance relevant to the two concurrent EEPRU evaluations relating to cefiderocol and CAZ-AVI (namely MLB, NDM, VIM and IMP). This database was then searched using a series of keywords and phrases to identify relevant studies. The search strategy is presented in Appendix 1.3.2.
 - Screening, citation searching and reference checking of studies retrieved by a search for cost-effectiveness models (66 references) (see Appendix 1.3.1)
 - Keyword search of the Endnote library provided by Shionogi as part the EEPRU evaluation of cefiderocol (1261 references),
 - Screening the list of key references provided by Shionogi as part the EEPRU evaluation of cefiderocol (45 references),
 - Keyword search of references provided by Pfizer as part of the EEPRU evaluation of CAZ-AVI (299 references),
 - Screening the studies included in two systematic review articles provided by Shionogi as part the EEPRU evaluation of cefiderocol (Zasowski et al., 2020;⁶⁹ Bassetti et al., 2020).⁶⁸
3. In addition to the two previous approaches, the RCTs identified for the intervention were examined for any additional data relating to this question (see Appendix 6.1).

Identified studies were assessed for relevance against pre-specified inclusion criteria listed in Table 11.

Table 11: Inclusion criteria for the review of susceptibility and clinical outcomes

Item	Inclusion criteria	Exclusion criteria
Population	cUTI or HAP/VAP Any infective pathogen	Other sites
Exposure	Treatment with any antibiotic that the isolate is susceptible to	Treatment with an antibiotic that the isolate has intermediate susceptibility to
Comparison	Treatment with any antibiotic that the isolate is not susceptible to (resistant or intermediate/increased exposure)	No comparison provided
Outcomes	Mortality, hospitalization, length of stay (LOS), bloodstream infections (BSI) or other subsequent infections, health related quality of life (HRQoL)	Short term outcomes such as clinical cure
Setting	MDS or ES UK studies (only applied to search update)	Not UK (only applied to search update)
Study design	Experimental or observational studies that assessed susceptibility to treatment prospectively or retrospectively	Published prior to 2010

cUTI, complicated urinary tract infection; ES, empiric setting; HAP, hospital-acquired pneumonia; MDS, microbiology-directed setting; VAP, ventilator-associated pneumonia; UK, United Kingdom

5.6.1.2. Results

1. Systematic review update of Bassetti et al. (2020)

The searches for the systematic review update yielded 172 citations, the screening process did not result in any studies that met the inclusion criteria.

2. Searching and screening additional databases

Eight studies were extracted in total, of which four and five studies reported outcomes in patients with cUTIs and HAP/VAP, respectively. None of the studies were conducted in the UK. None of the studies on patients with cUTIs included patients who received microbiology-directed treatment. In studies on patients with HAP/VAP, three studies only included patients receiving empiric treatment ^{70 71 72}, one study ⁷³ included patients both on microbiology directed and empiric treatment (it did not report outcomes conditional on the setting), and one study ⁷⁴ did not report whether treatment was microbiology-directed or empiric. Of the three studies conducted solely in the ES, one reported ICU mortality, hospital mortality, mechanical ventilation, LOS and ICU LOS ⁷⁰, one study reported 30-day mortality only ⁷¹, and one reported Kaplan-Meier curves for 30-day mortality ⁷².

3. Review of the RCTs identified in Review 1 for any subgroup data

The four RCTs (Table 3) were also examined for data on clinical outcomes contingent on susceptibility to treatment. No analyses were identified in these RCTs.

5.6.2. Review question 5

What is the long-term risk of mortality (and other outcomes) for patients with carbapenem-resistant cUTI or HAP/VAP?

5.6.2.1. Methods

The previous reviews did not identify any long-term mortality data. Given the paucity of data in this area, the scope of this review question was widened to include any carbapenem-resistant infections treated with any treatment, under the assumption this data could be generalised to MBL *Enterobacteriales* and *Pseudomonas aeruginosa* infections. A focussed search was conducted to identify UK studies reporting long-term (>3 months) mortality and other outcomes such as hospitalisation, subsequent infection, costs and adverse events for patients with carbapenem-resistant (including multi-drug resistant (MDR) and extensively-drug resistant (XDR)) cUTI or HAP/VAP. The search strategy comprised terms for (Carbapenem Resistance OR mechanisms) AND (sites [UTI/HAPVAP]) AND filters. The search scope was limited using terms for the UK, and the search was run from 2010 to ensure clinical practices were contemporary. Since no UK studies were identified, the search was expanded to include studies from Europe. The search strategy is presented in Appendix 1.3.3. The inclusion criteria for this review are reported in Table 12. Studies were assessed for eligibility against the inclusion criteria by one reviewer.

Table 12: Inclusion criteria for the review of the long term risk of mortality for patients with carbapenem-resistant cUTI or HAP/VAP

Item	Inclusion criteria	Exclusion criteria
Population	CR, XDR or MDR cUTI or HAP/VAP infections	Infections at sites other than cUTI or HAP/VAP
Exposure	Any treatment or no treatment	
Outcomes	Mortality measured more than 3 months after treatment Other long-term outcomes such as hospitalisations, subsequent infections, costs, adverse events	Outcomes measured at or before 3 months after treatment
Setting	UK, expand to Europe if no UK studies	
Study design	Experimental or observational studies or datasets	Studies published prior to 2010

CR, carbapenem resistant; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; MDR, multidrug resistant; VAP, ventilator-associated pneumonia; XDR, extensively drug-resistant

5.6.2.2. Results

The electronic database searches, following the removal of duplicates, identified 76 records relating to long term outcomes for patients with carbapenem-resistant cUTI or HAP/VAP. After examination of the title and abstracts, 76 records were excluded because they did not meet the inclusion criteria.

5.6.3. Review question 6.

What are the important safety implications of cefiderocol?

5.6.3.1. Methods

A comprehensive review of the safety of comparators was not possible within the timeframe of this evaluation. Adverse events included in the model for the intervention and comparators are described in Section 8.2.2.2. Clinical advisors to EEPRU indicated that cefiderocol is predominantly a safe treatment, but that colistin and aminoglycosides have significant adverse events relating to AKI. Another key adverse event related to antibiotic use is the emergence of *C. difficile* in a patient's digestive tract, which can lead to diarrhoea and serious damage to the colon. EEPRU conducted a review of the RCT trial evidence for cefiderocol to establish whether it supported the clinical view that cefiderocol is a safe treatment. EEPRU were especially interested in establishing safety comparative to toxic alternatives (colistin and aminoglycosides) and the other "safer" treatments used in the HVCSSs.

Rates of serious treatment-related adverse events, nephrotoxicity adverse events, and *C.difficile* infections were extracted from the included RCT publications and/or their ClinicalTrials.gov national clinical trial record. Only RCTs relating to the sites of interest were reviewed, due to time and resource constraints. Only RCTs were considered as these give comparative data. In the absence of nephrotoxicity events, other kidney and renal adverse events were extracted. The data was then synthesised narratively for any important safety signals.

A pooled analysis of CREDIBLE-CR, APEKS-NP and APEKS-cUTI was presented by Shionogi in their submission to NICE,³⁸ but since comparators in the studies differed, EEPRU preferred to consider the data from each RCT separately.

5.6.3.2. Results

The extracted adverse event data in the RCTs for Cefiderocol are presented in Table 13. Across three RCTs, the proportion of patients with serious adverse events was lower with Cefiderocol compared to: imipenem/cilastatin (4.7% vs 8.1%; APEKS-cUTI),³³ meropenem (2.0% vs 3.3%; APEKS-NP),¹³ and BAT (which comprised colistin-based regimens n=30 (61%); non-colistin based regimens (n=19

(39%)) (1% vs 10%, Bassetti et al. 2019/20 CREDIBLE).³⁴ A statistical significance for the between-group differences was not reported by any RCT.

None of the included studies reported specifically on nephrotoxicity. Related adverse events included AKI and renal disorder. All three RCTs reported both of these adverse events. The proportions of patients with either AKI or renal disorder was 0.0% for both cefiderocol and the comparator in the two RCTs that did not use colistin in the comparator arm.^{13,33} The proportions of patients with AKI and renal disorder was greater with the comparator in the RCT by Bassetti *et al.*³⁴ where colistin was used within the comparator arm (BAT 8.2% vs cefiderocol 0.0% and 2.0% vs 0.0% respectively). A statistical significance for the between-group difference was not reported by any RCT.

One study reported *C. difficile* infections. The proportion of patients with *C. difficile* was greater with the comparator (meropenem) compared to cefiderocol (1.3% vs 0.7%).¹³ A statistical significance for the between-group differences was not reported.

Other adverse events were generally very low across the studies, with slightly greater proportions of patients experiencing adverse events with cefiderocol compared to the comparator in all studies. Statistical significance for the between-group differences was not reported.

Table 13. Adverse event data in the RCTs of Cefiderocol

Author (date) Acronym	Intervention and comparator	Site	Serious Treatment related AE (total safety pop) n(%)		BAT therapies used	Nephrotoxicity n(%)		C Diff infection n(%)		Any other category that is important (name, n/N and %)	
			Intervention	Comparator		Intervention	Comparator	Intervention	Comparator	Intervention	Comparator
Portsmouth et al (2018) APEKs- cUTI	Cefiderocol v imipenem/ cilastatin	cUTI	(n=300) 14 (4.7%) (SAE)	(n=148) 12 (8.1%) (SAE)	-	Acute kidney injury 0 Renal disorder 0	Acute kidney injury 0 Renal disorder 0	0	0	Investigations 5 (1.7)	Investigations 2 (1.4)
Wunderink et al. (2021) APEKs- NP	Cefiderocol v Meropenem	HAP/VAP/HC AP, cUTI, or BSI/sepsis	(n=148) 3 (2.0)	(n=150) 5 (3.3)	-	Acute kidney injury 0 Renal disorder 0	Acute kidney injury 0 Renal disorder 0	1 (0.7)	2 (1.3)	Respiratory, thoracic and mediastinal disorders 18 (12.2) Investigations 4 (2.7)	Respiratory, thoracic and mediastinal disorders 14 (9.3) Investigations 4 (2.7)
Bassetti et al. (2019;202	Cefiderocol v BAT	HAP/VAP/HC AP, cUTI, or BSI/sepsis	(n=101) 1 (1%)	(n=49) 5 (10%)	Colistin based regiment	Acute kidney injury 0	Acute kidney injury 4	0	0	Respiratory, thoracic, and mediastinal	Respiratory, thoracic, and mediastinal

0) CREDIBLE-CR					s n 30 (61%); Non-colistin based regimens n 19 (39%)	Renal disorder 0	(8.2) Renal disorder 1 (2.0)			disorders 7 (7) Infections and infestations 29 (29) Investigations 8 (7.9)	disorders 2 (4%) Infections and infestations 11 (22) Investigations 2 (4.1)
Cefi pooled data (from Shionogi submission) (n549 v n 347)			NR	NR		Acute kidney injury 0 Renal disorder 0	Acute kidney injury 4 (1.2) Renal disorder 1 (0.3)	1 (0.2)	2 (0.6)	Investigations (Alanine aminotransferase increased; Gamma-glutamyltransferase increased; Aspartate aminotransferase increased) 17 (3.1)	Investigations (Alanine aminotransferase increased; Gamma-glutamyltransferase increased; Aspartate aminotransferase increased) 8 (2.3)

AE, adverse events; BAT, best available therapy; BSI, bloodstream infections; cUTI, complicated urinary tract infections; HAP, hospital-acquired pneumonia; IAI, intra-abdominal infections; VAP, ventilator-associated pneumonia

5.7. Overview and critique of evidence in Shionogi submission to NICE

In their submission,³⁸ Shionogi include evidence on cefiderocol from RCTS, non-RCTs and susceptibility studies. EEPRU checked that the evidence submitted by Shionogi, which met EEPRU's inclusion criteria, had been identified by EEPRU searches and included in our evidence review.

Shionogi presented clinical data from RCTs and observational studies, including CREDIBLE-CR³⁴ and compassionate use data. In both cases, outcomes were not reported by site and by pathogen-mechanism, so could not be used in EEPRU's evaluation (see also Appendix 6.1 for more details about CREDIBLE-CR).³⁴

Shionogi state that use of *in vitro* susceptibility studies has a number of advantages (see Section 2.3.1.2 of the company submission).³⁸ EEPRU are largely in agreement that given the difficulties with conducting RCTs of new AMs, *in vitro* evidence may provide useful information that can contribute to estimates of comparative efficacy. However, EEPRU also identified a number of drawbacks to this approach, as noted in the Discussion (Section 5.8) and in Section 5.1.2.

Several *in vitro* susceptibility studies were listed by Shionogi in Section 2.3.1 of the company submission,³⁸ but it was unclear whether these were identified by a systematic review. The main studies cited were SIDERO WT⁴² and SIDERO CR,⁴² both of which were the subject of subsequent data requests made by EEPRU to Shionogi, and were then included in EEPRU's synthesis (see Section 4.5). SENTRY, a surveillance study which publishes some data through an open access portal²⁷ was noted in the submission, but Shionogi did not submit data from this source in response to EEPRU's data request, and data relating to cefiderocol was not available to EEPRU via the open access portal. The UK susceptibility studies^{75,76} referred to by Shionogi were not eligible for inclusion in EEPRU's review, since they did not report data for comparators and were only published as meeting or conference abstracts.

Shionogi also noted that they are applying to EUCAST for the breakpoint for cefiderocol to be changed. This has already been discussed in Section 4.5.1 of this report, and two analyses were planned relating to this: one using EUCAST breakpoints for cefiderocol and comparators, and one using CLSI breakpoints for cefiderocol and comparators.

Shionogi also presented PK and PD data. EEPRU did not review PK and PD data, as discussed in Table 4.

Shionogi included a pooled analysis of adverse event data. EEPRU did not use this analysis, but did use the individual relevant studies as discussed in Section 4.6.4.

5.8. Discussion and conclusions: Cefiderocol clinical evidence review

There are evidential challenges when evaluating the use of new AMs to treat infections caused by MDR pathogens. RCTs are of generally low relevance. They tend not to recruit patients with MDR pathogens, since it would be unethical to randomise patients to potentially ineffective existing treatments in the comparator arm. Therefore, relative treatment effects between the intervention and comparator cannot be generalised to MDR pathogens, as this would overestimate the efficacy of the comparator.

Since it was anticipated that RCTs were unlikely to be the primary source of evidence, three approaches to estimating comparative efficacy between the intervention and comparators were considered. In Approach 1 and 2, RCTs and observational studies (respectively), with data for patients with HAP/VAP or cUTI infections caused by MBL *Enterobacterales* or *Pseudomonas aeruginosa aeruginosa*, could be used to construct a NMA to compare the intervention and comparators. In Approach 3, *in vitro* susceptibility studies could be used to indicate the proportion of MBL *Enterobacterales* or *Pseudomonas aeruginosa aeruginosa* isolates that are susceptible to treatment; additional evidence would be required to link susceptibility to clinical outcomes in cUTI and HAP/VAP.

Approaches 1 and 2 were not pursued since insufficient evidence from RCTs and observational studies was identified during the mapping review. The key limitations of the RCTs and observational studies that were identified included small numbers of MBL infections, and data not being reported for the sites of interest.

In Approach 3, relatively large samples of MBL *Enterobacterales* and *Pseudomonas aeruginosa aeruginosa* isolates obtained from a range of clinical sites of infection were available from *in vitro* susceptibility studies, and susceptibility (unlike clinical outcomes) was expected to generalise across sites. Therefore, a NMA was conducted. Three studies (SIDERO CR, SIDERO WT and Johnston et al.) reporting data for cefiderocol and at least one comparator met the inclusion criteria and were synthesised. Data from PHE was included alongside these studies in the synthesis as although this data did not include cefiderocol it was considered highly relevant to estimating the comparative effectiveness of other AMs in the UK. No data was available for fosfomycin from the review, or from the PHE data. Therefore, a separate search was conducted for fosfomycin studies and ten were included alongside the PHE data and the cefiderocol studies.

Separate networks were produced for MBL *Enterobacterales* and *Pseudomonas aeruginosa aeruginosa*, and these were run using both EUCAST and CLSI breakpoints, since the CLSI breakpoint for cefiderocol is 4mg/L whilst for EUCAST it is 2mg/L. Additionally, relative treatment effects for comparators may differ when using CLSI or EUCAST breakpoints.

The main NMAs used the EUCAST breakpoints. The between-study SDs indicated high heterogeneity. In the MBL *Enterobacterales* EUCAST analysis, cefiderocol was associated with a lower susceptibility

relative to colistin (OR, 0.32 95% CrI: 0.04 to 2.47), but the result was not statistically significant. Fosfomycin had a similar OR (OR 0.34, 95% CrI: 0.06 to 1.96) compared to colistin as cefiderocol. The remainder of the treatments were also associated with lower susceptibility than colistin, but the results were not statistically significant. Four studies contributed to the NMA of MBL *Pseudomonas aeruginosa aeruginosa* infections with EUCAST breakpoints. Cefiderocol was associated with a lower susceptibility relative to colistin (OR 0.44 95% CrI: 0.03, 3.94), but the result was not statistically significant. The remainder of the treatments were associated with no susceptibility. The EUCAST network results were selected as the base case source of evidence for the economic model as these are more commonly used in England.

Sensitivity analyses were performed using CLSI breakpoints. In these analyses, where the breakpoint for cefiderocol is higher, cefiderocol was associated with a higher susceptibility relative to colistin, rather than a lower susceptibility. However, the results were very uncertain in some of the NMAs due to sparse data and large number of treatment arms were with either zero or 100% susceptibility. These scenario analyses were run in the economic model.

Sensitivity analyses were also conducted to test assumptions about the inclusion of comparators in the network, and to assess the impact of missed data on the analysis. The estimates of comparative efficacy from the EUCAST networks were very similar in these sensitivity analyses, and it was not necessary to run these scenarios in the economic model. However, the ORs from the CLSI networks were noticeably lower for cefiderocol in two sensitivity analyses (when including missed data from Kohira *et al.* in the CLSI *Enterobacterales* network, and when only using the comparators specific to the pathogen in the CLSI *Pseudomonas aeruginosa* network). Further, the OR for fosfomycin was higher in a third sensitivity analysis (when only using the comparators specific to the pathogen in the CLSI *Enterobacterales* network). These scenarios were also considered in the economic modelling – see Section 8.2.3.2 for further discussion.

Additional scenarios were performed, where the PHE data was used for comparators, but the relative treatment effect for fosfomycin was ascertained from a network including only the fosfomycin studies (since these were obtained from a separate review), and the cefiderocol relative treatment effect was ascertained from a network including only the cefiderocol studies (i.e. the SIDERO studies) rather than from the analysis including all studies. This was in case the separate review of fosfomycin studies introduced bias, should studies of fosfomycin be systematically different from studies of cefiderocol, e.g. in the isolates selected for testing. Sensitivity analyses were conducted to test the effect of assumptions about the inclusion of comparators in the network. Results from these analyses were similar when using a single network for cefiderocol and fosfomycin, so were not used in the economic model.

Review 4 (link between susceptibility and clinical outcomes) identified two studies that reported mortality or hospital LoS conditional on susceptibility to empiric treatment and were selected for use in the model for the ES. No useful evidence relating to the MDS was identified. Review 5 did not identify any relevant literature, but an unpublished study (CARBAR) was submitted by Shionogi that contained useful data. Review 6 indicated that cefiderocol does not appear to increase the risk of AKI, *C. difficile*, or any other serious adverse event, compared to non-toxic comparators (i.e. comparators that were not colistin or an aminoglycoside). No study reported a comparison of cefiderocol exclusively to colistin or aminoglycosides. Event rates were generally very low or zero.

Strengths

The clinical review was conducted using a mapping approach based on robust systematic searches to capture relevant literature. This allowed EEPRU to focus resources from a relatively early stage on a viable approach to deriving clinical efficacy estimates, whilst still conducting a comprehensive search despite a paucity of high quality evidence. Data extractions were checked by a second reviewer to ensure data integrity, and statistical analyses were performed using standard NMA approaches. At all stages of the clinical review, clinical advisors were consulted where there was uncertainty, and the resulting methods of synthesis have attempted to account for clinical sources of heterogeneity where feasible. Susceptibility studies, whilst not reporting clinical outcomes, have the advantage of testing all the treatments in the same sample of isolates, thereby reducing the chance of heterogeneity in patient samples between arms introducing confounding. They also tend to include a higher numbers of patients/isolates compared to RCTs and observational studies.

Limitations

There are limitations to the clinical review, largely due to the availability of evidence and time available to conduct the evaluation.

A lack of availability of relevant RCT or observational evidence to inform clinical outcomes has resulted in the use of *in vitro* susceptibility data, which can be considered a surrogate outcome. This subsequently required a link to be made between susceptibility and clinical outcomes using published data and expert elicitation. No pre-specified criteria for judging the suitability of the surrogate or the linked evidence were applied. The data available to evidence the link between susceptibility and clinical outcomes was sparse and was not specifically for the pathogen-mechanism of interest but rather a wider population of carbapenem-resistant patients. For the MDS, expert elicitation was used to derive the link between susceptibility and clinical outcomes (see Chapter 5).

Other limitations relate to the review methods applied in this evaluation. Because this was the first evaluation of this type commissioned by NICE, and because EEPRU could not foresee the evidence and synthesis requirements at the inception of the project, no registration with PROSPERO was

performed. The statistical plan was made in response to the available data, rather than being formulated *a priori*, since the types of heterogeneity that would be encountered and their importance were largely unknown at the project outset. Due to time constraints, many stages of the review process were done by only one reviewer, which introduces a risk of inaccuracy. Data were checked by a second reviewer for the susceptibility review, but study selection and risk of bias assessment were conducted by only one. Since there was no suitable risk of bias tool available, EEPRU created a bespoke tool. This was done by consulting other available tools, but no face validity checks were performed by experts in susceptibility testing, and no other validation of the tool has been undertaken. This could be an area of future research. To allow for this, risk of bias scores were not used in the statistical synthesis to weight studies, subgroup studies or exclude studies, and instead aspects of clinical heterogeneity were considered in sensitivity analyses individually. Agreeing on the choice of comparators for pathogen-mechanisms was a challenge throughout the project, and some inconsistencies were introduced into the review by this issue. Sensitivity analysis have been used in the NMA to explore how respecifying these affects the NMA outputs, and in most instances the impact was small. Given the resources available in the project, there were limits to the extent to which these could be implemented in the economic model. However, the most impactful scenarios have been incorporated into the modelling scenarios.

Due to the time constraints available for the evaluation, the review initially only included studies that reported data for cefiderocol and at least one comparator, whereas ideally all susceptibility evidence for all comparators would have been sought to construct the network, regardless of whether cefiderocol had also been tested. As there was no data for fosfomycin in the cefiderocol studies, and the numbers in the PHE data were too small to use, a separate search was conducted for fosfomycin studies, which may introduce bias if studies reporting data for fosfomycin are systematically different to those reporting data for cefiderocol. Equally, the PHE data did not strictly meet the inclusion criteria for the review, since they did not report estimates for cefiderocol. To minimise the impact of these potential concerns, sensitivity analyses were planned using each source separately in the economic model, as well as using the network including all studies. In terms of statistical techniques, whilst EEPRU undertook consistency checks, further investigations relating to the high heterogeneity in the network were not undertaken due to time constraints.

There were also some limitations introduced by susceptibility testing and implementation in clinical practice in England, and available susceptibility data. Setting clinical breakpoints is a subjective process conducted by relevant experts taking into account a range of evidence, which may have been generated differently for different comparators. Therefore, any given breakpoint may not reflect the true activity of a treatment in clinical practice, and the extent to which it does may vary between treatments. Breakpoints also change over time as pathogens increasingly acquire resistance. EEPRU were not able to resolve whether it is better to use breakpoints contemporaneous to the sample collection date, or apply current breakpoints to the available data (where data allowed), and for pragmatic reasons used

data as reported in the published reports. Laboratory methods of susceptibility testing recommended by EUCAST and CLSI have also changed over time; before 2016 BSAC had its own set of methods, which may have affected the estimates of susceptibility derived before and since then, as practice did not change immediately. As noted in 5.5.1, PHE data were a mixture of BSAC, CLSI and EUCAST methods and breakpoints, which could potentially affect the estimates of susceptibility derived. The data entering the synthesis did not match practice in England in that CLSI laboratory methods were used rather than EUCAST laboratory methods; it is unclear to what extent CLSI laboratory methods produce the same absolute values as EUCAST methods, and therefore applying EUCAST breakpoints to data derived using CLSI methods may affect relative estimates of efficacy. Clinical advisors also noted that *in vitro* susceptibility to meropenem in particular does not always indicate how well a patient will respond to this treatment in clinical practice. A similar issue arose for fosfomycin because there is no clinical breakpoint for *Pseudomonas aeruginosa aeruginosa* isolates. In this case, the epidemiological cut off, which differentiates between isolates with and without resistance mechanisms but does not link to expected clinical outcomes, was used by the MBL *Pseudomonas aeruginosa aeruginosa* studies identified by the review. In addition, the evidence available for fosfomycin in *Pseudomonas aeruginosa* included very small studies.

5.8.1. Conclusions

Susceptibility estimates have been used to estimate the clinical effectiveness of cefiderocol and its comparators in the HVCSSs. In the EUCAST networks for MBL *Enterobacterales* and *Pseudomonas aeruginosa aeruginosa*, cefiderocol had lower susceptibility relative to colistin, but the result was not statistically significant, and heterogeneity was high. In the CLSI network, where the breakpoint for cefiderocol is higher (4mg/L compared to EUCAST's 2mg/L), cefiderocol was associated with a higher susceptibility relative to colistin, rather than a lower susceptibility. However, the results are highly uncertain. There are a number of limitations to the evidence available and the analyses done, which should be borne in mind when interpreting the evidence.

For the economic evaluation, the base case analysis uses the full EUCAST networks to provide relative efficacy of cefiderocol and comparators. Scenario analyses are conducted using the CLSI networks, and using PHE data for the available comparators with separate networks including only cefiderocol studies and fosfomycin studies providing the relative efficacy for cefiderocol and fosfomycin respectively.

6. Structured expert elicitation

The review in Section 5.6.1 did not identify any studies that informed clinical outcomes in HAP/VAP and cUTI patients conditional upon susceptibility, following microbiology-directed treatment. In the absence of empiric evidence, outcomes were informed by eliciting judgments of individuals who have

expertise on the subject matter. The outcomes of interest were consistent with those available for the ES, and included mortality, hospital LoS, and the type of ward these patients would stay on in hospital.

6.1. Methods

A structured elicitation process was used to improve accountability and transparency. Specifically, the reference methods for HTA developed at York⁷⁷ were employed. The full elicitation protocol describes the process used and is presented in Appendices 9-10.

6.1.1. Approach to elicitation

Clinical experts were recruited to take part in the elicitation exercise, and their beliefs were elicited individually and remotely using an application developed in R, SHINY package.⁷⁸

Experts were trained in the approach to elicitation prior to the task, using an online training webinar (slides are presented in Appendix 11). Experts were asked to express their uncertainty about the outcomes of interest using a histogram (chips and bins approach).⁷⁹ This approach has been shown to work well for experts not trained in probabilities and statistics.⁷⁷ Experts were first asked to express the range for their beliefs, the minimum, which is the value such that the experts believe that there is a 1% probability that the proportion is less than that value; and the maximum, a value, such that the experts believe that there is a 1% probability that the proportion is more than that value. Grids were then generated based on this range and experts were asked to place ‘chips’ on this grid to represent their beliefs. Once experts had completed the grid, a summary of their answers was relayed to them. This provided the following information:

Your answers imply that (example quantities given)

- There is a 17% probability that the proportion of patients is between 19 and 20%
- There is a 50% probability that the proportion of patients is between 20 and 21%
- There is a 33% probability that the proportion of patients is between 21 and 22%

Once experts were individually asked to express their beliefs, these were then aggregated using linear opinion pooling. First, a probability distribution was fitted to each expert’s beliefs from the histogram and then these were pooled, assuming that each expert contributed equally to the group overall distribution.

This overall distribution was then relayed back to experts, and they were given the opportunity to revise their own beliefs on the histograms they previously completed. This approach has been shown to generate less biased parameters when the quantities elicited are unobserved by the experts.⁷⁷ Following this revision, expert’s beliefs were aggregated using the same approach, linear opinion pooling, and the final group distributions were used in the model.

6.1.2. Expert recruitment

Experts recruited to take part in the elicitation exercise included medical consultants, ICU consultants, pulmonary consultants and microbiologists. The literature suggests that around 10 experts should be included in an individual elicitation, and that recruitment should strive for a representative sample.⁷⁷ To this end we sought to recruit experts from across the UK using our clinical leads. We approached experts directly and asked for their participation. Experts that agreed to participate were invited to attend a training webinar. The majority of experts attended this session, with a few choosing to view the pre-recorded slides instead. Experts' identities were known to the modelling team, however in aggregating, feeding back and reporting, all experts identities were anonymised.

6.1.3. Parameters elicited

The elicitation was conducted to inform outcomes in HAP, VAP and cUTIs caused by carbapenem-resistant GNB of interest, following microbiology-directed treatment. The elicitation exercise was used to inform outcomes in two distinct reports where the pathogens of interest included *Enterobacterales* OXA-48, MBL *Enterobacterales* or MBL *Pseudomonas aeruginosa*.

For each of the three sites of infections, we elicited outcomes depending on whether the infectious pathogen is susceptible to treatment. Therefore, outcomes only depend on whether a patient is susceptible to treatment or not, and not to the specific treatment given. The outcomes of interest were 30-day mortality, LoS in hospital, and the type of ward these patients would stay on in hospital.

As background information we presented several related studies to experts (see Appendix 10 for details). In these studies, infecting pathogens were not confirmed to be susceptible to the antibiotics administered; however, in our assessment, they are likely to have been susceptible.

For HAP, VAP and cUTI experts were first provided with some context, as follows (example given is HAP only, the questions were repeated separately for each site):

“The following questions refer to outcomes in patients with HAP caused by carbapenemase-producing *Enterobacterales* (CPE) with an OXA-48 or MBL resistance mechanism, or by *Pseudomonas aeruginosa* with a MBL resistance mechanism, who receive a treatment to which they are susceptible as microbiology-directed treatment.”

Then, the following questions were asked of experts:

Question 1. In this patient population, what proportion of patients will still be alive 30 days after starting microbiology directed treatment?

Question 2. In the patient population described, what will be the average length of stay?

Question 3. In the patient population described, what proportion of hospital stay would be spent on each of the following wards? This number should represent the average for all such patients, regardless of their outcome.

The questions were repeated for patients who are not susceptible. Specifically, the experts were provided the following context:

“The following questions refer to exactly the same patients as the previous section - with HAP caused by CPE with an OXA-48 or MBL resistance mechanism, or by *Pseudomonas aeruginosa* with a MBL resistance mechanism.

In these patients, what would be their outcomes if they were **not susceptible to any existing antibiotics (including CAZ-AVI and cefiderocol)**, and they received multi-drug salvage therapy instead?”

6.2. Results

6.2.1. Completion rate

Eleven experts agreed to take part in the elicitation task and took part in the training. Of these eleven, 9 experts attempted the task. The experts included medical consultants (n=2), microbiologists (n=5), ICU consultants (n=1) and pulmonary consultants (n=1). Seven experts completed the task, while two terminated it before answering all questions. Responses from the two experts who terminated the task before answering all questions, were included in the analysis for all outcomes where they provided an estimate for both susceptible and not susceptible populations. Following the elicitation task, experts were sent group summaries and asked if they would like to revise their responses. Only two experts responded that they reviewed the group summaries, and one adjusted their initial responses in light of group summaries.

Two experts were removed from the sample in the base case analysis. They both indicated that the probability of survival was lower in patients who were susceptible to treatment than those who were not susceptible, for two sites of infection. This was judged to be implausible.

6.2.2. Group summaries and use in the modelling

Pooled summaries for each elicited quantity are shown in Appendix 9. The group summaries on 30-day mortality indicate that survival is the lowest for VAP patients and highest for cUTI patients, and that susceptibility to treatment increases the probability of survival, for all three sites of infection. The group summaries on LoS indicate that the LoS is the shortest in patients with cUTIs and the longest for patients with VAP. For all three sites of infection, susceptibility to treatment decreased the LoS. The group summaries for the proportion of time spent on different types of wards indicate that patients with VAP spend the most time in ICU and the least time on general medical wards, followed by HAP, then cUTIs.

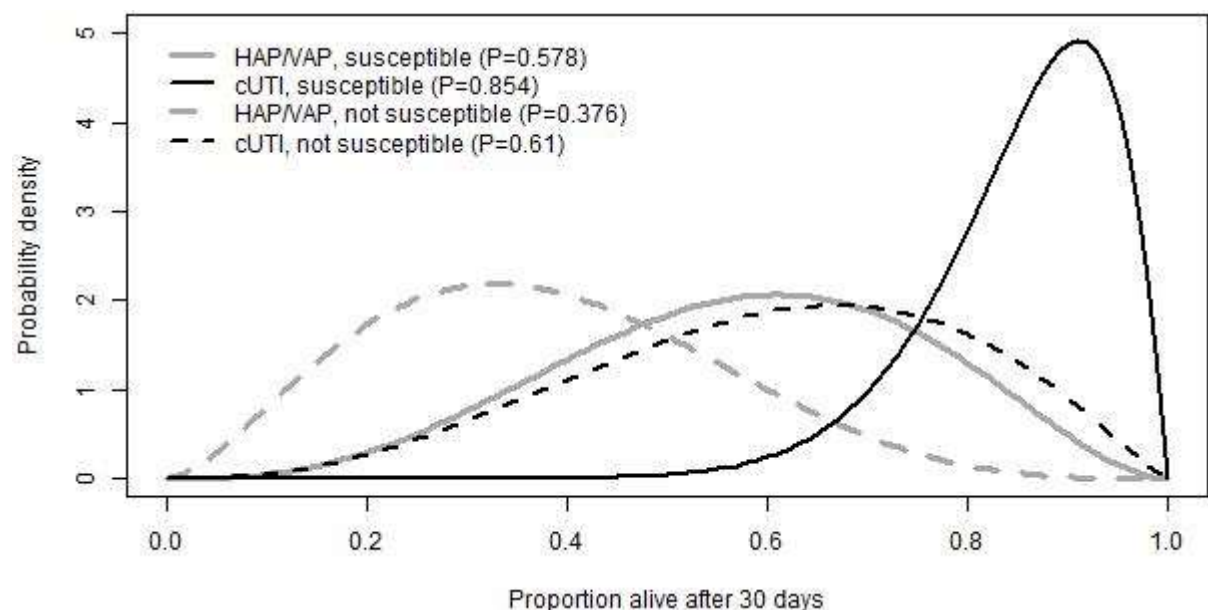
Furthermore, patients who are susceptible to treatment are expected to spend more time on the general medical ward and less on ICU and HDU, for all three sites of infection.

In the model, outcomes of HAP and VAP were modelled together, and so experts' responses were pooled. When pooling, outcomes for HAP and VAP were weighted by their relative occurrence in Tumbarello et al. (2013) - 0.283 (28/99) for HAP and 0.617 (71/99) for VAP. Tumbarello was chosen as the study where participants were the most representative of patients in the HVCSs that reported the proportion of patients with HAP that was ventilator-associated.

The pooled results for expert beliefs are shown in Figure 6 and Figure 7 and summarised in cUTI, complicated urinary tract infection; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia

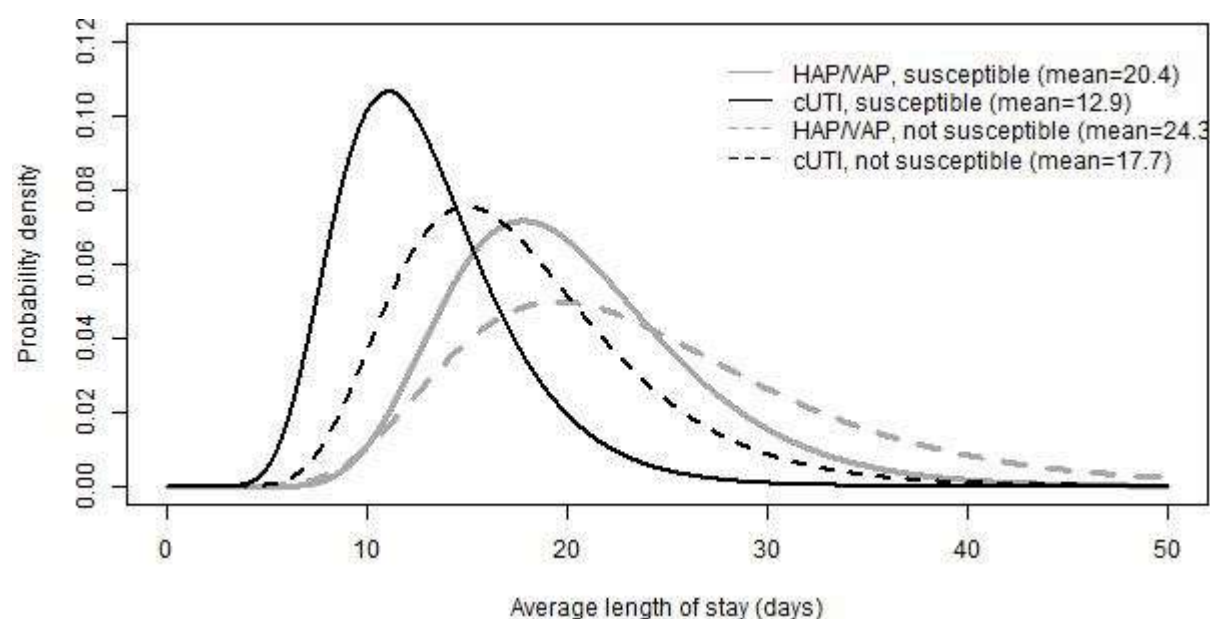
Table 14.

Figure 6. 30-day survival with HAP/VAP combined.



cUTI, complicated urinary tract infection; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia; P, proportion

Figure 7. Expected LoS with HAP/VAP combined.



cUTI, complicated urinary tract infection; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia

Table 14. Proportion (%) of hospital stay spent on ICU, HDU and general medical ward.

	ICU	HDU	General medical ward
HAP/VAP, susceptible	49.90	14.94	35.16
HAP/VAP, not susceptible	58.92	17.21	23.86
cUTI, susceptible	15.00	17.00	68.00
cUTI, not susceptible	23.33	18.33	58.33

cUTI, complicated urinary tract infection; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia; HDU, high dependency unit; ICU, intensive care unit

6.2.3. Validation of experts' estimates

We explored alternative sources of evidence to inform LoS in the model, in order to validate the elicitation results. In particular, we considered two UK-based studies that reported LoS in patients with carbapenem resistant organisms – CARBAR⁸⁰ and Merrick⁸¹, and the study by Muscedere⁷⁰ that was used to derive the relative reduction in the LoS associated with appropriate empiric therapy in the ES (see Section 8.2.3.8 for details).

The mean LoS in CARBAR⁸⁰ was 47.2 days. The median LoS in Muscedere⁷⁰ in patients who received appropriate and inappropriate empiric treatment was 27.9 and 42.2 days, respectively. This was

estimated to equate to the mean LoS of 43.1 days and 85.7 days, respectively (see Section 8.2.3.8 for details). The LoS in both studies was considerably longer than experts' estimates (~20 and ~24 days from the start of microbiology directed treatment in susceptible and resistant patients, respectively). However, the LoS in both studies was measured from hospital admission, rather than from the start of microbiology directed treatment following infection onset.

CARBAR reported that the average time between hospitalisation and infection was 8 days (median) for all patients, 16.8 days (mean) time for infections diagnosed from sputum samples and 13.9 days for UTI-related samples. In addition, the median time between infection onset and microbiology directed treatment in CARBAR was 5 days. Assuming that 13 (8 + 5) to 21.8 (16.8+5) days passed between admission and administration of microbiology directed treatment, the LoS from the start of microbiology directed treatment in CARBAR (25.4 to 34.2 days) was comparable to experts' estimates. Muscedere did not report the time between admission and infection onset, and so could not be directly compared to experts' estimates. In Merrick ⁸¹, the median LoS after infections caused by carbapenem resistant organisms was 24 days, comparable to the mean estimates from experts. The authors did not report the mean.

7. Existing economic evidence

7.1. Assessment of existing cost-effectiveness evidence and modelling approaches

A series of reviews of existing cost-effectiveness evidence and modelling approaches was conducted:

- A review of existing cost-effectiveness evidence for cefiderocol with a focus on studies that include decision-analytic models. The aims were to establish the existence of potentially policy-relevant models to guide NICE and NHS decisions; and to identify relevant analytical methods and data sources.
- A review of existing approaches to modelling resistant pathogens in the target population, currently and over time. The aim of this review was to identify methods that could be adopted for this purpose in EEPRU's modelling.
- A review of existing cost-effectiveness models in HAP/VAP to understand modelling approaches and data sources.
- A review of existing cost-effectiveness models in cUTI. Again, the purpose was to understand modelling approaches and data sources.

Each review involved searches of bibliographic databases using standardized search terms, selection of studies based on explicit inclusion criteria and data extraction using an agreed template. Details of each review are provided in Appendix 12. Here the key results of each review are outlined.

7.1.1. Review 1: existing cost-effectiveness evidence for cefiderocol

A total of 89 potentially relevant papers or abstracts were identified for the review from the searches. All the publications were screened using their titles and abstracts, and the only study included was in the form of a poster and provided limited detail regarding the sources of clinical evidence and how these were used in the modelling.⁸² This, together with the study's US focus, means it provides no basis to inform the current evaluation of cefiderocol.

7.1.2. Review 2: review of existing approaches for resistance modelling

Nine studies were included in this review. Five economic evaluations of ceftazidime/avibactam were included in this group. None of these assessed the implications of changes in resistance over time. Three analyses made assumptions (rather than drawing on evidence) about the proportions of patients with resistant infection in the relevant population, and the impact of resistance on clinical parameters.⁸³⁻
⁸⁵ The other two studies drew on evidence from observational studies to quantify the impact of resistance on relevant parameters in the modelling.^{85,86}

The other four studies in this review provided some indications of how resistance could be captured. One study assessed the appropriateness of alternative empiric therapies based on susceptibility data from a specific Taiwanese hospital.⁸⁷ Another looked at Procalcitonin-guided antibiotic stewardship and estimated the correlation between the percentage reduction in days of antibiotic use resulting from the Procalcitonin-guided test and antibiotic resistance.⁸⁸

The other two studies in this review attempted to deal with resistance through mechanistic infectious disease modelling. One used hypothetical data for illustrative purposes.⁸⁹ The other used the combination of a dynamic transmission model and a treatment pathway model as a generic framework to evaluate antibiotics for different indications and pathogens.⁹⁰ In principle, such a model could be capable of quantifying not just the direct health effects of a new antibiotic, but also the indirect impacts via any reduction in transmission of relevant pathogens. It could also reflect changes in resistance over time in response to different stewardship strategies and the introduction of new AMs. However, whether the model can achieve this in practice will inevitably depend on the available evidence and the assumptions necessary to address the evidence gaps.

7.1.3. Review 3: existing cost-effectiveness models in HAP/VAP

This review used an earlier systematic review⁹¹ to extract information on the characteristics of three relevant studies including target population, modelling assumptions, model structure and key evidence.⁹²⁻⁹⁴ All of these studies included standard cost-effectiveness models and did not consider the impact of alternative therapies on resistance patterns over time. One study attempted to include transmission rates in the modelling, but this was not extrapolated to estimate population-level health effects.⁹⁴ As a UK study, one study provided some potentially useful evidence sources for the current evaluation.⁹²

7.1.4. Review 4: existing cost-effectiveness models in cUTI

One study was identified⁹⁵ in addition to the models in cUTI identified in Review 2.^{82,84,85,87,90} As for Review 3, the UK-based studies provided some insights on evidence sources. The additional study,⁹⁵ was US-based and used micro-simulation to track patients allowing for treatment switching as microbiological information becomes available. A surveillance dataset was used to sample isolates and to determine susceptibility to different treatments. This use of susceptibility data rather than standard *in vivo* evidence from RCTs and other designs is novel and has the potential to address modelling challenges.

8. Methods for EEPRU quantitative assessment of value

8.1. Overview of EEPRU approach

The quantitative economic analysis developed for this evaluation comprises three components: an assessment of the INHEs of introducing cefiderocol within the HVCSs at the patient level; an assessment of INHEs within the HVCSs at the population level; and an assessment of how population-level INHEs within the HVCSs might appropriately be rescaled to reflect expected usage across the NHS. An overview of each component is provided below, and the methods for each component are described in the following sections. In line with the NICE Reference Case, the model perspective is the NHS and Personal and Social Services, health benefits are expressed in terms of quality-adjusted life-years (QALYs) and both costs and QALYs are discounted at a rate of 3.5% per annum.

The patient-level component of the model is structured similarly to models developed as part of other NICE activities, and characterises the likely comparative effectiveness of cefiderocol and existing AM usage scenarios; also the impact of cefiderocol and existing AM usage scenarios on costs, HRQoL and mortality over the lifetime of the patient.

The population-level component aggregates the patient-level predictions to the population level accounting for the size of, and growth over time in, the eligible patient population in England within each HVCS. This component also reflects how resistance is likely to develop to cefiderocol and existing AMs over time. The previous EEPRU framework outlined two broad approaches to modelling this: mechanistic dynamic transmission modelling which attempts to explain the way in which susceptible and resistant pathogens spread through the population; and statistical forecasting models that predict the number of people with infections with specific resistance profiles without explicitly modelling the underlying mechanistic processes of pathogen transmission and resistance acquisition.¹⁹ We considered both approaches, but ultimately used a forecast-based approach, for reasons detailed below.

The use of a transmission model was considered but not pursued on three grounds. Firstly, developing a mechanistic transmission model that characterises the spread of carbapenem-resistant organisms, with an adequate level of detail to model the introduction of cefiderocol, and that is appropriately calibrated to historical epidemiological data, was not considered feasible within the time and resources available for this 9-month project. Secondly, our clinical advisors considered that the direction and magnitude of the effects of the new treatments on transmission were uncertain and not well evidenced (see Section 9.3). Thirdly, advice during our previous EEPRU work ¹⁹ indicated that transmission modelling in AMR is an evolving science where the degree of parameter and structural uncertainty can lead to instability in model predictions and that, although there is no guarantee that a forecast-based approach will offer more certain or robust predictions, it should offer greater transparency.

The final quantitative assessment performed is to rescale the population-level INHEs observed in the HVCSs to reflect expected usage. This part of the quantitative assessment takes a very pragmatic approach seeking to identify the range of clinical scenarios in which cefiderocol is expected to be used, enumerate the corresponding population sizes using the best available evidence, and rescale the population-level INHEs estimated for the HVCS accordingly.

The literature on the economic evaluation of AMs has described a range of elements of value associated with these products that are not relevant to and, therefore, do not feature in evaluations of other drugs and health technologies.^{19,96} Following presentation of the quantitative assessments of value, we therefore discuss whether these additional elements of value might be delivered via use of cefiderocol, the extent to which they are captured by our quantitative assessments and, where they are not captured, whether they are likely to substantively modify the estimates of value presented (see Section 9.3).

8.2. Modelling direct patient net health effects in HVCS

8.2.1. Relationship with decision problem

8.2.1.1. Population

The patient populations modelled align with the decision problem outlined in Section 3. These are summarised in Table 15.

Table 15: HVCS patient populations modelled

Site	Pathogen	Mechanism	Setting
HAP/VAP	<i>Enterobacterales</i>	MBL	Microbiology-directed
HAP/VAP	<i>Pseudomonas aeruginosa</i>	MBL	Microbiology-directed
HAP/VAP	<i>Enterobacterales</i>	MBL	Risk-based empiric treatment
HAP/VAP	<i>Pseudomonas aeruginosa</i>	MBL	Risk-based empiric treatment
cUTI	<i>Enterobacterales</i>	MBL	Microbiology-directed
cUTI	<i>Pseudomonas aeruginosa</i>	MBL	Microbiology-directed

cUTI, complicated urinary tract infection; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia; MBL, metallo-beta-lactamases

8.2.1.2. Intervention

Cefiderocol is considered as monotherapy only due to a lack of *in vivo* or *in vitro* evidence about how it performs in combination with other agents. The clinical advisors confirmed that monotherapy was more likely to be used in practice, but indicated that combination therapy was more likely for *Pseudomonas aeruginosa*.

8.2.1.3. Comparators

A wide range of drugs is considered relevant in the HVCSs, and different drugs were considered relevant depending on the site, pathogen, mechanism and setting. The full list of comparators is provided in Section 3. Due to the paucity of data available to inform the comparative effectiveness assessment (see Section 5), and our reliance on *in vitro* susceptibility data to inform comparative effectiveness, it was possible to take a simplified approach to modelling these comparators rather than conducting a fully incremental analysis of all available AM options as is typically recommended in economic evaluation. The approach taken is documented in the following section.

8.2.2. Model structure

The model structure differs according to the setting (MDS or ES) but not the site, pathogen or mechanism of resistance. We describe the structure for the MDS first as it is more straightforward and forms part of the ES model structure.

Due to the paucity of *in vivo* data relevant to the modelled HVCSs (see Section 5.4), we have assumed that differences across treatments in *in vitro* susceptibility are predictive of *in vivo* clinical outcomes. This was considered reasonable by the clinical advisors to this project, and evidence relating to the treatment susceptibility as a surrogate for clinical outcomes is reviewed in Section 5.6.1. We link susceptibility to time in hospital and mortality. We do not model the development of infection sequelae such as sepsis. This would have required a range of additional evidence including the rate of development of sepsis, how this relates to susceptibility to the treatment administered, and mortality and hospitalisation outcomes conditional upon whether a patient developed sepsis. Given the sparsity of evidence available, including these additional parameters was not considered appropriate. We would, however, expect 30-day mortality and hospitalisation outcomes to implicitly reflect the possibility that patients may develop additional complications including sepsis. Repeat infection following discharge was also not explicitly modelled (though will be implicitly reflected in the mortality data) as these were considered unlikely to be a significant driver of population-level INHes in the HVCSs.

As well as differences in effectiveness, we model differences in treatment safety. We focus on nephrotoxicity and, in particular, the occurrence of AKI as this was considered to have the most significant implications for the modelling in terms of driving treatment choices (with clinicians keen to avoid highly nephrotoxic comparator drugs) and influencing INHes as cefiderocol is expected to be associated with lower rates of nephrotoxicity than some comparators.

Ototoxicity was raised by our clinical advisors as a safety concern associated with use of aminoglycosides. This was not modelled as it was expected that significant hearing impairment associated with aminoglycosides would be rare in this patient group.⁹⁷ Reduced rates of *C. difficile*

infection were highlighted by a number of stakeholders as a potential benefit of the new drugs. This was not included in the modelling as rates of *C. difficile* are very low⁹⁸ (Section 5.6.3).

Shionogi's manufacturer submission did not include an economic model. However, it suggested modelling the benefits of improved empiric therapy choice using data linking time to appropriate therapy to key outcomes (mortality, hospitalisation). This approach was not pursued as it was not clear how patients who never receive appropriate therapy (e.g., because they are not susceptible to any available treatment options) should be reflected in this type of model structure. In particular, it was unclear how a model based around time to appropriate therapy could accommodate all comparisons of interest, i.e., use of cefiderocol in the ES, use of cefiderocol in the MDS, and no use of cefiderocol. The latter two treatment pathways would both involve a similar time taken to reach the MDS, but if cefiderocol were used in the MDS a higher proportion of people would be expected to receive appropriate therapy at this point.

8.2.2.1. Model structure for microbiology directed setting

In the MDS, each patient's susceptibility to available treatment options is known, and treatment can be tailored accordingly. Based on feedback from our clinical advisors, the two main reasons for initiating treatment with cefiderocol (provided patients are susceptible to it) within the MDS HVCSs would be that patients are either: (i) not susceptible to any other available treatment options (i.e., patients are completely MDR to relevant existing treatment options); or (ii) that the only other treatments to which they are susceptible carry an elevated risk of nephrotoxicity. We include colistin and aminoglycosides within the category of nephrotoxic drugs as our clinical advisors indicated that they are likely to be associated with elevated levels of nephrotoxicity. To reflect these considerations, patients within the MDS are divided into three categories based on their susceptibility to existing therapies and, within each category, further subdivided according to their susceptibility to cefiderocol. Table 16 shows these subgroups, how they determine treatment choice under existing care, and how that would change if cefiderocol was to become available to this patient group. The groups for which a switch to cefiderocol is expected are highlighted in bold.

In the group of patients who are susceptible only to colistin or an aminoglycoside, and susceptible to cefiderocol, cefiderocol offers a safety advantage. In the group of patients who are not susceptible to any available treatment options and, in the absence of the new treatment under evaluation, would receive multi-drug salvage therapy, cefiderocol offers a safety and efficacy advantage. This is because, for many patients, multi-drug salvage therapy would be expected to include a colistin or aminoglycoside component. Throughout the modelling, isolates classed as intermediate resistant are grouped with those which are resistant as patients infected with intermediate resistant and resistant pathogens are expected to experience similar outcomes in the HVCS based on feedback from EEPRU's clinical advisors, and much of the data relating mortality and hospitalisation to susceptibility follows this grouping. Our

clinical advisors noted that it may be possible to overcome intermediate resistance via higher dosing, but also considered that it would be difficult to evidence this within the model. Given the diverse range of data sources informing susceptibility and the link between susceptibility and outcomes, and the level of reporting within these studies, it was not feasible to explore the implications of differential outcomes between intermediate resistant and resistant patients.

In the MDS the model is, therefore, driven by the proportion of individuals within each category of “susceptibility to existing drugs” and the proportion of individuals susceptible to cefiderocol. This is based on susceptibility data as documented in Section 8.2.3.2. The comparison made within the model is between the overall MDS cohort who receive tailored therapy with the new drug available (column four of Table 16) and the overall MDS cohort who receive tailored therapy under existing treatment options only (column 3 of Table 16).

Table 16: Subgroups within the MDS and their treatment choices

Susceptibility to existing drugs	Susceptibility to cefiderocol	Therapy under existing care	Therapy with new drug available
Susceptible to one or more non-colistin/aminoglycosides option	Susceptible	Non-colistin/amino	Non-colistin/amino
	Resistant	Non-colistin/amino	Non-colistin/amino
Susceptible only to colistin or aminoglycosides	Susceptible	Colistin/amino-based	Cefiderocol
	Resistant	Colistin/amino-based	Colistin/amino-based
Not susceptible to any available treatment options	Susceptible	Multi-drug salvage	Cefiderocol
	Resistant	Multi-drug salvage	Multi-drug salvage

Notes: orange indicates that clinician initiates treatment with drug with poor safety, red indicates that clinician initiates treatment with drug with poor efficacy (and possibly safety). Bold indicates patient groups for whom susceptibility evidence would initiate a switch to cefiderocol. Amino, aminoglycoside.

Importantly, the fact that the susceptibility profile is known prior to initiation of treatment in the MDS, alongside the assumption that susceptibility is the sole predictor of treatment effectiveness, means that we do not need to model each individual treatment option within the MDS. For example, it is not relevant (to clinical outcomes) whether a patient is susceptible to fosfomycin or aztreonam as susceptibility to these treatments would be assumed to result in the same outcomes. Although there are differences in the costs of therapies, these are modest in relation to other costs such as that of hospitalisations which may include periods in the ICU/HDU. In practice, patients may receive a combination of agents, but this is not modelled explicitly due to a lack of evidence. EEPRU’s clinical advisors considered it reasonable to assume that, in the MDS, patients susceptible to a single AM within

a multi-agent regimen perform as well as those susceptible to all components of that regimen (i.e. it does not matter if you are susceptible to drug A, drug B or drug A and B, as long as you are susceptible to one of the agents received).

Following receipt of treatment in the MDS, patients are modelled to experience one of four alternative 30-day outcomes which determine their long-term outcomes (Figure 8). A decision tree is used to determine the distribution of patients across these categories at 30 days. This is as shown in Figure 9. Probabilities highlighted in bold differ by treatment in this figure. In the MDS we only model one line of treatment explicitly, though hospitalisation and mortality evidence will reflect the fact that some patients entering the MDS receive multiple lines of therapy.

All patients face a risk of death due to their infection and comorbidities ($p_{\text{bgrrdD30d_MDS}}$). The risk differs according to whether patients have received a treatment to which they are susceptible or not. In the MDS, given that treatments are tailored according to patients' known susceptibility profiles, only patients infected with a fully MDR infection (who receive multi-drug salvage treatment) are expected to face the elevated risk of death of those non-susceptible to treatment. The efficacy advantage of cefiderocol is, therefore, driven by the proportion of people who, rather than having “multi-drug salvage”, are given cefiderocol (see Table 16), as these patients switch from experiencing the mortality of non-susceptible patients to experiencing the mortality of susceptible patients.

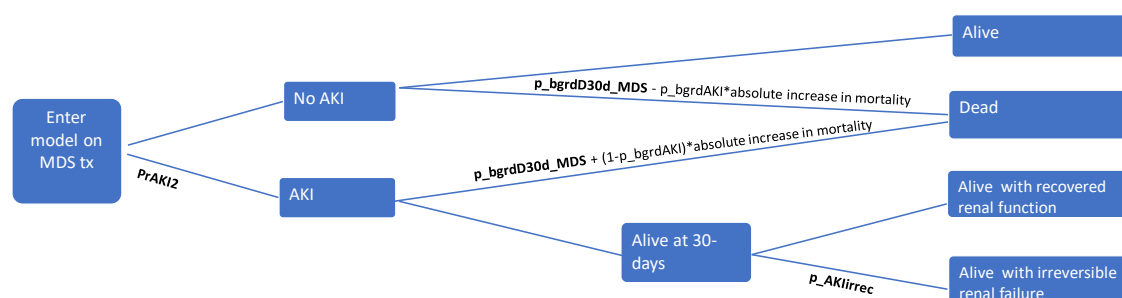
In addition, patients face differing drug-related risks of experiencing an AKI. Patients who experience an AKI face an elevated risk of death compared to those who do not. When modelling the effect of AKI on mortality, we account for the fact that the available mortality data already reflect both the underlying risk of AKI associated with currently available non-colistin/aminoglycoside AMs, and the background risk of AKI associated with patients underlying comorbidities and infection (see Figure 9). Patients who experience an AKI and survive until 30 days face a risk of adverse long-term outcomes according to whether they have: (i) recovered their renal function; or (ii) suffered irreversible renal failure i.e., developed CKD.

Figure 8: 30-day outcomes in the MDS

1- Dead
2- Alive no AKI
3- Alive post_AKI with recovered renal function
4- Alive post_AKI with irreversible renal failure

AKI, acute kidney injury

Figure 9: Decision tree used to calculate impact of AKIs on 30-day outcomes in MDS

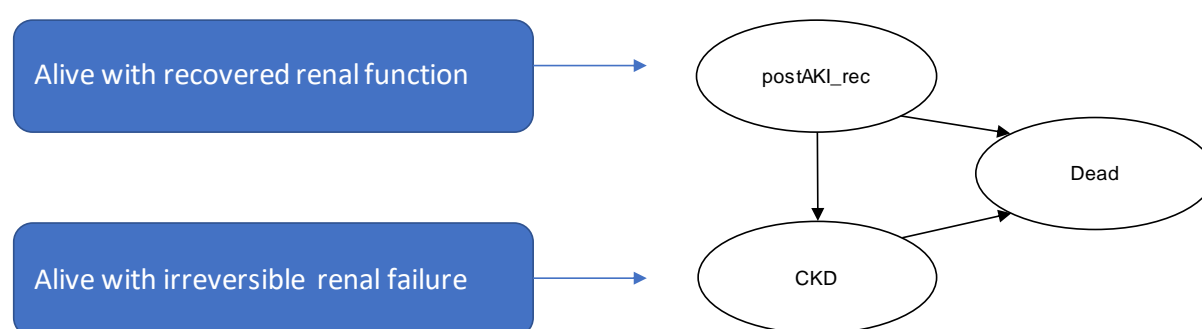


The absolute increase in risk of mortality associated with an AKI is estimated by applying OR_AKI_death to p_bgrdD30d_MDS and then subtracting p_bgrdD30d_MDS

At 30 days, patients who are discharged alive without renal dysfunction are assigned a comorbidity-adjusted QALY outcome estimated using an alive-dead area-under-the-curve approach. This is independent of the assigned treatment, as patients alive at 30 days without a history of AKI are assumed to experience similar outcomes regardless of the treatment they received for their infection.

Patients discharged with recovered renal function face the same HRQoL outcomes, but they face an additional risk of progressing to CKD and elevated mortality. Patients discharged with CKD or who develop CKD face further elevated mortality, reduced HRQoL and additional health care costs. The experience of the two groups of patients with a history of AKI is modelled as a semi-Markov process (with transition probabilities dependent on time in model) for all transitions as shown in Figure 10.

Figure 10: Markov model used to calculate post-30-day outcomes in patients with recovered renal function and irreversible renal failure



AKI, acute kidney injury; CKD, chronic kidney disease

8.2.2.2. Model structure for the risk-based empiric setting (ES)

The approach taken in the ES is similar to that taken in the MDS in terms of the possible 30-day outcomes patients can experience and the long-term implications of these outcomes. However, the

decision tree describing differences across comparators in the first 30-days is more complex for two reasons. Firstly, there is a need to model outcomes both in those correctly identified as having the pathogen-mechanism combination suspected, as well as those who were labelled as high-risk but in fact have a different causative pathogen or mechanism. Secondly, there is a need to model both the ES phase of treatment, and progression of some patients to the MDS for further treatment.

Unlike in the MDS, in the ES the susceptibility of patients to treatments provided is unknown at the time of initiating empiric treatment. It is, therefore, necessary to model the probability of susceptibility to individual treatment combinations as this determines clinical outcomes and, in particular, the need for further treatment. Since, as documented in 4.2.4, there are a number of feasible treatment combinations for these patients, to simplify the modelling we compare empiric use of cefiderocol in the ES to two alternative treatment options:

- (i) The non-colistin or aminoglycoside-based treatment combination with the current highest estimated susceptibility in the UK population.
- (ii) The colistin or aminoglycoside-based treatment combination with the current highest estimated susceptibility in the UK population.

When considering possible treatment pathways in the ES, three possible pathways are relevant:

ES1: empiric use of cefiderocol followed by existing treatments in the MDS.

ES2: empiric treatment using existing therapies followed by cefiderocol in the MDS.

ES3: use of existing therapies in both the ES and MDS.

The full list of comparators in the ES is summarised in Table 17 alongside their shorthand labels which are used in the results section.

Table 17: Comparator treatment pathways in the ES

Empiric treatment	MDS treatment	Shorthand label
Cefiderocol	Existing therapies	E1
Non-colistin or aminoglycoside-based	Existing therapies	E2nca
Colistin or aminoglycoside-based	Existing therapies	E2ca
Non-colistin or aminoglycoside-based	Cefiderocol used if indicated in the MDS (see Table 16)	E3nca
Colistin or aminoglycoside-based	Cefiderocol used if indicated in the MDS (see Table 16)	E3ca

ES, empiric setting; MDS, microbiology-directed

Repeated usage of cefiderocol in the MDS for patients who fail cefiderocol in the ES was not modelled as this was not considered to represent a priority use for cefiderocol.

Thirty-day outcomes in the ES are determined by a decision tree which comprises three-subcomponents:

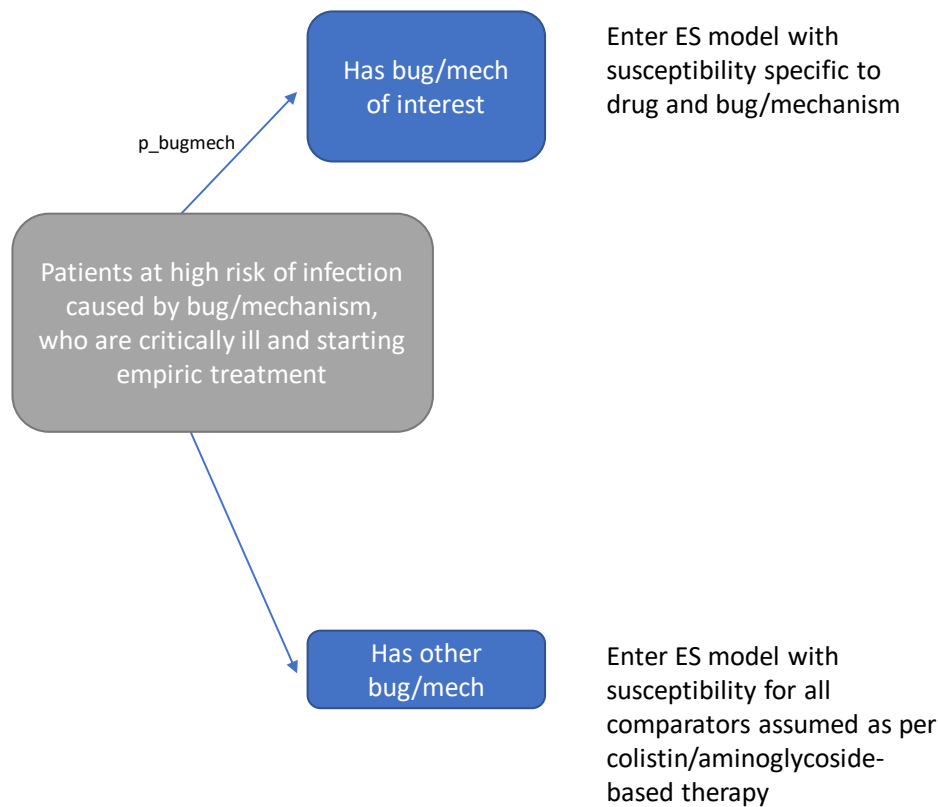
- (i) the risk of carrying the pathogen-mechanism of concern;
- (ii) outcomes at the point at which patients are assessed for MDS treatment, i.e. at around 3-5 days when susceptibility results report; and
- (iii) 30-day outcomes following MDS assessment.

Each of these is considered in more detail below.

- (i) Risks of carrying the pathogen-mechanism of concern

Patients may or may not have the suspected pathogen-mechanism of concern. We assume that patients who do not have the pathogen-mechanism of interest experience the same effectiveness outcomes regardless of the choice of empiric treatment (though safety differs), as our clinical advisors confirmed that these patients represented a broadly susceptible population (rather than a population enriched with pathogens carrying other resistance mechanisms), and that for this reason effectiveness is likely to be similar across all empiric treatment options considered. For simplicity we assume that patients who have a different pathogen-mechanism experience the susceptibility associated with colistin/aminoglycoside-based therapy in people with the pathogen-mechanism of interest regardless of the choice of treatment. Colistin/aminoglycoside-based therapy was chosen as more representative of outcomes across susceptible patients as this treatment class showed robust and high susceptibility across subgroups and scenarios. The structure of this element of the ES model is presented as Figure 11.

Figure 11: First component of 30-day outcomes model for ES: risk of carrying pathogen-mechanism of concern



ES, empiric setting

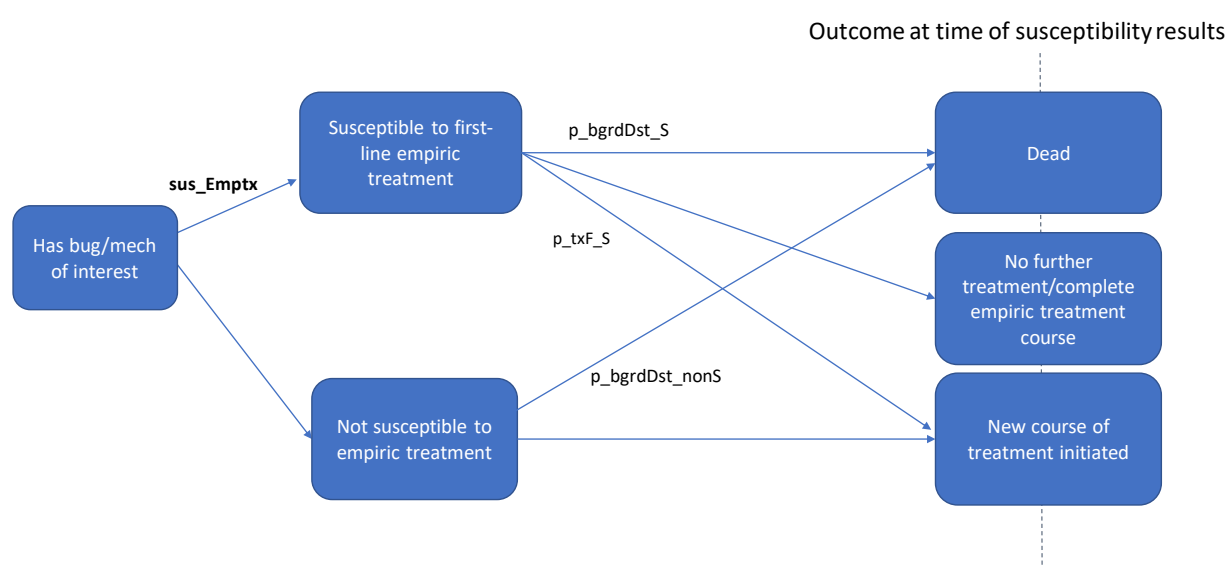
(ii) Outcomes at the point at which patients are assessed for MD treatment

At initiation of empiric treatment, patients are classified by the model as susceptible or non-susceptible to their empiric therapy. As in the MDS, susceptibility is the driver of differences in effectiveness across treatments. Note that we are able to model differences in susceptibility across treatments used in the ES dependent on whether a patient is susceptible or non-susceptible, even though clinicians will not observe this information until patients enter the MDS.

At the point at which patients' microbiology results become available, patients may have died, may require initiation of a new AM treatment (e.g. due to lack of efficacy) or may complete their course of empiric treatment. The probability of these three outcomes depends on whether patients were susceptible to their empiric treatment or not, but not directly on the choice of specific treatment. Patients

who have received empirically a treatment to which they are later found not to be susceptible are all assumed to require further treatment in the MDS, provided they survive until microbiology results are available. This assumption is based on evidence presented in Tumbarello *et al* 2013, which found that all patients who received inappropriate empiric treatment and survived until their microbiology results were received switched to appropriate therapy (further details on Tumbarello *et al* are provided in 8.2.3.4).⁷²

Figure 12: Second component of 30-day outcomes model for ES: outcomes at the point at which patients are assessed for MD treatment.



NB: mortality ($p_{bgrd_Dst_S}$ and $p_{bgrdDst_nonS}$) is also adjusted to reflected differences in mortality due to AKI, in the same way as shown in Figure 13, but this is not shown for parsimony.

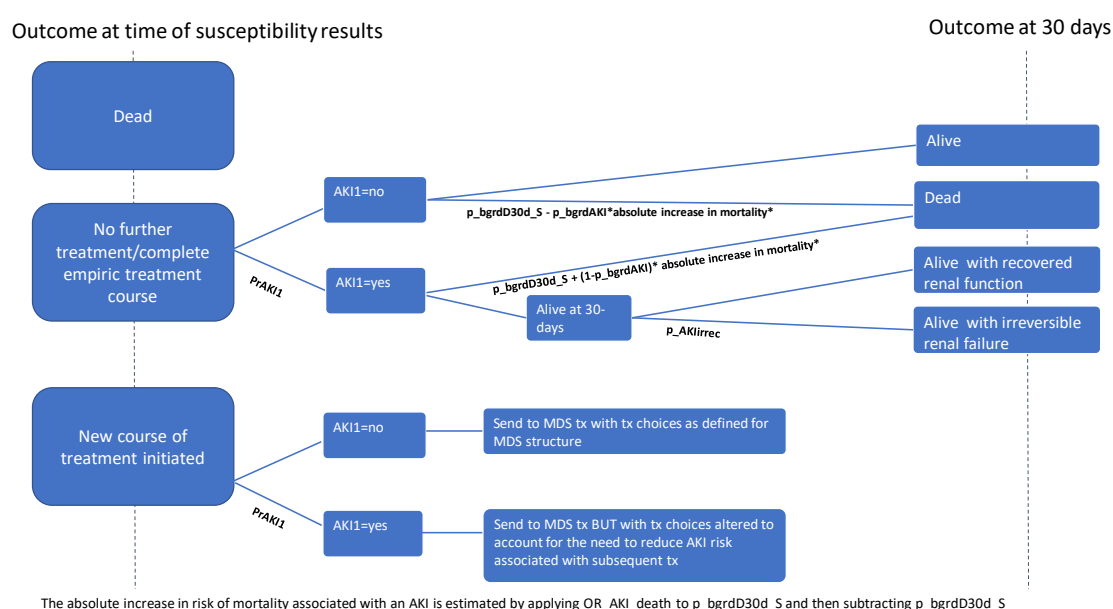
(iii) 30-day outcomes following assessment for MD treatment

People who survive until the time point of assessment for MD treatment enter the third part of the decision tree which is shown in Figure 13. Those requiring no further treatment face a risk of dying between this point and 30 days which depends on whether they experienced an AKI. Those surviving to 30 days face the possibility of entering the (i) alive; (ii) alive with recovered renal function or (iii) alive with irreversible renal failure health states described in Figure 13. Whilst patients may experience an AKI following empiric treatment, clinicians confirmed that in this patient group, where treatment options are limited, the AKI alone would not typically trigger a treatment switch, provided the treatment was effective.

Patients who require further treatment enter the MDS component of the model. Their outcomes depend on whether they experienced an AKI following first-line treatment (i.e. this is “remembered” within the model) as this determines both their outcomes (patients who experience an AKI experience elevated

mortality and the implications of reversible or irreversible kidney damage) and their choice of treatment in the MDS. Our clinical advisors informed us that patients requiring further treatment in the MDS, who experienced an AKI following treatment in the ES are unlikely to receive colistin- or aminoglycoside-based treatment in the MDS. Patients who fit this profile, and are only susceptible to colistin or aminoglycoside-based treatment are, therefore, assumed to receive multi-drug salvage therapy in the MDS, or the new drug if available. For these patients, multi-drug salvage therapy is assumed not to include colistin or an aminoglycoside. Instead, they are assumed to receive the outcomes of multi-drug salvage therapy without elevated risk of AKI.

Figure 13: Third component of 30-day outcomes model for ES: 30-day outcomes following assessment for MDS treatment



AKI, acute kidney injury

In the absence of evidence to support more detailed modelling, we assume that a patient's susceptibility to treatment is the same in the ES and MDS. In reality, patients entering the MDS who were already assessed as high-risk of carrying a highly resistant pathogen in the ES are likely to receive aggressive treatments in the ES which may change their resistance profile in the MDS. The nature of the effects on individual resistance are hard to predict as they are influenced by the treatment received in the ES, the effectiveness of this treatment and the development of acquired resistance. These are not, therefore, considered within the model.

8.2.3. Sources of evidence

8.2.3.1. Identification of evidence

Susceptibility evidence and evidence linking susceptibility to mortality and hospitalisation was obtained via the systematic reviews and structured expert elicitation as described in Sections 5.4, 5.5 and 5.6.1. Other key clinical parameters were obtained from existing systematic reviews where possible, otherwise clinical parameters were obtained from existing UK cost-effectiveness models. Quality of life weights (utilities) were obtained from a systematic review (described below) and cost parameters via targeted searches.

8.2.3.2. Clinical parameters – susceptibility evidence

The susceptibility data used in the model base case analysis are summarised in

Table 18. These represent the mean values of the samples used in the probabilistic sensitivity analysis, along with 95% percentile-based confidence intervals. Five key susceptibility parameters inform the model:

- One parameter describes susceptibility to cefiderocol in the MDS and ES.
- Two parameters describe susceptibility to colistin/aminoglycoside-based therapy and to non-colistin/aminoglycoside-based therapy in the ES.
- Two parameters describe the number of individuals in each category of susceptibility in the MDS as shown in Table 16 (namely, susceptible to a non-colistin/aminoglycoside AM, susceptible only to a colistin/aminoglycoside AM).

Susceptibility to existing drugs is obtained from both the analysis of PHE data and the NMA, as described in Section 4.5. These analyses can be combined to provide evidence on absolute rates of susceptibility to AMs for the HVCS. This evidence required further adjustment before it could be used in the economic model, with different adjustments for the ES and MDS. The methods employed to obtain estimates for these two settings are discussed in turn, with further details provided in Appendix 13. Of note, whilst evidence on susceptibility to meropenem was available, this was not used in the economic modelling. This is because clinical advice was that, for meropenem, susceptibility amongst carbapenem-producing pathogens was not a good surrogate predictor of clinical outcomes. This reflects advice in the literature.^{99,100} Hence, whilst meropenem is included as a comparator in the PICOS, it is assumed to have zero efficacy in the economic modelling (and so not actively modelled).

Susceptibility is estimated to be specific to the pathogen-mechanism subgroup of interest but is assumed to generalise across sites and settings. This was considered a reasonable assumption by our clinical advisors and preferable to further subgrouping the susceptibility data given the small sample sizes available to inform these parameter estimates for the HVCS.

Table 18: Susceptibility parameters by pathogen-mechanism subgroup (all evidence was from a combination of PHE data and the NMA)

Pathogen-mechanism subgroup	Description	Value	95% CI
<i>MBL Enterobacterales</i>	Proportion of isolates susceptible to one or more non-colistin/aminoglycosides option	91%	87% to 95%
<i>MBL Enterobacterales</i>	Proportion of isolates susceptible only to colistin or aminoglycosides	7%	4% to 12%
<i>MBL Enterobacterales</i>	Proportion of isolates susceptible to cefiderocol	67%	22% to 95%
<i>MBL Enterobacterales</i>	Proportion of isolates susceptible to the most effective non-colistin/aminoglycoside-based empiric treatment	Not applicable	Not applicable
<i>MBL Enterobacterales</i>	Proportion of isolates susceptible to the most effective colistin/aminoglycoside-based empiric treatment	96%	90% to 99%
<i>MBL Pseudomonas aeruginosa</i>	Proportion of isolates susceptible to one or more non-colistin/aminoglycosides option	28%	0% to 100%
<i>MBL Pseudomonas aeruginosa</i>	Proportion of isolates susceptible only to colistin or aminoglycosides	71%	0% to 100%
<i>MBL Pseudomonas aeruginosa</i>	Proportion of isolates susceptible to cefiderocol	98%	85% to 100%
<i>MBL Pseudomonas aeruginosa</i>	Proportion of isolates susceptible to the most effective non-colistin/aminoglycoside-based empiric treatment	28%	0% to 100%
<i>MBL Pseudomonas aeruginosa</i>	Proportion of isolates susceptible to the most effective colistin/aminoglycoside-based empiric treatment	100%	97% to 100%

CI, confidence interval; MBL, metallo-beta-lactamases

NB: For the MBL population the PICOS does not include any treatments in the ES that do not include colistin or an aminoglycoside.

Susceptibility for AMs used in the ES

Clinical advice, as reflected in the PICO, was that combination treatment was frequently used in the ES. Hence evidence on absolute susceptibilities for individual drugs needed to be converted to evidence on overall susceptibility to combination treatments, to identify the most effective combination treatments. This requires information on conditional susceptibility (e.g. for combination treatment of AM ‘X’ and AM ‘Y’, evidence is required on the susceptibility to AM ‘Y’ conditional on being resistant to AM ‘X’). For use in the model, the most effective ES treatment which did not include colistin or an aminoglycoside was considered, as well as the most effective ES which did. A discussion of the available evidence on conditional susceptibility is provided in Appendix 13.

For the base-case analysis, evidence on absolute susceptibilities for combination treatments and monotherapies was obtained from the NMA based on EUCAST studies (Section 4.5) applied to the absolute colistin susceptibility from the PHE data (colistin was chosen as the reference AM as it appeared in the majority of studies, and susceptibility to this AM was relatively constant overtime as illustrated by an analysis of PHE data; see Appendix 18). Where the NMA provided evidence for multiple AMs within the same class (such as aminoglycosides), the most effective AM was used. The assumption of independence of absolute susceptibilities was relaxed in scenario analyses, as detailed in Appendix 13 (relaxing this assumption was not possible for the *Pseudomonas aeruginosa* population due to an absence of evidence).

There are two main approaches for defining breakpoints for susceptibility evidence (which in turn affect relative and absolute rates of susceptibility): EUCAST and CLSI (see Section 5.1.1.1). The former was judged to be most relevant to the UK, hence evidence from studies using EUCAST breakpoints was used in the base-case. A scenario analysis included only CLSI studies.

Another scenario analysis used only evidence from PHE, as this represents UK-specific evidence. In this scenario, evidence for cefiderocol comes from the EUCAST NMA as no susceptibility evidence was available for cefiderocol from PHE. As there was insufficient evidence for fosfomycin in the PHE data, this scenario assumes that fosfomycin is not used (as fosfomycin and colistin are the only comparators for the *Pseudomonas* population, this scenario was only run for the *Enterobacterales*-MBL population). Additional scenarios were conducted in which evidence for all other treatments came from the PHE data with cefiderocol and fosfomycin evidence coming from their own separate networks. For each population there were two such scenarios; one which was restricted to EUCAST studies and one which was restricted to CLSI studies.

For the probabilistic sensitivity analysis (PSA) (which was performed for the base-case analysis only), two sources of uncertainty were considered:

- Uncertainty in the OR obtained from the NMA posterior distribution.
- Uncertainty in the absolute susceptibility of colistin (to which OR are applied), obtained from PHE data and modelled using a beta distribution.

As discussed in Sections 5.5.4.3 and 5.8 agreeing on the choice of comparators for pathogen-mechanisms was a challenge throughout the project, and some inconsistencies were introduced into the review and NMA by this issue. These were explored through a series of sensitivity analyses (see Sections 5.5.4.3 and 5.8) which indicated that the results of the NMA of CLSI studies was somewhat sensitive to these choices. Results for the CLSI *Enterobacterales* network varied according to the choice of comparators and inclusion of the Kohira *et al.* study, whilst results of the CLSI *Pseudomonas aeruginosa* network varied according to the choice of comparators. For the CLSI *Pseudomonas*

aeruginosa NMA, including only comparators specific to the pathogen resulted in changes to the odds ratios estimated from the NMA but these did not translate to substantive differences in absolute susceptibilities and so this scenario was not explored in the modelling. For the CLSI *Enterobacterales* network differences in absolute susceptibility were observed across both scenarios. Due to limitations on the number of scenarios that could feasibly be explored in this project, results are included for the CLSI scenario that contrasted most with the base case (restricting to pathogen-specific comparators, including Kohira et al. data). We note that of these CLSI *Enterobacterales* scenarios, the scenario included within the modelling has the most favourable susceptibility for cefiderocol.

Susceptibility for AMs used in the MDS

When microbiology test results are available it is assumed that patients will receive an AM to which they are susceptible (if they are susceptible to an AM). It was further assumed that, given their toxicity, use of either colistin or an aminoglycoside would be reserved for when a patient was not susceptible to any other relevant AMs. Hence, for use in the economic model, it was necessary to convert absolute susceptibility evidence for each AM into the proportion of patients falling into each of the following mutually exclusive groups:

1. Susceptible to an AM that is not colistin or an aminoglycoside
2. Susceptible only to colistin or an aminoglycoside
3. Not susceptible to any available treatment options

The AMs contributing to the first susceptibility grouping are:

- Fosfomycin (both populations).
- Aztreonam (*Enterobacterales*-MBL only).
- Tigecycline (*Enterobacterales*-MBL only).

In the ES susceptibility to a given AM was assumed independent of susceptibility to any other AM. This assumption could also be used to derive the proportion in each susceptibility group for the MDS. A discussion of the appropriateness of this assumption is provided in Appendix 13. This suggested that, in the MDS, the assumption of independence did not hold. Instead, evidence from PHE was used to estimate the bias arising when assuming independence to derive the proportion in each susceptibility group. This was quantified as a scaling factor which was then used to adjust estimates of the proportion in each susceptibility group obtained from the NMA using an assumption of independence of susceptibilities. Note that, for *Pseudomonas aeruginosa*, there is only one non-toxic AM in the MDS, so no adjustment is required. A scenario analysis that only used isolate-level data from PHE was also considered. Due to insufficient evidence, this scenario assumes that fosfomycin is not used.

For the PSA, two primary sources of uncertainty were considered:

- Uncertainty in the ORs obtained from the NMA posterior distribution.
- Uncertainty in the scaling factor used. This in turn had two components: variation in the true proportions in each susceptibility group from the PHE data (modelled using a Dirichlet distribution), and variation in the absolute susceptibility to each AM in the PHE data (modelled using a beta distribution).

Overview of options for including susceptibility data in the economic model

The evidence sources and assumptions used when generating susceptibility data for use in the economic model (for both cefiderocol and the comparators) are described in Table 19.

In MBL *Enterobacterales*, cefiderocol susceptibility is sensitive to the breakpoints used. In the scenarios using the EUCAST breakpoints, cefiderocol susceptibility is 65-69% whereas in the scenarios using CLSI breakpoints this increases to 87-98%. Empiric use of colistin/aminoglycoside-based therapy is associated with similar susceptibility across scenarios of 94-97%. In the MDS, comparator outcomes are similar across scenarios 1-3 with 91-97% of patients susceptible to a non-colistin/aminoglycoside-based treatment, and approximately 3-7% only to a colistin/aminoglycoside-based treatment. Use of the PHE data which does not include fosfomycin increases the proportion of patients susceptible only to a colistin/aminoglycoside-based treatment to 20%.

In MBL *Pseudomonas aeruginosa*, in most scenarios cefiderocol is associated with a high susceptibility of 98%-100%, which is comparable to the susceptibility for empiric use of colistin/aminoglycoside-based therapy (100% across scenarios). Scenario 4 which uses a lower baseline susceptibility for colistin, results in a lower susceptibility for cefiderocol (62%) than colistin/aminoglycoside-based empiric therapy (susceptibility 81%). Susceptibility to non-colistin/aminoglycoside-based empiric therapy varies markedly across scenarios (3-96%), with susceptibility to comparators much higher when evidence using the CLSI breakpoints is included. A similar pattern is observed in the MDS where the proportion of patients susceptible to a non-colistin/aminoglycoside-based treatment is much higher when evidence using the CLSI breakpoints is included.

As previously noted, to obtain absolute susceptibilities for each AM, ORs from the NMA were applied to the absolute PHE colistin susceptibility values. For the *Pseudomonas aeruginosa* population, colistin susceptibility was 100%, so a continuity correction was applied. As this baseline susceptibility was very high, resulting estimates for the other AMs could end up being large, even if the ORs were small. This effect was compounded by the skewed distributions for the odds ratios. Hence, even though fosfomycin was associated with very low odds ratios, it still had a resulting high susceptibility in some of the scenarios considered. Therefore, a scenario using a lower baseline colistin susceptibility level was run based on values from SIDERO WT.

Table 19 Sources and assumptions for susceptibility data

Scenario	Source of susceptibility data	Empiric setting: assume independence?
<i>Enterobacteriales</i>-MBL population		
Base-case	NMA: EUCAST studies	Yes
S1	NMA: CLSI studies	Yes
S2	PHE data, with cefiderocol and fosfomycin data from separate cefiderocol and fosfomycin networks (EUCAST studies).	Yes
S3	PHE data, with cefiderocol and fosfomycin data from separate cefiderocol and fosfomycin networks (CLSI studies).	Yes
S4	PHE data (cefiderocol from EUCAST NMA, excludes fosfomycin)	No
<i>Pseudomonas aeruginosa</i> population		
Base-case	NMA: EUCAST studies	Yes
S1	NMA: CLSI studies	Yes
S2	PHE data, with cefiderocol and fosfomycin data from separate cefiderocol and fosfomycin networks (EUCAST studies).	Yes
S3	PHE data, with cefiderocol and fosfomycin data from separate cefiderocol and fosfomycin networks (CLSI studies).	Yes
S4	NMA: EUCAST studies, absolute colistin susceptibility values from SIDERO WT	Yes

CLSI, Clinical Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility

Testing; NMA, network meta-analysis; PHE, Public Health England

Table 20 Susceptibility values used in the economic model

	Base-case	S1	S2	S3	S4
<i>Enterobacteriales</i>-MBL population					
Empiric treatment setting					
Susceptibility to the most effective non-colistin/ aminoglycoside	Not applicable				
Most effective non-colistin/ aminoglycoside	None				
Susceptibility to the most effective colistin/ aminoglycoside	96%	97%	95%	97%	94%
Most effective colistin/ aminoglycoside	Colistin + fosfomycin	Colistin + fosfomycin	Colistin + fosfomycin	Colistin + fosfomycin	Colistin + tigecycline
Microbiology-directed setting					
Susceptibility to a non-colistin/ aminoglycoside	91%	97%	91%	95%	77%
Susceptibility to colistin/ aminoglycoside	7%	3%	7%	4%	20%
Susceptibility to cefiderocol	67%	87%	69%	98%	65%
<i>Pseudomonas aeruginosa</i> population					
Empiric treatment setting					
Susceptibility to the most effective non-colistin/ aminoglycoside	28%	86%	34%	96%	3%
Most effective non-colistin/ aminoglycoside	Fosfomycin	Fosfomycin	Fosfomycin	Fosfomycin	Fosfomycin

Susceptibility to the most effective colistin/aminoglycoside based	99.51%	99.85%	99.64%	99.95%	81.34%
Most effective colistin/aminoglycoside based	Colistin + fosfomycin	Colistin + fosfomycin	Colistin + fosfomycin	Colistin + fosfomycin	Colistin + fosfomycin
Microbiology-directed setting					
Susceptibility to a non-colistin/aminoglycoside	28%	86%	34%	96%	3%
Susceptibility to colistin/aminoglycoside	71%	14%	66%	4%	78%
Susceptibility to ceftiderocol	97.83%	99.98%	97.46%	99.97%	62.37%

MBL, metallo-beta-lactamases

NB: S4 (MBL population): the PHE evidence does not include fosfomycin.

Three other sensitivity analyses of the NMA results were found to modify the relative differences in susceptibility across comparators: (see Section).

8.2.3.3. Clinical parameters – linking susceptibility to short-term mortality in the MDS

The remaining clinical evidence predicting 30-day outcomes in the MDS is presented Table 21. 30-day mortality differs across comparators via two mechanisms in the MDS. 30-day mortality does not differ in the MDS setting if infections are susceptible to existing treatments because patients will be treated with the correct AM, though it does differ if patients have infections resistant to existing options but susceptible to ceftiderocol, as their recovery will be more likely if they take ceftiderocol. In addition, patients mortality risk varies according to the AKI-rate associated with the AM used.

As documented in Section 5.6.1.2, several studies have explored the link between whether patients have been administered a treatment to which they are susceptible and their 30-day mortality outcomes in the infection sites of interest for the HVCSs. However, these studies have focused on the ES and none was available relating specifically to the MDS where outcomes are expected to differ substantively. Patients in the MDS who receive an inappropriate drug are much more likely to be MDR than patients receiving inappropriate treatment in the ES, and are more likely to be in critical state that reduces the possibility for further treatment.

This data gap is perhaps unsurprising as multi-drug resistance (including to colistin) remains rare and it may, therefore, be difficult to recruit or include sufficient patients in this setting. Given the absence of data to inform this important parameter, a structured expert elicitation exercise was conducted. The methods for the expert elicitation are described in Section 6. These estimates were elicited separately for cUTI, HAP and VAP as these infection sites are expected to have quite different mortality rates.

Separate estimates were not produced by causative pathogen-mechanism. This is because, amongst those receiving a treatment to which they are susceptible, outcomes are expected to be similar across the pathogen-mechanism combinations relevant to cefiderocol HVCSs. Similarly, amongst patients receiving multi-drug salvage therapy due to multi-drug resistance, outcomes are expected to be similar across the pathogen-mechanism combinations relevant to the cefiderocol HVCSs.

8.2.3.4. Clinical parameters – AKI risk and subsequent outcomes

Rates of nephrotoxic-drug induced AKI and their implications are assumed to generalise across sites, pathogens and mechanisms in the absence of subgroup-specific data. The evidence from the cefiderocol RCTs did not provide limited evidence on the safety implications of aminoglycoside/colistin use (see Section 5.6.3.2) and these data were not considered by our advisors to be generalisable to the highly comorbid patients who tend to acquire carbapenem-resistant infections. These parameters were obtained from existing systematic reviews where possible or, if not available, from UK-specific sources.

Several recent systematic reviews and meta-analyses estimated the pooled cumulative incidence of AKI in patients treated with colistin or polymyxins B,¹⁰¹⁻¹⁰⁴ and two reported differences in the rates of AKI between colistin or polymyxin B based therapy and other agents.^{102,103} The absolute risk of an AKI and the likelihood that an AKI resulted in irrecoverable kidney damage was derived from Sisay 2021,¹⁰¹ as this study had the most recent searches, included a broad range of study designs and was restricted to studies using the Risk Injury Failure Loss and End-Stage Renal Disease (RIFLE) criteria. The difference between colistin (or polymyxin B, a similar drug from the same class) based therapy and other agents was obtained from Chien et al 2020¹⁰³ as this review made some attempt to control for confounding. Chien et al 2020¹⁰³ included both RCTs and comparative cohort studies, but excluded studies considered poor quality as assessed by the Newcastle-Ottawa scale (in particular, the authors state that only cohort studies of parallel design with patients with comparable clinical characteristics were included). Alternative sources for these parameters are explored as scenario analyses.

The excess death rate from AKI was derived by comparing in-hospital mortality rates in the UK for individuals who experienced an AKI, as defined by the Acute Kidney Injury Network (AKIN) criteria, and individuals without AKI using the East Kent Hospitals University NHS Foundation Trust (EKHUFT) dataset from Kerr et al 2014.¹⁰⁵ The latter gathers admission records from three inpatient hospitals in the South of England. The analysis of the EKHUFT dataset was deemed more appropriate than that obtained using the HES dataset, as EKHUFT includes older and more comorbid patients that are, therefore, more similar to the patient population in this evaluation, and is more likely to include all AKIs than the HES dataset. The impact of AKI on mortality was estimated by the authors adjusting for a range of covariates including history of hospital admission, comorbidities and primary diagnosis. We assumed the relative increase in mortality associated with AKI observed in the Kerr et al. analysis applied to the baseline risk of mortality in our HVCSs despite the patients within our HVCSs exhibiting

a much higher baseline mortality risk. AKI is more prevalent in patients with poor prognosis and, although Kerr et al. attempted to adjust for these factors, the elevated mortality estimated was considered high by expert advisors. A scenario analysis was, therefore, run whereby the excess mortality associated with AKI was halved from the reported value.

Table 21: Parameters informing the 30-day MDS decision tree

Site	Parameter name	Description	Value	Uncertainty (measure)	Source
cUTI	p_bgrdS30d_MDS_S	30-day survival in cUTI patients receiving a treatment to which they are susceptible	0.854	Beta (12.10, 2.07) 95% CI (0.636 to 0.979)	Structured expert elicitation
cUTI	p_bgrdS30d_MDS_nonS	30-day survival in cUTI patients receiving a treatment to which they are resistant	0.610	Beta (3.55, 2.27) 95% CI (0.227 to 0.923)	Structured expert elicitation
HAP/VAP	p_bgrdS30d_MDS_S	30-day survival in HAP/VAP patients receiving a treatment to which they are susceptible	0.578	Beta (3.99, 2.91) 95% CI (0.226 to 0.888)	Structured expert elicitation
HAP/VAP	p_bgrdS30d_MDS_nonS	30-day survival in HAP/VAP patients receiving a treatment to which they are resistant	0.376	Beta (2.71, 4.51) 95% CI (0.090 to 0.726)	Structured expert elicitation
All	p_AKI_ca	Risk of AKI in patients receiving colistin or an aminoglycoside	0.45	95% CI: (0.41-0.49)	Sisay 2021 ¹⁰¹
All	OR_AKI_ca	Elevation in risk of AKI associated with colistin or aminoglycosides compared to other less nephrotoxic therapies	1.81	95% CI: (1.13, 2.92)	Chien 2020 ¹⁰³
All	OR_AKI_death	Odds ratio of mortality for AKI compared to no AKI	5.11	95% CI: (4.23, 6.17)	Kerr 2014 ¹⁰⁵
HAP/VAP	p_AKIrrec	Proportion of individuals who experience an AKI who have ESRD	0.003	0.002	Sisay, 2021 ¹⁰¹
cUTI	p_AKIrrec	Proportion of individuals who experience an AKI who have ESRD	0.001	0.002	

AKI, acute kidney injury; CI, confidence intervals; cUTI, complicated urinary tract infection; ESRD, end-stage renal disease; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia

8.2.3.5. Clinical evidence – linking susceptibility to 30-day outcomes in the ES

The evidence informing the decision tree predicting 30-day outcomes in the ES is presented in Table 22. The mechanisms database described in Section 5.6.1.2 was searched to identify papers providing quantitative estimates of the risk of carrying the pathogen-mechanism of interest among patients with specific characteristics. This was supplemented by papers known to the study team. Two searches were conducted. The first was to identify UK-specific studies. This had two concepts; the first was to identify ‘risk’ studies (any field containing any of “risk”, “prevalence”, “incidence”, “character*”, or “outbreak”), returning 1,696 studies. The second concept was for UK studies (abstract contains any of (“United Kingdom”, “Great Britain”, “England”, “UK”, “NHS”, “Trust”, “London”, “*Shire”), returning 119 studies. Combining both concepts provided 61 studies for the first search. The second search was expanded to identify non-UK risk models and returned 51 studies based on their title containing “Risk”. No risk models were identified from either search. Indeed, even in the wider population of patients at risk of a carbapenem resistant infection, there is a paucity of UK data available to estimate the risk of having a carbapenem resistant infection amongst patients with relevant risk factors.¹⁰⁶

The probability that a patient entering the ES who actually has the suspected pathogen-mechanism was obtained from SGSS data supplied by PHE as shown in Table 22 (for further discussion see Section 8.2.6.3). These data provide the number of tests for a given mechanism of resistance and the proportion of those tests that returned a positive result. For MBL mechanisms, separate tests are run for each specific type of mechanism (i.e. a separate test is run for IMP, VIM, NDM and in the case of *Pseudomonas aeruginosa* Dutch imipenemase, DIM). We assume when calculating these figures that, if MBL is suspected, all MBL mechanism tests are run. These data are unlikely solely to reflect the ES HVCSs of focus in the current analysis, for example testing may be conducted due to a suspicion in the lab rather than at the level of the treating clinician (e.g. a lab finding of carbapenem non-susceptibility might trigger a test), some tests may be run following treatment failure or may be run in the ES but at a lower level of suspicion than considered in our HVCSs.

Given these uncertainties in the available data, we also conducted a survey of the mailing list of the BSAC. This survey asked microbiologists and infectious disease specialists how many times they saw patients who would fall into our ES HVCSs of interest, and the proportion of those who actually had the pathogen-mechanism of interest. A survey was used in preference to the structured expert elicitation as this parameter was expected to vary according to local epidemiology and history of outbreaks of resistant infections, and it was not considered realistic that the expert elicitation exercise could include enough experts to adequately reflect this geographical heterogeneity. Unfortunately, the response to the survey was low with only 9 experts providing usable responses. On average, these experts reported that,

of the MBL *Enterobacterales* or *Pseudomonas aeruginosa* HAP/VAP cases seen where there was a high suspicion of the mechanism of interest, 71% of patients would be confirmed as having the mechanism. These values are used in a sensitivity analysis. Given the high level of uncertainty around this parameter, sensitivity analysis results are shown for a wide range of alternative values.

Mortality at the time of assessment for entry to the MDS conditional upon susceptibility status, and 30-day mortality among patients not requiring further treatment, was obtained from Tumbarello 2013.⁷² This study was conducted in 110 ICU patients with confirmed *Pseudomonas aeruginosa* pneumonia in a hospital in Italy, and compared 30-day mortality in patients who were susceptible to initial empiric treatment and those who were not. Surviving patients who were not susceptible to empiric treatment were switched to definitive therapy, on average approximately 62 hours after symptom onset. Tumbarello 2013⁷² was chosen as it reported a relatively high incidence of multidrug resistant strains in infecting organisms (42/110) compared to the other studies identified in the review and was the only study reporting Kaplan Meier curves (see Section 5.6.1 for details of review). No UK studies were identified.

The probability of requiring further treatment for susceptible patients was taken from the cefiderocol arm of the APEKS-NP study. Within the studies included in the cefiderocol evidence mappings, this was identified as the only study representing a predominantly empirically treated susceptible population of HAP/VAP patients that also reported subsequent treatment rates.

Table 22: Parameters informing the 30-day ES tree (HAP/VAP only)

Pathogen / mechanism subgroup	Parameter name	Description	Value	Uncertainty (measure)	Source
MBL <i>Enterobacterales</i>	p_bug_mech_EMBL	Proportion of people in ES who have the suspected pathogen-mechanism	0.15	92 (n)	PHE SGSS*
MBL <i>Pseudomonas aeruginosa</i>	p_bug_mech_PMBL		0.14	51 (n)	PHE SGSS*
All	p_bgrdDst_S	Proportion of patients who received a treatment to which they are susceptible who are dead at the point MDS results become available (assumed to be at 5 days based on CARBAR study)	0.03	0.02 (se)	Tumbarello 2013 ⁷²
All	p_bgrdDst_nonS	Proportion of patients who received a treatment to which they are not susceptible who are dead at the point MDS results become available (assumed to be at 5 days based on CARBAR study)	0.11	0.04 (se)	Tumbarello 2013 ⁷²
All	pmtxF_S	Proportion of patients who received a treatment to which they are susceptible who require further treatment	0.07	0.02 (se)	APEKS-NP ¹³
All	p_bgrdD30d_S	Proportion of patients who survive to MDS assessment, and do not require further treatment who die by 30 days	0.32	0.06 (se)	Tumbarello 2013 ⁷² outcomes from susceptible cohort

Abbreviations: ES, empiric setting; MBL, metallo-beta-lactamases; MDS, microbiology-directed setting; PHE, Public Health England; SGSS, Second Generation Surveillance System; se, standard error; n, number in sample.

* Note that the type of specimen within SGSS was used to determine whether an isolate should be considered as HAP/VAP. The original mapping between the type of specimen and infection type provided very low numbers of HAP/VAP making the estimation of the proportions of people with the pathogen-mechanism of interest highly uncertain. A sensitivity analysis was conducted using a revised mapping from specimen type to infection site, as this contained larger numbers and the estimates were more consistent across pathogen-mechanism subgroups these values were used for these parameters. These analyses are discussed in more detail in Section 8.2.6.3.

8.2.3.6. Clinical evidence – long-term mortality

All patients surviving to 30 days face an ongoing mortality risk based on the CARBAR⁸⁰ and Merrick⁸¹ studies. Both studies included UK patients with infections caused by carbapenem resistant organisms and were, therefore, considered relevant in terms of capturing the highly comorbid nature of patients who acquire these infections. Searches were conducted as described in Section 5.6.2, but did not identify any further evidence of relevance. A targeted search indicated a lack of data on long-term outcomes in both HAP/VAP and cUTI. It also seemed unlikely that outcomes in all-comer HAP/VAP and cUTI patients would reflect those of MDR patients who tend to have developed MDR infections as a result of multiple contacts with the health system, reflecting a wide range of comorbidities. We therefore chose to focus our review of long-term mortality on patients with resistant infections.

CARBAR⁸⁰ was used to inform mortality in the base case as it included more geographically diverse patients, had a longer follow up (2 years compared to 1 year in Merrick) and provided continuous survival estimates over time (i.e. Kaplan Meier curves). Merrick⁸¹ reported all-cause mortality at 1 year of 31% which is similar to the 1-year mortality in CARBAR of 34%.

Kaplan Meier curves from CARBAR were digitized and a published algorithm¹⁰⁷ was used to recover pseudo IPD from the Kaplan Meier curve for analysis. Parametric survival models were fitted to these data to facilitate extrapolation beyond the observed data. Data from 30 days onwards were used as these were of most relevance to the model. We followed guidance from the NICE Technical Support¹⁰⁸ document and fitted a range of parametric survival models: exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma. Model fit was assessed according to Akaike's Information Criteria (AIC), log-cumulative hazard plots, hazard plots, and visual assessment of the concordance between model predictions and Kaplan Meier plots. No specific external data were identified to support validation of long-term predictions, so probabilities of death predicted by each model were compared to general population mortality over 20 years to assess plausibility. A summary of these assessments is provided in Table 23. Overall, the Weibull, log-logistic and log-normal models were all considered plausible candidates and, in the absence of further evidence, log-normal was selected to offer a middle ground with the Weibull and log-logistic used in scenario analyses. Mortality is restricted so that it too remains above that in the general population within the model.

Table 23: Summary of survival analytic model fit to CARBAR⁸⁰ mortality data

Distribution	AIC	Visual assessment of fit	Comparison with external data and assessment of face validity
Exponential	953	Poor	No convergence with general population mortality
Weibull	935	Moderate	Converges towards general population mortality but annual probability of death always greater
Gompertz	952	Poor	Converges with general population mortality at 9 years
Log-logistic	938	Moderate	Converges with general population mortality at 15 years
Log-normal	953	Moderate	Converges with general population mortality at 13 years
Generalised Gamma	933	Poor	Rapidly accelerating mortality and divergence with general population mortality

AIC, Akaike's Information Criteria

In addition, patients alive with recovered renal function face an elevated risk of death and a risk of developing irreversible renal failure (CKD).¹⁰⁹ Patients alive with irreversible renal failure face the elevated risk of death of CKD-patients.

A recent body of evidence, with which our group of experts agreed, suggests that AKI and CKD are closely linked and interconnected, whereby CKD is a risk factor for experiencing subsequent AKI and AKI is a promoter or instigator of CKD. It was, therefore, considered important to capture the fact that AKI is not a 'self-limited process' and that patients with recovered renal function post-AKI are at risk of adverse renal outcomes and of developing CKD.

In our literature searches to identify evidence of the impact of AKI on the development of CKD and on long term survival, we looked for studies that would control for the confounding impact of comorbidities as stringently as possible, as we aimed to estimate the causal effect of AKI on subsequent outcomes. The US study by Bucaloiu 2012¹⁰⁹ was selected as it compared outcomes of patients with hospital-associated AKI (with recovered renal function) against a non-AKI patient population matched for a wide range of relevant clinical and demographic characteristics. 1,610 patients with AKI and 3,652 without were followed up from 90 days post-discharge to approximately 6 years. A limitation of this study is that the propensity score matching process excluded the most comorbid patients due to a lack of sufficiently closely matching controls, and the study excluded patients with impaired kidney function prior to hospitalisation. This evidence was used to inform the increased risk of death and the increased risk of developing CKD in patients with recovered renal function after an AKI. Relevant parameters are shown in Table 24.

There are a number of limitations to the approach taken to reflect the long-term implications of AKI within the model:

- 1) The CARBAR⁸⁰ mortality data will have included patients who experienced AKI and, therefore, including additional mortality risk associated with AKI and CKD development is likely to exaggerate mortality risk in the model.
- 2) The risk of CKD development is likely to be higher than estimated from Bucaloiu¹⁰⁹ in the highly comorbid patient group considered within the HVCSs.
- 3) The hazard ratios on mortality are applied multiplicatively despite the much higher baseline risk of death in the patient population considered within the HVCS.

Scenarios are explored to address each of these assumptions in turn:

- 1) CARBAR mortality rate is reduced by 10% reflecting an assumed AKI rate of 20% and an assumed excess mortality associated with AKI of 1.48 (95% CI 1.19, 1.82) based on Bucaloiu 2012.¹⁰⁹
- 2) Patients in the HVCSs face double risk of CKD compared to patients in Bucaloiu 2012.¹⁰⁹
- 3) Patients in the HVCSs face an absolute increase in mortality risk observed in Bucaloiu 2012.¹⁰⁹
- 4) All of the above applied simultaneously.

We did not account for life years accrued within the first 30 days in the model as these were expected to have a marginal effect on the model results.

Table 24: Post-30 day outcomes for patients with history of AKI

Site	Pathogen / mechanism subgroup	Parameter name	Description	Value	Uncertainty (measure)	Source
All	All	TPnoAKItoCKD	1-year absolute probability of experiencing CKD in non-AKI patients. Approach to computation: baseline risk of CKD development in non-AKI: 1218 events over a median follow-up of 4.3 years in 3652 individuals (=1218/(4.3x3652)).	0.078	SE for baseline risk assumed 10% of mean.	Bucaloiu 2012 ¹⁰⁹ (note that these probabilities are assumed to apply from the second cycle onwards as Bucaloiu measured outcomes from 90 days post-discharge)
All	All	TPAKItoCKD	1-year absolute probability of experiencing CKD in post-AKI patients with recovered renal function. Approach to computation: baseline risk of CKD development in non-AKI (0.078) multiplied by adjusted HR 1.91 (95% CI 1.75 – 2.09).	0.143	SE around HR of CKD development : 0.087, se for baseline risk assumed 10% of mean.	
All	All	AKIodeath	1-year probability of death in post-AKI patients with recovered renal function. Derived by multiplying the mortality from CARBAR by the HR of excess death adjusted for de novo CKD development from Bucaloiu 2012: 1.18 (95% CI 0.95- 1.46).	1.18 * mortality rate in non-AKI	SE 0.119 for HR	
All	All	TPCKDtodeath	1-year probability of death in CKD patients. Derived by multiplying AKI mortality by the HR of excess death in CKD patients compared to AKI patients in Bucaloiu 2012: 3.65 (95% CI 2.42, 5.52).	3.65 * mortality rate in AKI	SE 0.783 for HR	

AKI, acute kidney injury; CKD, chronic kidney disease; HR, hazard ratio; SE, standard error

8.2.3.7. Health-related quality of life

The HRQoL implications of the infection are not modelled as these are expected to be short-lived and, therefore, are not expected to impact substantively on the model results. However, to quality-adjust the life expectancy estimates accurately, we did consider it important to reflect the underlying comorbidities of the patients within the HVCSs. We did not identify any relevant utility data from existing models, most of which assumed that, post-infection, patients would return to the HRQoL of the general population. Therefore, we conducted a review of utility studies that provide evidence according to the Charlson Comorbidity Index (CCI). The CCI is a summary score of comorbidity based on 17 included comorbidities. The comorbidities considered in the CCI have been selected and then weighted based on their ability to predict 1-year mortality among hospitalised patients. Importantly, the CCI is reported within the CARBAR study for patients with infections caused by carbapenem resistant organisms, allowing utility values presented by CCI score to be re-weighted to reflect the CCI scores in a population similar to that included in our HVCSs.

The methods for this review are described in Appendix 1. This identified two studies reporting utilities by CCI in the general population. Both studies were based on large national surveys in France and Germany and estimated the SF-6D based on the SF-36 and SF-12, respectively. The French study was chosen in preference to the German study as the latter controlled for a number of variables likely to be associated with CCI (pain level, socio-demographic variables and health behaviours). Utility values by CCI score are reported in Table 25. These are weighted by the distribution of CCI scores observed in CARBAR,⁸⁰ also shown in Table 25. This produced an overall weighted utility score of 0.66 for the CARBAR population based on their comorbidities, this is intended to reflect their long-term quality of life rather than the immediate impact of infection. This was used to compute a multiplicative reduction in HRQoL associated with comorbidities by comparing the CARBAR population to the general population (assumed to have a CCI score of 0). This resulted in a utility-multiplier of $0.66/0.73 = 0.90$. This was applied to the age and gender-specific EQ-5D utilities of the general UK population. The latter were derived from a regression model estimated by Ara et al 2010¹¹⁰ using Health Survey for England (HSE) survey data for the years 2003 and 2006 ($n = 26,679$). This produced a baseline utility value of 0.73 for all patients.

Table 25 CCI-related utilities

CCI-score	SF-6D score ¹¹¹	Proportion of people within each CCI score (CARBAR)
CCI 0	0.729	20%
CCI 1-2	0.667	31%
CCI 3-4	0.621	21%
CCI 5+	0.615	28%

CCI, Charlson Comorbidity Index

Patients who have recovered their renal function post AKI are not expected to experience further disutility unless they develop CKD. The HRQoL decrement applied to the CKD patients is computed using pooled estimates from a systematic review and meta-analysis by Wyld *et al* (2011).¹¹² The authors reported decrements of 0.02 (-0.04, 0.09) for those in CKD pre-treatment, and of 0.11 (0.08, 0.15) for those with CKD in dialysis, where the latter was estimated to represent 2% of the diagnosed CKD population based on UK data.¹¹³ These were applied to the baseline utility value of 0.73 such that the utility of those with CKD pre-treatment was 0.71 and the utility of those with CKD in dialysis was 0.62.

8.2.3.8. Resource use and costs

The model includes costs relating to hospital stay, infection control during hospitalisation, AKI-related costs during hospitalisation, long-term costs associated with CKD and costs relating to use of existing AMs. The purchase price of cefiderocol is not included in the costings as the objective of the evaluation is to inform the payment for cefiderocol. Costs relating to testing (for pathogen, resistance mechanism or AM susceptibility) were not included as, in the HVCS populations, these tests were expected to be conducted to the same degree regardless of the introduction of cefiderocol.

An important cost driver in the model is time spent in hospital. Data on time in hospital for patients according to their treatment pathway and outcomes are presented in Table 26. As for 30-day mortality, we did not identify any studies in the MDS linking treatment susceptibility to duration or type of hospitalisation. This was, therefore, elicited as part of the structured expert elicitation exercise. LoS and the proportion of time spent in ICU or HDU was estimated conditional upon susceptibility for patients with cUTI and HAP/VAP separately. In the base case, all patients in the ES were assumed to spend 5 days in hospital prior to receipt of their microbiology results, the median wait reported in CARBAR.⁸⁰

The LoS for patients successfully treated in the ES was estimated from the LoS in patients who are susceptible to treatment in the MDS as estimated from the structured expert elicitation, the time to receiving MDS from CARBAR⁸⁰ and the relative reduction in the LoS associated with receiving appropriate empiric treatment from Muscedere 2012.⁷⁰ The proportion of time spent in the ICU for patients who received a treatment to which they are susceptible and who did not require further treatment was derived from Muscedere 2012.⁷⁰ The study was conducted in 350 adult ICU patients with VAP (any pathogen and resistance profile) in Canada who received empiric treatment with meropenem or meropenem + ciprofloxacin. The study reported hospital and ICU LOS in patients who were susceptible to their empiric treatment and those who were not. Muscedere⁷⁰ was chosen as it was the only study identified in the review in Section 5.6.1 that reported LOS conditional upon susceptibility in patients with HAP/VAP. The LOS reported by Muscedere 2012 was skewed. The mean LOS was derived by fitting a lognormal distribution to the reported median and interquartile range. The derived

mean LoS in patients who received appropriate and inappropriate treatment (43.1 days and 85.7 days, respectively) were used to derive the relative reduction in the LoS associated with receiving appropriate treatment. The derived mean LOS and stay in ICU were used to derive the proportion of hospital stay that was spent in ICU.

The additional hospitalisation costs associated with in-hospital AKI are informed by estimates derived from Kolhe *et al.* 2014.¹¹⁴ This study used the NHS costing system's relative value units that capture cost information associated with several cost items including LoS on wards, drugs, physiotherapy, radiology and medical staff costs.

Unit costs were obtained from standard sources and also considered those suggested in the manufacturer submissions. Where necessary, costs were adjusted to 2019/2020 prices using standard sources.¹¹⁵ The daily cost of cUTIs treated on general medical wards was derived from the weighted average cost of non-elective short stay for kidney or UTIs with/without interventions (LA04H to LA04S). The daily cost of HAP/VAP treated on general medical wards was derived from the cost of non-elective short stay bronchopneumonia with or without interventions (DZ23H to DZ23N). The daily cost of ICU was assumed to be the weighted average cost of non-specific, general adult critical care (CCU01) with zero to six organs supported (XC01Z to XC07Z), assuming that ventilation cost is reflected in the organ support costs. The daily cost of HDU was assumed to be the weighted average cost of medical adult patients in critical care (CCU03) with zero to six organs supported (XC01Z to XC07Z). Weighting was based on the overall volume of each type of organ support reported for the NHS. The daily cost of isolation was derived from Knight *et al.* 2018,¹¹⁶ and included the cost of gloves, aprons and infectious waste stream. It was assumed that all patients would be subject to isolation measures as they are either highly suspected of having or confirmed to have an MDR infection. One-off costs of stock disposal are not included as these are assumed to apply equally to all patients.

Table 26: Hospitalisation duration and unit costs

Site	Parameter name	Description	Value	Uncertainty (measure)	Source (costing year)
cUTI	los_MDS_S	LoS following treatment in the MDS for cUTI patients who received a treatment to which they are susceptible (days)	12.9	Lnorm (2.507, 0.321) 95% CI: (6.54 to 23.02)	Structured expert elicitation
cUTI	los_MDS_nonS	LoS following treatment in the MDS for cUTI patients who received a treatment to which they are not susceptible (days)	17.7	Lnorm (2.817, 0.334) 95% CI: (8.68 to 32.2)	Structured expert elicitation
cUTI	p_ICU_MDS_S	Proportion of time in hospital in ICU for cUTI patients who received a treatment to which they are susceptible	0.150	NA*	Structured expert elicitation
cUTI	P_ICU_MDS_nonS	Proportion of time in hospital in ICU for cUTI patients who received a treatment to which they are not susceptible	0.233	NA*	Structured expert elicitation
cUTI	p_HDU_MDS_S	Proportion of time in hospital in HDU for cUTI patients who received a treatment to which they are susceptible	0.170	NA*	Structured expert elicitation
cUTI	p_HDU_MDS_nonS	Proportion of time in hospital in HDU for cUTI patients who received a treatment to which they are not susceptible	0.183	NA*	Structured expert elicitation
HAP/VAP	los_prior_ast	Time from empiric treatment initiation to receiving microbiology results (days)	5**	NA	CARBAR ⁸⁰
HAP/VAP	los_txsucc1	Relative reduction in LoS for patients not requiring further treatment	0.503	NA	Muscedere 2012 ⁷⁰
HAP/VAP	LOS_ES_success	LoS in ES for patients not requiring further treatment (days)	12.8	Assume uncertainty as for LoS HAPVAP_MDS_S, with fixed time to MDS (5 days) and relative reduction in LOS (0.503)	Derived from structured expert elicitation and Muscedere 2012 ⁷⁰
HAP/VAP	p_ICU_tx_succ1	Proportion of time in ICU following receipt of empiric treatment for patients not requiring further treatment	0.300***	NA*	Derived from Muscedere 2012 ⁷⁰
HAP/VAP	los_MDS_S	LoS following treatment in the MDS for HAP/VAP patients who received a treatment to which they are susceptible (days)	20.4	Lnorm (2.971, 0.298) 95% CI: (10.88 to 34.97)	Structured expert elicitation

HAP/VAP	los_MDS_nonS	LoS following treatment in the MDS for HAP/VAP patients who received a treatment to which they are not susceptible (days)	24.3	Lnorm (3.118, 0.380) 95% CI: (10.73 to 47.63)	Structured expert elicitation
HAP/VAP	p_ICU_MDS_S	Proportion of time in hospital in ICU for HAP/VAP patients who received a treatment to which they are susceptible	0.499	NA*	Structured expert elicitation
HAP/VAP	P_ICU_MDS_nonS	Proportion of time in hospital in ICU for HAP/VAP patients who received a treatment to which they are not susceptible	0.589	NA*	Structured expert elicitation
HAP/VAP	p_HDU_MDS_S	Proportion of time in hospital in HDU for HAP/VAP patients who received a treatment to which they are susceptible	0.149	NA*	Structured expert elicitation
HAP/VAP	p_HDU_MDS_nonS	Proportion of time in hospital in HDU for HAP/VAP patients who received a treatment to which they are not susceptible	0.172	NA*	Structured expert elicitation
All	c_AKI	Increase in in-hospital cost associated with experiencing an AKI	£5,138	(4,724 – 5,548)	Kolhe 2014 ¹¹⁴ (2008 prices updated to 2019)
cUTI	c_genward	Unit cost per day for cUTI patient on general ward	£687.08	NA	NHS reference costs
HAP/VAP	c_genward	Unit cost per day for HAP/VAP patient on general ward	£870.51	NA	NHS reference costs
All	c_ICU	Unit cost per day for person in ICU	£1,689.09	NA	Derived from NHS reference costs and CARBAR
All	c_HDU	Unit cost per day for HDU	£1,299.67	NA	NHS reference costs
All	c_Isolation	Daily cost of isolation	£21.96	NA	Knight 2018 ¹¹⁶

Abbreviations: AKI, acute kidney injury; cUTI, complicated urinary tract infection; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia; HDU, high dependency unit; ICU, intensive care unit; LoS, length of stay; MDS, microbiology-directed setting

* Uncertainty around the proportion of time spent in ICU and HDU was not elicited to limit participant burden.

** The distribution of time spent in ICU/HDU and on a general ward were assumed to be as per the MDS for patients receiving a treatment to which they were susceptible.

*** No information on time spent in HDU reported, the ratio of the proportion of time spent in HDU to time spent in ICU was therefore assumed to be as per the MDS for patients receiving a treatment to which they were susceptible.

Following discharge, patients' long-term costs are determined by their health state. Patients alive without a history of AKI, or with recovered renal function, experience no further costs. Patients with irreversible renal failure (i.e., CKD) face a weighted average cost that reflects the CKD-severity distribution in England and requirement for dialysis. Kerr *et al.* 2012¹¹³ estimated the annual per patient NHS expenditure on CKD direct care, dialysis and transplants. The mean annual cost of direct CKD care per patient not on dialysis (that is anti-hypertensive drugs, primary care tests and consultations, nephrology consultations and cost due to excess incidence of cardiovascular events) was estimated at £278, whilst the annual cost of CKD-related care for a patient on dialysis was estimated at £31,933. These costs are similar to those proposed by Shionogi who estimate that patients with nephrotoxicity not experiencing dialysis face a cost of £173 in year 1 and £89 from year 2 onwards (based on assumed resource use), and £24-29,000 for those receiving dialysis (source unclear). As for quality of life, 2% of the diagnosed CKD population were estimated to be receiving dialysis based on UK data.¹¹³ The clinical advisors to EEPRU for this project indicated that this may be an overestimate, but use of a lower value is unlikely to substantially change the results of the modelling. Our clinical advisors expected that, in the highly comorbid group considered within the HVCs, transplant would be rare, the costs of transplant were not, therefore, included in the CKD cost estimates. This results in a weighted average cost of CKD of £911 per annum in 2019/20 prices.

We did not include differential rates of discharge to long-term care facilities in the base case analysis as no evidence was found comparing UK usage of care amongst those with and without AKI that adjusted for differences between patients with and without AKI. US data suggest that AKI is associated with an elevated risk of discharge to long-term care even with adjustment for other predictive factors. Liangos 2006¹¹⁷ found that 8.9% of patients without AKI will be discharged to long-term care, and this is elevated to 17.8% in those with an AKI (reflecting an adjusted odds ratio of 2.2 (95% CI 2.1, 2.2)). We combine this with information on the costs of long-term care and model a scenario based on this. We use a weekly cost of £1,049 (average of private sector nursing home, and local-authority own-provision residential care for older people¹¹⁵) and apply this for the lifetime of the patient. This is likely to be an overestimate as some patients may be discharged from long-term care and the full cost of this care may not fall on the NHS / PSS budgets.

We did not include the cost of end of life or palliative care as this was considered unlikely to substantially influence model outcomes.

Drug acquisition costs were based on the cost of the daily dose derived from published sources,^{118,119} the daily doses reported by WHO Collaboration Centre for Drug Statistics Methodology,¹²⁰ and the treatment duration derived from published literature.^{119,121-123} When more than one formulation or pack size was available, we based costs on the largest pack size and IV formulations. When the treatment duration was provided as a range, we used the longest duration, to reflect the high severity of infections.

When more than one AM was available for treatment in a particular setting (e.g. colistin or aminoglycosides for the treatment of HAP/VAP in MDS), the most expensive treatment was chosen to reflect that often combination or higher doses of therapy may be used. In the ES, patients who require a treatment switch following availability of their susceptibility results are assumed to receive 5 days of treatment, whereas those who do not require a treatment switch receive the full course.

The unit cost of all comparators is shown in Appendix 14. The drug acquisition costs used in the model are summarised in Table 27.

Table 27. Drug acquisition cost for a full course of treatment, or five days of treatment while awaiting sensitivity results in ES

	Colistin/ aminoglycoside- based treatment in ES	nca-based ES	Colistin/ aminoglycoside- based treatment in MDS	nca-based MDS	Salvage
MBL <i>Enterobacter ales</i>	<u>Full course:</u> £163.56 (colistin +fosfomycin) <u>Five-days:</u> £90.66	NA for empiric	£232.30 (amikacin)	£298.20 (tigecycline)	£397.78
MBL <i>Pseudomonas aeruginosa</i>	<u>Full course:</u> £163.56 (colistin +fosfomycin)** <u>Five-days:</u> £90.66	<u>Full course:</u> £9.66 (fosfomycin) <u>Five-days:</u> £9.66	£153.90 (colistin)	£9.66 (fosfomycin)	£397.78

ES, empiric setting; MBL, metallo-beta-lactamases; MDS, microbiology-directed setting

Drug administration costs were assumed to be included in the cost of hospital stay, where patients are assumed to be treated.

8.2.4. Model outputs and uncertainty analysis

Per patient lifetime costs, QALYs and NHEs are presented for each subgroup described in Table 16. For the subgroups of patients eligible for treatment in the MDS, incremental results are presented for the comparison of the overall MDS cohort who receive tailored therapy with the new drug available to the overall cohort who receive tailored therapy under existing treatment options only. For patients eligible for treatment in the ES, incremental results are presented for the pathway including cefiderocol as an empiric treatment, and the pathway including cefiderocol as an MDS treatment, each compared to the treatment pathways including only existing AMs. These estimates represent the INHEs offered by cefiderocol over and above existing therapeutic options.

Calculation of NHEs requires a measure of health opportunity cost in order to convert additional health-care costs (or savings) to health foregone (or accrued). We present estimates of NHEs using a measure

of health opportunity cost of £20,000/QALY as specified in the NICE scope for this evaluation,¹²⁴ with scenarios presented using £15,000 to reflect empirical estimates of health opportunity cost used by the Department of Health and Social Care (see for example¹²⁵) and £30,000/QALY to reflect the upper bound of the approval norm used by NICE in its technology appraisal process.¹²⁶

Results are presented using the base case assumptions and data sources outlined above. In addition, a series of scenarios is generated to address uncertain assumptions and reflect alternative plausible evidence sources. Parameter uncertainty is quantified using PSA the results of which are presented as distributions of INHEs.

8.2.5. Modelling direct population net health effects in HVCS

Two key drivers of estimates of population-level INHEs are the size of the affected population, and the efficacy of AMs in this population. Both drivers are expected to vary over time. Increasing rates of resistance to carbapenems (due to an MBL mechanism) will increase the population that could benefit from treatment with a newer AM. For cefiderocol, and potentially for the comparators, it is anticipated that resistance will change over time, with some of this change driven by changes in rates of AM use. The focus of this section is to describe the methods used to obtain quantitative estimates of changes in the affected population and AM efficacy over time. These estimates are used to generate predictions of the total population-level INHEs for cefiderocol over 20 years. This time horizon was chosen pragmatically to explore the long-term value of cefiderocol whilst avoiding additional uncertainties associated with very long-term population-level predictions.

There are four main aims of this section:

1. Predict how the number of people in each HVCS will change in the future.
2. Predict how rates of resistance to existing AMs will change within the HVCSs in the future if cefiderocol is not used ('current practice' scenario).
3. Predict how resistance will increase over time for cefiderocol within the HVCSs.
4. Predict the impact, if any, on resistance of reducing current levels of AM use due to the introduction of cefiderocol in the HVCSs.

There is a degree of overlap in the above aims. For example, aims 2 to 4 each involve the prediction of how resistance to an AM will change over time. In addition, for aims 1 and 2, the evidence sources were time-series data for the HVCSs. These time-series were made available by PHE and these were analysed using time-series methods. For aims 3 and 4, a range of potential evidence sources was considered. These sources included the published literature and publicly available surveillance data, and in general were for a population that was more broadly defined than the HVCSs. Evidence for a broader patient population was considered as it included evidence on both AM use and AM resistance, and so allowed for an estimate of how these two factors interact (this evidence was not available for the population of

interest). As there are distinct modelling challenges associated with each aim, they are discussed in turn. A brief overview is presented here, with more details provided in Appendix 15.

8.2.5.1. Predicting the future sizes of the HVCSs

The objective of this analysis was to statistically model changes in the number of patients within the HVCS over time, to inform a quantitative forecast of the number of patients presenting in the HVCS over the next 20 years.

Data on the number of infections over time for the mechanisms of interest were provided as a time-series by PHE. Two populations were included:

- *Enterobacterales* with an MBL mechanism
- *Pseudomonas aeruginosa* with an MBL mechanism.

Data were supplied for invasive infections which are predominantly infections where the specimen sample relates to a BSIs or cerebrospinal fluid infection. It was assumed that, for each pathogen-mechanism of interest, the trends in population size for invasive infections generalise to the HVCSs. This was considered reasonable by the clinical advisors to the project. The small number of invasive infections made it challenging to reliably identify if there was a trend in the growth of the HVCSs. As such, this analysis is supplemented by a secondary analysis which looks at trends in the number of screening isolates. These isolates are from screening specimen sites. Screening samples were broadly categorised as samples from swabs, wounds, and the lower gastro-intestinal tract. It includes potential infections as well as isolates from people who do not have infections but may be colonised by a MDR pathogen. These screening isolates were only used to confirm or refute the potential presence of a trend rather than inform the growth estimates as they may be influenced by screening policy changes over time which may not feed through to changes in identified infections. Data on both invasive infections and screening isolates were obtained from the AMRHAI national reference laboratory. These data were provided by PHE as monthly counts and are available from 2004 (*Pseudomonas aeruginosa*: from 2003) to April 2021. During 2018, guidance on which samples should be sent to AMRHAI changed, and charges were introduced. This led to a gradual “artificial” decrease in referrals. Further detail on the nature of this dataset is provided in Appendix 2.

Due to small numbers, data on invasive infections were aggregated to quarterly for analyses and restricted to October 2012 onwards. The last observations used were for March 2018 (inclusive), as after this point the observed numbers decreased. For screening isolates numbers were larger, so monthly data were used. For these, the first observation was set to be the first time-point for which there were no future months with zero counts (April 2013 for *Enterobacterales* and November 2014 for *Pseudomonas aeruginosa*).

Time-series (state-space exponential smoothing) models were used to forecast the isolate data. For the invasive isolates the use of other time-series models was also considered. Further details on the models considered and the justification and implementation of the state-space models is provided in Appendix 15. Three state-space models were considered. These varied with regards to the assumptions made about any long-term trends in the growth of the HCVS:

- No growth (no trend).
- Growth in the short-term that in the long-term changes to no growth (a ‘damped trend’ model; the degree of dampening is estimated from the data and influences how quickly the growth tends to zero).
- Persistent growth (trend that is not damped)

Within-sample goodness of fit statistics (Akaike’s information criteria, for which lower values indicate better fit) for the three models and the two datasets are provided in Table 28. Estimates of population growth are provided in MBL, metallo-beta-lactamases

Figure 14 (estimates are not shown for *Pseudomonas aeruginosa* as the best fitting model was always one without a trend). The two isolate datasets are very different with regards to absolute numbers. MBL, metallo-beta-lactamases

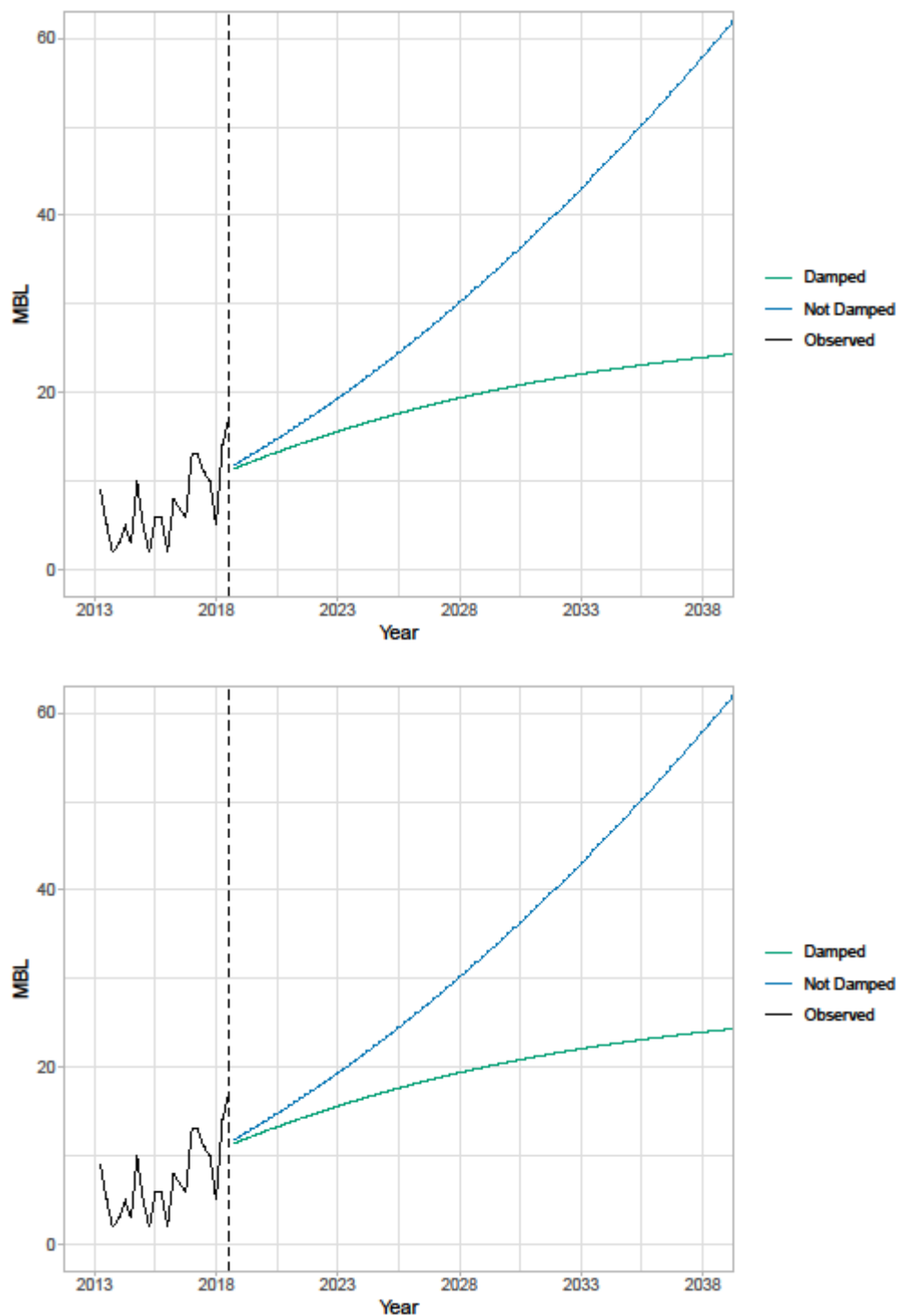
Figure 14 shows the change in population size over time for both the dataset of invasive infections and the screening isolates.

Table 28: Within-sample goodness of fit statistics

Model: <i>Enterobacteriales</i>- MBL	Invasive isolates	Screening isolates
No trend	93.49	192.95
Damped trend	97.71	193.81
Trend	95.08	185.76
Model: <i>Pseudomonas aeruginosa</i>	Invasive isolates	Screening isolates
No trend	443.55	134.49
Damped trend	444.75	136.87
Trend	447.93	141.23

MBL, metallo-beta-lactamases

Figure 14: Change in population size over time (top pane = invasive isolates, bottom = screening isolates).



MBL, metallo-beta-lactamases

For the invasive isolates, for both the *Enterobacterales* and *Pseudomonas aeruginosa* populations, the best-fitting model (based on within-sample fit) is one without a trend. Of the two models that include a trend, the trend model provided the best fit for the *Enterobacterales* population, whilst the damped trend model provided the best fit for the *Pseudomonas aeruginosa* populations. Differences between all three

models were very small. Visually, there was no evidence of a trend for the *Pseudomonas aeruginosa*, whilst for the *Enterobacterales* there was a potential trend.

For the screening isolates, the best model for the *Pseudomonas aeruginosa* was again one without a trend, whilst for the *Enterobacterales* it was a model with a non-damped trend. However, for the screening isolates it is unclear if long-term increases in *Enterobacterales* reflect genuine increases or the results of increased testing. It is also unclear if any genuine increases would persist into the future. For *Enterobacterales*, the largest relative change was for the screening isolates with a non-damped trend and the smallest (non-constant) change was for the invasive isolates with a damped trend model. As long-term estimates were very sensitive to the choice of model, and there were little statistical grounds to choose between the two models, both the damped trend and trend models for invasive isolates were considered within the decision analytic modelling for MBL *Enterobacterales*. It was assumed that there was no trend in the future size of *Pseudomonas aeruginosa*.

Details on how the estimates of future change in the HVCs were used in the economic model are provided in Appendix 15.

8.2.5.2. Predicting future rates of resistance for current practice

The objective of this analysis was to characterise historical changes in resistance to existing AMs amongst patients with MBL *Enterobacterales* and MBL *Pseudomonas aeruginosa* to inform a quantitative forecast of how resistance might change in the future.

This analysis used time-series data provided by PHE, obtained from the same evidence sources as described in the previous sub-section (i.e. the AMRHAI national reference unit). Analyses were restricted to comparators used in the economic model. Resulting data were available for:

Enterobacterales with MBL:

- Aminoglycosides (gentamicin, amikacin, tobramycin)
- Aztreonam
- Colistin
- Tigecycline
- *Pseudomonas aeruginosa* with MBL:
- Colistin

For AM classes with evidence from multiple AMs, the most resistant result was retained in the supplied data. It is not expected that retaining the least resistant result would have a noticeable impact on estimates of resistance over time. As already described, isolates that were reported as ‘intermediate’ resistant were assumed to represent resistant isolates for the purpose of this analysis. Hence any tested isolate was either categorised as ‘susceptible’ or ‘resistant’ for this analysis. Combining ‘intermediate’

and ‘resistant’ categories was based on advice from clinical advisors. It is, however, noted that current EUCAST guidance is to combine ‘intermediate’ and ‘susceptible’ when only two categories are used.¹²⁷ The methods used to generate forecasts are broadly the same as those considered in the previous section, and are discussed in more detail in Appendix 15. Due to the sparsity of the available evidence, trends in the resistance (or susceptibility) to comparator AMs were not incorporated in to the decision analytic model.

8.2.5.3. Predicting future resistance trajectories for cefiderocol

The time-series data on susceptibility provided by PHE (and detailed in the previous sub-section) do not include cefiderocol. In the absence of evidence for the drug of interest, trajectories for the development of resistance were identified for other AMs. Due to a lack of evidence, the searching to identify these trajectories were not restricted to the HVCS populations. Evidence linking these resistance trajectories to quantity of AM use was also sought. This was to enable a link with the economic modelling; differences in levels of cefiderocol use (for example, in response to an increases in the HVCS populations over time or when comparing use in the ES with use in the MDS) are expected to be associated with differences in the rate at which resistance is gained. To emphasise that the evidence used is for a different drug and patient population, it is referred to as ‘external AM use-resistance data’. Including an association between cefiderocol use and the development of resistance means that scenarios with increased levels of cefiderocol use will not automatically result in better long-term outcomes. There is a large body of literature demonstrating that AM use is associated with subsequent resistance.¹²⁸⁻¹³⁰ As there are no historic data on how resistance develops for cefiderocol (in either the PHE data described in the previous section or identified in the susceptibility searches of Section 4), any resistance trajectories used in the economic modelling will be subject to considerable uncertainty. This is particularly pertinent as the relationship between AM use and resistance has been shown to vary by both type of AM and geographical setting, and in some situations, there is no apparent relationship.^{129,131,132} In the company submission for cefiderocol, it was contended that the development of resistance may be lower for cefiderocol than historically observed for other AMs (Section 2.3.5). Conversely, as an AM with broad coverage, the development of resistance to cefiderocol may be similar to other broad-spectrum AMs (which is typically quicker than the development of resistance for narrow-spectrum AMs). This emphasises the importance of identifying the robustness of estimates of pNHB to different potential resistance trajectories.

Two approaches were used to identify external AM use-resistance data that may inform the use-resistance association. First, the entire database of studies that was used during the reviewing process (for both CAZ-AVI and cefiderocol) was searched. Studies were filtered to include those which included “use”, “usage”, “volume” or “consumption”, and these were searched for any relevant evidence. In addition, to identify any English studies (which may use evidence from PHE, or the online

portal ‘fingertips’), a Web of Science search was conducted with the terms “(AM* OR antibiotic* OR resistan*) AND (fingertip OR "Public health England")”. These searches were complemented by any studies that were identified via other reviewing activities or already known to the study team. As a result, three studies were identified that, whilst not using data in the public domain, provided information on a use-resistance relationship.¹³³⁻¹³⁵ Details of these studies are provided in Appendix 17. These existing studies informed the *de novo* analyses reported here by suggesting that ARIMA models would be suitable time-series models for capturing use-resistance associations, with a lag of one year between use and resistance when using annual data.

In addition, several studies used publicly available surveillance data.^{131,136-140} These data were re-analysed for this project to identify potentially useful associations. For this project there were two types of data of interest:

- English data on AM use and AM resistance, from the ‘AMR local indicators profile’.¹⁴¹
- European data on AM use and AM resistance from the European AM Resistance Surveillance Network (EARS-Net) and European Surveillance of AM Consumption Network (ESAC-Net), respectively.^{142,143} This is available as annual data.

Further details on these evidence sources is provided in Appendix 17. For cefiderocol, increases in resistance will be from a low starting point. Observed trajectories for external evidence which also showed an increase from a low starting point were only identified for the European data, so this was used in subsequent analyses.

Thirty countries from the European Union contribute data to EARS-Net on AM resistance for up to eight pathogens.¹⁴⁴ These data were further filtered based on the following criteria:

- Pathogen is included in the HVCSs (*Escherichia coli* as a *Enterobacterales* and *Pseudomonas aeruginosa*).
- Data were available for both AM use and AM resistance (cephalosporins of all types, and carbapenems).
- Countries with at least 5,000 isolates were tested, baseline resistance (average over the first three years of available data) was less than 3% (*Enterobacterales*) or less than 15% (*Pseudomonas aeruginosa*), with at least 10 years of observations for carbapenems and 15 years of observations for cephalosporins (these did not have to be consecutive).

This resulted in the following 23 pathogen-drug-country combinations:

- *Pseudomonas aeruginosa*, carbapenems: Finland, France, Ireland, Netherlands, Norway, Slovenia, Sweden.
- *Escherichia coli*, carbapenems: France, Greece, Netherlands, Norway.

- *Escherichia coli*, cephalosporins: Bulgaria, Croatia, Estonia, Finland, France, Greece, Ireland, Luxembourg, Malta, Norway, Slovenia, Sweden.

For these countries, ARIMA models were used to estimate the impact of increasing AM use (defined daily doses per 1,000 inhabitants per day) in a given year on resistance to that AM in the following year. Of the 23 combinations considered:

- Just under half provided a significant association (12 / 23; *Pseudomonas aeruginosa* = 4 / 7, *Escherichia coli* = 2 / 4 for carbapenems and 6 / 12 for cephalosporins).
- Of the 12 significant associations, seven were positive associations (increasing use led to an increase in resistance), whilst five were negative (decreasing use led to an increase in resistance). Four of the negative associations were for *Escherichia coli* cephalosporins, the remaining one was for *Pseudomonas aeruginosa*.

Hence this analysis resulted in up to seven significant positive associations that could be used to link increases in AM use to AM resistance in the economic model. Increases in AM use are driven by increases in the eligible population over time.

Projections of expected usage for cefiderocol from Section 8.2.6 were linked to these estimates of the relationship between usage and resistance to predict emergence of resistance to cefiderocol over time. Even under more extreme usage predictions and the strongest associations between usage and resistance emergence, this predicted small absolute increases in resistance up to 0.04% and 0.16% over 20 years for the MBL *Enterobacterales* and *Pseudomonas aeruginosa* populations, respectively (see Appendix 17 for more details). EEPRU considered that this may represent an underestimate of the potential for resistance emergence for two reasons. Firstly, the spread of MDR infections is influenced by international travel and the “importation” of MDR pathogens. Resistance emergence may, therefore, be influenced by cefiderocol usage outside the UK which is not accounted for in these projections.

Secondly, the relationships between usage and resistance characterised in the available data reflect all tested isolates in the community and hospital settings. Resistance emergence may be much higher within the HVCs where usage will be concentrated. For this reason, EEPRU has conducted a range of scenario analyses to characterise the potential emergence of resistance to cefiderocol. These were informed by considering the absolute increases in resistance for the drug-pathogen combinations and countries discussed above, where there was a statistically significant increase (see Appendix 17 for more details). The highest absolute increase in resistance (an annual absolute increase of 1.65%, leading to a projected 20-year increase of 33%) was used to bound these analyses. The second largest increase was 0.95% per year (19% over 20 years). Based on these considerations EEPRU ran analyses with resistance emergence reaching 1%, 5%, 10% and 30% at 20 years. It is noted that the upper scenario may be very extreme.

Of note, this analysis was focused on datasets which demonstrated an increase in resistance overtime. Hence any significant associations between AM use and decreasing resistance were not explored. As an alternative to an ARIMA model, a dynamic differential equations model was also developed. This was designed to incorporate AM use and resistance, as well as the spontaneous loss or gain of resistance over time as well as the impact of deaths. Details of this model are provided in Appendix 16; when evaluated in a simulation study it was shown to provide biased parameter estimates. This was potentially due to the non-identifiability of the model (due to the number of potential AM drivers considered), so this model was not considered further.

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.⁵ This provided an estimate of 2.4 DDD /1000 inhabitants for all AMs used in an inpatient setting. Drug use during the first year of the economic model for both CAZ-AVI and cefiderocol (combining results from both evaluations) for the sites cUTI, intra-abdominal infections (IAIs), HAP/VAP, and BSIs (all four in *Enterobacteriales*, *Pseudomonas aeruginosa*, and *stenotrophomonas*) was estimated to be 0.00018 DDD/1000 inhabitants, hence representing 0.01% of all hospital inpatient AM use. This estimate, as an upper-bound on the potential use of both cefiderocol and CAZ-AVI, was felt by the modelling team to have face validity.

8.2.5.4. Predicting the impact of reduced drug use on resistance

Introducing cefiderocol (compared with the situation when it is not available) may lead to a reduced use of comparator AMs. As the economic model includes an association between increased use of cefiderocol and increased resistance (as described in the previous subsection), then intuitively a decrease in AM use would be expected to lead to a decrease in resistance. However, AM use in the population of interest is only one of a multitude of potential drivers for increases in AM resistance. Other potential drivers include the number of invasive procedures, AM use in other countries, environmental factors, and AM use in animals.^{145,146} The existing evidence on the effect of reduced AM use on AM resistance is mixed,¹⁴⁷ with findings including no decrease, a decrease, and even an increase in AM resistance.¹⁴⁸⁻¹⁵⁰ Hence, whilst the introduction of a new AM is expected to lead to an increase in resistance over time, reducing AM use has less predictable effects on resistance. Due to the heterogeneity in the existing literature and the lack of evidence for the population and AMs of interest, it was assumed that reductions in use of existing AMs did not lead to reductions in resistance over time.

8.2.6. Extrapolation from HVCS to expected usage

An important part of understanding the value of cefiderocol is understanding the range of patients in whom it is expected to be used. This is also relevant to understanding how resistance to cefiderocol is likely to emerge over time (as higher usage is likely to contribute to higher resistance). To inform this assessment, we provide a qualitative description of the range of ways (outside of the HVCSs) that

cefiderocol is expected to be used. This is informed by discussions with our clinical advisors, the manufacturer submission for cefiderocol, and input by other stakeholders during the NICE process to identify patient groups in whom cefiderocol may offer significant improvements in HRQoL and mortality compared to existing therapies.

Following this, for those areas of usage considered by the clinical advisors and study team to be most significant in terms of population size and potential impact on INHEs, we have quantified the likely size of the populations who would receive cefiderocol. This is based on data from PHE, where available, and supplemented by data from the literature and expert opinion where necessary. These estimates are also compared to those provided by Shionogi in their manufacturer submission. These estimates are then used to rescale the population-level INHEs from the HVCSs.

8.2.6.1. Areas of expected usage

Infection sites and patient characteristics

Outside of the HVCSs, the following infection sites were considered to be most important in driving expected usage and gains in NHEs: BSI and IAI. Our clinical advisors emphasised the importance of cefiderocol in treating BSIs. The incremental value of cefiderocol (and AMs in general) in IAI is less clear as the quality of surgical procedures used to manage IAI was considered more important than the choice of AM and identifying MDR infections is more challenging. The clinical advisors also emphasised the importance of cefiderocol in treating patients who are immunocompromised (e.g. haematology, transplant), patients with cystic fibrosis and patients with burn injuries who are predisposed to acquiring resistant infections. In immunocompromised patients, BSIs are of particular concern, while in patients with cystic fibrosis, chronic respiratory infections are of particular concern. Patients with a higher propensity for renal complications and those with renal impairment may receive more significant benefits from cefiderocol, as renal complications may rule out or increase the toxicity of agents that remain effective in treating MDR infections (i.e. colistin, aminoglycosides).

MDR pathogens/mechanisms

Outside of the HVCSs, the following pathogen-mechanism combinations were discussed as relevant areas for usage for cefiderocol:

- Non-MBL *Pseudomonas aeruginosa*;
- *Stenotrophomonas* (which is inherently MBL);
- OXA-40/24, -51, -58, -143 and MBL *acinetobacter*;
- Pathogens with serine carbapenemases (e.g. OXA-48, KPC) or non-carbapenemase causes of carbapenem resistance (e.g. porin and efflux pump mechanisms).

Our clinical advisors considered that patients with non-MBL *Pseudomonas aeruginosa* had other effective treatment options available and that this was not, therefore, a priority area of usage for cefiderocol, but that *Stenotrophomonas* and OXA-40/24, -51, -58, -143 and MBL *Acinetobacter* were potentially important areas of usage, though the latter two groups were small. Use of cefiderocol in patients with other serine carbapenemases (e.g. OXA-48, KPC) or non-carbapenemase causes of carbapenem resistance (porin and efflux pump mechanisms) was not generally considered a priority by our clinical advisors due to the availability of other effective treatment options. The exception to this was infections that were MDR due to multiple types of carbapenem resistance (e.g. serine, porin and efflux pump) in whom cefiderocol may represent an important treatment option.

Empiric usage

During the course of these evaluations there was substantial debate about the appropriate definition of the ES. Stakeholders were broadly aligned that the risk-based ES should be driven by the severity of the clinical scenario rather than the site of infection alone.

The manufacturer and the clinical advisors to this project presented differing perspectives on how to define a patient as at high risk of carbapenem-resistance for the purposes of identifying patients that might appropriately receive risk-based empiric treatment with cefiderocol. As documented throughout this report, the clinical advisors to this project considered that it was appropriate to restrict usage in the ES to patients with a high risk of an infection caused by MBL *Pseudomonas aeruginosa* or MBL *Enterobacterales* where this high risk was based on one of three factors:

- The patient was previously hospitalised in a healthcare setting with high prevalence of *Enterobacterales* or *Pseudomonas aeruginosa* with MBL.
- There is an outbreak of infection with *Enterobacterales* or *Pseudomonas aeruginosa* with MBL on a ward where the patient has stayed during their current admission.
- Previous cultures (taken during the current or previous hospital stays) show that the patient was previously colonised/infected by *Enterobacterales* or *Pseudomonas aeruginosa* with MBL.

This view was based on the desire to restrict usage to those in whom benefit was most significant, thus controlling the emergence of resistance. The clinical advisors also expressed concerns that a broader definition could lead to stewardship challenges.

The manufacturer considered a broader definition of patients at high risk of a drug-resistant infection. This included patients at risk of resistance due to “*international travel and immunosuppression*”, and patients considered at risk of a range of types of carbapenem resistance “*including all classes of beta-lactamases (e.g. serine β -lactamase, metallo- β -lactamase), porin channels or efflux pumps related resistance mechanisms, alone or in combination.*” The manufacturer noted that, for many patients, the specific type of carbapenem-resistance may be unknown and there may just be a general suspicion of

carbapenem resistance. The manufacturer emphasised that, for this group, cefiderocol was particularly relevant due to its broad coverage.

The clinical advisors considered that usage under a broader suspicion of resistance should only be considered in exceptional cases. The appropriateness of a wider definition of empiric usage is, in principle, a question that could be addressed empirically, by assessing the health benefits of a more inclusive definition, against the health costs of treating more patients who do not have a resistant infection with cefiderocol and, therefore, contributing to higher levels of long-term resistance. This trade-off was not addressed quantitatively by EEPRU or the manufacturer, largely reflecting the difficulties in accurately quantifying the long-term implications of different levels of usage for the emergence of resistance to cefiderocol.

8.2.6.2. Population size estimates produced by the manufacturer

Shionogi estimates that there are 5,000 infections caused by MBL-producing pathogens per year in England. This is based on the calculations presented in Table 29.

Table 29: Manufacturer estimates of expected usage in infections caused by MBL-producing pathogens

Parameter	Value	Source
Infections caused by gram-negative pathogens in England	200,000	Estimate based on the annual rate of hospital acquired infections (HAIs) in England (243,746 ¹⁵¹ and 300,000 ¹⁵²) and the assumption that the majority of HAIs are caused by gram negative bacteria.
Proportion of gram-negative infections that are carbapenem resistant	8%	Specialist Pharmacy Service. ¹⁵³
Proportion of carbapenem resistant infections that produce MBL	33%	ESPAUR report ⁵ data on MBL rates in <i>Enterobacterales</i> ; Castanheira <i>et al.</i> ¹⁵⁴ data on MBL rates amongst carbapenem-producing <i>Pseudomonas aeruginosa</i> .
Total number of infections caused by MBL-producing pathogens	5,000	Calculation

ESPAUR, English Surveillance Programme for Antimicrobial Utilisation and Resistance; HAI, hospital-acquired infection; MBL, metallo-beta-lactamases

The manufacturer estimates that 750 infections caused by MBL-producing pathogens are critical and could be identified as high-risk of resistance. This is based on the calculations presented in Table 30.

Table 30: Manufacturer estimates of expected usage in infections caused by MBL-producing pathogens that are considered critically ill and could be identified as high risk at the point of empiric treatment

Parameter	Value	Source
Total number of infections caused by MBL-producing pathogens	5,000	See Table 29.

Proportion of infections considered critical	30%	Proportion of infections that are respiratory infections or BSIs amongst all health-care infections ¹⁵¹
Proportion of infections that would be considered at high suspicion of MBL production in the ES	50%	Expert opinion
Total number of infections caused by MBL-producing pathogens that would be eligible for treatment in the ES	750	Calculation

ES, empiric setting; MBL, metallo-beta-lactamases

In addition, the manufacturer provides a range of examples of increasing infection rates and rates of resistance which they assess as indicative of an annual growth rate in the number of patients eligible for cefiderocol of 5% per annum.

The company's estimate of the population size is based on uncertain evidence and a series of assumptions outlined in Table 29. The resulting estimate is uncertain, reflecting the sparsity of evidence about the prevalence of infections caused by pathogens with MBL. Similarly, the company's estimate of the annual growth rate is a rough estimate, higher than the growth rate in BSIs in general, and higher than the rate of increase in resistance in *Pseudomonas aeruginosa* or *Enterobacterales* infections which the company cite. The mark up is based on qualitative arguments, and is therefore considered to be highly uncertain.

The company's estimate represents the total number of MBL infections. In clinical practice, it is likely that not all MBL infections would be identified by clinicians as high risk of being MBL, or confirmed as MBL. As result, 750 infections is likely to be an overestimate of the number of infections that would be treated with cefiderocol in clinical practice in the ES. The manufacturer does not present an estimate of the number of infections that would be treated with cefiderocol in the MDS.

8.2.6.3. Quantitative extrapolation to expected usage

Current population sizes

The aim was to estimate the number of infections in the HVCs and other important areas of expected usage. Based on feedback from our clinical advisors, the majority of cefiderocol use in HAP/VAP and BSIs was expected to be in the ES and the majority of cefiderocol use in cUTI and IAI was expected to be in the MDS. Furthermore, cefiderocol was also expected to be used in certain hard to treat infections caused by *Stenotrophomonas*. We therefore set out to estimate the number of patients with the following characteristics:

- HAP/VAP and BSIs with suspected infection caused by *Enterobacterales* with MBL or *Pseudomonas aeruginosa* with MBL, according to the criteria outlined in Section 4.2.4; and

- cUTIs and IAIs caused by *Enterobacterales* with MBL or *Pseudomonas aeruginosa* with MBL, as confirmed by resistance mechanism testing; and
- HAP/VAP, cUTIs, BSIs and IAIs caused by *Stenotrophomonas*, resistant other treatment options.

The current population size was derived from SGSS data (AMR module) supplied by PHE. SGSS is a national database of laboratory data provided by approximately 98% of hospital microbiology laboratories in England.⁵ It contains resistance mechanism and antibiotic susceptibility testing for all submitted isolates. We analyse data for the period between October 2020 and April 2021 as from October 2020 reporting of acquired carbapenemse-producing GNB by laboratories become mandatory.

The SGSS dataset includes anonymised patient ID, specimen type, species, referral location, laboratory, resistance mechanism tested and mechanism results. The site of infection was not available directly; instead it was inferred from the specimen types.

Clinical advisors to the project highlighted that there is considerable uncertainty in the categorisation of infection sites according to the specimen type. To reflect this uncertainty we explored two separate classifications in scenario analyses, shown in

Table 31. The classification in Scenario 1 was derived by PHE, based on a set of specimens that map directly to infection sites. The scenario excluded all specimens from female patients in cUTIs except nephrostomy specimens, and all sputum samples. The sputum samples were removed following a clinical review (discussed in more detail in ESPAUR report 2021⁵) because a large number of sputum samples are considered to be contaminants without further evidence of clinical infection. The clinical advisors to EEPRU considered this classification to be conservative and a broader classification in Scenario 2 was derived with guidance from clinical advisors. Scenario 2 included sputum samples, and urine samples from both male and female patients where the medical requestor is ‘acute’ care, as a proxy for hospitalised patients. The scenario is likely to capture other relevant infections excluded from Scenario 1, but may include some specimens that do not relate to the infection types of interest.

Table 31: Classification of infection sites according to specimen type

	HAP/VAP	cUTIs	BSIs	IAIs
Specimen types in scenario I1	Lower respiratory tract (bronchial)	Urine/kidney specimens from all male patients, irrespective of setting (urine, CSU, MSU, urinary catheter, suprapubic aspirate, bladder, kidney, urethra, urine/kidney, spa, ureter, urethral swab, EMU, ileal/bladder conduit, perinephric, first void, pus associated kidney/urinary tract); Nephrostomy specimens in male and female patients	Blood samples (blood, plasma, dried blood spot, haematoma, cord blood, foetal blood)	Wound specimens (surgical and traumatic wounds)
Additional specimen types in scenario I2	Lower respiratory tract (alveolar lavage, trachea, BAL, chest, lung, lower respiratory tract, tracheal aspirate), sputum (sputum, endotracheal secretions, endotracheal aspirate, endotracheal tube, induced sputum), swab (lung swab)	Urine/kidney specimens in scenario 1 in all hospitalised* patients (both male and female), upper genital tract in male and female hospitalised* patients	Heart/heart valve (heart, heart valve, mitral valve), intra-vascular line (TIP-NOS, arterial line/tip, Hickman line, CVP line tip, aortic valve, Venflon, aorta, haemodialysis access, arterio-venous shunt), pacemaker, catheter swab, aortic tissue, heart valve prosthesis (cardiac prosthesis, heart valve prosthesis), vascular graft (vascular graft), liver/bile (bile, gall bladder), hip tissue, hip swab, skin/wound (pressure sore), bone (bone, bone/joint, vertebra), bone marrow, bone pin/plate (prosthesis pin, bone pin/plate, prosthesis plate), joint prosthesis (artificial joint), intervertebral disc (intervertebral disc), IUCD, peritoneum, foreign body, implant NOS, CSF shunt (ventriculo-atrial valve), bone biopsy sample	None

Abbreviations: BAL, bronchoscopy and bronchoalveolar lavage; BSIs, bloodstream infections; CSF, cerebrospinal fluid; CSU, catheter specimen of urine; cUTIs, complicated urinary tract infections; EMU, early morning urine; HAP/VAP, hospital-acquired pneumonia or ventilator associated pneumonia; IAIs intra-abdominal infections; IUCD, intra-uterine contraceptive device; MSU, midstream specimen of urine

* Specimens referred from acute care assumed to represent infections in hospitalised patients.

In the dataset, repeated entries were only removed if they were directly repeated for the same patient, species, specimen, referral location, laboratory, mechanism, and mechanism results. However, it is possible that reported numbers included multiple entries from the same infectious episode if multiple specimen samples were analysed (e.g. on different days). Furthermore, samples were likely to be tested

for multiple resistance mechanisms – specimens tested for MBL *Enterobacterales* included tests for IMP, VIM and NDM, and tests for MBL *Pseudomonas aeruginosa* included tests for IMP, VIM, DIM and NDM. When multiple resistance mechanisms were tested, each mechanism was recorded as an individual entry. When deriving the current population size for this report, the number of *Enterobacterales* and MBL *Pseudomonas aeruginosa* samples tested were divided by 3 and 4, respectively, under the assumption that each sample was tested for each resistance mechanism. Finally, on advice from clinical advisors, the number of specimens positive for *Stenotrophomonas* were multiplied by 0.15 to reflect the fact that the advisors estimated that approximately 15% of infections caused by *Stenotrophomonas* would be eligible to receive cefiderocol. The majority (85%) of *Stenotrophomonas* infections would not be eligible for treatment with cefiderocol as they may not require treatment with AMs at all or may be effectively treated with other AMs. Patients with *Stenotrophomonas* infections receiving cefiderocol were assumed to do so within the MDS.

The number of specimens *tested* for MBL was used to approximate the population size in ES. This reflects an assumption that all of the mechanism testing conducted was initiated following high suspicion of that resistance mechanism by the treating clinicians for the reasons specified in Section 4.2.4. The number of isolates *confirmed* to have the resistance mechanism was used to approximate the population size in the MDS. The derived population sizes are shown in Table 32. The specimen types included did not impact on the number of BSIs and IAIs.

It should be noted that the sum of population sizes for individual infection sites may overestimate the total population size, if the same infection presents at multiple sites. For example, BSIs are often sequelae of other infections. If a BSI develops from HAP/VAP following unsuccessful treatment with cefiderocol, it would likely be treated with an alternative AM, despite having the resistance mechanism of interest.

Table 32: Number of infections of interest (per annum)

		HAP/VAP (tested)	cUTIs (confirmed positive)	BSIs (tested)	IAIs (confirmed positive)	HAP/VAP (confirmed positive)	BSIs (confirmed positive)
MBL <i>Enterobacterales</i>	Scenario P1	25	62	155	51	NA	NA
	Scenario P2	157	84	155	51	NA	NA
<i>Pseudomonas</i> MBL	Scenario P1	6	17	13	12	NA	NA
	Scenario P2	87	10	13	12	NA	NA
<i>Stenotrophomonas</i> (MDS)	Scenario P1	NA	64	NA	38	100	63
	Scenario P2	NA	63	NA	38	547	63

BSIs, bloodstream infections; cUTIs, complicated urinary tract infections; HAP/VAP, hospital-acquired pneumonia or ventilator associated pneumonia; IAIs intra-abdominal infections; MBL, metallo-beta-lactamases; MDS, microbiology-directed setting

The estimates in Table 32 are associated with considerable uncertainty due to uncertainty in the completeness of the SGSS dataset (labs may not submit all specimens to SGSS), uncertainty in how accurately specimen types represent the infection sites of interest, uncertainty about whether all tested patients would fall within our the defined target population for empiric treatment, and the potential double counting of samples from the same infectious episode.

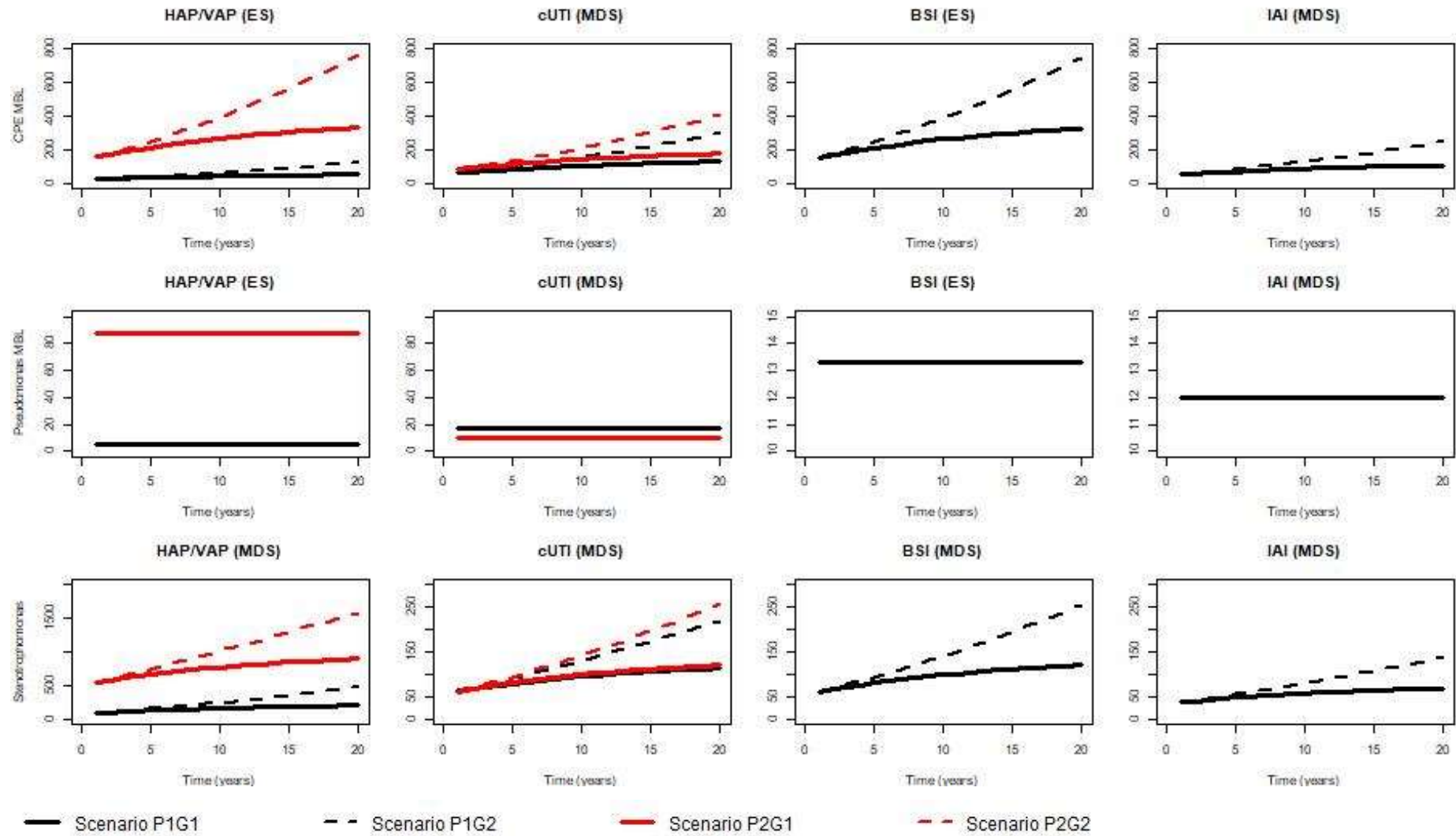
To provide an alternative estimate of the population size, we conducted a survey (previously described in Section 8.2.3) about the number of HAP/VAP infections eligible for treatment in the ES. The survey targeted infectious disease specialists and collected information about the participants' place of work (number of hospital beds, and the number of other infectious disease specialists), and the number of suspected and confirmed HAP/VAP infections caused by *Enterobacteriales* and MBL *Pseudomonas aeruginosa* they encountered per annum. The survey was disseminated to infectious disease consultants and microbiologists who were members of the BSAC, to clinical advisors to the project, and to experts recommended by the clinical advisors. The infection numbers were scaled to country-level estimates using the number of hospital beds per infectious disease specialist (derived from the survey responses) and the unweighted average number of hospital beds in England for four quarters in 2020/21.¹⁵⁵

In total, 25 participants started the survey, of which nine provided information required to estimate the total number of patients eligible for treatment in ES in England. The estimates varied considerably between experts (with responses implying 0 to 33,554 suspected and 0 to 26,843 confirmed infections in England). The weighted average (9,356 suspected and 6,669 confirmed infections) was considered to be implausibly high by clinical advisors to the project, possibly because of higher survey take up among experts who are more likely to encounter the infections of interest and these estimates were not, therefore, taken forward to the decision analytic modelling.

The population size over 20 years was derived by applying the year-on-year population growth detailed in Section 8.2.5 to the current annual population size (Table 32). The population size estimates are used to rescale the estimates of patient-level INHEs and are presented in

Figure 15. Four scenarios are used to model the eligible population over time. Scenario P1G1 is the most conservative, as it uses the conservative baseline number of infections (scenario P1 in Table 32), and the population growth derived from a time series model with a damped trend (see Section 8.2.5.1 for details). Scenario P2G2 is the least conservative, as it uses the larger baseline number of infections (scenario P2 in Table 32), and the population growth derived from a time series without a damped trend (see Section 8.2.5.1 for details). The difference between the scenarios is largely driven by the assumptions about long term growth in infection numbers. When using the model with a damped trend, the total population size across all sites of infection increased from between 605 and 1,280 (P1 G1 and P2G1) in year 1 to between 1,175 and 2,269 in year 20. The model with the non-damped trend increased the total population size substantially, from between 605 and 1,280 (P1G2 and P2G2) in year 1 to between 2,553 and 4,508 in year 20.

Figure 15. Population size



P1G1: baseline population based on PHE categorisation of infection sites, damped growth rate; P1G2: baseline population based on PHE categorisation of infection sites, growth rate not damped; P2G1: Baseline population based on clinical advisors' categorisation of infection sites, damped growth rate; P2G2: Baseline population based on clinical advisors' categorisation of infection sites, growth rate not damped.

In addition, we derive estimates of expected total drug usage for cefiderocol as these influence some of the scenarios relating to resistance emergence (see Section 8.2.5.3). Expected usage of cefiderocol was derived by adjusting the population size for the proportion of patients eligible for treatment with cefiderocol. In ES, all infections were assumed to be eligible for empiric treatment. In MDS, infections confirmed to have the relevant resistance mechanisms in Table 32 were adjusted for the proportion of patients who are not susceptible to non-colistin/aminoglycoside-based treatment, but were susceptible to cefiderocol. Susceptibility of infections caused by *Enterobacterales* and *Pseudomonas aeruginosa* with MBL were derived using the evidence described in Section 8.2.3.2. Susceptibility of *Stenotrophomonas* infections was derived from the average susceptibility of *Enterobacterales* with MBL and *Pseudomonas aeruginosa* with MBL infections, weighted by the proportion of infections caused by each microorganism (in Table 32). When deriving expected usage, susceptibility was assumed to be static over time for simplicity, as susceptibility changes over time were expected to have a small impact on usage.

The total expected usage over 20 years is shown in Table 33.

Table 33. Total number of patients initiating cefiderocol over 20 years.

	HAP/ VAP (MBL <i>Enterobacteriales</i>)	HAP/ VAP (Pseudo. MBL)	HAP/ VAP (Steno.)	cUTI (MBL <i>Enterobacteriales</i>)	cUTI (Pseudo. MBL)	cUTI (Steno.)	BSI (MBL <i>Enterobacteriales</i>)	BSI (Pseudo. MBL)	BSI (Steno.)	BSI (MBL <i>Enterobacteriales</i>)	IAI (Pseudo. MBL)	IAI (Steno.)
Scenario P1G1	830	111	618	125	339	351	5,110	266	365	104	237	215
Scenario P1G2	1,362	111	1,014	204	339	514	8,388	266	564	170	237	319
Scenario P2G1	5,186	1,740	2,743	170	203	352	5,110	266	351	104	237	207
Scenario P2G2	8,511	1,740	3,781	278	203	546	8,388	266	542	170	237	307

Abbreviations: BSIs, bloodstream infections; cUTIs, complicated urinary tract infections; HAP/VAP, hospital-acquired pneumonia or ventilator associated pneumonia; IAI, intra-abdominal infections; MBL, metallo-beta-lactamases; MDS, microbiology-directed setting; Pseudo., *Pseudomonas*; Steno., *Stenotrophomonas*

Scenarios: P1G1: baseline population based on PHE categorisation of infection sites, damped growth rate; P1G2: baseline population based on PHE categorisation of infection sites, growth rate not damped; P2G1: Baseline population based on clinical advisors' categorisation of infection sites, damped growth rate; P2G2: Baseline population based on clinical advisors' categorisation of infection sites, growth rate not damped.

Extrapolation of INHEs between populations

Population-level INHEs were derived by multiplying patient-level INHEs by the population size. Patient-level INHE, derived from the model described in Section 8.2, was conditional on the site of infection, the pathogen-mechanism and the treatment setting (ES or MDS). Patient-level INHEs for cUTIs in the MDS and for HAP/VAP in the ES were estimated by the model, for all infections caused by *Enterobacteriales* with MBL and *Pseudomonas aeruginosa* with MBL. Patient-level INHEs in BSI and IAIs were assumed to be the same as in HAP/VAP and cUTIs, respectively, based on feedback from our clinical advisors. BSI and HAP/VAP are both severe infections where ceftiderocol is expected to be used predominantly empirically. Although the consequences of IAI can be more severe than the consequences of cUTI as they are very difficult to treat (requiring a combination of ABs and surgery), on the other hand the benefits of ceftiderocol may be smaller due to the complexity of treating these infections and the lesser role of AMs compared to other treatment modalities in their management. Patient-level INHEs in infections caused by *Stenotrophomonas* were derived from INHEs in *Enterobacteriales* with MBL and *Pseudomonas aeruginosa* with MBL, weighted by the proportion of infections caused by each microorganism (in Table 32), based on feedback from our clinical advisors. All *Stenotrophomonas* were assumed to be treated in the MDS, again based on feedback from our clinical advisors.

Population-level INHEs in years 1-20 were discounted at an annual rate of 3.5% to account for the delayed start of treatment.

Probabilistic analysis

The parameters included in the probabilistic analysis were chosen pragmatically. The analysis incorporated uncertainty in the patient-level INHE (as described in Section 8.2) and uncertainty in the population growth. The probabilistic analysis did not reflect uncertainty in the current population size, instead this was explored in scenario analyses outlined above. Expected usage and the link between this and resistance was not made probabilistic for simplicity and due to the challenges in characterising with any accuracy the uncertainty around emergence of resistance, again this was explored via scenario analyses outlined in Section 8.2.5.

8.2.7. Additional elements of value for new AMs

The literature on the economic evaluation of AMs has described the different sources of value associated with these products.^{19,96} In EEPRU's earlier work on evaluation methods,¹⁹ the principles by which each of these 'elements of value' can be reflected in models focused on estimating the impact of new products on population NHEs was discussed.

In Section 9.3 we present a summary of how the different elements of value are conceptualised in the literature, within the manufacturer submission and how they are understood by our clinical advisory group. We summarise the extent to which each element of value is reflected in the quantitative assessments of value for the HVCs or quantitative evidence presented in the manufacturer submission. For each element of value for which a quantitative assessment was not conducted, we provide a discussion of the extent to which that element of value is likely to be quantitatively important in influencing the assessment of population-level INHs for cefiderocol. This is based on evidence from the literature, evidence presented in the manufacturer submission and the views of our clinical advisors.

8.2.8. Validation

To ensure the appropriateness of the decision problem, scope of the decision model, model structure and evidence used we consulted extensively: with microbiologists and clinicians involved in treating serious drug-resistant infections and in related research; those with expertise in transmission modelling; and experts in specific types of evidence. Given the complexity of the appraisal and the multiple components of the work this required, approximately ten separate calls on different aspects of the work.

A technical validation of the data analyses, synthesis and decision analytic modelling conducted by EEPRU was conducted. This comprised a review of the code by a second reviewer.

9. Results of quantification of value

9.1. Direct patient net health effects in HVCSS

9.1.1. MBL *Enterobacterales*, empiric setting, HAP/ VAP

The base case results are shown in Table 34 for patients correctly suspected as having MBL *Enterobacterales* (herein “with MBL *Enterobacterales*”), those wrongly suspected of having MBL *Enterobacterales* (herein “without MBL *Enterobacterales*”), and in the average patient suspected to have MBL *Enterobacterales* in the ES (whose outcomes are a weighted average of those with and without MBL *Enterobacterales*). There is no non-colistin/aminoglycoside based treatment combination in the PICOS for this patient population.

Amongst patients with MBL *Enterobacterales*, cefiderocol is associated with lower susceptibility (67% for cefiderocol compared to 96% for colistin/aminoglycoside-based therapy) but improved safety. Overall this results in slightly higher QALYs for cefiderocol (incremental difference 0.01). The safety advantage delivers a substantial QALY gain due to the reduced mortality associated with AKI in the short and long-term, almost offsetting the lower susceptibility. The lower susceptibility associated with cefiderocol results in a longer LoS, this overwhelms AKI-related cost savings and drives the £4,600 incremental costs associated with cefiderocol. The patient-level INHE is -0.22 QALYs when comparing cefiderocol to colistin/aminoglycoside-based therapy in patients with MBL *Enterobacterales*.

Amongst patients without MBL *Enterobacterales*, cefiderocol and colistin/aminoglycoside-based therapy are assumed to offer similar susceptibility but cefiderocol offers improved safety. This results in a patient-level INHE of 0.18 QALYs for cefiderocol compared to colistin/aminoglycoside-based therapy. This is driven by the QALY gain due to the reduced mortality associated with AKI in the short and long-term and a small cost saving associated with reduced risk of AKI.

In the average ES patient suspected of having MBL *Enterobacterales*, use of cefiderocol in the ES is associated with a patient-level INHE of 0.12 QALYs compared to colistin/aminoglycoside-based therapy. This reflects that the safety gains associated with avoiding colistin/aminoglycoside-based therapy across patients offset the lower susceptibility associated with cefiderocol in patients with MBL *Enterobacterales*.

Restricting the use of cefiderocol to patients who fail empiric treatment and require treatment in the MDS results in very similar INHE benefit as existing therapy. This is attributable to a number of factors. Many patients can be treated effectively in the ES with existing treatments or die prior to reaching the MDS (i.e. not all patients progress to the MDS), many patients do not have MBL *Enterobacterales* and are not, therefore, eligible to receive cefiderocol in the MDS, and amongst those with MBL

Enterobacterales the majority (91%) are susceptible to a non-colistin-based treatment option and, therefore, do not receive cefiderocol in the model.

Table 34: Per patient base-case results: MBL *Enterobacterales* HAP/VAP empiric setting (probabilistic, 2,000 simulations).

	E1	E2ca	E3ca	E1-E2ca	E1-E3ca
Patients with MBL <i>Enterobacterales</i>					
<i>Summary of in-hospital outcomes (proportions) across both lines of treatment available</i>					
Death	0.399	0.403	0.403	-0.004	-0.003
Survival no AKI	0.473	0.428	0.428	0.046	0.045
Survival AKI	0.127	0.169	0.169	-0.042	-0.042
Survival CKD	0.000	0.000	0.001	0	0
<i>Economic outcomes (all discounted)</i>					
Treatment costs	£101	£179	£178	-£78.38	-£76.83
AKI costs hospital	£1,954	£2,285	£2,283	-£330.79	-£328.95
Other costs hospital	£21,301	£16,319	£16,301	£4,981.96	£5,000.31
Long-term costs	£607	£623	£624	-£16.61	-£17.14
Total costs	£23,962	£19,406	£19,385	£4,556.18	£4,577.38
Life years	2.706	2.691	2.693	0.015	0.013
QALYs	1.901	1.891	1.893	0.01	0.009
Per person NHE	0.703	0.921	0.924	-0.218	-0.22
Patients without MBL <i>Enterobacterales</i>					
<i>Summary of in-hospital outcomes (proportions) across both lines of treatment available</i>					
Death	0.351	0.403	0.403	-0.052	-0.052
Survival no AKI	0.524	0.428	0.428	0.096	0.096
Survival AKI	0.125	0.169	0.169	-0.044	-0.044
Survival CKD	0.000	0.000	0.000	0	0
<i>Economic outcomes (all discounted)</i>					
Treatment costs	£30	£179	£179	-£149.26	-£149.26
AKI costs hospital	£1,672	£2,285	£2,285	-£612.30	-£612.30
Other costs hospital	£16,736	£16,319	£16,319	£417.03	£417.03
Long-term costs	£649	£623	£623	£26.12	£26.12
Total costs	£19,088	£19,406	£19,406	-£318.40	-£318.40
Life years	2.924	2.691	2.691	0.233	0.233
QALYs	2.054	1.891	1.891	0.163	0.163
Per person NHE	1.100	0.921	0.921	0.179	0.179
All patients presenting in the ES					
Total costs	£19,832	£19,406	£19,403	£425.9104	£429.1481
QALYs	2.031	1.891	1.891	0.140	0.139
Per person NHE	1.039	0.921	0.921	0.118	0.118

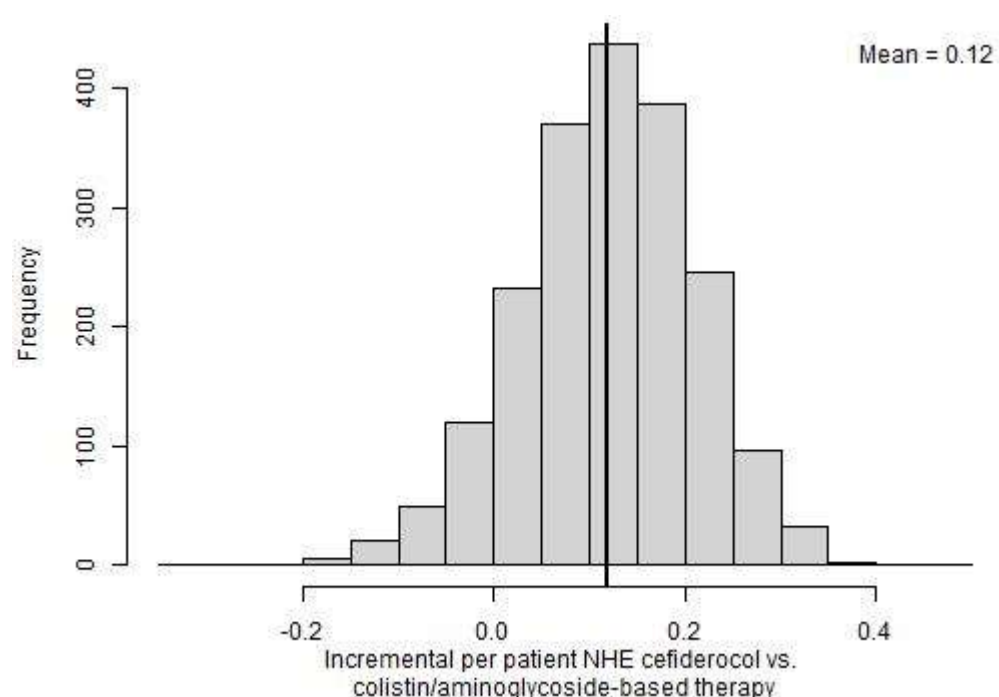
Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; ES, empiric setting; MBL, metallo-beta-lactamases; MDS, microbiology-directed setting; NHE, net health effect; QALYs, quality-adjusted life years

Comparators: E1 = empiric treatment with cefiderocol, followed by existing therapies in MDS if not susceptible; E2ca = colistin or aminoglycoside-based empiric treatment, followed by existing therapies MDS if needed; E3ca

= colistin or aminoglycoside-based empiric treatment, followed by cefiderocol MDS if needed. Net health effects derived using threshold of £20,000/QALY.

There is a large degree of parameter uncertainty around the patient-level INHEs of cefiderocol. The distribution of patient-level INHEs is shown in Figure 16. This reflects uncertainty in the probability a patient has MBL *Enterobacterales*, the relative susceptibility of these treatment options, their safety and the benefits of avoided AKIs.

Figure 16: Distribution of patient-level INHEs of cefiderocol compared to colistin/aminoglycoside-based therapy: MBL *Enterobacterales* HAP/VAP empiric setting (2,000 simulations)



NHE, net health effects

Scenario analyses that modified the base case INHE by more than 10% (and three scenario analyses requested by NICE marked by *) are shown in Table 35. The main areas of uncertainty relate to the probability that a patient has MBL *Enterobacterales*, the susceptibility scenarios, the impact of colistin/aminoglycoside-based therapy on AKI risk and its long-term implications, and long-term survival following discharge from hospital.

The results are very sensitive to the proportion of people with MBL *Enterobacterales*. When this proportion is 50% or more, the preferred treatment pathway is no longer to use cefiderocol empirically but to use colistin/aminoglycoside-based therapy empirically due to its susceptibility advantage amongst those with MBL *Enterobacterales* and reserve cefiderocol for use in the MDS (this is

associated with small INHE benefits as few patients both reach the MDS and require cefiderocol treatment).

The INHE associated with cefiderocol use increases to 0.18-0.20 when the CLSI breakpoints are used within the NMA (susceptibility scenarios S1 and S3), as this resulted in higher susceptibility to cefidericol of 87% under scenario 1 and 98% under scenario 3.

The results were sensitive to assumptions about AKI risk including use of alternative scenarios for absolute AKI risk and the increase in AKI risk associated with colistin/aminoglycoside-based therapy, as well as the short and long-term consequences of AKIs. Across these scenarios, the patient-level INHEs varied between 0.08-0.19 QALYs. Interestingly, scenarios that increased (reduced) the post-30 day consequences of AKI for mortality reduced (increased) the patient-level INHE. This suggests that survival duration following discharge from hospital is more important than differences in mortality between patients with and without history of AKI. This is further confirmed by the sensitivity of the model results to the parametric survival model used to predict long-term survival post-discharge. In particular, use of the Weibull model reduced the patient-level INHE to 0.08.

Changing the cost-effectiveness threshold had a small effect on the model results and using a lower discount rate of 1.5% for costs and outcomes increases the patient-level INHEs to 0.16.

Table 35: Per patient scenario analyses: MBL *Enterobacterales* empiric setting (deterministic)

Scenario name	Base case value/assumption	Scenario value/assumption	Optimal cefiderocol use	Patient-level INHE of Cefiderocol
Base case	-	-	Empiric (E1)	0.136
p_bug_survey	Probability patient has MBL <i>Enterobacterales</i> is 0.15	Probability patient has MBL <i>Enterobacterales</i> is 0.71 based on BSAC survey data	Reserve for use in MDS (E3ca)	0.002
p_bug_0	Probability patient has MBL <i>Enterobacterales</i> is 0.15	Probability patient has MBL <i>Enterobacterales</i> is 0.00	Empiric (E1)	0.196
p_bug_10	Probability patient has MBL <i>Enterobacterales</i> is 0.15	Probability patient has MBL <i>Enterobacterales</i> is 0.10	Empiric (E1)	0.157
p_bug_20	Probability patient has MBL <i>Enterobacterales</i> is 0.15	Probability patient has MBL <i>Enterobacterales</i> is 0.20	Empiric (E1)	0.118
p_bug_30	Probability patient has MBL <i>Enterobacterales</i> is 0.15	Probability patient has MBL <i>Enterobacterales</i> is 0.30	Empiric (E1)	0.079
p_bug_40	Probability patient has MBL <i>Enterobacterales</i> is 0.15	Probability patient has MBL <i>Enterobacterales</i> is 0.40	Empiric (E1)	0.040
p_bug_50	Probability patient has MBL <i>Enterobacterales</i> is 0.15	Probability patient has MBL <i>Enterobacterales</i> is 0.50	Reserve for use in MDS (E3ca)	0.001
p_bug_60	Probability patient has MBL <i>Enterobacterales</i> is 0.15	Probability patient has MBL <i>Enterobacterales</i> is 0.60	Reserve for use in MDS (E3ca)	0.002
p_bug_70	Probability patient has MBL <i>Enterobacterales</i> is 0.15	Probability patient has MBL <i>Enterobacterales</i> is 0.70	Reserve for use in MDS (E3ca)	0.002
p_bug_80	Probability patient has MBL <i>Enterobacterales</i> is 0.15	Probability patient has MBL <i>Enterobacterales</i> is 0.80	Reserve for use in MDS (E3ca)	0.002
p_bug_90	Probability patient has MBL <i>Enterobacterales</i> is 0.15	Probability patient has MBL <i>Enterobacterales</i> is 0.90	Reserve for use in MDS (E3ca)	0.003
p_bug_100	Probability patient has MBL <i>Enterobacterales</i> is 0.15	Probability patient has MBL <i>Enterobacterales</i> is 1.00	Reserve for use in MDS (E3ca)	0.003
S1	Susceptibility based on NMA of EUCAST studies	Susceptibility based on NMA of CLSI studies	Empiric (E1)	0.176
S3	Susceptibility based on NMA of EUCAST studies	PHE data, with cefiderocol and fosfomycin data from separate cefiderocol and fosfomycin networks (CLSI studies)	Empiric (E1)	0.197

p_AKI_Chien	Probability of AKI with colistin/aminoglycoside therapy based on Sisay 2021 (0.45)	Probability of AKI with colistin/aminoglycoside therapy based on Chien (0.32)	Empiric (E1)	0.105
OR_AKI_Wagenlehner	Odds ratio comparing AKI for colistin/ aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from all studies analysis in Chien 2020 (1.81)	Odds ratio comparing AKI for colistin/ aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from all studies analysis in Wagenlehner 2021 (2.23)	Empiric (E1)	0.194
OR_AKI_ChienRIFLE	Odds ratio comparing AKI for colistin/ aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from all studies analysis in Chien 2020 (1.81)	Odds ratio comparing AKI for colistin/ aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from RIFLE criteria studies analysis in Chien 2020 (1.61)	Empiric (E1)	0.100
OR_AKI_death_halved	Odds ratio of mortality for AKI compared to no AKI derived from Kerr (2014) (5.11)	Odds ratio of mortality for AKI compared to no AKI halved (2.56)	Empiric (E1)	0.081
double.ckd.risk	Risk of CKD as observed in Bucaloiu 2012	Risk of CKD doubled to reflect potential higher propensity for CKD in HVCS	Empiric (E1)	0.111
abs.increase	Odds ratios on mortality associated with nephrotoxicity from Bucaloiu 2012 are applied multiplicatively to underlying risk in HVCS	Absolute risk increases in Bucaloiu 2012 are assumed to apply	Empiric (E1)	0.175
all.aki.lt	Base case assumptions with respect to long-term effects of AKI	Applying a range of alternative assumptions to model the long-term effects of AKI	Empiric (E1)	0.177
reduce.carbar	CARBAR unadjusted baseline mortality	CARBAR adjusted to remove impact of AKIs	Empiric (E1)	0.153
loglogistic	Log-normal model fit to CARBAR survival data	Log-logistic model fit to CARBAR survival data	Empiric (E1)	0.116
weibull	Log-normal model fit to CARBAR survival data	Weibull model fit to CARBAR survival data	Empiric (E1)	0.080
lt.care	No costs of long-term care	Costs of discharge to long-term care	Empiric (E1)	0.157
thresh15*	Cost-effectiveness threshold £20,000	Cost-effectiveness threshold £15,000	Empiric (E1)	0.129

thresh30*	Cost-effectiveness threshold £20,000	Cost-effectiveness threshold £30,000	Empiric (E1)	0.143
dr1.5*	Discount rate for costs and benefits 3.5%	Discount rate for costs and benefits 1.5%	Empiric (E1)	0.161

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CLSI, Clinical Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; HVCS, high value clinical scenario; INHE, incremental net health effects; MBL, metallo-beta-lactamases; NMA, network meta-analysis; Public Health England; RIFLE, risk, injury, failure, loss and end-stage renal disease

Comparators: E1 = empiric treatment with cefiderocol, followed by existing therapies in MDS if not susceptible; E3ca = colistin or aminoglycoside-based empiric treatment, followed by cefiderocol MDS if needed.

NB: Net health effects derived using cost-effectiveness threshold of £20,000/QALY.

9.1.2. MBL *Enterobacterales*, microbiology-directed setting, HAP/VAP and cUTI

The base case results are shown in Table 36 for patients with MBL *Enterobacterales* in the MDS who have HAP/VAP or cUTI. The advantages of cefiderocol are smaller in the MDS as, once susceptibility results are known, many patients (91%) can be treated with a non-colistin/aminoglycoside-based option to which they are susceptible and do not receive cefiderocol. The patient-level INHE associated with cefiderocol are driven by avoided safety issues related to use of colistin and aminoglycosides in those susceptible to these agents (7% of the MDS cohort), and gains in efficacy and safety for those who are resistant to all available treatment options (1% of the MDS cohort). Overall, the patient-level INHE associated with using cefiderocol in the MDS are 0.02 QALYs for cUTI and HAP/VAP.

Table 36: Per patient base-case results: MBL *Enterobacterales* HAP/VAP and cUTI microbiology-directed setting (probabilistic, 2,000 simulations)

	MDS pathway with cefiderocol	MDS pathway without cefiderocol	Incremental values
HAP/VAP			
<i>Summary of in-hospital outcomes (proportions) across both lines of treatment available</i>			
Death	0.374	0.378	-0.004
Survival no AKI	0.496	0.490	0.007
Survival AKI	0.129	0.132	-0.002
Survival CKD	0.000	0.000	0.000
<i>Economic outcomes (all discounted)</i>			
Treatment costs	£280	£295	-£15
AKI costs hospital	£1,673	£1,712	-£39
Other costs hospital	£34,755	£34,822	-£67
Long-term costs	£632	£629	£3
Total costs	£37,339	£37,457	-£118
Life years	2.820	2.801	0.019
QALYs	1.981	1.968	0.013
Per person NHE	0.114	0.095	0.019
cUTI			
<i>Summary of in-hospital outcomes (proportions) across both lines of treatment available</i>			
Death	0.126	0.130	-0.004
Survival no AKI	0.646	0.638	0.008
Survival AKI	0.228	0.232	-0.004
Survival CKD	0.000	0.000	0.000
<i>Economic outcomes (all discounted)</i>			
Treatment costs	£280	£295	-£15.08
AKI costs hospital	£1,673	£1,712	-£39.11
Other costs hospital	£17,370	£17,427	-£57.10
Long-term costs	£903	£901	£1.44
Total costs	£20,225	£20,335	-£109.85

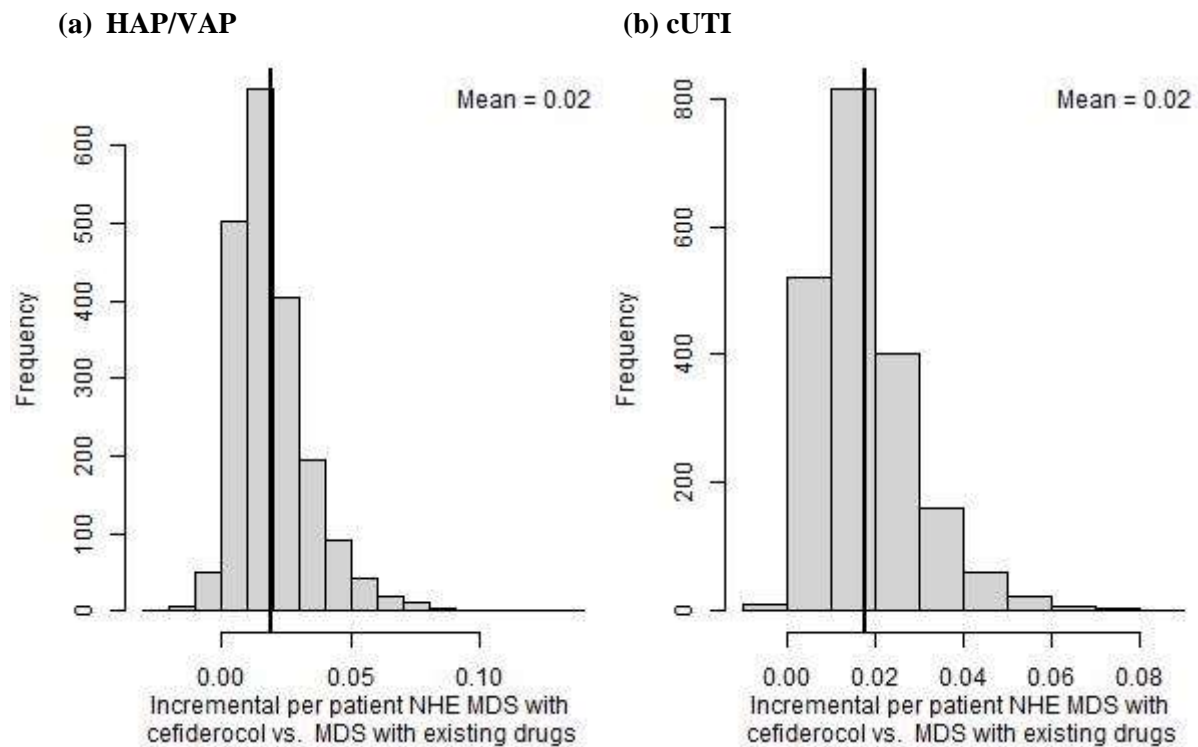
Life years	3.940	3.923	0.017
QALYs	2.769	2.757	0.012
Per person NHE	1.758	1.741	0.018

AKI, acute kidney injury; CKD, chronic kidney disease; cUTI, complicated urinary tract infections; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia; MBL, metallo-beta-lactamases; MDS, microbiology-directed setting; NHE, net health effect; QALYs, quality-adjusted life years

NB: Net health effects derived using threshold of £20,000/QALY.

There is a lower degree of uncertainty around the patient-level INHEs of cefiderocol compared to the existing treatment options in the MDS. The distribution of patient-level INHEs is shown in Figure 17.

Figure 17: Distribution of patient-level INHEs of introducing cefiderocol in to the MDS compared to existing therapies: (a) MBL *Enterobacterales* HAP/VAP and (b) MBL *Enterobacterales* cUTI (2,000 simulations)



MDS, microbiology-directed setting; NHE, net health effects

Scenario analyses that modified the base case deterministic INHE by more than 10% (and three scenario analyses requested by NICE marked by *) are shown in Table 37. The main areas of uncertainty relate to the susceptibility scenarios and long-term survival following discharge from hospital.

The patient-level INHEs were considerably higher when susceptibility was informed using PHE data for comparators (scenario S4) reaching 0.05 QALYs for both cUTI and HAP/VAP due to the lower

proportion of individuals susceptible to a non-aminoglycoside/colistin-based option in this scenario. Interestingly, when the NMA of susceptibility data that included studies using the CLSI breakpoints (scenario S1), and when the CLSI NMA results for cefiderocol are combined with the PHE data for comparators (scenario S3), the patient-level INHEs reduce to 0.01 in scenario S1 and 0.02 in scenario S2 for both cUTI and HAP/VAP. In these scenarios, although susceptibility to cefiderocol is higher, more individuals are susceptible to a non-aminoglycoside/colistin-based option thus reducing the proportion of patients who receive cefiderocol in the MDS.

The other scenario which had a large impact on results was use of the Weibull model to inform long-term mortality which reduced the patient-level INHEs to 0.02 in both HAP/VAP and cUTI.

Table 37: Per patient scenario analyses: MBL *Enterobacteriales* HAP/VAP and cUTI MDS (deterministic).

Scenario name	Base case value/assumption	Scenario value/assumption	Patient-level INHE of cefiderocol: HAP/VAP	Patient-level INHE of cefiderocol: cUTI
Base case	-	-	0.021	0.019
S1	Susceptibility based on NMA of EUCAST studies	Susceptibility based on NMA of CLSI studies	0.010	0.009
S3	Susceptibility based on NMA of EUCAST studies	PHE data, with cefiderocol and fosfomycin data from separate cefiderocol and fosfomycin networks (CLSI studies)	0.016	0.015
S4	Susceptibility based on NMA of EUCAST studies	PHE data (cefiderocol from EUCAST NMA, excludes fosfomycin)	0.052	0.048
OR_AKI_Wagenlehner	Odds ratio comparing AKI for colistin/ aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from all studies analysis in Chien 2020 (1.81)	Odds ratio comparing AKI for colistin/ aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from all studies analysis in Wagenlehner 2021 (2.23)	0.024	0.023
OR_AKI_ChienRIFLE	Odds ratio comparing AKI for colistin/ aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from all studies analysis in Chien 2020 (1.81)	Odds ratio comparing AKI for colistin/ aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from RIFLE criteria studies analysis in Chien 2020 (1.61)	0.019	Change <10% relative to base case
OR_AKI_death_halved	Odds ratio of mortality for AKI compared to no AKI derived from Kerr (2014) (5.11)	Odds ratio of mortality for AKI compared to no AKI halved (2.56)	0.017	0.016
double.ckd.risk	Risk of CKD as observed in Bucaloiu 2012	Risk of CKD doubled to reflect potential higher propensity for CKD in HVCS	0.018	0.017

abs.increase	Odds ratios on mortality associated with nephrotoxicity from Bucaloiu 2012 are applied multiplicatively to underlying risk in HVCS	Absolute risk increases in Bucaloiu 2012 are assumed to apply	0.024	0.023
all.aki.lt	Base case assumptions with respect to long-term effects of AKI	Applying a range of alternative assumptions to model the long-term effects of AKI	0.024	0.023
loglogistic	Log-normal model fit to CARBAR survival data	Log-logistic model fit to CARBAR survival data	0.019	Change <10% relative to base case
weibull	Log-normal model fit to CARBAR survival data	Weibull model fit to CARBAR survival data	0.015	0.015
lt.care	No costs of long-term care	Costs of discharge to long-term care	Change <10% relative to base case	0.022
thresh15*	Cost-effectiveness threshold £20,000	Cost-effectiveness threshold £15,000	0.023	0.021
thresh30*	Cost-effectiveness threshold £20,000	Cost-effectiveness threshold £30,000	0.019	0.018
dr1.5*	Discount rate for costs and benefits 3.5%	Discount rate for costs and benefits 1.5%	0.023	0.022

AKI, acute kidney injury; CKD, chronic kidney disease; CLSI, Clinical Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; HVCS, high value clinical scenario; INHE, incremental net health effects; MBL, metallo-beta-lactamases; NMA, network meta-analysis; PHE, Public Health England; RIFLE, risk, injury, failure, loss and end-stage renal disease

NB: Net health effects derived using threshold of £20,000/QALY.

9.1.3. MBL *Pseudomonas aeruginosa*, empiric setting, HAP/ VAP

The base case results are shown in Table 38 for patients with MBL *Pseudomonas aeruginosa*, those without MBL *Pseudomonas aeruginosa* and in the average patient suspected to have MBL *Pseudomonas aeruginosa* in the ES.

Cefiderocol is associated with similar susceptibility to colistin/aminoglycoside-based therapy but improved safety in both individuals with and without MBL *Pseudomonas aeruginosa*. The patient-level INHE gain is, therefore, similar in patients with MBL *Pseudomonas aeruginosa*, without MBL *Pseudomonas aeruginosa* and the overall ES population at 0.15-0.18 QALYs. The safety advantage delivers a small cost saving as cost savings associated with reduced rates of AKI are offset by longer time spent in hospital for patients receiving cefiderocol as preventing AKIs lowers early in-hospital mortality thus prolonging hospital stay. The safety advantage delivers a substantial QALY gain due to the reduced mortality associated with AKI in the short and long-term.

Amongst patients with MBL *Pseudomonas aeruginosa*, cefiderocol is associated with improved susceptibility and comparable safety to non-colistin/aminoglycoside-based therapy. The large difference in susceptibility between these comparators (99% vs. 28%) drives a large gain in patient-level INHE of 1.08 QALYs in this group. This reflects both the substantial QALY gain associated with this improved susceptibility (0.45) and the significant cost saving associated with a reduced LoS (£12,600). In patients without MBL *Pseudomonas aeruginosa*, cefiderocol and non-colistin/aminoglycoside-based therapy offer similar efficacy and safety.

In the average ES patient suspected of having MBL *Pseudomonas*, use of cefiderocol in the ES is associated with a patient-level INHE gain of 0.18 QALYs compared to colistin/aminoglycoside-based therapy and of 0.15 QALYs compared to non-colistin/aminoglycoside-based therapy.

Restricting the use of cefiderocol to patients who fail empiric treatment and require treatment in the MDS is associated with a smaller NHE benefit than the use of cefiderocol in the ES. This reflects that those without MBL *Pseudomonas aeruginosa* (86% of the cohort) are not eligible to receive cefiderocol in the MDS.

Table 38: Per patient base-case results: MBL *Pseudomonas aeruginosa* HAP/VAP empiric setting (probabilistic, 2,000 simulations). Note incremental values for cefiderocol used in the MDS only now shown for parsimony.

	E1	E2nca	E2ca	E3nca	E3ca	E1-E2nca	E1-E2ca
Patients with MBL <i>Pseudomonas aeruginosa</i>							
<i>Summary of in-hospital outcomes (proportions) across both lines of treatment available</i>							
Death	0.352	0.496	0.401	0.459	0.397	-0.143	-0.048
Survival no AKI	0.522	0.362	0.430	0.404	0.432	0.161	0.092
Survival AKI	0.125	0.142	0.169	0.137	0.170	-0.017	-0.044
Survival CKD	0.000	0.000	0.001	0.000	0.001	0.000	0.000
<i>Economic outcomes (all discounted)</i>							
Treatment costs	£15	£131	£167	£14	£156	-£116	-£152
AKI costs hospital	£1,684	£2,607	£2,270	£2,315	£2,255	-£923	-£586
Other costs hospital	£16,599	£28,276	£15,930	£27,331	£15,795	-£11,676	£669
Long-term costs	£648	£527	£625	£558	£629	£121	£23
Total costs	£18,946	£31,541	£18,992	£30,219	£18,836	-£12,594	-£46
Life years	2.917	2.273	2.701	2.439	2.717	0.644	0.216
QALYs	2.050	1.598	1.898	1.714	1.909	0.452	0.151
Per person NHE	1.102	0.021	0.949	0.203	0.968	1.082	0.154
Patients without MBL <i>Pseudomonas aeruginosa</i>							
<i>Summary of in-hospital outcomes (proportions) across both lines of treatment available</i>							
Death	0.349	0.349	0.401	0.349	0.401	0.000	-0.052
Survival no AKI	0.526	0.526	0.430	0.526	0.430	0.000	0.096
Survival AKI	0.125	0.125	0.169	0.125	0.169	0.000	-0.044
Survival CKD	0.000	0.000	0.001	0.000	0.001	0.000	0.000
<i>Economic outcomes (all discounted)</i>							
Treatment costs	£12	£22	£167	£22	£167	-£10	-£155
AKI costs hospital	£1,663	£1,663	£2,270	£1,663	£2,270	£0	-£608

Other costs hospital	£16,313	£16,313	£15,930	£16,313	£15,930	£0	£383
Long-term costs	£651	£651	£625	£651	£625	£0	£26
Total costs	£18,639	£18,649	£18,992	£18,649	£18,992	-£10	-£353
Life years	2.933	2.933	2.701	2.933	2.701	0.000	0.232
QALYs	2.061	2.061	1.898	2.061	1.898	0.000	0.162
Per person NHE	1.129	1.128	0.949	1.128	0.949	0.000	0.180
All patients presenting in the ES							
Total costs	£18,681	£20,429	£18,992	£20,247	£18,971	-£1,748	-£311
QALYs	2.059	1.997	1.898	2.013	1.900	0.062	0.160
Per person NHE	1.125	0.975	0.949	1.000	0.952	0.149	0.176

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; MBL, metallo-beta-lactamases; MDS, microbiology-directed setting; NHE, net health effect; QALYs, quality-adjusted life years

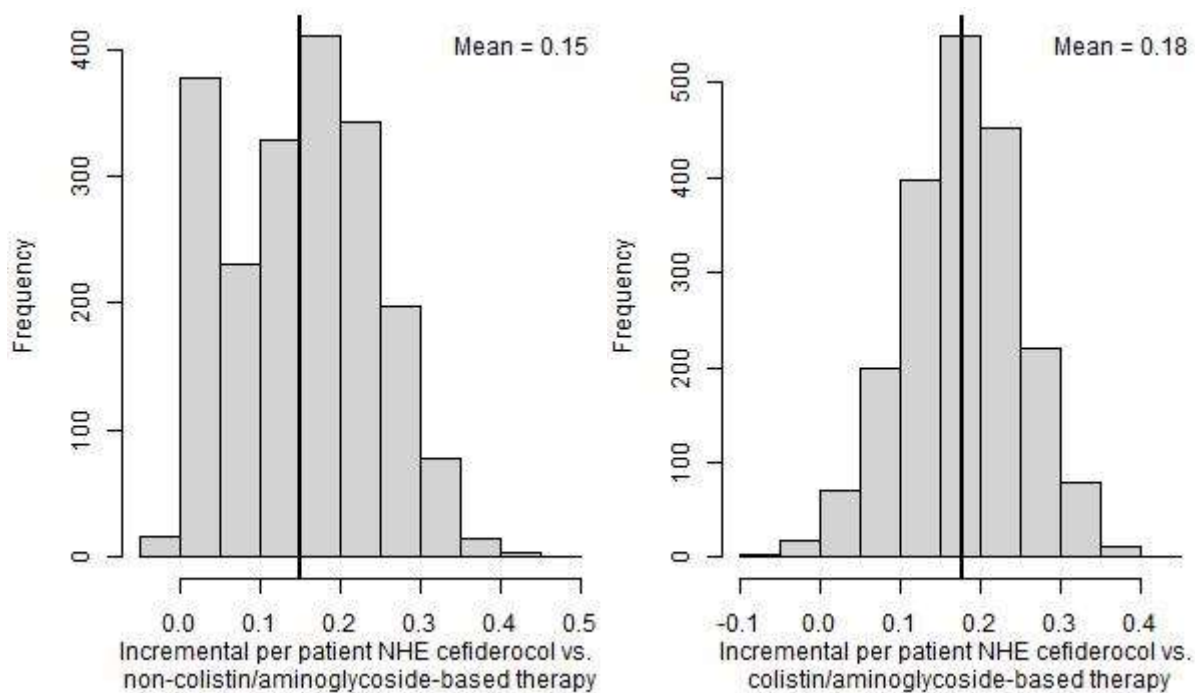
Comparators: E1 = empiric treatment with cefiderocol, followed by existing therapies in MDS if not susceptible; E2nca = non-colistin or aminoglycoside-based empiric treatment, followed by existing therapies MDS if needed; E2ca = colistin or aminoglycoside-based empiric treatment, followed by existing therapies MDS if needed; E3nca = non-colistin or aminoglycoside-based empiric treatment, followed by followed by cefiderocol in MDS if needed; E3ca = colistin or aminoglycoside-based empiric treatment, followed by cefiderocol MDS if needed. Net health effects derived using threshold of £20,000/QALY.

There is a large degree of parameter uncertainty around the patient-level INHEs of cefiderocol. The distribution of patient-level INHEs is shown in Figure 18. This reflects uncertainty in the probability individuals have MBL *Pseudomonas*, the relative susceptibility of these treatment options, their safety and the benefits of avoided AKIs. The cluster of values around 0 in the comparison of cefiderocol to non-colistin/aminoglycoside therapy is driven by samples where susceptibility to non-colistin/aminoglycoside-based therapy is high and the difference in mortality between those treatment successfully in the ES and MDS is minimal.

Figure 18: Distribution of patient-level INHEs of cefiderocol in MBL *Pseudomonas aeruginosa* HAP/VAP empiric setting compared to (a) non-colistin/aminoglycoside-based therapy and (b) colistin/aminoglycoside-based therapy and (2,000 simulations)

(a)

(b)



NHE, net health effects

Scenario analyses that modified the deterministic base case INHE by more than 10% (and three scenario analyses requested by NICE marked by *) are shown in Table 39. The scenarios which had the most marked effect on the study results were the likelihood that an individual has MBL *Pseudomonas aeruginosa* and the susceptibility scenarios.

When the probability the patient has MBL *Pseudomonas aeruginosa* was greater than 0.14 (the base case), the patient-level INHE increases as the preferred comparator switches to colistin/aminoglycosides and the safety advantage of cefiderocol is substantial. Two of the susceptibility scenarios reduced the patient-level INHEs associated with cefiderocol to less than 0.03 QALYs. These scenarios (S1, S3) used CLSI breakpoints and found non-colistin/aminoglycoside-based therapy (specifically fosfomycin monotherapy) to offer high levels of susceptibility (86-96%).

Table 39: Per patient scenario analyses: MBL *Pseudomonas aeruginosa* empiric setting (deterministic).

Scenario name	Base case value/assumption	Scenario value/assumption	Best existing treatment	Patient-level INHE of cefiderocol
Base case	-	-	Non-colistin/amino-based	0.145
p_bug_survey	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.14	Probability patient has MBL <i>Enterobacterales</i> is 0.71 based on BSAC survey data	Colistin/amino-based	0.177
p_bug_0	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.14	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.00	Non-colistin/amino-based	0.001

p_bug_10	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.14	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.10	Non-colistin/amino-based	0.106
p_bug_20	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.14	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.20	Colistin/amino-based	0.191
p_bug_30	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.14	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.30	Colistin/amino-based	0.188
p_bug_40	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.14	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.40	Colistin/amino-based	0.186
p_bug_50	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.14	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.50	Colistin/amino-based	0.183
p_bug_60	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.14	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.60	Colistin/amino-based	0.180
p_bug_70	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.14	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.70	Colistin/amino-based	0.178
p_bug_80	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.14	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.80	Colistin/amino-based	0.175
p_bug_90	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.14	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.90	Colistin/amino-based	0.173
p_bug_100	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 0.14	Probability patient has MBL <i>Pseudomonas aeruginosa</i> is 1.00	Colistin/amino-based	0.170
S1	Susceptibility based on NMA of EUCAST studies	Susceptibility based on NMA of CLSI studies	Non-colistin/amino-based	0.026
S3	Susceptibility based on NMA of EUCAST studies	PHE data, with cefiderocol and fosfomycin data from separate cefiderocol and fosfomycin networks (CLSI studies).	Non-colistin/amino-based	0.006
weibull	Log-normal model fit to CARBAR survival data	Weibull model fit to CARBAR survival data	Non-colistin/amino-based	0.123
thresh15*	Cost-effectiveness threshold £20,000	Cost-effectiveness threshold £15,000	Non-colistin/amino-based	0.173
thresh30*	Cost-effectiveness threshold £20,000	Cost-effectiveness threshold £30,000	Non-colistin/amino-based	0.116
dr1.5*	Discount rate for costs and benefits 3.5%	Discount rate for costs and benefits 1.5%	Non-colistin/amino-based	0.152

AKI, acute kidney injury; CKD, chronic kidney disease; CLSI, Clinical Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; HVCS, high value clinical scenario; INHE, incremental net health effects; MBL, metallo-beta-lactamases; NMA, network meta-analysis; PHE, Public Health England

9.1.4. MBL *Pseudomonas aeruginosa*, microbiology-directed setting, HAP/VAP and cUTI

The base case results are shown in Table 40 for patients with MBL *Pseudomonas aeruginosa* in the MDS who have HAP/VAP or cUTI. The advantages of cefiderocol in the MDS are relatively high in patients with MBL *Pseudomonas aeruginosa* as most patients are only susceptible to colistin/aminoglycoside-based treatment. The gains in patient-level NHE associated with cefiderocol are driven by avoided safety issues related to use of colistin and aminoglycosides in those susceptible to these agents (71% of the MDS cohort). Overall the patient-level gains in NHE associated with using cefiderocol in the MDS are 0.13 for HAP/VAP and 0.10 for cUTI.

Table 40: Per patient base-case results: MBL *Pseudomonas aeruginosa* HAP/VAP and cUTI microbiology-directed setting (probabilistic, 2,000 simulations)

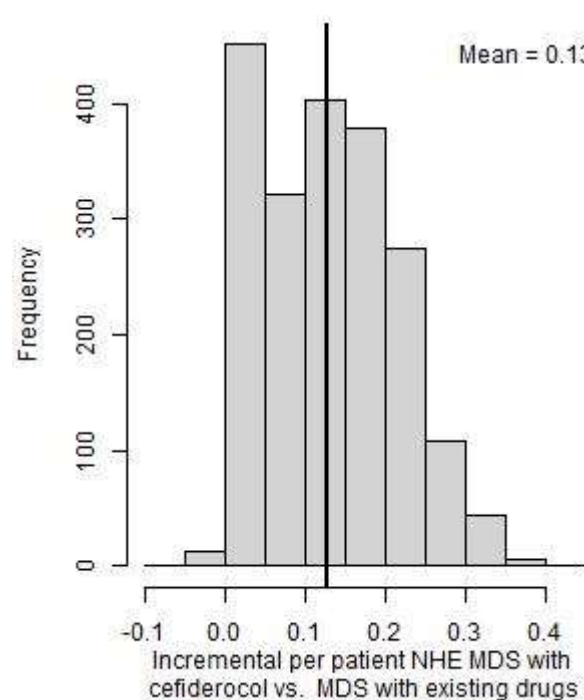
	MDS pathway with cefiderocol	MDS pathway without cefiderocol	Incremental values
HAP/VAP			
<i>Summary of in-hospital outcomes (proportions)</i>			
Death	0.373	0.404	-0.031
Survival no AKI	0.497	0.431	0.066
Survival AKI	0.129	0.164	-0.035
Survival CKD	0.000	0.000	0.000
<i>Economic outcomes (all discounted)</i>			
Treatment costs	£6	£114	-£108
AKI costs hospital	£1,667	£2,126	-£459
Other costs hospital	£34,724	£34,755	-£31
Long-term costs	£632	£621	£12
Total costs	£37,029	£37,616	-£587
Life years	2.825	2.685	0.140
QALYs	1.985	1.887	0.098
Per person NHE	0.133	0.006	0.127
cUTI			
<i>Summary of in-hospital outcomes (proportions)</i>			
Death	0.125	0.149	-0.024
Survival no AKI	0.648	0.562	0.086
Survival AKI	0.228	0.289	-0.062
Survival CKD	0.000	0.000	0.000
<i>Economic outcomes (all discounted)</i>			
Treatment costs	£6	£114	-£108
AKI costs hospital	£1,667	£2,126	-£459
Other costs hospital	£17,345	£17,375	-£30
Long-term costs	£904	£911	-£8
Total costs	£19,921	£20,526	-£605
Life years	3.946	3.839	0.107
QALYs	2.773	2.699	0.074
Per person NHE	1.777	1.673	0.104

AKI, acute kidney injury; CKD, chronic kidney disease; cUTI, complicated urinary tract infections; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia; MBL, metallo-beta-lactamases; MDS, microbiology-directed setting; NHE, net health effect; QALYs, quality-adjusted life years

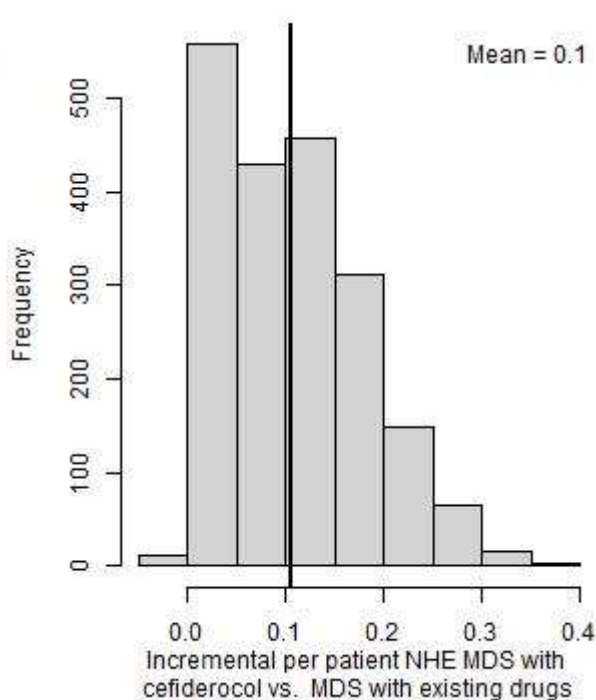
The uncertainty around the patient-level INHEs of cefiderocol compared to the existing treatment options in the MDS is shown in Figure 19 and is similar to that observed in the ES.

Figure 19: Distribution of INHEs of introducing cefiderocol in to the MDS compared to existing therapies: (a) MBL *Pseudomonas aeruginosa* HAP/VAP and (b) MBL *Pseudomonas aeruginosa* cUTI (2,000 simulations)

(a) HAP/VAP



(b) cUTI



MDS, microbiology-directed setting; NHE, net health effects

Scenario analyses that modified the base case INHE by more than 10% (and three scenario analyses requested by NICE marked by *) are shown in Table 41. The scenarios which had the most marked effect on results both in HAP/VAP and in cUTI were the susceptibility scenarios, scenarios relating to the rate and consequences of AKI, long-term survival following discharge from hospital and the costs of discharge to long-term care.

When susceptibility was informed by the CLSI NMA (scenario S1) and when the CLSI NMA results are combined with the PHE data (scenario S3), the patient-level INHEs decreased to 0.03 in scenario S1 and 0.01 in scenario S2 for both cUTI and HAP/VAP. In these scenarios, although susceptibility to

cefiderocol is slightly higher, more individuals are susceptible to a non-aminoglycoside/colistin-based option thus reducing the proportion of patients who receive cefiderocol in the MDS. The opposite is the case in scenario S4 where, although susceptibility to cefiderocol is slightly lower than the base case, fewer individuals are susceptible to a non-aminoglycoside/colistin-based option thus increasing the proportion of patients who receive cefiderocol in the MDS. Therefore, in this scenario INHE is higher.

The results varied according to the impact of colistin/aminoglycoside-based therapy on AKI risk and the long-term consequences of AKI with these scenarios resulting in patient-level NHE gains of 0.11-0.19 for HAP/VAP and 0.08-0.16 for cUTI.

Use of a Weibull model for long-term survival reduced the patient-level INHE to 0.10 in both HAP/VAP and cUTI.

Furthermore, inclusion of the costs of discharge to long-term care increase the INHE in cUTI and HAP/VAP to 0.17 QALYS.

Table 41: Patient-level scenario analyses: MBL *Pseudomonas aeruginosa* HAP/VAP and cUTI MDS (deterministic)

Scenario name	Base case value/assumption	Scenario value/assumption	Patient-level INHE of cefiderocol: HAP/VAP	Patient-level INHE of cefiderocol: cUTI
Base case	-	-	0.150	0.125
S1	Susceptibility based on NMA of EUCAST studies	Susceptibility based on NMA of CLSI studies	0.030	0.025
S3	Susceptibility based on NMA of EUCAST studies	PHE data, with cefiderocol and fosfomycin data from separate cefiderocol and fosfomycin networks (CLSI studies).	0.008	0.007
S4	Susceptibility based on NMA of EUCAST studies	NMA of EUCAST studies, absolute colistin susceptibility values from SIDERO WT	0.237	0.226
p_AKI_Chien	Probability of AKI with colistin/aminoglycoside therapy based on Sisay 2021 (0.45)	Probability of AKI with colistin/aminoglycoside therapy based on Chien (0.32)	0.125	0.105
OR_AKI_Wagenlehner	Odds ratio comparing colistin/aminoglycoside based therapy to non-colistin/aminoglycoside based therapy from all studies analysis in Chien 2020 (1.81)	Odds ratio comparing colistin/aminoglycoside based therapy to non-colistin/aminoglycoside based therapy from all studies analysis in Wagenlehner 2021 (2.23)	0.193	0.161
OR_AKI_ChienRIFLE	Odds ratio comparing colistin/aminoglycoside based therapy to non-colistin/aminoglycoside based therapy from all	Odds ratio comparing colistin/aminoglycoside based therapy to non-colistin/aminoglycoside based therapy from RIFLE	0.124	0.104

	studies analysis in Chien 2020 (1.81)	criteria studies analysis in Chien 2020 (1.61)		
OR_AKI_death_halved	Odds ratio of mortality for AKI compared to no AKI derived from Kerr (2014) (5.11)	Odds ratio of mortality for AKI compared to no AKI halved (2.56)	0.105	0.079
double.ckd.risk	Risk of CKD as observed in Bucaloiu 2012	Risk of CKD doubled to reflect potential higher propensity for CKD in HVCS	0.131	0.112
abs.increase	Odds ratios on mortality associated with nephrotoxicity from Bucaloiu 2012 are applied multiplicatively to underlying risk in HVCS	Absolute risk increases in Bucaloiu 2012 are assumed to apply	0.180	0.158
all.aki.lt	Base case assumptions with respect to long-term effects of AKI	Applying a range of alternative assumptions to model the long-term effects of AKI	0.181	0.158
weibull	Log-normal model fit to CARBAR survival data	Weibull model fit to CARBAR survival data	0.108	0.095
lt.care	No costs of long-term care	Costs of discharge to long-term care included	0.167	0.174
thresh15*	Cost-effectiveness threshold £20,000	Cost-effectiveness threshold £15,000	0.161	0.136
thresh30*	Cost-effectiveness threshold £20,000	Cost-effectiveness threshold £30,000	0.140	0.115
dr1.5*	Discount rate for costs and benefits 3.5%	Discount rate for costs and benefits 1.5%	0.169	0.144

AKI, acute kidney injury; CKD, chronic kidney disease; CLSI, Clinical Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; HVCS, high value clinical scenario; INHE, incremental net health effects; MBL, metallo-beta-lactamases; NMA, network meta-analysis; PHE, Public Health England; RIFLE, risk, injury, failure, loss and end-stage renal disease

9.2. Direct population net health effects in HVCS and broader areas of expected usage

Figure 20 shows the population-level INHE over 20 years derived using alternative assumptions about the population size (based on different categorisation of specimen types), population growth (derived with different models for the population growth predictions) and resistance emergence (reaching 1%, 10% and 30% at 20 years – 5% scenario not shown for parimony). Population-level INHE declines year on year in scenarios where the discount rate exceeds the rate of population growth in all period; rises and then declines in scenarios where the population growth rate exceeds the discount rate in earlier periods but then falls below the discount rate in later periods; and rises year on year in scenarios where

the rate of population growth exceeds the discount rate. Table 42 shows the total discounted population-level INHE aggregated over the 20 year period.

HAP/VAP and BSIs, and MBL *Enterobacterales* infections are the key drivers of population-level benefit consistently across all scenarios due to the population size. The impact of the population size is evident when comparing results across different scenarios, where different categorisations of specimen types (which determine the baseline number of infections) have the greatest impact, changing the total 20 year population-level INHE from between 710 to 1,333 to between 1,706 and 2,994 QALYs. Population growth scenarios and the resistance emergence scenario where 30% of the population is resistant after 20 years have similar impacts on population-level INHE. Resistance between 1% and 10% results in similar total INHE. The *Stenotrophomonas* populations account for 21-40% of the total population-level INHE depending on the scenario, due to their large population size. Of note, when the EEPRU clinical advisors' categorisation of infection sites is used, the current number of HAP/VAP *Stenotrophomonas* infections in which cefiderocol would be relevant increases to 547 (compared to 100 under the PHE classification). This introduces an additional element of uncertainty as no clinical evidence reviews or economic modelling were conducted for *Stenotrophomonas*.

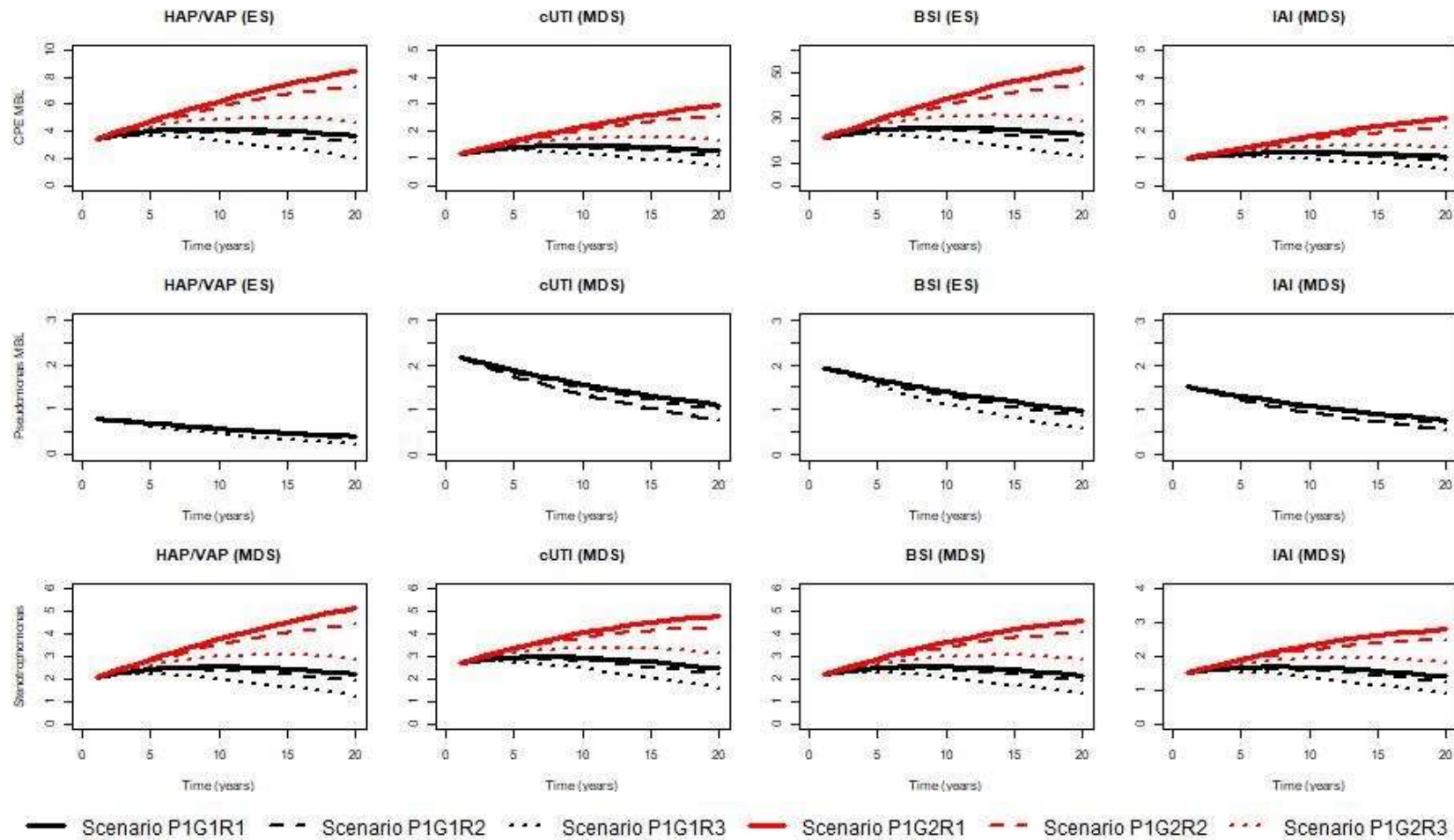
We also estimated how much of the value of cefiderocol accrues to patients initiating treatment in the first ten years of use, as this is the period of the contract for the delinked payment. Full results are presented in Appendix 20. Across scenarios relating to baseline population, population growth and resistance emergence, the proportion of value that accrues in the first 10 years of use is 41-58%. The proportion of value accruing in the first 10 years is less than might be expected for other pharmaceuticals. For a pharmaceutical where population size is expected to be stable over time we would expect 59% of the value to accrue in the first 10 years.

Following a request from NICE we also assessed the impact on the population-level results of using a 1.5% discount rate. These results reflect an assumption of zero emergence of resistance to cefiderocol and are intended to give an indication of the broad effect of a lower discount rate. Across the scenarios relating to population size and population growth the 20-year population-level INHE ranged from 1,267-4,282 when using a 1.5% discount rate. This indicates a substantive increase compared to the results observed using a 3.5% discount rate.

Figure 20. Population-level INHE (QALYs) over 20 years based on two population size scenarios.

P1: baseline population based on PHE categorisation of infection sites; P2: baseline population based on clinical advisors' categorisation of infection sites; G1: damped growth rate; G2: growth rate not damped; R1: 1% resistance after 20 years; R2: 10% resistance after 20 years; R3: 30% resistance after 20 years

a) PHE categorisation



b) Expert-guided categorisation of specimen types

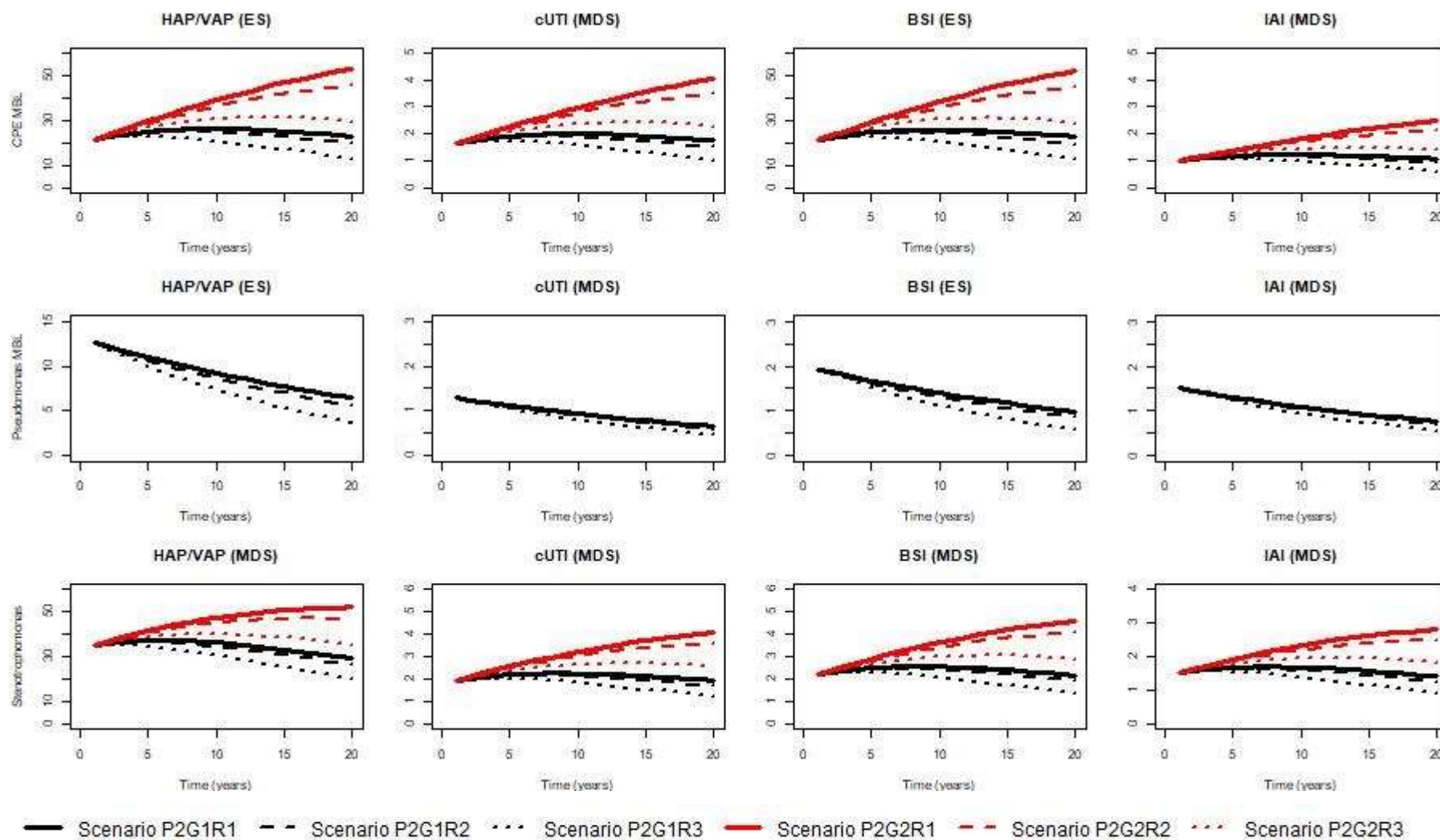


Table 42. Total population-level INHE across the first 20 years of usage

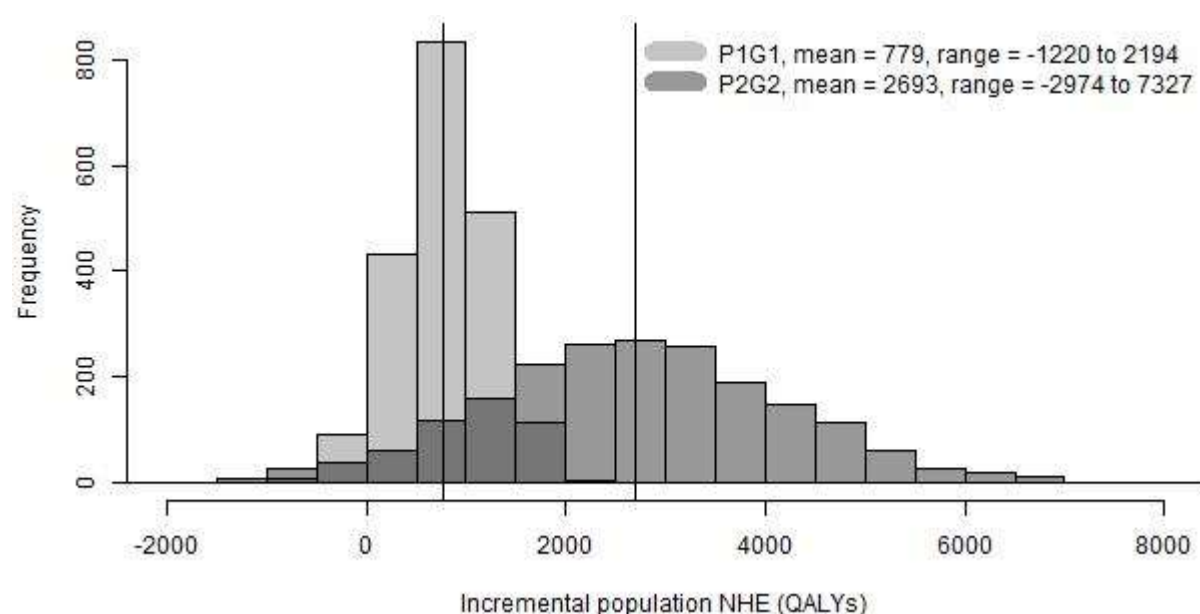
Baseline population	Pop. growth rate	Change in resistance	HAP/VAP (MBL CPE)	HAP/VAP (PA MBL)	HAP/VAP (Sten.)	cUTI (MBL CPE)	cUTI (PA MBL)	cUTI (Sten.)	BSI (MBL CPE)	BSI (PA MBL)	BSI (Sten.)	IAI (MBL CPE)	IAI (PA MBL)	IAI (Sten.)	Total
PHE categories of specimen types (scenario P1)	Model with damped effect G1)	1% (R1)	79	12	48	28	31	57	488	28	48	23	22	32	897
		5% (R2)	77	12	47	27	31	55	473	28	47	23	22	31	871
		10% (R3)	74	11	45	26	30	54	455	27	46	22	21	30	839
		30% (R4)	62	10	38	22	27	47	379	23	40	18	19	27	710
	Model without damped effect (G2)	1% (R1)	124	12	75	44	31	80	764	28	72	36	22	46	1,333
		5% (R2)	120	12	73	42	31	77	737	28	70	35	22	45	1,290
		10% (R3)	114	11	70	40	30	75	703	27	67	33	21	43	1,234
		30% (R4)	92	10	57	33	27	64	568	23	57	27	19	37	1,014
Clinical advisors' categories of specimen types (scenario P2)	Model with damped effect G1)	1% (R1)	496	185	694	38	19	43	488	28	48	23	22	32	2,116
		5% (R2)	480	180	679	37	19	42	473	28	47	23	22	31	2,059
		10% (R3)	461	174	660	35	18	40	455	27	46	22	21	30	1,988
		30% (R4)	385	151	584	30	16	35	379	23	40	18	19	27	1,706
	Model without damped effect (G2)	1% (R1)	775	185	925	59	19	64	764	28	72	36	22	46	2,994
		5% (R2)	748	180	902	57	19	62	737	28	70	35	22	45	2,903
		10% (R3)	714	174	874	55	18	59	703	27	67	33	21	43	2,788
		30% (R4)	577	151	763	44	16	50	568	23	57	27	19	37	2,332

BSI, bloodstream infection; CPE, carbapenem-producing Enterobacterales; cUTI, complicated urinary tract infection; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia; IAI, intra-abdominal infection; MBL, metallo-beta-lactamases; PHE, Public Health England; PA, Pseudomonas; Steno, Stenotrophomonas

There is a large degree of uncertainty around the population-level INHEs of cefiderocol. The distribution of population-level INHEs for two population size scenarios (P1G1, P2G2) under a scenario of no resistance emergence to cefiderocol, is shown in Figure 21. The distribution of population-level INHE reflects the patient-level INHE parameter uncertainty discussed in Sections 9.1.1-9.1.4, as well as uncertainty in the rate of population growth over time. The difference in dispersion (range) between two histograms indicates the uncertainty in population growth between the two scenarios.

Figure 21. Distribution of total population-level INHEs of cefiderocol (2,000 simulations)

P1G1: baseline population (point estimate) based on PHE categorisation of infection sites, growth rate damped (uncertain);
P2G2: baseline population (point estimate) based on clinical advisors' categorisation of infection sites, growth rate not damped (uncertain).



Patient-level scenario analyses that modified the total base case population-level INHE by more than 10% are shown in Table 43. The results are presented as the range based on most and least conservative assumptions about the population size (scenarios P1G1 and P2G2 in

Figure 15) and assuming zero resistance emergence. The scenarios assume that, where applicable, the same assumptions apply across populations, e.g., if a certain assumption is considered more appropriate for HAP/VAP ES patients it is also considered more appropriate for BSI ES patients.

Population growth impacts population-level INHE to a greater extent than scenarios in the patient-level model, as the variation in the total INHE across different population size scenarios of 904 to 3,016 QALYs (the base case range in Table 43) is more substantial than the variation across different rows in the table (e.g. 349 to 1,210 QALYs in the more conservative scenario about the population size).

The main areas of uncertainty relate to the probability that a patient has MBL, the susceptibility scenarios, the impact of colistin/aminoglycoside-based therapy on AKI risk and its long-term implications, and long-term mortality post-hospital discharge. These were the most impactful scenarios in patient-level results for MBL *Enterobacterales* in ES (Section 9.1.1 **Error! Reference source not found.**), the setting with the greatest population size.

Table 43: Population-level INHE (QALYs) for patient-level scenario analyses (deterministic) – range derived from different assumptions about the population size (scenarios P1G1 and P2G2 in Figure 15).

Base case value/assumption	Scenario value/assumption	HAP/VAP <i>Enterobacteriales</i> (ES)	HAP/VAP PA (ES)	HAP/VAP Sten. (MDS)	cUTI <i>Enterobacteriales</i> (MDS)	cUTI PA (MDS)	cUTI Sten. (MDS)	BSI <i>Enterobacteriales</i> (ES)	BSI PA (ES)	BSI Sten. (MDS)	IAI <i>Enterobacteriales</i> (MDS)	IAI PA (MDS)	IAI Sten. (MDS)	Total
-	-	80-782	12-186	49-930	28-60	19-32	57-64	492-770	28-28	49-72	23-37	22-22	32-46	904-3,016
Probability patient has MBL <i>Enterobacteriales</i> is 0.15, MBL Pseudo. is 0.14	Probability patient has MBL is 0.71 based on BSAC survey data	1-12	15-227	49-930	28-60	19-32	57-64	8-12	35-35	49-72	23-37	22-22	32-46	351-1,536
Probability patient has MBL <i>Enterobacteriales</i> is 0.15, MBL Pseudo. is 0.14	Probability patient has MBL is 0.30	46-451	15-241	49-930	28-60	19-32	57-64	284-445	37-37	49-72	23-37	22-22	32-46	674-2,424
Probability patient has MBL <i>Enterobacteriales</i> is 0.15, MBL Pseudo. is 0.14	Probability patient has MBL is 0.40	23-227	15-238	49-930	28-60	19-32	57-64	143-224	36-36	49-72	23-37	22-22	32-46	509-1,975
Probability patient has MBL <i>Enterobacteriales</i> is 0.15, MBL Pseudo. is 0.14	Probability patient has MBL is 0.50	1-9	15-234	49-930	28-60	19-32	57-64	5-8	36-36	49-72	23-37	22-22	32-46	349-1,537
Probability patient has MBL <i>Enterobacteriales</i> is 0.15, MBL Pseudo. is 0.14	Probability patient has MBL is 0.60	1-10	15-231	49-930	28-60	19-32	57-64	6-10	35-35	49-72	23-37	22-22	32-46	349-1,536
Probability patient has MBL <i>Enterobacteriales</i> is	Probability patient has MBL is 0.70	1-12	15-228	49-930	28-60	19-32	57-64	8-12	35-35	49-72	23-37	22-22	32-46	351-1,537

0.15, MBL Pseudo. is 0.14														
Probability patient has MBL <i>Enterobacterales</i> is 0.15, MBL Pseudo. is 0.14	Probability patient has MBL is 0.80	1-14	14-224	49-930	28-60	19-32	57-64	9-14	34-34	49-72	23-37	22-22	32-46	350-1,536
Probability patient has MBL <i>Enterobacterales</i> is 0.15, MBL Pseudo. is 0.14	Probability patient has MBL is 0.90	2-15	14-221	49-930	28-60	19-32	57-64	10-15	34-34	49-72	23-37	22-22	32-46	352-1,535
Susceptibility (<i>Enterobacterales</i> and PsA) based on NMA of EUCAST studies	Susceptibility based on NMA of CLSI studies	103-1,010	2-33	23-243	13-28	4-6	17-23	636-996	5-5	17-25	11-17	4-4	10-14	847-2,402
Susceptibility (<i>Enterobacterales</i> and PsA) based on NMA of EUCAST studies	Susceptibility based on PHE data, with cefiderocol and fosfomycin data from separate cefiderocol and fosfomycin networks (CLSI studies).	116-1,132	1-8	37-193	21-45	1-2	17-29	712-1116	1-1	21-31	18-28	1-1	11-15	958-2,600
Susceptibility (<i>Enterobacterales</i> and PsA) based on NMA of EUCAST studies	MBL <i>Enterobacterales</i> susceptibility based on PHE data	78-761	12-186	120-1,228	69-147	19-32	87-116	479-750	28-28	86-128	57-90	22-22	51-73	1,121-3,548

	(cefiderocol from NMA)													
Susceptibility (<i>Enterobacterales</i> and PsA) based on NMA of EUCAST studies	PsA MBL susceptibility based on NMA of EUCAST studies, absolute colistin susceptibility values from SIDERO WT	80-782	11-177	49-1,353	28-60	34-57	86-87	492-770	27-27	62-92	23-37	40-40	48-68	1,003-3,527
Probability of AKI with colistin/aminoglycoside therapy based on Sisay 2021 (0.45)	Probability of AKI with colistin/aminoglycoside therapy based on Chien (0.32)	61-601	11-168	44-791	25-54	16-26	49-56	378-592	26-26	42-63	21-33	19-19	28-40	730-2,459
Odds ratio comparing AKI for colistin/aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy from all studies analysis in Chien 2020 (1.81)	Odds ratio from all studies analysis in Wagenlehner 2021 (2.23)	114-1,114	12-182	57-1,175	32-69	24-41	70-78	701-1,097	28-28	60-88	27-42	28-28	40-57	1,210-3,982
Odds ratio comparing AKI for colistin/aminoglycoside-based therapy to non-colistin/aminoglycoside-based therapy	Odds ratio from RIFLE criteria studies analysis in	59-576	12-186	44-784	25-54	16-26	49-56	362-567	28-28	42-62	21-33	18-18	28-40	714-2,420

from all studies analysis in Chien 2020 (1.81)	Chien 2020 (1.61)													
CARBAR unadjusted baseline mortality	CARBAR adjusted to remove impact of AKIs	90-879	12-192	52-1,008	30-64	21-35	62-69	553-866	29-29	52-78	25-39	24-24	35-50	999-3,319
Risk of CKD as observed in Bucaloiu 2012	Risk of CKD doubled to reflect potential higher propensity for CKD in HVCS	65-638	11-173	43-816	25-53	17-28	51-57	402-629	26-26	43-63	21-32	20-20	29-41	764-2,565
Odds ratios on mortality associated with nephrotoxicity from Bucaloiu 2012 are applied multiplicatively to underlying risk in HVCS	Absolute risk increases in Bucaloiu 2012 are assumed to apply	103-1,006	13-199	56-1,108	33-71	24-40	70-78	633-991	30-30	57-85	28-43	28-28	40-57	1,131-3,720
Base case assumptions with respect to long-term effects of AKI	Applying a range of alternative assumptions to model the long-term effects of AKI	104-1,015	13-201	56-1,112	33-71	24-40	70-78	639-1,001	31-31	58-85	28-43	28-28	40-57	1,140-3,746
No costs of long-term care	Costs of discharge to long-term care	92-899	11-175	49-1,013	31-66	26-44	73-79	566-886	27-27	51-76	26-41	31-31	41-59	1,042-3,378

Log-normal model fit to CARBAR survival data	Loglogistic model fit to CARBAR survival data	68-667	11-173	44-837	26-55	18-30	53-60	420-657	26-26	44-65	21-33	21-21	30-43	794-2,655
Log-normal model fit to CARBAR survival data	Weibull model fit to CARBAR survival data	47-459	10-157	36-674	21-45	14-24	43-48	289-452	24-24	36-53	18-27	17-17	24-35	589-2,005
Odds ratio of mortality for AKI compared to no AKI derived from Kerr (2014) (5.11)	Odds ratio of mortality for AKI compared to no AKI halved (2.56)	48-466	11-176	40-678	22-48	12-20	39-47	293-459	27-27	37-55	19-29	14-14	23-32	593-2,043

BSI, bloodstream infection; CPE, carbapenem-producing Enterobacterales; cUTI, complicated urinary tract infection; HAP/VAP, hospital-acquired pneumonia or ventilator-associated pneumonia; IAI, intra-abdominal infection; MBL, metallo-beta-lactamases; PHE, Public Health England; PA, *Pseudomonas aeruginosa*; RIFLE, risk, injury, failure, loss and end-stage renal disease; Steno, *Stenotrophomonas*

9.3. Additional elements of value relevant to AMs

9.3.1. Conceptualisation of additional elements of value

The conceptualisation of each additional element of value, and how these additional elements of value may influence the INHEs associated with cefiderocol are presented in Table 44. These reflect the different viewpoints on the additional elements of value found in the literature, presented by the manufacturer, and discussed by the clinical advisors and other stakeholders to this project.

Table 44: Conceptualisation of additional elements of value

Element of value	What this represents	Specific pathways to INHEs ¹
Enablement value	Impact on population health from additional medical procedures being possible as a result of cefiderocol being available to manage otherwise resistant infections with few alternative treatment options.	<ul style="list-style-type: none"> • Improved treatment of post-operative infections • Improved treatment of pre-operative infections • Ability to treat MDR infections increasing number of procedures that can go ahead • Ability to treat MDR infections keeping wards open during an outbreak of MDR infections • Reduced use of hospital resources leading to enablement of procedures and health care for other patients
Diversity value	Impact on population health over time as a result of cefiderocol being available and adding to the range of treatments currently available. This can result in a reduction in selection pressure on and resistance to other available treatments, hence retaining their effectiveness for longer.	<ul style="list-style-type: none"> • Diverse prescribing² leading to reduced numbers of drug resistant infections over time • Reduced usage of existing drugs leading to reduced emergence of drug resistant infections over time
Insurance value	<p>Insurance value is presented in the literature in different ways.¹⁹ One relates to the impact on population health over time as a result of cefiderocol being ‘held back’ in reserve until resistance to existing treatments effectively eliminates the latter as options. Resistance to cefiderocol would be limited due to being used less.</p> <p>A second meaning is that cefiderocol would ameliorate a potentially catastrophic situation where multi-drug resistance becomes so widespread that cefiderocol is the only option across a large number of clinical scenarios. This is a low probability but high consequence outcome.</p>	<ul style="list-style-type: none"> • Restricting usage to preserve efficacy in the long term • Avoidance of catastrophic health losses, potential for differential societal valuation of this
Transmission value	The impact on population health over time as a result of cefiderocol reducing the rate of transmission of a given pathogen from patients treated with that product to other individuals,	<ul style="list-style-type: none"> • Reduced number of resistant infections

	potentially reducing the rate of resistant infections.	
Spectrum value	Benefits of cefiderocol replacing broad spectrum AMs and the problems associated with their over-use: potential collateral damage to the human microbiome resulting in a greater chance of developing resistance to AMs used in the future.	<ul style="list-style-type: none"> Reduced number of resistant infections

Abbreviations: INHE, incremental net health effect

¹ Enablement value may also include the benefits of antibiotics used prophylactically to prevent bacterial infections relating to treatments or procedures. The use of cefiderocol as a prophylactic is considered outside of the scope of the drugs license and is not, therefore, discussed further.

² For example rotation of AMs and mixing protocols where a fraction of the population receives different AMs.

9.3.2. Importance and quantification of additional elements of value

9.3.2.1. Enablement value

Improved treatment of pre- and post-operative MDR infections is included within our HVCSs and expected usage projections. There is some uncertainty as to whether the full benefits of treatment of pre-operative infections are reflected within our analysis. We assume that all patients who are alive at 30 days experience the same survival. If, however, the speed of resolution of an infection influences whether a procedure or treatment can go ahead, then it is possible that 30 day survival is longer for patients whose infection resolves more quickly as they may be more likely to receive procedures. The magnitude of this effect is uncertain due to uncertainties about the number of patients who experience infections pre-operatively, the impact of infection duration on the likelihood that operations will go ahead, and the implications of operations not going ahead (which will depend on the type of procedure, and whether the procedure is not conducted at all or delayed).

Enablement value may be also realised if the risk of MDR infection and clinicians' ability to treat an MDR infection influences a decision about whether to bring a patient in for a procedure. An example of this scenario was provided by our clinical advisory group, whereby if an MDR infection is known to be circulating in a haematology unit, certain patients may not receive planned procedures or treatments. This is particularly likely to apply for patients in whom existing antibiotics for MDR infections are not an option. Here, the specific example of myeloma patients was highlighted as such patients are predisposed to renal impairment which rules out key effective treatments for MDR infections such as colistin. There is uncertainty with respect to the 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 such as haematology. There is also uncertainty about the

consequences for patients not receiving planned therapy, as this will depend on the nature of the procedure/treatment and whether therapy is not received at all or delayed. These effects are not captured within the EEPRU modelling or any quantitative assessments submitted by the manufacturer.

A related way in which enablement value may be realised is if the availability of effective treatments for MDR infections allows wards to be kept open in the face of outbreaks. EEPRU considers it unlikely that cefiderocol would have this effect as most patients with drug-resistant infections do have alternative (albeit more toxic) treatment options - namely colistin. These effects are not captured within the EEPRU modelling or any quantitative assessments submitted by the manufacturer.

A final way in which enablement value may be realised is by use of cefiderocol freeing up healthcare resources. For example, use of cefiderocol may reduce time in hospital (alleviating pressure on beds) including time in the ICU/HDU. This may be particularly important where patients with MDR infections consume additional resources and staff time due to the need for additional infection control procedures including isolation measures. Any freed-up resources can then be repurposed to provide care for other patients within the hospital. To the extent possible, the impact of cefiderocol on resource use has been captured in the EEPRU modelling. When calculating the INHEs of cefiderocol we have translated cost savings to health benefits using standard measures of health opportunity cost (which allow monetary savings in health care resources to be translated to health gains across the NHS).

9.3.2.2. Diversity value

Our clinical advisors indicated that, within the HVCSs, diverse prescribing strategies (e.g. randomly allocating patients with similar clinical indications to different treatments) were unlikely to be appropriate given the lack of safe and effective alternative treatments. They were not supportive of the use of cefiderocol in broader populations as part of a diverse prescribing strategy due to the desire to reduce emergence of resistance to cefiderocol and concerns that the evidence for diverse prescribing was uncertain. This is in contrast to the views of the manufacturer who emphasised the potential role of cefiderocol in OXA and KPC populations where, due to the availability of other effective treatment options, it could be used as part of a diverse prescribing strategy. Diverse prescribing strategies were not, therefore, included in our quantitative assessments of population-level INHEs.

There is uncertainty about how reduced use of existing agents (e.g. colistin) due to availability of the cefiderocol will contribute to the emergence of resistance to these drugs. Due to these uncertainties this was not reflected in the EEPRU modelling. If reduced use of existing agents reduces resistance to existing drugs within areas of expected usage for cefiderocol this will, *reduce* the INHEs associated with cefiderocol. However, if resistance to existing agents reduces outside areas of expected usage for cefiderocol, this will *increase* the INHEs associated with cefiderocol. Given the potential for these

countervailing effects, and the wide range of factors driving resistance to existing drugs, this is not expected to have a large impact on INHEs.

9.3.2.3. Insurance value

Although we do not model a scenario where use of cefiderocol is completely held back to preserve its effectiveness, the scenarios modelled can be considered to reflect this form of insurance value as they involve heavily restricting usage to preserve long-term effectiveness.

It is generally agreed that the value of cefiderocol will depend on the trajectory of emergence of MDR infections over time. Within the HVCs, we have used statistical forecasting methods and explored uncertainty around these to understand the possibility that cefiderocol results in the avoidance of significant/catastrophic health losses. This is presented as distributions of population-level INHEs to inform the committee's deliberations about whether avoidance of these extreme events should be considered differentially to other forms of health losses. There is uncertainty around whether these distributions adequately reflect the uncertainty around high-consequence/low probability outcomes. An alternative approach proposed by the manufacturer (though not explored quantitatively in their submission) is to consider specific high consequence events and attempt to characterise their likelihood using evidence from the literature and expert opinion. Given the uncertainties about what these high consequence events might be, this was not considered feasible in the scope of this project though represents an interesting avenue for future research.

9.3.2.4. Transmission value

Our clinical advisors indicated that the direction of effect of introduction of cefiderocol on transmission was uncertain, but that overall the magnitude of effect was expected to be small. This reflects the fact that introducing a new effective drug for the treatment of MDR infections has a number of countervailing effects. If the drugs reduce time in hospital this is expected to reduce transmission. However, amongst MDR patients with poor prognosis, more effective treatments may, feasibly, increase time spent in hospital by reducing mortality. In addition, where use of the new drugs reduces mortality this will increase the number of people returning colonised to the community, as cefiderocol was considered unlikely to eradicate colonisation by the clinical advisors to this project. This may contribute to increased transmission in the community or via further hospitalisations in this highly co-morbid population.

The key drivers of transmission of MBL *Enterobacterales* and MBL *Pseudomonas aeruginosa* are broad and driven by transmission in populations beyond the HVCs (e.g. colonised individuals in the community and in the hospital, and importation of drug-resistance from abroad), making this a challenging area to model. Given the views of our clinical advisors that this would not be a key driver

of population-level INHE and these modelling challenges, we did not attempt to quantify transmission value using transmission modelling.

To support the committee in its decision making we do, however, provide a summary of the impact of each drug on time in hospital and time alive post discharge. Briefly, cefiderocol led to a short reduction in the hospital LOS (less than one day on average), and increased the length of life by 7 to 84 days (0.02 to 0.23 years) depending on the subgroup. We note that time post discharge is likely to include further periods spent in hospital given the patient population though we did not quantify these.

A number of advisors discussed the substantial impact of outbreaks of MDR infections in terms of disrupting healthcare provision and incurring large costs due to the need for more extensive infection control measures. However, no evidence was provided that cefiderocol would substantially impact on the likelihood of an outbreak or its spread. The possibility of outbreaks leading to large numbers of cases and the additional potential value of cefiderocol as a treatment in this scenario is discussed under insurance value.

9.3.2.5. Spectrum value

Our clinical advisors and other stakeholders did not consider spectrum value to be a significant consideration for cefiderocol which has a broad spectrum of activity. Therefore, this was not considered in our quantitative assessments of population-level INHE. The manufacturer, however, notes that *“cefiderocol is also expected to have low impact on the gut microbiota and cause minimal collateral damage to patients due to its narrow aerobic Gram-negative spectrum and predominantly renal clearance with negligible excretion into faeces. Therefore, it would likely not contribute to further disruption of the protective gut microflora and would not add to selective pressure for persistence of MDR and carbapenem-resistant pathogens in the GI tract or contribute to CDI.”*³⁸

9.3.3. Summary of additional elements of value

Table 45 summarises where EEPRU has been able to quantify the additional elements of value and, for those elements where this has not been feasible, provides an indication of their likely importance. Overall, EEPRU considers that the main areas of uncertainty are enablement value and transmission value. EEPRU considers it unlikely that transmission value is a significant driver of population-level INHE, though this remains an area of uncertainty. EEPRU considers that it is possible that, by treating pre-operative infections and offering the possibility of an effective low toxicity option for treating MDR infections, cefiderocol will facilitate additional or at least more prompt receipt of required treatments/procedures for certain groups. EEPRU considers that the magnitude of these population-level INHE remain highly uncertain.

Table 45: Summary of importance of additional elements of value

Element of value	Specific pathways to INHEs	Quantified in HVCS? <i>EEPRU assessment of importance if not quantified.</i>
Enablement value	<ul style="list-style-type: none"> Improved treatment of post-operative infections 	Quantified in HVCSs and extrapolation to expected usage
	<ul style="list-style-type: none"> Improved treatment of pre-operative infections 	Partially quantified in HVCSs and extrapolation to expected usage (<i>area of uncertainty</i>)
	<ul style="list-style-type: none"> Ability to treat MDR infections increasing number of procedures that can go ahead 	<i>Potential significant driver of population INHEs (area of uncertainty)</i>
	<ul style="list-style-type: none"> Ability to treat MDR infections keeping wards open during an outbreak of MDR infections 	<i>Unlikely to be significant driver of population INHEs</i>
	<ul style="list-style-type: none"> Reduced use of hospital resources leading to enablement of procedures and health care for other patients 	Quantified in HVCS
Diversity value	<ul style="list-style-type: none"> Diverse prescribing leading to reduced numbers of drug resistant infections over time 	<i>Diverse prescribing not considered appropriate for cefiderocol</i>
	<ul style="list-style-type: none"> Reduced usage of existing drugs leading to reduced emergence of drug resistant infections over time 	<i>Unlikely to be significant driver of population INHEs</i>
Insurance value	<ul style="list-style-type: none"> Restricting usage to preserve efficacy in the long term 	Quantified in HVCS
	<ul style="list-style-type: none"> Avoidance of catastrophic health losses, potential for differential societal valuation of this 	Quantified in HVCS (though no differential valuation applied)
Transmission value	<ul style="list-style-type: none"> Reduced number of resistant infections 	<i>Unlikely to be significant driver of population INHEs (area of uncertainty)</i>
Spectrum value	<ul style="list-style-type: none"> Reduced colonisation with drug-resistant bacteria, leading to reduced drug-resistance of future infections 	<i>Unlikely to be significant driver of population INHEs</i>

HVCS, high value clinical scenarios; INHE, incremental net health effect

10. Discussion of quantitative assessment of value

Table 46 summarises the patient-level INHEs for cefiderocol in the HVCs. Across subgroups, there is a high degree of uncertainty surrounding the benefits of cefiderocol.

For HAP/VAP patients treated empirically with cefiderocol due to suspected MBL *Enterobacteriales*, cefiderocol is associated with lower susceptibility but improved safety compared to colistin/aminoglycoside-based treatment in those who are correctly suspected of having MBL *Enterobacteriales* (patient-level INHE -0.22), and the same susceptibility but improved safety in those who have infections caused by other pathogens/mechanisms (patient-level INHE 0.18). As the proportion of patients who have MBL *Enterobacteriales* increases, the patient-level INHEs, therefore, reduce dramatically. Conversely, if the CLSI breakpoints are used to determine susceptibility, the patient-level INHEs increase to 0.20 QALYs reflecting the higher susceptibility to cefiderocol in this scenario. Scenarios examining a larger effect of colistin/aminoglycoside-based treatment on AKI risk, that reduce the implications of AKI for short-term mortality and shorten long-term survival for this patient group, also markedly effect the results (patient-level INHE 0.08-0.19).

For HAP/VAP patients treated empirically with cefiderocol due to suspected MBL *Pseudomonas aeruginosa*, cefiderocol is associated with comparable susceptibility and improved safety compared to colistin/aminoglycoside-based therapy and improved susceptibility compared to non-colistin/aminoglycoside-based therapy. The most significant source of uncertainty in this population is the effectiveness of non-colistin/aminoglycoside-based treatment. The synthesis of evidence using CLSI breakpoints indicated susceptibility to fosfomycin is similar to cefiderocol and, therefore, there is limited advantage of using cefiderocol, though we note that CLSI breakpoints are less relevant to the UK and that fosfomycin does not have established breakpoints for *Pseudomonas aeruginosa* making links with clinical outcomes more tenuous.

For patients treated in the MDS, the advantage of cefiderocol is much higher for MBL *Pseudomonas aeruginosa* than MBL *Enterobacteriales* as the latter patient group has a higher probability of being susceptible to a non-colistin/aminoglycoside-based treatment, and hence not requiring treatment with cefiderocol. There is a large degree of uncertainty in the patient-level INHE in the MBL *Pseudomonas aeruginosa* population. This reflects the differences across scenarios in the susceptibility to non-colistin/aminoglycoside-based treatments. This is much higher when the CLSI breakpoint studies are synthesised, and much lower when the baseline colistin susceptibility is set at the value from SIDERO WT.

Table 46: Summary of patient-level INHEs (QALYs) by HVCS subgroup, results presented as base case (scenario range)

	Empiric setting HAP/VAP	Microbiology-directed setting HAP/VAP	Microbiology-directed setting cUTI
MBL <i>Enterobacteriales</i>	0.12 (0.00-0.20)	0.02 (0.01-0.05)	0.02 (0.01-0.05)
MBL <i>Pseudomonas aeruginosa</i>	0.15 (0.01-0.19)	0.13 (0.01-0.24)	0.10 (0.01-0.24)

cUTI, complicated urinary tract infections; HAP/VAP, hospital acquired pneumonia or ventilator-associated pneumonia; MBL, metallo-beta-lactamases

In addition to these uncertainties, the modelling approach makes a number of important assumptions which were not amenable to sensitivity analysis or scenario testing within the scope of this project: (i) patients with intermediate resistance are assumed to respond as per those with resistant infections; (ii) patients receiving multi-AM regimens perform as well if they are susceptible to one component, two components or more components of the regimen; (iii) the use of meropenem in MBL *Enterobacteriales* and MBL *Pseudomonas aeruginosa* confers no clinical benefit; (iv) patients' AM susceptibility remains stable between the empiric and microbiology-directed settings; and (v) patients who are suspected to have MBL *Enterobacteriales* and MBL *Pseudomonas aeruginosa* who have another pathogen-mechanism are broadly susceptible and experience the same outcomes regardless of the choice of empiric treatment.

Due to the scope of work required to produce the population-level estimates of INHE, comprehensive reviews were not possible for all parameters and it is possible that additional evidence was missed. In particular, we were reliant on existing systematic reviews and meta-analyses to quantify the safety implications of alternative treatments. A preferred approach would have been to conduct a *de novo* systematic review and synthesis tailored to the current decision problem; however, this was not feasible. There were limitations to the evidence underpinning the model and, in particular, the surrogacy relationships between susceptibility and mortality/hospitalisation were informed by a combination of evidence of associations at the individual patient level, and structured expert elicitation.

EEPRU was unable to select a base case for the population-level results. Population-level results are, therefore, presented for two different approaches to estimating current MBL *Enterobacteriales* and MBL *Pseudomonas aeruginosa* infection numbers (based on different methods to classify infections from clinical specimen sites), two alternative approaches to forecasting increases in infections over time (based on whether observed trends are assumed to persist indefinitely or not), and three different trajectories with respect to resistance emergence (1%, 5% and 10% at 20 years).

These results are summarised in Table 47. These indicate that assumptions about baseline population size and growth are strong drivers of population-level INHEs which vary from 839 to 2,994 QALYs depending on the scenario. The results are particularly sensitive to the assumption about which clinical

specimen sites are indicative of HAP/VAP, with the more conservative definition provided by PHE indicating 131 HAP/VAP suspected MBL *Enterobacterales* or MBL *Pseudomonas aeruginosa*, or confirmed *Stenotrophomonas* would be eligible to receive cefiderocol per annum; and the broader definition provided by our clinical advisors indicating that 791 patients with HAP/VAP infections would be eligible. Of note, a substantial part of the value of cefiderocol (21-40% depending on scenario) is generated amongst patients with *Stenotrophomonas* who were outside of the HVCSs considered by EEPRU. Departures from the base case assumptions in the patient level model also had substantial effects on population-level INHEs.

Table 47: Summary of population-level INHEs (QALYs)

Baseline population	Population growth rate	Predicted patients initiating cefiderocol over 20 years	Range of population-level INHEs across resistance scenarios 1%, 5%, and 10% at 20 years (base case assumptions used for patient level model)
PHE categorisation of infection sites	Model with damped trends	8,671	839-897
	Model with persistent trends	13,488	1,234-1,333
Clinical advisors' categorisation of infection sites	Model with damped trends	16,669	1,988-2,116
	Model with persistent trends	24,969	2,788-2,994

INHEs, incremental net health effects; PHE, Public Health England

The population size estimates used to generate the estimates of population-level INHEs are subject to considerable uncertainties relating to the completeness of the national data, how accurately specimen types represent the infection sites of interest, whether all tested patients would fall within the HVCS populations for empiric treatment, the potential double counting of samples from the same infectious episode, and inherent uncertainties in forecasting population size over time.

In addition, estimates of population-level INHEs were generated using a number of strong assumptions about how evidence can be generalised between settings. Namely, that patient-level INHE of cefiderocol in patients with BSIs can be approximated based on outcomes in HAP/VAP patients, and that the patient-level INHE of cefiderocol in patients with IAIs can be proxied by that in patients with cUTIs. These assumptions were based on discussions with clinical experts.

Table 48 summarises where EEPRU has been able to quantify the additional elements of value and, for those elements where this has not been feasible, provides an indication of their likely importance. Overall, EEPRU considers that the main areas of uncertainty are enablement value and transmission value. EEPRU considers it unlikely that transmission value is a significant driver of population-level INHE, though this remains an area of uncertainty. EEPRU considers that it is possible that, by treating pre-operative infections and offering the possibility of an effective low toxicity option for treating MDR

infections, cefiderocol will facilitate additional or at least more prompt receipt of required treatments/procedures for certain groups. EEPRU considers that the magnitude of these population-level INHE remains highly uncertain.

Table 48: Summary of findings relating to additional elements of value

Element of value	Summary of importance in modifying quantitative estimates of population INHEs, * indicates areas of high uncertainty
Enablement value	Benefits of improved treatment of post-operative infections quantified Benefits of improved treatment of pre-operative infections partially quantified* Benefits of increasing number of procedures that can go ahead not quantified* Benefits of keeping wards open during MDR infection outbreaks unlikely to be a significant driver of population INHEs Benefits of reduced use of hospital resources quantified
Diversity value	Unlikely to be a significant driver of population INHEs
Insurance value	Quantified
Transmission value	Unlikely to be a significant driver of population INHEs *
Spectrum value	Unlikely to be a significant driver of population INHEs

INHEs, incremental net health effects

10.1. Conclusion

The quantitative assessment of value in this report indicates that cefiderocol is associated with a base case population-level INHE across its areas of expected usage of 839 to 2,994 QALYs over 20 years. These quantitative assessments of value were informed by a series of interlinked decision analytic models informed by evidence collated via systematic reviews of the literature and evidence synthesis, additional national data provided by PHE, structured expert elicitation and, where necessary, assumptions informed by clinical opinion.

This work has provided quantitative estimates of the value of cefiderocol within its areas of expected usage within the NHS. A broader and important question is “what would represent the “optimal” scope of usage for cefiderocol?” Further methodological and quantitative work is required to address this question.

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