NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Antimicrobial health technology evaluation

Cefiderocol for treating severe aerobic Gram-negative bacterial infections

Company evidence submission

**June 2021**

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* [Evaluation framework for antimicrobial evaluations](https://www.nice.org.uk/Media/Default/About/what-we-do/Life-sciences/evaluation-framework.pdf).

Policy Research Unit in Economic Methods of Evaluation in Health & Social Care Interventions (EEPRU) report: [‘Framework for Value Assessment of New Antimicrobials’.](http://www.eepru.org.uk/de-linking-reimbursement-of-antimicrobials-from-volumes-sold-assessing-alternative-arrangements-and-implications-for-nice-appraisal/)

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# *Executive summary*

Antimicrobial resistance (AMR) is a major and growing threat to public health.1 Infections by drug-resistant pathogens are associated with high levels of mortality and morbidity and an increasing economic burden. An estimated 700,000 deaths occur worldwide due to drug-resistant infections, with 33,100 lives lost per year in Europe.1, 2 Pathogenic bacteria are becoming increasingly resistant to the existing array of antimicrobials. It has been estimated that if significant action is not taken, then by 2050, 10 million lives will be lost each year due to AMR, greater than some of the current biggest causes of death, such as ischaemic heart disease (9.4 million), cancer (8.2 million) and stroke (5.8 million). In addition to this loss of life, the economic cost of AMR between 2016 and 2050 has been estimated at USD 100 trillion of economic output, representing a loss of 3.8% of the global annual gross domestic product (GDP).1

The levels of both public and private investment into antimicrobial development are insufficient to keep up with the development rate of resistance in key organisms worldwide. The inferior potential return on investment to drug companies investing in antimicrobials, coupled with incident eligible patient uncertainty, results in an unprofitable market, particularly for reserve antimicrobials, where there is a market failure (see *Appraisal context* section).1 The latest estimate of the cost of bringing a new antimicrobial to market, meeting post-marketing commitments, setting up a commercial organization and maintaining supply is around USD 1.7 billion, with typical annual sales of less than USD 50 million over the first 5 years of a product’s lifecycle (when they are likely to need high levels of financial support).3 Many companies have consequently withdrawn from antimicrobial development, and recently antimicrobial producers like Achaogen and Melinta have publicly reported financial difficulties. To encourage policies to incentivize funding for research into new antimicrobials, the World Health Organization (WHO) has published a list of priority pathogens that pose the greatest threat to human health.4 The critical group consists entirely of Gram-negative carbapenem-resistant bacteria, which pose a particular threat in hospitals and nursing homes, and among patients whose care requires devices such as ventilators and blood catheters.4

A pivotal, UK government-commissioned review into AMR, the O’Neill report, estimates that the world can avert the worst of AMR by investing USD 3–4 billion a year to take global action. The authors highlight that this is insignificant in comparison to the cost of inaction and is also a very small fraction of what G20 countries spend on healthcare today: about 0.05 percent.1

As noted in a prior report by the Policy Research Unit in Economic Methods or Evaluation in Health and Social Care Interventions (EEPRU), when assessing antimicrobials, it is important to consider aspects of value beyond those typically considered in NICE technology appraisals. Specifically, the STEDI value elements of:

1. **Spectrum value** – narrow-spectrum antimicrobials that target specific pathogens have benefits beyond broad-spectrum antimicrobials in reducing ‘collateral damage’ to patients’ microbiota
2. **Transmission value** – antimicrobials that rapidly resolve the infection minimize the risk the infection spreads through the population
3. **Enablement value** – antimicrobials allow patients to receive the surgical and medical procedures they require by resolving infections prior to the procedure that might otherwise prevent it and by being able to resolve infections that occur as a result of the surgery
4. **Diversity value** – broadening the range of available antimicrobials reduces selection pressure, extending the efficacy of existing antimicrobials
5. **Insurance value** – the benefit of having an effective antimicrobial will markedly increase in the case of a catastrophic event by treating individual patients’ infections, decreasing the spread of the multi-drug resistant pathogens that cause the outbreak, and by mitigating wider impacts on the provision of health services

As noted, for patients with a Gram-negative carbapenem-resistant infection, the currently available therapies are limited, with carbapenems already being the last line in therapy for MDR infections. The limited availability of therapies with activity against carbapenem-resistant pathogens therefore increases the chances of patients initially receiving an inappropriate therapy. Each of the currently available treatment options is associated with one or more significant limitations (Section 1.1.2.5). Commonly used therapies, such as ceftazidime/avibactam, ceftolozane/tazobactam or meropenem/vaborbactam, have gaps in the activity spectrum and documented limited efficacy against certain Gram-negative pathogens, particularly those producing metallo-β-lactamases. Metallo-β-lactamase-producing pathogens are a particularly hard to treat subset of an already difficult to treat group of carbapenem-resistant pathogens, requiring a cocktail of antimicrobials with undocumented or limited efficacy or activity data and safety concerns.

Colistin, which has *in vitro* activity against a broad range of Gram-negative carbapenem-resistant pathogens, was previously withdrawn from the market due to its unpredictable efficacy and toxicity profile often leading to kidney damage. It was necessary to re-launch the therapy due to the limited options available for the increasing number of resistant strains.

This difficulty in identifying effective treatments is compounded by the fact that UK data and clinical expert opinion states that in many hospitals it is not possible for patients to acquire the antimicrobial susceptibility test (AST) needed for a targeted antimicrobial therapy within the 2–3 days recommended by Public Health England.5 If a patient experiences a delay in receiving the initial *appropriate* therapy, they are at a greater risk of developing severe consequences such as sepsis, a life-threatening condition, with overall poorer health outcomes, irrespective of the initial infection site. This has potentially severe consequences associated with increases in longer-term morbidity resulting from organ damage, with increased risk of mortality.

In contrast to these therapies, and the other limited options currently available, cefiderocol:

1. is effective across the pathogens most prominently highlighted by WHO as a threat to public health, plus other carbapenem resistant pathogens
2. is well tolerated, as demonstrated by across the trial programme and compassionate use and early access programmes
3. has a chemical structure that results in a higher stability to hydrolysis across a wide range of bacterially produced β-lactamase enzymes (including carbapenemases) and a mechanism of cell entry that overcomes the primary mechanisms of resistance to β-lactam antimicrobials in Gram-negative bacteria
4. has received market authorization for use in the UK, European Union and US
5. has a reliable supply chain to ensure patient access is maintained

Cefiderocol is licensed for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options. When assessing cefiderocol’s value, EEPRU has communicated they will analyse in depth its value within two settings:

* **A ‘microbiology-directed’ treatment setting:** specifically, patients with a suspected or confirmed metallo-β-lactamase mechanism of resistance based on susceptibility testing. The infection sites considered for this setting are complicated urinary tract infection (cUTI) and pneumonia

**A ‘risk-based empiric’ setting:** patients with clinically urgent disease and with a suspected high risk of an infection caused by a metallo-β-lactamase-producing pathogen, where there is immediate need for effective, appropriate therapy. The infection site considered for this second setting is hospital-acquired pneumonia

Given the need to control the scope of the analysis, there is merit in prioritizing these two populations and indications. However, it is worth noting the following points:

Firstly, there are a number of other populations where the clinical community have indicated cefiderocol would have substantial added value over the currently available therapies. In the microbiology-directed treatment setting this includes infections caused by other pathogen species with MBL resistance (e.g. *Stenotrophomonas* and *Acinetobacter*), MBL infections in other infection sites, plus infections with *any* suspected or confirmed carbapenem resistance, including all classes of beta-lactamases (e.g. serine β-lactamase, metallo-β-lactamase) and porin channel- or efflux pump-related resistance mechanisms, alone or in combination (since cefiderocol can bypass all these mechanisms of resistance). In the risk-based empiric setting, where patients require rapid access to effective therapy to minimize the chance of death, it will often not be possible to distinguish between a suspicion of a metallo-β-lactamase producing pathogen and a pathogen that is carbapenem-resistant, with other or several concomitant mechanisms of resistance. In the risk-based empiric setting this includes suspected MDR-infected patients with sepsis. In such patients, where there is more ‘general’ suspicion of carbapenem resistance, cefiderocol is a suitable option due to its wide coverage of different potential pathogen types.

Second, in the microbiology-directed treatment setting, a further possibility is the use of ‘cycling’ or ‘mixing’ strategies (e.g. the option to use cefiderocol as well as other agents such as ceftazidime/avibactam for serine β-lactamase infections, and not being restricted to single options for certain pathogens) to increase overall antimicrobial heterogeneity and reduce selection pressure on the current limited number of antimicrobials active on these carbapenem resistant pathogens.

As noted in EEPRU’s initial report, there will be numerous challenges in robustly estimating the full incremental value of cefiderocol. For example, ethical practice requires that patients enrolled into double-blinded, randomized controlled clinical trials are confirmed as equally susceptible to the trial’s intervention and comparator regimens – a contrast to the treatment practice necessitated in the risk-based empiric setting. This means that this clinical trial evidence will not be sufficient to inform the relative treatment effect in the relevant patient population (i.e. patients with resistant infections).

Therefore, as EEPRU originally noted, the *in vitro* evidence of susceptibility used by clinicians to guide treatment decisions will be required to inform modelling efforts – a contrast to the approach typically adopted. Further complexities will be faced when attempting to:

* Predict the growth of carbapenem-resistant pathogen strains over time
* Estimate the growth of product-specific resistance to cefiderocol and other currently available alternative therapies, as well as cross resistance
* Identify how increased efficacy at the patient level will reduce persistence of resistant strains and therefore limit transmission and spread of resistant strains at the population level
* Estimate the wider aspects of value provided by a novel antimicrobial (the STEDI elements listed above)
* Extrapolate this estimated value to each of the wider populations where clinicians have indicated cefiderocol has substantial extra value

Estimate both the growth of each of these populations and the potential for other populations to emerge over time as resistance develops in populations where the need is *currently* less acute

In our submission, we provide data to support EEPRU’s analysis and some suggestions where we believe their anticipated approach (as outlined in the EEPRU protocol) could be meaningfully improved. We hope that the approach adopted is innovative and expansive in attempting to capture value. Nevertheless, we recognize that scarcity of both time and data may prevent the full value of a novel antimicrobial being comprehensively captured in a quantitative quality-adjusted life year (QALY) model. Therefore, we highlight the importance of EEPRU’s requirement to provide a very transparent account of whenever an element of value cannot be captured, or only captured partially. This expansive yet transparent approach is crucial given: the need to generate a comprehensive and accurate population net health benefit (PNHB) estimate for National Health Service England (NHSE), to inform the value of a subscription-based payment; and this pilot’s role in informing the approach adopted in future appraisals of antimicrobials both by NICE and by HTA agencies globally.

# *Appraisal context*

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| **Appraisal context summary**  Burden of disease  Antimicrobial resistance (AMR) is a major and growing threat to public health, with high mortality rate, considerable morbidity and significant economic burden.1, 2 There is a persistent threat that AMR will grow unless remedial action is taken1, 2   * In 2015, 874,541 disability-adjusted life years (DALYs) were attributable to infections due to antimicrobial-resistant bacteria worldwide2 * If significant action is not taken, it has been estimated that, by 2050:   + - 10 million lives will be lost each year due to AMR1     - The world will have an annual gross domestic product up to 3.8% lower than it otherwise would be1   Without new antimicrobials, more patients will eventually die from increasingly resistant infections that were previously treatable  Evaluating the benefit of antimicrobials  To estimate the full benefit of new antimicrobials, evaluation approaches outside of the framework currently used for other treatments and historically used for antimicrobials will be needed. These include the following:   * **Using *in vitro* data to allow projection and interpretation of clinical results from trials.** Due to the life-threatening nature of acute systemic bacterial infections, the efficacy of antimicrobials cannot be compared against placebo and thus requires an active comparator to investigate. Furthermore, for double blinded, randomized controlled trials, it is unethical to enrol patients with bacterial infections that are known or suspected to be resistant to the comparator drug in a trial. Therefore, only patients with susceptible infections can be recruited. However, this does not reflect the true unmet need or the expected patient population in which the approved antimicrobial will be used, which makes it difficult to generate reliable estimates of the likely clinical impact of a *new* antimicrobial. To only use clinical data would be to miss key comparative information, would not align with clinical practice, and would provide limited information for the target population (see Section 2.1). *In vitro* data are therefore of critical importance to the appraisal (supported by pharmacokinetics/pharmacodynamics [PK/PD], *in vivo*, and clinical trial data). These data are considered by the European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency (MHRA) and clinicians to be the pivotal evidence when evaluating efficacy and performing benefit–risk assessments6, 7 * **Incorporating additional measures of value.** These include diversity value, transmission value, enablement value, spectrum value and insurance value * **Taking a pragmatic approach to uncertainty.** NICE has acknowledged that for these pilot assessments of new antimicrobials, there will inevitably be a level of uncertainty in the evidence base and estimates of health gain, requiring a pragmatic, favourable stance on uncertainty, to ensure a sufficient reward for development. Such a stance would also be in line with anticipated revisions to the NICE methods, which will recommend a greater tolerance of uncertainty   Encouraging sustainable development  Under conventional funding arrangements, pharmaceutical companies have expectations of only a limited return on investment in antimicrobials, and relatively few companies are active in this space. Current incentives to develop novel antimicrobials are weak, with high development costs and low return on investment; those that do invest struggle to remain sustainable, with recent examples of companies developing antimicrobials publicly reporting financial difficulties  To encourage policies to incentivize research for antimicrobials, the World Health Organization (WHO) has published a list of priority pathogens that pose the greatest threat to human health4   * The most critical group includes Gram-negative carbapenem-resistant bacteria, which pose a particular threat in hospitals and nursing homes, and among patients whose care requires devices such as ventilators and blood catheters4   The UK government-commissioned O’Neill report on tackling multi-drug-resistant (MDR) infections globally recommended a range of policy responses to the international challenge of AMR as well as research and development in this area.1 It recommended including a global system of market entry rewards for new products, and urged national governments to find new ways of rewarding industry to help avoid over-use of new products1   * The National Institute for Health and Care Excellence (NICE), in conjunction with the Department of Health and National Health Service (NHS) England, is considering an insurance-based de-linked model in which a one-off, or series of ‘insurance’ payment(s) is made to reward innovation and to de-link revenue from the volume of antimicrobials sold   Objective  The objective of the overall antimicrobial HTA process is to estimate the population net health benefit of cefiderocol and other antimicrobials (rather than to make a decision on whether to approve them) in order to inform fixed payment levels for access and therefore provide an adequate incentive for new antimicrobials |

**The burden of antimicrobial resistance**

Antimicrobial resistance (AMR) is a major and growing threat to public health.1 Infections by drug-resistant pathogens are associated with high levels of mortality and morbidity and an increasing economic burden. An estimated 700,000 deaths occur worldwide as a result of drug-resistant infections, with 33,100 lives lost per year in Europe.1, 2 Pathogenic bacteria are becoming increasingly resistant to the existing array of antimicrobials. It has been estimated that if significant action is not taken, then by 2050, 10 million lives will be lost each year due to AMR, which exceeds some of the current biggest causes of death, such as ischaemic heart disease (9.4 million), cancer (8.2 million) and stroke (5.8 million). In addition to this huge loss of life, the economic cost of AMR between 2016 and 2050 has been estimated at USD 100 trillion of economic output, representing a loss of 3.8% of the global annual gross domestic product (GDP).1

The World Health Organization (WHO) has published a list of priority pathogens that pose the greatest threat to human health. These are provided in Table 1.4

Table 1: WHO priority pathogens

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| Priority level | Pathogens |
| Criticala | *Acinetobacter baumannii*, carbapenem-resistant |
| *Pseudomonas aeruginosa*, carbapenem-resistant |
| *Enterobacteriaceae*,b carbapenem-resistant, extended-spectrum β-lactamase-producing |
| High | *Enterococcus faecium*, vancomycin-resistant |
| *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and ‑resistant |
| *Helicobacter pylori*, clarithromycin-resistant |
| *Campylobacter* spp., fluoroquinolone-resistant |
| *Salmonellae*, fluoroquinolone-resistant |
| *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant |
| Medium | *Streptococcus pneumoniae*, penicillin-non-susceptible |
| *Haemophilus influenzae*, ampicillin-resistant |
| *Shigella* spp., fluoroquinolone-resistant |
| **Notes:** a, *Mycobacteria* (including *Mycobacterium tuberculosis*, the cause of human tuberculosis), was not subjected to review for inclusion in the WHO prioritization exercise as it is already a globally established priority for which innovative new treatments are urgently needed;  b, *Enterobacteriaceae* include: *Klebsiella pneumonia*, *Escherichia coli*, *Enterobacter* spp., *Serratia* spp., *Proteus* spp., and *Providencia* spp., *Morganella* spp.  **Source:** WHO, 2017.4 | |

The critical group consists entirely of Gram-negative carbapenem-resistant bacteria, which pose a particular threat in hospitals and nursing homes, and among patients whose care requires devices such as ventilators and blood catheters.4 These pathogens can cause severe and often deadly infections, such as bloodstream infections and pneumonia. They have become resistant to a large number of antimicrobials, including carbapenems and third-generation cephalosporins, which are the best available antimicrobials for treating serious bacterial infections and traditionally the last line of defence against MDR bacteria.

Antimicrobials should be used judiciously – and, in some cases, only as last-resort therapies – in an effort to slow down the rise in AMR. However, while the number of MDR pathogens is increasing, the number of effective antimicrobials to treat such infections are decreasing at an alarming rate and the few remaining active therapies are having to be used more often, therefore increasing exposure and increasing the chance of developing resistant pathogens. Among the active treatments is colistin that has previously been withdrawn from the market and not recommended in treatment guidelines due to poor safety profiles. Without new antimicrobials, a steadily increasing number of patients will die each year from increasingly resistant, untreatable infections that have previously been treatable.

Antibiotics are a distinct category of antimicrobial drugs in that they are used extensively across the healthcare system and are vital to supporting patient care in the case of chance infection and in enabling healthcare procedures and treatments across a range of therapy areas. If they lose their effectiveness, key routine medical procedures such as surgery, caesarean sections, joint replacements, and treatments that depress the immune system, such as cancer chemotherapy, could become too dangerous to perform. It is therefore vitally important, both to healthcare systems and to society as a whole, that there is a continuous development of new antimicrobials.

As bacteria evolve and adapt to their environment, resistance to all drugs is systematically and continuously emerging. This creates a constant need to:

1. Develop new safe and effective antimicrobials that can overcome known resistance mechanisms
2. Contribute to better infection control in the hospitals and increased antimicrobial diversity
3. Support good stewardship to preserve the overall effectiveness of existing antimicrobials

**Evaluating the benefit of antimicrobials**

To capture fully the benefit of new antimicrobials, evaluation approaches broader than the framework currently used for other treatments and historically used for the evaluation of antimicrobials should be considered. Problems of scale and confounding factors in trials make it difficult to generate reliable estimates of the likely clinical impact of a new antimicrobial. Therefore, to only use clinical data to inform decision-making would be to miss vital information, would not align with clinical practice and would provide limited information for the target population (Section 2.1). *In vitro* data are therefore of critical importance to the appraisal and must be used. Such data are considered the pivotal evidence for the benefit–risk assessment performed by the EMA and the MHRA, and used by clinicians to inform clinical decision making.6, 7

NICE has acknowledged that for these pilot assessments of new antimicrobials, there will inevitably be a level of uncertainty in the evidence base, and ultimately in the estimates of population net health benefit that will be the primary outcome of the exercise. Nevertheless, such areas of uncertainty or difficulty for appropriate modelling remain a part of health technology appraisal for new antimicrobials and should be addressed as well as current techniques will allow. A pragmatic approach to quantitative analyses should be used, but these should acknowledge their associated caveats and/or limitations. Where there are caveats and/or limitations to quantitative approaches, qualitative discussion, negotiation, and elicitation with a view to derive modifying factors to the existing quantitative estimates appears to be the next logical step. Such a stance would also be in line with the upcoming NICE methods review, which is expected to recommend a greater tolerance of uncertainty in areas of high unmet need.8

For a complete picture of the benefits associated with new antimicrobials, it is also crucial to consider several additional measures of value not usually considered within the health technology assessment (HTA) framework (see Section 2.5). These include:

* **Spectrum value:** The benefits of replacing broad-spectrum with narrow-spectrum antimicrobials that target specific pathogens to reduce ‘collateral damage’ to the patient’s commensal microbiota
* **Transmission value:** The benefits of minimizing the persistence of resistant pathogens within a patient’s microbiota and limiting onward spread of infection between patients and to the wider population
* **Enablement value:** The benefits of enabling surgical and medical procedures, which have a high risk of infection with resistant bacteria, to take place
* **Diversity value:** The benefits of access to a range of alternative antimicrobial treatments available covering the same pathogens, to reduce individual selection pressure and preserve the efficacy of existing antimicrobials

**Insurance value:** The benefits of having effective, low toxicity treatments available in case of a sudden and/or major outbreaks in the prevalence of resistant bacterial infections

These additional benefits will be discussed in more detail with relation to cefiderocol in Section 2.5, but should be considered throughout the appraisal process.

**The need for better ‘pull’ incentives**

Despite the critical importance of the development of new antimicrobials, both public and private investment in the research and development of novel antimicrobials is insufficient to keep up with the pace of development of resistance in key organisms worldwide. The potential return on investment to drug companies investing in the area, coupled with its uncertainty is unattractive, particularly for reserve antimicrobials. The latter are antimicrobials reserved for special situations when there is no other alternative, in order to preserve their activity and avoid or delay the emergence of resistance (in line with good stewardship practices) and, as they are curative therapies, when they are used their treatment duration is short. Paradoxically, clinical success may involve little use of the new treatment and therefore little revenue for the developing company, particularly in the first few years. The latest estimate of the cost of bringing a new antimicrobial to market, meeting post-marketing commitments, setting up a commercial organization and maintaining supply is around USD 1.7 billion, with typical annual sales of less than USD 50 million.3

Many companies have consequently withdrawn from antimicrobial development, and recently antimicrobial producers like Achaogen and Melinta have publicly reported financial difficulties. Only when the product is more widely used, i.e. when widespread resistance to pre-existing antimicrobials has emerged, does a new antimicrobial have the potential to become financially attractive. However, by this time the new antimicrobial may no longer have patent protection or will soon lose it.1 This represents a market failure: the expected value of new antimicrobials, when held in reserve, are not reflected in the revenue provided to manufacturers as a result of the low volumes of use, thereby disincentivizing the development of new products.9 This is particularly true when compared with the higher return on investment for treatments for most other diseases due to a general acceptance of protected pricing during the patent period for these products, and a high prevalence of conditions where demand for new products is high.

As described above, the WHO has published a list of priority pathogens that pose the greatest threat to human health, in order to encourage policies to incentivize funding for research into new antimicrobials.10 The O’Neill report on tackling MDR infections globally has also recommended a range of policy responses to the international challenge of AMR, with the aim of encouraging research and development in this area.

**The proposed UK (English) model from NICE/NHSE**

Many of the benefits associated with a new antimicrobial technology are not generated at the point of use (see below), and some benefits are associated with non-use. In these circumstances, payment at the point of use and/or payment by directly attributable results will not fairly remunerate producers of such products.

An alternative strategy is to develop a fixed payment for unlimited access to a new antimicrobial product which takes into account: i) trends in and the possibility of exogenous shocks to demand, such as outbreaks (i.e. increasing the number of eligible patients); ii) wider externalities; and iii) future population level benefits of prevention; meaning that it can be used (or not) in the manner that is optimal for the society being served while not providing inadequate reward to incentivize a manufacturer to develop and produce it.

Firstly, this strategy can provide remuneration while fairly accounting for positive externalities like reducing or delaying future AMR development. Secondly, fixed payments for unlimited access hedges the risk to payers of sudden exogenous shocks in demand for the antimicrobial product (i.e. from outbreaks which increase demand and associated budget impact). Thirdly, such a de-linkage provides guaranteed income for firms in a disease area with typically volatile and low demand and, if pitched at an appropriate level, can provide an adequate incentive to continue to develop and produce new antimicrobials.

As part of the UK’s 20-year vision for dealing with AMR, NHS England is committed to driving innovation that will support the development of new antimicrobials and support sustainable supply and access to products in the future. Moreover, one of their key commitments in the UK five-year national action plan to tackle AMR was to ‘Develop and test new models for national purchasing arrangements that de-link the price paid for antimicrobials from the volumes sold, using a NICE led healthcare technology assessment to support robust stewardship’. The idea of the payment approach is to move away from paying for individual packs of antimicrobials and, instead, make an annual payment based on the health benefits to patients and the value to the NHS now and in the future.

In 2014, in response to the critical threat of rising AMR, the UK government commissioned a review, to analyse the global problem of rising drug resistance and propose concrete actions to tackle it internationally.1 This report, by O’Neill and colleagues (2016) estimated that the broad estimate for the cost to tackle AMR globally is up to USD 40 billion over a 10-year period, including about USD 16 billion to overhaul the antimicrobials and tuberculosis research and development pipeline using new market incentives such as market entry rewards. In total, the O’Neill report estimates that the world can avert the worst of AMR by investing three to four billion USD a year to take global action. They highlight that this is insignificant in comparison to the cost of inaction and is also a very small fraction of what the G20 countries spend on healthcare today: about 0.05 percent.1

The world-leading work being conducted by NHS England, in collaboration with NICE and the Department of Health and Social Care (DHSC), represents the UK taking positive action in paying its fair share of this critical global initiative and demonstrating that this payment model can be beneficial for both health systems and industry; with NHS patients able to benefit from a secure supply of new antimicrobial drugs and pharmaceutical companies able to reliably forecast their return on investment.

**Objectives of this appraisal**

The objective of the overall AMR appraisal process is to estimate the population net health benefit of cefiderocol and other antimicrobials to inform fixed payment levels for access (rather than to make a decision on whether to approve them) and therefore incentivize the development of new antimicrobial therapies by providing sufficient reward to companies for investing in this development and to help to correct the current market failure.

# Decision problem: description of the technology and clinical care pathway

|  |
| --- |
| **Summary**  Cefiderocol is licensed for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options11  Cefiderocol is the first injectable siderophore cephalosporin12, 13, with high levels of stability and potent activity against bacteria producing carbapenemases, including metallo-β-lactamases13-18  Antimicrobials are often susceptible to resistance due to enzymes such as carbapenemases and other β-lactamases, and also porin channel mutations or overexpression of drug efflux pumps in pathogenic organisms1, 19; cefiderocol is able to overcome the two latter mechanisms of resistance via its additional mode of cell entry, through the bacteria’s natural active iron uptake mechanism20-22  Infections caused by MDR pathogens are more likely to be hospital-acquired (nosocomial) and occur predominantly in vulnerable/older patients, who are often severely sick and immunocompromised23, 24  Nosocomial MDR infections are particularly relevant as treatment options are limited25, which is especially the case for carbapenem-resistant pathogens and is why these are of particular interest  Currently, an antimicrobial susceptibility test (AST) is needed for a targeted antimicrobial therapy, the result of which can take much longer than the 2–3 days suggested by PHE.5, 26 Therefore, there are two main populations to consider, based on the urgency to treat the infection:   * + **‘Microbiologically-directed treatment’** where the patient is stable and the infection not immediately life threatening; therefore, the patient can wait for the results of the AST   + **‘Risk-based empiric treatment’** where there is strong suspicion of carbapenem-resistant infection and patients are critically ill, unstable and at risk of rapid deterioration and death, therefore requiring immediate treatment   Infections involving resistant pathogens are more difficult to treat and are more likely to require multiple different therapies before receiving an effective treatment, which has an impact on patient outcomes27  MDR infections are associated with a mortality risk 1.6–5.0 times higher than that of non-MDR/non-carbapenem-resistant infections,28-31 with mortality rates rising as high as 75% when looking at the most severe cases, such as patients who require a liver transplant32  The estimated burden of infections with antimicrobial-resistant bacteria in the UK and across Europe is substantial compared with that of other infectious diseases:   * + Length of stay for patients with carbapenem-resistant infections is significantly higher for patients with non-carbapenem-resistant infections5, 30, 33; length of stay is a key driver of economic burden (Section 3.2.1.3)   + The costs of carbapenem-resistance infections and carbapenem-susceptible infections have been explored in a UK hospital setting, with the costs of carbapenem-resistant infections being significantly higher than that of susceptible infections due to carbapenem-resistant infections being more challenging to treat, a delay in patient recovery, and an increase in patient morbidity and mortality (Section 3.3.2)34   MDR infections are predominantly managed with multiple drug combinations that include two or more of the following treatments:   * + Aminoglycosides (amikacin, gentamicin)   + Tetracyclines (tigecycline, minocycline)   + Carbapenems (ertapenem, imipenem/cilastatin, meropenem)   + β-lactam plus β-lactamase inhibitor combinations (ceftazidime/avibactam, ceftolozane/tazobactam, meropenem/vaborbactam, imipenem/ relebactam/cilastatin)   + Fosfomycin   + Polymyxins (colistin and polymyxin B)   Current treatment options may have suboptimal efficacy, limited pathogen coverage, ineffective incomplete coverage of mechanisms of resistance and/or significant safety and tolerability concerns (Section 1.1.2.5)  Given the lack of treatment options, there are few defined standard-of-care treatment regimens or guidelines defining the most appropriate treatment strategy, with combination therapy being common to cover gaps in spectrum and/or provide cover for poor efficacy  Colistin-based regimens are one of the few current treatment options available for patients with certain types of confirmed carbapenem-resistant infection. However, the efficacy of colistin and other polymyxin-based therapies are difficult to predict, and they are associated with renal adverse events (AEs) and subsequent sequelae. This may:   * + Prevent the treating clinician from using colistin – further minimizing the very limited number of options available for the patient   + Lead those patients treated with colistin to have impaired and sometimes total loss of renal function   + Result in the clinician reducing the dose and combine with additional therapies, in an effort to minimize the side effects, which risks undermining the overall efficacy, as a lower dose leads to less predictability in the concentration of the drug in the infection site, and a higher risk of not achieving the minimum inhibitory concentration (MIC) and therefore being ineffective, potentially selecting for the resistant pathogens   Increased use of colistin has also raised concerns about widespread and increasingly observed, treatment-emergent resistance to colistin, rendering it ineffective against infections leaving no other treatment options35  There is limited available epidemiological evidence, but data suggest that there are currently approximately 200,000 aerobic Gram-negative infections per year in England, of which 15,000 are carbapenem-resistant aerobic Gram-negative and 5,000 are aerobic carbapenem-resistant Gram-negative infections caused by metallo-β-lactamase-producing pathogens; approximately 2,500 are predictable metallo-β-lactamase infections, based on risk-factors (e.g., travel from areas with high prevalence of resistant infections), and 750 occur in patients who may be considered clinically 'critically ill' (Section 1.1.4)   * + These numbers have been increasing over recent years, and are highly likely to increase significantly in the future     - Furthermore, these do not account for infections caused by other types of resistance that could also warrant treatment with cefiderocol   + There are likely to be as many patients in these ‘other’ categories as in the 'metallo-β-lactamase' category as defined by the high value clinical scenarios (HVCSs) |

## Health condition and position of the technology in the treatment pathway

### Disease background

#### Introduction to infections

The human body harbours approximately 100 trillion bacteria, which constitutes a normal microbial flora.36 In healthy individuals, these bacteria do not usually cause infection and can co-exist with the host for long periods of time without causing harm.36 However, invasion of the host by pathogenic microorganisms and their subsequent proliferation can result in tissue injury.37 Pathogenic bacteria can infect any part of the body and cause infections such as bacterial meningitis, otitis media, eye infections, sinusitis, upper respiratory tract infection, pneumonia, skin infections, gastritis, and urinary tract infections. These infections can be acquired in the community setting (community-acquired infection), in the hospital setting (HAI or nosocomial infection), such as in intensive care units (ICUs), or in long-term care facilities (healthcare-associated infection) such as nursing homes and rehabilitation facilities.

Nosocomial infections primarily occur in vulnerable hospitalized patients, who are often ≥ 50 years of age, with a number of comorbidities, as well as the cause of their hospitalization. These patients could be awaiting a surgery, have recently received a transplant, been admitted to an ICU, be undergoing chemotherapy, or have been ventilated, with compromised immunogenicity and multiple comorbidities (e.g. heart disease, diabetes or kidney disease).23, 24

Some pathogens are more likely to cause certain infections than others:

* Complicated urinary tract infections (cUTI) are most commonly caused by *Enterobacterales* (*E. coli*, *K. pneumoniae*) as well as *P. aeruginosa, Proteus* spp., and *Serratia* spp.38
* Hospital-acquired and ventilator-associated pneumonia are most often caused by glucose non-fermenting bacteria (*P. aeruginosa*, and *A.* *baumannii*) as well as *Enterobacterales*, such as *K.* *pneumoniae39*
* Complicated intra-abdominal infections are mainly caused by *Enterobacterales*, *streptococci* and certain anaerobes (particularly *Bacteroides fragilis*)40

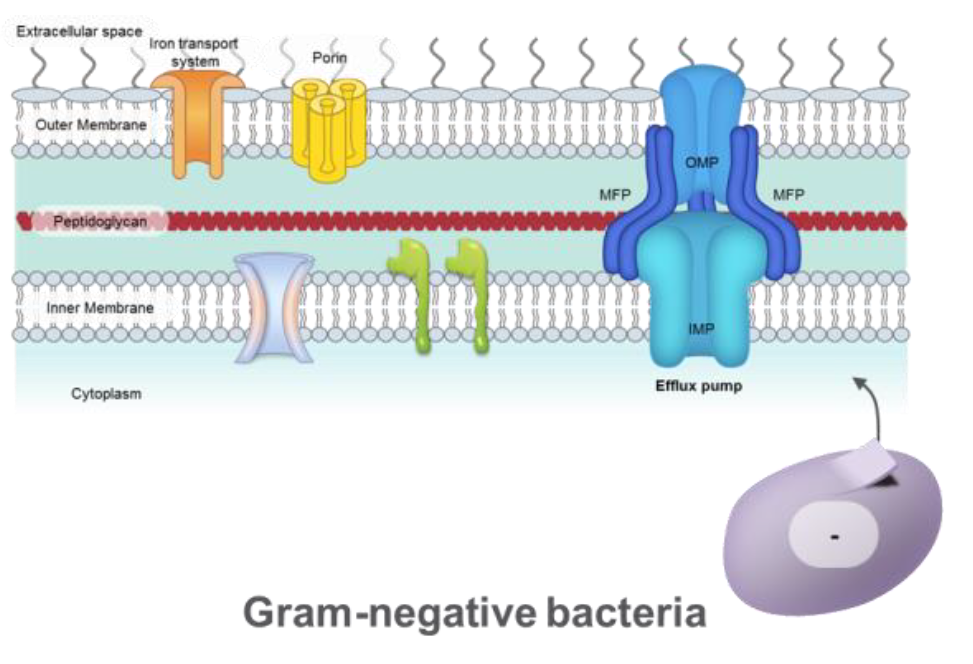
Bloodstream infections are caused by wide range of pathogens, both Gram-negative bacilli and Gram-positive cocci, as well as yeasts41

#### Overview of Gram-negative bacteria

Bacteria can be differentiated based on the characteristics related to cell wall properties (Figure 1). Classically this has been achieved through Gram staining, which allows categorization into Gram-negative and Gram-positive bacteria. Under the microscope, Gram-positive bacteria appear purple when stained and Gram-negative bacteria appear pink, due to their differing cell wall properties.42

Gram-negative bacteria can be classified into glucose fermenters and glucose non-fermenters (Figure 2).43 While glucose non-fermenting Gram-negative bacteria (non-fermenters) are usually found in nature, inhabiting the soil and water or the mucous membranes of humans and animals, they are harmful when colonizing and infecting immunocompromised people or when the infections are a consequence of trauma or invasive procedures (e.g. surgery, intravenous catheters, respiratory care equipment or endotracheal tubes).43 The glucose non-fermenting bacteria, *Pseudomonas* spp., *Acinetobacter* spp., *S.* *maltophilia*, and *B.* *cepacia*, are known for causing opportunistic healthcare-associated infection in critically ill or immunocompromised patients.44-46 Bacteria can also be differentiated based on cellular morphology (most commonly bacilli and cocci) and oxygen requirements (aerobes and anaerobes) (Figure 2).47 Aerobic Gram-negative pathogens are the most common causes of nosocomial infections and are most commonly seen in pneumonia, bloodstream infection (BSI) and UTI.48, 49

Figure 1: Cell wall properties of Gram-negative bacteria



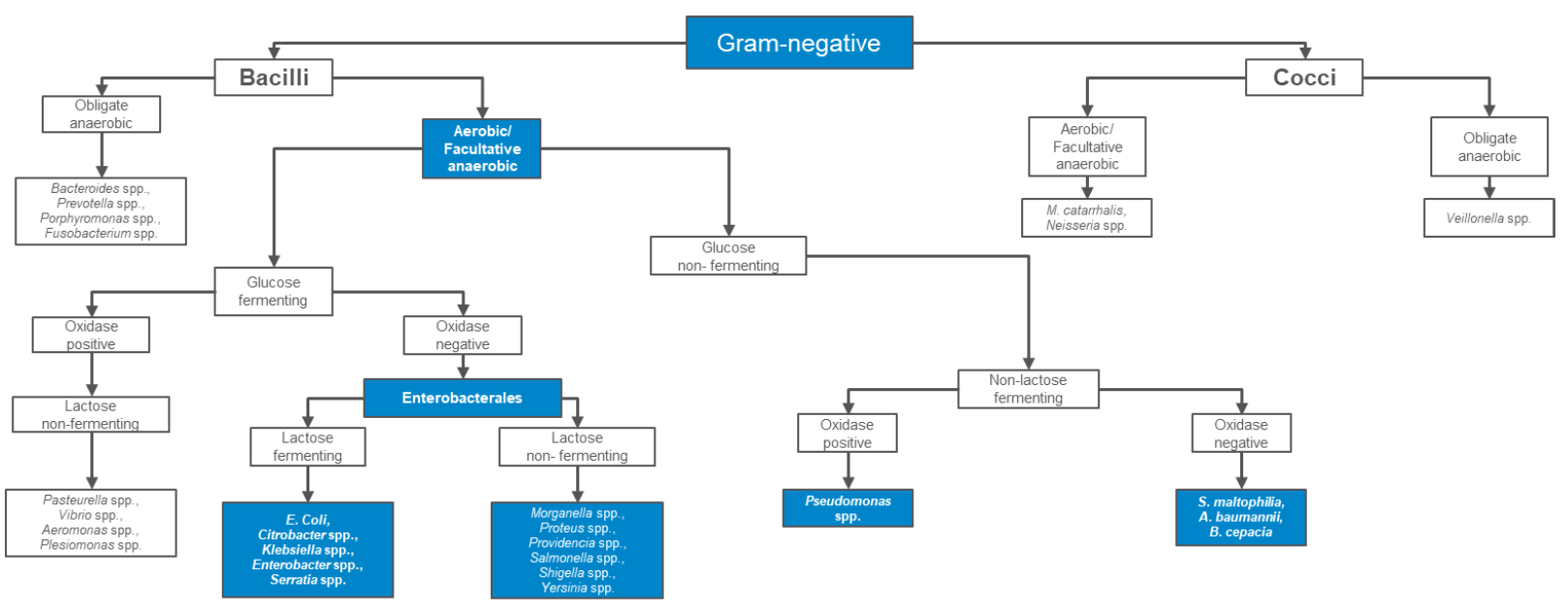
**Key:** IMP, inner membrane protein; MFP, membrane fusion protein; OMP, outer membrane protein.

**Source:** Silhavy *et al.*, 2010.50

Gram-negative pathogens are challenging to treat due to both their potential intrinsic resistance to antimicrobials (where resistance has naturally evolved in order for the pathogen to survive) and the emergence of acquired resistance (where pathogens were previously susceptible to the antimicrobial compound).51

Facultative anaerobes *E.* *coli* and *K.* *pneumoniae* are a cause of great concern with regard to AMR.52, 53 They can grow without the requirement of oxygen (as well as under aerobic conditions, i.e. in the presence of oxygen), which can allow facultative anaerobic pathogens to multiply more easily. Non-fermenters such as *P.* *aeruginosa*, *A.* *baumannii* and *S.* *maltophilia* are often resistant to a large number of antimicrobial treatments and also differ in their pathogenic potential and transmissibility.54 These pathogens are included in the list of the highest priority bacteria (carbapenem-resistant and extended-spectrum β-lactamase [ESBL]-producing *Enterobacteriaceae*, carbapenem-resistant *A.* *baumannii* and carbapenem-resistant *P.* *aeruginosa*) published by the WHO in 2017.10, 55 Although it is not on the WHO list of priority pathogens, *S.* *maltophilia* is also of particular concern in the UK, as it is one of the most prevalent species and is extremely difficult to treat, due to its intrinsic resistance.56

Figure 2: Classification of Gram-negative bacteria



**Notes:** Pathogens highlighted in blue are of interest when exploring the topic of carbapenem resistance.

**Source:** The Ohio State University, 201757; Adeolu *et al.*, 2016.58

#### Antimicrobial resistance

AMR is a natural occurrence, with many antimicrobials having been isolated from micro-organisms. AMR is selected during therapy because the use of antimicrobials inhibits or kills bacterial cells that are susceptible but allow the persistence and proliferation of any cells that are less susceptible due to mutations or acquisition of resistance genes. When penicillin, the first β-lactam antimicrobial, was introduced in clinical practice (1942), it revolutionized the treatment of infections and the conduct of safe surgical procedures.59 However, over the following two decades, bacteria became increasingly resistant to penicillin by regulating the expression of membrane proteins to restrict the amount of antimicrobial compound that enters the cell, and by expressing enzymes (e.g. β-lactamases) that destroy the β-lactam core of penicillin before it can be therapeutically active. While additional classes of antimicrobials were developed to respond to this challenge, with different mechanisms of action and/or a protection from cleavage by these enzymes, bacteria continued to evolve and developed increased resistance to new antimicrobials.

Two major genetic processes are involved in the development of AMR: 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 of mobile genetic elements such as plasmids and transposons.1, 19 The majority of pathogenic microorganisms appear to be able to develop resistance to at least some antimicrobial agents. Bacteria have developed many mechanisms of resistance including the following: 1) use of enzymes to inactivate antimicrobials by modification or hydrolysis; 2) protection of the antimicrobial target site, preventing antimicrobial binding, or modification of the target site resulting in decreased affinity for the antimicrobials; 3) decreased antimicrobial penetration, reducing antimicrobial uptake; 4) increased antimicrobial efflux exporting the antimicrobial out of the cell; and 5) resistance due to global cell adaptions.51 Resistance to multiple agents can develop via successive mutations, the dissemination and horizontal transfer 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 AMR genes. MDR bacteria can also spread rapidly within both hospitals and community settings, further contributing to increased antimicrobial use and heightened resistance60 and narrowing the choices available for antimicrobial treatment. Table 2 presents a traffic light chart of several of the newer antimicrobials and their activity across aerobic Gram-negative pathogens, clearly demonstrating the areas where there are limited treatment options. Table 2 presents the treatment landscape without cefiderocol, with the *in vitro* susceptibility data for cefiderocol presented in Section 2.3.1.2. These charts are frequently used by clinicians to guide their treatment decisions.

Table 2: *In vitro* comparison of antimicrobials for aerobic Gram-negative pathogens

|  |  | Ceftazidime/ avibactam | Imipenem/ relebactam | Meropenem/ vaborbactam | Ceftolozane/ tazobactam | Colistin |
| --- | --- | --- | --- | --- | --- | --- |
| *Pseudomonas aeruginosa* | *Pseudomonas aeruginosa*, wild-type |  |  |  |  |  |
| *Pseudomonas aeruginosa*, AmpC+ |  |  |  |  |  |
| *Pseudomonas aeruginosa*,  Porin loss (OprD-loss) |  |  |  |  |  |
| *Pseudomonas aeruginosa* Efflux pumps |  |  |  |  |  |
| *Pseudomonas aeruginosa* Carbapenem-R (Carbapenemase-negative) |  |  |  |  |  |
| *Pseudomonas aeruginosa*, MDR |  |  |  |  |  |
| *Pseudomonas aeruginosa*, XDR |  |  |  |  |  |
| *Pseudomonas aeruginosa*, MBL+ |  |  |  |  |  |
| *Enterobacteriaceae* spp. | *Enterobacteriaceae* spp. Wild-type |  |  |  |  |  |
| *Enterobacteriaceae* spp. ESBL+ |  |  |  |  |  |
| *Enterobacteriaceae* spp. OXA-48-like+ |  |  |  |  |  |
| *Enterobacteriaceae* spp. KPC+ |  |  |  |  |  |
| *Enterobacteriaceae* spp. Carbapenem-R (Carbapenemase-negative) |  |  |  |  |  |
| *Enterobacteriaceae* spp.  MBL+ (VIM, IMP, NDM) |  |  |  |  |  |
| *Acineto-bacter* | *Acinetobacter baumannii*, wild-type |  |  |  |  |  |
| *Acinetobacter baumannii*, Carbapenem-R |  |  |  |  |  |
| *Stenotro-phomonas* | *Stenotrophomonas maltophilia* (wild-type is Carbapenem-R via MBL production) |  |  |  |  |  |
| **Key:** CP, carbapenemase; CR, carbapenem resistant; IMP, imipenemase; MBL, metallo-β-lactamase; MDR, multi-drug resistant; NDM, New Delhi MBL; VIM, Verona integron-encoded MBL; XDR, extensively drug resistant.  Green, *in vitro* activity > 80%; yellow, *in vitro* activity 50-80%; red, *in vitro* activity < 50%; grey, not available.  **Notes:** OXA-48, KPC, and MBL are types of carbapenemase; AmpC are types of cephalosporinase.  **Source:** Thalhammer *et al.*, 2018.25 | | | | | | |

Given that bacterial evolution and adaptation to the environment are continuous and incremental processes, systematically leading to the emergence of resistance for all drugs, there is therefore a constant need to develop new and effective antimicrobials. However, antimicrobial development has come close to a standstill in recent decades due to a lack of viable pathways for innovators to bring new treatments to the market.61 Today, the development of AMR is a major public health threat, leading to increased mortality and morbidity, and significant economic burden.10, 52, 60-62

#### Carbapenem resistance

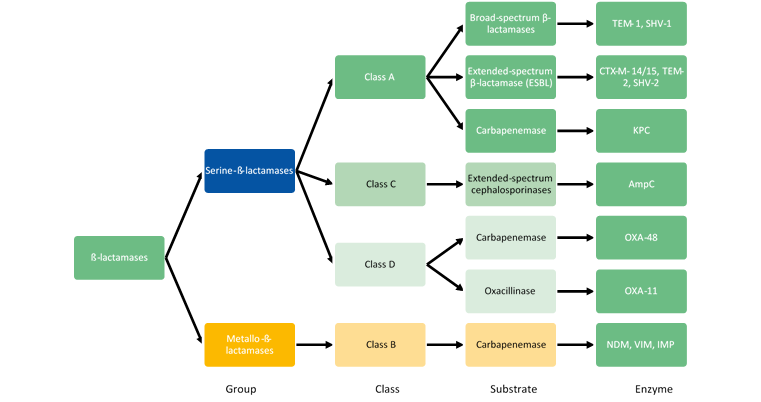
Carbapenems were first introduced in 1985. Their stability against enzyme cleavage and a broad spectrum of activity against Gram-negative, Gram-positive, anaerobic, and aerobic bacteria made them valuable, particularly for difficult-to-treat MDR pathogens.63 However, their use led to new mechanisms of resistance,64, 65 such as the ability of bacteria to transfer resistant genes to members of their own, or even different, species. Carbapenem resistance thus became a global problem of interspecies transmission. Even for colistin, an antimicrobial with a non-specific mechanism of activity and known neural and renal toxicities limiting its usage, plasmid-mediated resistance genes (*mcr1* through to *mcr9*) emerged, in part driven by farming usage.66 Plasmids can transmit colistin resistance more easily than other mobile elements between bacteria, leading to the development of colistin-resistant strains of carbapenem-resistant *Enterobacterales* that are resistant to almost all other antimicrobials and for which there is no treatment option.67-71

In recent years, the introduction of new treatments such as ceftolozane/tazobactam and ceftazidime/avibactam have been quickly followed by the emergence of new, resistant strains of bacteria. Due to their potent efficacy, broad-spectrum activity, and relative resistance to hydrolysis by the majority of β‑lactamases, they are usually reserved for use when other options have failed. The resistance to carbapenems is therefore of great concern.

A key driver for carbapenem resistance is the widespread use of broad-spectrum antimicrobials. Such overuse promotes the development of cross-resistance to antimicrobials (individual level) and an increase in MDR pathogens (wider public health level). Additional drivers for the increase in carbapenem-resistant Gram-negative pathogens may include a poor hospital/healthcare setting of infection control, exposure in densely populated environments to patients with infections caused by carbapenem-resistant pathogens (e.g. in a hospital ward) and inappropriate antimicrobial prescribing (the target of antimicrobial stewardship programs).72

In order to gather more data on carbapenem-resistant Gram-negative infections in the UK (as well as data for carbapenem susceptible Gram-negative infection), a retrospective chart review from 10 sites in England, Scotland and Wales was conducted. This study, CARBAR, is of critical importance as it provides UK-specific data on the epidemiology and distribution of pathogens across the UK, which is of particular importance for carbapenem-resistant infections, where data are currently limited. Further details on the methods of CARBAR are available in the publications, presented in Appendix C.7.1. For hospital acquired infections, the most frequently occurring carbapenem-resistant pathogens in the UK are *P.* *aeruginosa* (26.4%), *E.* *coli* (21.3%), *Stenotrophomonas maltophilia* (18.2%; *S.* *maltophilia* are intrinsically carbapenem-resistant), *K.* *pneumoniae* (10.9%), and *Acinetobacter baumannii* (1.9%), which combined represent 78.7% of the carbapenem-resistant isolates in the UK.56 The costs of carbapenem-resistance infections compared carbapenem-susceptible infections have been explored in a UK hospital setting, with the costs of carbapenem-resistant infections being more than double (£49,537 vs £19,299) that of susceptible infections due to carbapenem-resistant infections being more challenging to treat; a delay in patient recovery, and an increase in patient morbidity and mortality (Section 3.3.2).34

Figure 3: Classification of carbapenemases/β-lactamases



**Source:** Adapted from Thalhammer *et al*., 201825

#### Metallo-β-lactamases

Metallo-β-lactamases are enzymes that confer resistance to all prior β-lactams with the exception of monobactams. Active-site zinc ions activate a nucleophilic water molecule which opens the β-lactam ring (through hydrolysis) and render it ineffective.73

The rise in prevalence of the metallo-β-lactamases is a particular concern, both in the UK and globally, as metallo-β-lactamases are insensitive to all clinically available β-lactamase inhibitors (Table 2).74 The most common metallo-β-lactamases identified in clinical isolates in the UK (and globally), are subclass B1 enzymes: imipenemase (IMP), Verona integron-encoded metallo-β-lactamase (VIM), and New Delhi metallo-β-lactamase (NDM).75-78 Metallo-β-lactamases can be present in *Enterobacterales*, *Pseudomonas* spp., *Acinetobacter* spp., and *S.* *maltophilia*. One of the key challenges in designing metallo-β-lactamase inhibitors is the diversity among metallo-β-lactamase enzyme subtypes, which share less than one-third sequence identity at their active sites.79, 80 There is limited evidence on the optimal treatment for infections caused by metallo-β-lactamase-producing Gram-negative bacteria.79 Many metallo-β-lactamase-producing pathogens have multiple drug resistance mechanisms, leaving few obvious treatment options.79, 81, 82 Currently, colistin-based regimens are the mainstay of treatment for infections due to metallo-β-lactamase producers.79 The development of new treatments is key to the future armamentarium against metallo-β-lactamase Gram-negative infections.79, 81

#### Importance of antimicrobial preservation and good stewardship practice

While AMR is a naturally occurring phenomenon, the misuse and overuse of antimicrobials also drives this process by selecting for these resistance mechanisms.83 The widespread use of broad-spectrum antimicrobials, such as carbapenems in a hospital setting and other antimicrobials (e.g. cephalosporins, penicillins) more broadly, has contributed to the rapid increase in AMR that we currently see; however, resistance is an ecological problem that must be addressed on multiple fronts. Infections caused by carbapenem-resistant Gram-negative bacteria are associated with higher mortality rates compared with those involving susceptible strains and can vary between 30% for non-bacteraemia cases to 70% for patients with bacteraemia receiving liver transplant.84 The on-going emergence of resistance could ultimately render standard hospital procedures such as surgeries, unfeasible due to the danger of patients dying from MDR/pan-drug resistant (PDR) infections, without appropriate and fast-acting treatment options.9

The current treatment options available for these patients address only a subset of resistance mechanisms and pathogens and/or may be associated with severe adverse events (AEs). For example, the polymyxin class of antimicrobials is associated with reports of nephrotoxicity in up to 60% of patients.85

As discussed in the Appraisal contextSection, AMR has a significant impact in terms of clinical and economic burden, and is therefore of critical importance to address. In an attempt to preserve antimicrobial susceptibility, many countries have put in place stewardship programs to control usage of certain antimicrobials. Recommendations for stewardship strategies include the timely availability of standardized open data on antimicrobial consumption and resistance, quantitative targets for improvement of antimicrobial prescribing, and education of health professionals.86 It is suggested that antimicrobial stewardship strategies should follow WHO recommendations.87

### Clinical pathway

#### Clinical guidance and rationale for treatment

Public Health England (PHE) outline their best practice guideline for antimicrobial stewardship in their ‘Start Smart – Then Focus’ toolkit. This guidance states that, in patients with severe and life-threatening infections (particularly where the cause of infection is uncertain) antimicrobials should be started within 1-hour of diagnosis (or as soon as possible), in line with local prescribing advice. Therefore, in the risk-based empiric setting, the current treatment approach involves initial administration of empirical therapy with broad-spectrum antimicrobials based upon the individual patient profile, and using *in vitro* susceptibility data to guide appropriate treatment decisions based on suspected pathogens and resistance (such as the ‘traffic light chart’ in Table 2), followed by de-escalation to the most appropriate narrow-spectrum antimicrobial agent when the microbiological assessment is complete (i.e., following identification of the underlaying pathogen and susceptibility testing).88 In the microbiology-directed setting, where patients are stable with less severe infections, PHE state that local prescribing guidance should recommend narrow-spectrum antimicrobials that cover the expected pathogens.

While clinical guidelines pertaining to the management of carbapenem-resistant Gram-negative infections are commonly infection site specific, the British Society for Antimicrobial Chemotherapy, the Healthcare Infection Society and the British Infection Association Joint Working Party issued guidelines for the general management of infections caused by MDR and carbapenem-resistant Gram-negative bacteria.89 In general, if carbapenem-resistant is suspected, they recommend that a combination of agents with partial activity against carbapenemases are used; however, there is limited evidence of the efficacy of these combinations in these pathogens. As outlined in the EEPRU protocol90, and confirmed by a UK clinical expert, the key risk factors for carbapenem-resistant include: microbiologic history, recent history or long-term care admission, regular hospital-based treatment, epidemiological links to other carriers, international travel, immunosuppression, recent broad-spectrum antimicrobial exposure, admission to augmented care/high-risk units, and local epidemiology (e.g. previous history of outbreaks). Increasing age and prior use of antibiotics are also risk-factors for resistant infections.91 However, it is important to note that there are patients who do not meet these risk-factors, but who should still be considered as clinically high value; if the risk factors are too tightly defined then there is a risk that patients who do not meet these criteria, but who are still in high clinical need, may be missed.

Specific treatments for the HVCSs outlined by EEPRU (along with the issues associated with these treatments) are presented in Table 3, Section 1.1.2.5.

#### Infection management

The estimated burden of infections with antimicrobial-resistant bacteria in Europe is substantial compared with that of other infectious diseases.2 A study based on EARS-Net data from 2015 estimated that infections due to antimicrobial-resistant bacteria (including carbapenem-resistant and colistin-resistant infections) accounted for 33,110 attributable deaths and 874,541 disability-adjusted life years (DALYs).2 Infections with colistin-resistant or carbapenem-resistant pathogens accounted for 38.7% of the total DALYs caused by antimicrobial-resistant bacteria. This DALY burden is also increasing, with colistin-resistant or carbapenem-resistant pathogens accounting for 18% of the total burden in 2007, rising to 28% of the total burden in 2015.2

Hospital acquired bacterial infection has an impact on key outcomes for patients compared to non-infected patients, such as longer treatment, extended hospital admission, additional healthcare professional visits, healthcare resource use, AEs, greater disability (morbidity) and increased risk of death (mortality).60 The extent of the clinical burden depends on several factors, including the severity of the infection, the infection site, the causal pathogen and the characteristics of the affected patient; the burden also increases for MDR compared to non-MDR pathogens and for carbapenem-resistant compared to non-carbapenem-resistant pathogens.92

Infections can have a severe impact on a patient’s risk of mortality. This risk is affected by the severity of the infection, the type and resistance profile of causal pathogen, the infection site, the patient’s condition and the time to the patient receiving an effective therapy. The risk also increases as a result of pathogen multidrug resistance. The mortality risk associated with MDR infections is between 1.6 and 5.0 times higher than that associated with infections caused by non-MDR pathogens.28-31 For carbapenem-resistant Gram-negative infections, mortality is reported to range between 26% and 75%.32, 93, 94 Data specific to different infection sites showed that the highest hospital mortality rate was in patients with bacteraemia (60.0%) followed by pneumonia (43.3–48.6%), and UTI (17.6%).95, 96 In cUTI, mortality rates can range between 30% and 40% in case of severe sepsis or septic shock (occurring in 10–30% of cases).97

Patient factors such as health status and functional status can further increase the risk of mortality. Mortality associated with carbapenem-resistant infections can even reach 100% in severe cases such as mechanically ventilated patients with carbapenem-resistant Gram-negative with bacteraemia.95 Admission to a hospital (which has a high prevalence of MDR Gram-negative pathogens) and inpatient stays due to invasive procedures (e.g. surgery, ventilators, catheters) both increase the risk of infection and thus the risk of poor clinical outcomes.28

Another important patient factor is the patient’s renal function. This is a concern for all treatments that normally would be excreted by the kidneys as these substances will be retained in the body in cases of impaired renal function. This limits the number of possible treatment options, affecting the dosing and pharmacokinetics/pharmacodynamics (PK/PD) of these antimicrobials. Different antimicrobial dosing regimens for patients with renal failure may avoid severe side effects; however, this may lead to a lack of efficacy against the acquired infection.98

#### Time to antimicrobial susceptibility test (AST)

An antimicrobial-resistant infection with a Gram-negative pathogen can have a significant impact on the individual patient due to the consequences of using inappropriate therapies, potentially leading to treatment failure and treatment-related AEs while delaying a positive treatment effect.28, 99

The PHE guidance states that the clinical diagnosis and continuing need for antimicrobials should ideally be reviewed within 48−72 hours. Currently, the results of an AST are needed for clinicians to make a targeted prescription; however, these results often take more than 3 days to come through.5, 26, 88, 100 In fact, in an analysis of the CARBAR UK study dataset, the median time to patients receiving an appropriate therapy (i.e. receiving the results of their AST) was 4 days, which implies that for a significant proportion of patients these results took longer than the maximum recommended time in the PHE guidance.5 In many instances, the antibiogram is not ever retrieved.101 This delay in results increases the time to patients receiving an effective therapy, increasing the risk of patients experiencing poor clinical outcomes.

Many patients with infections involving resistant pathogens are more difficult to treat and are therefore more likely to receive multiple courses of inappropriate therapies before an effective treatment is initiated with MDR and carbapenem-resistant infections, with an estimated 14.1–78.9% of patients receiving inappropriate therapies.102-106 Furthermore, where carbapenem-resistant infection is suspected in critically ill patients, an antimicrobial regimen is started immediately, despite incomplete information on pathogen susceptibility, and the chosen antimicrobial (or combination of antimicrobials) is that which has the highest likelihood of success. The selection of antimicrobial(s) should be guided by the risks factors for resistance, such as knowledge of local epidemiology (local resistance profile and local pathogen distribution) and potential exposure to resistant infections (e.g., transferred from a long-term care facility with known resistance, or coming back from carbapenem-resistant endemic countries), as well as by site of infection and patient-specific factors, such as severity of illness, previous antimicrobial exposure, travel, comorbidities and previous colonization data. Treatment may be de-escalated to a more targeted treatment once the AST results have been obtained.88 This further emphasizes the critical importance of ASTs and the need for new antimicrobials, such as cefiderocol, with a wider spectrum of activity targeting MDR / carbapenem-resistant strains in the start smart approach.

|  |
| --- |
| **Key consideration for the economic model:**   * The time to effective therapy is likely to often be significantly longer than the 2–3 days recommended by the PHE guidance, as seen in real-world data * Delays to receiving AST results have a significant impact on the time it takes patients to receive an effective therapy, with implications for patient outcomes, including five-times-higher mortality risk, twice-longer hospital stays, and an increased risk of readmission compared with patients initially receiving appropriate therapy (see Section 1.1.2.4) * It is therefore critical to consider the time to receiving an effective therapy as part of the economic modelling – further discussion and appropriate references to consider are presented in Section 3.2.1.3 * Cefiderocol is optimally positioned to contribute to, and maximize the PHE’s ‘Start Smart Then Focus’ approach, with wide, but not broad coverage |

#### Impact of time to effective treatment on disease burden

Delayed effective therapy – either due to the initial treatment not being appropriate; the antibiogram being delayed or unavailable, or for any other reason – is a key determinant of the success of treating certain MDR infections.26 This is of particular concern in the risk-based empiric setting, where the pathogen is not known but there is an urgent need to start treating patients. The use of initial inappropriate therapy and/or a delay in starting an effective antimicrobial therapy can have a detrimental impact on the patient’s clinical outcomes such as mortality, the severity of the infection, hospital length of stay, risk of treatment failure, and hospital costs.26, 27 This is particularly well demonstrated for BSI and sepsis, as well as pneumonia.

As discussed in Section 1.1.2.3, the PHE ‘Start smart – then focus’ toolkit suggests that clinicians should receive AST results within 48–72 hours. While the ‘Sepsis 6’ guidance by the UK Sepsis Trust, suggests that prescribing an antimicrobial within 1-hour significantly increases a sepsis patient’s chances of survival. These support the use of empiric therapy in clinical practice and highlights the importance of time to effective therapy. However, although the PHE guidance provides a target time to receive test results, in clinical practice this target is frequently not met.5 This means that the majority of patients are likely to be impacted by a delay to receiving an effective therapy, which is of critical importance in the risk-based empiric setting, where patients are at risk of death.

As a result of this delay in test results, the current treatment approach for patients with bacterial infections involves initial administration of risk-based empirical therapy with broad-spectrum antimicrobials followed by treatment review, which may result in de-escalation to narrow-spectrum antimicrobials once these results become available.88, 100 Increasing AMR has also made the empiric antimicrobial selection more difficult, particularly as fewer appropriate treatments for resistant pathogens are available.107 This is particularly the case in carbapenem-resistant and metallo-β-lactamase-producing infections, where the number of available treatment options is extremely limited (Table 2). As a result, many patients with severe bacterial infections receive inadequate therapy and consequently experience delays in receiving appropriate antimicrobials, while inadequate prescribing may simply drive resistance to the antimicrobials that are used. As the severity of infection increases, patients are more likely to be cycled through a number of therapies in the attempt to successfully treat the infection, which leads to a difficult trade-off between selecting an antimicrobial with sufficiently broad coverage and maintaining stewardship. This emphasizes the need to identify appropriate risk factors to aid clinicians in their decision making. Moreover, patients for whom the initial therapies have failed and who have reached last-resort antimicrobials are exposed to the additional burden associated with severe AEs and toxicity.27

A delay in effective treatment may also lead to sepsis, a life-threatening condition, irrespective of the initial infection site. A range of studies have suggested that inappropriately treated patients have a five-times-higher mortality risk, twice-longer hospital stays, and an increased risk of readmission compared with patients initially receiving appropriate therapy. Sepsis is also associated with a number of serious, long-term consequences, such as organ failure, gangrene and amputation, which have a significant impact on the patients, and also significant financial burden for the NHS (Section 3.2.2 and Section 3.3.3.2); further emphasizing the urgent need for timely treatment.

#### Issues with current treatments

As presented in Table 2 (Section 1.1.1.3), there are limited treatment options that are effective across carbapenem-resistant Gram-negative infections and there is no defined standard of care. Treatment options for carbapenem-resistant *Acinetobacter baumannii* (CRAB), *Stenotrophomonas maltophilia*, extensively drug resistant (XDR) *Pseudomonas*, and metallo-β-lactamase-producing pathogens are further limited; other than cefiderocol, there are no approved active drug available with activity against these pathogens, with few agents still in development.15 As presented in Table 2, current therapies also have gaps in their activity profile, which limits their usefulness in the high-risk empiric setting, as well as against specific pathogens in the microbiology-directed setting. As a result, treatments are often used off-label and/or in combination with other therapies, to try and expand the coverage of the therapy given to patients, despite their being limited or no scientific evidence to support this use.

Table 3 presents a summary of the key comparators highlighted in the NICE scope, updated in line with the EEPRU protocol and discussions at the stakeholder engagement meeting, and the major issues associated with these treatments.

Table 3: Issues with current treatments defined in the EEPRU protocol

| Current treatments (as defined by the EEPRU protocol) | Key issues | | | |
| --- | --- | --- | --- | --- |
| Limited evidence to establish efficacy | Tolerability concerns | Supply issues | Off-label use or unlicensed in certain populations |
| Colistin-based regimens [microbiology-directed and risk-based empiric treatment settings] | While colistin has good *in vitro* data, it can have poor tissue penetration depending on site of infection (particularly in the lung), making dosing difficult and response unpredictable.108, 109 Therefore, independent of the organism or resistance mechanism, colistin is problematic, and achieving effective drug concentrations at the site of infection results in significant, serious side effects  As presented in Section 2.3.4.1, in CREDIBLE-CR, patients with infections caused by MBL-producing pathogens treated with BAT (6 out of 7 patients received a colistin-based regimen) had low rates of clinical and microbiological eradication | Colistin and colistin-based regimens are associated with severe adverse events, including neurotoxicity, nephrotoxicity, and ototoxicity28, 110  Renal failure is also a particular issue; reported in up to 60% in patients treated with colistin111  Due to colistin’s relatively poor efficacy in many situations, it is often prescribed in combination with other relatively toxic antimicrbials, which in turn further compounds colistin’s already unfavourable side-effect profile  Due to its poor safety profile, colistin is not an option for a number of patients who are in poor condition and may not be able to cope with the high levels of toxicity  In the BAT arm of CREDIBLE-CR, the one patient to die of drug related toxicity, was a patient on a polymyxin regimen | NA | Colistin had previously been withdrawn from the market and not recommended for use (due to high toxicity)  More recently, the increasing emergence of MDR Gram-negative bacteria and lack of effective alternative options (Table 2) has led to its reintroduction in clinical practice66, 112  The SmPC for colistin recommends that consideration should be given to co-administration with other antimicrobial agents whenever this is possible, and that it should only be used when other antimicrobials are not effective or not appropriate113 |
| Tigecycline + colistin [microbiology-directed (MBL-CPE) and risk-based empiric treatment settings] | Suboptimal concentrations of tigecycline have been found in both serum and pulmonary epithelial lining fluid, and this has prompted many physicians to use either combination therapy or high-dose tigecycline to treat CRE infection114  *Pseudomonas* are naturally resistant to tigecycline is (due to their broad substrate efflux pumps), as are *Enterobacterales*  Rapid development of resistance to tigecycline via upregulation of efflux has been observed in Acinetobacter spp.  A pooled analysis of clinical studies of tigecycline versus comparator agents showed an increased mortality associated with tigecycline, suggesting poor efficacy115 | The EMA have recommended that tigecycline should only be used within its licensed indications due to safety concerns, which highlights the poor safety profile associated with tigecycline  As above for colistin | NA | Tigecycline is only licensed for use in complicated skin and soft tissue infections (cSSTIs) and complicated intra-abdominal infections (cIAIs), and it is recommended that it is not used outside of this license due to safety concerns; therefore, this treatment is not relevant to a wide number of infections sites, including EEPRU’s HVCSs |
| Fosfomycin + colistin [microbiology-directed (MBL-CPE) and risk-based empiric treatment settings] | Fosfomycin is not active against *A.* *baumannii* or *S.* *maltophilia*  *Pseudomonas* are inherently resistant to fosfomycin  Evidence to support the use of fosfomycin for MBL-producing pathogens is extremely limited116  Resistance to fosfomycin develops rapidly and therefore it is generally recommended to be used in combination116 | Fosfomycin is recommended for restricted use by the EMA following re-evaluation of its safety and effectiveness117  As above for colistin | Although a UK license for fosfomycin is held with the MHRA, no UK packaged product is currently available, and all supplies must be imported as unlicensed special products, which has implications for the available supply | NA |
| Aztreonam + colistin [microbiology-directed (MBL-CPE) and risk-based empiric treatment settings] | Aztreonam is active against MBLs; however, due to the frequent co-production of serine β-lactamases within MBL-producing *Enterobacterales*, which can hydrolyze aztreonam, it only remains active against roughly 30% of these isolates118  Gram-negative bacilli carrying an MBL also commonly carry additional β-lactamases, including ESBLs, AmpC, or serine carbapenemases, that also inactivate aztreonam119 | As above for colistin | Supply of aztreonam is managed by one factory in India, this has implications for the available supply of aztreonam | Aztreonam is not licensed, meaning that there is limited evidence to assess the efficacy and safety of this product |
| Aminoglycosides (gentamicin, amikacin, tobramycin) [microbiology-directed (MBL-CPE) and risk-based empiric treatment settings] | The efficacy of aminoglycosides is hindered by increasing rates of resistance and reduced lung concentrations with systemic administration120-122; therefore, they are generally only used in combinations  Limitations of aminoglycosides include lack of activity against NDM-1-producing *Enterobacterales, S.* *saprophyticus*, *Enterococci*, and increasing resistance rates of ESBLs-producing Gram-negative organisms, *P.* *aeruginosa*, and *A.* *baumannii*116  Aminoglycosides have demonstrated limited activity against MBL-producing *Enterobacterales116* | Evidence suggests an increased risk of aminoglycoside-associated ototoxicity in patients with mitochondrial mutations123; hearing loss associated with aminoglycoside use in irreversible122  Aminoglycosides are also associated with nephrotoxicity120-122 and neuromuscular blockade124  Aerosol delivery, in addition to systematic administration, has been considered to improve efficacy for VAP; however, there is a risk of respiratory complications and evidence to support this use is lacking102 | NA | NA |
| Fosfomycin + meropenem [microbiology-directed (MBL-*pseudomonas*) and risk-based empiric treatment settings] | As above for fosfomycin  At normal doses, meropenem is unlikely to be active against carbapenem-resistant pathogens and had limited activity against carbapenem-resistant *A. baumannii*, *P. aeruginosa* or *S. maltophilia*125  Resistance to meropenem is an issue, which is why a newer fixed dose combination of meropenem/vaborbactam was developed; however, this has limited activity against Class D beta-lactamases, carbapenem-resistant *A.* *baumannii*, *P.* *aeruginosa*, or *S.* *maltophilia*, and no activity against Class B (MBLs)125, 126  Due to meropenem’s lack of activity against MBLs, the only active treatment in this combination would be fosfomycin, and would therefore only be as effective as fosfomycin monotherapy | As above for fosfomycin | As above for fosfomycin | NA |

A recent literature review of current and future therapeutic approaches for severe MDR Gram-negative infections in critically ill patients reported that the availability of newly approved antimicrobials such as ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, plazomicin (which is not available in the EU) and eravacycline are reported to have suboptimal activity against some pathogens especially against carbapenem-resistant *A.* *baumannii*, metallo-β-lactamase-producing pathogens and *S.* *maltophilia*.121 As part of the future treatments, this literature review lists cefiderocol as one of the most promising future therapeutic options for infections caused by serious carbapenem-resistant aerobic Gram-negative infections including *Enterobacterales*, *P.* *aeruginosa, A. baumannii* and *S.* *maltophilia*.121

Currently available therapeutic options, predominantly colistin, are also associated with pharmacokinetic limitations, such as high toxicity and low plasma levels.127 Among the more severe adverse events associated with current treatment options are neurotoxicity, nephrotoxicity (including acute kidney failure) and ototoxicity.28, 110

While it covers a broad spectrum of Gram-negative pathogens, colistin is associated with severe adverse events.28, 110 Renal failure is a particular issue associated with colistin and is reported to reach up to 60% in patients treated with colistin.111 In a recent systematic literature review and meta-analysis of 237 studies representing 35,569 patients, colistin was associated with double the odds of developing renal toxicity (OR: 2.23; 95% CI: 1.58, 3.15; p < 0.001), which has a significant impact on patients’ quality of life, leading to the development of acute kidney injury and increased hospital length of stay, long-term renal failure and death.128

Despite a recognition of inconsistent clinical efficacy – poor lung, bone, and CNS penetration, which makes dosing to reach concentrations above MIC difficult and response unpredictable, and an increased potential for renal toxicity – colistin is reported as being the most widely used antimicrobial for managing carbapenem-resistant Gram-negative infections129, 130 and is the last treatment available for some pathogens. Recognition of colistin’s relatively poor efficacy in many situations has seen it being prescribed more often than not in combination with other relatively toxic antimicrobials, which in turn compounds colistin’s already unfavourable side-effect profile.

The widespread use of colistin had been reduced (colistin had previously been withdrawn from the market and not recommended for use in treatment guidelines), due to the high rates of renal toxicity and the availability of new antimicrobials. However, in recent years, the increasing emergence of MDR Gram-negative bacteria, and lack of effective alternative options (Table 2) have led to its reintroduction in clinical practice.102, 110

Recently, colistin resistance has been identified as emerging in *A*. *baumannii* and *K*. *pneumoniae*, metallo-β-lactamase-producing *P*. *aeruginosa*, and *E*. *coli*.126 The resistance to colistin is also increasing with the emergence and worldwide spread of a colistin-resistance genes.131, 132 Multiple outbreaks in carbapenemase-producing, colistin-resistant isolates have been observed in Europe (including England) and North America.110

For patients who are unable to tolerate colistin, or who fail on colistin, treatment options are limited (Table 2; Section 1.1.1.3), with clinicians likely having to attempt combinations of antimicrobials that they suspect will fail. For this reason, and the potential for the development of resistance to colistin, antimicrobials with potent activity across carbapenem-resistant Gram-negative infections, especially metallo-β-lactamase-producing pathogens, CRAB and *S.* *maltophilia*, such as cefiderocol are of critical importance.

A UK clinical expert also acknowledged aztreonam-containing regimens (including with ceftazidime/avibactam), as a treatment option in the UK.

However, there are also a number of issues associated with this ceftazidime/avibactam. As shown in Table 2 (Section 1.1.1.3), ceftazidime/avibactam has limited effectiveness against a number of key pathogens, including *P*. *aeruginosa, A*. *baumannii, S. maltophilia* and metallo-β-lactamase-producing pathogens. Recent clinical case reports in the USA and the EU/EEA have also demonstrated the emergence of ceftazidime/avibactam resistance in CRE. This is further suggested in the CARBAR study, which identified a resistance rate of 40% from the 20 patients treated. There have also been reports of the development of within treatment resistance. These reports are of particular concern since it is under three years since the initial launch of ceftazidime/avibactam.

There are also supply-side issues with some current antimicrobials; for example, ceftolozane/tazobactam (Zerbaxa®) is currently being recalled from all markets worldwide (following bacterial contamination that occurred during the manufacturing process), which has led to global supply disruptions.133 This is not an isolated incident, with ceftazidime/avibactam also facing supply issues, both currently and historically.134 This presents a significant risk, particularly in the case of an outbreak that would put increasing pressures on the supply chain of other products. The security of the supply chain for antimicrobials is another reason why it is of critical importance to have multiple treatment options available (Section 2.5).

Given the sparsity of available treatment options and increasing rate of AMR it is worth noting that, unlike more conventional technology assessments, the choice is not whether cefiderocol should largely displace other therapies but rather the value of having an additional antimicrobial to use whether because:

* Current interventions are judged unlikely to be efficacious for the patient as a first line therapy
* The patient is contraindicated to colistin-based regimens
* The first line therapy has failed and no alternative treatments are available as a second line option

There is value in diversifying the antimicrobials being used, reducing the rate at which AMR develops to current interventions and therefore extending the useful life of the currently available therapies

### Long-term effects of treatment and infection

In the context of carbapenem-resistant infections, patients typically have very few treatment options available to them (Section 1.1.2), particularly in the risk-based empiric setting. The EEPRU protocol lists colistin, often in combination with other treatment options, alongside few other options, as potential treatment strategies within current UK standard of care.90 All these treatment strategies are known be, to varying extents, associated with renal toxicity. A natural consequence, therefore, of the way that patients are currently treated for this decision problem is the long-term burden of kidney injury, impairment, and failure.

The consequences of renal complications are not likely to be limited to the period of treatment, and in many cases are even life-long.135 Considerably more patients are expected to need long-term care following renal complications during antimicrobial treatment, which can cost up to £1,288 per patient per week (see Sections 3.3.3.2 and 3.3.3.2) and impacts both the mortality and morbidity of patients (See Appendix F and Figure 15 panels a and d). Furthermore, a small proportion of patients with renal complications will have progressive kidney issues like renal failure (whether reversible or irreversible), which further impact costs, survival, and quality of life for patients.

As presented in Section 2.4.1 and Appendix E, despite clearance of cefiderocol being predominantly via the kidneys, the renal side effect profile of cefiderocol is such that renal complications are not expected, with a very small number of patients in CREDIBLE-CR or the APEKs trials exhibiting cefiderocol-related renal complications, and these were shown to be transient. By contrast, the expected incidence of acute renal injury per day of colistin therapy is considerably higher (See Section 3.2.2 and Appendix F for discussion on data sources and appropriate modelling approaches).

Patients who recovered from infections may also face long-term consequences, which may be influenced by how quickly they have received an appropriate therapy. As discussed in 1.1.2.4, this is a particularly critical issue to prevent patients developing sepsis, and to prevent patients with sepsis dying, as a first step, but also from experiencing organ failure and gangrene, with the associated long-term effects for patients.

Due to the factors discussed here, a critical aspect of the value of cefiderocol is the lack of renal complications and neurotoxicity compared to current treatments, as well as the wide coverage of aerobic Gram-negative pathogens, increasing the likelihood of patients receiving an effective therapy earlier. We therefore recommend that the downstream consequences of renal complications and other long-term effects of infection on patients must be explicitly modelled by EEPRU to avoid underestimating the value of cefiderocol. Some suggested data sources and approaches to help EEPRU achieve this are provided in Section 3.3.3.2, and Appendix F.

### Epidemiology data

#### Objective

Based on the HVCSs, it is necessary to estimate the number of patients/infections within these two populations that could be treated with cefiderocol in England:

* Metallo-β-lactamase cases that are confirmed/suspected based on testing results
* *Enterobacterales* and *Pseudomonas* spp., plus other pathogen species (e.g. *Stenotrophomonas maltophilia*)
* cUTI, plus all other infection sites
* Metallo-β-lactamase cases that are suspected due to risk factors, in patients considered ‘critical’
* *Enterobacterales* and *Pseudomonas* spp., plus other pathogen species (e.g. *Stenotrophomonas maltophilia*)
* hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP), plus any other infection types considered ‘critical’ (e.g. BSI)

Any other patient types that are considered ‘critical’ (e.g. elderly and co-morbid)

Alongside these HVCS populations, it is also necessary to estimate the number of other patients/infections that could be considered to have ‘limited treatment options’ and thus be suitable for treatment with cefiderocol. As previously outlined (e.g. in response to the Evaluation Protocol), these include:

* Other types of carbapenem-resistant pathogens, apart from metallo-β-lactamase (e.g. those caused by serine β-lactamase, porin and efflux pump mechanisms) that are identified based on testing results

Other cases of carbapenem resistance, apart from metallo-β-lactamase, that are suspected due to risk factors in ‘critical’ patients

For all the patient populations described above, it will be necessary to estimate patient numbers currently and into the future, potentially over the next 10–20 years.

#### Response

The epidemiology in this area is challenging. These factors contribute to the difficulty of forecasting patient numbers for this NICE evaluation:

* Inherent complexities of the condition(s) under consideration, including the spectrum of pathogen species, resistance mechanisms and infection sites. This is also a highly dynamic area, with changes over time further compounding the challenge
* Limited evidence base, across the range of types of infection occurring in England relevant for NICE. Surveillance data in England are often focused on certain individual ‘priority’ pathogen types (often without information on the mechanism of resistance), record cases of colonization/infection rather than clinical infection, or are sampled rather than comprehensive data

Geographic variation. Due to the localized nature of infection types, the available data are not easily transferable (i.e. across countries, and between localities or hospitals – and even between departments within individual hospitals - in England)

There are no published estimates of the total number of patients in England with carbapenem-resistant Gram-negative infections, i.e. those patients eligible to receive cefiderocol.

Shionogi is aware of one independent estimate that has been developed. A Specialist Pharmacy Service (SPS) monograph on cefiderocol was issued in 2020 by the Northwick Park Medicines Information Centre. NICE have access to Prescribing Outlook and can access it from [www.sps.nhs.uk](http://www.sps.nhs.uk/) (<https://www.sps.nhs.uk/articles/po-2020-bnf-5-infections/>).136

##### Gram-negative infections

The total number of Gram-negative infections in England is unclear.

In 2011–12 there were an estimated 243,746 patients acquiring at least one HAI per year in England, with the majority being caused by Gram-negative bacteria.137 This survey may have underestimated the total number of HAIs by only capturing infections acquired by patients once admitted to hospital, rather than also counting patients that were admitted with infections. It is also quite an old survey; improved awareness, detection and surveillance would likely result in a higher number of patients being detected today.

NICE estimated 300,000 patients in England acquire a HAI per year in 2014.138

**Conclusion:** there are currently likely to be **at least 200,000 infections caused by Gram-negative pathogens per year in England**.136

##### Resistance levels

The estimated total number of resistant infections in England in 2019 was 65,162, based on a bacteraemia AMR rate of 21%.78 This estimate includes both Gram-negative and Gram-positive cases and encompasses a broad range of resistance types (not just carbapenem resistance). The proportion of *Enterobacterales* isolates that were carbapenemase-producing ranged from approximately 7% to 11% between 2014 and 2017.78 The proportion of *Pseudomonas* spp. BSI cases that were carbapenem resistant between 2015 and 2019 was 8%.78

The European Centre for Disease Prevention and Control (ECDC) has reported a wide range of resistance rates between countries and over time indicating that, for *Enterobacterales* at least, the UK resistance rates have historically been low. However, as outlined above, these figures are likely to represent an underestimate of the total number of resistant infections, due to under-reporting at that time, plus the absence of *Pseudomonas* (which appears to have a much higher rate of carbapenem resistance) from the sample.

In CARBAR, the proportion of patients with Gram-negative pathogens that had carbapenem-resistant isolates was 8%.139

**Conclusion:** based on an overall carbapenem resistance rate of approximately 8%,136 there are currently likely to be **at least 15,000 infections caused by carbapenem-resistant Gram-negative pathogens per year in England.136**

##### Resistance mechanisms

The estimated proportion of carbapenem-resistant *Enterobacterales* that produce metallo-β-lactamase is 43%,78 as referred to in the EEPRU Evaluation Protocol.

The proportion of carbapenem-resistant *Pseudomonas* spp. that are metallo-β-lactamase across Europe can be estimated at approximately 20%.140

100% of *Stenotrophomonas maltophilia* are carbapenem resistant due to their innate type of metallo-β-lactamase.

The prevalence of metallo-β-lactamases (in particular NDMs) has been growing, so the historical figures above are likely to be an underestimate of the proportions today. Based on this evidence we conclude that approximately one third of all carbapenem-resistant infections are caused by metallo-β-lactamase-producing pathogens.

**Conclusion:** there are currently likely to be **at least 5,000 infections caused by metallo-β-lactamase-producing pathogens per year in England.**

The distribution of these metallo-β-lactamase-positive infections across species is difficult to determine. Based on data from CARBAR, the majority (46%) could be *Pseudomonas*, with significant proportions being *Enterobacterales* (19%), *Stenotrophomonas* (27%) and *Acinetobacter* (4%).139

##### Risk factors

The epidemiological information on carbapenem-resistance risk factors is even more sparse than that on carbapenem-resistance itself.

The CARBAR study provides some evidence on one of the risk factors, namely repatriation from countries with high rates of carbapenem resistance. 27% of patients with carbapenem-resistant infections had travelled abroad in the 12 months prior to hospitalization, 75% of whom (i.e. 20% of the total) were also known to have been hospitalized whilst abroad.139 This suggests that one fifth of carbapenem-resistant cases may be predicted based on this particular risk factor. The importance of this risk factor may increase as international travel resumes post-COVID (see longitudinal trends section below).

Expert opinion suggests that most patients with a carbapenem-resistant and/or metallo-β-lactamase-positive infection will have a risk factor, and that approximately half will have a sufficiently clear risk profile to warrant high suspicion and thus risk-based empiric treatment.

**Conclusion:** there may currently be **at least 2,500 patients with an infection caused by metallo-β-lactamase-producing pathogens that can be predicted** with reasonable reliability using risk factors.

##### Critically ill patients

European Point Prevalence Survey data report that in 2011, respiratory infections and BSIs accounted for 23% and 8% of all HAIs, respectively.137 This evidence suggests that overall, about 30% of infections may be considered ‘critical’ requiring immediate antimicrobial treatment.

**Conclusion:** there may currently be **at least 750 patients in England that are considered ‘critically ill’ and with a suspected infection caused by a metallo-β-lactamase-producing pathogen.**

##### Longitudinal trends

Infection rates in England have increased over time. ESPAUR data indicates an increase of 16.9% in BSI between 2015 and 2019, which equates to an increase of 4.2% per year.78

AMR rates in England have also increased over time. ESPAUR reported an increase in the proportion of BSIs that were resistant of 18% in 2015 and 21% in 2019, which equates to an increase of 0.6% per year.78

ESPAUR data also indicate a steadily increasing rate of carbapenemase-producing *Enterobacteriaceae* (CPE) isolates and noted a 39% increase in the rate of *Klebsiella* spp. resistance between 2015 and 2019.

EARS-Net highlights that rates of carbapenem resistance vary according to pathogen, indicating that between 2015 and 2019, the resistance rate in *Pseudomonas* rose by 3.6% per year, whereas rates for *Enterobacterales* rose more slowly.141

Growth in ‘provision of care’ (e.g. intensive care, cancer, renal) as the population ages may further increase the prevalence of infection in the future. Similarly, inadequate infection control in the future could increase numbers of resistant infections; for example, the incidence of *Acinetobacter* infections is typically quite erratic, with outbreaks associated with poor infection control.

Finally, the impact of COVID-19 should be considered. To date, COVID-19 has resulted in an increased number of secondary infections and patients on ventilators in hospital, leading to an increase in VAP. Compromised infection control and antimicrobials stewardship during the crisis may allow resistant pathogens to flourish, particularly at the international level, i.e. in countries where resistance is endemic and healthcare systems are poorly resourced (e.g. India).142 As international travel resumes, it is likely that the domestic frequency of resistant infections in repatriated patients will increase; local populations who regularly visit such areas, returning with a greater number of these highly resistant pathogens, and tourists bringing such pathogens into the country more regularly.

In addition, the population of England is forecast to grow by an average of 0.41% per year between 2021 and 2033.143

A conservative estimate of the combined effect of increased infection rates plus increasing proportions of resistance is a growth rate for the number of resistant infections of 5% per year. Over a 10-year period, this equates to a compound increase of 55%.

**Conclusion: Over the next 10 years, the number of patients eligible for cefiderocol could increase by approximately 50%.**

#### Overall summary

There is limited evidence in this area, but available data suggest:

* There are currently approximately 5,000 Gram-negative infections caused by metallo-β-lactamase-producing pathogens per year in England
* Of these, approximately 750 are predictable infections caused by metallo-β-lactamase-producing pathogens that occur in patients who may be considered clinically ‘critical’

These numbers are highly likely to increase significantly in the future

These ‘HVCS’ figures, which focus on estimated numbers of infections caused by metallo-β-lactamase-producing pathogens, do not account for infections caused by pathogens with other types of resistance that result in limited treatment options, which could also warrant treatment with cefiderocol. Based on the prevalence of these other types of pathogen/resistance (i.e. serine β-lactamases, porin channel, and efflux pump mechanisms) there are likely to be at least as many patients in these other categories, as in the ‘metallo-β-lactamase’ target category included in the HVCSs.

## Description of the technology being appraised

A summary of cefiderocol is presented in Table 4. The SPC and EPAR are presented in Appendix B.

Table 4: Technology being appraised

|  |  |
| --- | --- |
| **UK approved name and brand name** | Cefiderocol (FETCROJA®) |
| **Mechanism of action** | The mechanism of action of cefiderocol is presented in more detail in Section 1.2.2. A summary is presented here.  The antimicrobial activity of cefiderocol is based on inhibition of Gram-negative bacterial cell wall synthesis.20 In contrast to bacteriostatic agents, which only suppress the growth of bacteria, the activity of cefiderocol results in cell death (bactericidal effect). Furthermore, cefiderocol has a higher binding affinity than ceftazidime for multiple PBPs, with particularly high affinity for PBP3 (1.5–12.5 times higher than ceftazidime).144  In addition to the normal mechanisms of cell entry via porin channels, Cefiderocol uses the bacteria’s own active iron uptake mechanism (siderophores) to enter the periplasmic space of Gram-negative bacteria where it binds to PBPs and kills the bacteria, acting like a ‘Trojan horse’ (Figure 4).20-22 This unique mechanism of cell entry for cefiderocol is based on the fact that bacterial cells require iron for growth.20, 21  Cefiderocol has been designed to chelate iron to form an iron complex similar to a bacterial catecholate siderophore.20, 21 When bound to iron, the cefiderocol–iron complex mimics a bacterial siderophore–iron complex and is actively transported through the outer membrane using the bacteria’s active iron transporters.20, 21, 145 Cefiderocol uptake is increased under the low iron conditions that occur during infections (Figure 5).146 Even in the absence of forming a complex with iron, cefiderocol can still function as an antimicrobial agent by entering the bacterial periplasm via passive diffusion through porin channels.22  Due to its unique mechanism of cell entry (via active iron transporters) and higher stability to both serine- and metallo-type carbapenemases (key enzymes rendering resistance to β-lactam antimicrobials), cefiderocol overcomes most common mechanisms of resistance in Gram-negative pathogens.20, 21, 147 |
| **Marketing authorization/CE mark status** | Cefiderocol received marketing authorization by the EMA on 23 April 2020.  Cefiderocol was launched in the UK on 15 September 2020. |
| **Indications and any restriction(s) as described in the summary of product characteristics (SmPC)** | The indication for cefiderocol is ‘for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.’  It is recommended that cefiderocol should be used to treat patients that have limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases. |
| **Method of administration and dosage** | Cefiderocol is administered by intravenous infusion over 3 hours.  For patients with a creatinine clearance (CrCL) ≥ 90 mL/min, the following dosing regimens are recommended for a duration in accordance with the site of infection (e.g. for cUTIs the recommended treatment duration is 5–10 days; for hospital-acquired pneumonia the recommended treatment duration is 7–14 days):  Normal renal function (CrCL ≥ 90 to < 120 mL/min): 2 g every 8 hours  Augmented renal clearance (CrCL ≥ 120 mL/min): 2 g every 6 hours  For patients with renal impairment (CrCL < 90 mL/min) the following dosing regimens are recommended:  Mild renal impairment (CrCL ≥ 60 to < 90 mL/min): 2 g every 8 hours  Moderate renal impairment (≥ 30 to < 60 mL/min): 1.5 g every 8 hours  Severe renal impairment (CrCL ≥ 15 to < 30 mL/min): 1 g every 8 hours  End-stage renal disease (CrCL < 15 mL/min): 0.75 g every 12 hours  Patient with intermittent haemodialysis: 0.75 g every 12 hours (as cefiderocol is removed by haemodialysis, it should be administered at the earliest possible time after completion of haemodialysis-on-haemodialysis days) |
| **Additional tests or investigations** | No additional tests or investigations are anticipated, beyond what is already performed in clinical practice. |
| **List price and average cost of a day of treatment** | NHS indicative price: £1,319 (hospital only)  £791.40 per day of treatment received, considering 6 vials per day |
| **Patient access scheme (if applicable)** | NA |

### Introduction to cefiderocol

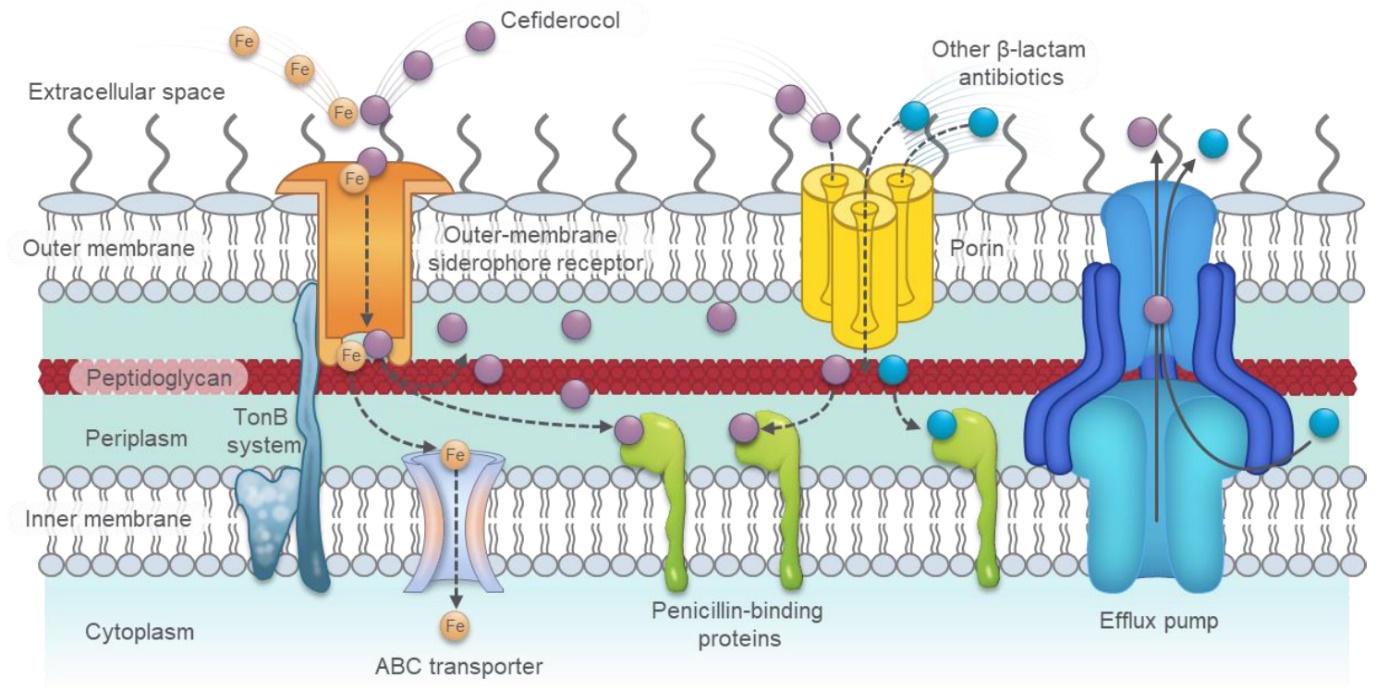
Cefiderocol (FETCROJA®) is the first injectable siderophore cephalosporin, which incorporates features of other cephalosporin antimicrobials but is distinct from other β-lactam antimicrobials due to its iron chelation. via the siderophore portion of the molecule. This difference classifies cefiderocol as a siderophore cephalosporin.12, 13

### Mechanism of action

The antimicrobial activity of cefiderocol is based on inhibition of aerobic Gram-negative bacterial cell wall synthesis. Like other β-lactams, cefiderocol binds and inhibits penicillin-binding proteins (PBPs) in the bacterial periplasm, inhibiting the synthesis of peptidoglycan (a critical component of the bacterial cell wall structure) and causing the bacteria to rupture and die.20 In contrast to bacteriostatic agents, which only stop the growth of bacteria, the activity of cefiderocol results in cell death (bactericidal effect). Furthermore, cefiderocol has a higher binding affinity than ceftazidime for multiple PBPs, with particularly high affinity for PBP3 (1.5–12.5 times higher than ceftazidime).144

Cefiderocol uses the bacteria’s own active iron uptake mechanism to enter the periplasmic space of aerobic Gram-negative bacteria where it binds to PBPs and kills the bacteria, acting like a ‘Trojan horse’ (Figure 4).20-22 This unique mechanism of cell entry for cefiderocol is based on the fact that bacterial cells require iron for growth.20, 21 The low levels of free iron in the human body during an infection induce pathogens to upregulate iron acquisition factors, such as by secretion of iron-binding small molecules called siderophores into their environment, and the production of membrane-bound active iron transporters.21, 148-151 Bacterial siderophores tightly bind to host iron and form a chelated iron complex, which then penetrates through the outer membrane via active iron transporters located in the aerobic Gram-negative outer membrane.20, 21

Figure 4: Cefiderocol mechanism of cell entry

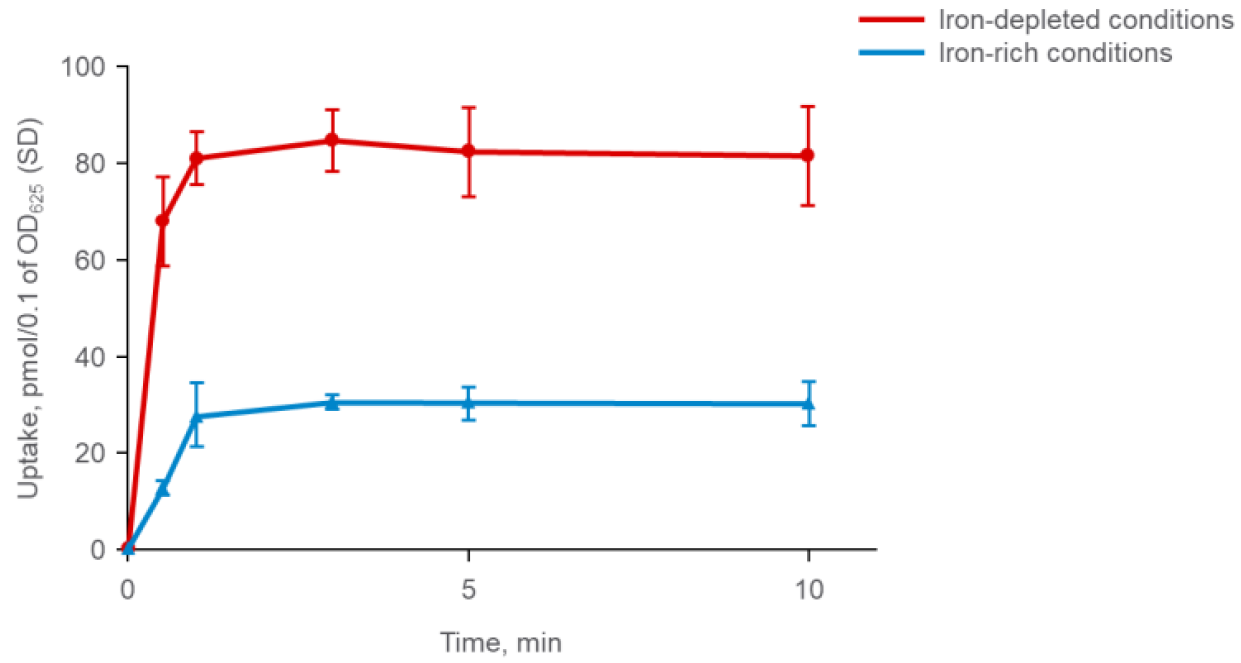


**Source:** Adapted from Zhanel *et al.*, 2019.21

Cefiderocol has been designed to chelate iron to form an iron complex similar to a bacterial catecholate siderophore.20, 21 When bound to iron, the cefiderocol–iron complex mimics a bacterial siderophore–iron complex and is actively transported through the outer membrane using the bacteria’s active iron transporters.20, 21, 145 Cefiderocol uptake is increased under the low iron conditions that occur during infections (Figure 5).146 Even in the absence of forming a complex with iron, cefiderocol can still function as an antimicrobial agent by entering the bacterial periplasm via passive diffusion through porin channels.22

Due to its unique mechanism of cell entry (via active iron transporters) and higher stability to both serine- and metallo-type carbapenemases (key enzymes rendering resistance to β-lactam antimicrobials), cefiderocol overcomes most common mechanisms of resistance in aerobic Gram-negative pathogens (Section 1.2.3).20, 21, 147

Figure 5: Uptake of cefiderocol in iron-depleted conditions



**Key:** OD, optical density; SD, standard deviation.

**Source:** Ito *et al.*, 2016.146

### Cefiderocol and mechanisms of resistance

Resistance to antimicrobials generally takes two forms: chemical (i.e. the pathogens produce enzymes, including carbapenemases, which ‘chop up’ and deactivate antibiotics) and mechanical (i.e. the pathogens develop porin and efflux channel mechanisms, which limit antibiotics within the inner membrane). Cefiderocol has a specific structure, which may make it difficult for carbapenemases to break its chemical bonds. As discussed in Section 1.2.2 cefiderocol can also use a unique ‘iron-based’ method of cell entry, which can effectively bypass the porin/efflux removal mechanisms. Therefore, it may also be more difficult to develop resistance against without compromising the bacteria’s ability to thrive. This unique iron moiety may also mean that emergence of cross-resistance associated with cefiderocol is likely to be low: in preclinical studies, spontaneous mutations that conferred resistance to cefiderocol occurred at a similar frequency as that for other β-lactam antimicrobials but tended to be in genes associated with the iron uptake pathway and did not affect other antimicrobials that cannot exploit this unique mechanism of cell entry. Such ‘iron uptake’ mutants are also observed to grow weakly under iron-limited conditions and so are unlikely to persist in the environment once selection pressure is removed.

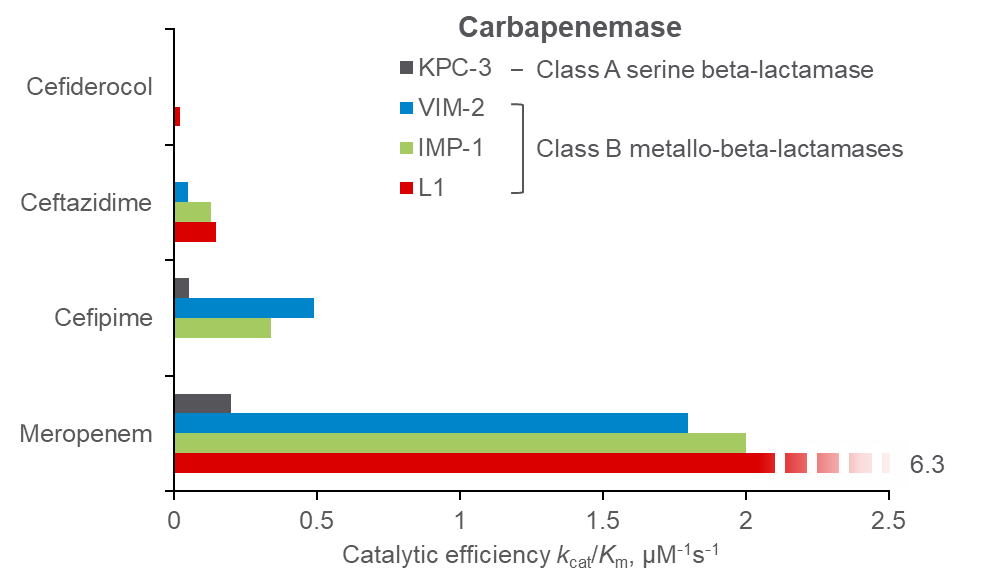
To date, surveillance data suggests a low level/rate of resistance against cefiderocol. This evidence, presented in Section 2.3.5 supports the biologically plausible reasons for low resistance outlined above.

### Stability of cefiderocol against β-lactamases

The structure of cefiderocol also presents higher stability to hydrolysis across a wide range of bacterially produced β-lactamase enzymes (including carbapenemases of the serine β-lactamase and metallo-β-lactamase classes) and thus overcomes the primary mechanism of bacterial resistance to β-lactam antimicrobials, without adding a β-lactamase inhibitor.20, 21

Cefiderocol has demonstrated higher levels of stability and more potent activity against carbapenemases, including against metallo-β-lactamases, than other β-lactamases (Figure 6).13-18 Compared with the activity of other existing antimicrobials, as presented in Table 2, this demonstrates a significant value for cefiderocol.

Figure 6: Stability of cefiderocol and other treatments against carbapenemases



**Notes:** The lower catalytic efficiency of carbapenemases indicates higher stability of the drug.

**Source:** Ito-Horiyama *et al.*, 2016.16

### How cefiderocol addresses the issues with current treatments

As discussed in Section 1.1.2.5, current treatments are associated with a range of issues: tolerability concerns; not being licensed for use in certain populations; having limited evidence to support efficacy in certain pathogens; and having issues with supply. Table 5 summarizes how cefiderocol overcomes these issues, with links to where the supporting evidence is presented within this dossier.

Table 5: How cefiderocol addresses the issues with current treatments

| Issue | How it is addressed |
| --- | --- |
| Limited evidence to establish efficacy | Cefiderocol has demonstrated efficacy across a wide range of aerobic Gram-negative pathogens, including all key pathogens in the WHO list of priority pathogens and S. *maltophilia*, as well as the specific HVCSs defined by EEPRU (Section 2.3) |
| Tolerability | Cefiderocol has been demonstrated to be a safe therapy option for patients (Section 2.4.1) |
| Supply issues | As described in dialogue with, and submission to, NHSE for the selection phase of this project, cefiderocol has a reliable supply chain to ensure patient access is maintained |
| Unlicensed | Cefiderocol is licensed for people receiving treatment in secondary or tertiary care settings in whom resistant aerobic Gram-negative infection is suspected/confirmed, with limited treatment options (i.e. carbapenem-resistant pathogens and metallo-β-lactamase-producing pathogens) (Section 1.3.1) |

## Decision problem

### NICE decision problem

The submission covers the technology’s full marketing authorization for this indication:

For the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options

The decision problem outlined by NICE, along with suggested considerations provided by Shionogi, are presented in Table 6. Further to the NICE decision problem, EEPRU have developed a protocol to present the planned approach to their analysis of certain high-value clinical scenarios (HVCSs), which has subsequently been updated in slides presented at a stakeholder engagement meeting and further updated in a document shared with Shionogi. The HVCSs defined by EEPRU are discussed further in Section 1.3.2 and the relevant comparators for these HVCSs have been discussed in Table 3, Section 1.1.2.5.

Table 6: The decision problem

|  | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
| --- | --- | --- | --- |
| **Population** | People receiving treatment in secondary or tertiary care settings in whom resistant aerobic Gram-negative infection is suspected/confirmed, with limited treatment options. | People receiving treatment in secondary or tertiary care settings in whom resistant aerobic Gram-negative infection is suspected/confirmed, with limited treatment options. | NA |
| **Intervention** | Cefiderocol | Cefiderocol | NA |
| **Comparator(s)** | Clinical management without cefiderocol | Clinical management without cefiderocol | NA |
| **Outcomes** | The outcome measures to be considered include:  All-cause mortality  Clinical cure (complete resolution of signs/symptoms of the index infection such that no further antimicrobial therapy is needed)  Microbiological eradication  Emergence of resistance  Hospital days  ICU days  Readmission rate within 90 days of treatment  Number of treatment days  Health-related quality of life  Adverse events (including those associated with *Clostridium difficile* infection and renal toxicity) | Additional outcomes to be included:  *In vitro* susceptibility data  PK/PD data  Time to effective therapy, i.e. the time to receiving an antimicrobial that is sensitive to the causal pathogen  Treatment-related mortality  Outcomes considered to be less relevant:  All-cause mortality | As summarized by the EMA, the most appropriate measure of treatment effect is likely to be a combination of clinical trial evidence (using ‘cure-focused’ endpoints, which were the primary measures for all cefiderocol trials), *in vitro* susceptibility/activity data, PK/PD data, and real-world case studies and other observational data.  Susceptibility data from surveillance studies provide important information on the activity profiles of different antimicrobials. In the absence of susceptibility testing results in the clinical setting (i.e. at the ‘suspected’ stage), these data represent a key measure informing the likely treatment effect.  Of further value are PK/PD studies. Given the high diversity of possible pathogens, mechanisms of resistance and infection sites, it is difficult and/or impractical to generate clinical data for each possible situation. Regulatory authorities, such as the EMA, have recognized this, and consider such PK/PD data and models to be pivotal to the assessment of efficacy of new antimicrobials. PK/PD data demonstrate the ability of each drug to reach different infection sites in concentrations deemed to be effective for each pathogen/mechanism of resistance.  Time to effective therapy (and the negative impact of initially inappropriate therapy) is an important measure in the ‘suspected’ clinical setting. It is a determinant of outcomes such as mortality and has an impact on NHS HCRU/costs.  All-cause mortality (including 90-day mortality) is undoubtedly compounded and therefore the results need to be heavily contextualized when they are being interpreted. Considering that the infections were all in hospitalized patients, but not necessarily all hospital-acquired infections (i.e. the infection may or may not have been the primary diagnosis requiring admission to hospital), all-cause mortality rates are confounded – particularly over longer time periods. They are poorly correlated with the effect of treatment of the original infection, especially as time progresses, due to other determinants of mortality (such as new/secondary infections, any background conditions, among other factors). Similarly, very immediate mortality rates are likely to be poorly correlated with antimicrobial treatment (which needs approximately 48 hours to take effect and have an impact on the infection) and are thus more likely to be determined by pre-existing co-morbidities. It is also worth remembering that dual- or triple-therapy with antimicrobials will lead to a multiplication of side effects, which is particularly important as these are extremely fragile patients. Many of these antimicrobials also have Gram-positive and Gram-negative effects, which more greatly impact the patient’s microbiome, leading to further damaging effects on the patient’s reserve (unlike cefiderocol, which only acts on aerobic Gram-negative pathogens). |
| **Subgroups to be considered** | A selection of high-value clinical scenarios (unspecified) | Relevant subgroups include a selection of high value clinical scenarios, in line with those stated in the EEPRU protocol document (see Section 1.3.2).90 | We understand the need for a choice of subgroups but the value of cefiderocol additionally lies beyond these subgroups in line with its indication and high *in vitro* activity across a range of aerobic Gram-negative pathogens (see Section 1.3.3) which includes all WHO critical priority pathogens and *S. maltophilia*, which is also of particular concern in the UK.  In the microbiology-directed treatment setting high clinical value is expected to also result from including cefiderocol as an option for patients with pathogens producing KPC or OXA carbapenemases, and carbapenem-resistant *Pseudomonas aeruginosa*. This should lead to diversity value by reducing the overuse of the limited available options currently available.  In the risk-based empiric setting we believe the current EEPRU approach has taken an unrealistically focussed approach to defining the population – patients suspected as having an infection caused by an MBL-producing pathogen. Whilst there are risk factors for carbapenem resistance, these factors may not be specific to certain resistance mechanisms. For example, international travel and immunosuppression are risk factors for unspecified carbapenem resistance,91 rather than for MBLs or SBLs specifically. Therefore, the empiric HVCS for cefiderocol might be better described in terms of a suspicion of carbapenem resistance in general, rather than suspicion of MBL specifically. |
| **Special considerations including issues related to equity or equality** | Guidance will include consideration of the optimal stewardship scenarios. | NA | NA |
| **Key:** EMA, European Medicines Agency;HCRU, healthcare resource unit; ICU, intensive care unit; MBL, metallo-β-lactamase; NA, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PD, pharmacodynamics; PK, pharmacokinetics; SBL, serine β-lactamase. | | | |

### High-value clinical scenarios selected by EEPRU

As discussed in the EEPRU protocol90, two HVCSs have been identified to allow EEPRU to focus their quantitative assessment of cefiderocol within these areas, while providing a narrative synthesis beyond these scenarios. It is worth noting that the HVCSs proposed by EEPRU are very unlikely to cover the majority of the population for which cefiderocol is indicated and where it is expected to be used, with a number of other patient populations for which cefiderocol will be equally as valuable. The two HVCSs identified by EEPRU are:

* **A confirmed setting, where treatment is microbiology-directed (‘microbiology-directed setting’:**
* Complicated urinary tract infections (cUTI) or hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) with suspected or confirmed metallo-β-lactamase mechanisms of resistance (*Enterobacterales* and *Pseudomonas* spp.) of the following subtypes: NDM, VIM, and IMP
* **A suspected setting, where treatment is risk-based and empiric (‘risk-based empiric setting’):**
* HAP/VAP suspected to be caused by metallo-β-lactamase producing *Enterobacterales* or *Pseudomonas* spp. (NDM, VIM, IMP), which may include a nested analysis of patients who progress to blood stream infections (BSI)

### Other high-value clinical scenarios

Cefiderocol should be considered to offer high value wherever there are limited treatment options. The range of clinical scenarios in which this is the case can be determined primarily by comparing cefiderocol’s high levels of *in vitro* activity across the range of aerobic Gram-negative pathogens with different resistance mechanisms (i.e. where it has activity, and others do not). Other factors, such as *in vivo* effectiveness (i.e. influenced by PK/PD profiles), tolerability, and supply, can also determine when treatment options are limited. These scenarios will be of high value to both patients and clinicians. These scenarios will include:

* In the microbiology-directed treatment setting:
* Other species of pathogen (not only *Enterobacterales* and *Pseudomonas*) that have metallo-β-lactamase resistance (e.g. *Stenotrophomonas*, *Acinetobacter*)
* Other infection sites (not only cUTI or HAP/VAP) that have metallo-β-lactamase infections
* Infections with any suspected or confirmed carbapenem resistance (not just metallo-β-lactamase), 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
* In the risk-based empiric setting:
* As above: other species of metallo-β-lactamase pathogen
* Other infection sites (not only HAP/VAP) that would be considered to make the patient’s condition ‘critical’ (e.g. BSI/sepsis)

Other factors (not only infection site) that would be considered to make the patient’s condition ‘critical’ (e.g. age, immunosuppression)

Whilst there may currently be more treatment options for this broader group of infection types in the microbiology-directed setting (compared to metallo-β-lactamases in the HVCSs), the range of efficacious options available to clinicians remains narrow (and will narrow further as resistance develops). At the individual patient/infection case level, options may be further constrained by other factors, such as tolerability concerns and interactions with other medicines, or supply issues. The possible presence of multiple resistance mechanisms can also be a factor; for example, a *Pseudomonas* infection that is MDR upon panel testing may be caused by metallo-β-lactamase and/or serine β-lactamase mechanisms, and certain options that could be effective against serine β-lactamase would not be effective against metallo-β-lactamases, and vice versa, whereas the broad coverage of cefiderocol can overcome this problem.

In the empiric setting, the risk-factors presenting for certain patients may result in suspicion of unspecified carbapenem resistance rather than any particular resistance mechanism. Furthermore, panel testing may suggest that one or more of these resistance mechanisms is present, without indicating specifically that it is likely to be metallo-β-lactamase. In both of these scenarios, the broad coverage of all aerobic Gram-negative pathogen/resistance types provided by cefiderocol represents an advantage over the other limited treatment options (such as ceftazidime/avibactam, as suggested in the EEPRU protocol)90 (Section 2.3.1.2).

A UK clinical expert also suggested that there were a number of HVCSs, outside of those specified by EEPRU, that would be important to consider for UK clinical practice. These included patients with *A.* *baumannii* or *S.* *maltophilia* infections, as the only alternative treatment for these patients would be colistin or co-trimaxazole; this is highlighted in Table 2, which shows the coverage of current antimicrobials and demonstrates the key areas where existing treatments aren’t optimal. Other key HVCSs that were presented as being particularly relevant in UK clinical practice were patients who had recently had renal replacement therapy (RRT; noting that often patients who have had RRT have other comorbidities such as obesity or diabetes) and haematology oncology patients, such as those who have recently received bone marrow transplants or intense chemotherapy for the treatment of Hodgkin’s lymphoma or non-Hodgkin’s lymphoma. If an effective treatment is given at the first-line, these haematology oncology patients would likely not have further complications. However, as they progress, they would likely develop other, more complex issues with more resistant pathogens.

In the microbiology-directed treatment setting, a further possibility is the use of ‘cycling’ or ‘mixing’ strategies (e.g. use of cefiderocol alongside other agents such as ceftazidime/avibactam for serine β-lactamase infections) to increase overall antimicrobial heterogeneity and reduce selection pressure for bacteria to develop resistance to any single antimicrobial.

|  |
| --- |
| **Key consideration for economic model:** It is important to remember that the true value of cefiderocol lies in the entire licensed patient population that includes patients outside of the HVCSs, due to high *in vitro* activity across aerobic Gram-negative pathogens – particularly in pathogens where there is virtually no active alternative (e.g. CRAB, *Stenotrophomonas*, etc.), and when treating critically ill patients with suspected aerobic Gram-negative carbapenem-resistant infection who are at risk of rapid clinical deterioration and death and cannot afford to wait for antibiogram test results. |

# Evidence to support positioning and assessment of clinical effectiveness

|  |
| --- |
| **Summary**  Unlike other therapeutic areas, the evaluation of the effectiveness of an antimicrobial relies on the combined consideration of *in vitro*, pharmacokinetic/pharmacodynamic (PK/PD) and clinical data   * The most important factors to consider with an antimicrobial are the pathogen’s susceptibility to the drug (demonstrated by *in vitro* studies) and the drug’s concentration at the infection site regardless of its location (demonstrated by *in vivo* PK/PD studies) * Clinical studies provide primarily supportive safety and efficacy evidence to the pivotal *in vitro* and PK/PD data * In the context of AMR, the standard clinical trial approach aimed at demonstrating superiority over existing treatments is neither feasible nor appropriate   ***In vitro* studies (Section 2.3.1)**  Cefiderocol has demonstrated high levels of *in vitro* activity against aerobic Gram-negative isolates and carbapenem-resistant pathogens, including all of the WHO priority pathogens and *Stenotrophomonas maltophilia* (Section 2.3.1.2)  Cefiderocol demonstrates higher levels of activity in aerobic Gram-negative isolates and provides a wider coverage in carbapenem-resistant pathogens than its comparators (Section 2.3.1.2)   * + Therefore, cefiderocol provides value to patients across a wide range of aerobic Gram-negative infections, in line with its licensed indication   Cefiderocol has the potential to reduce the time to effective therapy for patients, thereby improving outcomes, due to its wide aerobic Gram-negative coverage  **PK/PD studies (Section 2.3.2)**  As for other cephalosporins, the amount of time in which free or non-protein bound antimicrobial concentrations exceed the MIC of the organism (%fT > MIC) in the relevant infection site is the best predictor of efficacy for cefiderocol   * A dosing regimen delivering 75% T > MIC succeeded in reducing the number of viable bacterial cells in both murine thigh infection and murine lung infection by at least 90%, regardless of the isolate used to induce the infection (*E. coli*, *K. pneumoniae*, *P. aeruginosa*, *A. baumannii* or *S. maltophilia*). This is in comparison to colistin, which is known to have poor penetration in the lung108, 109   Probability of target attainment (PTA) for 75% fT > MIC was above 97% for an MIC of 4 mg/L regardless of the site of infection or the renal function   * The dosing regimen therefore ensures sufficient drug exposure to maximize the efficacy of cefiderocol, which was supported by cefiderocol exposure in clinical trials152   ***In vivo* data (Section 2.3.3)**  Cefiderocol demonstrated potent efficacy against MDR and carbapenem-resistant strains, including carbapenemase- and ESBL-producers, such as NDM-1, KPC, IMP, VIM and OXA where reference substances such as carbapenem and β-lactam/β-lactamase inhibitor combinations were less effective153  Cefiderocol was also shown to be an effective alternative treatment option for *S. maltophilia* infections (which are intrinsically metallo-β-lactamase-producing pathogens) in the lower respiratory tract, particularly for strains resistant to empiric antimicrobials154  **Clinical data (Section 2.3.4 and Section 2.4):**  Cefiderocol demonstrated similar rates of clinical cure and microbiological eradication to best available therapy (BAT) across different infection sites (cUTI, hospital-acquired pneumonia [HAP]/ventilator-associated pneumonia [VAP] or BSI/sepsis) as well as different pathogens (carbapenem-resistant *A. baumannii*, carbapenem-resistant *K. pneumoniae* or carbapenem-resistant *P. aeruginosa*)   * Clinical and microbiological efficacy was higher for patients treated with cefiderocol compared with patients treated with BAT for cUTI, all metallo-β-lactamase-producing pathogens and carbapenem-resistant *Enterobacteriaceae*, with improvements in mortality for these patients   Overall, the cefiderocol group had a similar adverse event and tolerability profile to current therapy, with no significant differences compared with BAT, with the exception of renal-related toxicity   * No renal-related toxicity was reported for patients treated with cefiderocol compared with 10% of patients treated with BAT (with this being the cause of death for one patient)   In patients with infections caused by metallo-β-lactamase-producing aerobic Gram-negative pathogens, cefiderocol demonstrated numerical differences in terms of both clinical cure and microbiological responses compared with BAT at test of cure (TOC) and mortaltiy  Cefiderocol has demonstrated consistently high efficacy across all aerobic Gram-negative pathogens including all key carbapenem-resistant pathogens and WHO priority pathogens, with similar (numerically higher) clinical cure and microbiological eradication rates at TOC  In real-world clinical data from compassionate use, cefiderocol was shown to successfully treat severely ill patients infected with carbapenem-resistant aerobic Gram-negative pathogens when no other treatment options were available, regardless of pathogen or infection site  **Elements of value beyond those typical of medicines assessed by NICE**  As a novel antimicrobial, the introduction of cefiderocol offers aspects of clinical value beyond those typically offered by medicines conventionally assessed by NICE.  **Enablement** Patients with MDR bacterial infections may not be able to receive certain surgical or medical procedures that they require, such as chemotherapy. By addressing infection better than alternative options, cefiderocol will enable patients to subsequently receive the additional healthcare interventions they require and/or make the conduct of those interventions more straightforward and successful. Additionally, cefiderocol will help to address infections that occur following required medical procedures. Were pathogens that are resistant to all available antimicrobials to become common, then numerous interventions might be considered unviable due to the risk of a previously addressable infection.  **Diversity** Having a diverse range of available antimicrobials helps to reduce the rate at which pathogens develop resistance to specific antimicrobials – preserving their efficacy. When used within carbapenem-resistant infections, cefiderocol will help to diversify the available treatment options (such as KPC or other carbapenem-resistant mechanisms of resistance), reducing resistance pressure on current antimicrobials and therefore helping preserve their efficacy for longer.  **Transmission** Resistant pathogens not only have the potential to affect the individual currently suffering with the infection but also others, through onward transmission. Research indicates that the longer patients remain in hospital, the higher their risk of contracting resistant pathogens. Cefiderocol reduces the onward transmission of resistant pathogens by effectively treating them earlier – benefitting other individual patients and minimizing the risk of an outbreak. Additionally, effective treatment with cefiderocol might reduce the population prevalence of specific pathogens over time, relative to the scenario in which it was not available.  **Insurance** The reports by O’Neill *et al.* and the WHO describe future catastrophic scenarios where AMR has developed to levels that would be devastating for a well-functioning health system. This could occur steadily over time or as a result of a catastrophic event whereby MDR is so widespread that cefiderocol is the only effective antimicrobial for a number of patient populations. Cefiderocol will have value in mitigating the damage that would result from this otherwise high-consequence situation. |

## Identification and selection of relevant studies to support positioning and assessment of clinical effectiveness

Unlike other therapeutic areas, the evaluation of the effectiveness of an antimicrobial relies on the combined consideration of *in vitro*, pharmacokinetic/pharmacodynamic (PK/PD) and clinical data. The most important factors to consider with an antimicrobial are the pathogen’s susceptibility to the drug (demonstrated by *in vitro* and susceptibility studies) and the drug’s exposure to the infection site regardless of its location (demonstrated by *in vivo* PK/PD studies). *In vitro* data are therefore considered the pivotal evidence to support the granted regulatory approval of antimicrobials9, including for the benefit–risk assessment performed by the EMA.6, 7 *In vitro* data also form a core part of the information used by physicians (antibiograms) when making everyday treatment decisions regarding patients with nosocomial infections.

Unlike many investigational drugs, due to the high mortality rate of systemic bacterial infections if not adequately treated, efficacy of new antimicrobials cannot ethically be compared against placebo. Therefore, Phase III double-blinded, randomized controlled trials use an active comparator, and only patients with infections caused by pathogens that are equally susceptible to treatments in both arms can be enrolled. This limits the trial’s value in assessing the intervention’s relative efficacy in highly resistant populations, where they are expected to be used in clinical practice, aligned with stewardship principles. Also, due to the large amount of heterogeneity in terms of infection sites, causal pathogens, mechanisms of resistance, and underlying diseases, it would not be practically possible to undertake a comparative study that was large enough to balance all of these confounding factors. Thus, in the context of AMR, the standard clinical trial approach aimed at demonstrating superiority over existing treatments is not feasible. *In vitro* susceptibility data (where this relative efficacy can be ethically assessed) are of particular importance in the assessment of the effectiveness of antimicrobials, as are PK/PD data (which can confirm the bioavailability of an antimicrobial at effective concentrations in the different infection sites), as these provide the most effective way of establishing relative effectiveness between different antimicrobials at a population level. Consequently, clinical studies should be used only to provide supportive efficacy and safety evidence to complement the pivotal *in vitro* data.

## List of relevant evidence to support positioning and assessment of clinical effectiveness

The key evidence to support the effectiveness and positioning of cefiderocol comes from the *in vitro* susceptibility studies, supported by the PK/PD data. This includes the following sources presented in Table 7.

Table 7: Sources of evidence for cefiderocol by population

| Type of evidence | Microbiologically-directed treatment setting | Risk-based, empiric treatment setting |
| --- | --- | --- |
| *In vitro* susceptibility studies | SIDERO-WT (2014-2019)  SIDERO-CR  SENTRY (2020)  UK-specific independent *in vitro* susceptibility validation studies  Several other independent *in vitro* susceptibility validation studies conducted across a number of other countries, including Ireland, Italy, Germany, Greece, Spain, Switzerland, France and the US | |
| PK/PD data | A population pharmacokinetic (PK) analysis was performed using a total of 3,427 plasma concentration data from:  Single ascending dose (SAD)/multiple ascending dose (MAD) study (1203R2111)  PK according to renal function study (1222R2113)  Phase II APEKS-cUTI study (1409R2121)  Phase III APEKS-NP study (1615R2132)  Phase III CREDIBLE-CR study (1424R2131) | |
| Clinical efficacy data | CREDIBLE-CR (Phase III, open-label, randomized, parallel-group, active-controlled non-inferential/descriptive clinical study in patients with serious infections caused by carbapenem-resistant aerobic Gram-negative pathogens for HAP/VAP/HCAP, cUTI and BSI/sepsis) | NA |
| Real-world, observational data from the cefiderocol compassionate use programme (case studies) | |
| Safety and tolerability data | Pooled analysis of all patients treated with cefiderocol across the clinical trial programme (CREDIBLE-CR, APEKS-NP and APEKS-cUTI) | |

As discussed in Section 2.1, clinical trial data are limited in their ability to assess the effectiveness of antimicrobials. Despite facing these same limitations, the CREDIBLE-CR study does provide evidence that is reflective of the microbiology-directed treatment setting, and therefore can be considered as supporting evidence to the *in vitro* data, alongside real-world, observational data from the cefiderocol compassionate use programme (case studies).

Additional clinical evidence is available from the APEK-cUTI and APEKS-NP studies. However, overall, these studies are not reflective of the risk-based empiric setting, nor are they reflective of the microbiology-directed treatment setting, as the patients enrolled in these studies were carbapenem susceptible patients. Therefore, as these studies do not present evidence in a relevant patient population, we do not believe that they should be considered here. A summary of the key details and results of these studies are presented in Appendix K for completeness.

Therefore, the *in vitro* data for cefiderocol is the only evidence available for the risk-based empiric setting and must be used to inform decision making for this population. The *in vitro* data should also be considered the primary source of evidence for the microbiology-directed treatment setting, although clinical data from CREDIBLE-CR can also be used as supporting evidence in this setting.

As CREDIBLE-CR is the only clinical study that is relevant to this submission, and there was significant heterogeneity between the cefiderocol studies, it was not appropriate to consider a meta-analysis of these studies. However, as the incidence of adverse effects for patients treated with cefiderocol is not affected by the population that the patient belongs to, a pooled analysis of safety was performed using data from CREDIBLE-CR, APEKS-cUTI, APEKS-NP and compassionate use cases of cefiderocol. As the largest pool of data for patients treated with cefiderocol, these should be considered the most robust data for the safety profile of cefiderocol. A summary of this analysis is presented in Section 2.4.1 and Appendix E.4.

As discussed in Section 2.1 and earlier in this section, clinical trial data are extremely limited in their ability to assess the effectiveness of antimicrobials in the target carbapenem-resistant population, and particularly in the risk-based empiric setting. As a result of this, and the wide range of potential pathogens and infection sites, there is often significant heterogeneity between clinical trials of antimicrobials, in terms of study design, included patient populations, included pathogens, included infection sites, outcome definitions and timepoints for assessments. Therefore, indirect treatment comparisons (ITCs) are not robust in this setting, and results of any analyses would be difficult (if not impossible) to accurately interpret. Indeed, in many cases, ITCs would not be possible due to the significant levels of heterogeneity and the lack of appropriate links between interventions, which is the case for CREDIBLE-CR. For completeness, a brief discussion of the ITCs considered and undertaken for cefiderocol are presented in Appendix K.

## Evidence to support clinical effectiveness

### *In vitro* evidence

#### Methodology of the in vitro evidence

Table 8 presents a summary of the methods SIDERO *in vitro* studies.

Table 8: Summary of the SIDERO surveillance studies

|  |  |
| --- | --- |
| SIDERO-WT *in vitro* studies | |
| Scope | Systematic surveillance studies of cefiderocol *in vitro* activity compared to key antimicrobials against a total of 30,459 aerobic Gram-negative isolates collecting isolates from three consecutive 12-month periods from 2014 to 2015 (SIDERO-WT-2014), from 2015 to 2016 (SIDERO-WT-2015), and from 2016 to 2017 (SIDERO-WT-2016) as well as cumulative. SIDERO studies have continue to include more isolates every year. To date there are 38,288 samples tested (analysis pending). Between 2013 and 2018, SIDERO-WT and SIDERO-Proteeae European isolates were used in another analysis, evaluating the activity of cefiderocol and comparators against 20,911 isolates (*Enterobacterales* and non-fermenters) with different infection sites. |
| Geographic location | North America and Europe |
| Comparator treatments | Ceftolozane/tazobactam, ceftazidime/avibactam, cefepime, ciprofloxacin, colistin, and meropenem |
| Included pathogens | Carbapenem susceptible and carbapenem non-susceptible pathogens: *Enterobacteriaceae* (including but not limited to *Escherichia coli*, *K.* *pneumoniae*, *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp.), non-fermenters (including but not limited *P.* *aeruginosa*, *A.* *baumannii*, *S.* *maltophilia*, *B.* *cepacia*), and *Proteeae* (*M.* *morgannii*, *P.* *vulgaris*, *P.* *mirabilis*). |
| SIDERO-CR *in vitro* studies | |
| Scope | *In vitro* study from 2014–2016 evaluating the activity of cefiderocol against a total of 1,873 MDR and CarbNS isolates Gram-negative Bacilli. SIDERO-CR 2014/2016 European isolates were used in another analysis, evaluating the activity of cefiderocol and comparators against 457 CarbNS *Enterobacterales* isolates and 413 MDR-Gram-negative bacteria. |
| Geographic location | World-wide (Europe, North America, Latin America, Asia, South Pacific, Africa, and the Middle East) |
| Comparator treatments | Ceftolozane/tazobactam, ceftazidime/avibactam, cefepime, ciprofloxacin, colistin, and meropenem |
| Included pathogens | CarbNS *Enterobacteriaceae*, MDR *A.* *baumannii*, MDR *P.* *aeruginosa*, *S.* *maltophilia* and *B.* *cepacia*. The test isolates of MDR non-fermenters were defined to be resistant to meropenem, amikacin and ciprofloxacin. |
| **Key:** CarbNS, carbapenem-non-susceptible.  **Sources:** Longshaw *et al.*, 2019155; Longshaw *et al.*, 2020156; Hackel *et al.*, 2017157; Hackel *et al.*, 2018.158 | |

As discussed in Section 2.1 and Section 2.2 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.

#### Results from the in vitro evidence

|  |
| --- |
| **Key consideration for economic model:** *In vitro* evidence can be analysed after the fact to establish whether or not the pathogen was in fact susceptible to each potential treatment, as is done in clinical practice to select the optimal treatment for each patient. *In vitro* studies are therefore both in the correct patient populations and are powered to detect differences between prospective treatments.  There are multiple *in vitro* studies with cefiderocol, including those looking at UK isolates only. However, SIDERO-WT and SIDERO-CR represent the largest isolate sample and therefore the most robust set of *in vitro* data, also including data on rare pathogens and key resistance mechanisms such as metallo-β-lactamase-producing pathogens, of particular relevance to the HVCSs.  Overall, the data are consistent across other surveillance studies, demonstrating cefiderocol bactericidal activity in carbapenem-resistant isolates, including those from metallo-β-lactamase-producing pathogens. Other relevant sources of data are presented in more detail in Appendix C.6.  Below are the key points surrounding the use of *in vitro* evidence in the context of this NICE appraisal and cost-effectiveness modelling (See Sections 2.3.1 and 3.2.1.1):   * *In vitro* data can be used to power a cost-effectiveness model (Section 3.2.1.1) * The use of *in vitro* data avoids many of the issues with using clinical trial data (Section 2.1) * *In vitro* data are the most robust way to compare activity across medicines, which is particularly relevant in the risk-based empiric patient population (Section 2.1) * *In vitro* data are routinely used to inform clinical practice, risk profiling and decision making (Section 1.1.1.3 and Section 1.1.2.1) * *In vitro* data permit more analysis of more targeted populations, by pathogen and infection site, allowing a closer proxy to the HVCSs defined by NICE and EEPRU (Section 3.2.1.1) |

Currently, there is incongruity in existing cefiderocol breakpoints proposed by EUCAST, the Clinical and Laboratory Standards Institute (CLSI) and the FDA. For example, for *Enterobacterales*, EUCAST: susceptible ≤2mg/L, resistant >2mg/L; CLSI: susceptible ≤4mg/L, intermediate 8mg/L, resistant >16mg/L; and FDA: susceptible ≤2mg/L, intermediate 4 mg/L, resistant >8mg/L depending upon which pieces of data different groups chose to consider. Practically, this means that an *Enterobacterales* isolate with an MIC of 4 mg/L that is reported as resistant by EUCAST breakpoints would be considered fully susceptible to cefiderocol by CLSI and the FDA, where the breakpoint for resistance is 16 mg/L.

In addition, the removal of the intermediate category and the introduction of the Area of Technical Uncertainty (ATU) by EUCAST has an impact on interpreting levels of resistance. Breakpoints may be revised as surveillance data develops, and Shionogi is working with EUCAST and CLSI to review the breakpoints as more surveillance and clinical data become available.

##### SIDERO-WT study results

In the SIDERO-WT longitudinal surveillance studies, cefiderocol demonstrated *in vitro* activity against the majority of aerobic Gram-negative clinical isolates at an MIC of < 4 μg/mL (only exception was *B. multivorans* with an MIC90 of 32 μg/mL) with a higher breadth of coverage than other antimicrobials included in these studies including ceftazidime-avibactam and colistin. The SIDERO-WT programme included five multinational surveillance studies testing a total of 9,205 aerobic Gram-negative bacterial clinical isolates in 2014–2015, 8,954 in 2015–2016, 10,470 in 2016–2017, 7,829 in 2017–2018 and 9,327 in 2018–2019. To date, there are 45,785 samples tested (analysis of final year pending). At the moment, the results for 30,459 aerobic Gram-negative isolates collected between 2014 and 2017 have been published and are presented within this submission. An analysis of these data, using CLSI breakpoints, is presented in Appendix C.4.

An additional analysis of the data for the EU isolates was performed based on EUCAST breakpoints for cefiderocol. A total of 20,909 isolates were included, of which 4,068 were carbapenem non-susceptible.

Overall, 97.49% of all isolates were sensitive to cefiderocol, compared with 80.41% for ceftolozane/tazobactam, 87.68% for ceftazidime/avibactam and 80.41 for colistin. Of significant note for this appraisal and when considering comparators to cefiderocol, when carbapenem non-susceptible isolates were analysed, 92.26% were sensitive to cefiderocol, compared with only 25.57% for ceftolozane/tazobactam, 40.39% for ceftazidime/avibactam and 79.82 for colistin. Additional details on % isolates sensitive to the different drugs by pathogen are presented in the table below.

With regards to *in vitro* activity across different pathogens, cefiderocol demonstrated potent activity against *Enterobacteriaceae* (97.87%) and non-fermenters including *A. baumannii*, *P. aeruginosa*, *S. maltophilia* and *B. cepacia* (96.73%), higher than that observed for other available treatments.

Table 9: Analysis of cefiderocol in SIDERO-WT EU isolates using EUCAST breakpoints

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Cefiderocol  S ≤ 2 mg/L | | All infection sites | | | | | |
| CarbNS | | | Total isolates | | |
| n | N | % | n | N | % |
| *Enterobacterales* | *E.* *coli* | 14 | 18 | 77.78 | 3,504 | 3,527 | 99.35 |
| *Klebsiella* | 335 | 450 | 74.44 | 4,634 | 4,823 | 96.08 |
| Other *Enterobacterales* | 81 | 100 | 81.00 | 5,492 | 5,577 | 98.48 |
| All *Enterobacterales* | 430 | 568 | 75.70 | 13,630 | 13,927 | 97.87 |
| Non-fermenters | *Pseudomonas* | 853 | 877 | 97.26 | 3,348 | 3,377 | 99.14 |
| *Acinetobacter* | 1,556 | 1,712 | 90.89 | 2,443 | 2,645 | 92.36 |
| *Stenotrophomonas* | 803 | 806 | 99.63 | 816 | 819 | 99.63 |
| Other non-fermenters | 100 | 104 | 96.15 | 135 | 140 | 96.43 |
| All non- *Enterobacterales* | 3,323 | 3,500 | 94.94 | 6,754 | 6,982 | 96.73 |
| Total pathogens | | 3,753 | 4,068 | 92.26 | 20,384 | 20,909 | 97.49 |
| **Key:** CarbNS, carbapenem-non-susceptible.  **Source:** Data on file. | | | | | | | |

Table 10: Analysis of comparators in SIDERO-WT EU isolates using EUCAST breakpoints

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Ceftolozane/tazobactam  S ≤ 2 mg/L *Enterobacterales;* S ≤ 2 mg/L *Pseudomonas;* no breakpoint *Acinetobacter* | | All infection sites | | | | | |
| CarbNS | | | Total isolates | | |
| n | N | % | n | N | % |
| *Enterobacterales* | *E. coli* | 3 | 18 | 16.67 | 3,439 | 3,527 | 95.50 |
| *Klebsiella* | 16 | 450 | 3.56 | 3,945 | 4,823 | 81.80 |
| Other *Enterobacterales* | 1 | 100 | 1.00 | 5,055 | 5,577 | 90.64 |
| All *Enterobacterales* | 30 | 568 | 5.28 | 12,449 | 13,927 | 89.39 |
| Non-fermenters | *Pseudomonas* | 583 | 877 | 66.40 | 3,059 | 3,377 | 90.58 |
| *Acinetobacter* | 99 | 1,712 | 5.78 | 930 | 2,645 | 35.16 |
| *Stenotrophomonas* | 260 | 806 | 32.26 | 270 | 819 | 32.97 |
| Other non-fermenters | 68 | 104 | 65.38 | 104 | 140 | 74.29 |
| All non- *Enterobacterales* | 1,010 | 3,500 | 28.86 | 4,363 | 6,982 | 62.49 |
| Total pathogens | | 1,040 | 4,068 | 25.57 | 16,812 | 20,909 | 80.41 |
| Ceftazidime/avibactam  S ≤ 8 mg/L *Enterobacterales;* S ≤ 8 mg/L *Pseudomonas;* no breakpoint *Acinetobacter* | | All infection sites | | | | | |
| CarbNS | | | Total isolates | | |
| n | N | % | n | N | % |
| *Enterobacterales* | *E.* *coli* | 9 | 18 | 50.00 | 3,512 | 3,527 | 99.57 |
| *Klebsiella* | 356 | 450 | 79.11 | 4,724 | 4,823 | 97.95 |
| Other *Enterobacterales* | 41 | 100 | 41.00 | 5,507 | 5,577 | 98.74 |
| All *Enterobacterales* | 406 | 568 | 71.48 | 13,743 | 13,927 | 98.68 |
| Non-fermenters | *Pseudomonas* | 586 | 877 | 66.74 | 3,069 | 3,377 | 90.88 |
| *Acinetobacter* | 236 | 1,712 | 13.79 | 1,067 | 2,645 | 40.34 |
| *Stenotrophomonas* | 320 | 806 | 39.70 | 330 | 819 | 40.29 |
| Other non-fermenters | 95 | 104 | 91.35 | 131 | 140 | 93.57 |
| All non- *Enterobacterales* | 1,237 | 3,500 | 35.34 | 4,590 | 6,982 | 65.74 |
| Total pathogens | | 1,643 | 4,068 | 40.39 | 18,333 | 20,909 | 87.68 |
| Colistin  S ≤ 2 mg/L *Enterobacterales;* S ≤ 2 mg/L *Pseudomonas;* ≤ 2 mg/L *Acinetobacter* | | All infection sites | | | | | |
| CarbNS | | | Total isolates | | |
| n | N | % | n | N | % |
| *Enterobacterales* | *E.* *coli* | 17 | 18 | 94.44 | 3,510 | 3,527 | 99.52 |
| *Klebsiella* | 311 | 450 | 69.11 | 4,606 | 4,823 | 95.50 |
| Other *Enterobacterales* | 70 | 100 | 70.00 | 2,436 | 5,577 | 43.68 |
| All *Enterobacterales* | 398 | 568 | 70.07 | 10,552 | 13,927 | 75.77 |
| Non-fermenters | *Pseudomonas* | 860 | 877 | 97.95 | 3,339 | 3,377 | 98.87 |
| *Acinetobacter* | 1,445 | 1,712 | 84.40 | 2,366 | 2,645 | 89.45 |
| *Stenotrophomonas* | 540 | 806 | 67.00 | 550 | 819 | 67.16 |
| Other non-fermenters | 4 | 104 | 3.85 | 5 | 140 | 3.57 |
| All non- *Enterobacterales* | 2,849 | 3,500 | 81.40 | 6,260 | 6,982 | 89.66 |
| Total pathogens | | 3,247 | 4,068 | 79.82 | 16,812 | 20,909 | 80.41 |
| **Key:** CarbNS, carbapenem-non-susceptible. | | | | | | | |

##### SIDERO-CR study results

The SIDERO-CR-2014-2016 study including carbapenem-resistant *Enterobacteriaceae* and carbapenem-resistant non-fermenters demonstrated the potent *in vitro* activity of cefiderocol with an MIC90 ranging between 0.25 and 8 μg/mL. For MIC of ≤ 4 μg/mL, cefiderocol showed activity against 96.2% of these pathogens and demonstrated higher *in vitro* activity than other available treatments (Table 11). Cefiderocol suppressed the growth of 97.0% of carbapenem-resistant *Enterobacteriaceae*, 99.2% of MDR *P. aeruginosa*, 90.9% of MDR *A. baumannii* and 100% of *S. maltophilia* (Table 11).

Table 11: *In vitro* activity data for all tested clinical strains of cefiderocol versus ceftazidime-avibactam, ceftolozane-tazobactam, and colistin (SIDERO-CR 2014–2016)

| Organism | Cefiderocola | Ceftazidime/ avibactama | Ceftolozane/ tazobactama | Colistina |
| --- | --- | --- | --- | --- |
| CarbNSb *Enterobacteriaceae* (N = 1022) | 97.0 | 77.0 | 1.7 | 77.8c |
| MDRb *P. aeruginosa* (N = 262) | 99.2 | 36.3 | 24.1 | 99.6 |
| MDRb *A. baumannii* (N = 368) | 90.9 | 18d | 3.6d | 94.6 |
| *S. maltophilia* (N = 217) | 100 | 56.9d | 37.6d | 67d |
| **Key:** CarbNS, carbapenem-non-susceptible; MDR, multi drug resistant.  **Notes:** NA, CLSI, EUCAST, and FDA MIC breakpoints were not available for the agent.  a, ratios (%) susceptible strains were calculated by using the following MIC criteria: cefiderocol MIC ≤ 4 μg/mL, ceftazidime/avibactam MIC ≤ 8 μg/mL, ceftolozane/tazobactam MIC ≤ 2 μg/mL for *Enterobacteriaceae*, ≤ 4 μg/mL for non-fermenters, colistin MIC ≤ 2 μg/mL; b, carbapenem-resistant strain was defined as meropenem MIC ≥ 2 μg/mL for *Enterobacteriaceae*, ≥ 4 μg/mL for non-fermenters; c, Includes 39 *Serratia* species that are intrinsically resistant to colistin; d, Data on file.  **Source:** Hackel *et al.*, 2018158; Yamano *et al.*, 2019159; Data on file. | | | | |

In addition to demonstrating high activity of cefiderocol against different drug-resistant species, the SIDERO-CR study showed antimicrobial activity against isolates stratified per resistance determinants detected through the polymerase chain reaction (PCR) method. For European isolates from the SIDERO-CR-2014–2016 study, cefiderocol demonstrated potent activity against a wide variety of carbapenem-non-susceptible and MDR-Gram-negative bacteria harbouring a range of metallo-β-lactamases and serine β-lactamases, even when considering the more stringent EUCAST breakpoints valid in Europe (MIC of ≤ 2 μg/mL).

The most common subclasses of carbapenemase were KPC for *Enterobacterales*, VIM for *P. aeruginosa*, and OXA-23-like and OXA-24/40-like for *A. baumannii.*156 *Enterobacterales* OXA-48-like producers showed the highest susceptibility to cefiderocol (88.2%), followed by KPC (83.6%), VIM (79.0%), and NDM producers (51.4%).156 For *P. aeruginosa*, GES, VIM, and NDM producers had a 100% susceptibility to cefiderocol.156 As for *A. baumannii*, the greatest susceptibility to cefiderocol was seen in GES and OXA-58 producers (100%), followed by OXA-23-like (96.3%), OXA-24/40-like (93.2%) and NDM producers (66.7%).156 Carbapenemase profiles varied across European countries.156

Cefiderocol exhibited *in vitro* activity against a variety of carbapenem-non-susceptible aerobic Gram-negative bacteria in SIDERO-CR-2014–2016 European isolates. Overall, 772/870 (88.7%) had a cefiderocol MIC of ≤2mg/L; 547/634 (86.3%) of *Enterobacterales* and *P.* *aeruginosa* isolates were susceptible to cefiderocol and 224/236 (94.9%) of *A.* *baumannii* isolates had a cefiderocol MIC of ≤2mg/L.

Of carbapenem-non-susceptible *Enterobacterales*, 81.6% were cefiderocol susceptible (MIC90≤4mg/L) (Table 12). The proportion of all *Enterobacterales* isolates susceptible to comparators was similar for colistin (76.4% susceptible) and ceftazidime/avibactam (76.6% susceptible). Of *K.* *pneumoniae* isolates (n=332), 82.8% were susceptible to cefiderocol, while 71.7% were susceptible to colistin and 88.9% to ceftazidime/avibactam.

Table 12: *In vitro* activity of cefiderocol and comparators against CarbNS and MDR aerobic Gram-negative bacteria with ≥ 10 European isolates (SIDERO-CR 2014–2016)

| Species/carbapenemase (n) | Antimicrobial | MIC interpretation  % susceptible |
| --- | --- | --- |
| *Enterobacterales* (457) | Cefiderocol | 81.6 |
| Cefepime | 0.9 |
| Ceftazidime/avibactam | 76.6 |
| Ceftolozane/tazobactam | 0.4 |
| Ciprofloxacin | 4.2 |
| Colistin | 76.4 |
| Meropenem | 4.2 |
| *P.* *aeruginosa* (177) | Cefiderocol | 98.3 |
| Cefepime | 13.6 |
| Ceftazidime/avibactam | 34.5 |
| Ceftolozane/tazobactam | 22.6 |
| Ciprofloxacin | 4.2 |
| Colistin | 76.4 |
| Meropenem | 4.2 |
| *A. baumannii* (236) | Cefiderocol | NA |
| Cefepime | 4.7 |
| Ceftazidime/avibactam | NA |
| Ceftolozane/tazobactam | NA |
| Ciprofloxacin | 0 |
| Colistin | 93.6 |
| Meropenem | 0.8 |
| **Key:** CarbNS, carbapenem-non-susceptible.  **Source:** Longshaw *et al.*, 2020.156 | | |

Similar proportion of *Enterobacterales* were susceptible to cefiderocol (81.6%; 79.0% of VIM producers; 51.4% of NDM producers; based on EUCAST breakpoint values) compared with comparator antimicrobial agents, including colistin (76.4%; 93.5% of VIM producers; 78.4% of NDM producers) and ceftazidime/avibactam (76.6%; 1.6% of VIM producers; 2.7% of NDM producers). Of *P.* *aeruginosa* isolates, 98.3% were susceptible to cefiderocol (100% of VIM producers), similar to colistin (100%). Against *A.* *baumannii*, 94.9% had cefiderocol MIC ≤2 mg/L and 93.6% of isolates were susceptible to colistin.

Table 13: *In vitro* activity of cefiderocol and comparators against carbapenemases produced by CarbNS and MDR aerobic Gram-negative bacteria in European isolates (SIDERO-CR 2014–2016)

| Species/carbapenemase (n) | Antimicrobial | MIC interpretation  % susceptible |
| --- | --- | --- |
| *Enterobacterales* | | |
| VIM (62) | Cefiderocol | 79.0 |
| Cefepime | 1.6 |
| Ceftazidime/avibactam | 1.6 |
| Ceftolozane/tazobactam | 0 |
| Ciprofloxacin | 6.5 |
| Colistin | 93.5 |
| Meropenem | 4.8 |
| NDM (37) | Cefiderocol | 51.4 |
| Cefepime | 0 |
| Ceftazidime/avibactam | 2.7 |
| Ceftolozane/tazobactam | 0 |
| Ciprofloxacin | 0 |
| Colistin | 78.4 |
| Meropenem | 0 |
| *P. aeruginosa* | | |
| VIM (73) | Cefiderocol | 100 |
| Cefepime | 4.1 |
| Ceftazidime/avibactam | 6.8 |
| Ceftolozane/tazobactam | 0 |
| Ciprofloxacin | 0 |
| Colistin | 100 |
| Meropenem | 1.4 |
| GES (12) | Cefiderocol | 100 |
| Cefepime | 33.3 |
| Ceftazidime/avibactam | 75.0 |
| Ceftolozane/tazobactam | 0 |
| Ciprofloxacin | 0 |
| Colistin | 100 |
| Meropenem | 0 |
| NDM (6) | Cefiderocol | 100 |
| Cefepime | 0 |
| Ceftazidime/avibactam | 0 |
| Ceftolozane/tazobactam | 0 |
| Ciprofloxacin | 0 |
| Colistin | 100 |
| Meropenem | 0 |
| **Source:** Longshaw *et al.*, 2020156 | | |

As mentioned above, there are currently differences in breakpoints for cefiderocol defined by EUCAST and CLSI, where EUCAST defined an isolate with MIC > 2 µg/mL resistant, and CLSI defined resistance as MIC > 4 µg/mL. Considering the data from CREDIBLE-CR trial, a significant proportion of patients with pathogens with MICs of 4 µg/mL and above had a clinical or microbiological success (Table 14).

Table 14: Clinical and microbiological success by pathogen, infection site and CR mechanism in the CREDIBLE-CR study

| Pathogen | Infection site | CR mechanism | MIC to CFDC | Outcome |
| --- | --- | --- | --- | --- |
| *K. pneumoniae* | HAP/VAP | NDM-1 | 4 | Success |
| *K. pneumoniae* | cUTI | NDM-1 | 4 | Success |
| *K. pneumoniae* | BSI/sepsis | NDM-1 | 4 | Success |
| *K. pneumoniae* | cUTI | NDM-1 | 4 | Success |
| *E. coli* | cUTI & BSI | NDM-5 | 16 | Success |
| *E. cloacae* | HAP/VAP | NDM-1 | 16 | Failure, died |
| *A. baumannii* | HAP/VAP | OXA-23 | 16 | Failure, died |
| *A. baumannii* | BSI/sepsis | NDM-1 | 4 | Success |
| *A. nosocomialis* | HAP/VAP | OXA-72 | > 64 | Failure, died |
| *P. aeruginosa* | cUTI | IMP | 4 | Success |

##### Other *in vitro* susceptibility studies

Several independent validation studies were carried out to determine cefiderocol activity against difficult-to-treat carbapenem-resistant pathogens gathered from various countries including the UK, Ireland, Italy, Germany, Greece, Spain, Switzerland, France and the US. In these studies, cefiderocol demonstrated consistently higher activity against aerobic Gram-negative pathogens regardless of the geographical origin compared with the other drugs included in the study. Cefiderocol also consistently showed high activity levels in all aerobic Gram-negative pathogens (MDR or carbapenem-resistant) and different mechanisms of resistance.

There are two publications where UK isolates were analysed.160, 161 The most recent,160 included highly resistant isolates from the UK, shared with PHE as part of the genotyping process, and providing additional stratification analysis of susceptibility by carbapenemase, considering both EUCAST and CLSI breakpoints, demonstrating the inconsistency in breakpoints for cefiderocol.

##### Summary of pathogen coverage

Cefiderocol has wide aerobic Gram-negative coverage, including pathogens affecting patients with limited treatment options (such as carbapenem-resistant *A.* *baumannii*, carbapenem-resistant *P.* *aeruginosa*, *S.* *maltophilia*, carbapenem-resistant *Enterobacterales*, and *Burkholderia cepacia*).157, 158 In a recent analysis of the global clinical antimicrobial pipeline by WHO, cefiderocol was reported to be the only antimicrobial providing coverage against all three critical priority pathogens: carbapenem-resistant *A. baumannii*, carbapenem-resistant *P.* *aeruginosa*, and carbapenem-resistant *Enterobacterales,* regardless of the mechanism of resistance*.*162

##### Expected comparative susceptibility: summary analysis

To determine susceptibility of aerobic Gram-negative bacteria to cefiderocol, multinational surveillance studies (SIDERO) were conducted over four consecutive years (2014–2018) using systematically collected clinical isolates from approximately 100 clinical laboratories in North American and European countries. A separate multinational surveillance study of *Proteeae* clinical isolates was also conducted. The antibacterial activity of cefiderocol was determined in iron-depleted cation-adjusted Mueller-Hinton broth (ID-CAMHB) medium, a method approved by the CLSI. Comparators were tested in parallel using standard cation-adjusted Mueller-Hinton medium according to CLSI recommendations.

In February 2020, EUCAST defined a new clinical breakpoint for cefiderocol of 2 μg/mL for *P. aeruginosa* and *Enterobacterales.* For *A. baumannii* and *S. maltophilia*, there was insufficient evidence referring to PK/PD breakpoints of 2 μg/mL (Table 15), which were used for this analysis. For the comparators, EUCAST breakpoint (version 9.0) were used in the analysis. In the absence of species-specific breakpoints, PK/PD breakpoints were applied. For colistin, PK/PD breakpoints were not available, so the analysis considered the *Pseudomonas* breakpoint of 2 μg/mL as an arbitrary breakpoint for *Stenotrophomonas* spp. and *Burkholderia* spp.

Table 15: EUCAST breakpoints for cefiderocol

| Species | Sensitive (≤) | Resistant (>) |
| --- | --- | --- |
| PK-PD breakpoints | 2 μg/mL | 2 μg/mL |
| *Enterobacterales* | 2 μg/mL | 2 μg/mL |
| *Pseudomonas aeruginosa* | 2 μg/mL | 2 μg/mL |
| *Acinetobacter baumannii* | 2 μg/mL | 2 μg/mL |
| *Stenotrophomonas maltophilia* | 2 μg/mL | 2 μg/mL |

In total and for all infection sites, 20,911 isolates were collected between 2013 and 2018 from 11 European countries. Out of the 20,911 isolates, *Enterobacterales* represented 66.5% of the pathogens, *Acinetobacter* spp. 12.7%, *Burkholderia* spp. 0.7%, *Pseudomonas aeruginosa* 16.1% and *Stenotrophomonas maltophilia* 3.9%.

Susceptibility for cefiderocol and the comparators was estimated in different subgroups of pathogens. Suspected MDR/carbapenem-resistant infections were defined as pathogens resistant to both ciprofloxacin and cefepime simultaneously.

Theoretical success in suspected MDR/carbapenem-resistant infections was estimated for each antimicrobial agent tested by combining the ECDC epidemiological data of Gram-negative pathogen distribution in each individual infection site with the susceptibility to each antimicrobial agent.

Table 16 and Table 17 (A-D) below summarize the results of such analyses for four different infection sites and the respective relevant comparators:

Table 16: Susceptibility to cefiderocol and comparators in all sites of infections for MDR3 pathogens

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | All infection sites | | | | |
| Cefiderocol | Meropenem (< MIC 8 mg/L) | Ceftolozane/ tazobactam | Ceftazidime/ avibactam | Colistin |
| *Enterobacterales* | *E.* *coli* | 96.49 | 98.52 | 87.27 | 98.15 | 98.89 |
| *Klebsiella* | 85.83 | 74.00 | 41.08 | 92.00 | 86.17 |
| Other *Enterobacterales* | 88.17 | 92.83 | 48.75 | 82.08 | 65.59 |
| All *Enterobacterales* | 89.02 | 82.78 | 54.53 | 54.53 | 86.74 |
| Non-fermenters | *Pseudomonas* | 97.74 | 40.23 | 46.80 | 47.56 | 98.12 |
| *Acinetobacter* | 88.69 | 11.64 | 5.54 | 12.83 | 85.47 |
| *Stenotrophomonas* | 99.82 | 3.09 | 28.36 | 37.45 | 76.36 |
| Other non-fermenters | 94.67 | 81.33 | 52.00 | 89.33 | 2.67 |
| All non-*Enterobacterales* | 92.58 | 17.12 | 18.52 | 25.73 | 86.67 |

Table 17: Theoretical success of antimicrobial therapy in Gram‐negative MDR pathogens in gastrointestinal site of infections (A) Pneumonia; (B) cUTI; (C) BSI; (D) Gastrointestinal

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| (A) Pneumonia | *Citrobacter spp.* | *Enterobacter spp.* | *E. coli* | *Klebsiella spp.* | *Proteus spp.* | *Serratia spp.* | Other *Enterobac-terales* | *Acineto-bacter spp.* | *P. aeruginosa* | *S. maltophilia* | *Pseudomonas spp.* | Other non-*Enterobac-terales* | *Total success in GN* |
| % pathogen | 1.26 | 7.85 | 13.81 | 17.90 | 3.77 | 4.08 | 1.73 | 13.66 | 27.32 | 5.02 | 2.20 | 1.41 |
| **Antimicrobial susceptibility** | | | | | | | | | | | | |
| Cefiderocol | 1.15 | 7.16 | 13.50 | 14.97 | 3.44 | 3.72 | 1.57 | 12.17 | 26.54 | 5.01 | 2.14 | 1.34 | 92.70 |
| Meropenem (2) | 1.07 | 6.69 | 13.50 | 11.53 | 3.21 | 3.48 | 1.47 | 0.66 | 3.87 | 0.07 | 0.31 | 0.21 | 46.09 |
| Meropenem (8) | 1.17 | 7.31 | 13.81 | 13.14 | 3.51 | 3.80 | 1.61 | 1.40 | 10.46 | 0.19 | 0.84 | 1.05 | 58.29 |
| Ceftolozane/ tazobactam | 0.74 | 4.62 | 11.95 | 7.51 | 2.22 | 2.40 | 1.02 | 0.64 | 13.27 | 1.48 | 1.07 | 0.64 | 47.55 |
| Ceftazidime/ avibactam | 1.12 | 7.00 | 13.66 | 16.25 | 3.36 | 3.64 | 1.54 | 1.83 | 13.37 | 1.78 | 1.08 | 0.64 | 65.27 |
| Colistin | 0.60 | 3.77 | 13.81 | 15.29 | 1.81 | 1.96 | 0.83 | 11.43 | 26.64 | 4.20 | 2.14 | 0.03 | 82.52 |
| (B) cUTI | *Citrobacter spp.* | *Enterobacter spp.* | *E. coli* | *Klebsiella spp.* | *Proteus spp.* | *Serratia spp.* | Other *Enterobac-terales* | *Acineto-bacter spp.* | *P. aeruginosa* | *S. maltophilia* | *Pseudomonas spp.* | Other non-*Enterobac-terales* | *Total success in GN* |
| % pathogen | 1.84 | 5.12 | 47.51 | 15.75 | 10.37 | 0.79 | 4.07 | 1.97 | 11.02 | 0.00 | 1.05 | 0.52 |
| **Antimicrobial susceptibility** | | | | | | | | | | | | |
| Cefiderocol | 1.67 | 4.66 | 46.33 | 13.73 | 9.45 | 0.72 | 3.71 | 1.81 | 10.69 | 0.00 | 1.02 | 0.50 | 94.28 |
| Meropenem (2) | 1.47 | 4.09 | 46.03 | 10.90 | 8.29 | 0.63 | 3.25 | 0.18 | 2.67 | 0.00 | 0.25 | 0.06 | 77.84 |
| Meropenem (8) | 1.55 | 4.32 | 46.92 | 11.97 | 8.75 | 0.66 | 3.44 | 0.23 | 4.01 | 0.00 | 0.38 | 0.10 | 82.34 |
| Ceftolozane/ tazobactam | 0.90 | 2.50 | 40.13 | 6.36 | 5.07 | 0.38 | 1.99 | 0.60 | 5.01 | 0.00 | 0.48 | 0.45 | 63.87 |
| Ceftazidime/ avibactam | 1.43 | 3.98 | 46.33 | 14.49 | 8.06 | 0.61 | 3.16 | 0.35 | 5.34 | 0.00 | 0.51 | 0.52 | 84.79 |
| Colistin | 1.35 | 3.75 | 46.03 | 13.61 | 7.60 | 0.58 | 2.98 | 1.79 | 11.02 | 0.00 | 1.05 | 0.00 | 89.77 |
| (C) BSI | *Citrobacter spp.* | *Enterobacter spp.* | *E. coli* | *Klebsiella spp.* | *Proteus spp.* | *Serratia spp.* | Other *Enterobac-terales* | *Acineto-bacter spp.* | *P. aeruginosa* | *S. maltophilia* | *Pseudomonas spp.* | Other non-*Enterobac-terales* | *Total success in GN* |
| % pathogen | 0.95 | 8.04 | 26.00 | 23.17 | 4.73 | 3.78 | 3.07 | 9.69 | 14.42 | 2.36 | 1.18 | 2.60 |
| **Antimicrobial susceptibility** | | | | | | | | | | | | |
| Cefiderocol | 0.81 | 6.84 | 21.33 | 18.66 | 4.03 | 3.22 | 2.62 | 9.69 | 12.75 | 2.36 | 1.04 | 2.40 | 85.76 |
| Meropenem (2) | 0.63 | 5.36 | 25.14 | 13.13 | 3.15 | 2.52 | 2.05 | 0.52 | 0.58 | 0.03 | 0.05 | 0.65 | 53.81 |
| Meropenem (8) | 0.89 | 7.59 | 25.43 | 15.59 | 4.47 | 3.57 | 2.90 | 0.95 | 4.33 | 0.03 | 0.35 | 2.60 | 68.70 |
| Ceftolozane/ tazobactam | 0.39 | 3.35 | 23.12 | 9.07 | 1.97 | 1.58 | 1.28 | 0.26 | 5.77 | 0.65 | 0.47 | 0.39 | 48.30 |
| Ceftazidime/ avibactam | 0.71 | 6.03 | 25.43 | 21.78 | 3.55 | 2.84 | 2.30 | 1.17 | 5.48 | 0.42 | 0.45 | 2.38 | 72.53 |
| Colistin | 0.71 | 6.03 | 26.00 | 18.79 | 3.55 | 2.84 | 2.30 | 8.26 | 14.13 | 0.02 | 1.16 | 0.22 | 84.01 |
| (D) Gastro-intestinal | *Citrobacter spp.* | *Enterobacter spp.* | *E. coli* | *Klebsiella spp.* | *Proteus spp.* | *Serratia spp.* | Other *Enterobac-terales* | *Acineto-bacter spp.* | *P. aeruginosa* | *S. maltophilia* | *Pseudomonas spp.* | Other non-*Enterobac-terales* | *Total success in GN* |
| % pathogen | 3.43 | 12.57 | 32.00 | 22.29 | 1.71 | 1.71 | 0.57 | 1.71 | 14.29 | 3.43 | 2.29 | 4.00 |
| **Antimicrobial susceptibility** | | | | | | | | | | | | |
| Cefiderocol | 2.97 | 10.90 | 30.55 | 19.67 | 1.49 | 1.49 | 0.50 | 1.48 | 13.88 | 3.47 | 2.22 | 3.60 | 92.16 |
| Meropenem (2) | 2.06 | 7.54 | 31.27 | 14.45 | 1.03 | 1.03 | 0.34 | 0.05 | 4.49 | 0.00 | 0.72 | 0.29 | 63.27 |
| Meropenem (8) | 2.63 | 9.64 | 31.27 | 16.91 | 1.31 | 1.31 | 0.44 | 0.11 | 7.35 | 0.00 | 1.18 | 0.50 | 72.64 |
| Ceftolozane/ tazobactam | 0.69 | 2.51 | 28.00 | 9.22 | 0.34 | 0.34 | 0.11 | 0.08 | 7.35 | 0.00 | 1.18 | 0.65 | 50.48 |
| Ceftazidime/ avibactam | 2.51 | 9.22 | 31.27 | 20.75 | 1.26 | 1.26 | 0.42 | 0.19 | 7.76 | 0.00 | 1.24 | 0.96 | 76.83 |
| Colistin | 2.97 | 10.90 | 30.91 | 20.29 | 1.49 | 1.49 | 0.50 | 1.47 | 14.29 | 0.00 | 2.29 | 3.44 | 90.01 |
| **Key:** BSI, bloodstream infection; cUTI, complicated urinary tract infection; GN, Gram negative; MDR, multi-drug resistant. | | | | | | | | | | | | | |

Regardless of the infection sites, cefiderocol demonstrated the highest theoretical success compared with meropenem, ceftolozane/tazobactam, ceftazidime/avibactam or colistin, for pre-emptive therapy in suspected MDR/carbapenem-resistant infections.

Table 18: Theoretical percentage of success for Gram‐negative antimicrobial therapy on aerobic Gram‐negative pathogens in different infection type

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Pneumonia | cUTI | BSI | cIAI |
| Cefiderocol | 92.7 | 94.3 | 85.8 | 92.2 |
| Meropenem (2 mg/L) | 46.1 | 77.8 | 53.8 | 63.3 |
| Meropenem (8 mg/L) | 58.3 | 82.3 | 68.7 | 72.6 |
| Ceftolozane/ tazobactam | 47.6 | 63.9 | 48.3 | 50.5 |
| Ceftazidime/ avibactam | 65.3 | 84.8 | 72.5 | 76.8 |
| Colistin | 82.5 | 89.8 | 84.0 | 90.0 |
| **Key:** BSI, bloodstream infection; cIAI, complicated intra-abdominal infections; cUTI, complicated urinary tract infection. | | | | |

|  |
| --- |
| **Key considerations for economic model:**   * As cefiderocol has a wide coverage of aerobic Gram-negative pathogens, its use in clinical practice could help to reduce time to effective therapy, particularly in the risk-based empiric setting, which is critical in improving patient outcomes * Given that carbapenems are broad-spectrum antimicrobials that also cover anaerobic and Gram-positive pathogens, the use of cefiderocol against aerobic Gram-negative bacteria in the appropriate patient could contribute to antimicrobial stewardship and the preservation of existing antimicrobials |

### PK/PD evidence

Optimized dosing of antimicrobials is a key component of antimicrobial stewardship to drive successful clinical outcomes and reduce the likelihood of resistance emerging. In the critical care setting it is essential to have confidence in the PK and PD properties of antimicrobials as they are being used in patients with altered and changeable pharmacokinetics, a low physiological reserve and often in the presence of multi-drug resistant opportunistic pathogens.163 Shionogi has established a robust pharmacokinetic and pharmacodynamic knowledge base for cefiderocol to demonstrate pharmacokinetic and pharmacodynamic confidence with recommended dosing regimens, in conjunction with *in vitro* potency. Alongside UK and global PK/PD expert advice, an ongoing investigational programme will continue to build and develop our understanding of optimized dosing of cefiderocol in critically-ill patient populations.

A population PK analysis was performed to develop a model using a total of 3,427 cefiderocol plasma concentration samples. Details on the methods and the studies that provided the samples for this analysis, along with the detailed results, are presented in Appendix C.5.

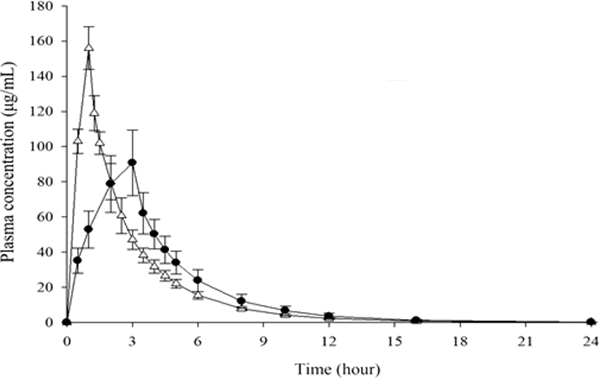
Probability of Target Attainment (PTA)

As for other beta-lactams, the fraction of the dosing interval (fT) that antimicrobial levels are maintained above pathogen minimum inhibitory concentration (MIC) is critical for efficacy.164

The extended infusion dosing regimen for cefiderocol was developed to optimize time above MIC for all pathogens and infection sources.165

In immunocompetent rat lung infection models, cefiderocol doses over a 3-hour infusion period versus a 1-hour infusion period achieved greater efficacy.166 Humanized exposures of cefiderocol in neutropenic murine thigh infection models produced a similar reduction in bacterial density.167

Figure 7: Mean (SD) plasma concentrations of cefiderocol following single-dose administration of 2g infused over 1 hour and 3 hours



**Key:** Triangle, 2g single infusion over 1-hour; circle, 2g infusion over 3-hours.

**Source:** Matsumoto *et al.*, 2017166

Population pharmacokinetic analysis has been performed using over 3,000 samples from 425 patients with pneumonia, blood stream infections/sepsis, complicated urinary tract infection or acute pyelonephritis to demonstrate that the recommended cefiderocol dosing regimens, adjusted for renal function, provide adequate exposure in patients, irrespective of their infection sites.168 These data demonstrate a high probability of achieving 100% fraction of time above MIC in plasma and in other tissues such as epithelial lining fluid for aerobic Gram-negative pathogens with MICs up to 4 µg/mL (Table 19).

Table 19: PTA for 100% fT > MIC

| Probability of target attainment (PTA) for 100% fT > MIC or 100% fT > MIC, ELF | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Target | Renal function group | Dose regimens with 3-hour infusion | MIC (µg/mL) | | | | | | |
| 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 |
| Pneumonia patients | | | | | | | | | |
| 100% fT > MIC (plasma) | Augmented renal function | 2 g q6h | 100 | 100 | 100 | 99.7 | 95.9 | 79.8 | 37.0 |
| Normal renal function | 2 g q8h | 100 | 100 | 99.9 | 98.3 | 91.2 | 64.6 | 23.2 |
| Mild renal impairment | 2 g q8h | 100 | 100 | 99.9 | 99.7 | 98.2 | 85.9 | 46.4 |
| Moderate renal impairment | 1.5 g q8h | 100 | 100 | 100 | 100 | 99.5 | 94.8 | 66.7 |
| Severe renal impairment | 1 g q8h | 100 | 100 | 100 | 100 | 100 | 99.5 | 81.8 |
| ESRD | 0.75 g q12h | 100 | 100 | 100 | 100 | 100 | 98.3 | 77.1 |
| 100% fT >MIC, ELF (ELF) | Augmented renal function | 2 g q6h | 100 | 100 | 100 | 99.8 | 91.8 | 53.9 | 10.2 |
| Normal renal function | 2 g q8h | 100 | 100 | 100 | 99.5 | 87.0 | 41.8 | 6.0 |
| Mild renal impairment | 2 g q8h | 100 | 100 | 100 | 99.7 | 93.1 | 58.8 | 14.4 |
| Moderate renal impairment | 1.5 g q8h | 100 | 100 | 100 | 100 | 95.8 | 65.6 | 17.5 |
| Severe renal impairment | 1 g q8h | 100 | 100 | 100 | 99.9 | 97.7 | 74.5 | 24.7 |
| ESRD | 0.75 g q12h | 100 | 100 | 100 | 99.9 | 93.8 | 61.9 | 20.0 |
| BSI/sepsis patients | | | | | | | | | |
| 100% fT > MIC (plasma) | Augmented renal function | 2 g q6h | 100 | 100 | 100 | 99.4 | 93.6 | 71.6 | 28.5 |
| Normal renal function | 2 g q8h | 100 | 99.9 | 99.5 | 96.2 | 85.8 | 54.0 | 14.1 |
| Mild renal impairment | 2 g q8h | 100 | 100 | 99.8 | 99.4 | 96.0 | 78.0 | 36.1 |
| Moderate renal impairment | 1.5 g q8h | 100 | 100 | 100 | 99.9 | 98.7 | 91.2 | 55.8 |
| Severe renal impairment | 1 g q8h | 100 | 100 | 100 | 100 | 100 | 98.3 | 74.7 |
| ESRD | 0.75 g q12h | 100 | 100 | 100 | 100 | 100 | 96.8 | 68.0 |
| cUTI patients | | | | | | | | | |
| 100% fT >MIC (plasma) | Augmented renal function | 2 g q6h | 100 | 100 | 100 | 100 | 98.0 | 88.3 | 51.1 |
| Normal renal function | 2 g q8h | 100 | 100 | 99.9 | 99.4 | 95.1 | 77.6 | 34.3 |
| Mild renal impairment | 2 g q8h | 100 | 100 | 100 | 99.8 | 98.9 | 93.2 | 59.4 |
| Moderate renal impairment | 1.5 g q8h | 100 | 100 | 100 | 100 | 99.8 | 97.7 | 79.1 |
| Severe renal impairment | 1 g q8h | 100 | 100 | 100 | 100 | 100 | 99.7 | 90.1 |
| ESRD | 0.75 g q12h | 100 | 100 | 100 | 100 | 100 | 99.4 | 85.7 |
| **Key:** BSI, bloodstream infection; cUTI, complicated urinary tract infection; ESRD, end-stage renal disease; fT, fraction of time interval; MIC, minimum inhibitory concentration; PTA, probability of target attainment; q#h, every # hours.  **Notes:** Shaded cells are indicates > 90%.  **Source:** Katsube *et al.*, 2020.168 | | | | | | | | | |

Augmented renal clearance (ARC)

As cefiderocol is expected to be used in seriously ill and/or ventilated patients, a significant proportion of whom are at risk of ARC, this has been modelled for cefiderocol using the Monte Carlo simulation. The Monte Carlo simulations of patients, with creatinine clearance (CrCL) up to 185 mL/minute calculated by the Cockcroft-Gault equation, demonstrated that a more frequent administration of cefiderocol (i.e., 2 g every 6 hours, infused over 3 hours) would provide adequate drug exposure for > 90% of patients with ARC (i.e. > 120 mL/ minute of CrCL) infected with strains with an MIC of ≤ 4 μg/mL.169

Lung penetration

In bacterial pneumonia, source control is not possible, and antimicrobials must be relied upon to do the heavy lifting to achieve a successful therapeutic outcome. Colistin is well known to have issues with poor penetration in the lung.108, 109 Therefore, a robust understanding of cefiderocol PK/PD, including penetration into lung tissue was initially built through accepted animal models and mathematical simulations before being demonstrated in the plasma and lungs of patients with hospital acquired pneumonia. Cefiderocol concentration ratios in epithelial lining fluid (ELF) to free plasma of 0.422 have been determined in patients with hospital acquired pneumonia.169 Figure 8 demonstrates the probability of target attainment in epithelial lining fluid, against 4,862 carbapenem resistant aerobic Gram-negative isolates from Europe and North America in SIDERO-WT-2014-2016.157

Figure 8: PTA for ELF 100% fT > MIC in patients with pneumonia



**Key:** MIC, minimum inhibitory concentration.

**Source:** Katsube *et al.*, 2020168

### *In vivo* activity

To support the pivotal *in vitro* data and supporting PK/PD and clinical efficacy data, the *in vivo* activity cefiderocol has been studied in a variety of animal infection models by various Gram-negative bacterial strains which try to simulate the limited free iron conditions that occur in humans with infectious diseases. In these studies, cefiderocol demonstrated potent efficacy against MDR and carbapenem-resistant strains including carbapenemase-producers where reference substances such as carbapenem and β-lactam/β-lactamase inhibitor combinations were less effective. The animal models consisted of mice and rats and included systemic infections (acute septicaemia), as well as local site infections such as neutropenic murine pneumonia, immunocompetent murine UTI, neutropenic murine thigh infection and immunocompetent rat pneumonia. Infection pathogens were carbapenem-resistant *Enterobacteriaceae*, *P. aeruginosa* and *A. baumannii*, including carbapenemase- and ESBL-producers such as NDM-1, KPC, IMP, VIM and OXA.153

Nakamura *et al.* (2021) evaluated the *in vivo* efficacy of cefiderocol against *S. maltophilia* in two lung infection models. Cefiderocol was shown to be an effective alternative treatment option for *S. maltophilia* infections in the lower respiratory tract, particularly for strains resistant to empiric antimicrobials (trimethoprim/sulfamethoxazole, minocycline).154

### Clinical evidence

As discussed in Section 2.2, the clinical evidence for antimicrobials is of limited use when assessing the effectiveness of treatments. However, despite facing the same limitations, the CREDIBLE-CR study does provide evidence that is reflective of the microbiology-directed treatment setting, and therefore can be considered as supporting evidence to the *in vitro* data for this population. A summary of the methods and baseline characteristics are presented below, with further detail available in Appendix C.6.1 and the CREDIBLE-CR CSR.

|  |
| --- |
| **Key consideration for economic model:** Unlike many investigational drugs, due to the high mortality rate of systemic bacterial infections if not adequately treated, efficacy of new antimicrobials cannot ethically be compared against placebo. Therefore, Phase III double blinded, randomized controlled trials use an active comparator, and only patients with infections caused by pathogens that are equally susceptible to treatments in both arms can be enrolled. This limits the trial’s value in assessing the intervention’s relative efficacy in highly resistant populations, where they are expected to be used in clinical practice, aligned with stewardship principles. Also, due to the large amount of heterogeneity in terms of infection sites, causal pathogens, mechanisms of resistance, and underlying diseases, it would not be practically possible to undertake a comparative study that was large enough to balance all of these confounding factors. Thus, in the context of AMR, the standard clinical trial approach aimed at demonstrating superiority over existing treatments is not feasible. Clinical data have value as supportive data to the *in vitro* evidence, especially when confounding factors are considered as far as possible. |

#### CREDIBLE-CR

##### CREDIBLE-CR methods

CREDIBLE-CR is a non-inferential/descriptive Phase III, open-label, randomized, parallel-group, active-controlled clinical study to investigate the efficacy of cefiderocol or best available therapy (BAT) in the treatment of serious infections caused by carbapenem-resistant aerobic Gram-negative pathogens for HAP/VAP/HCAP, cUTI and BSI/sepsis. Full details of the study methods are presented in Appendix C.6.1.1. Briefly, patients (n = 152) were randomized 2:1 to receive either cefiderocol, 2 g, administered intravenously (IV) over 3 hours every 8 hours (q8h) or BAT. Patients with cUTI received cefiderocol as monotherapy, whereas for patients with HAP/VAP/HCAP or BSI/sepsis, physicians could choose to add one additional antimicrobial: the majority of patients in CREDIBLE-CR received cefiderocol as monotherapy.

BAT was chosen by the investigator before randomization and could include up to three antimicrobials with aerobic Gram-negative coverage used in combination. Due to the enrolment of patients with a broad range of carbapenem-resistant aerobic Gram-negative bacteria and infection types, BAT was considered to be the appropriate comparator, reflecting the lack of consensus over standard of care and the variation in the combinations of antimicrobials within clinical practice. This was also in accordance with the regulatory guidance by EMA. The majority of patients receiving BAT were treated with colistin-based regimens.

The primary endpoint of the study was the clinical cure rate at TOC in the carbapenem-resistant microbiological intent-to-treat (micro-ITT) population for HAP/VAP/HCAP and BSI/sepsis, and microbiological eradication at TOC in carbapenem-resistant Micro-ITT for cUTI. Of note, the study was not designed to provide inferential hypothesis testing but was instead intended to provide descriptive statistics only of the aggregated data, due to limited number of patients. Given that BAT could not be standardized across geographical regions and could have been different even among hospitals in the same country, blinding was not possible.

As supporting evidence to the pivotal *in vitro* data for cefiderocol, full details of the descriptive statistical analyses and study populations from the CREDIBLE-CR study are available in the CREDIBLE-CR CSR and publications, available as part of the reference pack. The patient disposition diagram is presented in Appendix C.2.

The relevance of the clinical trial data to support cefiderocol in this submission is discussed in Section 2.1 and Section 2.2. As the only clinical trial appropriate to be considered as supporting evidence to the pivotal *in vitro* data for cefiderocol, a quality assessment of the CREDIBLE-CR study using the NICE checklist is presented in Appendix C.3.

CREDIBLE-CR was considered to be a high-quality study and was conducted according to Good Clinical Practice; however, being an open-label study that was not powered to detect statistically significant differences between treatment arms, there remains some risk of bias with any clinical trial results in this setting.

##### CREDIBLE-CR baseline characteristics

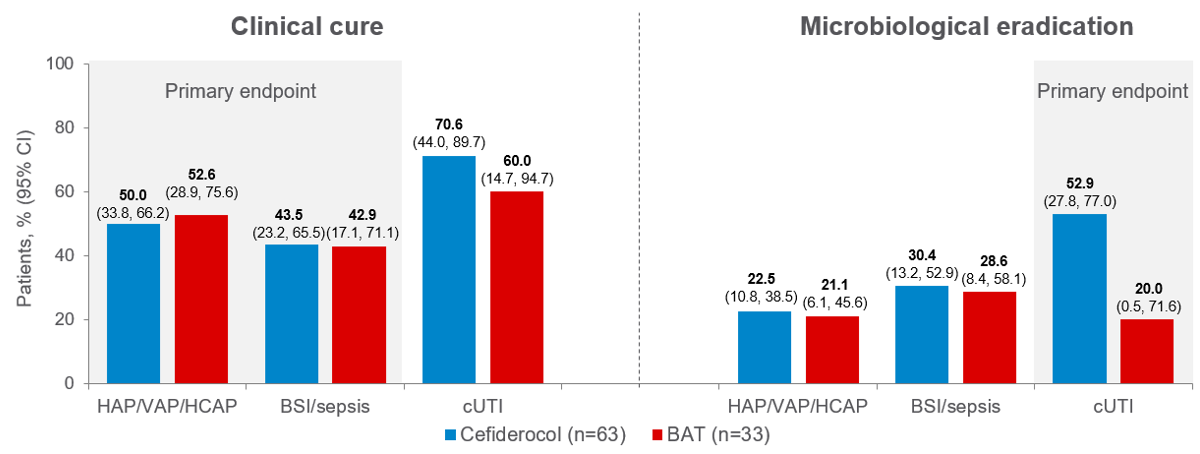
Full details on the baseline characteristics of patients in CREDIBLE-CR, including a breakdown of baseline pathogens are presented in Appendix C.6.1.2. Overall, the study included a heterogeneous population including three infection types (HAP/VAP/HCAP, BSI/sepsis, and cUTI), a wide variety of carbapenem-resistant pathogens also including non-fermenters (*Acinetobacter* spp. and *Stenotrophomonas* spp.), and a high number of patients with life-threatening or end-of-life conditions with a high risk of mortality.

Baseline demographics were generally statistically balanced between the two treatment arms, with some clinical exceptions that can influence the results. There was a higher proportion of patients of ≥ 65 years old (63.4% versus 44.9%) and of patients with moderate (22.8% versus 16.3%) and severe renal impairment (19.8% versus 14.3%) in cefiderocol group compared with the BAT group (see Appendix C.6.1.2). There was also an imbalance in the baseline pathogens between the trial arms. The cefiderocol arm contained more patients with multiple pathogens and more non-fermenters, particularly *Stenotrophomonas* *maltophilia*. The most common pathogens were *A. baumannii* and *K. pneumoniae* (see Appendix C.6.1.2). Of note, all infections caused by *S. maltophilia* were randomized to the cefiderocol arm.

##### Primary efficacy endpoint: clinical cure rate for HAP/VAP/HCAP and BSI/sepsis, and microbiological eradication for cUTI (at TOC)

Results of clinical cure and microbiological eradication were similar between the two arms. However, even in these very-difficult-to-treat patients, cefiderocol has consistently demonstrated numerically higher clinical cure in cUTI and BSI/sepsis and a numerically higher microbiological eradication rate than those seen in the BAT arm across all infection sites (pneumonia, BSI and cUTI). It is worth noting that for microbiological eradication there were a high proportion of patients with indeterminate results (cefiderocol: 48.8%; BAT: 50.0%). The proportion of patients with persistent infection was therefore lower (cefiderocol: 20.0%; BAT: 26.3%).

Figure 9: Clinical cure and microbiological eradication by clinical diagnosis at TOC



**Key:** BAT, best available therapy; BSI, bloodstream infection; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; TOC, test of cure; VAP, ventilator-associated pneumonia.

**Source:** Bassetti *et al.*, 2020.80

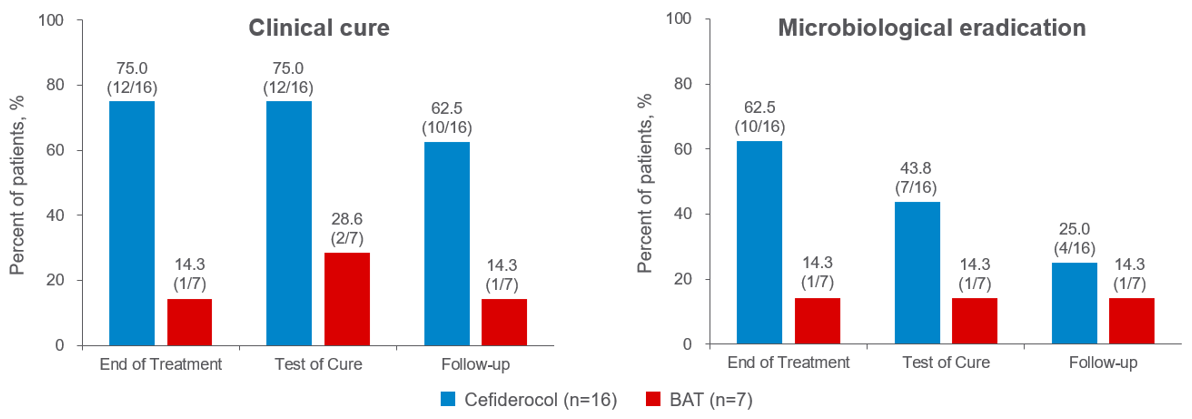
##### Efficacy across pathogens

As presented in Section 2.3.1, cefiderocol has demonstrated consistently high levels of efficacy across all aerobic Gram-negative pathogens in the SIDERO *in vitro* studies, including all key carbapenem-resistant pathogens and WHO priority pathogens. These results were supported in CREDIBLE-CR, with similar (numerically higher) clinical cure and microbiological eradication rates across all key pathogens (see Appendix C.6.1.3).

##### Efficacy data for patients with metallo-β-lactamase infections in CREDIBLE-CR

In patients with infections caused by metallo-β-lactamase-producing aerobic Gram-negative pathogens, cefiderocol demonstrated numerical improvements in terms of both clinical cure and microbiological responses (Figure 10) at different time points. These results were observed regardless of infection site and pathogen. Despite the small sample size, these results support the findings of the *in vitro* data (Section 2.3.1.2) and provide further evidence of the effectiveness of cefiderocol in this population. The results for microbiological eradication have the same consideration as for the overall population, discussed above, whereby a patient not meeting this outcome does not necessarily have persistent infection, due to indeterminate results.

Figure 10: Clinical and microbiological outcomes in metallo-β-lactamase producing aerobic Gram-negative pathogens (CR micro-ITT Population)



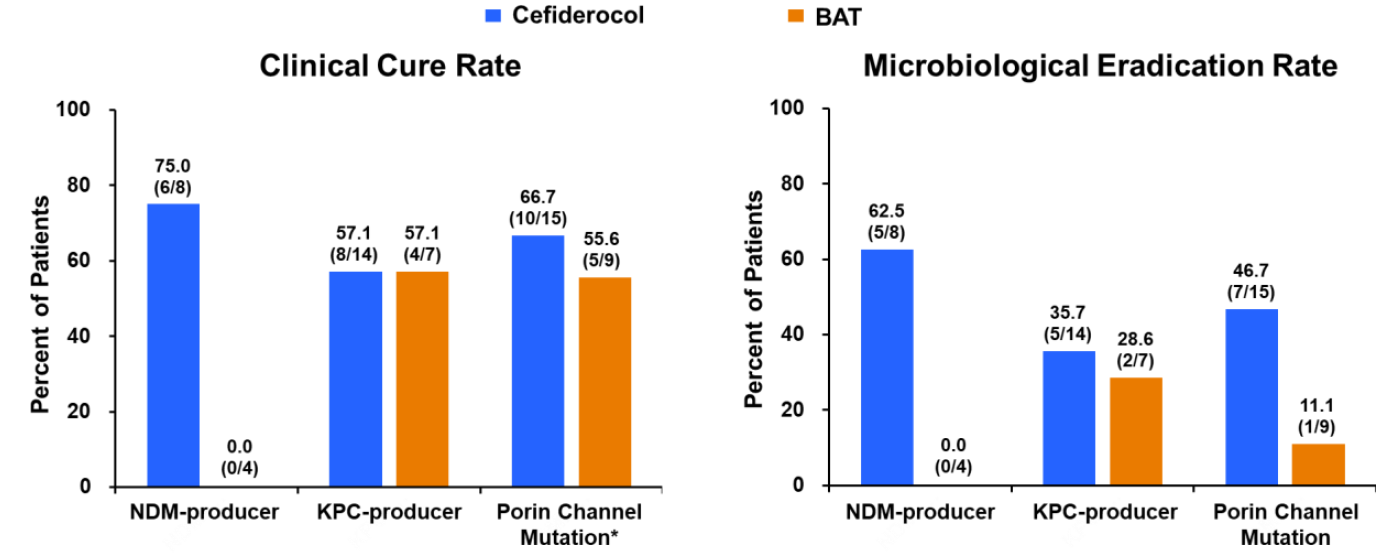
**Key:** CR, carbapenem-resistant; micro-ITT, micro-biological intent-to-treat.

**Source:** CREDIBLE-CR CSR; Bassetti *et al.*, 2020.80

In the most difficult-to-treat pathogens: New Delhi metallo-β-lactamase (NDM) producers, *Klebsiella pneumoniae* carbapenemase (KPC) producers and porin channel mutations; cefiderocol demonstrated similar or improved rates of clinical cure and microbiological eradication compared to BAT. Six out of eight patients with NDM-producing *Enterobacteriaceae* in cefiderocol the arm had a clinical cure and microbiological response. Of the four in the BAT arm, none responded (Figure 11).

There were 14 KPC producers in the cefiderocol group and seven in the BAT group, with similar clinical cure and microbiological eradication between treatment groups (Figure 11). Porin channel mutations were present in 15 pathogens in the cefiderocol group and nine in the BAT group, with similar rates of clinical cure. However, microbiological eradication was demonstrated in seven out of 15 pathogens in cefiderocol arm and one out of nine in BAT arm (Figure 11).

Figure 11: Clinical and microbiological outcomes in *Enterobacteriaceae* by carbapenemase or porin channel mutation (TOC; CR micro-ITT Population) at TOC



**Key:** NDM, New Delhi metallo-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase

**Notes:** \*OMPK35/36-deficient. Only patients with molecular data are included.

**Source:** CREDIBLE-CR CSR.

#### Other available clinical data including a data from compassionate use and early access programmes

Cefiderocol has been provided upon request from attending physicians to patients with serious carbapenem-resistant aerobic Gram-negative infections who have no other treatment options.170 The criteria for fulfilling compassionate use requests are highly restrictive including that all other available treatments must be ruled out through susceptibility testing and/or evidence of treatment failure in efficacy or safety, and patients must be unable to enrol in clinical studies of cefiderocol.170 To date, over 200 patients worldwide have been treated with cefiderocol within this programme. Full details for this evidence are presented in Appendix C.6.2. Cefiderocol has been provided upon request from attending physicians to patients with serious carbapenem-resistant aerobic Gram-negative infections who have no other treatment options.170 The criteria for fulfilling compassionate use requests are highly restrictive including that all other available treatments must be ruled out through susceptibility testing and/or evidence of treatment failure in efficacy or safety, and patients must be unable to enrol in clinical studies of cefiderocol.170 To date, over 200 patients worldwide have been treated with cefiderocol within this programme. Full details for this evidence are presented in Appendix C.5.2.

Across the case series and case reports of compassionate use of cefiderocol, which cover a wide range of pathogens and infection sites (Appendix C.6.2), cefiderocol was shown to be a life-saving therapy for most patients with aerobic Gram-negative infections who have exhausted all other treatment options. There was a high microbiological eradication rate, a small number of adverse events and the majority of patients were alive at discharge.171 Cefiderocol has demonstrated efficacy across all key pathogens (including A. *baumannii*, P. *aeruginosa*, A. *xylosoxidans*, and K. *pneumoniae*) and across multiple sites of infections, including HAP/VAP, cUTI, BSI, bones and joints, with the majority of patients having infections caused by MDR or XDR pathogens. Evidence from the use of cefiderocol in compassionate use programmes supports the pivotal *in vitro* data and clinical trial data, and demonstrates the value of cefiderocol in clinical practice.

### Emergence of resistance to cefiderocol

It is important to remember that *in vitro* studies designed to drive resistance to an antimicrobial do not necessarily translate across to *in vivo* infections, where multiple pressures on a microbe impact on its potential for survival, not only that of an antimicrobial. Uptake of iron is essential for bacterial growth and it has been observed that cefiderocol-resistant mutants with non-functional iron uptake grow more slowly than their wild type parents on iron-limited conditions. Further studies are necessary to understand whether the development of resistance to cefiderocol without prior exposure to this compound is a more widespread phenomenon.172

As discussed in Section 1.2.3, resistance to antimicrobials generally takes two forms:

* The pathogens produce carbapenemases, which degrade antibiotics
* The pathogens develop porin and efflux channel mechanisms, which remove antibiotics)

Cefiderocol may be able to bypass elements of both of these mechanisms of resistance. As discussed below, current surveillance data suggest a low background rate of existing cross-resistance with other antimicrobials, while preclinical studies and the low numbers of treatment emergent resistant isolates from the clinical trial programme support the biologically plausible reasons for low resistance outlined in Section 1.2.3.

*De novo* resistance against cefiderocol is usually due to mutations in membrane sensors or iron uptake genes, which do not confer cross-resistance to antimicrobials not using the bacteria’s iron uptake system to gain cell entry.173, 174 Mutations in membrane sensors or iron uptake genes were not observed for *Klebsiella* or *Pseudomonas* isolates in *in vitro* chemostat models reflecting humanized dosing levels.174 This is supported by evidence from the clinical trial programme where mutations in the iron uptake genes or PBP-3 were not consistently found by whole genome sequencing for most isolates that showed a ≥ 4-fold shift in MIC compared to baseline, and their frequency was not higher than for antimicrobials in the comparator arm.173 The isolates also usually remained susceptible to cefiderocol.173

Therefore, the risk of treatment emergent, transmissible resistance to cefiderocol, which compromises the susceptibility to other antimicrobials, is considered to be low.173 The SIDERO multinational surveillance studies identified isolates that were already resistant to cefiderocol at baseline; however, the vast majority of these involve the presence of β-lactamases, such as PER-1, which are rare in clinical practice.173

A study evaluating the frequency of resistance of *P*. *aeruginosa* to cefiderocol reported that mutations in the bacterial iron uptake systems were associated with a 4-fold elevated cefiderocol MIC (from 0.5 to 2 μg/mL) although none of the mutations appeared in the responsible iron transporter gene *piu*A.13, 17, 175 Of note, frequencies of resistance to cefiderocol were lower than those to ceftazidime.18, 175 Although the information is currently limited on resistance mechanisms to cefiderocol, no cross-resistance was observed between cefiderocol and ceftazidime.20

Even in the absence of forming a complex with iron, cefiderocol can still function as an antibacterial agent by entering the bacterial periplasm by passive diffusion through porin channels.22 While to date there has been no report on resistance in P. *aeruginosa*.

In comparison to cefiderocol, recent clinical case reports in the USA and the EU/EEA have demonstrated the emergence of ceftazidime/avibactam resistance in CRE, and the CARBAR study has also identified a resistance rate of 40% from 20 treated patients. These reports are of particular concern since it is under three years since the initial launch of ceftazidime/avibactam. As a result, the ECDC issued a warning on the emergence of ceftazidime/avibactam resistance very shortly after its launch;176 cefiderocol has received no such warning.

Both from first principles and the evidence observed to date there is a strong rationale to believe resistance to cefiderocol will develop more slowly than the historical trends observed for other antimicrobials. If, as previously communicated, EEPRU use historic data on resistance development to model the growth of resistance to cefiderocol, this is likely to provide a pessimistic estimate of cefiderocol’s clinical benefit over time.90

## Safety and tolerability

In order to provide the largest sample size for safety and tolerability data for cefiderocol, a pooled analysis of data from the CREDIBLE-CR, APEKS-NP and APEKS-cUTI study has been performed. As the adverse effects of cefiderocol for patients is not affected by the population that the patient belongs to, these data provide the most robust and relevant source of safety data for cefiderocol. This evidence is presented in Section 2.4.1 and is supported by the safety data from the CREDIBLE-CR study to confirm the results in the population of interest (Section 2.4.2). Additional detail on this pooled analysis, including a breakdown by study, is presented in Appendix E.4.

|  |
| --- |
| **Key considerations for the economic model (see Sections 3.2.2 and 3.3.3.2):**   * Adverse events in this context can have significant long-term consequences; renal issues following colistin therapy are of particular relevance and with implications on both overall survival and long-term health care resource use * Downstream impacts on patient outcomes need to be taken into account to avoid overlooking a considerable proportion of the value of introducing a new, less toxic, antimicrobial treatment, such as cefiderocol, to UK clinical practice |

### Overall safety data for cefiderocol

#### Summary of exposure to cefiderocol

Table 20 presents a summary of the dose and exposure to cefiderocol of patients within the clinical trial programme. Nearly half the patients are from the APEKS-cUTI trial that had a maximum treatment duration of 14 days. Therefore, the majority of patients were treated with cefiderocol between 7 to 14 days for cUTI. Patients in the APEKS-NP and CREDIBLE-CR studies had longer treatment durations; 52 patients received treatment with cefiderocol between 14 and 22 days (mostly coming from CREDIBLE-CR CR study).

Table 20: Dose and duration of exposure to cefiderocol

|  |  |
| --- | --- |
| Duration of exposure | Total (N = 549) |
| < 5 | 30 |
| 5 to < 7 | 21 |
| 7 to ≤ 14 | 435 |
| > 14 to | 52 |
| ≤ 21 | 11 |
| **Notes:** CREDIBLE-CR: 2 g cefiderocol (over 3-hours) 3 times daily (every 8 hours) for 7–14 days (may be extended up to 21 days; APEKS-cUTI: 2 g cefiderocol (over 1-hour) 3 times daily (every 8 hours) for 7–14 days; APEKS-NP: 2 g cefiderocol (over 3 hours) 3 times daily (every 8 hours) for 7–14 days (may be extended up to 21 days)  **Source:** EU Risk Managing Plan for Fetcroja.177 | |

#### Summary of adverse event data across the clinical trial programme for cefiderocol

In a pooled adverse event analysis, patients treated with cefiderocol experienced less treatment emergent-adverse events (67.1%) than patients treated with BAT (72.6%). The most common adverse reactions for cefiderocol were diarrhoea (8.2%), constipation (4.6%), pyrexia (4.0%) and UTI (4.7%). In total, 10.2% of patients treated with cefiderocol experienced treatment-related AEs compared to 13.0% of patients treated with BAT. Table 21 presents a breakdown of the treatment-related adverse events for patients treated with cefiderocol and BAT, by system organ class and preferred term. This demonstrates that cefiderocol has a manageable safety profile that was comparable or more favourable than comparators, with particular improvements in renal toxicity.

Table 21: Subjects with treatment related adverse events by system organ class and preferred term (all Phase II/III studies; Safety Population)

| System Organ Class - Preferred Term; n (%) | Cefiderocol (N=549) | BAT (N=347) |
| --- | --- | --- |
| Any Treatment Related AEs | 56 (10.2) | 45 (13.0) |
| Blood and lymphatic system disorders | 0 | 2 (0.6) |
| Disseminated intravascular coagulation | 0 | 1 (0.3) |
| Thrombocytopenia | 0 | 1 (0.3) |
| Cardiac disorders | 0 | 1 (0.3) |
| Tachycardia | 0 | 1 (0.3) |
| Ear and labyrinth disorders | 1 (0.2) | 0 |
| Ear discomfort | 1 (0.2) | 0 |
| Gastrointestinal disorders | 16 (2.9) | 11 (3.2) |
| Diarrhoea | 9 (1.6) | 8 (2.3) |
| Nausea | 3 (0.5) | 1 (0.3) |
| Vomiting | 1 (0.2) | 2 (0.6) |
| Abdominal pain upper | 1 (0.2) | 0 |
| Ascites | 1 (0.2) | 0 |
| Constipation | 1 (0.2) | 0 |
| Dry mouth | 1 (0.2) | 0 |
| Stomatitis | 1 (0.2) | 0 |
| Upper gastrointestinal haemorrhage | 1 (0.2) | 0 |
| Lip oedema | 0 | 1 (0.3) |
| General disorders and administration site conditions | 7 (1.3) | 2 (0.6) |
| Oedema peripheral | 2 (0.4) | 0 |
| Infusion site pain | 2 (0.4) | 0 |
| Feeling hot | 1 (0.2) | 0 |
| Oedema | 1 (0.2) | 0 |
| Pyrexia | 1 (0.2) | 0 |
| Infusion site erythema | 1 (0.2) | 0 |
| Hyperthermia | 0 | 1 (0.3) |
| Multiple organ dysfunction syndrome | 0 | 1 (0.3) |
| Hepatobiliary disorders | 1 (0.2) | 2 (0.6) |
| Hepatic failure | 1 (0.2) | 0 |
| Hepatic function abnormal | 0 | 1 (0.3) |
| Hepatocellular injury | 0 | 1 (0.3) |
| Immune system disorders | 1 (0.2) | 1 (0.3) |
| Drug hypersensitivity | 1 (0.2) | 0 |
| Anaphylactic reaction | 0 | 1 (0.3) |
| Infections and infestations | 9 (1.6) | 14 (4.0) |
| Clostridium difficile colitis | 2 (0.4) | 4 (1.2) |
| Oral candidiasis | 2 (0.4) | 0 |
| Candiduria | 2 (0.4) | 0 |
| Clostridium difficile infection | 1 (0.2) | 2 (0.6) |
| Pseudomembranous colitis | 1 (0.2) | 1 (0.3) |
| Sepsis | 1 (0.2) | 1 (0.3) |
| Fungal infection | 0 | 1 (0.3) |
| Septic shock | 0 | 1 (0.3) |
| Systemic candida | 0 | 1 (0.3) |
| Vaginal infection | 0 | 1 (0.3) |
| Urinary tract infection fungal | 0 | 1 (0.3) |
| *Pseudomonas* infection | 0 | 1 (0.3) |
| *Candida* infection | 0 | 1 (0.3) |
| Investigations | 17 (3.1) | 8 (2.3) |
| Alanine aminotransferase increased | 6 (1.1) | 1 (0.3) |
| Gamma-glutamyltransferase increased | 6 (1.1) | 1 (0.3) |
| Aspartate aminotransferase increased | 5 (0.9) | 1 (0.3) |
| Transaminases increased | 2 (0.4) | 0 |
| Liver function test increased | 2 (0.4) | 0 |
| Hepatic enzyme increased | 1 (0.2) | 3 (0.9) |
| Blood creatinine increased | 1 (0.2) | 1 (0.3) |
| Blood pressure increased | 1 (0.2) | 0 |
| Blood creatine increased | 0 | 1 (0.3) |
| Blood alkaline phosphatase increased | 0 | 1 (0.3) |
| Metabolism and nutrition disorders | 1 (0.2) | 1 (0.3) |
| Hypokalaemia | 1 (0.2) | 0 |
| Metabolic acidosis | 0 | 1 (0.3) |
| Musculoskeletal and connective tissue disorders | 1 (0.2) | 0 |
| Myalgia | 1 (0.2) | 0 |
| Nervous system disorders | 5 (0.9) | 5 (1.4) |
| Dysgeusia | 2 (0.4) | 1 (0.3) |
| Headache | 1 (0.2) | 3 (0.9) |
| Dizziness | 1 (0.2) | 0 |
| Paraesthesia | 1 (0.2) | 0 |
| Status epilepticus | 0 | 1 (0.3) |
| Psychiatric disorders | 1 (0.2) | 0 |
| Confusional state | 1 (0.2) | 0 |
| Renal and urinary disorders | 0 | 5 (1.4) |
| Acute kidney injury | 0 | 4 (1.2) |
| Renal disorder | 0 | 1 (0.3) |
| Reproductive system and breast disorders | 0 | 1 (0.3) |
| Vulvovaginal pruritus | 0 | 1 (0.3) |
| Respiratory, thoracic and mediastinal disorders | 3 (0.5) | 1 (0.3) |
| Pleural effusion | 2 (0.4) | 0 |
| Acute respiratory failure | 1 (0.2) | 0 |
| Asthma | 1 (0.2) | 0 |
| Respiratory arrest | 0 | 1 (0.3) |
| Skin and subcutaneous tissue disorders | 7 (1.3) | 1 (0.3) |
| Rash | 2 (0.4) | 0 |
| Pruritus | 1 (0.2) | 1 (0.3) |
| Drug eruption | 1 (0.2) | 0 |
| Erythema | 1 (0.2) | 0 |
| Palmar erythema | 1 (0.2) | 0 |
| Rash maculo-papular | 1 (0.2) | 0 |
| Vascular disorders | 1 (0.2) | 0 |
| Hypertension | 1 (0.2) | 0 |
| **Key:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; BAT, best available therapy; INC, increase from baseline; PT-INR, prothrombin time-international normalized ratio; ULN, upper limit of normal; Percentage is calculated using N’ as the denominator, where N’ is the number of subjects with valid postbaseline measurement. | | |

#### Mortality across the cefiderocol clinical trial programme

Table 22 presents the pooled mortality data across the clinical trial programme for cefiderocol. There was no difference in the proportion of deaths for patients treated with cefiderocol compared to the comparators used in these trials (13.5% for patients treated with cefiderocol compared to 12.7% treated with comparators). This is further supported by the first Periodic Benefit Risk Evaluation Report (PBRER) for cefiderocol, which confirmed that there was no excess mortality associated with cefiderocol across all patients who have been treated to date (including patients included in the clinical trials and from post-authorization sources, including global compassionate use programmes, regional early access programs and other regional temporary authorizations for use, data from peer-reviewed publications, and spontaneous reports).

Table 22: Pooled mortality data across the clinical trial programme for cefiderocol (safety population)

|  |  |  |
| --- | --- | --- |
| n (%) | Cefiderocol (N=549) | Comparator (N=347)a |
| Deaths | 74 (13.5) | 44 (12.7) |
| **Notes:** a, CREDIBLE-CR: best available therapy; APEKS-NP: high-dose meropenem; APEKS-cUTI: imipenem/cilastatin.  **Sources:** Bassetti *et al.*, 202080; Wunderink *et al.*, 2019;178 Wunderink *et al.*, 2020;179 Portsmouth *et al.*, 2018.180 | | |

### CREDIBLE-CR

As supporting evidence to the data from the overall cefiderocol safety data from the pooled clinical trial programme, a summary of safety data from the CREDIBLE-CR study is presented below, with additional detail in Appendix E.1.

#### Summary of adverse events in CREDIBLE-CR

Most patients (> 90%) in both groups were reported to have AEs (Table 23). Treatment-related AEs were reported for 14.9% of cefiderocol-treated patients and 22.4% of BAT-treated patients (Table 23). Approximately half of the patients in both groups had serious adverse events (SAEs). Treatment-related SAEs were lower in the cefiderocol arm than in the BAT arm. Discontinuation due to AEs was 9.9% in the cefiderocol group and 6.1% in the BAT group, and discontinuations due to treatment-related AEs occurred in three patients in the cefiderocol group and two patients in the BAT group (Table 23). AEs leading to death were reported for 33.7% of patients in the cefiderocol group and 18.4% in the BAT group (Table 23). A single patient could have more than one AE that led to death.

Table 23: Summary of TEAEs (safety population)

|  |  |  |
| --- | --- | --- |
| Safety event, n (%) | Cefiderocol (N = 101) | BAT (N = 49) |
| Any AE | 92 (91.2) | 47 (95.9) |
| Treatment-related AEs | 15 (14.7) | 11 (22.9) |
| SAEs | 50 (49.5) | 23 (46.9) |
| Treatment-related SAEs | 1 (1) | 5 (10.2) |
| Discontinuation due to AE | 10 (9.9) | 3 (6.1) |
| Discontinuation due to treatment-related AE | 3 (3) | 2 (4.1) |
| Deaths | 34 (33.7) | 9 (18.4) |
| **Key:** AE, adverse event; BAT, best available therapy; EOT, end of treatment; SAE, serious AE; TEAE, treatment-emergent adverse event.  **Source:** Data on file | | |

#### Renal-related toxicity in CREDIBLE-CR

Of note, renal-related toxicity was reported in the BAT group (n = 5), where one patient had in additional to acute kidney injury, metabolic acidosis and respiratory arrest leading to the death of the patient. In cefiderocol arm, none of the patients experienced renal-related toxicity (Table 24).

Table 24: Renal and urinary disorders

|  |  |  |
| --- | --- | --- |
| System organ class Preferred term, n (%) | Cefiderocol (N = 101) | BAT (N = 49) |
| Renal and urinary disorders | 0 | 5 (10.2) |
| Acute kidney injury | 0 | 4 (8.2) |
| Renal disorder | 0 | 1 (2.0) |
| **Key:** BAT, best available therapy.  **Source:** Data on file | | |

#### Mortality in CREDIBLE-CR

No statistically significant differences in mortality rates were identified in the CREDIBLE-CR study. There were some numerical differences between the cefiderocol and BAT groups; however, the study was descriptive and not powered to test differences in clinical efficacy or mortality between the test arms. As such, none of the differences described are statistically significant, are unexplained and could be due to chance. No statistically significant difference in all-cause mortality at day 14, day 28 or end of study was observed in the APEKS-NP study which was a larger, randomized and double blinded study where all-cause mortality at day 14 was the primary endpoint. An assessment of all-cause mortality in CREDIBLE-CR at different timepoints is presented in Appendix E.1.1. and mortality for patients with metallo-β-lactamase-producing pathogens is presented in Section 2.4.2.4.

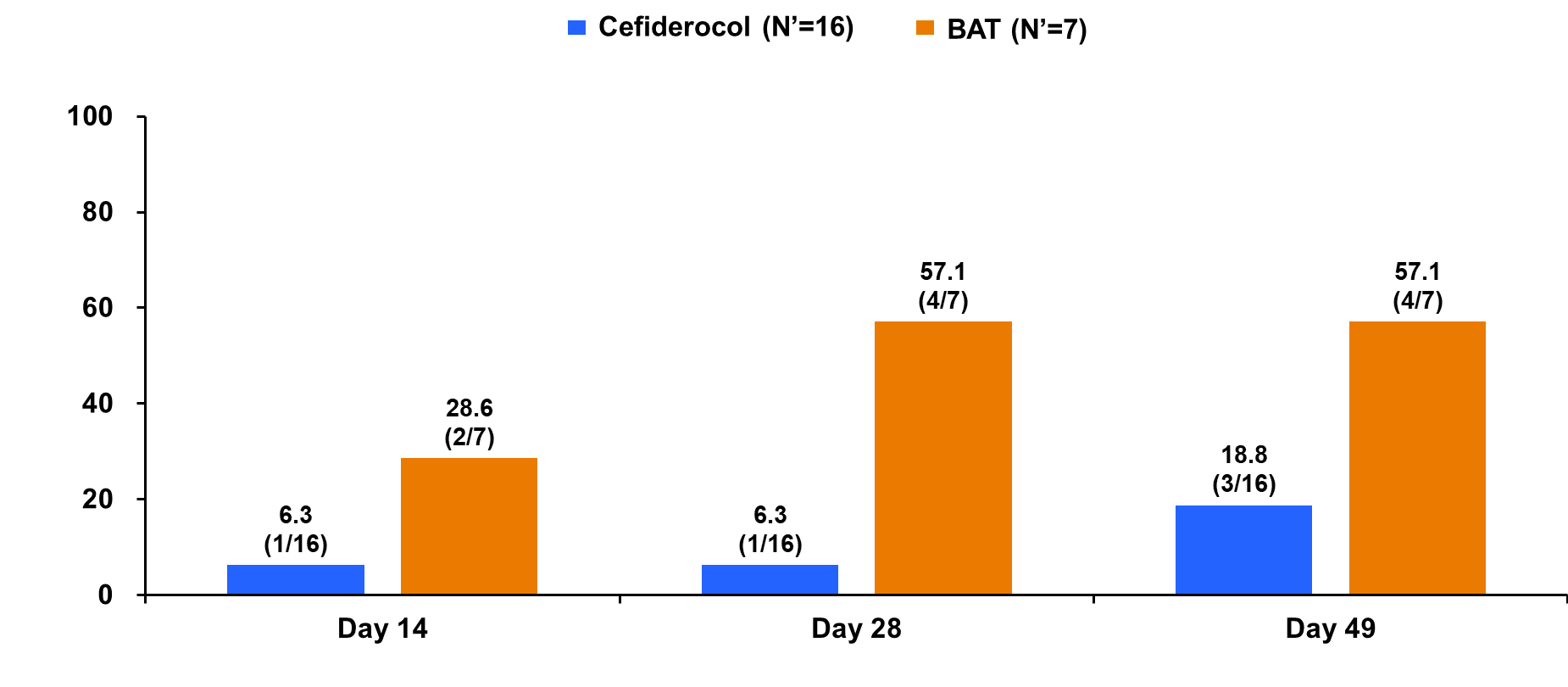
The numerical differences in all-cause mortality between the study arms (although not significant) appear to be largely observed in the sub-group of patients characterized as having infections caused by *Acinetobacter* spp. infections (Appendix E.1.3). Treatment arms were not stratified by suspected pathogen type at randomization and at baseline, patients with *Acinetobacter* treated with cefiderocol were more likely to be in ICU and have a history of shock than those in the BAT arm. Patients with infections caused by A. *baumannii* and with a history of shock (both shock at baseline and a history of shock up to 31 days before baseline), had mortality rates much higher than in patients without a history of shock; this was observed for both treatment groups (Appendix E.1.4) but no difference in mortality was observed in patients with history of shock without *Acinetobacter*. Patients with a history of septic shock or ongoing shock at baseline are at a high risk of mortality.181 Therefore, given that the proportion of patients with a history of shock was higher for the cefiderocol group than for the BAT group, this imbalance may provide an explanation for a large proportion of the numerical differences in mortality rates seen.

In an extensive assessment of the numerical mortality differences by Shionogi, DSMB, and an independent blinded adjudication committee, it was determined that no death was due to an adverse drug reaction. The proportion of all-cause mortality due to aerobic Gram-negative infection in each treatment group was similar (cefiderocol: 16 out of 34 [47%]; BAT: 4 out of 9 [44%]) as well as due to progression (cefiderocol: 18 out of 34 [53%]; BAT: 5 out of 9 [55%]). All-cause mortality in a population with such severe illnesses is difficult to assess, and there was marked heterogeneity within each treatment group for underlying diagnoses and prognoses. The investigators providing direct patient care, the DSMB and the blinded adjudication committee did not identify any death as being an adverse drug reaction to cefiderocol. The cause of the numerical difference in mortality (although not significant) is therefore unknown and could be due to chance. As part of the assessment of cefiderocol, the EMA concluded that there were no significant differences in mortality between cefiderocol and comparators and that the cause of the imbalance in the CREDIBLE-CR data was unexplained.

#### Mortality in patients with metallo-β-lactamase pathogens in CREDIBLE-CR

In the most difficult to treat infections caused by metallo-β-lactamase-producing pathogens, all-cause mortality was numerically lower in patients treated with cefiderocol compared to patients in the BAT arm (Figure 12).

Figure 12: All-cause mortality rates for patients with metallo-β-lactamase-producing pathogens in CREDIBLE-CR



**Key:** BAT, best available therapy; MBL, metallo-β-lactamase.

**Source:** CREDIBLE-CR CSR.

There is a biologically plausible reason that this numerical difference could reflect a real difference in efficacy between cefiderocol and the BAT arm, namely the comparative *in vitro* activity/efficacy evidence, which indicates the limited activity of many agents against metallo-β-lactamase pathogens.

More specifically to colistin, these data include several HAP/VAP patients, and while penetration into the lung for cefiderocol is not an issue165, 168, it is acknowledged that colistin can have poor tissue penetration in certain infection sites, including the lung, which may go some way to explain this result.

## Additional value elements for cefiderocol

As a novel antimicrobial, and due to certain characteristics particular to cefiderocol (i.e., the prospect of improved efficacy due to broader Gram-negative pathogen coverage), the introduction of cefiderocol presents a number of additional value elements that are not captured within the usual health technology assessment framework but provide a substantial benefit to the NHS and society as a whole and therefore should be considered.

***Enablement value***

Firstly, without access to effective antimicrobials patients with bacterial infections may not be able to receive certain surgical or medical procedures that they require, such as gut surgery, joint replacements, and treatments that depress the immune system, such as chemotherapy and stem cell transplant for cancer. By addressing the infection, effective antimicrobial interventions enable patients to subsequently receive the additional healthcare interventions they need.182

Second, many antimicrobials are also used in advance of surgery, such as prior to bone and joint replacement procedures, in order to reduce the risk of infection.

Thirdly, effective antimicrobials help to prevent infections that may occur following required medical procedures, giving clinicians confidence to proceed with these procedures.182, 183

Ardal and colleagues (2018) investigated the impact of increased AMR on the 10 most common surgical procedures and immunosuppressing cancer chemotherapies that rely on antimicrobial prophylaxis in the US.183 They identified relevant meta-analyses and reviews of RCTs to estimate the efficacy of antimicrobials in preventing infections and estimated the impact of reduced efficacy of antimicrobial prophylaxis in terms of the number of infections and infection related deaths that would result. They found that a 30% reduction in the efficacy of antimicrobial prophylaxis would result in 120,000 surgical site infections and infections following chemotherapy and 6,300 related deaths annually. If we hold all else equal and adjust for the relative population size of England and Wales compared to the US then a 30% reduction in efficacy would result in approximately 21,600 additional infections and 1,100 additional deaths per annum in England and Wales. Similarly, in the future, if pathogens resistant to all available antimicrobials become common, then numerous interventions might be considered unviable due to the risk of a previously addressable infection. Indeed, O’Neill and colleagues (2016) note that “if they [antimicrobials] lose their effectiveness, key medical procedures (such as gut surgery, caesarean sections, joint replacements, and treatments that depress the immune system, such as chemotherapy for cancer) could become too dangerous to perform.”1

***Diversity value***

Having a diverse range of antimicrobials available also helps to reduce the rate at which pathogens develop resistance to specific antimicrobials, thereby preserving their efficacy.184-186 When used to treat carbapenem-resistant infections alongside other effective agents, cefiderocol will help to diversify the available treatment options, reducing resistance pressure on the currently available antimicrobials and therefore helping to preserve their efficacy for longer. For example, cefiderocol may have a valuable role to play in preserving the range of effective existing antimicrobials against infections caused by carbapenem-resistant pathogens with KPC, with OXA and by carbapenem-resistant *P. aeruginosa*. Furthermore, if in the future additional novel antimicrobials are developed to treat metallo-β-lactamase infections, then hospitals may be able to cycle between cefiderocol and the subsequently launched antimicrobial, which would allow each of these treatments to further preserve the other’s effectiveness.

***Transmission value***

Resistant pathogens not only have the potential to affect the individual currently suffering with the infection, but also others through onward transmission of the resistant pathogen.187, 188 The literature suggests that the longer infected patients remain in hospital, the higher the risk that they transmit resistant pathogens.189 Cefiderocol could reduce the onward transmission of resistant strains by y resolving infections earlier (e.g. in cases where it is a more effective agent than alternatives). This provides significant benefits to other individual patients by reducing their risk of acquiring a resistant pathogen. Additionally, effective treatment with cefiderocol might reduce the population prevalence of certain specific resistant strains in the long term, in comparison to the scenario in which it was not available. When considering the impact of cefiderocol on the onward transmission of resistant strains it is therefore important to consider the reduced time to treatment resolution. This will likely have benefits at the patient level and, over time, at the population level.

**Spectrum value**

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.190 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. This is not the case for other antimicrobials, such as carbapenems, which have a disruptive effect on the gut microbiota and can lead to colonization with carbapenem-resistant pathogens. Also, the different PK of the components of antimicrobial-inhibitor combinations means that inhibitors are excreted through the kidney while active antimicrobials like meropenem, imipenem or ceftazidime can get into the gut and add to selective pressure. Persistent gut colonization of hospitalized patients with carbapenem-resistant pathogens presents an infection control risk, which cefiderocol could minimize.

***Insurance value***

The reports by O’Neill and colleagues (2016) and the WHO describe future catastrophic scenarios in which AMR has developed to levels that are devastating to otherwise well-functioning health systems.1, 10, 62 This could either occur steadily over time or because of a specific event, whereby multi-drug resistance becomes so widespread that there are many more cases of resistant infection combined with significantly fewer treatment options, and potentially, cefiderocol is the only effective antimicrobial for a large number of patient populations.90 Novel antimicrobials therefore have additional value in mitigating the potentially massive amount of damage that would result from this otherwise high consequence scenario, e.g. potential closure of wards or even hospitals, and an exponentially negative ‘enablement’ effect on other health services. This benefit could occur in terms of minimizing the risk and impact of local outbreaks, such as those that have occurred relatively recently in hospitals in both Manchester and London.191-194 Conversely the outbreak could occur in multiple regions, with the associated health and financial consequences impacting both the health system and wider society.

## Ongoing studies

The following studies of cefiderocol are currently ongoing and anticipated to have data available within the next 12-months:

* ARES STUDY: A retrospective chart review study including patients with carbapenem-resistant *A. baumannii* within the early access (EAP) programme

PROVE STUDY: A multi-site, retrospective chart review study of cefiderocol real-world outcomes and safety in patients with aerobic Gram-negative bacterial infections in the US and Europe

## Implications of the clinical data for the economic analysis

Based on available clinical evidence, several recommendations to EEPRU and NICE for reasonable approaches to incorporate into their valuation of cefiderocol can be made.

Firstly, *in vitro* data from SIDERO, complemented by UK epidemiology data, should be used to determine or influence efficacy for empiric high-value populations, as these are the best available data pertaining to those patients (Section 1.1.4 and Section 2.3.1). Data from PK/PD can be used alongside these data to extrapolate to other infection sites, including for the HVCSs defined by EEPRU and the other identified HVCSs.

Secondly, the efficacy data from CREDIBLE-CR are suitable for use in decision making in the microbiology-directed treatment setting and provides an important signal for comparative efficacy between cefiderocol and colistin (Section 2.3.3). Evidence from compassionate use and EAPs can be used to complement the evidence provided here. However, as discussed in Section 2.1, data from ITCs would not be suitable to use for comparative data.

Thirdly, time to effective therapy is an important indicator, and the potentially non-linear association that it has with length of stay should be considered for modelling.

Finally, the downstream effects of renal toxicity on patient outcomes are considerable and their avoidance through the introduction of cefiderocol to the treatment pathway should be considered a vital part of cefiderocol’s value (Section 3.2.2 and Section 3.3.3.2).

Epidemiology is a difficult topic in the context of infectious disease and eligibility for treatment with cefiderocol within the high value populations defined by NICE. Nevertheless, Shionogi have provided some estimates (Section 1.1.4), which we believe to be credible and clinically supported. We offer these to support EEPRU and NICE in their efforts to understand the expected annual incidence of patients within the various high value populations of interest to this decision problem.

In addition to these recommendations, there are some areas in which data could not be found to populate likely model inputs that are important for capturing the value of cefiderocol. A summary of these is provided in Appendix I.2. Firstly, we had difficulty establishing market shares for comparator therapies within the high value populations, including the frequency of combined use. Secondly, we could not retrieve any data on the proportion of post-infection long-term care patients that are fully or partly funded by the NHS compared with those going into private care facilities. Finally, some infection-patient-specific outcomes with respect to renal impairment (time on dialysis following colistin-related renal failure, transplant rates for infection survivors, proportions of dialysis patients requiring long-term care post recovery) could not be found. We suggest that these areas are candidates for data collection or expert elicitation, as they may considerably influence estimates of value associated with new treatments.

Lastly, although for the most part we agree with the approaches proposed by EEPRU in their protocol, there are some areas where we believe some changes could be made to reflect the situation more accurately in clinical practice and more fully capture the value of antimicrobials in this setting. These are presented in Section 3.4.

# Cost effectiveness

Much of the important discussion relating to estimating the net health benefit of cefiderocol in the populations of interest for EEPRU and NICE is included in the clinical sections above. The cost-effectiveness section focuses predominantly on providing appropriate data and recommending appropriate approaches to informing analyses of population net health benefit (PNHB), and more detailed discussion on technical points relating to this decision problem. The below box provides a summary of the economics section, as well as cross references to the pertinent sections and discussions relating to PNHB of cefiderocol throughout the document.

|  |
| --- |
| **Cost-effectiveness: Summary and key points**  Evaluation of the cost-effectiveness of antimicrobials has been attempted in the past, though not for cefiderocol specifically in the context of the HVCSs defined by NICE and EEPRU. Methods to capture value are improving with some more recent positive developments (Section 3.1)  Incorporating analyses of both epidemiology and *in vitro* susceptibility data is critically important when estimating incremental efficacy in resistant infections. This is because most clinical trials are designed to demonstrate non-inferiority in populations that often do not represent the target populations for treatments due to ethical concerns (See Sections 2.3 and 3.2.1). For instance, some clinical trials for treatments for carbapenem-resistant populations include only patients that are confirmed to be carbapenem susceptible (See Section 2.3.3)  Expected time to effective therapy is an important metric in risk-based empiric settings (that is, settings in which carbapenem resistance is suspected) to determine the utility of an antimicrobial treatment (See Section 3.3.1)   * This metric in part reflects the population-level probability that the underlying infection in the empiric setting is susceptible to the treatment initially given. If the probability of being susceptible is higher, then across a cohort, the time to effective therapy received will be shorter. The probability of initially receiving an inappropriate therapy (and having to wait for an appropriate therapy to eventually be given) is reduced, thus reducing the cohort expected value for time to effective therapy and improving the survival probabilities. In turn, time to effective treatment is one determinant of outcomes such as survival and long-term morbidity, in a treated population * Time to effective treatment is also, to a more limited extent, determined by the average time it takes to determine whether the treatment given was appropriate or not. For those initially inappropriately treated, time to receipt of test results determines the ability of the physician to change the treatment from the inappropriate baseline treatment to an appropriate one. (Section 1.1.2.3) * Both time to effective treatment in general and time to test results influence the total time the average patient spends in hospital, which is particularly important when considering the daily cost of a patient in an ICU, the daily probability of death whilst in an ICU, and the daily probability of transmitting disease.   The tolerability of treatments in the antimicrobial context, particularly with respect to colistin-based regimens, is an important factor in evaluating the cost-effectiveness of treatments that would displace it. Of particular importance is capturing the longer-term consequences of different treatments’ toxicity on patient mortality and morbidity (Sections 2.4, 3.2.2, 3.2.3 and 3.3.3.2)  Capturing wider value elements – spectrum, transmission, enablement, diversity, and insurance (STEDI) – quantitively is challenging, given data constraints and the forward-looking nature of some elements like insurance. We propose some approaches and scenarios that may be helpful in determining the value to the NHS of different strategies for the introduction of cefiderocol over a 10-year system time horizon (Sections 2.5 and 3.4)  Epidemiological data are of primary importance to the expected PNHB of introducing a new treatment. They are key to understanding the uncertainty surrounding the decision problem. We report some expert and data-led efforts to quantify patient numbers in Section 1.1.4   * Epidemiology data are required to determine the baseline incidence of eligible patients to calculate the PNHB, and any cost offsets associated with the introduction of cefiderocol to clinical practice in England * Epidemiology data and forecasting are required to power the dynamic forecasting of future incidence, in different ‘states of the world’ to capture STEDI value aspects (Sections 2.5 and 3.4)   The considerable uncertainty surrounding estimates of historical antimicrobial use and resistance development across the NHS, as well as around the forecasting of future use/resistance, is an important issue that requires thorough and careful exploration (Sections 2.3.5 and 1.1.4). This uncertainty influences the estimation of the amount that cefiderocol will be used in England, how this will change over time, and how effective the medicine will be   * A pragmatic approach to capturing epidemiology should be taken, using a combination of expert elicitation and analysis of the available data (Section 1.1.4)   When evaluating insurance value as well as other decision uncertainty, NICE should retain their usual risk neutral stance (See Sections 2.5 and 3.4) |

## Published cost-effectiveness studies

No cost-effectiveness studies of cefiderocol in the HVCSs defined by EEPRU (See Section 1.3) have been conducted to date. However, studies of different products (or cefiderocol) in different contexts do provide a useful source of data and thought on the capturing of value for new antimicrobial treatments. These studies are summarized in Appendix F and outlined in Table 25.

Table 25: Summary list of published cost-effectiveness studies

| **Study** | **Year** | **Summary of model** | **Patient population (average age in years)** | **QALYs (intervention, comparator)** | **Costs (currency) (intervention, comparator)** | **ICER (per QALY gained)** |
| --- | --- | --- | --- | --- | --- | --- |
| Gill *et al. 195* | 2020 | Cohort-based decision tree model | US adult patients with confirmed carbapenem resistance cUTI, or pneumonia (mean age 63.5 years) | PSA results from 5,000 iterations. Cefiderocol (10.88); colistin-based regimens (10.29) | PSA results from 5,000 iterations. Cefiderocol ($25,542.81); colistin-based regiments ($16,859.88) | PSA results from 5,000 iterations. ICER = $14,616 |
| Simon *et al.* 92 | 2019 | Cohort-based decision tree model, including modelling of renal issues and BSI/sepsis development | Adults (mean age 61 years) | CAZ-AVI (1.76); Colistin-based therapy (1.26) | CAZ-AVI ($156,300); Colistin-based therapy ($108,800) | $95,000 |
| SMC (meropenem/ vaborbactam) 196 | 2020 | Cohort-based decision tree model | Adults (mean age 63.5 years) | Meropenem/ vaborbactam (1.574); BAT (1.241) | Meropenem/ vaborbactam (£30,643); BAT (£28,600) | £6,146 |
| Naik *et al. 197* | 2021 | Cohort-based decision tree model | Adults (mean age 60.5 years) | Confirmed setting: ceftolozane/ tazobactam (8.93); meropenem (8.33)  Early treatment setting: ceftolozane/ tazobactam (7.78); meropenem (7.06) | Confirmed setting: ceftolozane/ tazobactam ($153,182); meropenem ($145,935)  Early treatment setting: ceftolozane/ tazobactam ($161,961); meropenem ($158,546) | Confirmed setting: $12,126  Early treatment setting: $4,775 |
| BIanchini *et al. 198* | 2020 | Cohort-based decision tree model | Adults (mean age 60 years) | BLBLI (11.5): Colistin-based therapy (8.3) | BLBLI ($16,200): Colistin ($3,500) | $3,900 |
| Gordon *et al. 199* | 2020 | Dynamic disease transition model | - | 7.7–10.3 QALYs per patient, for the introduction of a new antimicrobial dependent on antimicrobial efficacy | - | - |
| Tichy *et al. 200* | 2020 | Patient-level, sequential simulation model | Not specified | CAZ-AVI (3.439); meropenem (3.089) | CAZ-AVI ($18,394); meropenem ($17,140) | $3,581 |
| **Key:** BAT, best available treatment; BLBLI, β-lactam β-lactamase inhibitor; CAZ-AVI, ceftazidime/avibactam; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.  **Notes:** All values in $ refer to USD. | | | | | | |

### Patient population

The patient populations relevant to this decision problem are discussed in Section 1.3.2, whilst the potential broader populations are discussed in Section 1.3.3.

The epidemiology surrounding infections caused by carbapenem resistant and/or metallo-β-lactamase-producing pathogens in the UK is a difficult topic, in which there are very little usable data. This is discussed in Section 1.1.4.

### Intervention technology and comparators

The topic of cefiderocol and its comparators as technologies is discussed in Sections 1.2 and 1.3. A summary is provided below.

|  |
| --- |
| **Key points for cost-effectiveness: intervention and comparator(s)**  We consider colistin-based regimens, aminoglycosides, and combination with aztreonam, to be the relevant comparators in the microbiology-directed and risk-based populations defined by NICE and EEPRU  We expect that in both the microbiology-directed and risk-based settings, cefiderocol will predominantly be used as a monotherapy, avoiding cross resistance development (See Section 2.3.4.1)  Microbiology-directed setting:   * Aztreonam has supply issues, meaning that in some cases cefiderocol may be used as an alternative in clinical practice, particularly for metallo-β-lactamases (See Section 1.1.2.5) * Colistin is toxic with potentially life-long renal or other consequences for patients (Sections 3.2.2 and 3.3.3.2). These can lead to a need for long-term care, which is associated with elevated mortality and morbidity and additional cost to the NHS (Section 3.2.3) * Cefiderocol is associated with good safety and low rates of renal toxicity, avoiding these consequences (Section 2.4.2.2). Therefore, cefiderocol has value in its ability to offset these issues   Risk-based setting:   * In the empiric settings (infections suspected to be caused by metallo-β-lactamase-producing pathogens), both aztreonam-containing and colistin-based regimens are still determined by NICE and EEPRU as the current standard of care. These treatments have the same limitations as defined above. * Susceptibility data for cefiderocol show its value in a risk-based setting * Introducing cefiderocol into the pathway in the empiric settings provides a less toxic and more broadly effective alternative to colistin-based therapies, preserving colistin-based regimens as a last-resort treatment to be used in a microbiology-directed setting |

## Clinical parameters and variables

As Shionogi will not be submitting a cost-effectiveness model for this submission, the focus of this and subsequent sections is on the presentation of recommendations for data inputs and modelling approaches. This is to provide constructive input to the collaborative effort towards providing precise and reliable estimates of the value that new antimicrobial treatments bring to the NHS.

The clinical parameters reviewed and recommended within this section include:

* Presentation and critique of the relevant *in vitro* susceptibility data to which we have access; we suggest these are the only relevant data on the efficacies of cefiderocol and BAT for treating infections suspected to be caused by carbapenem-resistant (and metallo-β-lactamase-producing) pathogens in the risk-based setting
* Presentation of data on the importance of time to effective therapy, as well as time to antibiogram and/or testing for metallo-β-lactamase
* Presentation and critique of the data from CREDIBLE-CR, which we suggest are the best available data on the efficacy of both cefiderocol and BAT for treating infections caused by carbapenem-resistant (and metallo-β-lactamase-producing) pathogens in the microbiology-directed setting.

Presentation and critique of data on the life-long downstream consequences of renal toxicity during antimicrobial treatment

Following the presentation of these factors, we produce a set of recommendations or minimum requirements to appropriately capture of the value of cefiderocol or similar treatments.

Finally, as per NICE guidance on discounting of health benefits in special circumstances201, and the Green Book guidance on Life and Health202, we recommend a 1.5% discount rate be applied to health effects, instead of the 3.5% used in the NICE reference case. We believe cefiderocol meets the criteria of a treatment effect that is both substantial in restoring health and sustained over a very long period (even beyond the extent of the patient lifetime), outlined in the NICE guidance.201 Section 9.3 of the Green Book recommends QALYs be discounted at a rate of 1.5%.202

### Measuring the efficacy of different treatments

As discussed in Sections 2.3 and 2.4 and in Appendix C, clinical trial data cannot always reliably be used on their own to estimate the incremental efficacy of different antimicrobial treatments, even when using an indirect treatment comparison. In the risk-based empiric setting, a better approach is to use *in vitro* data. (See Sections 2.3.1 and 3.2.1.1) In the case of the microbiology-directed setting CREDIBLE-CR study data, *can* be used to measure incremental efficacy due to its (albeit descriptive) trial design (See Sections 2.4.1 and 3.2.1.4). Therefore, this section includes presentation of the relevant *in vitro* susceptibility data, as well as the relevant comparative efficacy data from CREDIBLE-CR.

#### In vitro data

The *in vitro* data that we recommend for use by NICE is from the SIDERO study (See Section 2.3.1.2), stratified by pathogen, mechanism of resistance and infection site. This is because it is the only source of data that compares cefiderocol with other relevant comparators in the exact same isolate, and includes all types of Gram-negative pathogens in the same study (e.g. *Enterobacterales, Pseudomonas, Stenotrophomonas, Acinetobacter*). Other surveillance studies do not include cefiderocol, or all these pathogens as the other medicines have gaps in their activity spectrum and therefore, those pathogens/mechanisms of resistance where there they are not active, are not included in the surveillance studies. SIDERO, as with all other *in vitro* data studies does not account for susceptibilities to combination regimens that are not in a fixed dose combination formulation. Consequently, there are some comparisons for which there is no trial or *in vitro* data available, and assumptions will have to be made to model cost-effectiveness.

When combining the SIDERO data with UK epidemiology, by infection site, a weighted probability of *in vitro* activity per drug in pneumonia, or BSI can be computed which is comparable across treatments. This reflects the context of a critically ill patient with a suspected carbapenem-resistant infection that requires immediate treatment. The SIDERO data provide an estimate of the probability that the pathogen is susceptible to each drug; weighting it by pathogen distribution in the UK refines this to reflect the UK context. SIDERO is also the largest longitudinal surveillance study to date allowing comparison between cefiderocol and other treatment options across a wide range of pathogens (See Section 2.6 for more discussion of ongoing studies).

However, as observed in clinical trials, not 100% of the patients that have a documented susceptible pathogen will then have a positive treatment outcome. Estimates of the final expected clinical responses in the suspected patient population can be made by applying the clinical effectiveness rates from clinical studies in the carbapenem-resistant setting to the weighted likelihood of *in vitro* activity. This integrates local epidemiology, pathogen susceptibility, and likelihood of responding to treatment to provide an overall efficacy/usefulness estimate which can be used to estimate PNHB.

Table 26 compares the susceptibility of carbapenem-resistant pathogens (*Enterobacterales,* and *Pseudomonas aeruginosa*) to cefiderocol and comparators.155, 158, 159 In most underlying contexts, the susceptibility profile of cefiderocol is superior to the comparators, demonstrating its broad spectrum and ability to cover virtually all populations. When comparing to colistin-based regimens, the profile of cefiderocol is superior across all pathogens. Whilst the data presented here is specific to *Enterobacterales* and *Pseudomonas*, the same pattern (superior susceptibility profile) is also observed for other pathogen species (e.g. *Stenotrophomonas* and *Acinetobacter*).

Appendix M presents the case for carbapenem-susceptible infections. This is relevant in the risk-based empiric setting because some risk-based setting patients may be ‘false-positives’ – i.e. carbapenem susceptible or non-metallo-β-lactamase-producing but treated as if resistant or metallo-β-lactamase producing. This indicates a similar situation to the carbapenem resistant population, suggesting no consequence and in fact some immediate incremental benefit to treating false-positive risk-based empiric HVCS patients.

Table 26: susceptibility of different pathogens to cefiderocol and comparators – carbapenem-resistant infections

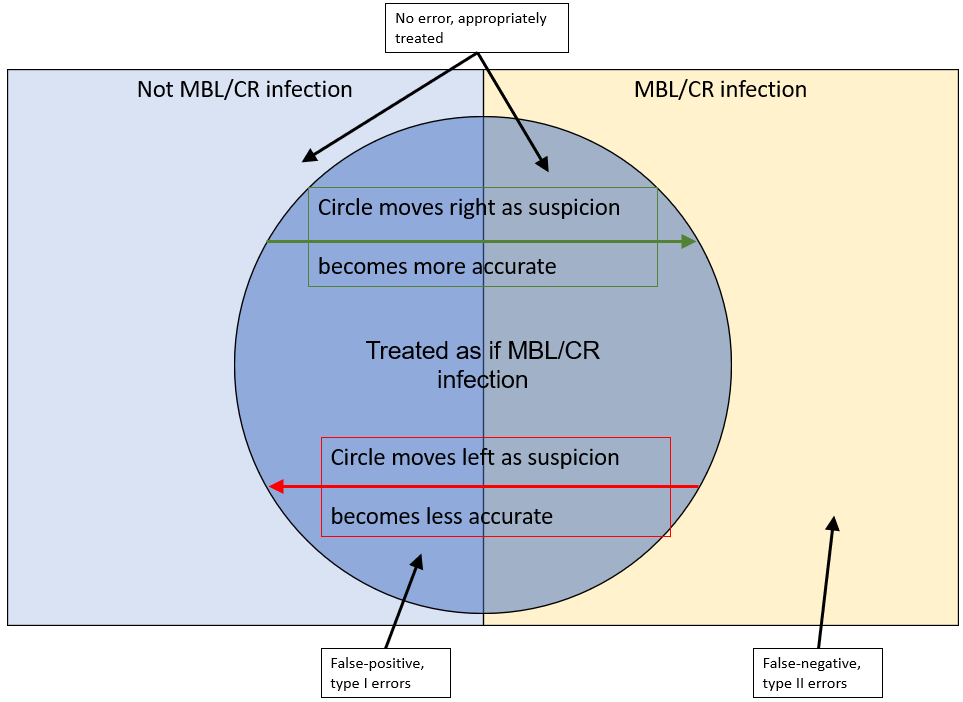
|  |  |  |
| --- | --- | --- |
| Intervention | *Enterobacterales* | *Pseudomonas aeruginosa* |
| ***cUTI*** | | |
| Cefiderocol | 75.0% | 97.9% |
| Ceftazidime/avibactam | 70.0% | 62.9% |
| Ceftolozane/tazobactam | 3.0% | 60.8% |
| Colistin & colistin based regimens | 68.0% | 100.0% |
| ***Pneumonia*** | | |
| Cefiderocol | 71.3% | 98.4% |
| Ceftazidime/avibactam | 71.9% | 68.6% |
| Ceftolozane/tazobactam | 5.1% | 68.6% |
| Colistin & colistin based regimens | 65.2% | 98.3% |
| ***BSI and sepsis*** | | |
| Cefiderocol | 74.8% | 97.9% |
| Ceftazidime/avibactam | 77.2% | 63.9% |
| Ceftolozane/tazobactam | 8.7% | 63.9% |
| Colistin & colistin based regimens | 67.7% | 97.9% |
| **Key:** BSI, bloodstream infection; cUTI, complicated urinary tract infection. | | |

#### Diagnostic precision and accuracy

The superior susceptibility profile of cefiderocol highlights the interaction between accurate prediction of high value population patients in the risk-based empiric setting and the cost-effectiveness of newer technologies that are targeted at those populations. The more precise the estimation of carbapenem resistance / metallo-β-lactamase production, the more frequently the most cost-effective initial treatment decision can be made. Equally, the more frequently the risk factors associated with the target populations can be identified and used to predict the characteristics of the underlying infection, the fewer patients that are in fact carbapenem resistant or metallo-β-lactamase-producing will be ultimately treated as if they are not. Figure 13 attempts to characterize the uncertainty in the risk-based empiric setting. This diagram was presented and discussed with a clinical expert in an interview. The expert stated that it is important to characterize both the accuracy (the position of the circle) and the precision (size of the circle) when estimating the high value populations for cefiderocol and determining the cost-effectiveness. The expert noted that for cUTI and blood stream infections, the pathogen and resistance mechanism are more easily identified than for HAP/VAP, so accuracy and precision are both likely to be higher than for HAP/VAP.

Cefiderocol has higher susceptibility values according to the SIDERO results for European patients with pneumonia. Consequently cefiderocol, which covers virtually all infections, has incremental value in the risk-based empiric setting defined by NICE and EEPRU via its ability to reduce the number of patients given an inappropriate therapy in the risk-based setting. We therefore recommend that the relationship between diagnostic uncertainty and susceptibility profiles be incorporated into the cost-effectiveness modelling strategy undertaken by EEPRU and NICE.

Figure 13: Risk of errors in taking action on the suspicion of high value populations



**Key:** CR, carbapenem-resistant; MBL, metallo-β-lactamase.

#### Time to effective therapy

Time to effective therapy is a useful indicative metric in understanding the underlying efficacy in the context of risk-based empiric treatment. This is because those treatments that have a higher probability of being effective will have, on average, a shorter time to effective treatment received. Those that immediately receive an appropriate therapy reduce aggregated values through having a time to appropriate therapy of 0. Consequently, as the cohort-level probability of the pathogen being susceptible to the antimicrobial in the risk-based empiric setting increases, the average time to effective treatment in that population decreases. For those that are not initially appropriately treated, time to confirmation of susceptibility is the primary determining factor of time to appropriate treatment. Therefore, time to appropriate treatment reflects the uncertainty surrounding risk-based empiric clinical decision making, the efficacy of different available treatments, and the rapidity of susceptibility confirmation as well as the clinical response to that confirmation. In the context of calculating PNHB, therefore, time to effective therapy could be a useful proxy to many of the cost-effectiveness drivers for which there is a paucity of data. We therefore recommend that EEPRU should investigate the usefulness of time to appropriate treatment for cost-effectiveness modelling.

Some evidence suggests that delays in provision of an appropriate treatment can lead to disproportionate increases in length of stay. 203 We consulted a clinical expert on this relationship, and the expert agreed with this concept.

There is some literature surrounding the topic of treatment appropriateness and length of stay. A detailed review and the derivation of the values in Table 27 is provided in Appendix H.2.1. To summarize, this literature suggests considerable variation by infection site, clinical setting, and appropriateness of treatment received. Following consideration of this literature, some suggested model input values for EEPRU are provided in Table 27.

Table 27: Suggested model inputs - Length of stay (days) in hospital by appropriateness of treatment received

|  |  |  |
| --- | --- | --- |
| **Appropriateness of the initial treatment, Treatment setting** | **Pneumonia** | **BSI and sepsis** |
| Appropriate initial treatment (CS or CR) | 10 | 15 |
| Inappropriate initial treatment, confirmed CR infection | 17 | 22 |
| **Key:** BSI, blood stream infection; CR, carbapenem-resistant; CS, carbapenem-susceptible; cUTI, chronic urinary tract infection. | | |

#### CREDIBLE-CR data

As discussed in Sections 2.3.4.1 and 2.4.1, the data from CREDIBLE-CR are useful because of the trial design. We recommend that the proportion of patients achieving clinical cure at 7 days after the last treatment completion day (TOC) be used. This provides enough time for the treatment to take effect and for the patient to respond, whilst at the same largely avoiding confounding through patients’ underlying mortality and morbidity (See Section 2.4.2.3).

Figure 9 in Section 2.3.4.1 summarizes the TOC outcomes for cefiderocol and BAT from the CREDIBLE-CR study in the general confirmed carbapenem resistant population. The performance of cefiderocol and BAT at TOC in the ITT population is comparable across this wider population.

The high-value clinical scenarios for cefiderocol as defined by EEPRU and NICE revolve around production of metallo-β-lactamase. A subgroup analysis of the CREDIBLE-CR data suggests a considerable increment in efficacy using the TOC endpoint (See Figure 12 in Section 2.4.2.4).

### Measuring the long-term consequences of different treatments

In some microbiology-directed settings (e.g. confirmed high clinical value patients with metallo-β-lactamase-producing infections), colistin-based regimens are a prominent comparator to cefiderocol. When consulted on this, the clinical expert highlighted some other particularly vulnerable microbiology-directed populations outside of the HVCS outlined by EPPRU. These included current renal replacement therapy and haemato-oncology patients. These patients already have, or are particularly vulnerable to, renal toxicity, and in many cases colistin is the only effective therapy available to treat their infection.

This is of concern given the well documented increased risk of acute kidney injury (AKI) and renal impairment (RI) associated with a colistin-based regimen 204 205. Figure 14 provides some literature data on incidence of AKI per day of colistin treatment received. This illustrates that the incidence is considerable.

Figure 14, panel a, provides data for incident AKI per day of colistin received against a control, whilst panel b provides colistin against colistin with ascorbic acid. As the duration of treatment suggested in Table 27 for HAP/VAP and BSI/sepsis patients is between 10 and 20 days, it is likely that AKI for colistin patients is commonplace in the cefiderocol high value populations. The consequences of these episodes are likely to be both long-term and expensive (See Section 3.3.3 for more details), and considerably more common in colistin patients compared to cefiderocol patients.

Previous literature has associated AKI with increased risk of hospitalization, increased length of stay, increases in short and long-term resource use, as well as short and long-term mortality.135 Zeng *et al.* (2014) define AKI using stages, based on serum creatine per the Kidney Disease Improving Global Outcomes (KDIGO) work group206, the RIFLE (Risk, Injury, Failure, Loss, and ESRD) criteria207, the Acute Kidney Injury Network (AKIN) criteria208, and creatine-kinase (CK) criteria. The percentage chance of hospitalization (USA study of more than 25,000 patients) for Stage 1, Stage 2, and Stage 3 AKI were 70.9%, 17.1%, and 12.0% respectively. These stages were also associated with considerable elevations of in-hospital mortality (no AKI: 0.6%, Stage 1: 5.3%, Stage 2: 13.4%, Stage 3: 35.4%; p < 0.001). Furthermore, in the sample examined, a considerably higher proportion of AKI patients were discharged into rehabilitation facilities or other medical institutions compared to non-AKI patients (37%, 12% respectively). This suggests that long-term health care resource use beyond just that associated with treating a serious infection is associated with AKI.

Renal failure is also an important consideration. A small proportion of renally impaired colistin patients are expected to enter either reversible or irreversible kidney failure, meaning some amount of renal replacement is required. The overall survival of patients after HAP/VAP and after sepsis are unlikely to be equal to that of the general population. Figure 15, panels b and c, provide some evidence of outcomes beyond infection in sepsis and pneumonia patients, respectively. We therefore recommend that EEPRU consider modelling what happens to patients after they recover from their infection, as this is likely to be an important factor influencing estimates of QALYs gained and lost.

Figure 15 (panel a) demonstrates the long-term overall survival of patients on renal replacement therapy pre- and post-kidney transplant209, whilst panel d provides estimates of overall survival in long-term care (which is required more frequently amongst patients with AKI/RI/requiring RRT) and demonstrates the need to consider long-term survival of patients and not to assume general population mortality post-infection.210 The cost associated with renal replacement is discussed in Section 3.3.3.2 (our estimates are £36,289.37 in the first year and £19,007.26 subsequently).211 From these data, a differential in the incidence of renal complications is likely to be associated with a differential in both overall survival and health care resource use costs over the lifetime of treated patients.

As discussed in Section 1.1.2.4, one key difference between the different available treatments in each setting is the expected time to receiving effective treatment. Reducing the probability of inappropriate treatment in an empiric setting through using a drug with a higher probability of susceptibility will reduce the expected (i.e. for the average treated patient) time to appropriate medication received. There is likely to be a relationship between time to effective treatment and clinical outcomes, both in the short-term (e.g. death from infection) and long-term, discussed in Sections 1.1.2.4 and 3.3.1. For instance, failure to appropriately treat sepsis may lead to septic shock, organ failure, and gangrene, with both respiratory and blood stream infections known to causes sepsis,212-214 as well as the relationship between sepsis and long-term cognitive deficits.215-217 Furthermore, in those patients with HAP/VAP, development of BSI/sepsis is an increasing possibility the longer the infection goes untreated with effective medicine.218-220 Consequently, if the expected time to receiving effective treatment for a risk-based empirically treated HAP/VAP case is reduced, so is the probability of developing sepsis, and subsequently any sequalae. These factors suggest a strong link between differences in time to effective treatment and long-term (potentially life-long) morbidity and mortality.

In conclusion, capturing downstream consequences on patients is likely to be a considerable portion of appropriately evaluating the cost-effectiveness of cefiderocol in those scenarios where there is likely to be a difference between arms in AKI (e.g. metallo-β-lactamase-producing infections where colistin-based regimens are the best current option).

Figure 14: Incidence of acute kidney injury per day of colistin therapy received.

|  |  |
| --- | --- |
| a) Miano *et al*. (2018) | b) Dalfino *et al*. (2015) |

**Notes:** Percentage chance AKI with subsequent days of colistin treatment. **a)** Retrospective cohort study of 150 propensity-matched patient. Patients were treated for multidrug-resistant *Pseudomonas*, *Klebsiella*, or *Acinetobacter* spp. **b)** A prospective, observational, cohort study involving patients with severe sepsis or septic shock who received colistin was performed. Solid black line represents patients who received colistin only. Solid grey line represents patients who received colistin plus ascorbic acid. Dashed line is for the whole cohort of patients.

### Post-infection survival

The overall survival of patients after HAP/VAP and after sepsis are unlikely to be equal to that of the general population. Figure 15 panels b and c provide some evidence of outcomes beyond infection in sepsis and pneumonia patients, respectively. We therefore recommend that EEPRU considers modelling what happens to patients after they recover from their infection, as this is likely to be an important factor influencing estimates of PNHB.

Figure 15: Long-term overall survival of patients after discharge from hospital

|  |  |
| --- | --- |
| a) Heldal *et al*. 2009 | b) Wang *et al*. 2014 |
| c) Holter *et al*. 2016 | d) Padrón-Monedero *et al*. 2020 |
| **a)** Kaplan-Meier plot of overall survival of patients on either a waiting list for a kidney transplant (blue line; N = 286) or who had received a kidney transplant (pink line; N = 233). Retrospective study of patients aged 70 or over, who started dialysis between 1990 – 2005, and were on the waiting list for a kidney transplant. Patient data was received from the Norwegian Renal Registry. Patients were censored from the waiting list plot at the time of transplantation, dotted line shows the time at which the two plots cross. **b)** Kaplan-Meier plot of overall survival of sepsis (N = 970) and non-sepsis (N = 28,694) patients in the USA. Population-based data from 30,239 community-based dwellings, adults aged 45 years and over. **c)** Kaplan-Meier plot of long-term survival of 259 patients discharged from hospital, following treatment for community-acquired pneumonia. Patients were submitted to general hospitals between 2008 – 2011, median age of 66 years, Norway. **d)** Retrospective cohort study of 689 patients in a nursing home, Spain.Adjusted cumulative all-cause mortality among plot, light grey line represents cumulative all-cause mortality of patients who did not suffer a fall. | |

## Cost and healthcare resource use identification, measurement, and valuation

Accurate estimates of healthcare cost and real resource use are important to capture the health benefits and cost offsets offered by cefiderocol. Cefiderocol has demonstrated a shorter time to effective therapy, greater overall survival, and long-term quality of life compared to comparator treatments in the HVCS and wider populations available in the UK clinical practice today (see Section 2.3). the below sections list the costs and resource use values we recommend for use by EPPRU.

### Time to effective treatment

As discussed in Section 1.1.2.2, the time to antibiogram outlined in PHE guidance (48 to 72 hours), is likely to be an underestimate of clinical practice. 88, 100 Time to effective treatment correlates with an increased risk of mortality in patients with aerobic Gram-negative bacteraemia26, and inappropriate treatment selection is associated with an increase in hospital stay, hospital costs, chance to be discharged to a hospice, and mortality; described in more detail in Section 3.3.3.

### Treatment costs

The de-linkage deal disassociates the use of the cefiderocol with the amount paid for it. Expected time on treatment for cefiderocol. Treatment costs for non-de-linked comparator treatments are listed in Appendix H.1.

The costs of carbapenem-resistance infections vs. carbapenem-susceptible infections have been explored in a UK hospital setting, with the costs of carbapenem-resistant infections being more than double (£49,537 vs £19,299) that of susceptible infections due to carbapenem-resistant infections being more challenging to treat; a delay in patient recovery (the increase in hospital-related costs per day in hospital explored in the below Sections), and an increase in patient morbidity and mortality.34

#### Time on treatment

For pneumonia patients, time on treatment for cefiderocol was 10.4 days for responders and 12.6 for non-responders requiring salvage therapy.221 BSI/sepsis patients, time on treatment for cefiderocol was 11.4 days and 12.6 days for responders and non-responders respectively.221 More details are provided in Appendix H.2.

More detailed reporting of our estimated time on treatment is provided in Appendix H.2. To summarize, for comparator therapies time on treatment was varied with respect to cefiderocol time on treatment. Some treatments like colistin had a longer time on initial therapy for responders (12.9 days221), whilst others like ceftazidime/avibactam had considerably shorter (7.7 days).222 However, very little data were found on time on treatment or time to salvage therapy for non-responders. Consequently, it may be necessary to assume this value or use structured elicitation to gain an understanding on it.

### Healthcare and resource use costs

An important aspect of capturing the value of a new antimicrobial product is accurately estimating displacement of resources, both whilst the patient is in hospital and after they recover.

We suggest that the following categories are particularly important to consider for each potential population:

* In-hospital costs
* Initial infection costs
* Cost to the NHS per day in hospital
* Transmission of disease (leading to hospitalization)
* Additional days in hospital due to renal toxicity
* Time ventilated and/or isolated
* Costs beyond the individual patient
* Closing a ward or hospital due to an outbreak
* Offsetting elective procedures due to infection risks
* Long-term costs to the NHS after infection resolution
* Renal replacement
* Long-term care
* Repeat infection

Cost to the NHS of end of life / palliative care during clinical failure

#### In hospital costs

The latest NHS reference costs (2018/2019)223 show that the national average unit cost for sepsis ranges from £494 to £3,476 and for pneumonia from £433 to £2,370, depending on complications and comorbidity score and number of interventions. The number of additional days in hospital for the inappropriate treatment of carbapenem-resistant and carbapenem-susceptible infections is 7 and 5.5 days respectively (Table 27; see Appendix H.2). Each additional day in hospital increases in-hospital costs, and an increase in time to effective treatment is known to increase mortality and likelihood of discharge to a hospice.203

One estimated risk of hospital-acquired pneumonia (HAP) per day in hospital is 0.32%, based on a study of 1,302 admitted to the Ninewells Hospital and Royal Victoria Hospital, NHS Tayside, Dundee between 2012 and 2013. Subject to some caveats and assumptions, this probability of transmission could be applied to the number of patients in hospital, to provide an estimation of new HAP patients generated. This phenomenon is one aspect in which this decision problem is inherently non-linear. The prevention of extended hospital stays due to improved time to effective therapy can prevent an agglomeration of HAP patients, meaning that there is a non-linear association between efficacy and outcomes.

Simon *et al*. estimates that the average number of additional days in hospital as a result of nephrotoxicity – increased risk of nephrotoxicity with days on colistin in outlined in Section 3.2.2 – is 5.2 days for patients who require renal replacement therapy (RRT) and 2.3 days for patients who do not require RRT, this is in addition to the number of days in hospital due to infection. We recommend EEPRU use the NHS reference costs for non-elective short stay General Renal Disorders without Interventions, with CC Score 3-5 (LA09N) as a proxy for additional days in hospital for nephrotoxicity without RRT, and non-elective short stay General Renal Disorders with Interventions, with CC Score 0-2 as a proxy for additional days in hospital for nephrotoxicity with RRT. Resource use costs for nephrotoxicity are outlined in Appendix H.3.

We recommend that our estimates of resource use per day in hospital, and post-infection are used, as well as factoring in modifiers to length of stay.

#### Long-term costs to the NHS after infection resolution

Renal replacement therapy is routinely used to treat patients with severe AKI.224, 225 Annual costs of nephrotoxicity, without RRT, have been estimated to be £173.32 in the first year and £89.80 in subsequent years.211 Assumed annual cost of nephrotoxicity, with RRT, and considering the cost of dialysis and kidney replacement, were estimated to be £36,289.37 in the first year and £19,007.26 in subsequent years. Details on the calculations used to estimate the costs of nephrotoxicity, both with and without RRT, and given in Appendix H.3. Utility values associated with nephrotoxicity and RRT, used by Simon *et al*., and which we encourage EEPRU to consider, are listed in the description of Simon *et al*. in Appendix F.1.1.

Zeng *et al*. (2014), describes a 3-fold increase in the probability of patients being discharged into long-term care vs. returning to home in patients who experience renal impairment (37% discharge to long-term care) vs. patient who did not experience renal impairment (12.3%).135 The weekly cost of one patient in long-term care (local authority own-provision residential care for older people (65+)) described in the PSSRU report (2020) is £1,288 establishment cost plus personal living expenses and external services per permanent resident week.226 We recommend that EEPRU incorporate simulation of patients going into care following treatment into their model, to capture the incremental value that cefiderocol has in terms of avoiding renal consequences.

The risk of repeat infection, following discharge from hospital is an important factor which can repeatedly elevate the mortality of a patient, as well as increasing cost to the NHS. Any factors influencing the risk of repeat infection must, therefore be taken into consideration to appropriately capture the value which a new antimicrobial brings to the system. Finally, the cost implications associated with the downstream consequences of delayed effective treatment should be captured, as medicines with a higher probability of being effective in the empiric setting will reduce the amount of patients initially treated with ineffective medicine. Because of this, less patients will face the consequences associated with delayed treatment, such as developing BSI/sepsis from HAP/VAP, the resource use consequences of this sepsis progressing, and the post-infection consequences.

#### End of life and palliative care costs

An increase in mortality is associated with length of stay in hospital203, post-infection versus general population227, 228, and renal replacement therapy.209 We recommend that EEPRU consider the increase rate of mortality in these scenarios, as well as the associated end-of-life and palliative care costs, as per standard NICE methods.

### Adverse reaction unit costs and resource use

Adverse reactions are discussed further in Appendix E. The main adverse reaction of interest with respect to cost-effectiveness in this context is renal impairment, which we are recommending should be captured via tracking its lifelong consequences on a patient. However, another factor which has been treated in previous analyses as an adverse event is *Clostridium difficile* infection. Cefiderocol may be associated with lower rates of CDI due to its aerobic Gram-negative only coverage (See section 2.5). However, rates of CDI are low for all comparators being considered by NICE and EEPRU, so the increment in PNHB associated with CDI is likely to be small. Although we do not consider CDI to be a major driver of the incremental PNHB of cefiderocol in the HVCSs defined by NICE and EEPRU, we do suggest that it could be one area of uncertainty warranting investigation. Consequently, we consider the only critically important adverse events to include in the cost-effectiveness modelling to be those summarized in Section 3.2.2 and the associated sections.

### Cost of comparator treatments

Comparators outside of the de-linkage deal still incur a cost to the NHS, and these costs will be offset by the introduction of cefiderocol. Therefore, we agree with Section 6.1 of the EEPRU cefiderocol protocol which states that the cost of “linked” comparators should be taken into consideration in the modelling approach.

## Consideration of the provisional approach outlined by EEPRU

Shionogi recognizes: i) the complexity of undertaking an evaluation in this extremely challenging therapeutic area; ii) the collaborative approach EEPRU and NICE have adopted in sharing the planned approach to undertaking the value assessment; and iii) that these plans are as yet unfinalized (the process requires this manufacturer submission be completed before EEPRU have finalized their approach). In that context of collaboration, we highlight below some of the specific proposals raised by EEPRU to date that may lead to a flawed estimate of cefiderocol’s value to the NHS –providing brief suggestions for improvement. Specifically, we discuss: i) the selection of the HVCVs (and the potential exclusion of the risk-based empiric population); ii) the approach of splitting the patient and population models (rather than using a dynamic model); and similarly, iii) the approach to incorporating the additional value elements.

***Selecting the HVCSs***

At the stakeholder engagement meeting in April, EEPRU raised the possibility that detailed quantitative analysis might be only undertaken in the confirmed metallo-β-lactamase population. Contrary to the EEPRU protocol the risk-based empiric treatment population would therefore not be included for detailed quantitative analysis. One reason given for this was the analytic challenge of modelling the expected value quantitatively, given the absence of directly relevant clinical trial data and the reliance – at least in part on *in vitro* data. Omitting this population from detailed analysis would severely inhibit the reliability of the overall value assessment. The reasons for this are: a) its clinical relevance (it is one of the populations prioritized by NHS England in their response to the draft scope)229; and b) the need to have more than one population modelled in depth if EEPRU are meaningfully to extrapolate value from the prioritized populations to the wider populations of relevance. Unless more than one population is modelled in depth it is very difficult to see how EEPRU can credibly determine whether other populations have greater per patient health benefits than patients in the microbiology-directed setting. Furthermore, the difficulties noted by EEPRU in estimation in the empiric context will arise in future evaluations and the opportunity to learn how best to deal with estimating this major source of value needs to be addressed now to inform future approaches as well as to deal fairly with cefiderocol.

We believe that EEPRU should revert from this suggestion and instead adopt the approach outlined in their protocol – including the risk-based empiric treatment Model. Although the data are necessarily sparser, the original EEPRU report anticipated the need to draw on expert opinion and *in vivo* data. In Section 3.2.1.1 we outline an approach, previously reviewed by EUnetHTA, that enables this. It draws on both *in vivo* and *in vitro* data to account for the fact that some patients who are susceptible will still not be treated successfully.

***Splitting the patient and population level models***

Shionogi were surprised to see that, contrary to the analytic approach in their original report and the model recently published by Gordon *et al.*, EEPRU are not undertaking their analysis with a dynamic transmission model.90, 199 We understand this is in part a result of resource constraints. While the practicalities of scope are important, we are concerned that the analytic approach will in effect assume the *population* growth of resistant strains is exogenous to the *patient* level effectiveness of cefiderocol (that population patterns of resistance can affect patient outcomes but patient outcomes will not affect the evolution of population patterns of resistance). As outlined in Section 2.5 there is strong evidence to suggest that increased duration in hospital stay, which could result from less effective therapies, results in higher transmission. It is therefore important that the benefits of improved efficacy at the patient level, reducing the time in hospital, not only result in estimates of improved outcomes at the patient level but are analytically enabled to influence the population growth trajectories of resistant strains.

Practically we encourage EEPRU to both investigate the impact of increased effectiveness on transmission and ensure that this influences not only the patient level model estimates but also those of the population model. Additionally, we encourage EEPRU to consider the heterogenous clustering of resistant strains between regions within the country. In hospitals, growth of resistant strains is likely non-linear and therefore modelling at ‘the average’ is likely to provide a flawed estimate of the aggregate population health benefit of a novel antimicrobial. Indeed, the distribution of resistant strains may be multi-modal. We would encourage EEPRU to explicitly consider the distribution of resistant strains across different regions and ensure the approach adopted to the analysis accounts for its likely complex nature and the potential nonlinear dynamics of the transmission risk within hospitals.

Additionally, as discussed in Section 2.3.5, resistance to cefiderocol is likely to develop more slowly than to historic antimicrobials. Instead of solely relying on historic trends to estimate the development of resistance to cefiderocol over time Shionogi recommend EEPRU explore the impact of a range of values; treating the data from historically launched antimicrobials as the most pessimistic in reference to expectations for resistance to cefiderocol.

***Partial consideration of the additional value elements***

The discussion above considers the implication of the proposed model structure for estimating transmission value. The approach suggested in the EEPRU protocol to the diversity, enablement and insurance value may also fail to capture the full value offered by a novel antimicrobial (we recognize this will always be a challenge).

In terms of diversity value, it is our understanding that this value, along with the other value elements, will only be estimated for the HVCS. For cefiderocol, in these contexts where treatment options are extremely limited, cefiderocol’s role in diversifying options may exist but in limited manner (as it may well become the option of choice). As discussed in Section 2.5, cefiderocol’s diversity value is likely to be much more substantial in the OXA and KPC populations (and potentially non-carbapenemase producing *Pseudomonas* species) where, though limited, alternative treatment options exist. In these populations, excluded from the HVCS, cefiderocol may have a role in reducing selection pressure on current antimicrobials and extending the time period for which they remain useful treatment options. We would encourage EEPRU to consider how diversity value may differ from one population to another.

With regards to enablement value, we note that the EEPRU protocol considers the enablement value of addressing *post* procedure complications. However, the proposed approach does not consider the value of addressing infections existing *prior* to the required procedure, preventing it from occurring (discussed in Section 2.5). We would recommend EEPRU investigate this, identifying via the literature and through discussions with clinical experts the magnitude of its importance. Shionogi’s discussions with clinical experts to date indicate this is a critically important contribution. For example, a number of patients with haematological malignancies may not be able to receive a stem cell transplant were it not for the availability of antimicrobials capable of effectively addressing current pathogens.

In terms of insurance value, and specifically cefiderocol’s potential ability to, “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.”, we have concerns about the reliance on probabilistic sensitivity analysis. The protocol does not outline the proposed approach in depth, it could be that EEPRU plan to: 1) identify from the literature and expert interviews the range of high consequence/low probability outcomes (see provisional suggestions in Section 2.5); 2) estimate the cost and health consequences of each; and 3) estimate the probability of each occurring in a world with and without cefiderocol. If done in this manner, with explicit characterization and incorporation of differing high consequence events, then we would agree with the approach. We believe this would be far more transparent than an alternative interpretation of the summarized approach. The latter would be that no explicit consideration will be given to differing specific high consequence events and instead that the analysis in general will be run probabilistically and the ‘worst outcomes’ for population net health, driven in general by the most pessimistic parameter values will be considered to capture states of the world with high consequence outcomes.

More generally we recognize that time, data and analytic constraints will prevent the full quantitative incorporation of these wider elements of value. We endorse EEPRU’s ambition to provide a very transparent account of where they have and have not managed to quantify the wider value elements.

## Validation

Shionogi will not be providing a cost-effectiveness model as a part of this submission. However, several recommendations have been provided both on approaches to capturing cost and value, along with data sources. To establish the extent to which clinical experts would support the use of these approaches and data sources, we consulted a clinical expert.

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# Appendices

Appendix B: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix C: Identification, selection and synthesis of clinical evidence

Appendix D: Subgroup analysis

Appendix E: Adverse reactions

Appendix F: Published cost-effectiveness studies

Appendix G: Health-related quality-of-life studies

Appendix H: Cost and healthcare resource identification, measurement and valuation

Appendix I: Suggested approached for EEPRU

Appendix J: Checklist of confidential information

Appendix K: Additional information on indirect and mixed treatment comparisons

Appendix L: Potential health state utility values for use in cost-effectiveness modelling

Appendix M: Susceptibility data from SIDERO for carbapenem-susceptible patients