FRAMEWORK FOR VALUE ASSESSMENT OF NEW ANTIMICROBIALS

Implications of alternative funding arrangements for NICE Appraisal

Authors: Claire Rothery¹, Beth Woods¹, Laetitia Schmitt¹, Karl Claxton¹,², Stephen Palmer¹, Mark Sculpher¹

¹ Centre for Health Economics, University of York
² Department of Economics and Related Studies, University of York
CORRESPONDENCE TO:

Claire Rothery
Centre for Health Economics
University of York
claire.rothery@york.ac.uk

Mark Sculpher
Centre for Health Economics
University of York
mark.sculpher@york.ac.uk

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**CONTRIBUTION OF AUTHORS**

All authors contributed to the conception of the research study. CR, BW and LS carried out the analysis with input from KC, SP, and MS. CR led the writing of the report with input from LS.
1. EXECUTIVE SUMMARY

Antimicrobial resistance (AMR) is a complex issue of major global concern, and infectious organisms are now becoming increasingly resistant to the array of existing antimicrobials (AMs) available. At the same time, the pharmaceutical and biotechnology industry is becoming reluctant to develop novel AMs because of their expected limited return on investment. The problem is compounded further by public health and conservation goals that require AMs to be used judiciously and, in some cases, only as last resort therapies, in an effort to curb the rise in AMR. This is increasingly difficult for multi-drug resistant (MDR) pathogens where the number of available AMs is decreasing at an alarming rate, to the point that more patients will eventually die from previously treatable infections.

The O’Neill report on tackling drug-resistant infections globally recommended a range of policy responses to the international challenge of AMR and research and development in this area, including a global system of market entry rewards for new products [1]. It also urged national governments to find new ways of rewarding industry to help avoid over-use of new products. One policy that is being considered in the UK is an insurance-based delinked model, where a one-off or series of ‘insurance’ payments is made to reward innovation and to delink revenue from volume of antimicrobials sold. This model would be based on a payment that reflects the expected value of a new product to the National Health Service (NHS) over a specified period, and with the possible addition of ‘cap and collar’ arrangements to meet an agreed maximum and minimum payment, respectively, in order to share risk and unexpected variations in use. The precise specification of the UK insurance-based delinked model is yet to be determined, but it is likely to be specific to the profile of risk for particular AMs and their expected patterns of resistance over time.

Central to the proposed alternative funding arrangements of new AMs is the necessary prerequisite to characterise the expected value of a new product over an appropriate time horizon. This involves taking into account the same values as other health technologies; namely, the health benefits accruing at a population level, the expected costs borne by the payer, and the opportunity costs associated with expenditure on the new intervention; but also to reflect the additional elements of
value for AMs, including diversity value (benefits of having a range of treatments available to reduce selection pressure and preserve the efficacy of existing AMs); transmission value (benefits of avoiding the spread of infection in the population); enablement value (benefits of enabling surgical and medical procedures to take place); spectrum value (benefits of replacing broad spectrum with narrow spectrum AMs that target specific pathogens); and, potentially, insurance value (benefits of having treatments available in case of sudden, or major, increase in prevalence of infections) [2], [3].

The aims of this research project are: i) to develop a framework that captures the expected value of a new AM; ii) consistent with this framework, to assess the implications of an insurance-based approach to reimbursement for the evidence and evaluation methods used as part of the National Institute for Health and Care Excellence (NICE) technology appraisal programme; iii) to illustrate the framework using one or more case studies to highlight methods and evidence issues and alternative ways of addressing these; iv) to suggest any changes that might be required to the methods used in the NICE technology appraisal programme; and v) to make recommendations on each of these topics and identify any remaining issues and areas for further research.

Conceptual framework for value assessment of new AMs

The value assessment of new AMs follows the same principles of other health technologies as set out, for example, in NICE’s methods guide for technology appraisal [4]; but the challenges for AMs involve adequately reflecting the expected rate of growth in AMR and associated outcomes over time. The starting point for the evaluation is the need to determine the range of treatment protocols about usage of the new and existing AMs for particular indication(s) (diversity value), including: mixing strategies, rotation of AMs, sequence of use, or preserving use to last line. Once these are defined, the expected value of a new product may be estimated conditional on a particular policy strategy about usage. Each of these strategies will give rise to different resistance trajectories that are driven by exposure to the AMs. This involves modelling to estimate the infection transmission dynamics and associated resistance and economic outcomes for each strategy, which, in turn, results in different payoffs in total population health benefits and costs for each alternative strategy. This may be used to identify the optimal strategy that maximises the expected population net health benefit. The acquisition cost of the new AM may be excluded from the total costs in order to allow a separate decision on payment to be negotiated based on the estimated expected population net health benefits (i.e., value) of the alternative strategies (see Sections 3.2 and 7.2).
Implications for NICE technology appraisal

Although the principles of value assessment for new AMs are not dissimilar to other health technologies, the quantification of health benefits and costs is challenging (see Sections 3.4 and 3.5) and has important implications for NICE appraisal (see Section 8). Firstly, it is anticipated that the scoping process will be a crucial component for the evaluation and may need to be a longer element of the process than is currently the case for other technologies. In part this is because of difficulties in defining the relevant population(s) and potential subgroups for the new product due to quite general marketing authorisations that may be centred on pathogens, providing limited signals regarding the clinical indications for use. Identifying all relevant comparative strategies will need careful consideration of the range of ways the new and existing products could be used now and in the future. The limited evidence base, the extensive use of non-inferiority studies for new AMs, the potential need to rely on non-clinical microbiological outcomes from pharmacokinetic/pharmacodynamic studies, and the reliance on surveillance data will need to draw on more clinical and epidemiological expertise at scoping than for existing appraisals (see Section 4). The principal methods for modelling the infection transmission dynamics and resistance outcomes over time also require careful consideration at the scoping stage (see Section 5) in order to avoid later problems with modelling that is not fit for purpose, or unable to provide credible predictions of historical data on infection and resistance rates; this will need to draw heavily on the expertise of infectious disease modellers and epidemiologists with an understanding of the mechanisms of resistance for specific AMs.

Secondly, a process similar to NICE’s Multiple Technology Appraisal (MTA) or Diagnostic Assessment Programme is likely to be more suitable to the assessment stage of new AMs compared with the Single Technology Appraisal (STA) arrangements. This is in part due to the challenges associated with assembling the evidence to support decision-making (see Sections 3, 4 and 5) and modelling the expected costs and health benefits over an appropriate time horizon of the full range of ways that the products could be used (see Section 5); but it is also due to a strong reliance on the use of ‘real world’ evidence based on surveillance data, or data collected routinely in the NHS, rather than manufacturers’ regulatory trials. The modelling expertise in this field is currently limited and any programme of NICE assessment of new AMs will need to focus on academic groups with the necessary skillsets to undertake this type of modelling.
Thirdly, some areas of the NICE methods guide for technology appraisal may need to be extended to deal with the complexities of assessing new AMs. These include the greater reliance on non-clinical studies and observational data (see Section 4); the potential use of dynamic transmission modelling rather than cohort static modelling (see Section 5); the more extensive and systematic use of expert elicitation methods and model calibration for inferring values for unobservable parameters (see Section 5); use of population net health benefit as a measure of value instead of incremental cost-effectiveness ratios; presenting the expected value of a new product assuming a zero acquisition cost in order to provide an indication of the maximum acquisition cost consistent with the product being cost-effective to the NHS; and the need for levels of payment to reflect both the expected value and the implications of uncertainty for the decision (see Section 7).

Fourthly, there are a number of implications for the appraisal of new AMs that are distinct from the assessment (see Section 8). These include, additional considerations outside of NHS costs and health effects such as the innovative nature of the new product and potential cost savings outside the NHS; the ‘insurance value’ associated with avoiding major catastrophic health consequences if AMR becomes substantially worse than expected; the appropriate measure of opportunity cost used to guide decisions; defining research recommendations, with specific reference to routine data collection in the NHS and appropriate study designs, and whose responsibility it is for conducting research; a need for an interdisciplinary appraisal committee with diverse expertise that includes mathematical modellers, epidemiologists, data experts, clinical experts, and health economists; and greater interaction between the committee and the relevant assessment group regarding the details of the evidence, comparisons and modelling than is currently the case for other technologies. The time required for this type of engagement is expected to be much longer than the current STA process but this can be justified, for appropriate products, on the basis of their anticipated impact on population health benefits and NHS costs. There is also a need formally and quantitatively to characterise some of the above factors, such as the insurance value if considered relevant, against health gain in terms of standard quality-adjusted life years (QALYs) and to reflect any trade-offs in the measure of opportunity cost used to guide decisions.

Implications of uncertainty for funding decisions
The assessment of new AMs using the value framework proposed here would be subject to a number of uncertainties, which have implications for funding decisions (see Section 7). Typical sources include evidential uncertainty and the need for further research, but also future uncertainties that will only reveal with the passing of time (e.g., duration of lag phase before
resistance emergences to the new product; availability of new and existing AMs in the future; and impact of stewardship and conservation policies to improve resistance outcomes). These uncertainties create an ‘option value’, where some flexibility in the timing of funding decisions is a desirable characteristic. Upfront commitment of payment (or a series of periodic payments) under an insurance-based delinked scheme may lead to irreversible sunk costs to the NHS. At the same time, there are also irreversible consequences if funding decisions are delayed due to the nature and scale of AMR over time. This means that consideration should be given to the appropriate timing of funding decisions. If additional research is valuable to reduce the consequences of uncertainty, or if there is a need to wait until future uncertainties are revealed over time, then a decision must be made on how to balance the value of delaying a decision (or restricting the product’s use to specific settings or circumstances) until better information becomes available, against the value of providing early access to the new product and avoiding potential irreversible consequences of not acting today. The appropriate timing depends on the contractual arrangements in place e.g., whether there is a renegotiation strategy in place to revisit the evidence and to revise the decision at a later point in time (or once resistance levels, or clinical need, reaches a certain threshold). Given these uncertainties, there is a strong case for periodic reconsideration of payment for new AMs as additional evidence emerges.

List of recommendations
The final section of this report (see Section 9) provides a summary of the recommendations intended to be helpful to the Department of Health and Social Care, NICE and other relevant stakeholders. These recommendations are based on the conceptual framework for value assessment of new AMs (Section 3); assessment of the clinical effectiveness of AMs (Section 4); modelling the infection and resistance outcomes (Section 5); implications of uncertainty for funding decisions (Section 7); and the implications of the value assessment framework and alternative funding arrangements for NICE policy, process and methods (see Section 8).
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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AETS</td>
<td>Agencia de Evaluación de Tecnologías Sanitarias, Health Technology Assessment Agency, Spain</td>
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<tr>
<td>AM</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>AMR</td>
<td>Antimicrobial resistance</td>
</tr>
<tr>
<td>AWMSG</td>
<td>All Wales Medicines Strategy Group</td>
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<tr>
<td>AWR</td>
<td>Approval with research</td>
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<tr>
<td>AWS</td>
<td>Approval with surveillance</td>
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<tr>
<td>BAT</td>
<td>Best available therapy</td>
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<tr>
<td>DHSC</td>
<td>Department of Health and Social Care</td>
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<tr>
<td>DIMDI</td>
<td>German Institute of Medical Documentation and Information</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>EUCAST</td>
<td>European Committee on Antimicrobial Susceptibility Testing</td>
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<tr>
<td>HAS</td>
<td>Haute Autorité de Santé, Health Technology Assessment Agency, France</td>
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<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>HTA</td>
<td>Health Technology Assessment</td>
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<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
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<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IQWiG</td>
<td>The Institute for Quality and Efficiency in Healthcare, Germany</td>
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<tr>
<td>JCVI</td>
<td>Joint Committee on Vaccination and Immunisation</td>
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<tr>
<td>MDR</td>
<td>Multi-drug resistant</td>
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<tr>
<td>MIC</td>
<td>Minimum inhibitory concentration</td>
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<tr>
<td>MRC</td>
<td>Medical Research Council</td>
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<tr>
<td>MTA</td>
<td>Multiple Technology Appraisal</td>
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<td>NHS</td>
<td>National Health Service</td>
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<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
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<tr>
<td>NIHR</td>
<td>National Institute for Health Research</td>
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<tr>
<td>NMA</td>
<td>Network meta-analysis</td>
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<tr>
<td>OIR</td>
<td>Only in research</td>
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<tr>
<td>ONS</td>
<td>Office of National Statistics</td>
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<td>PD</td>
<td>Pharmacodynamics</td>
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<td>PK</td>
<td>Pharmacokinetics</td>
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<td>Acronym</td>
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<tr>
<td>QALY</td>
<td>Quality-adjusted life years</td>
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<tr>
<td>R&amp;D</td>
<td>Research &amp; Development</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>SMC</td>
<td>Scottish Medicine Consortium</td>
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<tr>
<td>STA</td>
<td>Single Technology Appraisal</td>
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<tr>
<td>TOC</td>
<td>Test of cure</td>
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<tr>
<td>UDR</td>
<td>Usual drug resistant</td>
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<tr>
<td>VBP</td>
<td>Value-based payment</td>
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<tr>
<td>ZI</td>
<td>National Health Care Institute Netherlands/Zorginstituut Nederland</td>
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2. INTRODUCTION

Antimicrobial resistance (AMR) is a complex issue of major global concern. It occurs when microorganisms such as bacteria, fungi and parasites become prone to adapt to the environment and develop resistance upon antimicrobial drug exposure. Infectious organisms are now becoming increasingly resistant to the array of existing antimicrobials (AMs) available. At the same time, the pharmaceutical and biotechnology industry is becoming reluctant to develop novel AMs because of their expected limited return on investment. The problem is compounded further by public health and conservation goals that require AMs to be used judiciously and, in some cases, only as last resort therapies, in an effort to curb the rise in AMR. A potential market failure exists in such contexts if the expected value of new AMs, when held in reserve, is not reflected in revenue to manufacturers as a result of the low volumes of use, dis incentivising the development of new products. This is increasingly difficult for multi-drug resistant (MDR) pathogens where the number of available AMs is decreasing at an alarming rate, to the point that more patients will eventually die from previously treatable infections.

Health systems internationally, individually, and collectively face the challenge of managing antimicrobial resistance, which is on the rise. The international dimension partly reflects the fact that use of new and existing AMs internationally will influence resistance patterns and, therefore, the potential value of different policies within a given jurisdiction; and this is quite unlike other healthcare technologies. A key element of this is to ensure that new antimicrobial products are available to provide treatments in the face of drug resistance. Given that most pharmaceuticals are developed to the point of launch by commercial manufacturers, the extent to which these products are appropriately funded by health systems to incentivise research and development has been a key concern in public policy. The O’Neill report on tackling drug-resistant infections globally recommended a range of policy responses to the international challenge of AMR and suggested market failures relating to research and development in antimicrobials [1]. It urged national governments to find new ways of rewarding manufacturers to help avoid over-use of new products. One policy to have been considered in this area in the UK is to remove the link between what the NHS pays for new AMs and the volume of their use. In other words, for the NHS to pay for new products using a mechanism (e.g. a periodic ‘insurance’ payment) that does not depend on how much of that product is actually used. Such funding arrangements have the potential to reward manufacturers appropriately for the development of new AMs, and not penalising them with policies for the sparing use of AMs or
holding new products ‘in reserve’ until any point in the future where therapeutic options are very limited.

These alternative funding arrangements may have important implications for how NHS decisions are made regarding the funding of new AMs. In particular, the process of assessment and appraisal of new drugs by the National Institute for Health and Care Excellence (NICE) is typically based on acquisition costs defined per unit consumed. Regardless of any new pricing arrangements of AMs in the NHS, any decision about whether to fund these products at a given acquisition cost needs an assessment of its impact on health and other potential sources of value. It is unclear whether the methods used by NICE’s technology appraisal programme are suitable for this purpose or need further development or extension. This report describes research undertaken to inform policy decisions by NICE on the future appraisal of new AM products.

2.1. AIMS AND OBJECTIVES

The aim of the project was to assess the implications for the NICE technology appraisal programme of an insurance-based approach to the reimbursement of new AMs. The specific objectives were:

- To develop a framework that captures the expected value of a new AM. This involves defining and characterising all relevant costs and health benefits to be considered as part of NICE assessment;
- Consistent with this framework, to assess the implications of an insurance-based approach to reimbursement for the evidence and evaluation methods used as part of NICE assessment;
- To illustrate the framework using one or more case studies to highlight methods and evidence issues and alternative ways of addressing these;
- To suggest any changes that might be required to the methods used in the NICE technology appraisal programme;
- To provide brief consideration of remaining issues and to make recommendations for further research.

The report is structured as follows. Section 3 provides an overview of the proposed conceptual framework for value assessment of new AMs. Section 4 assesses the evidence available on the
clinical effectiveness of new AMs. Section 5 provides an overview of modelling approaches used to reflect infection and resistance outcomes over time. Section 6 is a case study illustrating the value assessment framework. Section 7 considers the implications of uncertainty for alternative payment mechanisms of new AMs. Section 8 considers the implications of the value assessment framework for NICE policy, process and methods. Finally, Section 9 provides a full list of recommendations from each of the above sections.

3. OVERVIEW OF THE CONCEPTUAL FRAMEWORK FOR VALUE ASSESSMENT OF NEW ANTIMICROBIALS

3.1. INTRODUCTION

The overarching purpose of the proposed conceptual framework for value assessment is to help inform funding decisions for new AMs in the UK. This is particularly important given the consideration being given to new payment mechanisms for these products on the part of the NHS, but the conceptual framework is relevant whatever the approach to payment. Fundamental to this is the need to reflect the value of a new AM since this is a necessary prerequisite for any payment arrangement. Therefore, the framework seeks to characterise the expected value of a new AM over an appropriate time horizon. The evaluation of a new AM should consider the same values as any other health technology appraisal; namely, the health benefits accruing at a population level, the expected costs borne by the payer, and the opportunity costs associated with expenditure on the new intervention. This section presents an overview of how the expected value of new AMs may be determined. The approach taken is consistent with the methods used for the economic evaluation of other healthcare technologies; however, AMs are expected to differ from other technologies in the way that value accrues to the population. The following sections describe what constitutes value for new AMs, illustrates how this value can be reflected within the assessment of population health effects, and discusses the implications for the evidence and evaluation methods used as part of NICE technology appraisal.

3.2. ESTABLISHING THE EXPECTED VALUE OF NEW ANTIMICROBIALS

The value assessment of new AMs follows the same principles of Health Technology Assessment (HTA) for technological innovations as set out, for example, in NICE methods guide for technology appraisal [4]. This involves assessing the expected value of a new AM
over an appropriate time horizon. Here the term ‘value’ refers to the expected impact of the new AM on population net health\(^1\) by taking account of the expected benefits to patients and/or the wider population and expected costs borne by the payer, relative to the comparator options available, as well as the expected opportunity costs in terms of forgone health gain when resource allocation decisions allocate resources away from other potential and actual healthcare uses. The framework is consistent with the principles of economic evaluation but the challenge for the evaluation of AMs is the need to reflect adequately the expected rate of growth in resistance and associated outcomes over time.

The starting point is the need to determine the range of potentially relevant alternative strategies for the usage of the new AM for a particular indication (or multiple indications). These alternative strategies can be described as the policy choices or usage scenarios representing the different ways that the AM may be used in clinical practice. In principle, the relevant alternatives include all options that might be considered worthwhile. This could include different treatment protocols such as mixing strategies, combination therapy, rotation of AMs, or holding back on the use of an AM.

The same considerations apply to existing forms of management including current AMs (i.e. ‘comparators’). There will be a range of options for how the patients with the relevant indication can currently be managed. Some of these strategies may not be currently used in many patients or even at all and there is likely to be considerable geographical variation in current routine practice. In order to assess the value of a new AM, it needs to be compared with the best current management using existing AMs (i.e. the most cost-effective), and this can appropriately be defined as ‘standard of care’. Unless there is clarity regarding an appropriate standard of care (e.g. based on earlier NICE appraisal), the comparators for an appraisal of a new AM need to include the full range of ways in which existing AMs can be delivered for a given indication.

Once the alternative strategies are defined, then the need is to characterise the expected value of a new AM conditional on a particular policy choice regarding its usage, e.g., only use the

\(^1\) Other considerations may be reflected in the benefit measure; however, the focus here is on health given that this is NICE’s current focus. NICE also weights health gain to patients with very short life expectancies higher than that accruing to others, and this would also presumably apply to AMs.
new AM as a last line therapy, and to compare this to the available alternatives under consideration.

Each of these different strategies about usage will give rise to different resistance trajectories that are driven by exposure to the new and existing AMs, as well as a number of other HTA considerations (see Section 3.4). Therefore, there is a need to define all relevant health benefits and costs over an appropriate time horizon for each alternative strategy. This will involve modelling the infection transmission dynamics and associated economic and resistance outcomes for each strategy over the time horizon. This in turn will result in different payoffs in total health benefits and costs for each of the alternative strategies (see Box 1). Appropriate models will also be able to estimate the volumes of use of new and existing AMs under different strategies. This will reflect the inevitable uncertainties in resistance over time and will allow, for example, for the chance of high volumes of use of a new AM even under strategies where it is held back in case of extensive resistance to other products.

The total costs would normally include the acquisition costs of all AMs being compared and any other costs associated with its use. This includes any expected resource savings such as reduced length of hospital stay or avoiding subsequent costly clinical events. However, for the purposes of helping to inform the value-based payment for the new AM, the drug acquisition cost of the new AM would be excluded from the total costs. The main reason for keeping the drug acquisition cost outside of the analysis is that the overarching purpose of the value assessment framework is to help inform future antimicrobial funding strategies that delink payment from usage; this could apply, however, to any value-based pricing arrangement. Therefore, the framework seeks to characterise the expected value of a new AM without the inclusion of the drug acquisition cost of the new AM. This approach also reflects the possible distinction between NICE’s role in assessment of the expected value and a separate decision (e.g. by Department of Health and Social Care or NHS England) on the appropriate value-based payment (see Section 8).

Given that the framework would be applied with an initial assumption of a zero acquisition cost, standard ‘decision rules’ for cost-effectiveness analysis [5], which are generally used by NICE [4], would need to be adapted to inform decisions about the appropriate value-based payment. This involves a number of elements:
There needs to be an assessment of opportunity costs, which is the health gain forgone elsewhere by resources not being available for other activities because they are accommodating the additional costs of the new AM. NICE’s range of ‘cost-effectiveness threshold’ (£20,000-£30,000 per QALY gain) purports to reflect opportunity cost in part, but also factors such as innovation [4]. Recent empirical research provides a central empirical estimate, based on the NHS’ marginal productivity, of approximately £13,000 per QALY [6] and this is supported by ongoing research based on further waves of data and an exploration of key assumptions. Health impact assessments by the Department of Health and Social Care (DHSC) now routinely use £15,000 per QALY as an estimate of health opportunity cost (for example, see [7]) This can be interpreted as the NHS generating 1 additional (fewer) QALY in population health per £15,000 additional (lower) expenditure.

A new AM can only be considered to be of potential value to the NHS (i.e. potentially cost-effective) if it offers positive health benefits net of any associated opportunity costs it imposes at zero acquisition cost compared to current alternatives.

In the anticipated case of there being a number of strategies for using a new AM and existing management options, then these can be ranked in terms of expected net health benefit.

To inform decisions about an appropriate value-based payment for the new AM, net health benefit should be expressed at the population level. This will reflect the size of the indicated population plus the indirect effect on individuals who do not receive the product but experience indirect effects through any changes in resistance over time. When there are multiple indications, net population health benefit can be aggregated across indications.

Each strategy with the new AM and with existing treatments can be presented in terms of its expected population net health benefit and usage volumes over time. The maximum value-based payment that would not result in a negative impact on overall population health can then be calculated based on the difference in expected population net health benefit between the selected strategy for the new AM and the best of the comparators.

The value-based payment may be expected to relate to the strategy with the new AM that is expected to achieve the highest population net health benefit at zero acquisition cost. However, as usage levels will vary by strategy and identifying a value-based
payment will inevitably involve some negotiation, this may not be the case and less effective strategies with the new AM may be chosen as long as these offer, at zero acquisition cost, higher expected population net health compared to strategies using existing treatments.
Box 1: Calculation of value-based payment using illustrative numbers

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

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

Column D shows the expected net health benefit in terms of QALYs PPT. This is calculated as \(QALYs = \frac{\text{Cost}}{k}\), where \(k\) is the estimate of health opportunity cost expressed as £15,000 per QALY. Column E details the expected population net health benefit in QALYs assuming a population with the potential to benefit 6000 patients over the time horizon of the analysis. AM(N)3 represents the best of the strategies involving the new AM, with an expected population net health benefit of 54,104 QALYs for the new AM. To calculate the maximum the NHS could pay for the new product before a net reduction in population health, the difference in population net health benefit between AM(N)3 and the best of the strategies using existing treatments is calculated (54,104 – 50,400 = 3,704 QALYs). Based on a health opportunity cost of £15,000 per QALY, the NHS would require £55,560,000 of additional expenditure to generate this gain in population health from other activities (3,704 x 15,000). Put differently, this amount of resource would, if taken out of the system to fund the new AM, reduce population health by 3,704 QALYs. This would be a total payment relating to the management of the estimated number of patients with potential to benefit over the time horizon of the analysis but could be readily expressed as a per annum payment. Note that the estimated population is not necessarily the number who would receive the new AM, as this would depend on the details of each strategy with the new product.
3.3. Attributes of Value for Antimicrobials

The rise in AMR has led to a growing literature on this important topic. Recent reports have highlighted a number of attributes of value of particular relevance to antimicrobials [2,8]. These attributes can be separated into those that are typically included in standard HTA evaluation and those that are considered additional for AMs. The typical elements include: (i) health gain to patients treated, which is measured as life extension and quality of life gain relative to comparators; (ii) short- and long-term costs associated with introducing a new AM into the healthcare system relative to its comparators; (iii) innovative or novel action value associated with addressing an area of unmet need, e.g., new mechanism of action which adds distinctive benefits that are not captured in the health gain to patients; (iv) aspects that relate to non-health objectives of the healthcare system, e.g., productivity gains or impact on caregivers. The principles of including these elements of value for AMs are the same as those used for standard HTA evaluation of other technologies and, therefore, they are not discussed further in this report.
The additional attributes of value² for new AMs that have been proposed in the literature include [2], [3]:

- **Diversity value** – this refers to the benefits of having a range of treatment options available in order to reduce selection pressure (e.g., by withdrawing the use of an existing AM for a period of time) and to preserve the efficacy of existing AMs. This is because the use of AMs has been associated with the development of resistance, and strains resistant to a formerly used drug may decrease in frequency, or even disappear altogether, in the off period. Furthermore, strategies to coordinate the use of different drugs may make it difficult for specific pathogens to adapt to their environment and hinders their resistance development to AM agents.

- **Transmission value** – this refers to the benefits of avoiding the spread of the pathogen to the wider population, i.e., reduced onward transmission of an infection to other individuals in the population if the patient with the infection is treated successfully. This means that there are population-level effects in addition to those accruing to individuals treated. This is very different from non-communicable diseases where reducing prevalence of a condition makes no difference to the risk faced by others.

- **Enablement value** – this refers to the benefits associated with enabling other treatments or procedures to take place, e.g., surgical and medical procedures that may not be possible if AMs were not available to prevent or treat surgical site or post-procedure infections.

- **Spectrum value** – this refers to the benefits of replacing broad spectrum AMs, which are specifically designed to protect against a wide variety of bacterial pathogens, with narrow spectrum AMs that target a specific type of pathogen causing the infection. The use of broad spectrum AMs has become commonplace for treating many different types of infection because the exact nature of the organism causing the infection may not become known in a timely manner and there is a desire not to delay treatment. However, the overuse of broad spectrum AMs can cause collateral damage to the human microbiome (where susceptible species in microbiome, e.g. on the skin, gut or lungs, are replaced by resistant species ready to cause infection in the future) resulting in a greater chance of developing resistance to the AMs used.

² Some of these additional attributes of value are not specific to antimicrobials; they may also be applicable, for example, to the evaluations of vaccinations and diagnostic technologies.
• Insurance value – this refers to the value of having AMs available in case of a sudden or major increase in the prevalence of infections with pathogens resistant to existing AMs. This suggests two components to the insurance value: i) the conservation value associated with strategies that hold back on the use of an AM for future need, e.g., strategies to preserve the use of a new AM until resistance to all other existing AMs worsens and the prevalence of infections cannot be contained; and ii) there is additional value associated with avoiding major catastrophic health consequences if the build-up of AMR becomes substantially worse than expected, i.e., insuring against some exogenous shock to the system that could spike the prevalence of resistant infections.

The question that now remains is how can these additional attributes of value be reflected within HTA evaluation of AMs? Before addressing this question, it is worth noting that a recent review of HTA assessment of antibiotics across the EU since the year 2000 until April 2016, which included 5 nations and 8 different HTA agencies (HAS from France, IQWiG and DIMDI from Germany, ZI from Netherlands, AETS from Spain, SMC from Scotland, NICE from England and AWMSG from Wales), found that there are no guidelines or methods advice specific to the economic evaluation of antibiotics [8]. The review also examined whether HTA agencies consider the additional attributes of value associated with antibiotics. The conclusion was that some HTA reports for specific antibiotics raised related issues, but the values were not explicitly quantified or included in reimbursement recommendations, nor were they systematically considered across antibiotics or agencies [8]. The following section examines the specific challenges associated with AMs for HTA evaluation. Section 3.5 illustrates how the additional attributes of value may be reflected in estimates of population health effect.

3.4. Health Technology Assessment of Antimicrobials

To date, the approach taken to the HTA evaluation of AMs in the UK has focused only on the short-term effects of treatment for particular indications on patients directly infected. The time horizon for the economic evaluations has typically been very short, e.g., 10 days, 6 months or 1 year, to match outcomes in the associated clinical study. Studies to date have also not addressed the positioning of the new agent relative to a range of comparators. Instead they have restricted the analysis typically to only one comparator drug, which may not match that used across clinical practice in the UK. Most of the analyses have adapted the same class of decision-analytic models used for non-communicable diseases, such as Markov models, and have
ignored the indirect effects that arise from averted infections in the population. In fact, most studies to date have ignored the problem of resistance altogether and have not evaluated strategies to reduce emergence of resistance or transmission of resistant organisms.

Table 1 presents a comparison of the challenges associated with the HTA evaluation of AMs compared to standard NICE guidance for the methods of technology appraisal of other technologies. The table focuses on the different aspects of NICE appraisal, such as indication(s), population, perspective, comparators, evidence base and modelling approaches, with a view to identifying how the evaluation of AMs is likely to differ compared to other technologies.

The marketing authorisation of new technologies generally specifies the therapeutic indications for use. For AMs, this is unlikely to be a single indication, but rather a large array, reflecting the spectrum of activity against a wide variety of bacterial pathogens. Pathogen-specific indications are also permitted by the European Medicines Agency [9] and indications may receive regulatory approval simultaneously, in quick succession or over time.

Cost-effectiveness is typically assessed in standard NICE appraisal for an ‘average’ patient in the licensed indication, with potential subgroups of the population analysed separately. However, for AMs the benefits of treatment extend beyond the patient treated to the wider population. Treatment protocols in one subgroup of the population may also affect outcomes, including the emergence and transmission of resistance, in another subgroup. Different settings, such as the community, hospital or Intensive Care Unit (ICU), also affect the inflow of infections and spread of resistance in the population.

The perspective of the analysis reflects the scope of the costs and benefits and the individuals who are affected by the outcomes of interest. In the case of AMs, both direct and wider health effects and costs by avoiding the spread of infection to the population should be considered (transmission value). The appropriate time horizon of the analysis should be sufficiently long to reflect important differences in costs and effects between the technology and comparators. For standard NICE appraisal, this is typically a patient lifetime horizon. For AMs, the effects need to be evaluated in the short- and long-term and these effects can arise from complex infectious disease dynamics. In this respect, AMs differ from other drug treatments and the
effects are considered in the context of an indefinite time period. The timescale for the analysis is also affected by the discount rate and is also relevant to the methods used by the Joint Committee on Vaccination and Immunisation (JCVI) for vaccination programmes [10] (see Section 3.6.6).

The choice of comparators in NICE technology appraisal is determined by established standard practice in the NHS, which is usually defined as the ‘average’ way standard of care is used. A new cost-effective technology is expected to replace standard of care. In contrast, a new AM is expected to be used in addition to the existing AMs. The appropriate comparators are established standard practice, but this is likely to vary considerably by geography depending on local resistance levels, costs of AMs, physician habits and other factors. In order to reduce the selection pressure and preserve the efficacy of existing AMs (diversity value), the treatment protocols for the new AM and comparators will usually include heterogeneous prescribing, including: rotation of AMs; mixing protocols, with a fraction of the population receiving the new AM and a fraction receiving an existing AM; and combination therapy, where the AMs may be used together. The availability of diagnostic tests may also considerably modify the value of a new AM. For multi-drug resistant (MDR) pathogens, where antimicrobial resistance is shown by a species of organisms resistant to multiple antimicrobial drugs, there may be no alternative ‘active’ comparator available.

In terms of the clinical evidence base, non-inferiority Randomised Controlled Trials (RCTs) are the norm for AMs. These trials only tend to include patients infected with pathogens susceptible to both the new AM and a comparator of best available therapy, i.e., in usual-drug resistant (UDR) pathogens as opposed to MDR pathogens, where it is difficult to enrol patients into trials when resistance is known or suspected. This means that there is limited efficacy data for MDR pathogens. The use of non-clinical pharmacokinetic/pharmacodynamic data and in-vitro microbiological data may be required to predict response for MDR pathogens (see Section 4).

The modelling approach commonly used in NICE appraisal is cohort decision-analytic models such as decision trees, Markov models or partitioned survival models, where the overall health benefits can be estimated by summing across the individual benefits. This is because the majority of NICE appraisals deal with non-communicable diseases, whereby reducing the
prevalence of the condition makes no difference to the risk faced by others. In contrast, for AMs the models generally and ideally need to be transmission models that reflect between-host dynamics in order to account for indirect population benefits. These models can capture how susceptible and resistant strains of bacteria spread through the population over time. The models may also need to reflect the mechanisms of resistance in order to predict the prevalence of infections and resistance patterns in the population over time for alternative treatment protocols (see Section 5).

In terms of measuring and valuing health effects and costs, the approach used in standard NICE appraisal is applicable to AMs. However, there are likely to be greater challenges in measuring health-related quality of life (HRQoL) in short-term infections. Generic, preference-based measures of HRQoL, such as the EQ-5D, are generally not collected in clinical trials. Characterising the uncertainty in costs and effects over the modelled time horizon is key for quantifying the decision uncertainty associated with the use of a new AM. For AMs, there are a number of additional uncertainties over and above those seen for other technologies; these include, uncertainty in the stock of future AMs available, uncertainty in the prevalence of infections and resistance patterns to AMs over time, the lag period before resistance to a new AM develops, irreversible impacts of the intervention on resistance and its consequences over time and the availability of new evidence to resolve uncertainties (see Section 7).
Table 1: Comparison of the HTA evaluation of antimicrobials with standard NICE guidance for other technologies

<table>
<thead>
<tr>
<th>Standard NICE HTA</th>
<th>HTA evaluation of antimicrobials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication(s)</strong></td>
<td></td>
</tr>
</tbody>
</table>
| • Marketing authorisation of new technology generally specifies therapeutic indication(s) for use | • Likely to be multiple indications  
• Pathogen-specific indications permitted by European Medicines Agency  
• Indications may receive regulatory approval simultaneously, in quick succession or succession over time |
| **Population**    |                                  |
| • Cost-effectiveness assessed for ‘average’ patient in licensed indication  
• Subpopulations analysed separately | • Benefits of treatment extend beyond the patient treated to the wider population  
• Different settings: Community, hospital setting, long-term care facility. Setting affects the inflow of infections and spread of resistance  
• Treatment protocols (on or off-label) in one subgroup may affect outcomes in other subgroups |
| **Perspective**   |                                  |
| • Direct health effects and costs for NHS and personal social services | • Direct and wider health effects and costs for NHS and personal social services by avoiding the onward spread of infection |
| **Comparator(s)** |                                  |
| • Appropriate comparator(s) is established standard practice (standard of care) in NHS  
• Cost-effective technology expected to replace standard of care | • Lack of comparator for multi-drug resistant pathogens  
• Established standard practice varies by geography and local variation depending on local resistance patterns, costs, physician habits, other factors  
• Treatment protocols for new AM and comparators include heterogeneous prescribing: rotation of AMs, mixing protocols, combination therapy  
• New AM is expected to be used in addition to existing AMs  
• Availability of diagnostic tests may considerably modify value of AMs |
| **Time horizon**  |                                  |
- Sufficiently long to reflect all important differences in costs and effects between the technology and comparators
- Typically, lifetime horizon

| Time horizon should be sufficiently long to reflect all important differences in costs and effects between the alternative comparators
| ‘Lifetime’ time horizon does not apply
| Indefinite time horizon due to long-term dynamic effects but limited by temporal uncertainty in parameters
| Time horizon set by the discount rate for costs and effects

### Clinical evidence

- RCTs usually available directly comparing the technology with relevant comparator(s) on clinical endpoints
- Non-randomised studies may exist in isolation or supplement RCT data, with potential bias explored
- When surrogate data are only available, evidence to support surrogate-to-final endpoint relationship must be quantified, with associated uncertainty

| Non-inferiority RCTs are the norm for AMs in usual drug resistant pathogens. Clinical response rate at test-of-cure is resolution of infection (cure), failure or indeterminate
| Non-clinical pharmacokinetic/pharmacodynamic data and in-vitro microbiology data used to predict response for resistant pathogens. Microbiological response rates at test-of-cure may be surrogate for predicting clinical cure in specific patient populations

### Modelling approach

- Models synthesise available evidence. Use of cohort models, typically decision trees, Markov models, partitioned survival models, some use of individual simulation models that don’t reflect transmission dynamics.
- Occasionally transmission modelling e.g., vaccines, HIV

| Models may need to reflect mechanisms of resistance development
| Predict prevalence of infections and resistance patterns in populations over time for alternative treatment protocols
| Transmission models (most commonly compartmental models) reflect between-host dynamics (based on properties of within-host dynamics). Models capture how susceptible and resistant strains of pathogens spread through population over time

### Measuring and valuing health effects

- Changes in HRQoL reported directly from patients and HRQoL weights (utilities) based on UK public preferences using a choice-based method. EQ-5D is preferred measure in adults
- When EQ-5D data are not available, mapping from other instruments to EQ-5D may be used

| Difficulty in measuring HRQoL in short-term severe infections
| EQ-5D data or other preference-based measures are not collected in clinical trials
| Limited data sourced from literature of utility values by indication. Likely to be no data for pathogen-specific indication.
### 3.5. Reflecting the Attributes of Value for Antimicrobials in Population Health Effects

Consistent with the standard approach to HTA evaluation and NICE appraisal, each of the additional attributes of value associated with AMs can be reflected in the estimates of population health effect (see Box 3). Although there is limited evidence that this has been attempted in existing literature and there may be evidential challenges in doing so, it is in principle possible. Diversity value can be reflected in the range of alternative strategies or treatment protocols being compared, representing the different ways that the new and existing AMs may be used. Conditional on these strategies about usage, population health effects are generated through avoiding or treating infections. This includes, firstly, the direct health

<table>
<thead>
<tr>
<th>Resource use and costs</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Resource use that falls on the NHS and personal social services. Valued using prices relevant to NHS</td>
<td></td>
</tr>
<tr>
<td>- Use list price for technology and comparator(s)</td>
<td>- Characterise uncertainty in costs and effects over the modelled time horizon</td>
</tr>
<tr>
<td></td>
<td>- Identify parameters that have a substantial impact on cost-effectiveness results</td>
</tr>
<tr>
<td></td>
<td>- Explore impact of structural assumptions by separate scenarios</td>
</tr>
<tr>
<td></td>
<td>- Characterise uncertainty in costs and effects over modelled time horizon, identify key determinants of cost-effectiveness, explore alternative assumptions with separate scenarios</td>
</tr>
<tr>
<td></td>
<td>- Additional uncertainties for AMs:</td>
</tr>
<tr>
<td></td>
<td>- Uncertainty in the prevalence of infections and resistance patterns over time;</td>
</tr>
<tr>
<td></td>
<td>- Uncertainty in the stock of future AMs;</td>
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<tr>
<td></td>
<td>- Uncertainty in the lag period before resistance to new AM develops;</td>
</tr>
<tr>
<td></td>
<td>- Irreversible impacts of AMs on resistance and its consequences over time;</td>
</tr>
<tr>
<td></td>
<td>- Availability of new evidence to resolve uncertainties</td>
</tr>
</tbody>
</table>

- Justification for not using EQ-5D should be supported through construct validity tests and responsiveness in a particular patient population

- All resource use that falls on the NHS and personal social services, including the implications of onward transmission of infections to the wider population. Valued using prices relevant to NHS

- Exclude acquisition price of new AM for separate assessment of value-based payment
outcomes and costs associated with treating the infection; secondly, the indirect benefits to the population of reduced infection rates by avoiding the onward spread of pathogens to the wider population – transmission value; and, thirdly, the indirect benefits to individuals associated with enabling other treatments or procedures to take place – enablement value. These population health effects can be estimated through appropriate modelling, ideally using dynamic transmission models that are capable of reproducing both the direct and indirect effects (see Section 5).

Each of the different strategies about usage of the new and existing AMs will create changes to the trajectory of resistance over time, which is driven by exposure to the AMs. Resistance to the new AM will develop over time, e.g., through acquired resistance during treatment where a susceptible strain of bacteria can become replaced with a resistant strain, that benefits from a survival advantage following treatment. The resistance trajectory of the existing AMs will also change over time through direct infection in the population by a resistant strain or through acquired resistance. These changes in turn will feed back into changes in the estimates of population health effect. For example, if exposure to the AM increases the pool of resistant pathogens, then AMR will increase in the population; whereas if the treatment reduces the pool of infections, then the risk to uninfected individuals will decrease.

The population health effects associated with the use of narrow spectrum AMs to replace broad spectrum AMs – spectrum value – are derived from preventing collateral damage to the microbiome. For opportunist pathogens, susceptible species in the microbiome (e.g. on the skin, gut or lungs) are replaced by resistant species ready to cause infection in the future. Therefore, the benefits of spectrum value are through avoiding future resistant pathogens that could cause infections unrelated to the one for which the patient has been treated. This is likely to be very difficult or impossible to model since it requires estimation of the impact of the alternative AM treatment strategies on health outcomes and costs of other future resistant infections.

The remaining attribute of value that may be relevant is insurance value. As described in Section 3.3, there are two components to the insurance value: i) the conservation value of strategies that hold back on the use of a new AM for future need; and ii) the value associated with avoiding major catastrophic health consequences if AMR becomes substantially worse.
than expected. The first of these can be reflected by including in the evaluation a full range of alternative strategies about usage. This would include preserving the use of the new AM as last line and until resistance to all other existing AMs worsens and the prevalence of resistant infections cannot be contained. Therefore, this strategy becomes one of the many different policy options about usage and can be quantified in terms of population health effects in the same way as the other diverse strategies.

The second component to the insurance value may be partly modelled through its impact on population health effects. Insuring against some exogenous shock to the system that could spike the prevalence of resistant infections may be modelled as an uncertain future parameter with a low probability of occurrence, but one that changes the trajectory of resistance substantially and, therefore, the resulting population health effects. However, these health effects associated with avoiding a major catastrophic event may also be valued differently by society than other health effects. In other words, there may be a non-linear relationship between the scale of health effects and some measure of societal value for these effects. There may be a case to undertake research to quantify this relationship (e.g. by eliciting public preferences) and deriving higher weights for the benefits of avoiding catastrophic events, but this is external to the modelling approach used.

The approach to re-weighting the health effects is not dissimilar to the approach used in current NICE appraisal for technologies that meet the criteria for special consideration as a life-extending treatment at the end of life [4]. In the absence of information on the relationship between effects and on the likelihood of catastrophic events, the best that could be done is to quantify the risk of extreme events and to present the corresponding health impact to decision makers in order to allow them to come to some judgement on the potential adjustment factor. A similar concern has been recognised by the JCVI for the cost-effectiveness methodology for vaccination programmes [10]. NICE’s reference case methods for the technology appraisal programme indicates that there should be no differential weighting of QALYs, although their end of life criteria is an exception to this. Any additional re-weighting of benefits would presumably need an explicit policy decision by NICE/DHSC.
Box 3: Attributes of value for antimicrobials reflected in population health effects

3.6. OPERATIONALISING THE CONCEPTUAL FRAMEWORK

The first step required to operationalise the conceptual framework is to define clearly the decision problem and its separate components; for example, the population, setting, indications, appropriate comparators, potential subgroups, perspective, appropriate time horizon and discount rate for costs and health benefits. Addressing these fundamental issues related to the decision problem itself will help to define the scope and boundaries of the assessment. A scoping process similar to that used by the NICE technology appraisal programme may be used for this purpose (see Section 8). The scoping process may also highlight issues related to the available evidence base on clinical effectiveness of AMs (see Section 4) and principal methods for modelling the infection transmission dynamics and associated resistance outcomes and measures of population health effects and costs (see Section 5).
3.6.1. **Indications**

The scope would include information about the marketing authorisation of the new AM. In particular, it should include a description of the licensed indication(s) for use and whether pathogen-specific indications are permitted. In most cases, the licensed indications will describe the specific types of clinical infections to be treated by the new AM (e.g., complicated intra-abdominal infection, hospital-acquired pneumonia), but it may also include a pathogen-specific indication when the new treatment has been shown to have clinical efficacy against particular pathogens (including multi-drug resistant organisms). The dose regimen, duration of treatment courses and the circumstances of use applicable to each indication are usually defined by the marketing authorisation. The scoping process should help to refine the indications for use and ensure that the new AM is only used for the specified indications. Adherence to this should follow in the same way as NICE guidance for other technologies, but additional stewardship and policing of the use of AMs for specific indications may be required to exclude ‘leakage’ to other indications as well as to ensure uptake for the recommended indications in order to reduce the build-up of resistance to the new AM in the population.

3.6.2. **Population and setting**

The scope should clearly define the setting and population for whom the new AM is to be used. This is generally specified by the indications, but it may need to be narrowed down given the potential for very broad use of the AMs with multiple clinical indications and potential pathogen-specific indications. Careful consideration should also be given to the specific setting of AM use, such as community, hospital or restricted to ICU use, since the proportion inflow of infections and transmission dynamics is expected to differ depending on the setting. For example, hospitals tend to have higher AM usage and infections are quickly transmitted through the institutional environment or through healthcare workers, creating greater opportunity for bacterial species opportunistically to colonise sterile sites such as the bloodstream or lower respiratory tract. In contrast, community use may only be heightened in certain populations such as children/elderly or where there is a higher contact rate due to more shared space. The scope may also highlight potential subgroups of the population, such as those with renal impairment, or specific settings where the AM use might be expected to give rise to different outcomes from the overall population.
3.6.3. Comparators

The choice of comparators is fundamental to the decision problem and will have an important impact on the evaluation conducted, the approach to data collection and the interpretation of the findings. The range of potentially relevant comparators is likely to be large, reflecting the many different ways that the new and existing AMs may be used. One important alternative to the new AM will be ‘existing care’ for a particular indication, which represents what would be done in the absence of the new AM under evaluation. However, as noted in Section 3.4, established standard care is likely to vary considerably by geography depending on local resistance levels, physician habits, and other factors. This may mean that different decisions about which alternative (or strategy) to offer may need to be made for individuals in different localities where the effects of the AMs are likely to differ due to differences in resistance levels by locality. Similarly, the choice of alternatives may be restricted according to different subgroups. These could be defined by patient characteristics but are more likely to be defined by bacterial strain type (e.g., single-resistant or multi-resistant to specific AMs), transmission risk, or resistance outcomes over time. Again, the effects of the alternative comparators are likely to differ in these subgroups and for which different decisions about the use of the new and existing AMs can be made.

The comparators should also reflect the treatment protocols typically seen in practice and ones that can reflect the diversity value of AMs, which include rotation and mixing strategies, diagnostic test-and-treat or interim empiric treatment, and combination therapy with different AMs. There may also be a question about the sequence in which the treatments should be offered and whether the new AM should be preserved as a last line therapy. In this case, the relevant comparative choices are the alternative strategies, e.g., combinations, sequences of treatment, rotation of AMs, diagnostic criteria. This choice of comparators is likely to represent one of the most difficult challenges to define as part of the scoping process. There is no simple method to identify all potentially relevant comparators, but consideration must be given to the precise setting, population, indications, and relevant subgroups in order to minimise the chances of an important alternative being excluded from consideration.
3.6.4. Perspective

The choice of perspective on outcomes determines the scope of the costs and health benefits. In the context of offering guidance on the use of AMs in the NHS, it would be expected that the perspective on costs would be that of the NHS and personal social services. Although the case for a broader perspective has been widely argued, this would be in line with current NICE guidance for technology appraisals [4]. Again, following NICE’s current position, the perspective to be adopted for outcomes (and associated costs) should focus on health effects and consider the direct effects to the individual treated for the infection, the potential indirect effects to the wider population through avoiding the onward spread of infection and resistant outcomes, and any potential indirect effects to individuals associated with enabling other treatments or procedures to take place. The scope of the evaluation is likely to depend on the particular indication, population, setting and the potential to confer benefits that go beyond treating the direct infection. All potentially relevant health effects from the new AM should ideally be identified during the scoping process.

In situations where AMs are expected to confer benefits that go beyond the objective of gains in population health, e.g., where there could potentially be broader impact on parents of children/carers, or benefits that are considered socially valuable but are not directly captured in the health benefits, then these could be quantified and weighted to reflect their social value. Importantly, any analysis seeking to include a broader perspective must also quantify the trade-off between health gain and non-health related benefits (i.e. some form of weighted ‘value function’). Importantly, any such wider definition of benefit or value would also need to be reflected in the measure of opportunity costs since other types of NHS expenditure also have such wider impacts.

3.6.5. Time horizon

There are three potentially relevant time horizons for the value assessment of AMs: i) the analytic or model time horizon, representing the period over which the differences in costs and health outcomes between the alternative strategies are compared; ii) the technology time horizon, representing the period over which the new and existing AMs are used (i.e., ‘anticipated shelf-life’); and iii) the contractual time horizon, representing the period over which any contractual terms (and subsequent reviews) are defined in relation to alternative
funding arrangements that delinks payments for new AMs from their usage. The latter contractual time horizon falls outside the assessment of expected value of new AMs; therefore, it is only discussed further as part of Section 7 of this report.

The analytic time horizon should be sufficiently long to reflect the important differences in costs and effects between the alternative strategies being compared. This commonly involves adopting a lifetime horizon for most technologies, particularly those differing in mortality effects. However, for AMs, this time horizon, in principle, could be indefinite due to the long-term dynamic effects on infection rates and resistance outcomes. In practice, it should be long enough for the modelled infection and resistance outcomes to attain an equilibrium point (or length of time to plateau) across the different strategies, which will depend on the interventions and characteristics of the infection.

The appropriate time horizon for the analysis is also set by the discount rate that is used for costs and effects. A lower discount rate means that the effective period of analysis is extended further into the future. Therefore, the discount rate is critical to the appropriate time horizon for the evaluation. This issue is not specific to AMs as a similar issue arises in assessing the value of immunisation programmes for infectious diseases. The working group for JCVI examining the cost-effectiveness methodology for vaccination programmes extensively reviewed the issue of the appropriate time horizon and discount rate and concluded that there was no simple methodological solution [10]. The group proposed that immunisation programmes should be evaluated using an indefinite timescale and a sensitivity analysis should be undertaken to highlight the extent to which the estimated cost-effectiveness is influenced by the choice of discount rate and time horizon. This recommendation would also seem appropriate for the evaluation of AMs.

The technology time horizon will not be indefinite due to changes in treatment protocols over time. For example, the development of resistance to the existing AMs will change the availability of the alternative comparators. Similarly, emergence of resistance to the new AM will start to appear over time. This is usually after a lag phase when the new AM is first introduced to the market, which is often followed by a relatively rapid increase in the proportion of organisms that are found to be resistant to the AM before an equilibrium phase is reached [11]. The length of this period of time will depend on the microbiological response of the new
agent to the range of pathogens that the therapy is expected to target. The time to emergence
and development of resistance to both the new and existing AMs will also depend on the
stewardship policies in place, including policies related to hospital control of infections and
prescribing policing to reduce selection pressure. Other new information may also become
available in the future which will affect the value of the new AM. Therefore, the total expected
value of a new AM will depend on its anticipated shelf-life and that of the comparators used in
the evaluation.

Specifying an appropriate technology time horizon is a proxy for a complex and uncertain
process of future changes [12]. Some assessment is possible based on historical trends in the
frequency of resistance to particular AMs and, where there are limited or no data available for
a new AM, it may be necessary to extrapolate past trends from other analogous AMs that
exhibit similar mechanisms of resistance in order to infer likely changes in the patterns of
resistance over time. Some judgement about how fast the field is changing in terms of resistance
outcomes, availability of AMs, future innovations, stewardship policies and new data and
information becoming available, which would change the treatment protocols over time is
necessary in order to evaluate the total value of a new AM. Sensitivity or scenario analyses
should also be undertaken to highlight the extent to which the value of a new AM is influenced
by the technology time horizon. Careful assessment of the expertise needed to specify
alternative scenarios would be necessary (see Section 8).

3.6.6. Discount rate

The total expected value of a new AM should reflect the present value of the stream of costs
and benefits accruing over the analytic time horizon. The UK Treasury recommends that future
costs and benefits of public sector goods are discounted at a rate of 3.5% per annum [13]. For
this reason NICE considers it usually appropriate to discount costs and health effects for new
technologies at the same annual rate of 3.5% [4].

The discount rate is considered to comprise three main elements: i) a catastrophic risk
premium; ii) a rate of pure time preference; and iii) the diminishing marginal utility of future
consumption when per capita consumption is expected to increase over time [14]. The most
recent JCVI guidance for immunisation programmes recommends that health impacts (both
benefits and the displacement effects of expenditure) should be discounted at the lower rate of 1.5% per annum [10]. This is based on the argument that it is consistent with the catastrophic risk premium and future time preference components of the discount rate, but it excludes the part related to the diminishing marginal utility of future consumption with anticipated higher levels of consumption, since there is currently no agreement that future increases in health have a declining value over time [10]. Alternatively, a lower rate for health benefits can be justified based on the assumption that the value of health gains and losses will be valued more highly as income grows over time.

Resources used today to generate health outcomes at some future time point are effectively forgone in the short-term (e.g. they could be deposited in a bank at a positive real rate of interest) but it is argued in the updated JCVI guidance that additional expenditure from the healthcare budget already leads to an opportunity cost in terms of the health that could have been generated elsewhere by the displaced expenditure and, therefore, the third element of the discount rate does not apply such that it follows that expenditure from the health budget should be discounted at 1.5% per annum, while non-health benefits should be discounted at 3.5% per annum [10].

The appropriate discount rate for health effects and costs has been a source of debate over a number of years for health technologies in general [14–16]. In particular, the issue about whether health effects and costs should be discounted at the same or different rate and what discount rates should be applied. These issues are compounded further for AMs because the use of the new AM is not going to remain stable over time but instead it is likely to rise as resistance to the existing portfolio of AMs increases. This means that time-varying discount rates may be more appropriate, i.e., the discount rate does not remain the same over time [17].

There is no easy answer to the question of the most appropriate discount rate for use with AMs. The conventional practice on discounting invariably does not matter as long as the problems being addressed do not have very long-term consequences. However, given that the analytic time horizon for AMs is effectively indefinite, time-varying rates are potentially very important. The appropriate discount rates to use for health effects and costs in the evaluation of AMs is an area where further research is needed to reach a consensus view. In the absence
of this information, sensitivity analysis is required to understand the extent to which the expected value of a new AM is influenced by the choice of discount rate.
3.7. **Recommendations**

- The indication(s) for the use of a new AM should be well-defined and clearly stated. A scoping process similar to that used by the NICE Technology Appraisal programme may be used to refine the indications for use. Where pathogen-specific indication(s) have been permitted by the European Medicines Agency, the selected pathogens should be clearly stated, including those that demonstrate multidrug resistance to specific agents. To ensure the adherence of AM use in the specified indication(s) only, additional stewardship and policing is likely to be required to reduce the emergence of resistance to the new AM.

- The population for whom a new AM is being considered should be stated as clearly as possible. Where the benefits of treatment are expected to extend beyond the individual treated to the wider population, this should be clearly described. Different settings (e.g., community or hospital) affect the flow of infections and spread of resistance in the population; therefore, the setting should also be well-defined. Any potential subgroups of the population, or specific settings, where AM use might be expected to differ from the overall population and in whom treatment protocols may be expected to differ require consideration.

- The scoping process should help to define the range of alternative comparator strategies about usage of a new AM and relevant existing AMs. When alternative AMs are available, the new AM is expected to be used in addition to existing AMs. The relevant comparators are likely to include a range of treatment protocols that reflect heterogeneous prescribing patterns across different settings; these include, rotation of available AMs, mixing protocols and combination therapies. Identifying all potentially relevant comparators requires consideration of the precise setting, population, indications and relevant subgroups for use. Treatment protocols that include off-label use of AMs should be considered if they are deemed relevant and expected to affect resistance patterns over time.

- Following the existing NICE position, the potential impact on health effects and costs that would be expected from the introduction of a new AM should be considered from the perspective of NHS and personal social services. The direct health effects and costs for the treated infection should be considered. Where the
benefits and costs are expected to extend beyond the individual treated to the wider population, the indirect health effects and costs of reduced onward transmission of infection should be given consideration. Indirect effects to individuals of enabling other procedures to take place, which were not possible for some patients without the introduction of the new AM, may also be considered. The methods used to identify and define the health effects and costs associated with both the new AM and the relevant comparators should be clearly described. Other suggested attributes of value can be reflected through these health effects or by differential weighting some effects.

- The approach used to model the expected rate of resistance and associated outcomes for a new AM and its relevant comparators should be clearly stated and justified. Models should predict the prevalence of infections and susceptible and resistant strains of pathogens in the population over time for each comparative strategy over an appropriate time horizon. The model time horizon should be sufficient to capture all important differences in health effects and costs between the comparative strategies; an appropriate discount rate should be used to discount costs and effects to present value. Sensitivity analysis on the model time horizon and discount rate should be conducted.

- Following existing NICE guidance, the economic evaluation should take the form of a cost-effectiveness analysis, with quality-adjusted life years (QALYs) used as the main outcome measure. The expected population net health benefit of each strategy should be compared to the available alternatives. This should allow the potentially best strategy to be identified for each indication based on the one that maximises the expected population net health benefit compared to existing approaches to treatment, initially assuming zero acquisition cost. Where there are multiple indications, results should be aggregated across all relevant indications to determine the total expected value. In negotiating a payment for access to a new AM, the NHS will obtain value until the health opportunity cost of the value-based payment just equals the additional population net health benefit of the new AM compared to current care.
4. ASSESSING THE CLINICAL EFFECTIVENESS OF ANTIMICROBIALS

4.1. INTRODUCTION

The efficacy variables for AMs include both clinical outcomes and non-clinical microbiological response outcomes. Clinical outcomes (e.g., resolution of signs and symptoms of infection) are related to the indication, while microbiological outcomes (e.g., eradication rate of the bacterium) are related to the pathogen. The primary judgement of antimicrobial effect is clinical or microbiological response. For some indications, the assessment of response to therapy will be based primarily on clinical outcomes, whereas for other indications (e.g., urinary tract infections) the microbiological response is the preferred efficacy variable [9]. In some cases, both the clinical and microbiological outcomes are regarded to be of equal importance for the judgement of efficacy [9]. This section examines the sources of data available to inform both clinical and microbiological outcomes, the correlation between these outcomes, how this information may be used to inform the clinical effectiveness of AMs and a discussion on the limitations of the information available.

4.2. CLINICAL EFFICACY OUTCOMES FROM PHASE III TRIALS

Clinical trials for AMs tend to be designed primarily for regulatory purposes. These trials have significant challenges in demonstrating the superiority of a new agent over an existing one, particularly for acute severe infections. The challenges arise because, if resistance is known or suspected to the new agent or comparator(s), it would be considered unethical to use a substandard control; the only possible exception is if all available alternative treatments have been exhausted for the infecting strain. This means that trials tend to include only individuals infected with pathogens expected to be susceptible to both the new agent and comparator(s). Furthermore, the feasibility of demonstrating superiority in clinical trials for AMs is reduced because significant effort is placed on using preclinical in-vitro microbiological data and pharmacokinetic/pharmacodynamic approaches to determine optimised dosing of AMs to reduce resistance and achieve clinical cure (see Section 4.3). There are also additional issues associated with the timing and enrolment of individuals with severe and rapidly fatal infections caused by specific resistant pathogens into trials as rapid point-of-care diagnostics are needed [18]. For these reasons, new AMs are usually evaluated using non-inferiority clinical trials in usual drug resistant (UDR) pathogens.
Non-inferiority trials aim to demonstrate efficacy and safety between the new agent and an active comparator that is considered best available therapy (BAT) for the indication being studied. These trials are designed under the expectation that treatment response rates between the new agent and comparator will lie within a maximum clinically acceptable difference (non-inferiority margin) to be sufficient to differentiate the effect of the new agent and comparator. The implications of the choice of non-inferiority margin for NICE appraisal deserves particular attention and should be tailored to the indication. Both the European Medicines Agency [9] and the US Food and Drug Administration [19] provide guidelines and detailed methodology for computing appropriate non-inferiority margins for the evaluation of bacterial infections.

The primary judgement of clinical efficacy usually occurs at a protocol-defined time point after completion of treatment, which is known as the ‘test-of-cure’ (TOC) visit. At this visit, the clinical outcome measure is typically categorised as cure (i.e., complete resolution of signs and symptoms of infection), failure or indeterminate. In some cases, other endpoints such as mortality or return to baseline status may be used. These outcomes tend to be indication-specific (e.g., community acquired bacterial pneumonia, complicated intra-abdominal infection, complicated urinary tract infection) and stratified by patients’ baseline characteristics when appropriate.

These trials provide evidence that a new AM is not inferior to BAT in terms of clinical efficacy for a given indication. However, there are a number of limitations associated with non-inferiority trials as a source of efficacy data for informing economic evaluation or HTA decisions of AMs. Firstly, the comparator is unlikely to match BAT in the population or setting of the decision. Established standard treatment practice is likely to vary significantly by geography and local variation patterns. Therefore, treatment protocols include very heterogeneous prescribing and there is unlikely to be one BAT. Furthermore, the trials are not addressing the positioning of the new agent relative to the comparator therapies available. This means that there is likely to be an absence of direct head-to-head trial evidence comparing the relevant comparators under evaluation. Secondly, the major unmet need for new AMs is to treat multi-drug resistant (MDR) infections but the trials are predominantly conducted in UDR pathogens. Thirdly, the trials are designed primarily for regulatory purposes and the hypothesis-based approach on a non-inferiority margin is limited for informing funding decisions. Fourthly, the very nature of non-inferiority studies creates a risk of generating experimental ‘noise’, leading to invalid conclusions; for example, these studies are at risk of
biocrecp where successive use of a less efficacious treatment as the active comparator can result in degradation over time of the acceptable efficacy of new AMs [20]. Poor quality design of non-inferiority trials such as ill-defined, non-standardised endpoints or poor adherence to study procedures can also produce false positive results [18], [21].

In the absence of superiority studies for demonstrating clinical efficacy of new AMs, and notwithstanding the limitations of non-inferiority trials as noted above, the only source of evidence in the short-term to inform HTA decisions on clinical effectiveness for a new AM relative to an alternative treatment option is likely to come from these non-inferiority studies, which have been conducted to support the marketing authorisation of the new AM. The European Medicines Agency guideline for treatment of bacterial infections stipulates a preference that each clinical indication for use is supported by at least two randomised and controlled studies, with most confirmatory studies of efficacy based on a specific non-inferiority margin between agents [9]. Recommendations for the design of non-inferiority studies and the identification of the non-inferiority margin should follow established guidelines. These include guidance documents published by the European Medicines Agency [9], the US Food and Drug Administration [19], the CONSORT extension statement for non-inferiority trials [22], the ICH E9 and E10 guidelines [23], [24] and the SPIRIT guidance for protocols of clinical trials [25].

Where the comparator of the trials is not matching BAT in the population and setting of interest, or where there is a range of alternative treatment options representing the different treatment protocols to be evaluated, the analysis of clinical effectiveness for HTA evaluation should be based on all available evidence relevant to all comparators, as described in Section 3. A systematic and transparent approach to obtaining and using this evidence should be pursued in the same way as the HTA evaluation of any other technology [4]. When the comparison of the different treatment protocols has not been evaluated within a single clinical trial, network meta-analysis (NMA) provides a method to combine evidence on clinical outcomes from comparative trials for multiple different treatments [26]. Multiple treatment protocols are compared in NMA using both direct comparisons of interventions within trials and indirect comparisons across trials based on a common comparator [27], [28]. The principles of NMA for the evaluation of clinical effectiveness of AMs is the same as good practice recommendations for standard NMA of other technologies. However, the application to AMs
is likely to present a significant challenge with limited data available to connect the network for all potential treatment protocols. When relevant data are not available for including in the NMA, the analysis may need to be restricted to a narrative overview that critically appraises the clinical efficacy data that is available from individual studies and takes into account the uncertainty associated with the lack of direct or indirect evidence for all relevant treatment protocols.

Non-inferiority trials for AMs are not usually focused on the study of resistant pathogens for which the need for new therapeutic options is expected to be greatest, particularly in MDR pathogens [18]. This means that clinical outcomes associated with infections due to UDR pathogens should always be supported by non-clinical microbiological outcomes and preclinical pharmacokinetic/pharmacodynamic data to assess the activity of a new agent against pathogens that are resistant to other antimicrobial agents (see Section 4.3). Alongside the clinical phase III studies, microbiological in-vitro data are often collected where baseline bacterial isolates across different sites of the infection of the population included in the trial are shipped to the laboratory for confirmation to identify baseline pathogens associated with the infection and to report the range of susceptibility to the agents used in the trial. This provides useful parallel information of resistance to the AMs included in non-inferiority trials, but is often limited by the size of the study and the baseline pathogens identified.

4.3. NON-CLINICAL MICROBIOLOGICAL RESPONSE OUTCOMES

Non-clinical microbiological evaluation of AMs is important for identifying activity against pathogens that are resistant to new therapeutic agents. In its simplest form, this involves susceptibility testing where the antimicrobial agent is placed on a petri dish (in-vitro) where the bacterium is growing; some agents will kill the bacterium, while others will prevent it from multiplying so that the host immune system overcomes it, and some bacterium will be found to be resistant to the agent. The minimum inhibitory concentration (MIC) represents the lowest concentration of an agent which inhibits visible growth of bacterium.³ The non-clinical assessment of AM activity typically involves collecting several thousand isolates from hospitalised patients with a specific pathogen. These are then left in overnight incubation with

³ Minimum bactericidal concentration (MBC) is the lowest concentration of an agent required to kill the bacterium.
the test agent to determine susceptibility of the organisms to the agent. The range of antibiotic concentrations used for determining MICs is universally accepted to be in doubling dilution steps, e.g., 0.5, 1, 2 and 4 concentration units (see Box 4). Lower values of MIC indicate that less drug is required to inhibit growth of the organism. The range of susceptibility to the agent is typically reported as MIC50 (or MIC90) corresponding to the agent inhibiting 50% (or 90%) of the particular strain of bacteria (see Box 4). Thus, the MIC is often thought of as a threshold value for drug effect.

**Box 4: Distribution of MIC values**

- Isolates tested with antimicrobial to determine susceptibility of the organisms to the agent
- Bacterial isolates collected from hospitalised patients with different pathogens
- Isolates tested with antimicrobial to determine susceptibility of the organisms to the agent
- Record the minimum inhibitory concentration (MIC) for each isolate for each pathogen
- Identify the number of isolate for each pathogen strain with MIC (Mg/L) of 0.002 0.004 0.008 0.015 0.03 0.06 0.12 0.25 0.5 1 2 4 8 16 32 64 128 256 512
- Lower MIC values indicate less drug is required to inhibit growth of organism, i.e. lower values suggest bacteria is more susceptible to the agent
- MIC50 (or MIC90) gives the MIC which inhibits 50% (or 90%) of pathogen strain

There are a number of drawbacks to the use of the MIC value as a measure of effect: i) it is limited to a single efficacy endpoint; ii) it is evaluated at a snapshot point in time and at a fixed concentration of dose; and iii) it does not take account of the entire time course of effect, which may vary between treated individuals and bacterial strains; therefore, it neglects any dynamic changes in growth and susceptibility over the studied time period [29]. These limitations are overcome by using pharmacokinetic/pharmacodynamics (PK/PD) relationships that are linked to the MIC value of drug in relation to a specific bacterium. Pharmacokinetics (PK) describe
the relationship between drug dosing and the drug concentration-time course in body fluids resulting from the administration of the drug dose, while pharmacodynamics (PD) describe the relationship between drug concentration and the observed effect on the bacterium. The combined PK/PD relationship is used to characterise the relationships between dose, exposure and response to treatment. It should also be noted that there is a small literature on the use of PK/PD data for economic models (e.g. [30]).

Antimicrobial agents are categorised on the basis of the PK/PD measure that is most predictive of efficacy. Three common measures (indices) are used for this purpose:

i. The duration of time that the unbound (free or non-protein bound) drug concentration remains above the minimal inhibitory concentration (f/T>MIC), e.g., the percentage of a 24-hour time period that the free drug concentration exceeds the MIC;

ii. The ratio of the maximal unbound drug concentration to the MIC (f/C\text{max}/MIC); and

iii. The ratio of the area under the unbound drug concentration-time curve to the MIC (f\text{AUC}/MIC).

These indices have become the gold standard for evaluating PK/PD of antimicrobials and to guide optimal dosing schedules for maximum bacterial kill and minimal emergence of resistance. They have also been used to predict therapeutic outcomes against the range of pathogens encountered clinically in different patient populations and to develop strategies that minimise the development of bacterial resistance (see Box 5).

Susceptibility testing breakpoints for antimicrobials are used to define the MIC value that separates bacterial organisms into either: Susceptible (S), Intermediate (I) or Resistant (R) to the agent under evaluation, based on the fact that MIC increases for resistant isolates. The European Committee on Antimicrobial Susceptibility Testing (EUCAST), for instance, sets the breakpoints for AMs taking into consideration a number of relevant factors, which include the dose-effect relationship, MIC distribution, PK/PD outcomes, and variability in outcomes between individuals in targeted pathogen populations. The susceptibility breakpoint is the MIC value that separates low and high probability of clinical success for a given dosing regimen and pathogen. For example, the susceptibility breakpoints for Zavicefta (ceftazidime-avibactam) for the pathogens of Enterobacteriaceae and Pseudomonas aeruginosa are shown in Figure 1. The breakpoints suggest that Zavicefta is unlikely to inhibit growth of these particular bacterial strains for an MIC value greater than 8 mg/L, and therefore unlikely to result in clinical cure.
Different pathogens will have different breakpoints, and this may vary by antimicrobial agent. The activity of the new AM is also independent of being UDR or MDR to other antimicrobial agents.

Figure 1: Susceptibility testing breakpoints for Zavicefta (ceftazidime-avibactam) for the pathogens of *Enterobacteriaceae* and *Pseudomonas aeruginosa*.

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Susceptible</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>≤8 mg/L</td>
<td>&gt;8 mg/L</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>≤8 mg/L</td>
<td>&gt;8 mg/L</td>
</tr>
</tbody>
</table>

Source: EMA Summary of Product Characteristics for Zavicefta [31].

Estimates of the microbiological response of the new AM and comparators should be reported to establish the susceptibility of agents to pathogen-specific indications. For MDR pathogens, PK/PD analyses and microbiological response data may provide important supportive information of the likely efficacy of new AMs against particular pathogens. A pathogen-specific indication for use of a new AM that is not qualified by site of infection is permitted by the European Medicines Agency if the new agent has shown to have efficacy against particular pathogens that express resistance at different body sites [9].
Box 5: PK/PD modelling for target attainment to minimise the development of resistance

- PK/PD modelling is used to generate dosing strategies that maximise the likelihood that a regimen will achieve the desired target (e.g., 50% $fT>MIC$) against the range of pathogens encountered clinically in the patient population of interest.

  **Pharmacokinetics (PK):**
  - Relationship between drug dosing and the drug concentration-time profile.
  - $C_{max}$, $T_{max}$, AUC, $\text{Log Concentration}$.

  **Pharmacodynamics (PD):**
  - Relationship between drug concentration and effect.
  - $E_{max}$, $E_{0}$, EC$\text{_{50}}$.

  **PK/PD:**
  - Effect vs. Time.

- PK model is typically developed based on phase I/II trial data:
  - Covariate model based on how PK parameters change with respect to observable physiological signs (e.g., renal impairment, hepatic impairment) and patient demographics.

- PD model is developed based on how the drug affects the bacteria.

- Interrelationship between PK and PD model is then defined.

- The small sample size of phase I/II studies has led to increased use of population PK/PD simulation models. Monte Carlo simulation (MCS) is used to 'expand' the sample size of the phase I/II studies to provide predictions of the likely result of different dose and dosing schedules.

- Population PK/PD simulation modelling used to determine optimal dosing schedule for a specific pathogen to reduce resistance and achieve clinical cure.

  - For particular dose/schedule against a specific pathogen.
  - Drug inhibits pathogen above MIC.
  - Work out % of time in 24-h period above MIC.
  - Is it ≥50% target? MCS is simulating lots of PK/PD curves for different MICs.
  - Probability of target attainment 50%$T>MIC$.
  - Different dosing schedules.
4.4. Correlation Between Microbiological Response Outcomes and Clinical Outcomes

Clinical response outcomes for AMs are related to the indication, whereas microbiological response outcomes are related to the pathogen. An important question that arises is how well microbiological response outcomes, derived from the results of susceptibility testing, predict clinical outcomes in individuals with infection. In general, a positive correlation between these outcomes would be expected, i.e., where susceptibility is determined from in-vitro susceptibility testing for a specific agent against particular pathogens, higher rates of clinical response to therapy would be expected; similarly, if resistance is determined by susceptibility testing, this would be expected to be an independent risk factor for clinical failure in individuals with the infection. However, results of prospective studies that have assessed both clinical responses and microbiological eradication rates have shown that it is not always possible to presume that what happens in-vitro can be extrapolated to therapeutic outcomes of clinical success or failure [32], [33]. One study found that in 56% of cases considered a clinical success at the end of treatment among patients with severe pneumonia, several pathogen strains were not eradicated in these patients, i.e., patients remained colonised with a resistant bacterial strain as determined by susceptibility testing of the organism [32]. Other studies have also found no predictive value for clinical outcomes based on the results generated by susceptibility testing [33].

The correlation between microbiological and clinical response outcomes varies by pathogen and indication. There are no clear criteria for when in-vitro activity can become a good proxy for clinical outcomes. A “90-60 rule” has been suggested, but there are few data to validate this [34]. This rule suggests that infections with susceptible strains are associated with favourable clinical response to therapy approximately 90% of the time, whereas infections with resistant strains respond favourably approximately 60% of the time. In some scenarios, however, there may be much higher failure rates when an AM is used to treat a resistant pathogen; for example, infections in critically ill patients.

Clinical endpoints that reflect whether the infection has been treated successfully or not for the individual patient may be regarded as more informative than intermediate endpoints from a healthcare practitioner’s perspective. However, microbiological outcomes are likely to provide the most useful information on the emergence and prevalence of resistance to a new AM. In
the absence of a final clinical endpoint for the evaluation of clinical effectiveness of AMs, there is a potential need to extrapolate from imperfect proxies, or intermediate outcomes, to infer clinical endpoint. The principles of extrapolating intermediate-to-final clinical outcomes are the same as good practice recommendations for how this relationship is quantified for other technologies [35]. In the absence of a relationship for new AMs, consideration should be given to generalising the relationship observed for existing AMs of a similar class if appropriate. The uncertainty associated with the relationship between intermediate and final endpoints should be explored and quantified.

4.5. MICROBIOLOGICAL SURVEILLANCE DATA

The combination of traditional clinical trial endpoints and non-clinical microbiological outcome data provides the necessary information needed to inform the clinical effectiveness of AMs. However, the extent of this information being available is likely to be limited due to the need to get new AMs to market as quickly as possible. This means that marketing authorisation decisions for AMs are increasingly being made when the evidence base to support their use is least mature. As a consequence, there is an important need to collect microbiological surveillance data on the effectiveness and safety of new AMs (this can be seen as a form of ‘real world’ data).

Microbiological surveillance data provides a rich source of information on the susceptibility and resistance of AMs to different pathogens. A number of ongoing global antimicrobial surveillance programmes collect in-vitro susceptibility data for defined bacterial groups and indications, including the British Society for Antimicrobial Chemotherapy (BSAC) Resistance Surveillance Programme [36], the Study for Monitoring Antimicrobial Resistance Trends (SMART) [37], and the English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) [38]. These surveillance programmes collate resistance data, which are collected by local hospital laboratories that send routine susceptibility test results to their national database. The BSAC collects a broad selection of organisms from both community- and hospital-acquired infections in the UK and Ireland, while SMART monitors the in-vitro susceptibility and resistance patterns of intra-abdominal and urinary tract infections worldwide. ESPAUR collects data on both resistance and antibiotic prescribing in the English NHS, as well as antimicrobial stewardship activities. Data are available on trends in resistance for England through several annual reports from ESPAUR, which are supplemented by freely
available Excel files containing the data used for the reports [38]. This surveillance data are likely to provide the most reliable information on the emergence of, or changes in, the prevalence of resistance to both new and existing AMs. Investment in data collection infrastructure in the form of data linkage for the surveillance of AMR is also underway with the funding of two Health Protection Research Units (HPRUs) in healthcare associated infections and antimicrobial resistance by the UK National Institute for Health Research [39], [40].

The continued coordination and collection of surveillance data from networks of centres recruiting individuals with infections is needed. This information should be collected across geographies, patient groups, infection sites and pathogens given the wide variation in resistance patterns even at a local hospital level. This also means that consistent criteria for inclusion of bacterial organisms by the collaborating centres are required. Large, well-established surveillance networks will help detect trends in the emergence and patterns of resistance over time; examples include the European Antimicrobial Resistance Surveillance Network (EARS-Net) [41] and the Global Antimicrobial Resistance Surveillance System (GLASS) [42]. Clinical trial networks may also present a potential solution to the challenges of recruiting sufficient numbers of patients with specific types of resistant infections into a single clinical trial [2]. The EMA guideline for the evaluation of treatment of bacterial infections also recommends a commitment from manufacturers to undertake post-approval studies of susceptibility and resistance to a new AM over a period of approximately 3-5 years [9].
4.6. **Recommendations**

- Estimates of the clinical effect of a new AM and its relevant comparator(s) should be informed by RCTs when available. For most bacterial infections, efficacy and safety is demonstrated through non-inferiority trials in patients infected with pathogens expected to be susceptible to both the new AM and the comparator(s). The implications of the choice of non-inferiority margin for NICE appraisal deserves particular attention and should be tailored to the indication. The test-of-cure visit after completion of treatment should categorise clinical outcomes as cure of infection (complete resolution of signs and symptoms), failure or indeterminate for each indication of use.

- Where the comparator(s) of the trials are not matching best available therapy in the population and setting of interest, this should be clearly stated and justified. In the absence of direct head-to-head RCTs comparing the relevant comparators under evaluation, network meta-analysis should be conducted if appropriate.

- Recommendations for the design of non-inferiority studies and identification of non-inferiority margins should follow established guidelines. Given the constraints associated with the evaluation of AMs, the design of RCTs to inform funding decisions represents an important area for further evaluative research.

- Estimates of the microbiological response (e.g., rates of bacterial eradication) of the new AM and comparator(s) should be reported to establish the susceptibility of the agents to pathogen-specific indication(s). Microbiological outcomes of cultures collected during clinical studies should be reported for each comparator and pathogen when available. The microbiological evaluation of a new AM should aim to identify the precise mechanism of action and the activity against pathogens that are resistant to other comparator drugs.

- The correlation between microbiological outcomes and clinical response outcomes should be explored if appropriate. For MDR pathogens, PK/PD analyses and microbiology response data may provide important supportive information of the likely efficacy where the new AM has shown to have efficacy against particular pathogens that express resistance at different sites. When the use of final clinical
Endpoints is not possible and intermediate outcomes are used to infer clinical response, evidence to support the intermediate-to-final outcome relationship should be provided with an explanation of how the relationship is quantified. In the absence of a relationship for new AMs, consideration should be given to generalising the relationship observed for existing AMs if appropriate.

- The use of microbiology surveillance data should be used as a source of information on susceptibility and resistance to pathogens. A number of ongoing global antimicrobial surveillance programs collect in-vitro susceptibility data for defined bacterial groups and indications. Microbiology surveillance data should be collected at a local level given the variation in resistance patterns. This information is likely to be the most reliable information on the emergence of, or change in, the prevalence of resistance to a new AM and its comparators over time.

- The coordination and collection of surveillance data from networks of centres recruiting patients with infections across geographies, patient groups, infection sites and pathogens should be established further, with a need for consistent criteria for inclusions of bacterial pathogens by the collaborating centres. Large well-established surveillance networks should help detect trends in the emergence and patterns of resistance over time.
5. MODELLING THE INFECTION AND RESISTANCE OUTCOMES

5.1. INTRODUCTION

The framework for establishing the expected value of a new AM is consistent with the principles of economic evaluation, but the most challenging aspect is estimating the population health effects. This involves adequately reflecting the expected rate of growth in resistance and associated outcomes over time, including the infection transmission dynamics and measurements of attributes of value. Estimation is likely to require modelling studies, where mechanistic dynamic transmission models can provide a valuable tool through which the mechanisms of resistance and infection transmission dynamics can be methodologically reflected. The model by itself, however, cannot address important policy questions without appropriate parameter estimation and empirical evidence that are transparently integrated to reflect plausible and realistic outcomes in the population or setting of the decision problem.

The first step in the development of a model should be an understanding of the mechanisms of resistance and the epidemiological data available for a new AM and its comparator strategies so that the important determinants of the transmission dynamics of the infectious pathogen can be reflected. Once the conceptual model is developed and appropriately parameterised with empirical data where possible, the second step involves evaluating and comparing the epidemiological and economic impact of the alternative policy interventions. This section examines the underlying mechanisms of resistance, the types of resistance models used to characterise competition between susceptible and resistant bacterial strains, a comparison of statistical forecasting and mechanistic dynamic transmission modelling approaches to predict the evolution of resistance in a population over time, and the sources of data available to parameterise the models. This section also discusses the methods available to address the evidential and modelling challenges.

5.2. MECHANISMS OF RESISTANCE

An understanding of the underlying mechanisms by which resistance to the AMs develops is fundamental for enabling the infection dynamics to be modelled appropriately. Bacteria have developed robust mechanisms to adapt to the environment and to develop resistance upon AM exposure. Resistance emerges through a number of biological processes [43–45]. For example, the resistance can be acquired by genetic mutations in the chromosome and by horizontal gene
transfer where the acquisition of a gene by a means other than direct inheritance from a parent cell (vertical gene transfer) is transmitted between pathogens in plasmids and other forms. This process can provide the host cell with new genetic material conferring antimicrobial resistance and can occur through several mechanisms, which include transformation (some pathogens take up free DNA from the environment), transduction (DNA from a donor bacterium is packaged into a virus particle and transferred to a recipient bacterium during infection), and conjugation (plasmid is transferred between two bacterial cells) [43]. Antimicrobial use can influence this by either exerting a selection pressure favouring the emergence of resistance (i.e. conferring a survival advantage to resistant pathogens that benefit from favoured gene transfer) or by inducing transfer of the determinants of resistance between organisms.

The role of antimicrobial use in driving the emergence of resistance is specific to each AM and to each organism. Therefore, the correlation between consumption and resistance for any specific AM is complicated by different factors. One of the main factors is the relative fitness of resistant and susceptible strains of the pathogen, where fitness refers to the rate of replication of the surviving pathogen under the prevailing environmental conditions. Other factors are multiple resistances, where genetic material that confers resistance to several different AMs are selected through the use of any one AM [46], cross-resistance, where the propensity of a genetic change that confers resistance to one specific AM also affects resistance to a different AM [47], or transmission rates of pathogens between hosts and the environment. These confounding factors mean that a uniform approach to eliminating resistance is not possible, e.g., it is not possible to assume that reducing usage of antimicrobials once resistance has developed will result in complete eradication of resistance. For some organisms, the persistence of antimicrobial resistant strains is maintained in the absence of the AM through, for example, compensatory mutations. This is the case when the potential reduction in relative fitness that followed the mutation conferring resistance is compensated by another genetic mutation that restores the pathogen’s fitness. Strategies intended to reduce the development and spread of AMR are generally aimed at lowering the selection pressure by limiting or suspending the use of particular AMs for a period of time. This is based on the assumption that resistant strains will be outnumbered by susceptible strains once the selective advantage conferred by AMs to the resistant strains is diminished - provided the latter are less fit than susceptible strains [43].
AM use exerts selective pressure on the human microbiota, increasing the risk of resistant organisms in individuals, which are then spread through cross-transmission between individuals. The mechanisms that drive the transmission of resistance between individuals are summarised in Box 6. Primary resistance occurs when an uninfected individual becomes infected with a resistant strain (new infection by a resistant organism). Exposure to AM treatment drives resistance predominantly through either target selection or collateral selection. This is known as acquired resistance during antimicrobial treatment. Target selection occurs when genetic mutations conferring antimicrobial resistance are selected during treatment such that susceptible strains of the bacterium become resistant. Transmission of these resistant strains can occur during (before cure is achieved) or following inadequate treatment (re-emerge after treatment failure) [48]. Collateral selection (also known as bystander selection) occurs in a person taking AMs for any reason, and susceptible sub-types present in his/her microbiome are replaced by resistant ones that can cause infection in the future. Transmission of these resistant strains can be between asymptomatic carriers, where an individual becomes colonised with the resistant strain without causing immediate infection, but the resistant strain is present to cause infection in the future [48]. Acquired resistance in the absence of direct AM usage may also occur through antimicrobial residuals present in the environment (e.g., hospital), where even low quantities of residuals can change the fitness of susceptible strains [49]. Other between-host dynamics that are based on the properties of within-host strain co-existence of susceptible and resistant strains include, replacement infection (when an individual is infected with one strain there is potential for a novel strain to replace the resident strain), strain conversion (when a predominant strain may convert from susceptible to resistant or vice-versa), or superinfection (when an individual becomes infected with susceptible and resistant strains) [50].
Mathematical models have been used to model the competition between susceptible and resistant bacterial strains. These include within-host models of bacterial growth that focus on the mechanisms for the emergence of resistance, microbial fitness, competition between susceptible and resistant strains, and within-host tolerance to different treatment protocols (e.g., drug concentration, dose, duration, combinations of therapies) on bacterial populations [50]. Population-level models, which reflect between-host dynamics, have also been used. These focus on how susceptible and resistant strains spread through the population over time. These models have conceptualised the spread of resistance in different settings such as transmission within hospitals and ICUs, within the community setting, and transmission between individuals in the community and hospital setting. These models have predominantly been used to evaluate the effectiveness of different treatment protocols (e.g., comparing cycling or mixing programmes) and infection control programmes (e.g., hand hygiene, patient isolation, movement of healthcare workers, stewardship and screening) to reduce AMR [51]. Spicknall et al., (2013) [50] provides a review of the generic model structures and assumptions that have been used with regard to within- and between-host competition between susceptible and resistant strains, while van Kleef et al., (2013) [51] provides a systematic review of
transmission models that have been used to improve our understanding of the epidemiology of healthcare associated infections.

The conceptual framework for value assessment of new AMs focuses on population-level models since the aim is to predict the evolution of resistance in the population over time and the associated outcomes for the alternative treatment protocols. Between-host models are based on the properties of within-host dynamics and are determined by the extent of strain co-existence within a host, e.g., resistant and susceptible strains can co-exist at equal levels, one strain may predominate over the other, or an individual may be infected exclusively by either a resistant or susceptible strain [50]. Competition between the strains within an individual will give rise to different results, e.g., strain conversion, replacement infection, or superinfection. This means that different model structures are used to model the underlying mechanisms of resistance and no simple generic form of model structure is available.

Population-level models typically consist of mutually exclusive compartments and reflect the dynamic changes in the uninfected population and those infected with susceptible and resistant strains. In its simplest form, individuals belong in one of three states: uninfected, X; infected with a susceptible strain, S; and infected with a resistant strain, R. These compartments are the minimal set that govern the infectious disease process and are used to model the flow of the population over time and, therefore, the development of AMR over time for a single antimicrobial (see Box 7). The model makes specific assumptions about the transmission of susceptible and resistant bacterial strains among the population and course of the infection, e.g., the fitness cost associated with resistance may translate into a lower rate of transmission of resistant strains relative to susceptible ones, or the spontaneous clearance rate of the infection in the absence of AMs may be different for susceptible and resistant strains.
Box 7: Basic compartment model for a single antimicrobial treatment; a) infection status modelled; b) colonisation status modelled separately from infection status.

The mechanisms of resistance should be clearly defined in the model structure. For example, primary resistance (infection by a resistant strain) should be separated from ‘acquired resistance’ during treatment, where a fraction of individuals initially infected with a susceptible strain may develop resistance during treatment (target selection). Similarly, conversion may be possible if the susceptible strain outcompetes the resistant strain, i.e., the resistant strain can convert to a susceptible strain. The resistance gene may, however, be retained by the strain. In this case, the conversion may be quickly reversed under exposure to a specific antibiotic that allows the resistance gene to be re-expressed.
Often a distinction is also made between infected, as defined by clinical symptoms, and colonised individuals, with stable bacterial presence without clinical symptoms, although both contribute to pathogen cross-transmission. Colonisation status may also be distinguished by strain phenotype (susceptible or resistant). In some cases, both uninfected and colonised individuals may become infected (see Box 7), whilst in other cases it is assumed that infection requires colonisation with the pathogen first.

When multiple AM treatments are considered, the structure of the model increases in complexity, with the number of mutually exclusive compartments for the infectious state increasing exponentially. For example, for a simple two treatment model with antimicrobials A and B, the probability of an individual to become infected at any one point in time is related to the number of individuals in the population who are infected or colonised with a strain resistant to drug A, drug B or both drugs AB. This means that the number of model compartments for the infected states (and colonised states if the distinction is implemented) increases from two (single treatment model) to four (two treatment model), i.e., those individuals may have a strain susceptible to both available AMs, resistant to drug A or B, or resistant to both available drugs AB. Similarly, if another drug C is added into the mix, the number of infected (and colonised) states increases from four to eight, i.e., infected (colonised) individuals may have a strain susceptible to all three available AMs, resistant to drug A, B or C, resistant to two of the available drugs AB, AC or BC, or resistant to all three drugs ABC.

In hospitals patients are often treated with multiple drugs simultaneously. This means that the number of parameters in the model also greatly increases due to more transitions being allowed between the health states. This has implications for the number of treatment protocols that can be feasibly evaluated. Treatment strategies may include partial or mixed use of AMs, combination therapy, cycling or periodic switch in therapies, or test and treat strategies with choice of AM dependent on resistance status. In these cases, if only two AMs are considered but evaluated in different ways of use, the model structure may be tractable. However, if more than two treatments are considered, or treatment strategies lead to different rates of emergence of multi-drug resistance, the combination of possible policy options and modelled health states can quickly become very large.
5.4. STATISTICAL FORECASTING MODELS AND DYNAMIC TRANSMISSION MODELS FOR PREDICTING THE EVOLUTION OF RESISTANCE IN THE POPULATION OVER TIME

An important distinction is often made between statistical forecasting approaches and mechanistic dynamic transmission models used to predict the number of infected individuals in the population over time with susceptible and resistant bacterial strains.

5.4.1. Mechanistic dynamic transmission models

In a mechanistic dynamic transmission model, the probability that an individual acquires the pathogen at any one point in time (the force of infection) is related to the number of infectious (infected and colonised) individuals in the population, which will change over time and feed back into the future force of infection [52]. Therefore, a mechanistic model cyclically re-estimates the force of infection from the proportion of susceptible and infectious individuals in the population at each point in time.

Mechanistic models attempt to explain the way in which susceptible and resistant pathogens spread in the population, through either transmission or other means such as acquired resistance due to AM exposure. These models can capture the impact of different AM policy strategies on: i) the pathogen’s ecology, e.g., the impact of selection pressure on the competition between susceptible and resistant strains or other differences between serotypes; ii) direct effects on treated individuals, e.g., potential to acquire resistance during treatment; and iii) disease transmission among individuals and those who may not engage with treatment but still contribute to the transmission process, e.g., asymptomatic individuals colonised with a bacterial strain, or transmission via a healthcare worker or the environment.

Transmission risk in mechanistic models is likely to depend on a large number of factors. These include: individual characteristics, e.g., immunity due to prior AM exposure or vaccination status; differences between serotypes; contact patterns, e.g., sexual contact patterns or household groupings; risky behaviours; physical characteristics, e.g., open wounds or incontinence; current treatment status, e.g., part-way through treatment may mean that infectiousness is reduced, or AM receipt may increase the load of the resistant pathogen increasing the risk of onward transmission; and location, e.g., hospital admission increases the transmission risk. The transmission risk will also depend on the implementation of risk
reduction policies by individuals, patients and healthcare workers. Therefore, the transmission parameters in the model should take on values according to the characteristics that determine the force of infection, and additional health states may need to be added to the model to reflect differences in long-term outcomes associated with different treatment strategies.

Pathogens predominantly spread within a certain setting, e.g., hospital or community, but the dynamics within a given setting (e.g. hospital) may also be impacted by transmission dynamics outside that setting (e.g. intensive care units). In some circumstances, modelling of resistance and transmission dynamics within and between multiple settings is required. For example, there may be an associated feedback effect, whereby a treatment policy in the hospital setting may directly influence the frequency of resistance, or transmission risk, within incoming patients from the community, which in turn feeds back into resistance frequencies in the community [53]. If the interaction with the external setting only impacts the setting of interest via a feedback loop, then simplifications that avoid modelling multiple settings may be possible. However, if the alternative AM policy strategies are expected to have consequences outside the setting in which they are implemented, then the long-term effects may need to be explicitly reflected in a joint model of multiple settings [54].

The resistance mechanism of collateral selection may have important implications for modelling. Exposure to antimicrobials and the resultant disruption of the intestinal microbiota are known to predispose individuals to be colonised by other resistant pathogens in the future. Therefore, treatment for the infection of interest may have significant effects on the development of other types of resistance in the future. This is related to the spectrum value attributed to AMs, e.g., if a narrow spectrum AM replaces a broad spectrum AM, the negative effects outside the infection of interest may be reduced. Failure to reflect this mechanism of resistance in the modelling may result in the omission of an important ‘externality’ of treatment, particularly if collateral selection is expected to be an important driver of resistance. Collateral selection may be modelled by differentiating between individuals colonised and infected due to ‘other’ AM exposure and modelling the associated transmission dynamics. However, this will not be sufficient to understand the impact of the alternative AM policy strategies on future resistance outside the pathogen of interest. This is likely to be very difficult or impossible to model with little available evidence to inform the transmission dynamics. When possible, consideration should be given to the likely direction and magnitude of effect
qualitatively by taking into consideration the nature of the policy change, e.g., implications on the development of resistance of moving from broad spectrum to narrow spectrum use.

5.4.2. Statistical forecasting models

Statistical forecasting models differ from dynamic transmission models in that they predict numbers of infected individuals and future resistance trends without explicitly modelling the underlying mechanistic processes of pathogen transmission and resistance development.

These models predict the number of infected individuals with susceptible and resistant strains over time by statistically extrapolating past epidemiological trends to the future, using historical data on the frequency of pathogens across strain sub-types. Costs and health outcomes associated with incident infections are estimated for each alternative AM treatment strategy.

The main goal of a statistical forecasting model is to make projections on the future emergence and spread of AMR and the associated health and economic burden of resistance. However, despite the rise in AMR, very few studies to date have attempted such a task. The two most recent studies are those by Nouvellet et al (2016), which adopted a scenario-based approach to make assumptions about future rates of resistance and disease burden in *Escherichia coli* [55], and Colson et al (2018), which compared structured expert judgment and statistical forecasting methods to quantify uncertainty about future AMR in various invasive infections [56]. These studies, however, have not compared the impact of alternative policy strategies about the use of a new AM relative to existing comparators on infection and resistance rates over time, nor have they considered acquired resistance to a new AM.

5.4.3. Choosing between statistical forecasting and mechanistic dynamic transmission modelling approaches

No simple generic modelling approach can be prescribed that minimally meets the analytic requirements given the range of different infections, pathogens and treatment protocols. The statistical forecasting approach is generally perceived to be a much simpler modelling approach compared to the development of a mechanistic dynamic transmission model. In the statistical modelling approach, alternative scenarios are usually used to address key uncertainties and to
explore how future resistance is likely to develop over time. However, this inevitably means that some judgement needs to be taken about what is the most credible scenario, or a weighted scenario approach is required, where the weights are quantitatively informed by judgements from experts or using an expert elicitation exercise.

In the absence of modelling of mechanistic processes, the statistical modelling approach extrapolates trends using time series and regression-based methods. However, the extent to which this approach can reasonably predict future trends in resistance, and the impact of alternative policy strategies on resistance, depends crucially on the availability of long time series data with sufficient information on covariates, e.g., level of granular detail in the available dataset at a hospital or patient level and how covariates of the local setting or patient can explain change in effect.

The statistical forecasting approach to date has generally not considered acquired resistance during treatment. This means that differences in effect are driven solely by the development of new infections and not through acquired resistance because of AM treatment. To date, these models have also assumed no resistance to the new AM therapy due to an absence of past epidemiological data for the new treatment. This implies that there are no negative consequences from using the new treatment. However, alternative scenarios could be explored within the statistical modelling approach that makes assumptions about the expected rate of growth in resistance to the new therapy over time. Where there are limited or no data available for a new AM, that has yet to be introduced in real-life, it may be necessary to examine the data available for other analogous AMs seen in the past that exhibit similar mechanisms of resistance in order to infer likely changes in the emergence of resistance over time until additional information on the new AM becomes available.

The simplicity of the statistical modelling approach has, perhaps, the advantage that models appear more transparent in their assumptions. For instance, one may fit a trend to past usage and allow it to go forward to predict the baseline trend and then evaluate several scenarios regarding resistance appearance under new AM, e.g. same/lower/higher as existing drug, depending on the expected level of drug usage.
The exploration of various scenarios can be useful for gaining better intuition and insight into the key determinants of resistance outcomes and the implications of plausible future scenarios [55]. Importantly, the attributes of the specific infections, pathogens and interventions and their implications for the development of resistance are likely to determine the appropriateness of the statistical forecasting approach, as well as the availability of past epidemiological and microbiological outcome data.

Mechanistic dynamic transmission models are capable of reproducing both the direct and indirect effects arising from alternative AM policy strategies, including acquired resistance during treatment to the new AM. Therefore, mechanistic dynamic models have the added advantage over statistical models that they can explicitly model the complex relationships between infected and non-infected individuals, competition between susceptible and resistant bacterial strains, target and collateral selection during AM treatment, transmission risk according to characteristics that determine the force of infection, and other non-linear effects.

The complexity of mechanistic dynamic modelling is determined by the mechanistic level of detail that is added to the conceptualisation of the model structure. Structural considerations can be easily addressed through appropriate specification of health states and the allowed transitions between states. However, uncertainties about the underlying mechanisms of co-existence and emergence of resistance make the application of mechanistic models to specific systems problematic. Bacteria have evolved diverse mechanisms of resistance to AMs and these are not well understood. Evaluating the impact of the interventions on disease transmission and resistance may prove to be particularly difficult for new AMs where there is limited information or understanding of resistance mutations, fitness costs for transmission and emergence of resistance. Thus, mechanistic models require knowledge of the parameters that drive the mechanisms of resistance, many of which are non-measurable and not well understood.

Mechanistic models have typically been used to date to explore the population biology of drug resistance or to evaluate the effectiveness of treatment protocols to reduce AM resistance (e.g., cycling or mixing protocols). They have been very rarely used to model long time series of data on resistance or to address policy questions about AM use. This is largely due to the lack of observed data on key quantities such as contact and transmission rates, as well as the
difficulties in informing fitness costs and other determinants of resistance. The potential for a high level of structural complexity also makes the findings from dynamic transmission models difficult to interpret. Disentangling the impact of important drivers of resistance is much more challenging compared to statistical models. For these reasons, mechanistic models need to be carefully planned, parameterised appropriately with available data, and all assumptions listed in a clear and transparent format.

Importantly, both statistical and mechanistic approaches should be able to provide credible predictions of historical data on infection and resistance rates. To date, both approaches have struggled to achieve this. Colson et al (2018) showed, however, that structured expert judgment to elicit future rates of resistance produced forecasts that were considered more biologically credible and less dependent on arbitrary technical assumptions about model form and parameterisation than statistical forecasting methods to quantify uncertainty about future AMR in various invasive infections [56]. The statistical forecasting approach makes explicit use of historical data, but extrapolation based on these data alone is not able to anticipate changes in AM use, the emergence of new resistant strains, or the introduction of new AMs [56]. Similarly, mechanistic dynamic transmission models have struggled to reproduce credible historical data on infection and resistance patterns both in terms of quantitative predictions and qualitative trends such as the co-existence of susceptible and resistant strains [57]. This is particularly the case for many commensal pathogens that pose a significant public health threat and are important targets for new AMs. When historical data on infection and resistance rates cannot be reproduced, there should be careful consideration of the potential direction of bias informed by an understanding of the determinants of key outcomes.

5.5. METHODS EMPLOYED TO PARAMETERISE THE MODELS

A systematic literature review of policy models evaluating the effectiveness of at least two alternative treatment protocols for the use of AMs, and reported in the literature between 2011 and 2017, was conducted to identify common model parameters and issues and challenges related to the sources of data required to parameterise models (see Appendix A.1 for details of the literature review).

Most studies to date that have taken a mechanistic dynamic transmission modelling approach are population-based and evaluated at an aggregate level, i.e., the population is divided into
compartments that represent the average values of individuals in a particular state (e.g., non-infected, infected with a susceptible or resistant strain) and tracked over time. Fewer studies have used individual-based models, which track individuals explicitly over time. In these models, individuals are treated as discrete entities that enable the simulation of a richer heterogeneity of individual trajectories by allowing more realistic and complex patterns of disease evolution and resistance to emerge. In an individual-based model, the transitions between different states may be conditioned on previous events and prior individual history. This enables better incorporation of heterogeneity in individual characteristics, contact patterns, disease history and history of AM use. However, the latter models pose significant challenges for parameterisation due to the need for very granular levels of detail on individual histories.

Parameter measurement and estimation for infectious disease models is challenging. Table 2 provides an overview of the typical parameters and potential sources of data used to inform these parameters based on the policy models identified in the literature. These parameters are population-level, epidemiological including infection risk, transmission risk, fitness costs and natural history; treatment-related parameters including treatment outcomes and acquired resistance during treatment; healthcare related parameters including vaccination rates and impact on infection risk; costs and health-related quality of life. It must be noted, however, that Table 2 is not an exhaustive list since the parameters of any model should take on values according to the characteristics of the pathogen, indication, infection, endemic situation and interventions. In view of the many attributes for specific infections and interventions, a generic guide to model parameterisation and sources of data is not possible.

Where possible, model parameter values should represent the entirety of the existing data and evidence available that is, however, expected to be very setting-specific. This can be informed using standard methods for systematic review and evidence synthesis, whilst also reflecting uncertainty in the available evidence. A large literature exists on methods guidance regarding parameter estimation, and the same general principles should be applied to the evaluation of AMs. However, unlike the evaluation of other health technologies, information on epidemiological parameters, treatment outcomes, and infection and resistance rates is largely reliant on routine, survey or observational surveillance data. As discussed in Section 4.5, surveillance data provides a rich source of information on the susceptibility and resistance of
AMs to different pathogens. There is a number of ongoing global antimicrobial surveillance programmes collecting and providing relevant data. Hospital surveillance data also provides an important source of information to further understanding of epidemiological parameter values, varying from routinely collected hospital data to strain or genotype data, as well as longitudinal data on colonisation and infection status. The use of observational data can present particular challenges when comparing the effects associated with different treatment protocols. However, various statistical methods are available to try to minimise the risk of bias and potential confounding variables, including regression methods to adjust for estimated treatment effects, propensity score matching and instrumental variables [58].
Table 2: Typical sources of data used to parameterise the models

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Source of data</th>
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<tbody>
<tr>
<td><strong>Epidemiological</strong></td>
<td></td>
</tr>
<tr>
<td>Population size, initial distribution of population across health states</td>
<td>Routine data, surveillance or observational data</td>
</tr>
<tr>
<td>Birth and death rate, population entry and exit rate</td>
<td>National statistics, routine data, observational or survey data</td>
</tr>
<tr>
<td>Rate of transmission between different groups</td>
<td>Calibration, contact data (survey, electronic data or observational data) combined with calibration of rate of transmission per effective contact</td>
</tr>
<tr>
<td>Infection clearance rates</td>
<td>Observational data on natural history carriage</td>
</tr>
<tr>
<td>Fitness cost on transmission risk, clearance rates</td>
<td>In-vitro studies or models of bacterial growth</td>
</tr>
<tr>
<td>Rate of infection in colonised individuals</td>
<td>Longitudinal data on colonisation and infection status</td>
</tr>
<tr>
<td>Disease progression</td>
<td>Observational data</td>
</tr>
<tr>
<td>Duration of immunity</td>
<td>Observational data</td>
</tr>
<tr>
<td><strong>Antimicrobial treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Treatment rates</td>
<td>Routine data, survey data or observational data for existing antimicrobials, assumption required for new antimicrobial</td>
</tr>
<tr>
<td>Treatment outcomes: success rates, failure rates, rates of acquired resistance</td>
<td>Some data on repeated testing of patients for development of resistant isolates, possibility of calibration to resistance data</td>
</tr>
<tr>
<td><strong>Other health-care related</strong></td>
<td></td>
</tr>
<tr>
<td>Vaccine rate</td>
<td>Routine data</td>
</tr>
<tr>
<td>Vaccine effects: reduction in rate of colonisation, infection, duration or severity of infection</td>
<td>Trial and observational data on vaccine effects</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td></td>
</tr>
<tr>
<td>Costs of treatment</td>
<td>Standard sources for cost of antimicrobials and administration and monitoring costs</td>
</tr>
<tr>
<td>Costs of infection health states</td>
<td>Trial and observational data</td>
</tr>
<tr>
<td><strong>Health-related quality of life (HRQoL)</strong></td>
<td></td>
</tr>
<tr>
<td>HRQoL for asymptomatic individuals</td>
<td>General population norms, adjusted for co-morbidities (colonised are expected to be asymptomatic)</td>
</tr>
<tr>
<td>HRQoL for infected individuals (by stage as appropriate)</td>
<td>Trial and observational data</td>
</tr>
</tbody>
</table>

One of the main challenges for model parameterisation relates to the lack of direct data on transmission risks and fitness costs. Risk of transmission depends on the contact rate and the risk of infection per contact. This risk will differ for various individual characteristics and contact patterns, including age and setting (e.g. hospital, school, community). Infection risk
may depend on serotype and complex mechanisms of competition between serotypes, as well as immunity. Serological studies of bacteria, longitudinal data on carriage status and models exploring the different assumptions about the effect of age and serotype competition may be used directly to estimate infection risk [59–62]. Contact rates and patterns of contact may be estimated using survey data [63], [64], electronic data capture and direct observations [65]. In the absence of direct data on the rate of transmission of infection, model calibration to survey and surveillance data on the prevalence of infections and resistance is used to estimate the transmission risk per contact [65–67]. Information on fitness costs for transmission and cure parameters is generally reliant on in-vitro studies or models of bacterial growth of resistant and non-resistant strains [68]. The fitness costs of a pathogen are context-specific and will vary depending on the drug-specific mutations that create the resistance to the pathogen, i.e., the magnitude of fitness costs is specific to the AM agent to which the pathogen has developed resistance, rather than to the pathogen itself. In the absence of direct data on fitness costs, formal elicitation methods combined with expert review of available data may be required to establish effects on key parameters such as transmission and clearance and how these parameters change over time e.g., due to compensatory mutations.

5.5.1. Calibration for model fitting to data

For unknown parameters such as transmission risks, or where accurate parameter estimation is difficult or impossible to achieve, model calibration may be used. This involves inferring values for unobservable parameters by calibrating model outputs to empirical data that are available (e.g., prevalence rates of infection). It may also be used to explore variations within plausible bounds of the model parameters to identify combinations of the parameter values that provide a better fit to the empirical data. This involves adjusting the unobserved or unavailable parameter values in order to obtain consistency between model outputs and observable data. The ability of the model to reproduce observed infection incidence, trends or natural history also helps to establish the model’s credibility. Difficulty in calibrating across multiple parameter sets may suggest that the model structure, approaches or assumptions are incorrect [52].

The process of model fitting to observed data is similar to the estimation of coefficients in a regression analysis. One important step in the process is the choice of calibration target, which could be a single parameter value such as mean prevalence rate or a series of parameter values.
Importantly, the model and behavioural patterns should represent the same conditions of the population from which the empirical data were obtained to use as targets [69]. Metrics used to quantify the goodness of fit to the data include the least squares criterion (minimisation of the sum of the squared prediction errors between the observed data and predicted values), chi-squared criterion (divides the least squares error by its standard deviation to overcome different levels of certainty), maximum likelihood estimation (identification of the set of parameter values that makes the observed data most likely), Bayesian calibration methods to generate a range of plausible values rather than a single best fit value (frequently uses Markov Chain Monte Carlo simulation to update prior values, which could be derived from experts), or a combination of these methods [69]. Applications of calibration model fitting to surveillance data on prevalence and resistance outcomes can be found in Opatowski et al., 2008 [66], Hurford et al., 2012 [67], Chan et al., 2012 [70] and Pelat et al., 2016 [65].

5.5.2. Expert elicitation for parameter estimation and forecasting of resistance outcomes

In the absence of data for a particular model parameter, expert elicitation may be used where relevant experts are asked to provide their judgement regarding the magnitude of a given parameter and its uncertainty. In its simplest form this could involve asking experts for ‘best guess’ estimates, but more formal methods of expert elicitation are readily available that involve asking for probabilistic belief statements about unknown quantities and using formal processes to combine judgements from multiple experts [71]. Where some limited data may be available for a given parameter, expert elicitation may be used to supplement this information and a large literature exists on expert elicitation in Bayesian statistics [71]. Expert beliefs may also be validated by comparing elicited judgments to observed data where possible. The use of performance scores for creating and validating combinations of expert judgments is known as the classical model or structured expert judgment [72].

The process of expert elicitation involves identifying the relevant experts and the quantities or groups of parameters to be elicited, including any time period over which the quantity is to be elicited. There is also need to apply specific methods for elicitation (e.g., use of a probability grid such as a histogram of values on which the expert marks a series of crosses to show their belief in the likelihood of each value), to synthesise the elicited quantities across experts (e.g., a Delphi panel to reach consensus or mathematical synthesising techniques such as linear
pooling and fitting of probability distributions to pooled elicited values) and to validate experts’ assessments and scores where possible [73].

The classical model of expert elicitation has been used by Colson et al., 2018 to elicit projections of future rates of antibiotic resistance with uncertainty for nine different pathogen-antibiotic combinations in four European countries and to empirically validate the experts’ assessments against current data on a set of calibration questions [56]. This work showed that experts have extensive domain knowledge and are able to take account of background health system patterns when making their judgements, e.g., anticipated changes around antibiotic use and infection control policies, availability of new agents coming to the market, or new resistance mechanisms emerging. Structured expert judgement was shown to provide a very useful tool for understanding uncertainty about future resistance rates compared to statistical forecasting methods for making similar predictions [56].

5.5.3. **Uncertainty in model predictions**

Statistical and mechanistic dynamic transmission models can be either deterministic or stochastic. Deterministic models are evaluated at mean parameter values and no randomness in any parameter is assumed. This may be adequate if the population at risk is large and an understanding of how sensitive the model outputs might be to changes in particular inputs is required. However, ideally, a stochastic modelling approach is likely to be more appropriate to take into account the role of chance in determining transmission patterns and other events.

Models are developed and informed using a combination of evidence from existing studies, expert elicitation, direct estimation from data, and model assumptions. This information is very unlikely to be complete and, therefore, is subject to uncertainty. There are two broad sources of uncertainty: i) parameter uncertainty relating to uncertainty in the estimates used for the parameter values; and ii) structural uncertainty relating to the biological properties, relationships and different judgements used to construct the statistical or underlying mechanisms of transmission. Accurate parameter measurement for infectious disease models and resistance outcomes is very challenging and where possible this needs to be based on all available existing evidence with uncertainty. Deterministic sensitivity analysis will provide biased estimates in non-linear models while best- and worse-case scenarios, where all the parameters are set at extreme, but plausible favourable or non-favourable values, is very
difficult to interpret correctly due to the small probability that all values would take an extreme scenario simultaneously [74].

Uncertainty in parameter values can be more influential on model results in mechanistic models than in statistical models because of non-linear feedback effects, leading to different dynamic regimes [52]. For example, dynamic transmission models can be highly sensitive to small shifts in the parameter values, which may move a model from a stable equilibrium to oscillatory or even chaotic behaviour. This in turn can have important implications for the effectiveness of interventions if the change in parameter values is near a threshold point that is sufficient to alter the decision about which alternative intervention offers highest expected net benefits. In principle, probabilistic sensitivity analysis (PSA) is required where probability distributions are assigned to each of the model parameters to reflect the uncertainty in the evidence available to inform the estimates. Sampling from these distributions is then undertaken (usually using Monte Carlo simulation) to reflect the joint uncertainty in the model inputs and to propagate this uncertainty to the model outputs [74].

The process of PSA has become a standard component of economic evaluation of health technologies in order to reflect uncertainty in model inputs and to consider the implications for decision uncertainty [74]. However, its use in infectious disease modelling is challenging for a number of reasons. Firstly, many of the parameters relating to transmission dynamics and resistance mechanisms are correlated and, although PSA can handle this correlation, it must be preserved appropriately, and relationships informed by the correlation and covariance structure. This inevitably increases the computational expense of undertaking a PSA. Secondly, many of the model parameters are unknown and calibration methods are required to inform these parameters. This again adds to the computational expense of PSA, particularly when appropriate Bayesian methods are used to inform the calibration process. Nonetheless, despite these challenges, various methods have been developed such as meta-modelling or emulator approaches with the aim of approximating the Bayesian computation methods and reducing the computational load of PSA [75], [76]. Latin Hypercube Sampling as a means of performing PSA has also been used in the literature for infectious disease modelling. Therefore, PSA should not be precluded as a consideration for reflecting the joint uncertainty in model inputs and implications for decision uncertainty (see Section 8).
In some situations, model structural uncertainties can be expressed in terms of additional model parameters, e.g., a structural assumption may be treated as a parameter with missing information or set at an extreme value. Therefore, structural uncertainty may be treated in the same way as parameter uncertainty. Structural uncertainty may also be parameterised using expert elicitation techniques to make an explicit quantitative judgement about the uncertain parameter. In situations in which structural uncertainties cannot be parameterised, scenario analyses may be used where alternative scenarios represent plausible assumptions or judgements. Rather than parameterise these scenarios, the model output results are presented for each separate scenario. Model averaging may be used to combine the results across the different scenarios using some form of weighted average [77]. Alternatively, the results from the separate scenarios may be presented to decision makers with the reasons for differences identified and critically examined. However, inevitably this means that decision makers need to come to a view on the most plausible scenario or come to some judgement on the potential weighting of each scenario.

5.5.4. Model validation

There is a strong requirement for validation of model outcomes against historical data. This can include calibration to historical data by reproducing observed infection incidence, trends or natural history. However, models should also be validated by comparing the results of the model predictions against unrelated observations, i.e., observations from an alternative dataset than the one used for model fitting or used to inform parameters in the model.

In principle, there is no difference between model validation for infection and resistance modelling and for other health technologies. Standard model validation checks should take place such as model verification or debugging (e.g., setting parameter values to zero and checking that the corresponding results behave as expected), face validity (e.g., checking that any changes in inputs are in line with what is known or expected in model outputs and are not counter-intuitive), predictive validity (e.g., checking that the model behaves as expected such that any changes in input values produces outputs that are predictable) and convergent validity between models (e.g., checking whether models developed by different analysts, or taking a statistical or mechanistic approach, produce similar results or that any differences can be explained on the basis of different assumptions, model inputs or structure).
5.6. ASSESSING THE COST AND HEALTH-RELATED QUALITY OF LIFE OUTCOMES

The methods used to identify, measure, and value the costs and health-related quality of life outcomes associated with each alternative AM strategy are, in principle, the same as those used for other health technologies. Resource use and costs related to the infection and incurred over the period that the patient is treated should be included in the analysis. This includes drug acquisition costs and any other costs associated with its use such as administration and monitoring costs. However, for the purposes of helping to inform the value-based payment for the new AM, the drug acquisition cost of the new AM is excluded from the total costs (see Section 3.2). Total costs of treatment are expected to depend on the average treatment duration of the AMs.

Relevant health state costs such as those related to average length of hospital stay, with and without successful treatment, or other subsequent clinical events should be included. This may include costs related to surgical interventions, infection recurrence, drug adverse events and outpatient visits. Costs related to the need for second- or third-line treatment following treatment failure may also be considered, and this could include additional costs associated with diagnostic tests under empiric treatment of test-and-treat. The sources used to inform the costs should be relevant to the NHS and personal social services and identified in the usual way following NICE Technology Appraisal guidance, with justification provided and any discrepancies between sources explained [4].

The scoping stage should identify the principal measures of health outcomes that are relevant to the estimation of clinical effectiveness. This includes the measures of short-term clinical efficacy (see Section 4), attributes of value relevant to the AMs under evaluation (see Section 3), any adverse events that are important, and long-term clinical efficacy (e.g. reduced recurrent infections or reduced long-term mortality). Time to clinical response may also be an important factor, which will depend on the availability of rapid diagnostic tests and the speed of accurate diagnosis.

The measures of health benefit are usually quantified as an impact on health-related quality of life that translates into quality-adjusted life years (QALYs). This involves quality-adjusting the period of time the average individual is alive within the model using an appropriate ‘utility’ or preference score. The challenge for AMs is that the differential impact of the treatment
protocols in terms of utility values (e.g., EQ-5D) is likely to be absent from the trials and difficult to estimate directly from patients with severe infections. In the absence of utility data from the trials, external data sources will need to be sought to quantify the differential impact of the AMs on individual health status according to the different states of the model. Baseline utility values for asymptomatic individuals may be informed by the underlying utility of the general population and adjusted for any relevant co-morbidities (e.g., using a nationally representative UK sample using EQ-5D).

5.7. REPORTING RESULTS AND INFORMING DECISION MAKING

The presentation of results for the evaluation of a new AM should follow the same general guidelines and principles for reporting of expected cost-effectiveness of health technologies, in line with NICE Technology Appraisal guidance [4], although presenting the overall incremental results will need changes compared to standard ‘decision rules’ (see Section 3.2). All parameters used to estimate clinical and cost-effectiveness should be presented in clear tabular form with details of data sources and justification for values presented, as well as documentation of uncertainty in the input parameters. The total expected costs and QALYs for each alternative treatment protocol should be presented, and net health benefit of each strategy calculated as appropriate and compared to the available alternatives. This depends critically on the assessment of opportunity costs which is the health that is forgone elsewhere because resources are used to accommodate the additional costs of the strategy rather than on other NHS activities. This may be defined in terms of a cost-effectiveness threshold although the term ‘threshold’ for NICE and similar organisations usually involves other considerations such as social value ‘weights’.

An important component to the presentation of results to help inform decision making is a clear provision of information on the key determinants of value. This includes information on the estimated change in the incidence of infection and emergence of resistance due to the different treatment protocols, disaggregation of resistance outcomes according to source of resistance (e.g., primary resistance vs. acquired resistance during treatment) and strain type (susceptible or resistant) over time, route of transmission, disaggregation of health benefits and costs according to whether they are directly or indirectly prevented or achieved, indication and pathogen-specific outcomes, population and setting subgroups, as appropriate. The uncertainty
in the analysis and the presentation of results for different scenarios should also be transparently reported in order to assist the decision making of new AMs.
5.8. RECOMMENDATIONS

- The first step in the development of a model should be an understanding of the mechanisms of resistance and the epidemiological data available for a new AM and its comparators so that important determinants of transmission dynamics of the infectious disease epidemic and resistance to the AMs are reflected. The appropriate structure of the model should reflect the source and mechanisms of resistance and the nature of any competition between susceptible and resistant strains. Detailed scoping meetings or formalised model conceptualisation processes should support appropriate model scope and structure. The model structure, methods, assumptions and parameters should be clearly described, justified, and be reproducible. Uncertainty and sensitivity analysis on determinants of key outcomes is critical. Models may be used to support identification of evidence gaps and identify key areas for further research.

- There should be careful consideration and interpretation of surveillance data to assess the quality of the existing evidence base on disease burden and resistance to AMs. Where there are limited or no data available for a new AM, it may be necessary to examine the data available for other analogous AMs seen in the past that exhibit similar mechanisms of resistance to infer likely changes in the emergence of resistance over time until additional information on the new AM becomes available.

- Where there is a lack of direct data or accurate parameter estimation, model calibration approaches should be considered. There is a strong requirement for validation of model outcomes against historical data, including reproducing observed infection incidence, trends or natural history. Statistical and mechanistic modelling approaches should be able to provide credible predictions of historical data on infection and resistance rates. If this cannot be shown to be the case, there should be a detailed consideration of the potential direction of bias informed by an understanding of the determinants of key outcomes.

- The elicitation of scientific and technical judgements from experts can be a valuable addition to other forms of evidence to support effects on key parameters. Therefore,
consideration should be given to the expert review of available data, as well as formal expert elicitation techniques where there are limited data or alternative viewpoints.

- Given the difficulties associated with developing credible mechanistic dynamic models and concerns relating to the simplicity of statistical models for the prediction of resistance to different AM prescribing strategies, consideration should be given to the development of both statistical and mechanistic models. Differences in outcomes between these two modelling approaches should be clearly described, explained and justified.

- Models should be iteratively updated and re-evaluated as new data or considerations arise.

- Priorities for further research include exploring the practicalities of implementing policy models with the data currently available and exploring the possibility of combining Bayesian calibration, expert elicitation and statistical forecasting approaches.
6. CASE STUDY ILLUSTRATING THE VALUE ASSESSMENT FRAMEWORK

6.1. INTRODUCTION

A mathematical model was developed to illustrate how the expected value of a new AM can be quantified within the proposed value assessment framework. The model takes the form of a mechanistic dynamic transmission model, which was used to demonstrate the capacity to model endogenously infection transmission dynamics and emergence of resistance to both a new AM and an existing AM over an appropriate time horizon. The model seeks to capture the clinical and microbiological efficacy of the treatment strategies and to show how it impacts on the transmission of infection and the emergence of AMR over time. Both primary resistance (where an uninfected individual becomes infected with a resistant strain) and acquired resistance during treatment were modelled.

The analysis is not intended to be definitive or to guide policy decisions. Rather, it is an illustrative analysis to show how epidemiological outcomes can be translated into health effects and costs for each alternative strategy. Standard decision rules for cost-effectiveness analysis were applied to determine whether the additional or incremental health benefits of choosing one treatment strategy over another are sufficient to justify the additional costs. Probability sensitivity analysis (PSA) was used to incorporate evidential uncertainty and to show how this impacted on the probability that treatment strategies using the new AM are cost-effective.

The model was developed and parameterised using *Acinetobacter baumannii* as the case study pathogen. This is a multi-drug resistant pathogen associated with a range of severe nosocomial infections [78], [79]. The choice of model parameters was carefully chosen based on information in the literature; however, the model was used purely for illustrative purposes and does not aim to support decision-making pertaining to the treatment of infections by *A. baumannii*. The development of a *de novo* mechanistic model to support the evaluation of a new AM provides an opportunity to illustrate the level of data and assumptions required for model parameterisation.

6.2. RELEVANT LITERATURE

A number of mechanistic models have been developed in the literature, but these have been predominantly focused on informing policy decisions regarding current AM usage or treatment
duration and stewardship programmes to reduce AMR [53], [67], [80]. None of the policy models to date (see Appendix A.1) has been tailored to evaluate economic outcomes associated with introducing a new AM relative to the use of existing AMs on infection and resistance rates over time. This requires: (i) capturing the clinical and microbiological effectiveness of a new AM agent relative to its comparators; and (ii) linking epidemiological outcomes of infection and resistance to economic endpoints.

To our knowledge, Jansen et al. [81] and Jansen et al. [82] are the only studies that have supported an economic evaluation of comparative AM treatment strategies. These studies evaluated the cost-effectiveness of ertapenem and piperacillin/tazobactam for first-line treatment of complicated intra-abdominal infections and diabetic foot infections, respectively. Both studies used the same modelling approach, which involved a dynamic transmission model for the development of AMR and a decision tree to evaluate the cost-effectiveness of ertapenem relative to piperacillin/tazobactam for the treatment of infections.

The approach used by the authors to model the increase in AMR over time was, however, limited to considering primary infections by susceptible and resistant strains in the population over time, i.e., acquired resistance during treatment was not modelled. As a result, the modelled rate of increase in AMR solely stemmed from a substantially lower first-line cure rate in individuals infected by a resistant strain relative to individuals infected by a susceptible strain. The differential clearance rate led to a greater number of individuals with resistant infections over time, which fed back into a reduced probability of first-line treatment success among infected patients. Under this single mechanism of resistance, the comparative evaluation of the two AM treatment strategies was heavily dependent on the initial prevalence of individuals resistant to each AM therapy. With both treatments assumed to have similar levels of clinical success (as expected to be seen from non-inferiority trials), any comparative assessment undertaken under these same assumptions is expected to favour the new AM as less initial resistance has developed to the new agent. In addition, acquired resistance during AM treatment is a core determinant of AMR and this was not modelled by Jansen et al. [81], [82]. The studies considered second-line treatment after first-line clinical treatment failure but resistance to the treatments used as second-line was not considered in the modelling approach used. Furthermore, no distinction between clinical and microbiological response outcomes was considered (see Section 4).
Our aim was to develop an illustrative mechanistic model to evaluate a new AM compared with an existing AM that: (i) incorporates both microbiological and clinical success outcomes; (ii) models the emergence of AMR due to both primary resistant infections and acquired resistance during treatment; and (iii) links epidemiological outcomes with economic endpoints.

6.3. CASE STUDY

6.3.1. Pathogen and setting

The model was developed to assess the value of a new AM targeted at *Acinetobacter baumannii*, which represents a major cause of severe nosocomial infections, ranging from ventilator-associated pneumonia, bacteremia, urinary tract infections and meningitis in patients admitted to ICUs [78]. *A. baumannii* is known to have developed resistance to many different antibiotics, particularly carbapenems, which makes treatment and bacterial eradication highly difficult [79], [83] and, consequently, there is an acute need to develop new AMs against this pathogen in order to control the spread of infection in healthcare settings.

The model was developed to describe the transmission dynamics of *A. baumannii* in an ICU with a capacity of 15 beds. In order to inform NHS payments for the new AM, modelling results would need to be rescaled appropriately to the total number of ICUs in England where the new AM is to be made available, whilst accounting for heterogeneity in ICUs characteristics, as further discussed in Section 6.8.

In line with the overwhelming majority of mechanistic transmission dynamic models identified from the literature search (see Appendix A), infected patients were allowed to be discharged from the ICU, but dynamics of infection transmission upon patients discharge to other healthcare settings were not considered in the analysis.

6.3.2. Analysis time horizon

As discussed in Section 3, although the analysis time horizon is theoretically indefinite, in practice it is limited by the temporary uncertainty in parameters, especially with regards to resistance development to existing and new AMs. This suggests that payments would have to be re-negotiated over time as the evidence base evolves. In principle, the modelling could be
undertaken in a piecewise manner, by imposing changes in parameters at predefined periods of time. However, given the uncertainty about the magnitude and speed of change in parameters, in line with the dynamic models identified in the literature, the model used time-invariant parameters. For the purpose of the illustrative analysis, it was run for an arbitrary period of 10 years.

6.3.3. Treatment strategies

The model was developed to quantify the expected value of a new AM compared to an existing AM, tigecycline, which is a common therapy used for treating a range of infections caused by multi-drug resistant \(A. baumannii\) [84], [85]. Patients received first-line empiric treatment as a result of clinical presentation with infection symptoms (i.e., in the absence of testing whether the infection is caused by a resistant or susceptible strain of bacteria). If patients failed to respond to first-line treatment, a second-line diagnostic test-and-treat strategy was used. The second line was informed by i) history of empirical treatment failure, where failure refers to clinical failure to clear symptoms; and ii) susceptibility testing, where only those pathogens susceptible or intermediate-resistant to the alternative AM would receive the alternative treatment at second line. Susceptibility testing was performed after empirical treatment failure, leading to a short delay of three days on average before switching to the alternative AM [86]. If patients failed treatment with both available AMs (i.e., the new AM and tigecycline), or were identified as resistant to both available AMs following susceptibility testing, no further treatment was given.

Four comparator treatment strategies were considered (see Table 3): i) treatment with tigecycline for all treated cases and no second-line treatment available (base-case scenario, BC); ii) treatment with tigecycline for all treated cases followed by second-line test-and-treat (TS1); iii) treatment with the new AM for all treated cases followed by second-line test-and-treat (TS2); and iv) a mixed treatment strategy with random allocation of the two available AMs (tigecycline and the new AM) with fixed probability, i.e., 50% of treated cases receive tigecycline and 50% receive the new AM, followed by second-line test-and-treat (TS3). For simplicity, tigecycline is referred to as AM1, while the new treatment is referred to as AM2. In each of the latter three comparative strategies, if patients fail the treatment that is empirically given as first-line therapy, they will receive the alternative treatment in second line, i.e., if patients fail AM1 at first-line, they would receive AM2 at second-line, and \textit{vice-versa}.
<table>
<thead>
<tr>
<th>Treatment Strategies</th>
<th>First-line empiric treatment</th>
<th>Second-line test-and-treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case (BC)</td>
<td>100% of treated cases receive AM1 (tigecycline)</td>
<td>-</td>
</tr>
<tr>
<td>TS1</td>
<td>100% of treated cases receive AM1 (tigecycline)</td>
<td>If patients fail AM1 at first-line, they receive AM2 at second-line, and vice-versa.</td>
</tr>
<tr>
<td>TS2</td>
<td>100% of treated cases receive AM2 (new AM)</td>
<td>Double-resistant patients, who fail empiric treatment at first-line, receive no further treatment at second-line.</td>
</tr>
<tr>
<td>TS3</td>
<td>Mixed strategy with 50% of treated cases receiving AM1 and 50% receiving AM2, i.e., patients have an equal probability of receiving either AM1 or AM2</td>
<td>-</td>
</tr>
</tbody>
</table>

6.4. MODEL STRUCTURE

Two integrated models were developed: (1) a mechanistic model to describe the transmission dynamics of *A. baumannii* in a 15-bed ICU over a 10-year time horizon that differentiates between uncolonised individuals and those colonised and infected with *A. baumannii*; and 2) a Markov model to follow the outcomes of infected patients for 90 days after ICU discharge. The follow-up period after discharge was informed by the maximum period to spontaneous recovery, which was applied to all infected patients irrespective of their resistance status, such that after 90 days every patient discharged was either symptom-free or had died.

6.4.1. Mechanistic transmission dynamic model

A schematic representation of the model used to represent the transmission dynamics of the infection is presented in Figure 2. The model distinguishes between uncolonised (X), colonised (C) and infected (I) individuals. Colonised and infected individuals may host a strain that is either (i) susceptible to both available AMs (S); (ii) resistant to either AM1 (R1) or AM2 (R2); or (iii) resistant to both available AMs (R12). Individuals may acquire a resistant infection via direct infection (primary resistance) or as a result of AM treatment (acquired resistance). Following successful treatment (i.e., symptom clearance), the transitions of infected patients depend on whether the bacteria was eradicated or not, and the cause of eradication failure. If symptoms are cleared and the bacteria are fully eradicated, infected individuals transit back to the uncolonised health state. Failed eradication due to the acquisition of resistance during
treatment means that infected individuals transit to the colonised resistant states, whereas failed eradication due to causes other than resistance means that infected individuals transit to the colonised susceptible states.

In order to model the two lines of treatment, it was necessary to monitor the cause of treatment failure in each line. This was achieved by further separating the infected compartments according to history of treatment failure. This increased the number of infected compartments from 4 to 15 (See Appendix B.1). The complete representation of the model structure, the transitions between the 20 compartments and the set of ordinary differential equations governing the dynamic model are provided in Appendix B.1.

**Figure 2: Schematic structure of the dynamic transmission model for uncolonised (X), colonised (C) and infected (I) individuals**

Colonised and infected individuals may host a strain that is either (i) susceptible to both available antimicrobials (C° or I°, respectively); (ii) resistant to either drug 1 or 2 (C°1, C°2, I°1 or I°2 respectively); or (iii) resistant to both available antimicrobials (C°12, I°12 respectively). Permitted transitions are indicated by arrows. Individuals may acquire a resistant infection via direct infection (transitions from X to I°i with i = 1, 2 or 12) or as a result of antimicrobial treatment (transitions from C° to I°i or from C°i to I°12 with i = 1, 2). Following successful treatment, i.e. symptom clearance, the transitions of infected patients depend on whether the bacterium was eradicated or not, and the cause of eradication failure. If symptoms are cleared and the bacterium is fully eradicated, infected individuals transit back to X. Failed eradication due to resistance acquisition leads to transitions from I° to C°1i or from I°1i to C°12 with i = 1, 2, whereas failed eradication due to causes other than resistance leads to transitions from I° to C° with i = 1, 2, 12.
6.4.2. **ICU admission and discharge**

All individuals entered the ICU as uninfected (compartment X), with the exception of 5.3% who were admitted already colonised with *A. baumannii* [79]. Whilst those colonised predominantly harboured a susceptible strain (S), in line with recent surveillance data on susceptibility to tigecycline in the UK, it was assumed that 10.7% presented with a strain resistant to AM1 [87]. Patients could be discharged from any compartment but the discharge rate of those infected was more than twofold lower than those uninfected, with an average ICU stay of 25 days for infected individuals compared to 12 days for uninfected individuals [88]. However, the difference in ICU stay between infected and uninfected individuals was partially reduced by the excess mortality risk faced by infected patients at a rate of 0.009/day [84]. The ICU was assumed to be fully occupied at a constant rate such that discharges or deaths were balanced by new admissions.

6.4.3. **Colonisation and infection transmission dynamics**

Individuals could become colonised via cross-transmission with other patients in the ICU, where colonised and infected patients contributed equally to colonisation, i.e., had the same level of infectiousness. The cross-transmission rate of the bacteria was estimated as the product of a baseline cross-transmission coefficient in the absence of antibiotic exposure with a background antibiotic prescribing rate for prophylaxis [80], [89] and an excess risk of colonisation by *A. baumannii* associated with previous antibiotic exposure [79]. No fitness cost was applied to the transmission of resistant strains. Once individuals were colonised with a given bacterial strain, it was assumed that in the absence of treatment, they would not get colonised with another strain through *de novo* mutation or replacement infection, i.e., if they became infected it was by the same strain that colonised them [67], [90]. Infection could not occur without prior colonisation with the bacteria [67], [80] and, once infected, patients were immediately empirically treated. In addition, patients had a spontaneous rate of symptom clearance, but in the absence of AM treatment, they would remain colonised with the bacteria [80].
6.4.4. Clinical and microbiological response rates from treatment

It was assumed that treatment outcomes would be known only at treatment completion, i.e., infectiousness would not reduce half-way through treatment. If infected patients were prescribed an AM to which they were susceptible, their treatment outcome would depend on the joint-probability of (i) clinical success following treatment with the prescribed AM; (ii) acquisition of resistance (assumed to be on average twice as likely in the case of clinical failure compared to clinical success); and (iii) strain persistence for reasons other than resistance. Resistance, as well as strain persistence for other causes, would lead to microbiological eradication failure. Consequently, if infected patients were prescribed an AM that they were resistant to, they would remain colonised with the bacteria and continue to contribute to bacteria cross-transmission to uncolonised individuals. In contrast, clinical outcomes would depend on whether the infectious strain was intermediate- or complete-resistant to the AM received (see Section 4), as informed by a large-scale surveillance study in the UK on Acinotobacter susceptibility to tigecycline. Intermediate-resistant patients (57% of all resistant patients [87]) were assumed to face the same chance of clinical success as those infected by a susceptible strain, whereas complete-resistance (43% of all resistant patients [87]) was assumed to lead to clinical failure. The same proportion of intermediate- and complete-resistance was applied to patients who developed resistance to the new AM.

6.4.5. Transmission following infection

The clinical and microbiological outcomes following treatment drive the transitions between the modelled compartments. In the case of clinical failure, patients would remain infected and colonised. If they were infected by a susceptible strain and acquired resistance to the AM that they were empirically treated with, they would transit from the infected susceptible compartment to the compartment of infected single-drug resistant with empiric failure. If they did not acquire resistance, they would transit to the compartment of infected susceptible with empiric failure due to causes other than resistance. If patients were infected by a single-drug resistant strain and empirically treated with the AM that they were susceptible to, but acquired resistance, they would transit from the infected single-drug resistant compartment to the compartment of infected double-drug resistant with empiric failure or, alternatively, if failed due to other causes, they would transit to the compartment of infected single-drug resistant state with empiric failure due to other causes than resistance. If patients were infected by a
strain resistant to both AMs, they would transit to the compartment of infected double-drug resistant with treatment failure.

In the case of clinical success, patients would become symptom-free. In addition, if the bacteria were successfully eradicated, i.e. no acquired resistance during AM treatment or persistence of the bacteria due to other causes, patients would transit from their respective infected compartments back to the uncolonised compartment (X). In all other cases, i.e. clinical success with eradication failure, patients would transit to colonised compartments, where transitions would depend on whether eradication failure was a result of acquired resistance or persistence due to other causes.

Once in the infected failed compartments, patients would undergo second-line susceptibility testing. Only those patients susceptible or intermediate-resistant to the alternative AM would receive it at second-line. Treatment outcomes would be determined by the pathways described above, i.e., conditional on the resistance profile of infectious strains after first-line treatment failure. Double-resistant individuals that had failed empirical treatment were assumed to be infected with complete-resistant strains and did not receive further treatment.

6.4.6. Markov model

A Markov model using a daily cycle was linked to the dynamic model in order to follow the quality of life and survival of infected patients after ICU discharge to other (lower-cost) healthcare settings, in accordance with their treatment history and susceptibility profile. The modelled time horizon, T, was split into daily time steps that constituted T closed cohorts of discharged patients, who were followed for 90 daily cycles across the following seven health states (see Figure 3):

1- Uninfected⁴;
2- Infected treatment failed;
3- Infected treated with AM1 and susceptible to it;

---

⁴ Since pathogen transmission dynamics are not modelled outside of the ICU, uninfected patients are no longer distinguished between colonised and uncolonised.
4- Infected treated with AM1 and resistant to it;
5- Infected treated with AM2 and susceptible to it;
6- Infected treated with AM2 and resistant to it;
7- Dead

At cycle 0, individuals in state 1 “uninfected” correspond to discharges from compartments X and C, whereas individuals in state 2 “infected treatment failed” correspond to discharges from the infected compartments following treatment failure. Individuals in states 3 to 6 (“infected treated”) correspond to patients who were discharged whilst under first- or second-line treatment. Once their treatment outcome was revealed, “infected treated” patients moved to either state 1 “uninfected” (which is an absorbing state since infection transmission dynamics outside of the ICU are not modelled) or to state 2 “infected treatment failed”. If they transited to the latter state, they could only move to the “uninfected” state via spontaneous recovery. All infected individuals faced the same excess risk of death.

**Figure 3: Structure of Markov model**

![Markov model diagram]

6.4.7. **Input parameters**

The combined models were informed with parameters related to: (i) the dynamics of transmission in the ICU setting; (ii) treatment efficacy data including clinical and
microbiological response rates and the risk of acquired resistance; and (iii) costs and HRQoL parameters. Parameters for these three categories are presented in Table 4, Table 5 and Table 6, respectively. Parameter values were extracted from published literature using synthesised results from meta-analyses when available. When no estimate of uncertainty was provided, a range of 80-120% of the mean estimate was used.

Table 4: Parameters relating to the transmission dynamics of A. baumannii in an example ICU setting

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Mean (SE)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Number of beds in ICU</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>λ</td>
<td>Admission rate per bed</td>
<td>Based on rate of discharge and deaths</td>
<td></td>
</tr>
<tr>
<td>mc</td>
<td>Fraction of admitted patients colonized</td>
<td>0.053 (0.005)</td>
<td>[79]</td>
</tr>
<tr>
<td>mcr</td>
<td>Fraction of admitted colonized who are resistant to AM1 (tigecycline)</td>
<td>0.107 (0.0109)</td>
<td>[87]</td>
</tr>
<tr>
<td>γni</td>
<td>Daily discharge rate of uninfected individuals</td>
<td>0.083 (0.018)</td>
<td>[88]</td>
</tr>
<tr>
<td>γi</td>
<td>Daily discharge rate of infected patients</td>
<td>0.04 (0.009)</td>
<td>[88]</td>
</tr>
<tr>
<td>ω</td>
<td>Daily death rate of infected patients</td>
<td>0.009 (0.002)</td>
<td>[84]</td>
</tr>
<tr>
<td>β</td>
<td>Daily baseline cross-transmission rate in the absence of AM exposure</td>
<td>0.005 (0.001)</td>
<td>[89]</td>
</tr>
<tr>
<td>ρ</td>
<td>Daily antimicrobial prescribing rate for prophylaxis</td>
<td>0.12 (0.012)</td>
<td>[80]</td>
</tr>
<tr>
<td>a</td>
<td>Relative risk of colonisation in uncolonised individuals due to previous AM exposure</td>
<td>2.4 (0.58)</td>
<td>[79]</td>
</tr>
<tr>
<td>θ</td>
<td>Daily rate of colonised individuals becoming infected</td>
<td>0.11 (0.011)</td>
<td>[80]</td>
</tr>
<tr>
<td>η</td>
<td>Daily rate of spontaneous recovery</td>
<td>0.018 (0.002)</td>
<td>[80]</td>
</tr>
</tbody>
</table>
Table 5: Parameters relating to treatment efficacy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Mean (SE)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Gamma$</td>
<td>Daily rate of treatment outcome following infection (mean treatment duration=14.2 days)</td>
<td>0.0704 (0.027)</td>
<td>[85]</td>
</tr>
<tr>
<td>$\chi_i$</td>
<td>Probability of being prescribed AM$_i$ (i=1,2)</td>
<td>See treatment strategies in Table 3</td>
<td></td>
</tr>
<tr>
<td>cs$_1$</td>
<td>Clinical success under AM1</td>
<td>0.5954 (0.0438)</td>
<td>[84]</td>
</tr>
<tr>
<td>cs$_2$</td>
<td>Clinical success under AM2</td>
<td>cs$_1$ +/-10%</td>
<td>Non-inferiority margin</td>
</tr>
<tr>
<td>mes$_1$</td>
<td>Microbiological eradication success under AM1</td>
<td>0.4914 (0.0561)</td>
<td>[84]</td>
</tr>
<tr>
<td>mes$_2$</td>
<td>Microbiological eradication success under AM2</td>
<td>See scenario description in Table 7</td>
<td></td>
</tr>
<tr>
<td>$\varepsilon$</td>
<td>Proportion of resistant strains with complete resistance to either AM1 or AM2</td>
<td>0.43 (0.075)</td>
<td>[87]</td>
</tr>
<tr>
<td>r$_1$</td>
<td>Probability of acquiring resistance to AM1 during treatment</td>
<td>0.1247 (0.0485)</td>
<td>[84]</td>
</tr>
<tr>
<td>r$_2$</td>
<td>Probability of acquiring resistance to AM2 during treatment</td>
<td>Two possibilities were evaluated: r$_2$ = 0 or r$_2$ = r$_1$ /2</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Daily rate of delay for susceptibility testing results to report</td>
<td>3 (0.5)</td>
<td>[91]</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Ratio of resistance acquisition in the presence of clinical failure compared to clinical success</td>
<td>2 (0.5)</td>
<td>Assumption</td>
</tr>
</tbody>
</table>

Table 6: NHS cost and health-related quality of life parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>£ Mean (SE)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{c1}$</td>
<td>Tigecycline treatment cost (2 packs of 10 doses)</td>
<td>646</td>
<td>NHS basic cost for Tygacil (Reference cost)</td>
</tr>
<tr>
<td>$T_{c2}$</td>
<td>Treatment cost of new AM (AM2)</td>
<td>Set to 0 for the purposes of informing alternative funding arrangements for new AMs</td>
<td></td>
</tr>
<tr>
<td>diagC</td>
<td>Susceptibility testing cost</td>
<td>70 (7.1)</td>
<td>Merck website</td>
</tr>
<tr>
<td>BedC</td>
<td>Daily cost of stay in ICU</td>
<td>1383 (298)</td>
<td>[92]</td>
</tr>
<tr>
<td>hrqol$_X$</td>
<td>Baseline HRQoL utility value for ICU patients</td>
<td>0.6 (0.06)</td>
<td>Assumption</td>
</tr>
<tr>
<td>hd</td>
<td>Decrement in HRQoL utility due to infection-related symptoms</td>
<td>0.15 (0.015)</td>
<td>Assumption</td>
</tr>
</tbody>
</table>
6.4.8. **Parameterisation of the Markov model**

Patients discharged whilst receiving treatment were assumed to be discharged halfway through the treatment cycle and to continue treatment in another healthcare setting (e.g. general hospital), such that their treatment outcomes would reveal at the rate of $2\Gamma$. Daily rates of death, treatment outcome and spontaneous recovery (see Table 4 and Table 5) were converted into daily probabilities to inform the transitions of discharged individuals across the Markov states represented in Figure 3.

6.5. **ANALYSIS**

All analyses were undertaken for a modelled time horizon of 10 years. The base case scenario was run with tigecycline as a single treatment option. The numerically-obtained equilibrium prevalence of patients colonised by *A. baumannii*, and their distribution by susceptibility profile, were used to initiate the dynamic system and to evaluate the outcomes of the three comparative treatment strategies described in Table 3. Expected incremental costs and QALYs were estimated for five different efficacy scenarios regarding clinical and microbiological eradication success under the new AM2. Each of these five efficacy scenarios were evaluated for two separate scenarios regarding the risk of acquiring resistance during treatment with AM2.

6.5.1. **Resistance scenarios**

Acquired resistance during treatment with the new AM2 ($r_2$ parameter in Table 5) was assumed to be substantially lower than the existing AM (tigecycline). Two scenarios were evaluated: (i) acquired resistance to AM2 was set equal to zero; and (ii) acquired resistance to AM2 was set equal to half the risk of developing resistance to AM1. Importantly, it was assumed that during the modelled time horizon, no patient would enter the ICU colonised with a strain of *A. baumannii* resistant to AM2.

6.5.2. **Efficacy scenarios**

Clinical efficacy data for AM2 was assumed to come from non-inferiority trials with a $\pm 10\%$ margin of efficacy between the new AM2 and tigecycline, i.e., the chance of achieving clinical success (cs) following treatment with AM2 could be between 10% lower and 10% higher than
However, since the mechanisms of action of both treatments may be associated with different levels of efficacy in terms of eradiating the bacteria, irrespective of resistance acquisition (see, for example, the case of colistin compared to tigecycline in treating infections caused by *A. baumannii* [84]), two possibilities regarding microbiological eradication success (mes) were evaluated:

(i) bacterial persistence for causes other than resistance (ψ) was set equal for both drugs;

(ii) eradication success under AM2 (mes2) was the same as, or 10% lower than, AM1.

In the first case, owing to its lower risk of resistance acquisition, treatment with AM2 would lead to a greater probability of successful microbiological clearance than treatment with AM1.

In the second case, in order to compensate for the difference in the risk of resistance acquisition between the two treatments, the risk of bacterial persistence for causes other than resistance would be higher under AM2 than AM1.

The efficacy scenarios combining the assumptions about clinical and microbiological eradication success for AM2 are presented in Table 7. Among these five efficacy scenarios, S2 is the most optimistic with a 10% higher chance of clinical success and a 20% greater chance of successfully eradiating the bacteria when acquired resistance to AM2 is equal to zero and 15% when acquired resistance to AM2 is half that of AM1. Scenario S5 is the most pessimistic scenario, with a 10% lower chance of both clinical and eradication success.
Table 7: Efficacy scenarios for different combinations of clinical and microbiological eradication success rates

<table>
<thead>
<tr>
<th>Efficacy scenarios</th>
<th>Microbiological eradication success (mes) / bacterial persistence for OCTR (ψ)</th>
<th>Implication for microbiological eradication success of AM2 under alternative resistance scenarios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario</td>
<td>Probability of clinical success (cs)</td>
<td>% difference in mes₂ vs. mes₁ when r₂ = 0</td>
</tr>
<tr>
<td>S1</td>
<td>cs₂ = cs₁</td>
<td>ψ₂ = ψ₁</td>
</tr>
<tr>
<td>S2</td>
<td>cs₂ = 1.1* cs₁</td>
<td>ψ₂ = ψ₁</td>
</tr>
<tr>
<td>S3</td>
<td>cs₂ = 1.1* cs₁</td>
<td>mes₂ = mes₁</td>
</tr>
<tr>
<td>S4</td>
<td>cs₂ = 0.9* cs₁</td>
<td>ψ₂ = ψ₁</td>
</tr>
<tr>
<td>S5</td>
<td>cs₂ = 0.9* cs₁</td>
<td>mes₂ = 0.9 * mes₁</td>
</tr>
</tbody>
</table>

cs₁, clinical success for AM1 (tigecycline); cs₂, clinical success for AM2 (new AM); ψ₁, bacterial persistence for causes other than resistance under AM1; ψ₂, bacterial persistence for causes other than resistance under AM2; mes₁, microbiological success for AM1; mes₂, microbiological success for AM2; OCTR, other causes of bacterial persistence than resistance.

1 ψ = 1 - \( \frac{\text{mes}}{1 - \text{cs}} \) denotes bacterial persistence for other causes than resistance (OCTR). ψ₁ = 0.0943. If mes₂ ≥ mes₁, then ψ₂ > ψ₁ since \( r₂ > r₁ \).

6.5.3. Outcome measures

Expected incremental costs and QALYs for the three comparative strategies listed in Table 3 were compared with the base case strategy over the 10-year modelled time horizon based on four economic outcomes; three of which were computed during the hospitalisation period and one during the 90 days post-discharge.

The hospitalisation-related outcomes included:

(i) Costs of care associated with additional length of ICU stay for each case of infection;

(ii) Costs of treating the infection, which included the two treatment lines and the microbiological susceptibility test following first-line treatment failure (where the cost of AM1 was included but the cost of AM2 was set to zero to inform value-based pricing as discussed in Section 3.2).

(iii) QALYs associated with inpatient stay in the ICU.

The post-discharge outcome was based on the QALYs accrued by individuals during the 90-day follow-up after discharge from ICU. Adverse events from treatment and their consequences
on patients’ health-related quality of life and healthcare service resources, as well as potential costs consequences following patients discharge from the ICU, were not considered.

All economic outcomes were computed using a daily time step and discounted at an annual rate of 3.5% compounded daily. In order to adequately capture the consequences of infection-related excess mortality risk, whilst also satisfying the assumption of constant ICU occupancy (new admissions of uninfected individuals replaced infected patients who had been discharged or died), computation of the three hospitalisation-related economic outcomes at each time point \( t \) was adjusted for the number of infected patients who had died between times \( (t-1) \) and \( (t) \). This adjustment was required in order to avoid biasing the incremental results in favour of treatment strategies that would let infected patients die and be replaced by uninfected ones, rather than treat them. All the equations underpinning the computation of outcomes are provided in Appendix B.1.

6.5.4. Uncertainty analysis

PSA was undertaken in a subset of scenarios in order to capture evidential uncertainty in the parameter values. This consisted of fitting appropriate statistical distributions to the parameters and using Monte Carlo simulation to reflect the joint uncertainty in model outputs. Gamma distributions were fitted to rate parameters, as well as to costs and the infection-related decrement in HRQoL, while beta distributions were fitted to probability parameters and prevalence data. A lognormal distribution was fitted to the risk ratios associated with being colonised following prophylaxis treatment and acquired resistance conditional on treatment failure. The PSA simulation outputs \( (n=5,000) \) enabled the cost-effectiveness acceptability curve (CEAC) to be derived, which depicts the probability that a given treatment strategy is more cost-effective than the base case scenario for different values of the acquisition cost of AM2.

6.6. Results

6.6.1. Base case prevalence of colonised and infected individuals

Figure 4 depicts the equilibrium prevalence of individuals colonised and infected by \( A. baumannii \), representing 17% and 22%, respectively, of the ICU population under the base case. Among infected patients, about two thirds are under treatment, i.e. still infectious and
waiting for treatment outcome, and one third have failed treatment, with the only possibility of clearance due to a lower rate of spontaneous recovery.

With 0.57% of patients hosting a strain resistant to AM1 on admission (10.7% of those 5.3% who are admitted colonised) and a 12.5% chance of acquiring resistance to AM1 following treatment, under the base case strategy that only gives AM1 to patients, the equilibrium prevalence of colonised and infected patients with resistance to AM1 is unsurprisingly very high (accounting for 56% of colonised and 63% of infected). However, it should be noted that about 60% of these patients are assumed to be intermediate-resistant. For these individuals, AM1 can clear clinical symptoms but it cannot eradicate the bacteria.

The prevalence distribution is similar to that found elsewhere in the literature. For example, the estimated equilibrium distribution of ICU patients between uncolonised, colonised and infected under the base case strategy (61%, 17% and 22%, respectively) is similar to the baseline prevalence reported in Doan et al. [80], which also reports on an ICU setting for the same bacteria (57% uninfected, 25% colonised and 18% infected), but under different drivers of transmission dynamics.

Figure 4: Equilibrium prevalence of colonised and infected with A. baumannii under the base case strategy
6.6.2. Prevalence of colonised and infected individuals under the comparative strategies

Scenario where the risk of acquiring resistance to the new AM2 is set equal to zero

Figure 5 compares the prevalence of uncolonised, colonised and infected individuals (with a further distinction between infected individuals under treatment and those who failed treatment) for each of the three comparative strategies compared to the base case strategy under the scenario where the risk of acquiring resistance to AM2 is set equal to zero. The efficacy scenario, S1, which assumes that AM2 has the same clinical efficacy as AM1, but provides greater bacteria eradication owing to its zero risk of resistance acquisition (see Table 7), was chosen as the reference scenario for comparing the treatment strategies.

Figure 5: Prevalence of colonised and infected individuals with *A. baumannii* for each of the treatment strategies under efficacy scenario S1 and no risk of acquired resistance to AM2

The proportion of uncolonised individuals (black dashed line) is noticeably higher under each two-line comparative strategy compared with the base case, reaching as high as 71% under TS2 compared to 61% under the base case strategy. This reflects the lower colonization rate and, therefore, infection rate due to the second-line of therapy. In fact, the overall proportion of infected patients who failed treatment is lower under each two-line strategy compared with the base case. This, in turn, feeds back into a reduced rate of infection transmission and results in the prevalence of infected individuals being as low as 15% under TS2 (16% under TS3, 18%
under TS1) compared to 22% under the base case. It is worth noting that this dynamic outcome is jointly driven by the probability of clinical success, patients’ susceptibility profile, the time to treatment outcome, the delay in switching to the second-line of treatment, as well as discharge and death rates.

Among the three comparative strategies, the proportion who failed the first-line of treatment (purple full line) is the lowest under TS2 (17% of those infected, i.e., 2.6% of all ICU patients) and the highest under TS1 (21% of those infected, i.e., 3.9% of all patients). Whilst resistance mainly affects microbiological outcomes by preventing bacteria eradication, it also drives the difference in first-line rates of treatment success between the comparative strategies, since 43% of resistant strains are expected to exhibit complete-resistance leading to clinical failure. Under the combined assumptions of (i) a zero risk of acquiring resistance to AM2 and (ii) the absence of a resistant strain to AM2 among colonised patients upon admission, AM2 clearly benefits from a strong advantage over AM1. In contrast, since 0.57% of all admitted patients host a strain resistant to AM1 and patients can acquire resistance during treatment, the prevalence of a resistant strain to AM1 is always positive. The latter, however, dramatically drops when adding AM2 as an alternative treatment option, since this resistance scenario assumes that all infected individuals are susceptible to AM2.

Table 8 provides the distribution of resistant strains under each treatment strategy for efficacy scenario S1 and no risk of acquired resistance to AM2. It shows that drug positioning within treatment lines matters substantially in curbing the rise in resistant strains to AM1. Treatment strategy TS2, which gives AM2 to all treated cases at first-line achieves a much greater reduction in the prevalence of resistant strains compared to TS1 or TS3.

<table>
<thead>
<tr>
<th></th>
<th>R1/I</th>
<th>R1/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC</td>
<td>62.6%</td>
<td>56.3%</td>
</tr>
<tr>
<td>TS1</td>
<td>55.4%</td>
<td>50.0%</td>
</tr>
<tr>
<td>TS2</td>
<td>19.5%</td>
<td>18.1%</td>
</tr>
<tr>
<td>TS3</td>
<td>37.8%</td>
<td>34.0%</td>
</tr>
</tbody>
</table>

I, infected; C, colonised; R1/I, strain resistant to AM1 among infected patients; R1/C, strain resistant to AM1 among colonised patients.
Scenario where the risk of acquiring resistance to the new AM2 is equal to half the risk of acquiring resistance to AM1

Figure 7 presents the prevalence results under each of the three comparative strategies compared with the base case under the scenario where the risk of acquiring resistance to AM2 is equal to half the risk of acquiring resistance to AM1 and under efficacy scenario S1.

Figure 6: Prevalence of colonised and infected individuals with *A. baumannii* for each of the treatment strategies under efficacy scenario S1 and risk of acquiring resistance to AM2 set equal to half the risk of acquiring resistance to AM1

Whilst offering a second-line of treatment with an alternative AM undoubtedly helps boost the proportion of uncolonised and reduces the proportion of infected individuals, the change in the prevalence of colonised and infected individuals is less dramatic when the risk of acquiring resistance to the new AM2 is positive (6% in this case). Under TS2, which represents the best strategy for efficacy scenario S1, the proportion of individuals uncolonised, colonised and infected represent 65%, 16%, 19%, respectively, of ICU patients compared to 61%, 17% and 22%, respectively, under the base case.

As expected, differences in outcomes between the treatment strategies are less marked when compared to the scenario with no acquired resistance to AM2. For example, TS2 is only
marginally better than TS3. Table 9 shows the distribution of single- and double-resistant strains for each treatment strategy under the two scenarios of resistance acquisition.

Whilst under the resistance scenario where there is no acquired resistance to AM2, AM positioning plays an important role in curbing the rise in resistant strains, it matters less when acquired resistance to the new AM2 is set equal to half that of AM1. Although the mixing strategy, TS3, helps reduce the emergence of resistance to the new AM2 (i.e. R2 strains only accounts for 3.7% of all infectious strains under TS3 compared to 11.6% under TS2), it leads to a rise in double-resistance that is roughly as high as under TS2.

### Table 9: Prevalence of single- and double-resistant strains for each treatment strategy under efficacy scenario S1

<table>
<thead>
<tr>
<th></th>
<th>R1/I</th>
<th>R2/I</th>
<th>R12/I</th>
<th>Tot R/I</th>
<th>R1/C</th>
<th>R2/C</th>
<th>R12/C</th>
<th>Tot R/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC</td>
<td>62.6%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>62.6%</td>
<td>56.3%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>56.3%</td>
</tr>
<tr>
<td>Resistance scenario: no acquired resistance to AM2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS1</td>
<td>55.4%</td>
<td>0%</td>
<td>0%</td>
<td>55.4%</td>
<td>50.0%</td>
<td>0%</td>
<td>0%</td>
<td>50.0%</td>
</tr>
<tr>
<td>TS2</td>
<td>19.5%</td>
<td>0%</td>
<td>0%</td>
<td>19.5%</td>
<td>18.1%</td>
<td>0%</td>
<td>0%</td>
<td>18.1%</td>
</tr>
<tr>
<td>TS3</td>
<td>37.8%</td>
<td>0%</td>
<td>0%</td>
<td>37.8%</td>
<td>34.0%</td>
<td>0%</td>
<td>0%</td>
<td>34.0%</td>
</tr>
<tr>
<td>Resistance scenario: acquired resistance to AM2 equal to half that of AM1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS1</td>
<td>39.4%</td>
<td>0.8%</td>
<td>16.3%</td>
<td>56.4%</td>
<td>36.5%</td>
<td>0.7%</td>
<td>16.9%</td>
<td>54.0%</td>
</tr>
<tr>
<td>TS2</td>
<td>8.3%</td>
<td>11.6%</td>
<td>30.7%</td>
<td>50.6%</td>
<td>8.6%</td>
<td>10.5%</td>
<td>31.4%</td>
<td>50.6%</td>
</tr>
<tr>
<td>TS3</td>
<td>17.8%</td>
<td>3.7%</td>
<td>29.9%</td>
<td>51.3%</td>
<td>17.2%</td>
<td>3.3%</td>
<td>31.0%</td>
<td>51.5%</td>
</tr>
</tbody>
</table>

I, infected; C, colonised; R1, strain resistant to AM1; R2, strain resistant to AM2; R12, strain resistant to AM1 and AM2. Only 43% of resistant strains are complete-resistant strains.

### 6.7. Economic Results

#### 6.7.1. Scenario where the risk of acquiring resistance to the new AM2 is set equal to zero

Table 10 translates epidemiological estimates into the four economic outcomes defined in Section 6.5.3. The epidemiological quantities are the difference between each treatment strategy including the new AM and the base case, in terms of the prevalence of uncolonised, colonised and infected individuals, and number of clinical failures within the 15-bed ICU population over the 10-year follow-up period.

Expected incremental costs and QALYs of each strategy against the base case are presented for the five efficacy scenarios defined in Table 7. Incremental cost impacts, savings in this case, were expressed in QALY equivalents using a measure of health opportunity cost of
£15,000 per QALY gained [7], and aggregated with incremental QALY impacts into a measure of ICU-population incremental net health benefit. The latter was also expressed in monetary units (ICU-population incremental net monetary benefit) by valuing each QALY at the measure of health opportunity cost (£15,000 per QALY).

Table 10: Expected incremental net health benefit for each treatment strategy at ICU-population level compared with base case when acquired resistance to AM2 is set equal to zero under alternative scenarios about clinical efficacy

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario 1</td>
<td>TS1 vs. BC</td>
<td>-18,444</td>
<td>-534,856</td>
<td>0.66</td>
<td>14.17</td>
<td>51.72</td>
</tr>
<tr>
<td>Scenario 1</td>
<td>TS2 vs. BC</td>
<td>-456,280</td>
<td>-1,676,170</td>
<td>1.29</td>
<td>26.18</td>
<td>169.63</td>
</tr>
<tr>
<td>Scenario 1</td>
<td>TS3 vs. BC</td>
<td>-254,549</td>
<td>-1,226,549</td>
<td>1.05</td>
<td>21.67</td>
<td>121.47</td>
</tr>
<tr>
<td>Scenario 2</td>
<td>TS1 vs. BC</td>
<td>-22,030</td>
<td>-596,495</td>
<td>0.73</td>
<td>15.41</td>
<td>57.37</td>
</tr>
<tr>
<td>Scenario 2</td>
<td>TS2 vs. BC</td>
<td>-474,305</td>
<td>-1,871,043</td>
<td>1.46</td>
<td>29.74</td>
<td>187.56</td>
</tr>
<tr>
<td>Scenario 2</td>
<td>TS3 vs. BC</td>
<td>-267,599</td>
<td>-1,361,891</td>
<td>1.18</td>
<td>24.20</td>
<td>123.40</td>
</tr>
<tr>
<td>Scenario 3</td>
<td>TS1 vs. BC</td>
<td>-12,557</td>
<td>-433,667</td>
<td>0.66</td>
<td>14.19</td>
<td>44.60</td>
</tr>
<tr>
<td>Scenario 3</td>
<td>TS2 vs. BC</td>
<td>-468,233</td>
<td>-1,325,288</td>
<td>1.28</td>
<td>26.50</td>
<td>147.34</td>
</tr>
<tr>
<td>Scenario 3</td>
<td>TS3 vs. BC</td>
<td>-255,332</td>
<td>-1,007,883</td>
<td>1.05</td>
<td>21.91</td>
<td>107.18</td>
</tr>
<tr>
<td>Scenario 4</td>
<td>TS1 vs. BC</td>
<td>-14,943</td>
<td>-474,685</td>
<td>0.60</td>
<td>12.92</td>
<td>46.16</td>
</tr>
<tr>
<td>Scenario 4</td>
<td>TS2 vs. BC</td>
<td>-437,621</td>
<td>-1,488,970</td>
<td>1.12</td>
<td>22.52</td>
<td>152.07</td>
</tr>
<tr>
<td>Scenario 4</td>
<td>TS3 vs. BC</td>
<td>-241,388</td>
<td>-1,095,255</td>
<td>0.93</td>
<td>19.11</td>
<td>109.15</td>
</tr>
<tr>
<td>Scenario 5</td>
<td>TS1 vs. BC</td>
<td>-10,986</td>
<td>-406,670</td>
<td>0.57</td>
<td>12.40</td>
<td>40.81</td>
</tr>
<tr>
<td>Scenario 5</td>
<td>TS2 vs. BC</td>
<td>-434,260</td>
<td>-1,264,407</td>
<td>1.03</td>
<td>21.05</td>
<td>135.33</td>
</tr>
<tr>
<td>Scenario 5</td>
<td>TS3 vs. BC</td>
<td>-236,005</td>
<td>-948,062</td>
<td>0.87</td>
<td>18.10</td>
<td>97.90</td>
</tr>
</tbody>
</table>
The treatment cost of the new AM2 was set equal to zero to support value-based assessment for AM2.

Using a measure of health opportunity cost of £15,000 per QALY gained.

The cost savings relating to a shorter duration of stay in the ICU (estimated average cost of £1383 per day) is the key driver of the incremental net health benefit associated with the introduction of AM2. It contributes to about 65% of the total incremental net health benefit for each treatment strategy compared to the base case. In fact, as depicted in Figure 4 (reduced prevalence of infected individuals), all three comparative treatment strategies help curb the rate of cross-transmission and, consequently, the number of new infections. The latter are reduced by 5%, 17% and 12% under TS1, TS2 and TS3, respectively.

The incremental gain in QALYs during ICU stay for strategies compared with the base case is very modest and reflects the relatively high patient turnover in ICU. Over the 10-year time horizon, under each treatment strategy including the base case, patients contribute about 70-72 QALYs during their cumulative stay. Despite a smaller discharge rate, owing to their excess death risk, infected patients stay, on average, only 8.4 more days in ICU compared to uninfected individuals. Consequently, the loss in HRQoL incurred by each infected patient whilst in ICU is accumulated over a very short time period. As a result, the new AM2 only yields a maximum incremental gain of 1.5 QALYs for all patients admitted to ICU over 10 years.

Since the ICU is assumed to be constantly fully occupied at any given point in time, the same total number, N, of patients contribute to the total QALYs accrued in ICU. However, by reducing the numbers of primary infections under the comparative strategies, patients are discharged quicker and, therefore, more patients can be treated in the ICU. For example, under efficacy scenario S1, 64, 124 and 102 additional patients are treated under TS1, TS2 and TS3, respectively, over the modelled time horizon. The higher number of individuals admitted to the ICU, combined with a longer follow-up duration post-discharge (90 days compared with an average ICU stay of 19 days per patient) leads to substantially larger incremental QALY gains post-discharge, than during ICU stay, under the comparative strategies. Depending on the efficacy scenario, the incremental QALY gains post-discharge accounts for about 20% of the incremental net health benefit under TS2 and TS3 and 30% of the incremental net health benefit under TS1.
As expected, the incremental saving from reduced treatment cost under TS1 is very small (about 2% of incremental net health benefit) and reflects the reduction in the number of primary infections. In contrast, the reduction in treatment cost contributes more significantly to the incremental net monetary benefit of TS2 and TS3 (20% and 15%, respectively) since these strategies not only achieved a higher reduction in the number of primary infections, but the cost of AM2 was set equal to zero.

Under scenario S1, TS2 yields the highest incremental net monetary benefit (£2.5m compared with £0.8m under TS1 and £1.8 under TS3). TS2 is also the best treatment strategy under all other four efficacy scenarios. As expected, the difference in incremental net health benefit between the three comparative strategies is highest under S2, which is the most optimistic scenario for AM2, and lowest under S5, which is the most pessimistic scenario. Under S2, the expected incremental net monetary benefit of TS2 is higher than TS1 and TS3 by £2m and £0.8m, respectively, whereas under S5, it is higher by £1.4 and £0.6m, respectively.

**6.7.2. Scenario where the risk of acquiring resistance to AM2 is set equal to half the risk of acquiring resistance to AM1**

Table 11 presents the expected incremental costs and QALYs for each of the treatment strategies compared with the base case for the scenario under the different efficacy scenarios, when the risk of acquiring resistance to AM2 is set equal to half the risk of acquiring resistance to AM1.

As already demonstrated in Figure 7 and Table 9, the incremental net health benefit associated with adding another line of therapy is substantially reduced with a positive probability of patients’ acquiring resistance to the new AM2. However, even if the risk of acquiring resistance to AM2 is set equal to half the risk of acquiring resistance to AM1 (i.e. 6%), AM2 given in addition to AM1 would provide an incremental net health benefit of between 32 to 86 QALYs (£0.5m to £1.3) over 10 years compared to the base case.
In line with findings presented in Figure 7 and Table 9, the incremental difference in outcomes between the treatment strategies is much lower when acquired resistance to AM2 is half that of AM1, but the incremental net health benefit of each strategy is not reduced by the same proportion (e.g., reduction of 22-31% for TS1 compared to 40%-50% for TS2 and TS3, depending on the efficacy scenario considered). The added value of giving the new AM at first-line compared to second-line is highly susceptible to the risk of acquiring resistance to it. However, under the two resistance scenarios presented, TS2 remains the best treatment strategy under all five clinical efficacy scenarios.
Table 11: Expected incremental net health benefit at ICU-population level for each treatment strategy compared with base case when acquired resistance to AM2 is set equal to half the acquired resistance to AM1 under alternative scenarios about clinical efficacy

<table>
<thead>
<tr>
<th>Scenario</th>
<th>ICU-Population Incremental Treatment Cost*</th>
<th>ICU-Population Incremental cost for length of ICU stay</th>
<th>ICU-Population Incremental QALY gain in ICU</th>
<th>ICU-Population Incremental QALY gain post-discharge</th>
<th>ICU-Population Incremental Net health benefit (QALY)</th>
<th>ICU-Population Incremental Net Monetary Benefit (INHB)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS1 vs. BC</td>
<td>-8,848</td>
<td>-369,904</td>
<td>0.51</td>
<td>11.09</td>
<td>36.85</td>
<td>552,754</td>
</tr>
<tr>
<td>TS2 vs. BC</td>
<td>-473,328</td>
<td>-593,131</td>
<td>0.59</td>
<td>12.28</td>
<td>83.97</td>
<td>1,259,479</td>
</tr>
<tr>
<td>TS3 vs. BC</td>
<td>-246,366</td>
<td>-569,341</td>
<td>0.58</td>
<td>12.16</td>
<td>67.12</td>
<td>1,006,864</td>
</tr>
<tr>
<td>Scenario 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS1 vs. BC</td>
<td>-10,440</td>
<td>-397,268</td>
<td>0.55</td>
<td>11.76</td>
<td>39.49</td>
<td>592,383</td>
</tr>
<tr>
<td>TS2 vs. BC</td>
<td>-488,638</td>
<td>-580,696</td>
<td>0.66</td>
<td>14.04</td>
<td>86.00</td>
<td>1,289,957</td>
</tr>
<tr>
<td>TS3 vs. BC</td>
<td>-254,434</td>
<td>-576,919</td>
<td>0.63</td>
<td>13.29</td>
<td>69.35</td>
<td>1,040,210</td>
</tr>
<tr>
<td>Scenario 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS1 vs. BC</td>
<td>-5,840</td>
<td>-318,200</td>
<td>0.59</td>
<td>11.38</td>
<td>33.51</td>
<td>502,687</td>
</tr>
<tr>
<td>TS2 vs. BC</td>
<td>-483,394</td>
<td>-443,725</td>
<td>0.65</td>
<td>14.06</td>
<td>76.52</td>
<td>1,147,815</td>
</tr>
<tr>
<td>TS3 vs. BC</td>
<td>-249,425</td>
<td>-472,058</td>
<td>0.62</td>
<td>13.19</td>
<td>61.91</td>
<td>928,643</td>
</tr>
<tr>
<td>Scenario 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS1 vs. BC</td>
<td>-7,094</td>
<td>-339,756</td>
<td>0.47</td>
<td>10.35</td>
<td>33.94</td>
<td>509,128</td>
</tr>
<tr>
<td>TS2 vs. BC</td>
<td>-457,077</td>
<td>-598,091</td>
<td>0.51</td>
<td>10.43</td>
<td>81.28</td>
<td>1,219,233</td>
</tr>
<tr>
<td>TS3 vs. BC</td>
<td>-237,683</td>
<td>-556,025</td>
<td>0.52</td>
<td>10.95</td>
<td>64.39</td>
<td>965,807</td>
</tr>
<tr>
<td>Scenario 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS1 vs. BC</td>
<td>-5,604</td>
<td>-314,144</td>
<td>0.46</td>
<td>10.20</td>
<td>31.98</td>
<td>479,660</td>
</tr>
<tr>
<td>TS2 vs. BC</td>
<td>-454,839</td>
<td>-551,493</td>
<td>0.50</td>
<td>10.37</td>
<td>77.96</td>
<td>1,169,379</td>
</tr>
<tr>
<td>TS3 vs. BC</td>
<td>-235,812</td>
<td>-520,354</td>
<td>0.52</td>
<td>10.87</td>
<td>61.79</td>
<td>926,903</td>
</tr>
</tbody>
</table>

*The treatment cost of the new AM2 was set equal to zero to support value-based assessment for AM2.
‡Using a measure of health opportunity cost of £15,000 per QALY gained.
6.7.3. **Probability that introducing AM2 is more cost-effective than the base case**

The majority of the incremental net health benefit for the comparative strategies (between 60% to 80%) stem from a reduced length of ICU stay and, to a lesser extent, lower treatment costs. This is due to a reduction in the number of primary infections that are achieved at zero cost under AM2. It follows that, even at a measure of health opportunity cost of £0 per QALY gained, all comparative strategies appear more cost-effective than the base case across all Monte Carlo simulations (i.e., the probability that they are more cost-effective than the single-line base case treatment is always equal to 1).

The change in the probability that the comparative strategies are more cost-effective than the base case was evaluated as a function of the acquisition cost of AM2, using a measure of health opportunity cost of £15,000 per QALY gained. Figure 7 and Figure 8 show the probability that TS2 is more cost-effective than the base case for efficacy scenarios S1, S2 (optimistic) and S5 (pessimistic) when acquired resistance to AM2 is set equal to zero and half that of AM1, respectively. The results are only shown for TS2 since this treatment strategy provides the highest expected incremental net health benefit under all efficacy and resistance scenarios.

The probability that TS2 is more cost-effective than the base case drops faster under scenario S5 (pessimistic) compared to scenario S2 (optimistic), and the risk of acquired resistance to AM2 has a significant impact on the probability that TS2 is better than the base case. If the cost of AM2 reaches £10,000 per infected patient treated, TS2 would be expected to be more cost-effective than the base case with a 90% probability when acquired resistance to AM2 is set equal to zero, while this would drop to a 75% probability when acquired resistance to AM2 is half that of AM1. Above a cost of £10,000 per patient treated, the chance that TS2 provides greater value than the base case drops quickly below 50% when acquired resistance to AM2 is half that of AM1.
6.8. DISCUSSION

The case study developed in this section was used to demonstrate how to conceptually map out the quantification of wider population health benefits of a new AM over time, and to translate
dynamic epidemiological outcomes into economic endpoints. Unlike previous mechanistic models that focused solely on the clearance of infection-related symptoms, the present model examined the value of a new AM based on its capacity to clear symptoms and eradicate the bacteria. The latter outcome is central to evaluating the long-term population health benefits of a new AM as weak efficacy in eradicating bacteria in clinically successful patients may further increase the selection of multi-drug resistant strains [32].

Particular emphasis was placed on capturing the mechanisms of resistance on microbiological eradication success rates, which is a key determinant of prevalence of patients colonised with bacteria (some of whom will become infected). Therefore, the rate of bacteria cross-transmission between patients is important. Furthermore, in addition to the mechanism of resistance emergence embedded in the differential clearance rate of infected patients according to their susceptibility profile, the model also captured the impact of resistance acquisition during treatment. This second mechanism contributes to the emergence of resistance through conversion of susceptible bacterial strains into single-resistant and double-resistant strains during treatment. The impact of collateral selection associated with past AM exposure as discussed in Section 5 was also partially captured by incorporating prophylaxis treatment as an exogenous risk factor for being colonised.

The inclusion of both clinical and microbiological outcomes has allowed us to move away from the commonly used assumption that resistance systematically leads to clinical failure, which has frequently been invalidated in practice [32], [33], [85], [91]. In line with recent surveillance data on Acinobacter in the UK, it was assumed that only about 40% of resistant strains were fully-resistant to AMs [87].

Whilst the model was illustrative only and was not developed to inform real-world treatment decisions for infections caused by *A. baumannii*, it was designed to represent a biologically realistic model of the dynamics of bacteria transmission and incorporate clinical and microbiological efficacy outcomes. The prevalence of colonised and infected individuals obtained in the base case strategy was comparable to values reported in the literature [80].

A key objective of the model was to demonstrate that economic endpoints can be linked to epidemiological outcomes on infection transmission and emergence of AMR. The results
suggest that the addition of a new AM can substantially increase the rate of successfully treated and decolonised patients and consequently, sharply reduce the number of new primary infections. This would, in turn, generate substantial healthcare resources savings. The main source of savings is expected to be the reduced length of ICU stay per patient, which represented about 60% of the incremental net health benefit of the comparative strategies compared with the base case. Treatment costs are also expected to be lower as a result of the reduction in infection transmission rate. Unlike previous mathematical models, which have overwhelmingly focused on modelling infection dynamics within a single healthcare or community setting, the computation of economic endpoints in this context has enabled us to fully capture the benefits of treatment, including outcomes post-discharge from the ICU. QALY gains post-discharge accounted for 20% to 30% of the incremental net health benefit associated with TS2 and TS3 and 40% of the incremental net health benefit of TS1.

At the level of a 15-bed ICU followed over 10 years, the incremental ICU-population net benefit associated with adding a second line to treat nosocomial infections by *A. baumannii* in admitted patients was estimated to range from 41 to 188 QALYs (£0.5m to £2.9m), depending on the treatment strategy and on the expected clinical and microbiological efficacy of the new AM. Unsurprisingly, the greater the risk of acquiring resistance to the new AM, the less population benefit the latter would generate. In the scenario where the risk of acquiring resistance to the new AM was equal to half the risk of acquiring resistance to the existing AM, the new AM increased the incremental net health benefit by a maximum of 86 QALYs, valued at £1.3m (TS2).

PSA showed that, at a cost of the new AM up to £10,000 per infected patient treated, the probability that providing the new AM as an additional treatment option is more cost-effective than exclusively using the existing treatment (BC strategy) is high, ranging from 90% to 75%, depending on the risk of acquired resistance under the new AM.

In order to inform payments for the new drug, the modelled benefits would have to be rescaled to the total number of ICUs in the geographical area where the new AM is to be made available to treat nosocomial infections by *A. baumannii*. This rescaling should account for the heterogeneity in ICUs, in terms of differences in bed-capacity and occupancy rate, in the patient population admitted, and especially with regards to the prevalence of admitted individuals
colonised with the pathogen and in ICU care practice. The latter can impact, for example, on the discharge rate and the rate of routine susceptibility testing following clinical failure. The model could, therefore, be re-run with a different range of parameters that characterise heterogeneity between ICUs and the resulting results could be weighted in accordance with the distribution of these characteristics in England.

The extent to which this modelling can inform value-based assessment is, however, limited by a number of simplifying assumptions that were taken to limit the scope of the analysis and to parameterize the model. First, the potential transmission of the pathogen outside of the ICU is not modelled and, as a result, the prevalence of individuals colonised by the various susceptibility phenotypes of *A.baumanni* upon admission was considered an exogenous process. This is expected to be unrealistic, especially over a medium time-period of 10 years.

Second, the model does not capture the enablement value of AM as it ignores the clinical implications of delayed procedures associated with a patient contracting a nosocomial infection upon admission. The importance of modelling such implications is expected to depend on the primary reason for ICU admission. In the case of organ transplant, for instance, a delayed procedure is expected to have a major impact on the patient’s prognosis.

Third, adverse events from treatment were not considered and incremental analyses therefore assumed that the new AM would have a similar level of toxicity to the existing AM. There is, however, evidence that treatments such as tigecycline and colistin, both of which are used to treat *A. baumannii* infections, are associated with different risk of nephrotoxicity, leading to potentially irreversible kidney damage and death [84]. Whilst any differential long-term consequences associated with adverse events should be included in the analysis, it is worth highlighting that adverse events associated with the use of new agents may only become apparent only after their use in large populations. This argument further supports the expected need to re-negotiate delinked payments as the evidence base becomes more mature (See Section 7).

Fourth, patients who do not die from the infection are assumed to clear their symptoms following either successful treatment of spontaneous recovery after a maximum period of three months. In reality, because of resistance, patients may remain with symptoms, and thereby
require additional healthcare and suffer from health-related quality of life impairment, for a much longer period of time. This is expected to have important implications when defining the size of the population expected to benefit from the new drug in negotiating payments.

Fifth, the treatment strategies evaluated do not represent the full range of possible treatment options for *A. baumannii* infections.

The last category of limitation pertains to the parameterization of the model which involved important simplifications. First, whilst extensive standard model validation checks (e.g., face and predictive validity) were undertaken, model outcomes were not validated against historical data, which further highlights the conceptual nature of the model developed.

Second, although the assumption of time-invariant input parameters appears common practice in the dynamic models in the literature, the longer the modelled time horizon, the more this assumption ought to be challenged. For example, an improvement in environmental cleaning practices at hospitals may help to curb the rate of cross-transmission independently of treatment protocol [80]. Similarly, it was assumed that during the modelled time horizon no patient was admitted to the ICU with a strain resistant to the new AM. Whilst this is expected to be the case in the first years after the introduction of the new AM, the lag phase for the emergence of resistance to reach an equilibrium level is unknown.

A third simplification in parameterization is that microbiological outcomes did not distinguish between eradication at site of infection and in hosts’ microbiomes. If the bacteria were to be eradicated only from the site of infection, it would remain transmissible to other patients. The extent to which a drug’s bacterial eradication success rate at infection site, as informed by *in vitro* studies, reduces the risk of onwards transmission is, therefore, very uncertain. This level of uncertainty should ideally be appropriately reflected in the transmission value of new AMs.

Fourth, unlike most existing models where resistance is assumed to systematically lead to clinical failure, in order to better reflect clinical reality [22] clinical cure was allowed in the case of intermediary-resistance. However, since clinical outcome and resistance are not independent, the relationship between these two events has to be specified, which required a further assumption. It was also assumed that patients infected by an intermediary-resistant
strain would have the same cure rate (but not bacterial eradication) as those infected by a fully susceptible strain, which may not be validated in practice.

Fifth, a single set of values was assigned to represent the baseline HRQoL experienced by patients in the ICU and a decrement applied to infections, as well as discharge rate. In reality, these parameters are expected to be specific to the cause of admission to the ICU and the severity of infection caused by the bacteria. Finally, whilst PSA was performed to reflect evidential uncertainty, the variance was not known for a number of parameters. The estimated distribution of outcomes used to support the estimation of cost-effectiveness is strongly dependent on the assumed level of uncertainty around mean parameter values. The uncertainty analysis here would also need to be taken further using the approaches described in Section 7.

7. IMPLICATIONS OF UNCERTAINTY FOR ALTERNATIVE PAYMENT MECHANISMS OF NEW ANTIMICROBIALS

7.1. INTRODUCTION

The output of the value assessment framework for new AMs is an estimate of the total expected population net health benefit for each of the alternative strategies regarding usage of the new and existing AMs, considering the projections of AMR over the modelled time horizon. This characterises the value of a new product based on whether the additional health expected to be gained from its use exceeds the health forgone elsewhere in the NHS from diverting resources away from other activities in order to accommodate the additional costs of the strategy. The expected value of a new AM assumes zero drug acquisition cost or payment in order to guide decisions about appropriate levels of reimbursement and alternative funding mechanisms for new AMs.

The value of a new product in terms of its expected impact on population net health benefit is based on the balance of evidence currently available. However, uncertainty in the existing evidence is unavoidable. This uncertainty arises from a number of sources including: i) evidential uncertainty in key parameters that affect the pattern of resistance over time (e.g., uncertainty in infection transmission parameters, surveillance data and other epidemiological parameters), resource use and costs, health-related quality of life utility values; ii) structural uncertainty in resistance modelling and assumptions used to support the modelling (e.g., in the
understanding of the mechanisms of resistance); iii) uncertainty about the lag period before resistance to a new AM develops; iv) uncertainty about the stock of future AMs available; v) uncertainty about when new information on resistance patterns may become available and the likelihood that surveillance data and other forms of new evidence to resolve uncertainties is collected; vi) the level of payment that emerges from contract renegotiations and any potential price changes with existing comparator AMs; vii) uncertainty about the irreversible impacts of an intervention on resistance and its consequences over time; viii) uncertainty about implementation of stewardship and policy initiatives to improve resistance patterns; and ix) uncertainty about the technology time horizon for new AMs. This uncertainty ultimately leads to uncertainty in the expected value of the drugs and, therefore, has direct implications on the contractual arrangements or the specification of alternative payment mechanisms for new AMs. The following sections describe the alternative proposed payment mechanisms that have been discussed in the literature, the implications of uncertainty under an insurance-based reimbursement arrangement that delinks payment of AMs from usage, the coverage options available for new AMs, choosing between these options in light of the uncertainty and its implications under alternative payment mechanisms.

7.2. PAYMENT MECHANISMS FOR REIMBURSEMENT OF ANTIMICROBIALS

A growing literature exists on strategies to incentivise the development of new AMs under the viewpoint that the traditional pharmaceutical business model, where revenues are based on sales volume and price, is financially unattractive to developers [93–96]. This is because revenue and conservation goals (e.g., restricting use of AMs to encourage appropriate stewardship that would kerb AMR) are in direct contradiction to each other. The mechanisms proposed in the literature are generally characterised into two broad categories known as push and pull mechanisms. Push mechanisms focus on lowering the research and development (R&D) costs for new drugs, while pull mechanisms reward successful development and provide return on investment. However, much of the literature is predominantly focussed on incentivising AM development from the perspective of the pharmaceutical industry, while less meaningful consideration has been given to establishing a framework for future AM pricing from a purchaser (or reimbursement authority) perspective. From this latter perspective, the focus is on pull mechanisms to reward successful development of new AMs.
The pull mechanisms that have been proposed in the literature include: i) higher reimbursement where a premium price is paid to restrict use and provide a return on R&D; ii) monetary prizes to motivate development; iii) tradeable exclusivity vouchers to increase market exclusivity over an extended period; iv) premium price paid upon confirmation of diagnosis of resistant pathogens; v) options market where a differential price is paid dependent on the time point in the development process that the AM is reimbursed; vi) insurance-type delinked model where a one-off or series of payments is made to reward innovation and fully delink revenue from volumes sold; and vii) partial delinked model where smaller reward payments are used to top-up traditional unit-based revenues. The advantages and disadvantages of each of these strategies, as well as a thorough review of all the potential pull strategies that have been proposed in the literature are provided in Renwick et al., (2016) [95].

The insurance-based delinked model has been most frequently recommended in the literature and is the focus of discussions between the DHSC and the relevant stakeholders. This model is based on a payment that reflects the expected value of a new product over a specified period, and with the possible addition of cap and collar arrangements (where the cap is an agreed maximum payment and the collar is an agreed minimum payment such that if company revenue exceeds the agreed maximum the payer faces a reduced cost on further use; while if revenue is lower than the agreed minimum the company receives an additional top-up payment). The precise specification of the insurance-based delinked model in a UK setting is yet to be determined and is likely to be specific to the profile of risk for particular AMs and their expected patterns of resistance over time.

Importantly, the value of a new AM as estimated by the proposed value assessment framework is a necessary prerequisite to inform the insurance-based delinked model. Negotiating a payment based on expected population net health benefit (assuming that there is no uncertainty in that estimate) is illustrated in Figure 10. As explained in Section 3, the payment level plays a key role in determining whether the new AM is expected to be of value to the NHS. A maximum payment level should be chosen such that the additional population net health benefit for a particular strategy with a new AM, compared with the current best practice, is equal to zero. This would mean that the additional health benefits of the AM used in that way would just offset the health that could have been generated if the financial value of the payment had been used elsewhere in the NHS. This is commonly referred to as the value-based payment
(VBP) for the strategy. It describes the maximum payment that the NHS could afford in order to gain access to the new AM and use it in the way defined by the strategy without imposing negative net health benefit.

Figure 10 shows the population net health benefit of three alternative strategies using the new AM as a function of the value-based payment. The population net health benefit associated with current practice is shown as the horizontal line and does not vary with the payment for the new product. As discussed in Section 3, current practice should be the most cost-effective way of treating indicated patients with existing AMs. The proposed value framework would initially estimate the population net health benefit of the new AM assuming zero acquisition cost (zero value-based payment), which is the point at which each of the three alternative strategies with the new AM meets the vertical axis. Figure 10 shows that Strategy 3 is the most effective and potentially the highest value strategy for using the new AM. This strategy would be of value to the NHS as long payment for access remains below VBP₃, which is the value-based payment for that strategy. Given possible considerations about the feasibility of implementing a new AM in a given strategy and relating to payment negotiation with the manufacturer, it would make sense to present the value-based payments for each strategy involving the new AM (Strategies 1 and 2 in Figure 10).

In most circumstances, however, there is uncertainty and a number of other value-based payments exist, each of which have implications for the optimal usage strategy and the level of coverage that the NHS could reasonably afford to pay without imposing a loss to the health system. The implications of uncertainty and its role for the delinked payment model are described in the following sections.
Three different value-based payment levels exist (VBP1, VBP2 and VBP3) for the three different ways that the new AM may be used (Strategy1, Strategy2 and Strategy3, respectively). Strategy 3 is the most effective and will be of value to the NHS up until a value-based payment of VBP3, with payments for less effective strategies 1 and 2.

### 7.3. Implications of Uncertainty for Reimbursement of Antimicrobials

A number of important issues arise when decisions about reimbursement levels are based solely on the expected value of the new product without considering the level of uncertainty in the current evidence base and the future uncertainties that will reveal over time. The most obvious implication is that uncertainty can lead to incorrect or inappropriate decisions regarding the treatment strategy with the highest potential value since gaps in the evidence base, uncertain parameter values, and unknown assumptions mean that the estimates of the expected resistance levels, costs and health outcomes are uncertain. This uncertainty and scope for incorrect decisions, therefore, creates the potential for a loss in total population health benefit to the NHS.
Additional evidence has the potential to reduce this uncertainty either by investing in further research to resolve the uncertainties or waiting until additional information becomes available (e.g., waiting on microbiological surveillance data to be reported on the susceptibility and resistance of AMs to different pathogens by local hospital laboratories). The value of conducting research to address specific uncertainties, and the value of waiting on evidence to report that reduces uncertainty, can be considered equally important as supporting decisions about the best treatment strategy since new information can improve population health for the same reasons as access to a new intervention [97]. Therefore, some assessment of uncertainty, its consequences in terms of health lost from suboptimal decisions, and the need for further information is required. This assessment of uncertainty can be informed through methods of value of information analysis, which can also be used to inform the type and proposed design of research [98–100]. Some assessment of the likelihood that the research is conducted, the length of time for the research to report and the costs of conducting research are also required [98].

Allowing early access to a new AM until further research is conducted can affect the generation of new evidence. For example, it may reduce the prospects of conducting the research that would provide the evidence needed to reduce uncertainties, or it may create disincentive effects to invest in further research. This means that additional health outcomes for the population may be foregone as a consequence of making the decision too early [98]. Furthermore, it may mean that the emergence of resistance to the new AM can occur at a much faster pace before the necessary research has been conducted to fully understand the susceptibility of a range of pathogens to the new agent. In these circumstances, it may be better to delay the decision until further research is conducted.

Investing in research, however, is not the only way to resolve uncertainty. In fact, it represents a very costly activity, both in terms of the resources needed to undertake the research and in the delays waiting for the research to report. More importantly, research will not resolve all uncertainty. This is particularly true for the evaluation of AMs, where another important source of uncertainty is that in the future that will only reveal over time, i.e., uncertainties that will only unfold with the passing of time. This could include the lag phase before resistance emerges to a new AM. The length of this period of time will depend on a number of factors including; the microbiological response of the new agent to the range of pathogens that the therapy is
expected to target, which is unlikely to be known when the new AM is first introduced to the market; stewardship and conservation policies in place or new initiatives to improve resistance patterns; and the availability of other AMs to reduce selection pressure (e.g., uncertainty in the future stock of AMs available). This creates an option value, where some flexibility in the timing of the reimbursement or payment decision becomes a very desirable characteristic. In other words, if we commit resources today when the future is uncertain there may be a significant loss in population health benefits by not delaying that commitment until the uncertainties resolve. The key determinants of an option value are the ability to defer the decision until some later time point (i.e., there is some discretion to the timing of the payment decision) and whether the payment decision entails an irreversible commitment of resources.

The option value has implications for the upfront commitment of payment under a delinked insurance-based model. Any upfront payment made in advance for several years use of a new AM implies a sunk cost that cannot be recovered if a decision about the best treatment strategy or use of the new AM is changed in the future as uncertainties unfold over time. If there were no implications of the uncertainty and switching between strategies as new information becomes available was a costless activity, then there would be no concern about the sunk costs. However, large upfront costs can lead to negative net population health when taking account of the opportunity cost of the expenditure that may never be recovered. Even if these costs are annuitized into a series of periodic payments and allocated over the anticipated lifetime of the intervention, any switch between treatment strategies or changes in the decision about the use of the new AM before the end of the lifetime of the intervention will result in sunk costs that cannot be recovered. There may also be additional costs associated with the removal of the intervention from clinical practice if a decision about the therapy changes in the future (e.g., upfront costs associated with implementing stewardship policies, or policing the use of AMs, that may no longer be required). The concerns about uncertainty and the irreversible nature of sunk costs suggest that the purchaser needs some reassurance that the payment level for access to a new AM is sustainable, because decisions about the intervention cannot be reversed at a later point without incurring costs. The impact of the irreversible costs will depend on a number of factors including; the technology time horizon (i.e., its anticipated shelf-life); the shelf-life of the comparators included in the evaluation; the size or scale of the upfront payment relative to the total costs; the size of the population that can benefit from the intervention; and the level
of uncertainty resolved over time. With these considerations in place, it is clear that some flexibility in the timing of the investment of the new AM is a desirable characteristic.

The challenge for the evaluation of AMs is that the resolution of uncertainty is expected to be gradual over time. Therefore, some assessment is needed on the timing at which new information is likely to become available that would change the expected value of the AMs and the future value of research. For information on the frequency of resistance to a new AM over time, this could potentially be informed by examining historical trends associated with other analogous AMs that exhibit similar mechanisms of resistance to the new AM. However, a proxy for all potential future changes is also required, which includes the availability of the current stock of AMs, entry of new AMs, new stewardship and conservation initiatives, as well as price changes or price renegotiation over time. This proxy may be based on past empirical evidence, or on estimates elicited from experts (‘priors’), but it is clear that it will only ever be a proxy for a very uncertain and complex process of future changes [12].

There are also irreversible consequences if decisions about the use of the AMs are delayed, even though there are uncertainties. For example, it may be better to act now than to delay the decision until the uncertainties resolve. This is because, unlike other technologies, decisions about AMs are not homogeneous over time. The nature and scale of resistance and the disease changes over time such that a decision to delay treatment by two years does not simply move the same decision problem forward by two years; instead it means that a different decision problem is faced in two years’ time (e.g., the choice of comparator strategies is likely to change at a later time point). This means that failure to act now with regard to the payment decision could lead to irreversible impacts on the patterns and consequences of resistance over time, since decisions made in time period t, affect payoffs for all future time periods.

All of the above considerations have implications for the optimal timing of funding decisions. If additional research is valuable to reduce the consequences of uncertainty in the current evidence base, or if there is a need to wait until future uncertainties are revealed over time (e.g., a watchful waiting scenario), then a decision must be made on how to balance the value of delaying a decision about the use of a new AM (or restricting its use to specific settings or circumstances) until better information becomes available against the value of providing early access to the new product and avoiding potential irreversible consequences of not acting now.
The optimal timing of the decision also depends on the contractual arrangements in place regarding payments with the manufacturer, e.g., whether there is a renegotiation strategy in place to revisit the evidence and decision at a later point in time.

7.4. Coverage options for new antimicrobials

A framework exists for assessing whether a new technology should be adopted without waiting on further information to resolve uncertainties, adopted alongside further research that resolves uncertainties, used only in the context of research, or rejected without further research [98]. This framework by Claxton et al., (2012) [98] offers conditional coverage options to allow patients early access to promising new technologies and permit companies to make a return on investment, while limiting the risks associated with making reimbursement decisions until additional evidence or further information becomes available that reduces the consequences of uncertainty. Application of this framework to the context of AMs, however, requires careful consideration of how the uncertainties are likely to resolve over time, the extent to which they can be resolved via active research, the potential for irreversible impacts of the use of AMs on the patterns and consequences of resistance and how the principles apply under a delinked insurance-based payment model.

The combined effect of the considerations in Section 7.3 suggests five potential coverage options when making funding decisions about a new AM (based on the framework of Claxton et al., 2012 [98] but with application to AMs):

i. Approve based on existing information: The new AM is approved for general use in the indication(s) that the therapy is expected to target (or in specific subgroups of the population/settings in line with conservation or stewardship goals) on the basis of the evidence currently available and at an agreed payment level that represents value to the NHS. This decision may be reversed at a later point in time as new evidence and uncertainties are revealed over time, but the decision is made conditional upon the collection of new evidence or delayed until new information is revealed. Under this approved coverage decision, the agreed payment level is expected to demonstrate value to the NHS taking account of the uncertainties and irreversible consequences such that the contractual agreement on payment is not required to be renegotiated in the near future, although it could be renegotiated at a later point in time when new information becomes available.
ii. **Reject based on existing information**: The new AM is rejected for general use in the indication(s) that the therapy is expected to target on the grounds that the evidence currently available suggests that it does not represent value to the NHS and no agreement can be reached on an appropriate payment level that would make access to the therapy viable to the NHS. This decision may be reversed at a later point in time as new evidence and uncertainties are revealed and an appropriate payment level can be agreed to ensure that the AM represents value to the NHS.

iii. **Only in research (OIR)**: The new AM is approved for use only in a selected subset of the population/settings or selected indication(s) for use, or only in patients involved in research, on the basis that the evidence currently available is insufficient to demonstrate value to the NHS. The payment level is expected to be renegotiated (or reviewed) after a pre-specified period of time (or once resistance levels reach a certain threshold, or a threshold of clinical need is reached). OIR represents a low usage scenario in order to see how resistance develops over time, or other uncertainties resolve over time, before broader roll-out of the AM. The decision on the general use of the AM in the indication(s) that the therapy is expected to target would be made at a later point in time when sufficient new information becomes available and the payment level can be renegotiated to demonstrate value of the AM to the NHS. This option may involve appropriate incentives or risk sharing agreements between the payer and another party (e.g., manufacturer or another stakeholder) to encourage and reward investment in further research to resolve uncertainties in such a way that it represents value to both sectors.

iv. **Approval with research (AWR)**: The new AM is approved for general use in the indication(s) that the therapy is expected to target (or in specific subgroups of the population/settings in line with conservation or stewardship goals) at the agreed payment level but conditional upon the necessary requirement to collect additional evidence to support its use in the form of a well specified study design(s). The payment level is expected to be renegotiated when the research reports. This option means that the decision to approve the AM is revisited in the future once the research reports and sufficient uncertainties are resolved. Based on the new information, the decision is reconsidered and may be revised such that the positive coverage option is continued, expanded or withdrawn. This option is only expected to be feasible if there is potential
for renegotiation of the payment level and the payer can ensure that any research that is needed is conducted.

v. **Approval with surveillance (AWS):** The new AM is approved for general use in the indication(s) that the therapy is expected to target (or in specific subgroups of the population/setting in line with conservation or stewardship goals) at the agreed payment level, but conditional upon the necessary requirement to collect additional information to support its use in the form of microbiological surveillance data or other forms of reliable surveillance information on the emergence of, or changes in, the prevalence of resistance to the new AM. This means that the right infrastructure needs to be in place to ensure that the necessary information is collected (e.g., networks of centres recruiting individuals with infections; consistent criteria for inclusion of bacterial organisms by collaborating centres; databases and data linkage on the surveillance of AMR). The payment level is expected to be renegotiated after a pre-specified period of time (or once resistance levels reach a certain threshold, or a threshold of clinical need is reached) when sufficient surveillance information is reported. This option is very similar to AWR and means that the decision to approve the AM is revisited in the future once the new information reports and sufficient uncertainties are resolved. Based on the new information, the decision is reconsidered and may be revised such that the positive coverage option is continued, expanded or withdrawn. Like AWR, this option is only expected to be feasible if there is potential for renegotiation of the payment level after the pre-specified period (or resistance level threshold) and the payer is satisfied that the necessary infrastructure to collect the required surveillance information is in place. This option may involve risk sharing agreements between the payer and another party (e.g., manufacturer or another stakeholder) to invest in the appropriate infrastructure to resolve uncertainties in such a way that it represents value to both sectors.

Each coverage option is based on the balance of evidence supporting the value of a new AM, the value of additional evidence to reduce the uncertainties, the value of waiting until future uncertainties and surveillance information is revealed over time, the likelihood and timing of the new information becoming available, the irreversible consequences of delaying the decision until uncertainties resolve, and the implications of irreversible upfront costs. Trade-offs, which
can be expressed in terms of population net health benefit, occur under each coverage option (see Box 8), and the aim is to minimise the risks associated with each option.

Box 8: Criteria for choosing between the coverage options (see Claxton et al., 2012 [98])

- **Approve based on existing information:**
  a) Agreed payment represents value to the NHS;
  b) Research or waiting for uncertainties to resolve is not needed;
  c) Research or waiting for uncertainties to resolve is needed but the benefits of not delaying the decision are greater than the costs and consequences, OR, cannot delay decision.

- **Reject based on existing information:**
  a) No agreed payment is reached to represent value to the NHS;
  b) Research or waiting for uncertainties to resolve is not needed;
  c) Research or waiting for uncertainties to resolve is needed but the benefits of not delaying the decision are greater than the costs and consequences, OR, cannot delay decision, AND there are no significant irreversible costs and consequences;
  d) Agreed payment represents value to the NHS, but there are significant irreversible costs and consequences, AND research or waiting for uncertainties to resolve is needed but the costs and consequences are greater than the benefits, AND cannot delay decision.

- **Only in research (OIR):**
  a) Agreed payment represents value to the NHS, AND research or waiting for uncertainties to resolve is needed and the benefits of delaying the decision are greater than the costs and consequences, AND the research needed is not possible with approval;
  b) Agreed payment does not represent value to the NHS, AND research or waiting for uncertainties to resolve is needed and the benefits of delaying the decision are greater than the costs and consequences.

- **Approval with research (AWR)/Approval with surveillance (AWS):**
  a) Agreed payment is sufficient to represent value to the NHS, AND research or waiting for uncertainties to resolve is needed and the benefits of not delaying the decision are greater than the costs and consequences;
  b) Agreed payment does not represent value to the NHS, AND research or waiting for uncertainties to resolve is needed and the benefits of not delaying the decision are greater than the costs and consequences, AND research/collection of surveillance information is only possible with approval.

### 7.5. PAYMENT LEVELS LINKED TO COVERAGE OPTION

Under an insurance-based delinked model, payment could be provided at the point of approval, but is more likely to be divided into a series of periodic payments. If payment is given at the time of approval, it may not be possible to determine the AM’s true effectiveness compared to the available alternatives, or to predict how the uncertainties are expected to resolve over time. Instead it may be better to structure the payments over time and potentially to attach them to specific milestones, e.g., when certain sources of uncertainty are resolved. The coverage options assume a degree of flexibility in the payment level over time such that there is potential for renegotiation after a period of time or when a specific milestone is reached. Therefore, payment negotiation is not only linked to the expected value of a new product but also to the value of resolving uncertainties or waiting until new information becomes available.
This is shown in Figure 11 which includes the population net health benefit of a strategy using a new AM as a declining function of the payment level. As shown in Figure 10, based on expected values without uncertainty, the NHS is expected to derive value from the new AM until the point where the expected population net health benefit with the new AM is equal to that with no access (i.e. current treatment) at VBP*. Figure 11 also shows the value of addressing uncertainties through research or waiting for additional information, this being the distance from the optimal management (the new AM or existing treatment) and the black dotted line. At VBP* there is considerable value in resolving uncertainties as this is the payment level at which the value of the new product is marginal. The lower the payment for the new AM, the lower expected loss in population net health due to uncertainty, and at VBP** the value of resolving uncertainties is effectively zero5. Under these circumstances, the range of payment between VBP** and VBP* can be used to guide decision making and negotiation: a payment VBP** should secure immediate approval based on existing information; but a payment of VBP* may only be suitable with a policy such as only in research (see Box 8). An appropriate payment between VBP** and VBP* will depend on factors such as the feasibility of research, the timing of further research or other information being revealed, the potential for irreversible impacts of the use of AMs on the patterns and consequences of resistance and the principles of the delinked insurance-based payment model.

5 The cost of uncertainty will only fall to zero when there is no uncertainty regarding whether the strategy is more effective than current practice, only in the magnitude of effect.
The payment level not only changes the population net health benefit of each treatment strategy, but it also changes the value of resolving uncertainties. For a strategy that is expected to represent value (i.e., has positive mean population net health benefit), a reduction in the payment level will generally tend to reduce the value of resolving uncertainties resulting in greater benefits of early access to the treatment without waiting to resolve uncertainty.

Importantly, the relationship between payment and uncertainty changes the population net health benefit of each coverage option. The framework by Claxton et al., (2012) may be used to establish the population net health benefit under each of the potential coverage options in order to show the trade-offs between the options [98]. Figure 11 illustrates the payment thresholds (boundaries) for access to a new AM under each coverage option. The boundaries depend on the magnitude of payment and/or the flexibility to renegotiate payment over time, as determined by the coverage choice.
The coverage option on the outer envelope of the curves offers the highest population net health benefit at specific payment levels. This is determined by the value of resolving uncertainties, the significance of irreversible costs, and the significance of irreversible consequences associated with a delay in decision. The payment thresholds (boundaries) between the coverage options represent a switch in optimal coverage option. This depends on the magnitude of payment and/or the flexibility to renegotiate payment over time, as determined by the coverage choice.
7.6. RECOMMENDATIONS

- A distinction should be made between uncertainty that can be resolved by investing in further research and uncertainty that will only resolve with the passage of time. This includes uncertainty arising from gaps in the evidence base, uncertainty in parameter values, uncertainty about when new information on resistance is likely to become available, and the likelihood that surveillance data and other forms of new information are collected.

- When the evidence supporting a new AM is considered weak or uncertain, consideration should be given to the value of conducting further evaluative research to resolve uncertainties. The study design(s) should be clearly described, together with an estimate of how much uncertainty is likely to be resolved, the time frame for research to complete and report, and any other factors that may impact on the value of evidence generation.

- When the evidence supporting a new AM is only likely to be revealed over time without further evaluative research, some assessment is needed on the timing at which the future uncertainties are likely to be revealed and how much uncertainty is expected to be resolved. A proxy may be based on past empirical evidence, historical trends, or elicited from experts.

- Irreversible sunk costs associated with payment, or the potential for irreversible consequences from introducing a new AM into the NHS, should be clearly stated and the impact of these on population health outcomes fully explored.

- The optimal timing for funding decisions should be carefully considered. If additional research is valuable to reduce the consequences of uncertainty, or if there is a need to wait until future uncertainties are revealed over time (e.g., a watchful waiting scenario), then a decision must be made on how to balance the value of delaying a decision about the use of a new AM (or restricting its use to specific settings or circumstances) until better information becomes available against the value of providing early access to the new product and avoiding potential irreversible consequences of not acting today. The optimal timing also depends on the contractual arrangements in place, e.g., whether there is a renegotiation strategy in place to revisit the evidence and decision at a later point in time.
• Given uncertainties, there may be a strong case for periodic reconsideration of payment for new AMs as additional evidence emerges.
• Consideration should be given to how surveillance data is used to monitor the use of AMs in the NHS.
8. IMPLICATIONS OF THE VALUE ASSESSMENT FRAMEWORK FOR NICE POLICY, PROCESS AND METHODS

8.1. INTRODUCTION

The methodological and evidential challenges in evaluating new AMs under a de-linked funding scheme outlined in this report have important implications for how NICE would approach appraisal of these products. It would seem reasonable for the starting point for NICE’s process and methods for new AMs to be the existing programme of technology appraisal guidance, which has explicit methods [4] and processes [102]. It should be noted that there have recently been a number of changes to the process of technology appraisal programme, apparently to increase its efficiency (e.g. fast track appraisal [103]). Under a series of headings below, possible extensions or variations to the technology appraisal process are considered. Where appropriate, we consider the extent to which the arrangements in place for other NICE programmes, such as those relating to clinical guidelines and diagnostics, may be appropriate for AMs.

8.2. TOPIC SELECTION

NICE has a well-established process for selecting those technologies it will include in its technology appraisal programme. Given that not all newly licenced pharmaceuticals are appraised, there is a focus on selecting priority technologies that fall within the remit of the programme. Prioritisation is based on criteria including the likelihood of generating significant health benefit across the NHS, impact on other government policies, impact on NHS resources, inappropriate variation in use of the technology and the likelihood of adding value by issuing NICE guidance [102].

Depending on the anticipated numbers of new AMs reaching the market over time, it may be appropriate for topic selection for new AMs to have two levels. The first would be whether the product is considered potentially appropriate for NHS funding de-linked from the volume of the product used. It is not clear whether this decision would be taken by NICE or by the DHSC, but it would presumably consider whether the product is likely to have most value to the NHS by being held in reserve in case of future changes in resistance to existing products. Other considerations might include whether there is expectation of further product launches for similar indications, and the manufacturer’s attitude to being part of the de-linked arrangements.
The second level of topic selection would be to set priorities for appraisal amongst those new AMs considered potentially appropriate for the de-linked funding scheme. The need for this second level would depend on the time and resourcing available for the programme and numbers of potential products. As discussed below, there are reasons why the assessment and appraisal of new AMs is likely to be markedly more resource intensive than for other pharmaceuticals.

It should be noted that decisions will be necessary regarding NHS funding for new AMs that are not considered appropriate for the de-linked funding programme. For many of these products, the analytical and evidential challenges of estimating their impacts on population health will remain significant. It is not clear whether such products would be considered as part of NICE’s standard technology appraisal, be included in a new programme focussed on AMs despite not being considered for de-linked funding or not be appraised by NICE at all.

8.3. SCOPING PROCESS

Scoping the appraisal of a technology is a crucial part of NICE’s existing process, and is likely to be even more important for new AMs. Scoping involves defining one or more relevant population(s) for the product, potential subgroups, all relevant comparators, health outcome measures and any other special considerations or issues. In determining these features of an appraisal, the documented scope becomes a key reference point for all aspects of the assessment and appraisal. Considerations relating to populations, subgroups and comparators have been covered in Section 3. These factors point to the process of scoping being appreciably more involved than for standard technology appraisal.

In part, this is because of many new AMs being expected to have quite general marketing authorisations and to be centred on relevant pathogens, providing limited signals regarding the clinical indications for a new product. It is feasible that estimates of the gains in health outcomes from a new product will be needed for several populations. Furthermore, identifying relevant comparators will need to involve a careful assessment of the range of ways the new product could be used now and in the future. This would include holding the product back for potential use in the long term in case of major changes in resistance to current products. As such, the demands of selecting the full range of options for these appraisals is likely to be closer
to those of NICE’s Diagnostics Assessment Programme where the comparisons are often between different strategies involving existing and new tests [104].

The information available for new AMs at the scoping stage is likely to be limited compared with existing technology appraisals. For many new branded pharmaceuticals, the regulatory trials provide a key source of evidence about efficacy, albeit generally against a limited subset of comparators. As discussed in Section 4, the extensive use of non-inferiority studies for new AMs will provide more limited evidence. For new AMs, determining the range of ways in which a new product could be used in the NHS, whilst allowing for variation in existing clinical practice, will need to draw on more clinical and epidemiological expertise at scoping than for existing appraisals. This element of the process would also benefit from growing systematic data collection in AM use and resistance patterns across the NHS (see Section 8.4). Overall, it should be anticipated that scoping will be a longer element of the process than is currently the case, drawing on more extensive inputs from outside of NICE and using wider sources of evidence than the regulatory trials.

8.4. Evidence and Modelling

The stage in the NICE process where evidence is assembled to support decision-making consistent with the defined scope is also likely to have to be quite different than for current technology appraisal. This process of technology assessment (as distinct from appraisal or decision making) involves identification and synthesis of evidence relating to the relevant diseases and interventions (including resistance rates with new and existing products, clinical effectiveness, impacts on quality of life, prognosis, resource use and costs). It also incorporates modelling to bring this evidence together to estimate appropriate metrics to guide decisions; namely, long-term survival, QALYs and costs, expressed in terms of long-term population net health impacts.

Sections 3 and 5 have explained the challenges of modelling the expected costs and benefits of new AMs over an appropriate time horizon and reflecting the full range of ways the new and existing products could be used. This reflects the fundamental lack of knowledge about how to develop reliable dynamic models for many of the infections that are likely to be the target of new products. This will potentially lead to marked uncertainty about resistance patterns with new and existing products. Despite the challenges, however, NHS decisions about NHS
resourcing of these products are unavoidable, whether or not they are part of a ‘delinked’ funding scheme.

This raises the question about how the assessment phase of a NICE programme in this area should be organised. Under existing arrangements, most new branded pharmaceuticals appraised by NICE are considered under its Single Technology Appraisal (STA) process. A key feature of STAs is that the evidence identification, synthesis and modelling is conducted entirely by the product’s manufacturer, albeit with review by academic Evidence Review Groups and using approaches set out in NICE methods guide. A second feature is that the period from a formal referral to the final appraisal determination is rapid, up to 34 weeks from the formal referral to NICE, in an attempt to publish NICE guidance as close to a product’s regulatory approval as possible.

Reliance only on the manufacturers to undertake the technology assessment of new AMs seems infeasible, at least in the short term. This is mainly because the expertise to develop the models of new products suitable to guide funding decisions in this field is very limited and likely to be largely concentrated in relatively few academic groups. A process similar to NICE’s Multiple Technology Appraisal (MTA) scheme, which has now largely disappeared from the Technology Appraisal Programme, or the current Diagnostic Assessment Programme seems more suitable. With these programmes, the evidence identification, synthesis and decision modelling are undertaken principally by academic groups. With MTAs, the manufacturer(s) are also able make submissions of evidence and models which are summarised and reviewed by the academic groups and fed into the appraisal phase. Any programme of NICE assessment of new AMs focussed around academic groups would need to consider whether the existing groups providing technology input into the NICE Technology Appraisal Programme currently have the requisite experience and skillsets to undertake this type of work for new AMs. It is likely that one or more specialist groups for this programme will need to be recruited or used alongside the existing evidence review groups.

Another reason why manufactures are unlikely to be the main suppliers of the technology assessment for AMs relates to the source of evidence. Under the existing Technology Assessment Programme, evidence gathering and modelling largely relies on information from the manufacturers’ regulatory trials, as well as secondary (i.e. published) sources of evidence
relating to other trials and data such as resource use and health-related quality of life. The use of ‘real world’ evidence based on data collected routinely in the NHS is seen as central to recent key policy developments such as the reformed Cancer Drug Fund [105] and Accelerated Access [106]. As yet, however, there are few examples of such data being used as key elements of NICE technology appraisal, and demonstrating the necessary accessibility, completeness and reliability.

For the assessment of new AMs, the use of NHS data will be of fundamental importance. In addition to existing linked datasets such as the Hospital Episodes Statistics, ONS mortality data and primary care datasets such as the Clinical Practice Research Database, there will be a key role for AM surveillance data (see Section 4.5). Of particular note is the funding by NIHR of two Health Protection Research Units in healthcare-associated infections and AM resistance at Imperial College London and Oxford University. The units are looking into how to improve AM surveillance and modelling by linking existing NHS datasets. In its response to the O’Neill Report on AM resistance, the government has emphasised current and future investment in surveillance [107].

A key element of NICE programmes has been to define research recommendations as part of guidance [108]. Increasingly, there has been a focus on linking guidance to additional research with a view to undertaking reviews of guidance in the light of additional data – the Cancer Drugs Fund is an obvious example [105]. As discussed in Section 7, in the context of a programme to appraise new AMs, the need to identify the details and timing of new information expected to emerge in the future, and to define and prioritise appropriate research in the light of key uncertainties, and to update guidance accordingly, will be crucial. A key consideration is who would be expected to undertake (and to fund) such research. It is likely that appropriately designed studies involving new and existing antibiotics in selected centres in the NHS would be an important type of research. This might be expected to provide firmer evidence on the effectiveness of new products and resistance patterns. These studies would also be more feasible in the context of routinely collected and linked NHS data. Designing feasible and relevant research studies in this area would necessitate the involvement of clinical, epidemiological and health system expertise in healthcare-associated infections and AM resistance.
8.5. METHODS

NICE sets out its preferred methods for technology appraisals in its methods guide [4]. A key feature of the guide is the use of a ‘reference case’, representing the methods of assessment for effectiveness and cost-effectiveness that NICE wishes to see as the primary analysis in manufacturer and any academic submissions. Many of the methods challenges identified in this report are at a level of detail beyond that described in NICE’s reference case, but would still need to be incorporated into assessment for the Institute in this area. There are, however, some areas of the methods guide that may need to be extended to deal with the complexities of assessing new AMs.

8.5.1. Expert elicitation methods

It is clear from Sections 4 and 5 that major uncertainties can be expected in modelling the population health impacts of new AMs. These can be categorised into two broad areas: uncertainty in estimating parameters in the model (e.g. resistance rates, effect sizes) given potentially limited, low quality or even non-existent data (parameter uncertainty); and uncertainty in knowledge about how evidence links to an underlying understanding of disease, treatment effects and resistance (structural uncertainty).

For both types of uncertainty there is likely to be a key role for relevant experts to guide those undertaking the technology assessment. As discussed in Section 5, this would include formal expert elicitation where a sample of experts’ quantitative judgements regarding uncertain quantities are sought. Although these methods are mentioned in NICE methods guide, their use is likely to be more extensive with AMs than is currently the case. This will be supported by ongoing methods research on elicitation in health technology assessment, funded by the NIHR/MRC Methodology Research Programme [109].

8.5.2. Incremental cost-effectiveness ratio and net health benefit

NICE’s preferred approach to quantifying the cost-effectiveness of a product is the ICER. This represents the incremental cost per additional QALY of an option compared to the next least effective and costly alternative. As explained in Section 3, these standard ‘decision rules’ will need to be adjusted for new AM’s, although the principles of cost-effectiveness analysis
remain. This is because the value of new AMs needs to be assessed at the population level given the scope for indirect effects through changes in resistance. As shown in Sections 3 and 7, it is likely to be more appropriate to make more use of an alternative measure of cost-effectiveness, expected population net health benefit.

8.5.3. Dealing with a product’s acquisition price

Standard NICE assessment initially takes a product’s list price as the basis of its NHS acquisition cost. In the context of a de-linked funding arrangement between the NHS and a manufacturer, however, no acquisition cost will be available at the point of assessment. Assessment would presumably, therefore, be undertaken assuming a zero acquisition cost and provide the appraisal committee with the estimates of the potential cost-effectiveness of the range of alternative strategies on that basis. The NICE Appraisal Committee would then determine the range of expected population net health benefit for the new AM at zero acquisition cost. As discussed in Sections 3 and 7, this would provide the DHSC with an indication of the maximum acquisition cost (however that is specified) consistent with the new product being cost-effective for each of the strategies in which the new AM is being evaluated. As discussed in Section 7, the payment levels would need to reflect both the expected (best estimate of) cost-effectiveness, as well as the cost of uncertainty associated with the decision.

8.5.4. Dealing with other considerations

The NICE methods guide indicates that a range of factors other than NHS costs and health effects in terms of QALYs are considered as part of decision-making, including the degree of certainty in the evidence, the innovative nature of the technology and cost savings outside the NHS [4]. The only additional consideration to be formally and quantitatively factored into cost-effectiveness analysis relates to the appraisal of life-extending interventions for individuals with very short life expectancy [110]. For products meeting explicit criteria, analysis involves placing an additional weight on their incremental benefits to indicate a higher ‘social value’ associated with the health benefits accruing to this group of patients. As part of the value-based pricing initiative, the DHSC and NICE considered methods to reflect formally the burden of illness and wider social benefits in economic analysis [111], but this was not implemented.
In appraising new AMs, there may be consideration for some additional factors to inform decision making. One in particular that has been raised, the idea of the ‘insurance value’ associated with new products in this area (see Section 3). Under current arrangements, with the exception of the ‘life extending treatment at the end of life’, these additional considerations are dealt with qualitatively. That is, they are reflected in decisions about guidance but not formally reflected quantitatively in the cost-effectiveness. In the context of AMs, it is not clear how this might work given presumed remit of NICE and DHSC. That is, that NICE would be responsible for indicating the impact on population health of a range of strategies involving the new and existing AMs based on available evidence and appropriate analysis; and DHSC/NHSE would have the remit of agreeing funding arrangements associated with the new AMs. The latter is the ultimate ‘decision’ being supported, so these other qualitative considerations will presumably need to be considered at this stage by the ultimate funders.

The alternative would be for any other factors to be incorporated quantitatively into the cost-effectiveness analysis. As mentioned in Section 3, this requires a number of explicit analytic steps. The first is clarity regarding the additional characteristics of diseases, interventions or patients that are considered relevant to the decision, and how these are to be measured. The second is to be able to assess a given product for a specific disease in terms of that or those characteristics. The third is to quantify how these characteristics are to be traded-off against health gain in terms of standard QALYs. For example, how would QALYs for a particular AM (with the relevant characteristics) be weighted compared with those accruing to other types of patients. Finally, this trade-off would need to be reflected in the measure of opportunity cost used to guide decisions. In other words, unless these characteristics are considered to be rare in terms of interventions, if some health improvement is valued more highly than others, this should also be reflected when assessing the health that could be generated when resources are devoted to a specific new investment rather than to NHS services more generally.

8.6. APPRAISAL

The appraisal stage of the NICE process involves its advisory committees using the evidence and analysis generated during the assessment phase to determine appropriate guidance for the NHS. There may be a need for some changes in how appraisal would be undertaken for new AMs compared to that in the current appraisal programme. As discussed in Section 8.5.3, the nature of the committee’s ‘decision’ will be different because, at this stage of the process, a
zero acquisition price will need to be assumed for the new AM. The committee’s role is likely
to be to present its view on the most credible estimates of benefit, and the magnitude of
uncertainty, associated with the range of strategies being compared. Specifically, this would
be credible estimates of the expected population net health benefit for each of the options being
compared at zero acquisition cost and the implied value-based payment levels. Also, the
committee would indicate its most credible estimates of the cost of uncertainty associated with
each strategy.

NICE appraisal committees have an important role in defining research recommendations
[108]. As discussed in Section 8.4, the uncertainty associated with decisions about the funding
of new AMs is likely to be considerably greater than for most standard pharmaceuticals going
through NICE technology appraisal. There will, therefore, be a need to define research
recommendations more specifically, with reference to routine data collection in the NHS as
well as appropriate study designs. It would also need to take a view about information other
than research which would be expected to come to light over time and which may influence
the value of new AMs.

To establish its guidance the committee is likely to have to engage with the assessment group
regarding decisions about the evidence and what to include in the modelling. Under current
arrangements, NICE appraisal committees have to form a view about the most suitable
estimates of particular parameters (e.g. effect size of an intervention or the risk of adverse
events). There has always been scope for the committee also to ask for additional scenarios to
be modelled to inform its deliberations. Indeed, there are examples of this being undertaken
within a committee session [112], but this is not generally the case, particularly under the STA
process.

There can be expected to be a need for considerably greater interaction between the committee
and the relevant assessment group regarding the details of the evidence, comparisons and
modelling in the context of AMs. This has a series of implications. The first is that this will
be best achieved if assessment is undertaken by academic groups given the need to rapid
response and close collaboration, further enforcing the point made in Section 8.4. Secondly,
the time available for this type of engagement can be expected to be much longer than for the
STA process. Thirdly, as for the scoping stage, there will be a need for considerable clinical,
epidemiological, data and health system expertise to facilitate this interaction between assessment and appraisal. Although this could feed in entirely in terms of the membership of the assessment group, there would seem to be a strong case to use specialist committee members, in addition to standing committee members. This is the approach used by the Diagnostic Assessment Programme [104], although specialists should not be just clinical, but also include modellers, epidemiologists and data experts.

Taken together, NICE’s scoping, assessment and appraisal phases are likely to be more intensive than is currently the case for the branded drugs that the Institute currently considers. The cost implications of this will heavily depend on how many new AMs will be launched and prioritised for appraisal by NICE each year. In general, there seems to be a strong case to modulate the intensity and duration of NICE appraisal in accordance with expected impact in population health benefits and overall cost [113]. In which case, either the NICE prioritisation system focuses on AMs, the expected impact of which is suitable for more intensive appraisal, or there is room for more or less intensity in the process depending on the characteristics of the new AM being appraised.
8.7. **Recommendations**

- Topic selection for NICE appraisal for new AMs is likely to have two levels: (i) to assess whether the product is considered potentially appropriate for de-linked NHS funding; and (ii) to set priorities for appraisal amongst those new AMs considered potentially appropriate for the de-linked scheme.

- Overall, it should be anticipated that scoping will be a longer element of the process than is currently the case, drawing on more extensive inputs from outside of NICE and using wider sources of evidence than products’ regulatory trials.

- A process similar to NICE’s Multiple Technology Appraisal (MTA) or Diagnostic Assessment Programme seems more suitable to the assessment stage of new AMs than the Single Technology Appraisal (STA) arrangements. This would involve academic groups leading the evidence synthesis and modelling.

- Academic assessment would need to consider whether the existing assessment groups have the requisite experience and skillsets to undertake this type of work for new AMs. It is likely that one or more specialist groups for this programme will need to be recruited or used alongside the assessment groups.

- For the assessment of new AMs, the use of NHS data will be of fundamental importance. In additional to existing linked datasets there will be a key role for AM surveillance data.

- The need to define and prioritise appropriate research in the light of key uncertainties and to update guidance accordingly, will be crucial. Designing feasible and relevant research studies in this area would necessitate the involvement of clinical, epidemiological and health system expertise in healthcare-associated infections and AM resistance.

- Some areas of the methods guide may need to be extended to deal with the complexities of assessing new AMs. These include the more extensive and systematic use of expert elicitation methods; greater use of population net health benefit as a measure of value or cost-effectiveness; presenting value assuming a zero acquisition cost providing an indication of the maximum acquisition cost consistent with the product being cost-effective to the NHS; and the levels of payment would need to reflect both the expected cost-effectiveness and the cost of uncertainty associated with the decision.
There may be a need for some changes in how appraisal would be undertaken compared to that in the current appraisal programme. The committee’s role is likely to be to present its view on the most credible estimates of value, and the magnitude of associated uncertainties. There will also be a need to define specific research recommendations, with reference to routine data collection in the NHS as well as appropriate study designs.

There will be a need for greater interaction between the committee and the relevant assessment group regarding the details of the evidence, comparisons and modelling in the context of AMs. The time available for this type of engagement can be expected to be much longer than for the STA process. Specialist committee members would be needed including clinical and data experts, modellers and epidemiologists.

The intensity and duration of NICE appraisal is likely to be greater for new AMs, which can be justified by their selection for NICE review in terms of their expected impact on health benefits and costs.
9. **Summary of Recommendations**

Table 12 summarises the full list of recommendations made in each section.

**Table 12: Full list of recommendations**

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Recommendations</th>
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<tr>
<td>Decision problem (Section 3)</td>
<td>The indication(s) for the use of a new AM should be well-defined and clearly stated. A scoping process similar to that used by the NICE Technology Appraisal programme may be used to refine the indications for use. Where pathogen-specific indication(s) have been permitted by the European Medicines Agency, the selected pathogens should be clearly stated, including those that demonstrate multidrug resistance to specific agents. To ensure the adherence of AM use in the specified indication(s) only, additional stewardship and policing is likely to be required to reduce the emergence of resistance to the new AM.</td>
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<td>The population for whom a new AM is being considered should be stated as clearly as possible. Where the benefits of treatment are expected to extend beyond the individual treated to the wider population, this should be clearly described. Different settings (e.g., community or hospital) affect the flow of infections and spread of resistance in the population; therefore, the setting should also be well-defined. Any potential subgroups of the population, or specific settings, where AM use might be expected to differ from the overall population and in whom treatment protocols may be expected to differ require consideration.</td>
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<td>The scoping process should help to define the range of alternative comparator strategies about usage of a new AM and relevant existing AMs. When alternative AMs are available, the new AM is expected to be used in addition to existing AMs. The relevant comparators are likely to include a range of treatment protocols that reflect heterogeneous prescribing patterns across different settings; these include, rotation of available AMs, mixing protocols and combination therapies. Identifying all potentially relevant comparators requires consideration of the precise setting, population, indications and relevant subgroups for use. Treatment protocols that include off-label use of AMs should be considered if they are deemed relevant and expected to affect resistance patterns over time.</td>
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<td>Following the existing NICE position, the potential impact on health effects and costs that would be expected from the introduction of a new AM should be considered from the perspective of NHS and personal social services. The direct health effects and costs for the treated infection should be considered. Where the benefits and costs are expected to extend beyond the individual treated to the wider population, the indirect health effects and costs of reduced onward transmission of infection should be given consideration. Indirect effects to individuals of enabling other procedures to take place, which were not possible for some patients without the introduction of the new AM, may also be considered. The methods used to identify and define the health effects and costs associated with both the new AM and the relevant comparators should be clearly described. Other suggested attributes of value can be reflected through these health effects or by differential weighting some effects.</td>
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<td>The approach used to model the expected rate of growth in resistance and associated outcomes for a new AM and its relevant comparators should be clearly stated and justified. Models should predict the prevalence of infections and susceptible and resistant strains of pathogens in the population over time for each comparative strategy over an appropriate time horizon. The model time horizon should be sufficient to capture all important differences in health effects and costs between the...</td>
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comparative strategies; an appropriate discount rate should be used to discount costs and effects to present value. Sensitivity analysis on the model time horizon and discount rate should be conducted.

Following existing NICE guidance, the economic evaluation should take the form of a cost-effectiveness analysis, with quality-adjusted life years (QALYs) used as the main outcome measure. The expected population net health benefit of each strategy should be compared to the available alternatives. This should allow the potentially best strategy to be identified for each indication based on the one that maximises the expected population net health benefit compared to existing approaches to treatment, initially assuming zero acquisition cost. Where there are multiple indications, results should be aggregated across all relevant indications to determine the total expected value. In negotiating a payment for access to a new AM, the NHS will obtain value until the health opportunity cost of the value-based payment just equals the additional population net health benefit of the new AM compared to current care.

Following existing NICE guidance, the economic evaluation should take the form of a cost-effectiveness analysis, with quality-adjusted life years (QALYs) used as the main outcome measure. The expected population net health benefit of each strategy should be compared to the available alternatives. This should allow the potentially best strategy to be identified for each indication based on the one that maximises the expected population net health benefit compared to existing approaches to treatment, initially assuming zero acquisition cost. Where there are multiple indications, results should be aggregated across all relevant indications to determine the total expected value. In negotiating a payment for access to a new AM, the NHS will obtain value until the health opportunity cost of the value-based payment just equals the additional population net health benefit of the new AM compared to current care.

Estimates of the clinical effect of a new AM and its relevant comparator(s) should be informed by RCTs when available. For most bacterial infections, efficacy and safety is demonstrated through non-inferiority trials in patients infected with pathogens expected to be susceptible to both the new AM and the comparator(s). The implications of the choice of non-inferiority margin for NICE appraisal deserves particular attention and should be tailored to the indication. The test-of-cure visit after completion of treatment should categorise clinical outcomes as cure of infection (complete resolution of signs and symptoms), failure or indeterminate for each indication of use.

Where the comparator(s) of the trials are not matching best available therapy in the population and setting of interest, this should be clearly stated and justified. In the absence of direct head-to-head RCTs comparing the relevant comparators under evaluation, network meta-analysis should be conducted if appropriate.

Recommendations for the design of non-inferiority studies and identification of non-inferiority margins should follow established guidelines. Given the constraints associated with the evaluation of AMs, the design of RCTs to inform funding decisions represents an important area for further evaluative research.

Estimates of the microbiological response (e.g., rates of bacterial eradication) of the new AM and comparator(s) should be reported to establish the susceptibility of the agents to pathogen-specific indication(s). Microbiological outcomes of cultures collected during clinical studies should be reported for each comparator and pathogen when available. The microbiological evaluation of a new AM should aim to identify the precise mechanism of action and the activity against pathogens that are resistant to other comparator drugs.

The correlation between microbiological outcomes and clinical response outcomes should be explored if appropriate. For MDR pathogens, PK/PD analyses and microbiology response data may provide important supportive information of the likely efficacy where the new AM has shown to have efficacy against particular pathogens that express resistance at different sites. When the use of final clinical endpoints is not possible and intermediate outcomes are used to infer clinical response, evidence to support the intermediate-to-final outcome relationship should be provided with an explanation of how the relationship is quantified. In the absence of a relationship for new AMs, consideration should be given to generalising the relationship observed for existing AMs if appropriate.

The use of microbiology surveillance data should be used as a source of information on susceptibility and resistance to pathogens. A number of ongoing global antimicrobial surveillance programs collect in-vitro susceptibility data for defined
bacterial groups and indications. Microbiology surveillance data should be collected at a local level given the variation in resistance patterns. This information is likely to be the most reliable information on the emergence of, or change in, the prevalence of resistance to a new AM and its comparators over time.

The coordination and collection of surveillance data from networks of centres recruiting patients with infections across geographies, patient groups, infection sites and pathogens should be established further, with a need for consistent criteria for inclusions of bacterial pathogens by the collaborating centres. Large well-established surveillance networks should help detect trends in the emergence and patterns of resistance over time.

The first step in the development of a model should be an understanding of the mechanisms of resistance and the epidemiological data available for a new AM and its comparators so that important determinants of transmission dynamics of the infectious disease epidemic and resistance to the AMs are reflected. The appropriate structure of the model should reflect the source and mechanisms of resistance and the nature of any competition between susceptible and resistant strains. Detailed scoping meetings or formalised model conceptualisation processes should support appropriate model scope and structure. The model structure, methods, assumptions and parameters should be clearly described, justified, and be reproducible. Uncertainty and sensitivity analysis on determinants of key outcomes is critical. Models may be used to support identification of evidence gaps and identify key areas for further research.

There should be careful consideration and interpretation of surveillance data to assess the quality of the existing evidence base on disease burden and resistance to AMs. Where there are limited or no data available for a new AM, it may be necessary to examine the data available for other analogous AMs seen in the past that exhibit similar mechanisms of resistance to infer likely changes in the emergence of resistance over time until additional information on the new AM becomes available.

Where there is a lack of direct data or accurate parameter estimation, model calibration approaches should be considered. There is a strong requirement for validation of model outcomes against historical data, including reproducing observed infection incidence, trends or natural history. Statistical and mechanistic modelling approaches should be able to provide credible predictions of historical data on infection and resistance rates. If this cannot be shown to be the case, there should be a detailed consideration of the potential direction of bias informed by an understanding of the determinants of key outcomes.

The elicitation of scientific and technical judgements from experts can be considered as a valuable addition to other forms of evidence to support effects on key parameters. Therefore, consideration should be given to the expert review of available data, as well as formal expert elicitation techniques where there are limited data or alternative viewpoints.

Given the difficulties associated with developing credible mechanistic dynamic transmission models and concerns relating to the simplicity of statistical models for the prediction of resistance to different AM prescribing strategies, consideration should be given to the development of both statistical and mechanistic models. Differences in outcomes from these two modelling approaches should be clearly described, explained and justified.

Models should be iteratively updated and re-evaluated as new data or considerations arise.

Priorities for further research include exploring the practicalities of implementing policy models with the data currently available and exploring the possibility of...
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<th>Implications of uncertainty (Section 7)</th>
<th>A distinction should be made between uncertainty that can be resolved by investing in further research and uncertainty that will only resolve with the passage of time. This includes uncertainty arising from gaps in the evidence base, uncertainty in parameter values, uncertainty about when new information on resistance is likely to become available, and the likelihood that surveillance data and other forms of new information are collected.</th>
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<td>When the evidence supporting a new AM is considered weak or uncertain, consideration should be given to the value of conducting further evaluative research to resolve uncertainties. The study design(s) should be clearly described, together with an estimate of how much uncertainty is likely to be resolved, the time frame for research to complete and report, and any other factors that may impact on the value of evidence generation.</td>
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<td>When the evidence supporting a new AM is only likely to be revealed over time without further evaluative research, some assessment is needed on the timing at which the future uncertainties are likely to be revealed and how much uncertainty is expected to be resolved. A proxy may be based on past empirical evidence, historical trends, or elicited from experts.</td>
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<td>Irreversible sunk costs associated with payment, or the potential for irreversible consequences from introducing a new AM into the NHS should be clearly stated and the impact of these on population health outcomes fully explored.</td>
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<td>The optimal timing for funding decisions should be carefully considered. If additional research is valuable to reduce the consequences of uncertainty, or if there is a need to wait until future uncertainties are revealed over time (e.g., a watchful waiting scenario), then a decision must be made on how to balance the value of delaying a decision about the use of a new AM (or restricting its use to specific settings or circumstances) until better information becomes available against the value of providing early access to the new product and avoiding potential irreversible consequences of not acting today. The optimal timing also depends on the contractual arrangements in place, e.g., whether there is a renegotiation strategy in place to revisit the evidence and decision at a later point in time.</td>
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<td>Given uncertainties, there may be a strong case for periodic reconsideration of payment for new AMs as additional evidence emerges. Consideration should be given to how surveillance data is used to monitor the use of AMs in the NHS.</td>
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<th>Implications for NICE policy, process and methods (Section 8)</th>
<th>Topic selection for NICE appraisal for new AMs is likely to have two levels: (i) to assess whether the product is considered potentially appropriate for de-linked NHS funding; and (ii) to set priorities for appraisal amongst those new AMs considered potentially appropriate for the de-linked scheme.</th>
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<td>Overall, it should be anticipated that scoping will be a longer element of the process than is currently the case, drawing on more extensive inputs from outside of NICE and using wider sources of evidence than products’ regulatory trials.</td>
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<td>A process similar to NICE’s Multiple Technology Appraisal (MTA) or Diagnostic Assessment Programme seems more suitable to the assessment stage of new AMs than the Single Technology Appraisal (STA) arrangements. This would involve academic groups leading the evidence synthesis and modelling.</td>
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<td>Academic assessment would need to consider whether the existing assessment groups have the requisite experience and skillsets to undertake this type of work for new AMs. It is likely that one or more specialist groups for this programme will need to be recruited or used alongside the assessment groups.</td>
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For the assessment of new AMs, the use of NHS data will be of fundamental importance. In addition to existing linked datasets there will be a key role for AM surveillance data.

The need to define and prioritise appropriate research in the light of key uncertainties and to update guidance accordingly, will be crucial. Designing feasible and relevant research studies in this area would necessitate the involvement of clinical, epidemiological and health system expertise in healthcare-associated infections and AM resistance.

Some areas of the methods guide may need to be extended to deal with the complexities of assessing new AMs. These include the more extensive and systematic use of expert elicitation methods; greater use of population net health benefit as a measure of value or cost-effectiveness; presenting value assuming a zero acquisition cost providing an indication of the maximum acquisition cost consistent with the product being cost-effective to the NHS; and the levels of payment would need to reflect both the expected cost-effectiveness and the cost of uncertainty associated with the decision.

There may be a need for some changes in how appraisal would be undertaken compared to that in the current appraisal programme. The committee’s role is likely to be to present its view on the most credible estimates of value, and the magnitude of associated uncertainties. There will also be a need to define specific research recommendations, with reference to routine data collection in the NHS as well as appropriate study designs.

There will be a need for greater interaction between the committee and the relevant assessment group regarding the details of the evidence, comparisons and modelling in the context of AMs. The time available for this type of engagement can be expected to be much longer than for the STA process. Specialist committee members would be needed including clinical and data experts, modellers and epidemiologists.

The intensity and duration of NICE appraisal is likely to be greater for new AMs, which can be justified by their selection for NICE review in terms of their expected impact on health benefits and costs.
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A.1 APPENDIX A: LITERATURE REVIEW OF POLICY MODELS EVALUATING ALTERNATIVE TREATMENT PROTOCOLS

A systematic literature review of policy models evaluating the effectiveness of at least two alternative treatment protocols for the use of AMs was conducted to identify common model parameters, issues and challenges related to the sources of data required to parameterise models.

Search strategy

A PubMed database search was carried out on 23rd August 2017 to identify existing models on the effect of different antibiotic treatment pathways. The approach involved updating and adapting an existing PubMed search strategy reported in the review by Spicknall et al. (2013) [50]. The terms used were “(determinist* or stochast* or compartment* or mathematic* or simulat*) and model* and resistan*” and “(antibiotic* or antimicrob* or anti-microb* or antibact* or anti-bacter*)” in all fields. The search was further limited to “human” studies published in the English language. Exact searches are provided in Table A1. The search was conducted for the period January 2011 until 2017, where the small overlap with the search period used for Spicknall et al. (2013)’s review aimed at validating the present extended search by cross-checking the identification of key studies present in this previous review.

Table A1: Search terms for systematic search conducted in Pubmed (1946 to present)

<table>
<thead>
<tr>
<th>#</th>
<th>Searches</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>Search (determinist* OR stochast* OR compartment* OR mathematic* OR simulat*)</td>
</tr>
<tr>
<td>#2</td>
<td>Search model*</td>
</tr>
<tr>
<td>#3</td>
<td>Search resistan*</td>
</tr>
<tr>
<td>#4</td>
<td>Search (((antibiotic*) OR (antimicrob* or anti-microb*)) OR (antibact* or anti-bacter*))</td>
</tr>
<tr>
<td>#5</td>
<td>Search (((((determinist* OR stochast* OR compartment* OR mathematic* OR simulat*))) AND model*) AND resistan*) AND (((antibiotic*) OR (antimicrob* or anti-microb*)) OR (antibact* or anti-bacter*)))</td>
</tr>
</tbody>
</table>
A total of 437 records were retrieved from this search, and were combined with 66 references published pre-2011 identified in Spicknall et al (2013) [50]. Papers’ relevance to the research question was evaluated based on the PICOs criteria (Population; Intervention; Comparison; Outcome) presented in Table A2.

**Table A2: PICOs inclusion search terms**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Patients with or at risk of developing a bacterial infection in a high income setting (exclude studies in low- or middle-income countries).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions</td>
<td>Studies should compare more than one policy option, and the policy options should differ in some way in their use of antibacterials.</td>
</tr>
<tr>
<td>Comparator</td>
<td>Any.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Studies should use a modelling approach that aims to quantify effects on a population (rather than within an individual) and reflects interactions between individuals, any modelling approach is permitted. Studies should reflect infection rates and resistance rates over time.</td>
</tr>
</tbody>
</table>
Out of the combined 503 records, 444 were excluded based on title and abstract and a total of 59 papers were reviewed in full. Of these 59 papers, 36 were excluded, where the main reason for exclusion was that the model developed did not aim to support the evaluation of a policy. Twenty-three papers were deemed relevant to the research question: six from Spicknall et al (2013)’s review [50] and 17 came from the extended search. A succinct description of these 17 additional papers is provided in Table A3.
<table>
<thead>
<tr>
<th>Paper</th>
<th>Type (policy or conceptual model structure)</th>
<th>Decision problem / patient population</th>
<th>Comparators*</th>
<th>Outcomes</th>
<th>Time horizon</th>
</tr>
</thead>
</table>
| Campbell et al. 2014 [114]    | Conceptual, compartmental (adapted the model of Bergstrom 2004) | Closed hospital system in which patients are treated with AMs for a nosocomial infection                | - No treatment  
- Single therapy A or B  
- Mixing with 50:50 receiving A and B  
- Cycling where all patients receive a single drug for a certain time period, after each period all patients receive the alternative drug  
- Cocktail where all patients receive both drugs A and B simultaneously, but each at a reduced dosage | Trade-off between resistance to drug A, drug B, and AB (both) under the different intervention strategies. The model seeks conditions that maximise the frequency of uninfected patients. Results are presented in terms of trade-off strength to achieve an equilibrium in number of uninfected individuals for the different intervention strategies. | Not clear |
| Chan et al. 2012 [70]         | Policy/ Conceptual, compartmental            | General population at risk of Gonorrhoea in Canada and US.                                           | Tx of low-risk, Tx of med-risk, Tx of high-risk, Tx of 1/3 in each risk group.  
- Single therapy A  
- Random allocation of 2 agents: 50% therapy A, 50% therapy B  
- Combination therapy (A+B)  
- Single therapy A if resistance <5% infections, B if resistance >5% infections  
- Differential treatment strategies for different risk groups based on population resistance levels e.g. 20% threshold of resistance  
- Scenario of hypothetical point-of-care testing for presence of resistance to A or B resulting in accurate targeted therapy | Prevalence of gonorrhoea infection over time                                                                                                                                  | 50+ years |
<p>| Doan et al. 2016 [80]         | Conceptual, compartmental                   | Describing the transmission dynamics of <em>A. baumannii</em> in ICU (hypothetical 100-bed ICU). Incorporates the role of AM exposure and free- | In terms of AM use: (i) reduced AM prescribing rate; (ii) reduced AM treatment duration in patients infected with <em>A. baumannii</em>. Range of other interventions considered but not related to AM use e.g., improved compliance with hand hygiene, improved environment cleaning efficacy, isolation of infected patients. | Differentiates between patients colonised and infected with <em>A. baumannii</em>. Prevalence of colonized patients with and without AM exposure (AM exposure defined as receiving any AM or having received in the last 30 days). Note environment-patient transmission is | 1 year       |</p>
<table>
<thead>
<tr>
<th>Paper</th>
<th>Type (policy or conceptual model structure)</th>
<th>Decision problem / patient population</th>
<th>Comparators*</th>
<th>Outcomes</th>
<th>Time horizon</th>
</tr>
</thead>
</table>
| Hurford et al. 2012 [67] | Policy/Conceptual, compartmental            | Individuals at risk of colonisation and infection of *P. aeruginosa* in ICU in Canada (Mount Sinai Hospital) | -Before and after implementing an antimicrobial stewardship program with three main aims:  
1. Alter the fraction of uninfected patients that are prescribed antimicrobials;  
2. Shorten the duration of antimicrobial treatment;  
3. Use alternative types of antimicrobials – change in the probability of prescribing ceftazidime, ciprofloxacin, and meropenem to uninfected patients. | Number of patients colonized with *P. aeruginosa* and the prevalence of *P. aeruginosa* resistance (in first isolates) after implementation of antimicrobial stewardship program (collaborative daily review of all patients in ICU to advise on AM use based on efficacy, safety, targeting known pathogens with narrow spectrum AMs rather than broad spectrum, reducing costs and reducing treatment duration from 11-12 days to 8 days) | 6 years       |
<p>| Kardas-Sloma et al. 2011 [115] | Conceptual, agent-based, individual, spatial model | Patients and HCW at risk of community-associated MRSA (CA-MRSA) in a hypothetical ICU or general ward (community dynamics not included) | Examines AM prescription patterns. Consists of different hypothetical usage frequencies for 4 groups of AMs used for <em>S. aureus</em> strains. The explored values ranged from 5% to 80%, leading to 252 hypothetical AM prescription patterns. Values were compared to baseline scenario based on the frequency of use in French hospitals. | Prevalence of CA-MRSA among all <em>S. aureus</em> patient carriers (examines the spread of CA-MRSA among hospitalised patients using an agent-based individual level model) | 30 days      |
| Kardas-Sloma et al. 2013 [116] | Conceptual, 2 modelling parts: (i) agent-based, individual, spatial model for hospital setting (same as Kardas-Sloma 2011) | Individuals at risk of MRSA in a hypothetical ICU and in the community. Model was calibrated to reproduce French | Similar to Kardas-Sloma 2011 – examines different hypothetical usage frequencies for 4 groups of ABs used for <em>S. aureus</em> strains. 56 AM prescription patterns considered. | Prevalence of MRSA in ICU and community setting. Outcomes compared to data from the European Antimicrobial Resistance Surveillance System (EARSS) for MRSA frequency in France between the years 2002-2003. | 1 year       |</p>
<table>
<thead>
<tr>
<th>Paper</th>
<th>Type (policy or conceptual model structure)</th>
<th>Decision problem / patient population</th>
<th>Comparators*</th>
<th>Outcomes</th>
<th>Time horizon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sloma 2011; (ii) compartmental model for transmission in community.</td>
<td>data in both hospital and community setting</td>
<td>Comparator: Mixing of AMs (empirical treatment) - two broad-spectrum drugs A and B considered. Intervention: Informed Switching Strategies (ISS) based on the information from microbiological tests (i.e. test and treat) – switching to appropriate narrow spectrum AB. Information on resistance frequencies is used to inform ISS.</td>
<td>Prevalence of resistant mutations in hospital ward and the number of inappropriately treated patients</td>
<td>Not clear</td>
<td></td>
</tr>
<tr>
<td>Obolski et al. 2015 [53]</td>
<td>Conceptual, compartmental</td>
<td>Hospital unit but allowing for both-ways interaction with the community with regards to spread of resistance (not for transmission of infection). Focus on resistance modelling under different treatment strategies, i.e. no focus on a particular disease or pathogen. Use of data from a medical centre in Israel to inform frequencies of resistance to common AB in incoming hospital patients</td>
<td>Two different types of treatment strategy: First empirical strategy (i) $\text{mix}_2 = \text{mixing two common AM (AM}_i\text{ and AM}_j\text{)}$ with equal probability (ii) $\text{mix}_3 = \text{mixing AM}_i\text{ and AM}_j\text{ with a third restricted (last-resort with little resistance in pop) drug AM}_k\text{ - with equal probability between all 3 drugs}$ If empirical treatment failed, once resistance tests results are available, =&gt; if resistant to AM$i$, give AM$j$ with 100% probability under mix 2 or give AM$j$ or AM$k$ with 50% probability each under mix 3 (and conversely if resistant to AM$j$) =&gt; Only if resistant to both $i$ and $j$ give AM$k$ under mix 2</td>
<td>-Mean frequency of incorrectly treated patients -Frequency of double resistant infections -Mean emergence rate of triple resistance</td>
<td>20 -100 years</td>
</tr>
<tr>
<td>Paper</td>
<td>Type (policy or conceptual model structure)</td>
<td>Decision problem / patient population</td>
<td>Comparators*</td>
<td>Outcomes</td>
<td>Time horizon</td>
</tr>
<tr>
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<td>--------------------------------------------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Obolski et al. 2012 [49]</td>
<td>Conceptual, compartmental</td>
<td>Hospital unit. No focus on any pathogen nor disease but on strategy to administrate AB</td>
<td>Three treatment strategies using 2 AM:</td>
<td>Emergence of double resistance</td>
<td>600 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(i) Mixing: each patient receives a randomly selected AB (within the range of two AM considered here)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(ii) Cycling: All patients are treated with same AM at a given time t, with periodical switch of AM given over time</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(iii) Combining: administration of both AM to each patient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelat et al. 2016 [65]</td>
<td>Policy, compartmental with two sets of agents (patients and health-care workers)</td>
<td>Individuals at risk of colonisation with ESBL-producing enterobacteriaceae in an ICU in France</td>
<td>- Base case (56% patients receiving AMs at admission, AMs used for 8 days in uncolonised patients and 18 days in colonised patients)</td>
<td>Proportion of patients with colonisation in first 90 days Duration of persistence of colonisation within ward Probabilistic outcomes: proportion simulations with colonisation in ward for &gt;90 days, proportion of simulations without any colonisation</td>
<td>2.7 years</td>
</tr>
<tr>
<td>Saddler et al. 2013 [117]</td>
<td>Conceptual, compartmental</td>
<td>Broadly based on gonorrhoea dynamics (no country stated).</td>
<td>- Rate of detection and treatment (f) and proportion of detected cases tested for resistance (p) (who receive second-line treatment) varied in different combinations with f taking values 0, 0.6, 1 and p taking values 0.02, 0.2, 0.8.</td>
<td>Distribution of individuals across health states (susceptible, untreated (separated by each strain: S, R, R with compensated mutation mutation) treated (also separated by strain) and some aggregated groups of health states (proportion infected, proportion infected resistant). Basic reproductive value by strain Reaching specific scenarios: disease eradication, endemic S strain, endemic R strain.</td>
<td>150 years</td>
</tr>
<tr>
<td>Talaminos et al. 2016 [54]</td>
<td>Policy, compartmental</td>
<td>Individuals at risk of ESBL-producing and non-ESBL producing ST131 E coli colonisation or infection in the community, hospital</td>
<td>- Base case of 5% exposure to fluoroquinolones and cephalosporin in colonised individuals - No exposure to fluoroquinolones and cephalosporin in colonised individuals</td>
<td>Number of individuals infected with ESBL-producing E coli and with non-ESBL-producing E coli</td>
<td>1 year</td>
</tr>
<tr>
<td>Paper</td>
<td>Type (policy or conceptual model structure)</td>
<td>Decision problem / patient population</td>
<td>Comparators*</td>
<td>Outcomes</td>
<td>Time horizon</td>
</tr>
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<td>--------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Trecker et al. 2015 [118]</td>
<td>Policy, compartmental</td>
<td>General population at risk of Gonorrhoea in Canada and US.</td>
<td>- No tx</td>
<td>Gonorrhoea prevalence.</td>
<td>50 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Tx of low-risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Tx of med-risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Tx of high-risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Tx of 1/3rd of patients in each risk group.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wares et al. 2016 [119]</td>
<td>Policy/ conceptual, agent-based simulation</td>
<td>Outpatients receiving chronic hemodialysis (no country stated)</td>
<td>- AM usage</td>
<td>Colonised patients, contaminated chairs</td>
<td>2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- AM duration (implemented as sensitivity analyses)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xiridou et al. 2015 [68]</td>
<td>Policy, compartmental</td>
<td>Men who have sex with men in the Netherlands</td>
<td>- Single therapy A</td>
<td>Gonorrhoea prevalence, % strains resistant to different AMs.</td>
<td>40 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Single therapy A with increased proportion of pts. treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Combination therapy (A+B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Combination therapy (A+B) with increased proportion of pts. treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Single therapy A if resistance &lt;5% infections, B if resistance &gt;5% infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yahdi et al. 2012 [120]</td>
<td>Policy/ compartmental</td>
<td>ICU pts. at risk of VRE (no country stated)</td>
<td>- Current practice: partial implementation of preventive care in colonised individuals and AMs in infected individuals.</td>
<td>Distribution of individuals across health states (susceptible, colonised with prev care, colonised no prev care, infection - tx, infection – no tx).</td>
<td>Not clear.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- All colonised patients receive preventive care and all infected patients receive AMs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- No colonised patients receive preventive care and no infected patients receive AMs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Only comparators meeting inclusion criteria (i.e. varying AM usage or use of diagnostics) or the “baseline comparator” are recorded here. Note that in many cases, comparators were modelled as scenarios or sensitivity analyses rather than being explicitly defined as alternative comparators/policies.

Abbreviations: VRE, vancomycin-resistant enterococci; ESBL, extended-spectrum beta-lactamase-producing.
B.1 APPENDIX B: CASE STUDY MODEL STRUCTURE AND EQUATIONS

Structure of the compartment model

The complete structure of the dynamic transmission model is represented in Figure B1. The model distinguishes between uncolonised (X), colonised (C) and infected (I) individuals. Colonised and infected individuals may host a strain that is either (i) susceptible to both available antimicrobials (CS or IS, respectively); (ii) resistant to either drug 1 or 2 (CR1, CR2, IR1 or IR2 respectively); or (iii) resistant to both available antimicrobials (CR12, IR12 respectively). Permitted transitions are indicated by arrows. Individuals may acquire a resistant infection via direct infection (transitions from X to IRi with i = 1, 2 or 12) or as a result of antimicrobial treatment (transitions from CS to IRj or from CRi to IR12 with i= 1, 2). Following successful treatment, i.e. symptom clearance, the transitions of infected patients depend on whether the bacterium was eradicated or not, and the cause of eradication failure. If symptoms are cleared and the bacterium is fully eradicated, infected individuals transit back to X. Failed eradication due to resistance acquisition leads to transitions from IS to CRi or from IRi to CR12 with i= 1, 2, whereas failed eradication due to causes other than resistance leads to transitions from IS to CS or from IRi to CRi with i = 1, 2, 12.

In order to model the two lines of treatment, it was necessary to monitor the cause of treatment failure in each line. This was achieved by further separating the infected compartments according to history of treatment failure. This distinction was implemented using additional compartments denoted I^k_i and I^k_F, where i=1,2 denotes each AM treatment option, k denotes strain phenotypes, f denotes first-line failure and F denotes failure of both lines or that no further treatment is provided. The model is, therefore, structured around a total of one uncolonised compartment, four colonised compartments and 15 infected compartments.
Figure B1: Structure of compartment model
**Ordinary differential equations governing the dynamic model**

All parameters are defined in Tables 4-6 of Section 6, reproduced here for convenience.

**Duplicate Table 4 Section 6: Parameters relating to the transmission dynamics of A. baumannii in an example ICU setting**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Mean (SE)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Number of beds in ICU</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>λ</td>
<td>Admission rate per bed</td>
<td>Based on rate of discharge and deaths</td>
<td></td>
</tr>
<tr>
<td>mc</td>
<td>Fraction of admitted patients colonized</td>
<td>0.053 (0.005)</td>
<td>[79]</td>
</tr>
<tr>
<td>mcr</td>
<td>Fraction of admitted colonized who are resistant to AM1 (tigecycline)</td>
<td>0.107 (0.0109)</td>
<td>[87]</td>
</tr>
<tr>
<td>γ\text{uf}</td>
<td>Daily discharge rate of uninfected individuals</td>
<td>0.083 (0.018)</td>
<td>[88]</td>
</tr>
<tr>
<td>γ\text{l}</td>
<td>Daily discharge rate of infected patients</td>
<td>0.04 (0.009)</td>
<td>[88]</td>
</tr>
<tr>
<td>ω</td>
<td>Daily death rate of infected patients</td>
<td>0.009 (0.002)</td>
<td>[84]</td>
</tr>
<tr>
<td>β</td>
<td>Daily baseline cross-transmission rate in the absence of AM exposure</td>
<td>0.005 (0.001)</td>
<td>[89]</td>
</tr>
<tr>
<td>ρ</td>
<td>Daily antimicrobial prescribing rate for prophylaxis</td>
<td>0.12 (0.012)</td>
<td>[80]</td>
</tr>
<tr>
<td>a</td>
<td>Relative risk of colonisation in uncolonised individuals due to previous AM exposure</td>
<td>2.4 (0.58)</td>
<td>[79]</td>
</tr>
<tr>
<td>θ</td>
<td>Daily rate of colonised individuals becoming infected</td>
<td>0.11 (0.011)</td>
<td>[80]</td>
</tr>
<tr>
<td>η</td>
<td>Daily rate of spontaneous recovery</td>
<td>0.018 (0.002)</td>
<td>[80]</td>
</tr>
</tbody>
</table>
**Duplicate Table 5 Section 6: Parameters relating to treatment efficacy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Mean (SE)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Gamma$</td>
<td>Daily rate of treatment outcome following infection (mean treatment duration =14.2 days)</td>
<td>0.0704 (0.027)</td>
<td>[85]</td>
</tr>
<tr>
<td>$\chi_i$</td>
<td>Probability of being prescribed AM$_i$ (i=1,2)</td>
<td>See treatment strategies in Table 3</td>
<td></td>
</tr>
<tr>
<td>cs$_1$</td>
<td>Clinical success under AM1</td>
<td>0.5954 (0.0438)</td>
<td>[84]</td>
</tr>
<tr>
<td>cs$_2$</td>
<td>Clinical success under AM2</td>
<td>cs$_1$ +/-10%</td>
<td>Non-inferiority margin</td>
</tr>
<tr>
<td>mes$_1$</td>
<td>Microbiological eradication success under AM1</td>
<td>0.4914 (0.0561)</td>
<td>[84]</td>
</tr>
<tr>
<td>mes$_2$</td>
<td>Microbiological eradication success under AM2</td>
<td>See scenario description in Table 7</td>
<td></td>
</tr>
<tr>
<td>$\varepsilon$</td>
<td>Proportion of resistant strains with complete resistance to either AM1 or AM2</td>
<td>0.43 (0.075)</td>
<td>[87]</td>
</tr>
<tr>
<td>$r_1$</td>
<td>Probability of acquiring resistance to AM1 during treatment</td>
<td>0.1247 (0.0485)</td>
<td>[84]</td>
</tr>
<tr>
<td>$r_2$</td>
<td>Probability of acquiring resistance to AM2 during treatment</td>
<td>Two possibilities were evaluated: r$_2$ = 0 or r$_2$ = r$_1$ / 2</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Daily rate of delay for susceptibility testing results to report</td>
<td>3 (0.5)</td>
<td>[91]</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Ratio of resistance acquisition in the presence of clinical failure compared to clinical success</td>
<td>2 (0.5)</td>
<td>Assumption</td>
</tr>
</tbody>
</table>

**Duplicate Table 6 Section 6: NHS Cost and health-related quality of life parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>£ Mean (SE)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tc$_1$</td>
<td>Tigecycline treatment cost (2 packs of 10 doses)</td>
<td>646</td>
<td>NHS basic cost for Tygacil (Reference cost)</td>
</tr>
<tr>
<td>Tc$_2$</td>
<td>Treatment cost of new AM (AM2)</td>
<td>Set to 0 for the purposes of informing alternative funding arrangements for new AMs</td>
<td></td>
</tr>
<tr>
<td>diagC</td>
<td>Susceptibility testing cost</td>
<td>70 (7.1)</td>
<td>Merck website</td>
</tr>
<tr>
<td>BedC</td>
<td>Daily cost of stay in ICU</td>
<td>1383 (298)</td>
<td>[92]</td>
</tr>
<tr>
<td>hrqol$_X$</td>
<td>Baseline HRQoL utility value for ICU patients</td>
<td>0.6 (0.06)</td>
<td>Assumption</td>
</tr>
<tr>
<td>hd</td>
<td>Decrement in HRQoL utility due to infection-related symptoms</td>
<td>0.15 (0.015)</td>
<td>Assumption</td>
</tr>
</tbody>
</table>
\[ i = 1,2; k = S, R1, R2, R12; j = \emptyset, f_1, f_2, f, F; \]
\[ f_i = 1 - cs_i; \]
\[ d = \frac{1}{1 + \tau D}; \]
\[ r_i|cs = \frac{r_i}{\alpha f_i + (1 - f_i)}; r_i|cf = \alpha r_i|cs \]
\[ \psi_i = 1 - \frac{mes_i}{cs_i (1 - r_i|cs)} \]

\[
\frac{\partial X}{\partial t} = \lambda (1 - m_c)N - \beta X (1 + \rho a) (\sum_{k_j} C^k) - \gamma_n X
+ \tau [(1 - f_1) (1 - r_1|cs) (1 - \psi_1)] [X_1 (I^s + I^{R2}) + d(I^S_1 + I^{R2}_1)]
+ \tau [(1 - f_2) (1 - r_2|cs) (1 - \psi_2)] [X_2 (I^s + I^{R1}) + d(I^S_1 + I^{R1}_1)]
\]

\[
\frac{\partial C^s}{\partial t} = \lambda m_c (1 - m_{cr}) N + \beta X (1 + \rho a) (C^s + I^s) - \theta C^s + \eta I^s - \gamma_{nl} C^s
+ \tau [(1 - f_1) (1 - r_1|cs) \psi_1] (X_1 I^s + dI^S_1)
+ \tau [(1 - f_2) (1 - r_2|cs) \psi_2] (X_2 I^s + dI^S_1)
\]

\[
\frac{\partial C^{R1}}{\partial t} = \lambda m_c m_{cr} N + \beta X (1 + \rho a) (C^{R1} + I^{R1}_j) - \theta C^{R1} + \eta (I^{R1} + I^{R1}_j) - \gamma_{nl} C^{R1}
+ \tau (1 - f_1) r_1|cs (X_1 I^s + dI^S_1)
+ \tau (1 - f_2) (1 - r_2|cs) \psi_2 (X_2 I^{R1} + dI^{R1}_1)
\]

\[
\frac{\partial C^{R2}}{\partial t} = \beta X (1 + \rho a) (C^{R2} + I^{R2}_j) - \theta C^{R2} + \eta (I^{R2} + I^{R2}_j) - \gamma_{nl} C^{R2}
+ \tau (1 - f_2) r_2|cs (X_2 I^s + dI^S_1)
+ \tau (1 - f_1) (1 - r_1|cs) \psi_1 (X_1 I^{R2} + dI^{R2}_1)
\]

\[
\frac{\partial C^{R12}}{\partial t} = \beta X (1 + \rho a) (C^{R12} + I^{R12}_j) - \theta C^{R12} + \eta I^{R12}_j - \gamma_{nl} C^{R12}
+ \tau (1 - f_2) r_2|cs (X_1 I^{R1} + dI^{R1}_1)
+ \tau (1 - f_1) r_1|cs (X_1 I^{R2} + dI^{R2}_1)
+ \tau (1 - f_1) (1 - r_1|cs) (X_1 I^{R1} + dI^{R1}_1) + \tau (1 - f_2) (1 - f_2)) I^{R12}
\]

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\[ \frac{\partial l^k}{\partial t} = \theta C^k - (\tau + \eta + \gamma_1 + \omega)l^k \]

\[ \frac{\partial l^S_i}{\partial t} = \tau x_i f_i (1 - r_{i|c}) l^S - (\tau d + \eta + \gamma_1 + \omega)l^S_i \]

\[ \frac{\partial l^{R1}_f}{\partial t} = \tau x_1 [f_1 r_{1|c} l^S + (\epsilon + (1 - \epsilon)f_1)l^{R1}] - (\tau d + \eta + \gamma_1 + \omega)l^{R1}_f \]

\[ \frac{\partial l^{R1}_f}{\partial t} = \tau x_2 f_2 (1 - r_{2|c}) l^{R1} - (\tau d + \eta + \gamma_1 + \omega)l^{R1}_f \]

\[ \frac{\partial l^{R2}_f}{\partial t} = \tau x_1 f_1 (1 - r_{1|c}) l^{R2} - (\tau d + \eta + \gamma_1 + \omega)l^{R2}_f \]

\[ \frac{\partial l^{R2}_f}{\partial t} = \tau x_2 [f_2 r_{2|c} l^S + (\epsilon + (1 - \epsilon)f_2)l^{R2}] - (\tau d + \eta + \gamma_1 + \omega)l^{R2}_f \]

\[ \frac{\partial l^S}{\partial t} = \tau d [f_2 (1 - r_{2|c}) l^S_f + f_1 (1 - r_{1|c}) l^S_f] - (\eta + \gamma_1 + \omega)l^S \]

\[ \frac{\partial l^{R1}}{\partial t} = \tau d [f_1 r_{1|c} l^S_f + (\epsilon + (1 - \epsilon)f_1)l^{R1}_f + f_2 (1 - r_{2|c} * l^{R1}_f)] - (\eta + \gamma_1 + \omega)l^{R1} \]

\[ \frac{\partial l^{R2}}{\partial t} = \tau d [f_2 r_{2|c} l^S_f + (\epsilon + (1 - \epsilon)f_2)l^{R2}_f + f_1 (1 - r_{1|c} * l^{R2}_f)] - (\eta + \gamma_1 + \omega)l^{R2} \]

\[ \frac{\partial l^{R12}}{\partial t} = \tau d [f_2 r_{2|c} l^{R1}_f + f_1 r_{1|c} l^{R2}_f + l^{R12}_f] - (\eta + \gamma_1 + \omega)l^{R12} \]
**Formulas for computing outcomes**

i = 1,2; j = ∅, f₁, f₂, f, F; k = S, R1, R2, R12

In order to capture infection-related excess mortality risk, whilst satisfying the assumption of constant ICU occupancy whereby new admissions of uninfected individual replace patients who have been discharged or died, hospitalisation-related economic outcomes were first computed per patient and adjusted for the numbers of infected individuals who had died and were replaced by uninfected individuals in the previous time step. In a second step, these outcomes were scaled back to the analysis time horizon to ensure the same total number of patients in the ICU at each time point.

**Step 1: Computing outcomes per patient (pp)**

The adjustment factor the deaths in infected at each time point (cᵣ) is provided in equation (1)

(1) \( cᵣ = \omega \left( \int_{t}^{t+1} I^{i,k} - \int_{t-1}^{t} I^{i,k} \right) \)

The expression for the three hospitalisation-related economic outcomes “per patient” (pp) at each time step t are provided in equations 2-4b:

(2) \( \text{LosC}_{\text{pp}} = \frac{\theta \left( \int_{0}^{t} C^{i,k} - \int_{0}^{t-1} C^{i,k} \right)}{N_t - c_t} \times \left( \frac{1}{(\gamma_1 + \omega) - \gamma_{nt}} \right) \times \text{BedC} \times e^{-rt} \)

(3) \( \text{QALY}_{\text{atICU}} = \frac{\left( X_t + \sum_k C_{t}^k \right) \text{hrqol}_t + \sum_k I_t^k (\text{hrqol}_t - \text{hd})} {365} \times e^{-rt} \)

For simplicity, the expression for the treatment cost at time t (TreatCₜₚ) was broken down into two steps:

(4a) \( \text{CumulTc} = \theta \sum_{k,j} C_{t}^{k,j} * \sum_i Tc_i 
+ \tau \left( \left( I_{t}^{R1} + I_{t}^{R2} \right) * \left( \chi_2 f_2 * \left( \text{diagC} + Tc_2 \right) + \chi_2 f_2 * \left( \text{diagC} + Tc_1 \right) \right) 
+ I_{t}^{R12} * \left( \chi_1 f_1 \right) * \left( \text{diagC} + Tc_1 \right) \right) * e^{-rt} \)

(4b) \( \text{TreatC}_{t} = \frac{\text{CumulTc} - \text{CumulTc}_{t-1}}{N_t - c_t} \)
Step 2: Rescaling outcomes to the analysis time-horizon T

TreatCppₜ, LosCppₜ, QALY_atICUppₜ - which are all present values - were then summed across all daily time steps constituting the analysis time horizon (T) and multiplied by (N), the total number of patients in the ICU at each time point.

(5) \[ NPVTreatC = \int_{t=0}^{T} TreatCppₜ \times N \]

(6) \[ NPVLoSC = \int_{t=0}^{T} LosCppₜ \times N \]

(7) \[ NPVQALY_{atICU} = \int_{t=0}^{T} QALY_{atICUppₜ} \times N \]

Step 3: Computation of post-discharge outcomes

Individuals discharged at every daily time step that split the analysis time horizon constituted T cohorts were followed, using a daily cycle, for 90 days post discharge across seven Markov states. Death in non-infected was not modelled as only the excess fatality risk due to infection was relevant in the comparison of post-discharged QALY outcomes across treatment strategies.

Computation of post-discharge QALY outcome over 90 daily cycles (c) for each T discharged (closed) cohort was based on equation (8)

(8) \[ QALY_{postdis_{percohort,t}} = \sum_{c=0}^{90} \left[ (\text{DisNonIₗ}_c)_{\text{hrqol}_X} + \text{DisIₗ}_c(\text{hrqol}_X - \text{hd}) \right] / 365 \times e^{-rc} \]

where \( \text{DisIₗ}_c \) = “Infected treatment failed” + “Infected AM1S” + “Infected AM2S” + “Infected AM1R” + “Infected AM1R”.

This result was then summed across all T cohorts to generate the final post discharge outcome measure.

(9) \[ NPVQALY_{postdis} = \int_{t=0}^{T} QALY_{postdis_{percohort,t}} \]