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Assessing the Value of New Antimicrobials: Evaluations of Cefiderocol and Ceftazidime-Avibactam to Inform Delinked Payments by the NHS in England

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Abstract

Objectives The UK has recently established subscription-payment agreements for two antimicrobials: cefiderocol and ceftazidime-avibactam. This article summarises the novel value assessments that informed this process and lessons learned for future pricing and funding decisions.

Methods The evaluations used decision modelling to predict population incremental net health effects (INHEs), informed by systematic reviews, evidence syntheses, national surveillance data and structured expert elicitation.

Results Significant challenges faced during the development of the evaluations led to profound uncertainty in the estimates of INHEs. The value assessment required definition of the population expected to receive the new antimicrobials; estimating value within this heterogeneous population; assessing comparative efficacy using antimicrobial susceptibility data due to the absence of relevant clinical data; and predicting population-level benefits despite poor data on current numbers of drug-resistant infections and uncertainties around emerging resistance. Though both antimicrobials offer the potential to treat multi-drug resistant infections, the benefits estimated were modest due to the rarity of true pan-resistance, low life expectancy of the patient population and difficulty of identifying and quantifying additional sources of value.

Conclusions Assessing the population INHEs of new antimicrobials was complex and resource intensive. Future evaluations should continue to assemble evidence relating to areas of expected usage, patient numbers over time and comparative effectiveness and safety. Projections of patient numbers could be greatly enhanced by the development of national level linked clinical, prescribing and laboratory data. A practical approach to synthesising these data would be to combine expert assessments of key parameters with a simple generic decision model.

1 Introduction

The global spread of antimicrobial resistance (AMR), combined with a lack of new antimicrobial (AM) agents with efficacy against resistant bacteria, has created the public health challenge of untreatable infections. In recognition that few AMs under development target key resistant pathogens [1], a range of policies have been implemented to incentivise the development of new AMs that address unmet public health needs. To date, most of these policies have focussed on financial incentives that directly fund research and development (R&D) or lower R&D costs and

risks ('push incentives') [2]. Policy-makers are now exploring 'pull mechanisms' that reward the commercialisation of new AMs [3]. A wide range of pull mechanisms are being explored internationally including more favourable pricing arrangements for AMs, minimum revenue guarantees, and subscription style payments whereby total payment is independent of sales volume [4].

In the UK, a joint government and industry AMR working group, established in 2015, highlighted the need for a more appropriate payment model for new AMs [5]. The payment model should align payment with value, support AM stewardship goals by delinking payment from volume of drug sales, and generate predictable revenue smoothly over time. This objective is especially important because

Key Points for Decision Makers

NICE and NHS England recently completed a project to establish subscription-based payments for two new antimicrobials, cefiderocol and ceftazidime-avibactam. This required a novel approach to estimate population-level health benefits and costs, which informed the payment negotiations.

The estimates of value were highly uncertain due to the need to define acceptable usage of the antimicrobials, the need to model outcomes across highly heterogeneous populations, the paucity of directly relevant clinical evidence and reliance on in vitro susceptibility evidence; the absence of national data on the numbers of individuals with drug-resistant infections and the need to forecast numbers of drug-resistant infections over time.

Future evaluations to inform delinked payments should continue to assemble evidence relating to areas of expected usage, patient numbers over time and comparative effectiveness and safety. A practical approach to synthesising these data would be to combine expert assessments of key parameters with a simple generic decision model.

valuable AMs may be subject to strict stewardship, restricting use to cases of multi-drug resistance (MDR), making them unattractive to pharmaceutical companies under conventional payment models.

In 2019, the National Institute for Health and Care Excellence (NICE) and the National Health Service (NHS) England initiated a project to pilot a new healthcare technology evaluation process and delinked payment model for two AMs. A structured process [5] selected cefiderocol and ceftazidime-avibactam for inclusion within the project. The products were subject to evaluations by academics within the Policy Research Unit in Economic Methods of Evaluation in Health and Social Care Interventions (EEPRU).

NICE usually assesses the cost-effectiveness of a new drug by comparing the additional cost per quality-adjusted life year (QALY) associated with using the product for an average patient with a cost-effectiveness threshold. The drug price underpinning these calculations is then charged per unit of the product sold with total payments to manufacturers depending on both this price and volumes of use. The evaluations and decision-making processes associated with the delinked payment model differed from this approach and

were guided by the principles outlined in earlier work [6]. The delinked payment comprised an agreed overall annual payment that is independent of the volume of product sales. Value was defined as incremental net health effects (INHE) at the population (as well as individual) level as delinked payments to the companies should reflect overall value to the English NHS. Value should reflect impacts on treated patients as well as wider health benefits and costs (e.g. where using a new AM is expected to modify the number or nature of AMR infections in the future).

NICE established an Antimicrobials Evaluation Committee to consider the evidence and make recommendations on the level of population INHE offered by each product. These recommendations then informed the commercial negotiations between NHS England and the pharmaceutical companies to establish the terms of the delinked contracts that came into effect in July 2022.

The detailed evidence sources, methods and results of the evaluations have been published previously [7, 8]. This paper seeks to (i) provide a non-technical summary of the challenges associated with evaluating AMs and how these were addressed within the two appraisals; (ii) summarise the findings from the evaluations and identify key value drivers of relevance to future appraisals; and (iii) identify research priorities for evidence generation and modelling that could support more robust future decisions in relation to the pricing and reimbursement of new AMs.

2 Challenges in Quantifying the Value of New Antimicrobials and Approaches Taken

2.1 Overview of Methods

The evaluations undertaken used decision modelling to predict population INHE, informed by a series of systematic reviews, evidence syntheses, analyses of surveillance data and a formal structured expert elicitation (SEE) [9]. The decision models evaluated the costs and health benefits for patients throughout their lifetime, while a population-level model used a forecasting approach to combine the patient-level predictions for cohorts of patients expected to receive treatment in the next 20 years.

2.2 Defining the Patient Population for Modelling and Value Assessment

The licensed indications for both cefiderocol and ceftazidime-avibactam are broader than for other types of pharmaceuticals, covering a range of infection sites, organism types

and potential points in the clinical pathway.¹ To control the development of resistance to the AMs and preserve their long-term effectiveness, usage of both drugs within the UK is expected to be restricted to a subset of the licensed population with infections caused by MDR pathogens, though there is no clear agreement on how these pathogens should be defined. This is also reflected in international guidance; for example, the World Health Organisation places both AMs in its most restrictive ‘reserve’ category recommending these treatments only be used in last resort contexts (i.e. for life-threatening infections caused by MDR bacteria) [10].

Estimates of value should reflect long-term within-licence expected usage, which is challenging to define as it will depend on numerous factors including clinical guidelines, patterns of AMR and individual clinical decisions, all of which are likely to change over time. Quantifying the health and cost implications of this expected usage adds another layer of complexity, as it encompasses infections that differ in causative organism (pathogen, resistance mechanism), infection site and healthcare setting, amongst other patient characteristics.

The evaluations characterised the value of each drug across its range of expected uses via a two-step approach. First, decision modelling was used to assess value within a limited set of clearly specified scenarios considered to represent important uses of each drug. These indications were defined during the evaluation phase of the project and are referred to as the high-value clinical scenarios (HVCSs). Second, evidence from the HVCSs were re-scaled to provide quantitative assessments of value across all expected usage scenarios. This required additional assumptions about the likely similarities between the HVCSs and wider areas of expected usage (see Sect. 2.6).

The HVCSs were selected in consultation with stakeholders (including clinicians, microbiologists and pharmaceutical companies) to reflect areas of clinical use where resistance to existing AMs was significant, where cefiderocol and ceftazidime-avibactam were expected to offer significant improvements over existing treatments in terms of efficacy and/or safety and where sufficient evidence to inform quantitative modelling was expected to be available. The features of the HVCSs and the wider areas of expected usage are summarised in Fig. 1. The clinical populations of interest were defined according to the resistant pathogen type (including its resistance mechanism), the infection site (e.g. bloodstream) and the points in the clinical pathway where the new AMs were expected to be used, which we refer to as the treatment setting. Two treatment settings were

considered relevant: an empiric setting and a microbiology-directed setting. The empiric setting refers to treatment being initiated before confirmation of the causative pathogen due to the severity of the infection and strong suspicion that the pathogen is drug resistant. The microbiology-directed setting refers to treatment being initiated after confirmation that the infection is caused by a resistant pathogen, at which point AM susceptibility data (see Box 1) are available to inform treatment decisions.

2.3 Quantifying Value to Inform a Delinked Value-Based Payment

The evaluations used the principles described in Rothery et al. [6] to quantify the value of a new AM in health terms; that is its expected impact on population-level INHEs. The literature around the evaluation of antimicrobials has emphasised the multiple complex pathways by which new AMs may influence population health. For example, some authors have described these as the spectrum, transmission, enablement, diversity and insurance (STEDI) concepts of value [11, 12]. These broadly relate to long-term effects on the microbiome which can influence the likelihood of future resistant infections (spectrum), effects on the emergence and spread of AMR (transmission, diversity), effects on the delivery of procedures or other treatments (enablement) and the potential higher value of AMs in uncertain future states of the world where AMR is widespread (insurance). In principle, these effects on health and healthcare costs can be quantified using modelling methods [6]. However, in practice, it can be challenging to identify evidence that specific AMs will have these effects and to model their consequences. Section 2.7 discusses the extent to which cefiderocol and ceftazidime-avibactam are expected to deliver these effects and the extent to which these were quantified within the evaluations.

As for other pharmaceuticals, evaluations of new AMs should assess the products’ incremental value over-and-above existing therapeutic options. The present evaluations were therefore designed to capture the additional value of using cefiderocol or ceftazidime-avibactam over-and-above the clinical pathway that delivers the highest NHEs using existing AMs. Net health effects account for health benefits but also costs borne by (or savings accruing to) the NHS, converted to health foregone (generated) using a suitable measure of health opportunity cost [13]. A measure of health opportunity cost of £20,000/QALY is used within this paper as specified in the NICE scope for the evaluations [14, 15]. This means that for every £1 million of NHS budgetary spend on a particular programme, we expect that 50 QALYs will be foregone elsewhere within the NHS. As the purpose of the evaluation work was to inform a value-based payment

¹ Typically, pharmaceuticals are licensed for individual indications which include specification of the condition, its severity and the stage in the treatment pathway at which the treatment is licensed for use.

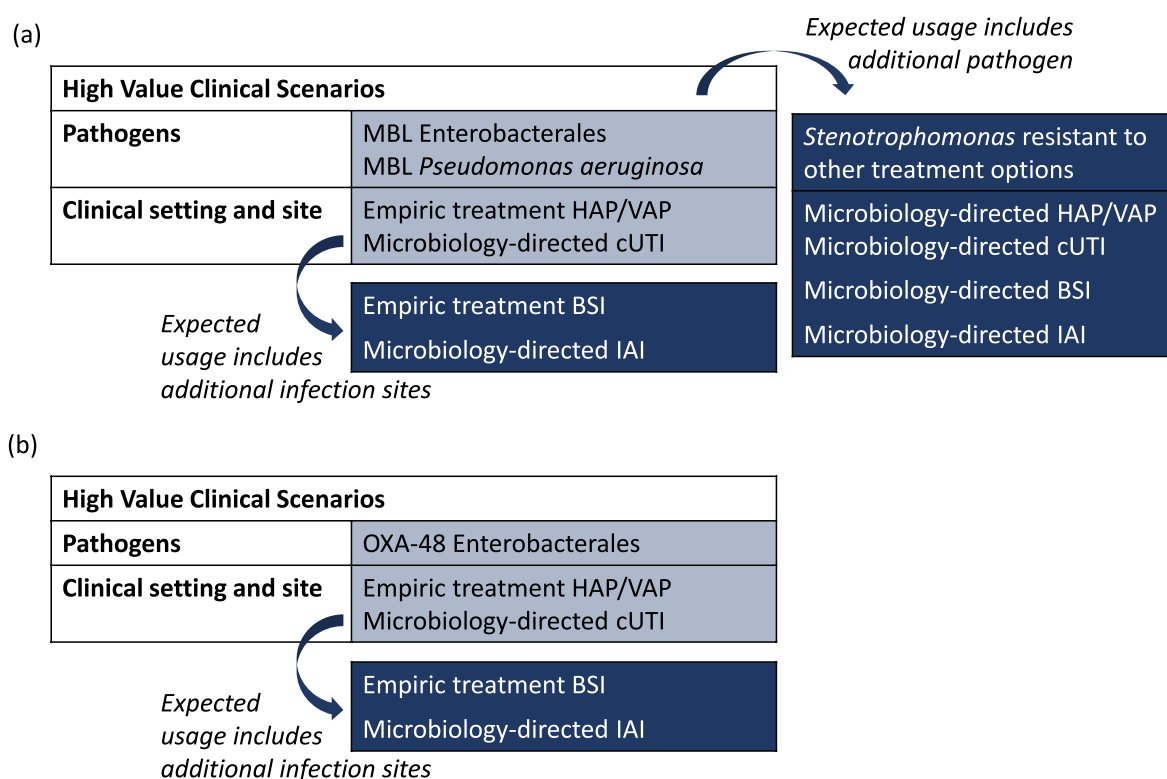


Fig. 1 High-value clinical scenarios and additional areas of expected usage **a** for cefiderocol and **b** for ceftazidime-avibactam. *BSI* bloodstream infection, *cUTI* complicated urinary tract infection, *HAP/V*

VAP hospital-acquired or ventilator-associated pneumonia, *IAI* intra-abdominal infections, *MBL* metallo-beta-lactamases, *OXA-48* oxacillinase-48

for the products, their drug acquisition costs were excluded from the calculation of population-level INHE.

This estimate of value, once monetised by a suitable measure of health opportunity cost, can inform the maximum appropriate payment for the products and thus set a starting point for commercial negotiations.

2.4 Assessing Comparative Effectiveness and Safety

Given the anticipated paucity of clinical evidence of direct relevance to the HVCSs, systematic reviews used a mapping approach that focussed on a broad evidence base for the products, including observational and in vitro data. Although the regulatory approval of both drugs was supported by multiple randomised controlled trials (RCTs), these trials were considered of low relevance to the expected clinical usage of the products because they tended not to include patients infected with MDR pathogens [6]. Relative treatment effects between the AMs and their comparators from these trials cannot be reliably generalised to infections caused by MDR pathogens, since the comparators are expected to show significantly diminished effects due to resistance. Whilst the mapping also identified several observational studies,

these included small numbers of patients of relevance to the HVCSs and exhibited high levels of heterogeneity with respect to prognostic factors, making any accounting for confounding very challenging.

In this context, in vitro microbiological data were also systematically reviewed, focussing on susceptibility studies (see Box 1). For both drugs, susceptibility studies conducted on the pathogen and resistance mechanisms of interest were systematically searched and synthesised using a network meta-analysis. The results of this network meta-analysis informed the decision modelling.

Although the susceptibility studies had high internal validity and covered many comparators, they were very heterogeneous in nature (e.g. the threshold value ‘breakpoints’ used to define resistance differed across studies and over time). The results of the network meta-analysis synthesising this evidence had wide credible intervals, and using this evidence to inform clinical efficacy within the decision model introduced a high degree of uncertainty.

Another key driver of uncertainty was the lack of evidence relating to the quantitative relationship between susceptibility and important patient outcomes such as

mortality and hospital length of stay.² Given the lack of directly relevant clinical evidence this element of the model was informed by a range of evidence of lower quality and/or relevance including clinical opinion, SEE and indirectly relevant clinical evidence.

An important potential advantage of new AMs is their ability to avoid the use of more toxic AMs such as colistin, which may represent the only alternative treatment to which an infection is susceptible. Clinical input indicated that the most important safety advantage of the new AMs was expected to be the reduced risk of acute kidney injury (AKI), and its sequelae, compared with colistin and aminoglycoside-based therapy. AKI risk was estimated using clinical data and assumptions required to generalise the available data across comparators, and the long-term consequences of AKI for health and healthcare costs were modelled.

Box 1: An introduction to susceptibility evidence

The objective of susceptibility studies is to classify bacterial samples taken from infected patients as susceptible or resistant to specific antimicrobials. This information can be used to better predict treatment response at the individual level to inform treatment decisions, and at the population level to inform regulatory decisions and guideline development. It is particularly important in understanding the likely effectiveness of antimicrobials against MDR infections as *in vivo* clinical data may be difficult to obtain. Susceptibility studies involve growing, in a laboratory setting, bacterial samples obtained from patients with infections. A range of antimicrobials are applied to these samples at increasing concentrations. The objective is to identify what concentration of drug is required to inhibit bacterial growth compared to a threshold value (a drug-specific breakpoint). The proportion of samples where the drug concentration required to inhibit bacterial growth exceeds the breakpoint represents the proportion of samples exhibiting resistance, and the complement of this proportion is the proportion of samples exhibiting susceptibility.

2.5 Quantifying Long-Term Population-Level Effects Within the HVCSs

To aggregate patient-level lifetime predictions of QALYs and costs to the population level, the size and expected growth of the eligible patient population in England for each HVCS was estimated. A central component of these predictions was understanding the emergence of resistance to the new and existing AMs over time.

² Producing estimates of clinical outcomes from susceptibility data also required additional assumptions. For example, patients' susceptibility to combination therapies was based on mathematically combining individual drug susceptibilities. For patients who received treatment empirically due to a suspected MDR infection but who had an infection caused by a different pathogen, assumptions about the susceptibility of that pathogen were made.

National-level laboratory data on samples tested for the pathogen/resistance mechanism combinations of interest were supplied to the study team by Public Health England (now the UK Health Security Agency). These data informed statistical forecasts of the number of resistant infections over time. As these laboratory datasets do not contain clinical information, infection sites and treatment setting had to be inferred from the available information. This introduced uncertainty in patient numbers and therefore the population-level predictions, as discussed in Sect. 3.

The emergence and spread of resistance to AMs is very difficult to predict [16]. In light of this, a broad range of scenarios were used to reflect the potential emergence of resistance to cefiderocol and ceftazidime-avibactam, informed by international data on the emergence of resistance to existing AMs. Changes in resistance to existing AMs within the HVCSs over time were not modelled due to a lack of evidence of temporal trends within the data supplied by Public Health England, though the available data were sparse.

2.6 Quantifying Long-Term Population-Level Effects Across Expected Usage

Population-level long-term INHEs for the HVCSs were re-scaled to reflect expected usage beyond the HVCSs. This re-scaling was based on population size estimates from the national-level laboratory datasets, and the use of expert opinion to inform which cost and QALY estimates from the HVCS were likely to represent the best proxies for the additional areas of expected usage (see Fig. 1). For example, the benefits and costs of using cefiderocol in the empiric setting to treat bloodstream infections suspected to be caused by MBL *Enterobacterales* were assumed to be best proxied by evidence on treating HAP/VAP in the empiric setting, where MBL *Enterobacterales* is the suspected causative organism.

2.7 Reflecting complex health effects of new antimicrobials

As discussed in Sect. 2.3, the wider value of AMs has been discussed within the literature using the STEDI concepts of value. Given the expected restricted use of both AMs, clinical advisors to the project did not anticipate that either AM would significantly impact on the number of future infections that are resistant to existing AMs at the patient or population level (i.e. spectrum, diversity and transmission value were not, on balance, expected to be significant sources of additional health benefits from these antibiotics). The potential for both AMs to deliver higher value in the future as the number of infections resistant to existing antibiotics rises (see Sect. 2.5) was reflected within the model. This was quantified by incorporating growth in the numbers of patients within the HVCS and additional areas of

Table 1 Summary of patient-level INHEs (QALYs) by HVCS. Results presented as base-case (scenario range across all scenarios considered)

	Empiric HAP/VAP	Microbiology-directed HAP/VAP	Microbiology-directed cUTI
Cefiderocol in MBL <i>Enterobacterales</i>	0.15 (0.00–0.23)	0.02 (0.01–0.06)	0.02 (0.01–0.06)
Cefiderocol in MBL <i>Pseudomonas aeruginosa</i>	0.15 (0.00–0.22)	0.15 (0.01–0.25)	0.15 (0.01–0.25)
Ceftazidime-avibactam in OXA-48 <i>Enterobacterales</i>	0.16 (0.00–0.26)	0.08 (0.05–0.12)	0.08 (0.05–0.12)

Measure of opportunity cost = £20,000/QALY.

cUTI complicated urinary tract infection; HAP/VAP hospital-acquired or ventilator-associated pneumonia; HVCS high-value clinical scenario; INHE incremental net health effects; MBL metallo-beta-lactamases; OXA-48 oxacillinase-48; QALYs quality-adjusted life years

expected use and by reflecting future states of the world where these growth trajectories were higher or lower (via the probabilistic sensitivity analysis). However, it is unlikely that this fully characterised these uncertainties, that is, insurance value may have been only partially reflected. It was considered plausible that use of cefiderocol and ceftazidime-avibactam could facilitate other treatments and procedures for certain patient groups. These enablement benefits were not reflected within the modelling due to a lack of evidence on how the availability of these antibiotics might influence broader clinical decision-making. This remains an important area of uncertainty and we return to this topic in the discussion.

3 Findings and Use Within Decision-Making

The patient-level results are presented in Table 1. These represent the expected additional INHEs of having access to cefiderocol or ceftazidime-avibactam within each indication compared with the best available alternative treatment. The patient-level INHEs are perhaps lower than might be expected in the context of severe infections which potentially have no effective treatment options. This reflects the susceptibility evidence which suggests that even in the context of the MDR infections considered within the HVCSs, many patients have infections caused by pathogens which are still susceptible to some treatments, albeit often more toxic treatments such as colistin. The health benefits therefore largely reflect those associated with safety, although for a small proportion of patients resistant to all available treatments, efficacy benefits (e.g., efficacy driven changes in survival) are expected and reflected within the models. Survival extensions were modest due to the profile of patients developing MDR infections in the UK who tend to be older and highly comorbid, and therefore, have relatively low life expectancies even after recovery [17].

In general, INHEs are higher in the empiric setting than the microbiology-directed setting. This is because, once susceptibility results are known, many patients within the model can be treated with a non-colistin or non-aminoglycoside-based AM to which they are susceptible and would,

therefore, not be expected to receive the new AMs. The exception to this is in patients with infections caused by metallo-beta-lactamase (MBL) *Pseudomonas aeruginosa*, where a high proportion of patients were estimated to be susceptible only to the more toxic treatments. Uncertainty in the estimated patient-level benefits is high, as shown in the scenario ranges. This is attributable to uncertainty in: the susceptibility evidence, the proportion of patients presenting in the empiric setting who have an MDR infection, the risk of kidney damage associated with different AMs and the long-term survival of patients with MDR infections.

Due to the uncertainties in the evidence base and the associated uncertainty in decision-making, the population-level results are presented for two different approaches to classifying infection site using laboratory specimen site data, two alternative statistical models for forecasting the number of MDR infections over time (a ‘persistent trend’ model whereby the observed trend is assumed to continue over time and a ‘damped trend’ model whereby population growth approaches zero over time) and a range of scenarios relating to emergence of resistance to cefiderocol and ceftazidime-avibactam. As presented in Table 2, across the population-level results there is a four-fold difference in population-level INHE.

The layers of uncertainty at the parameter, scenario and population-level collectively contribute to even broader uncertainties in INHEs than presented here. For example, for cefiderocol, combining the scenario analyses and population-size uncertainties suggested a range of total INHEs of 419–4864 (see the full reports for further analyses [7, 8]).

NICE’s Antimicrobials Evaluation Committee considered their preferred assumptions with respect to the estimation of population INHE [18, 19]. For both drugs, when taking into account available evidence and advice from clinical and infectious disease specialists, they preferred: the clinical advisor infection site classification; the use of persistent trend models to reflect population growth; a 5% increase in resistance to cefiderocol and ceftazidime-avibactam over 20 years; and introduction of an additional assumption that, due to toxicity concerns, 20% of people cannot have colistin or aminoglycosides even if no other effective AM is available.

Table 2 Summary of population-level INHEs (QALYs) across population-level base-case scenarios

Source of baseline population estimate	Statistical model used to reflect population growth rate	Cefiderocol		Ceftazidime-avibactam	
		Predicted patients initiating treatment over 20 years	Range of population INHEs across resistance scenarios	Predicted patients initiating treatment over 20 years	Range of population INHEs across resistance scenarios
PHE categorisation of infection sites	Model with damped trends	8671	896–1093	5287	531–673
	Model with persistent trends	13,488	1291–1625	11,742	1026–1390
Clinical advisors' categorisation of infection sites	Model with damped trends	16,669	2064–2499	9056	892–1134
	Model with persistent trends	24,969	2861–3559	20,112	1719–2342

Base-case scenario used for patient-level results, measure of opportunity cost = £20,000/QALY. The clinical advisors comprised clinicians and microbiologists involved in the treatment of highly resistant infections. PHE (now the UK Health Security Agency) is an executive agency of the Department of Health and Social Care and responsible for the collection and interpretation of national-level information relating to AMR.

INHE incremental net health effects, PHE Public Health England, QALYs quality-adjusted life years

Using these assumptions, the 20-year population INHE was estimated to be approximately 5400 QALYs for cefiderocol and 3700 QALYs for ceftazidime-avibactam.³

The Committee concluded that the population of patients eligible for each drug was under-estimated, and that some aspects of value had not been captured by the evaluations. In particular, the Committee considered that the model had not fully accounted for the emergence of resistant infections as the growth in the number of patients within some HVCSs was under-estimated and resistance to comparators within the HVCSs was assumed to be constant over time. In addition, the Committee's view was that there were likely to be pathways through which the AMs delivered value which had not been quantified. The Committee considered that both drugs were likely to deliver value by enabling other medical treatments and procedures to go ahead; by reducing the emergence of resistance; and by providing insurance that, in the face of a catastrophic increase in MDR infections, additional effective treatment would be available. Ultimately, the Committee concluded that, over the 20-year modelled time horizon, the INHE of cefiderocol would be approximately 16,200 QALYs, and that of ceftazidime-avibactam would be 8800 QALYs. These increased QALY estimates reflected subjective judgements formed by the committee on the basis of some evidence relating to ceftazidime-avibactam usage and deliberations by the committee on the likely magnitude of benefits not captured by the quantitative evaluations.

4 Priorities for Evidence Generation and Modelling

The challenges of conducting RCTs for new antibiotics in the patient populations expected to receive the treatments are well documented [6]. However, understanding where products are expected to be used (e.g. via mapping of HVCS) earlier on in the clinical development pathway may help to inform where alternative trial designs, additional data collection within trials or other forms of pre-launch evidence generation may be valuable to inform future value assessments.

Linking clinical, prescribing and microbiology (laboratory) data at national level would allow for more robust estimates of patient population size. It would also provide more detailed UK-specific data about pathogens' susceptibility to existing AMs and how this may change over time and in response to AM use, AM toxicity and how these link to long-term outcomes. Proposals to develop such data linkages are increasingly being considered by policy-makers to support a range of health policy objectives [20]. Undertaking analysis of these linked data is likely to require time and resources beyond those typically available within a NICE HTA process, and is therefore likely to require separate funding. However, the information collected could potentially inform multiple AM appraisals.

Post-approval evidence on new AMs, including cefiderocol and ceftazidime-avibactam, is being collected via the UK Antimicrobial Registry (UKAR) and the NHS England Blueteq high-cost drug management system [21]. This will provide information on usage patterns as well as clinical and safety outcomes. Although these data offer the opportunity to estimate many parameters more reliably, it is unlikely to provide robust information on the comparative effectiveness

³ This value is higher than the ranges within Table 2 as it also accounts for 20% of patients being ineligible for colistin/aminoglycosides.

and safety of the new drugs compared with existing AMs (as this would require appropriate controlling for confounders which are likely to be unobserved and/or difficult to capture). Post-approval, routine randomisation may provide one vehicle to assess comparative effectiveness, for example, using novel trial designs to allow for randomisation to be personalised according to an individual's susceptibility, toxicity profile and other factors [22]. However, amongst those individuals most able to benefit, such as those who are resistant to all alternative AMs and susceptible to the new agent, it is unlikely that randomisation would be considered ethical due to the lack of equipoise. In addition, whilst post-approval RCTs offer the potential to improve decisions about the preferred treatment option for individual patients, it is less clear whether the evidence collected should be used to adjust payments post-approval and who should pay for this evidence generation; we return to this topic in the discussion.

The contribution of new AMs to supporting the delivery of other treatments and procedures was identified as a potentially important source of unquantified value in the evaluations. Further work is required to identify the pathways through which new AMs may deliver these benefits and the evidence that could be used to assess their magnitude.

5 Informing Value-Based Payments in the Short Term

NICE and NHS England have recently launched a new model for assessing the value of those new antibiotics that qualify for subscription-style contracts. Under this new model, a points system based on clinical criteria will form the basis for assessing value and therefore payment level [23]. This clinical points approach aligns with proposals under discussion internationally [25, 26].

The move towards a clinical points system appears to reflect two intertwined factors [24]. Firstly, economic evaluation of AMs is resource intensive and this is likely to be particularly problematic given that international coordination is essential to achieve a pull incentive, and many countries do not have well-developed HTA capacity. Secondly, there is considerable uncertainty in the evidence available to inform the evaluations, and therefore in the resulting predictions of costs and INHEs arising from any economic evaluation.

For a subscription-based purchasing arrangement to align with the objective of maximising long-term population health, we would argue that it should: (i) be evidence-based; (ii) define value as the expected contribution of the new AM to population-level INHE; and (iii) ensure payment levels do not impose health opportunity costs that exceed the overall population-health benefits of the new AM. Although

NICE's move to a more pragmatic approach is a reasonable objective, it is not clear whether a clinical points-based approach adheres to these principles. Many of the scored attributes relate to product novelty and unmet need, neither of which maps clearly to health benefits or resource savings. Furthermore, it is unclear how other important aspects such as incremental clinical benefit will be assessed without conducting an exercise similar to the evaluations described here; that is, requiring a careful consideration of the nature and number of MDR infections in which the new AM is expected to be used, and consideration of how the evidence base that informed regulatory approval could shed light on comparative effectiveness and safety.

It seems likely that, to ensure payment levels are aligned with population-level INHE, some form of decision modelling will be required. More pragmatic approaches to this decision modelling could include subject-matter experts being presented with information on the key determinants of value as outlined in Table 3, and a view formed on likely parameter values through deliberation or SEE. These parameter values could then be fed into a simple transparent decision model.

Table 3 categorises evidence sources according to whether they are likely to be specific to the AM and pathogen in question, generalisable across products targeting the same pathogen, or generalisable across products targeting the same infection site. This may enable some aspects of the model to be developed as generic across appraisals. For example, the links between susceptibility/safety events and long-term outcomes could be developed for a series of important infection sites. Similarly, patient numbers could be estimated for key pathogens which represent important threats and for which several new products are in development.

The susceptibility, trial and observational evidence for new AMs and comparators should be identified via systematic review (which could be undertaken by the manufacturer or an independent group). Data on long-term outcomes and patient numbers would most appropriately be established from national-level data, or where this is not feasible from sub-national level datasets and/or the published literature.

In common with a clinical points-based system, a publicly available model would help manufacturers to better understand how value will be rewarded. By allowing companies (or public sector organisations involved in AM R&D) to undertake early value assessments of assets under development, the model could inform stop-go decisions in the clinical development process and help manufacturers to identify evidence priorities to support HTA.

Table 3 Value determinants and evidence required to support product value for new antimicrobials

Key determinants of value of new antimicrobials	Evidence required to support value assessment	Likely generalisability of evidence
Definition of areas of expected usage now and in the future	Susceptibility, trial and observational evidence for new anti-microbial and comparators to identify usage with potentially important incremental clinical and/or safety benefits	Antimicrobial and pathogen specific (and infection site specific for in vivo evidence)
Numbers of patients over time in areas of expected usage	National-level laboratory and dispensing data* Observational data* International resistance evidence on emerging threats	Pathogen and infection site specific (some evidence may be drug specific)
Comparative effectiveness, safety in areas of expected usage, link to long-term health outcomes and costs	Susceptibility, trial and observational evidence for new anti-microbial and comparators describing clinical and/or safety benefits Surveillance data on resistance to existing antimicrobials and how this is changing over time to inform new drug and comparator resistance emergence** Observational data on mortality and length of stay dependent on susceptibility and safety	Antimicrobial and pathogen specific (and infection site specific for in vivo evidence) Pathogen specific Infection-site specific
Implications of mode of delivery	Administration costs of new antimicrobial and comparators, link between mode of delivery and length of stay	Antimicrobial and infection-site specific

*In the long-term may be replaced by national-level linked clinical, prescribing and laboratory data

**Though this would ideally be linked to volume of use, methods have not yet been developed to quantify this link robustly.

6 Discussion and Conclusions

The evaluations of cefiderocol and ceftazidime-avibactam conducted to inform recent UK subscription payment agreements represented a first opportunity to quantify the population INHE of new AMs. The detailed methods for the evaluations have been published previously [7, 8]. The contribution of this paper is to provide a non-technical overview of the specific challenges associated with evaluating AMs and methods for addressing these, as well as the main drivers of population-level INHEs. Additionally, it highlights priorities for future evidence generation, modelling methods and the development of pricing and reimbursement policies. These insights have broad relevance to pricing and reimbursement decisions about AMs internationally.

The appraisals were resource intensive, and the resulting assessments of value were highly uncertain. This was for a range of reasons, most notably the need to identify the clinical parameters defining acceptable usage, the need to model outcomes across highly heterogeneous populations, the absence of directly relevant clinical evidence and reliance on *in vitro* susceptibility evidence to predict therapeutic benefit and the absence of national data on the numbers of individuals with specific profiles of MDR infections.

The Antimicrobials Evaluation Committee concluded that the most plausible population-level INHE for the drugs was 2–3 times higher than the quantitative evaluation results derived using Committee's preferred assumptions and parameter values. The re-scaling of the quantitative evaluation results was based on subjective judgements accounting for data relating to current usage of ceftazidime-avibactam and expert opinion from within the Committee. The discussion of additional sources of value within the NICE guidance documents contain several aspects of value which had already been quantified within the evaluations, casting doubt on the rigour of the approach taken by the Antimicrobials Evaluation Committee. The focus on the STEDI values throughout the process [11, 12] appears problematic given the difficulty all stakeholders faced when describing and evidencing how the specific AMs could deliver these potential benefits. In addition, the subjective basis for the final estimates of INHE (and associated payments) undermines one important objective of a pull incentive, which is to provide a clear signal of what health systems value and how this can be evidenced.

NICE and other international decision-makers considering implementing subscription-style contracts for new AMs are moving towards using a points system based on clinical criteria to determine payment levels. This reflects a range of concerns, some of which relate to the resource requirements of the evaluations which are likely to be considerable in terms of time, money and expertise. The resourcing for

each evaluation was equivalent to that of a NICE diagnostic assessment review (DAR) or multiple technology assessment (MTA). It was challenging to complete the work within this resource envelope, which is perhaps unsurprising given that MTA/DAR projects typically focus on a single indication (with other substantively different indications being scoped as separate projects), whereas the current work looked at several indications, and required estimation of population-level effects over time for multiple cohorts. Whilst other concerns relate to the uncertainty in the evidence and modelling, these concerns do not seem to justify moving to a clinical points-based system. The same evidential uncertainties relating to the potential magnitude of population health benefits remain, regardless of the mechanism used to measure and weight the dimensions of benefit.

Some have argued that payments for new antibiotics should be based on costs of drug development [25] rather than the value delivered by the new drug. Although this would incentivise investment in R&D, it would provide no incentive to develop products that deliver value to health systems and run the risk that any health benefits provided by these products are more than offset by the health opportunity costs associated with paying for them. Application of value-based rather than cost-based pricing may mean that the payments made for a specific product do not fully offset the sunk R&D costs. This is entirely appropriate and signals that the health system won't encourage R&D to the detriment of overall population health. Application of value-based pricing shouldn't prevent products that have already been developed being used. Once a product has been developed, R&D costs are 'sunk', so the manufacturer should be willing to supply the medicine as long as the payments cover the costs of production and supply.

We propose that one pragmatic approach to assessing population INHE to inform payments would be to develop a simple decision model that was applicable to a broad range of antimicrobials, and parameterised using expert assessments of key parameters. Under our proposals, these assessments would be informed by evidence relating to areas of expected usage, patient numbers over time, comparative effectiveness and safety and how these translate to costs and health outcomes, as well as any implications of mode of administration. In the medium term, the availability of national-level data linking clinical, prescribing and microbiology information would enable more robust value assessments. Post-approval trials with routine randomisation may also offer opportunities to improve comparative effectiveness and safety estimates in some contexts.

Despite the many opportunities to improve the evidence base underpinning value assessments for new antibiotics, there will remain profound uncertainty about the numbers of patients who may benefit from new antibiotics in the future. These numbers will depend on the emergence and spread of

AMR, which in turn depends on poorly understood biological processes as well as human activity across health and non-health sectors, within and outside the UK [16]. There is also profound uncertainty about the role and value of antibiotics as health systems evolve to mitigate the effects of AMR [27]. These concerns about uncertain futures in part seem to have driven some of the NICE committee decision-making about value and ultimately the payments. Further research to identify methods for quantifying these systemic risks, reflecting them within value assessments for new antibiotics and other interventions and using this to inform resource allocations decisions is warranted.

An important question is whether post-approval evidence should inform adjustments to payments (the contracts relating to payment for cefiderocol and ceftazidime-avibactam include a review at 3 years to inform the optional remaining 7 years of the contract). Although this would better align payments with value delivered to the NHS, it would add additional uncertainty to manufacturers regarding revenue in a context where investment conditions are already considered unfavourable. In the USA, the opposite has been proposed within the PASTEUR legislation, which allocates a value at an earlier stage of development, and allows payment contracts to remain unchanged, even if the targeted pathogen is no longer considered a significant threat at the time of approval [26]. Further research is required to assess the potential costs and benefits of conditional reimbursement in this context.

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Declarations

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Ethics Approval Ethics approval for the expert elicitation exercise was granted from the University of York Department of Health Sciences Research Governance committee (reference no.: HSRGC/2021/448/G; date of approval: 14 May 2021). No other activities required primary data collection, so no further ethics approval was required.

Consent to Participate The experts included within the expert elicitation exercise received a Participant Information Sheet and completed a Participant Consent Form. These materials were reviewed as part of ethics approval.

Consent for Publication (from patients/participants) Consent for publication of results relating to the elicitation exercise was sought as part of the overall consent to participate process.

Data Availability The only primary data collection for this study related to the expert elicitation; ethics approval for this element of the study does not permit data sharing. All queries should be sent to the corresponding author.

Code Availability The code is available from the authors by email request.

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