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A RESEARCH ROADMAP FOR STEDI

Capturing the Broader Value of Antibiotics

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Executive Summary

Capturing an antibiotic's full value requires an extended value assessment. To that end, a framework called STEDI has been conceptualised that describes antibiotic-specific value in addition to the value captured by the National Institute for Health and Care Excellence (NICE)'s standard Technology Appraisal (TA) methods. The STEDI framework is named after the initial letters of five broader value elements (Spectrum, Transmission, Enablement, Diversity and Insurance) and mostly captures an antibiotic's value beyond the value accrued to the treated individual.

In 2022, the NICE-NHS England AMR pilot was the first attempt to consider STEDI value formally during an HTA process. However, due to the complexity and uncertainty of this novel evaluation process, it fell short of fully quantifying each element. The process revealed substantial sources of uncertainty that hindered the implementation of the STEDI framework and highlighted the need for research on how these broader value elements can be operationalised. To capture the broader value of antibiotics using the STEDI framework, a clear and systematic roadmap is required to guide how and when the prevailing uncertainties can be resolved.

To this end, this report sets out a research roadmap to demonstrate how progress can be made towards appropriate quantitative assessment of the full value of new antibiotics, based on the STEDI framework. By exploring existing uncertainties and the key barriers to progress, we provide suggestions of research projects that should be explored in the short, medium and long term.

Phase 1 (short term, <1 years) will achieve clarity and consensus on the underlying concepts and definitions of each STEDI value element. This will ensure a shared understanding and language among all stakeholders involved in the HTA process. Key elements of this phase include refining concepts and definitions of each STEDI value element, identifying historical references cases to plug evidence gaps and support economic evaluation, reviewing existing data sources alongside what is needed, and specifying the types of methods that need further development.

Phase 2 (medium term, 1-3 years) will develop the science and methods associated with the quantification of individual value elements. This will be an intermediate pit stop on the road to a fully integrated model. Key elements include providing interim operational guidance on the STEDI value framework (including how it differs from usual TA, and how to handle trade-offs between different value elements and how to avoid double counting), analysis of historical data to identify key proxy parameters for STEDI estimation, definition of a data strategy (based on the previous analysis of availability and gaps), and further development of specific methods.

The third phase (>3 years) addresses the fundamental work that will improve data collection and analysis and develop complex integrated methods that will contribute to a full QALY-based evaluation of the STEDI value elements. This long-term goal will enable a comprehensive and holistic assessment of the broader value of antibiotics. This phase will involve updating the operational guidelines based on progress made across evidence, scientific understanding and methods, expanding data collection, and formalising a comprehensive methodological framework to fully capture STEDI value within economic evaluation.

See Figure 4 of the report for a visual summary of the roadmap.

The suggested actions require collective, interdisciplinary action. While the path towards a comprehensive value assessment of antibiotics may be challenging, we have identified various ways forwards and suggest that with meaningful stakeholder collaboration, significant progress can be made.

1 Introduction

1.1 Background

Antimicrobial resistance (AMR) occurs when infection-causing pathogens evolve, and antibiotics and other antimicrobial drugs become less effective or stop working altogether. Antibiotics are one of the backbones of modern medicine as they not only resolve the infection and limit its spread but also ensure that other medical procedures, such as chemotherapy or surgery, can continue and advance. The risk of rising resistance rendering antibiotics less effective is one of the biggest health threats of our time (Murray et al., 2022), affecting population health on a global, national and local level.

In 2019, the UK Government acknowledged the dangers of AMR, publishing a vision to contain and control it by 2040 (HM Government, 2019a) alongside an accompanying five-year National Action Plan (HM Government, 2019b). One key pillar within this plan was investing in innovation, supply, and access to novel antibiotics.

For such investment in novel antibiotics to be effective, it must overcome the pervasive market failure faced by new antibiotics. One option, which has been extensively discussed in this context, is a pull incentive in the form of a subscription-style model that would delink the payment to the manufacturer from the level of use of the new antibiotic. In a recent report, we explored how such a model could successfully be implemented within the English setting (Brassel et al., 2023). Our findings highlighted the need for setting the manufacturer's potential payment in line with the full value the antibiotic in question would produce.

Capturing an antibiotic's full value requires an extended value assessment. To that end, a framework called STEDI has been conceptualised that describes antibiotics' specific value in addition to the value captured by the National Institute for Health and Care Excellence (NICE)'s standard Technology Appraisal (TA) methods. The STEDI framework is named after the initial letters of five broader value elements (Spectrum, Transmission, Enablement, Diversity and Insurance) and mostly captures an antibiotic's value beyond the value accrued to the treated individual. The framework and its underlying concepts and definitions evolved from its original introduction by Karlsberg Schaffer et al. (2017), while Rothery et al. (2018a) transformed it into today's STEDI framework.

Previous studies have attempted to illustrate/quantify the parts of the STEDI framework, including transmission and diversity (Morton et al., 2019; Gordon et al., 2020), enablement (Teillant et al., 2015; Smith and Coast, 2013) and insurance value (Megiddo et al., 2019), with limited success. In 2022, the NICE-NHS England AMR pilot was the first attempt to consider STEDI value formally during an HTA process. However, due to the complexity and uncertainty of this novel evaluation process, it fell short of fully quantifying each element. The process revealed substantial sources of uncertainty that hindered the successful implementation of the STEDI framework and highlighted the need for research on how these broader value elements can be operationalised.

Building on the learnings (and in particular the challenges) from the pilot, NHS England have recently (July to October 2023) consulted on proposals for a pragmatic scoring system to be used to determine the value of new antibiotics (NHS England, 2023; Hofer and Hampson, 2023a; b). Scoring is points based, across a range of seventeen criteria. NHSE state that the criteria were developed using STEDI as a conceptual basis. The scoring system has been proposed in lieu of full methods and understanding of how the value of antibiotics (including but not limited to the STEDI elements) can be appropriately captured and quantified.

To allow for appropriate quantification of the broader value of antibiotics using the STEDI framework, a clear and systematic roadmap is required to guide how and when the existing uncertainties can be resolved.

1.2 Development of the roadmap

This research roadmap sets out how progress can be made towards appropriate quantitative assessment of the full value of new antibiotics, based on the STEDI framework. By exploring existing uncertainties and the key barriers to progress, we provide suggestions of research projects that should be explored in the short, medium and long term.

The roadmap was developed following a systematic approach to categorise, analyse, and evaluate the uncertainties in estimating the broader value of antibiotics, as outlined below.

1. In the first step, we developed a framework to classify sources of uncertainty into four domains, as depicted in Figure 1. Two of those domains (conceptual and scientific) are more theoretical, while the other two (evidence and methodological) capture practical uncertainties concerning the ability to measure STEDI value.

FORMS OF UNCERTAINTY AROUND STEDI VALUATION

PRACTICAL

| METHODOLOGICAL | There is not an agreed or reliable method for estimating the value element |

| EVIDENCE | There is a lack of robust, relevant and standardised evidence or data inputs required to estimate the value elements |

What/how can we measure?

| SCIENTIFIC | There is a lack of scientific understanding of the relevant microbiological processes, physiological phenomena or clinical contexts |

| CONCEPTUAL | There is not a consistent definition or concept of the value element within the field |

What do we want to measure?

THEORETICAL

FIGURE 1: OVERVIEW OF UNCERTAINTY DOMAINS AND EXPLANATIONS. SOURCE OHE.

2. We then analysed publicly available outputs from the NICE-NHSE-pilot, and other attempts to estimate STEDI values, and extracted relevant uncertainties concerning the value estimation of STEDI elements, classifying each uncertainty using the framework above.

3. We shared our results with an interdisciplinary group of seven experts (two microbiologists, two health economists from industry, two health economists from academia/charity, and one health economist specialising in advanced modelling). Through an online survey, we asked each expert for comments and further input on our findings and to rank each uncertainty domain according to its importance in estimating the STEDI value.

4. Finally, we facilitated a roundtable with the same experts to discuss the consolidated results and to identify solutions for the most relevant uncertainties.

The resulting roadmap summarises the main uncertainties underlying the estimation of each value element and describes three main phases (short, medium and long term) along a path that will pave the way towards a full future STEDI value estimation.

An overview of the project structure is provided in the appendix.

2 Where are we now?

Half a decade has passed since the STEDI framework (Rothery et al., 2018a) was formalised. Nevertheless, critical uncertainties that hinder its application remain.

Figure 2 ranks the importance of each uncertainty domain by value element based on our analyses and experts' insights elicited during the survey. Conceptual and evidence uncertainties are considered to be the primary sources of uncertainty for most STEDI value elements and as such are addressed first. Scientific and methods uncertainties, which were relatively seen as less important for most STEDI value elements, are addressed subsequently.

A full summary of the uncertainties discussed here is presented at the end of this Chapter in Table 2.
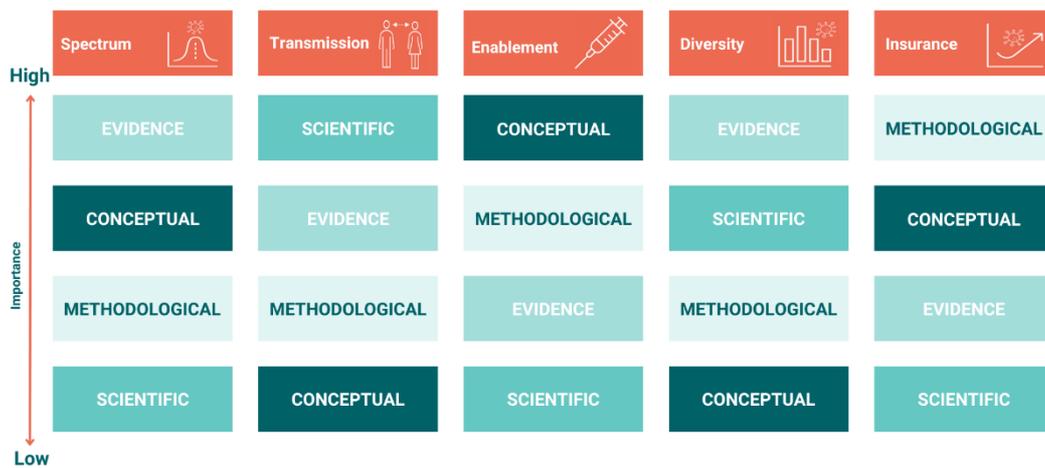
FIGURE 2: IMPORTANCE OF UNCERTAINTY DOMAIN BY STEDI ELEMENT: SURVEY RESULTS

2.1 Conceptual uncertainties

Conceptual uncertainty stems from different (interpretations of the) definitions and conceptualisation of the value framework. There are also unclarities regarding the operationalisation of the framework itself and its relation to the existing NICE technology appraisal methods. Resolving conceptual uncertainty is paramount to estimating STEDI value as it defines what to measure.

2.1.1 Definitions and concepts underlying the STEDI framework

The survey and feedback from the expert group revealed that some definitions of individual value elements are still unclear. Several value elements (e.g., spectrum and insurance) have different components with distinct characteristics that are relevant when assessing their value. It is easy to mix or confuse those components.

Table 1 provides definitions and examples of each STEDI value element. It is based on prior definitions and explanations (Karlsberg Schaffer et al., 2017; Rothery et al., 2018b; Towse and Silverman Bonnifield, 2022) and input from OHE's expert group attending the roundtable.

An antibiotic's broader value can accrue to the treated individual or the wider population and accumulate during treatment or further into the future, thus when conceptualising the different value elements, it may be helpful to consider to whom the benefits accrue and when they accrue. Figure 3 provides a visualisation of these distinct benefits by separating the direct benefit (benefit to the individual treated at the time of treatment) from the indirect benefit (externality to a wider population or future benefit to the individual). Only a few STEDI elements have a direct benefit, but population effects today and in the future feedback to the treated individual later in life assuming their survival. In addition, some elements have multiple mechanisms (e.g., spectrum value), making their conceptual separation even more challenging.

TABLE 1: STEDI DEFINITIONS AND EXPLANATIONS

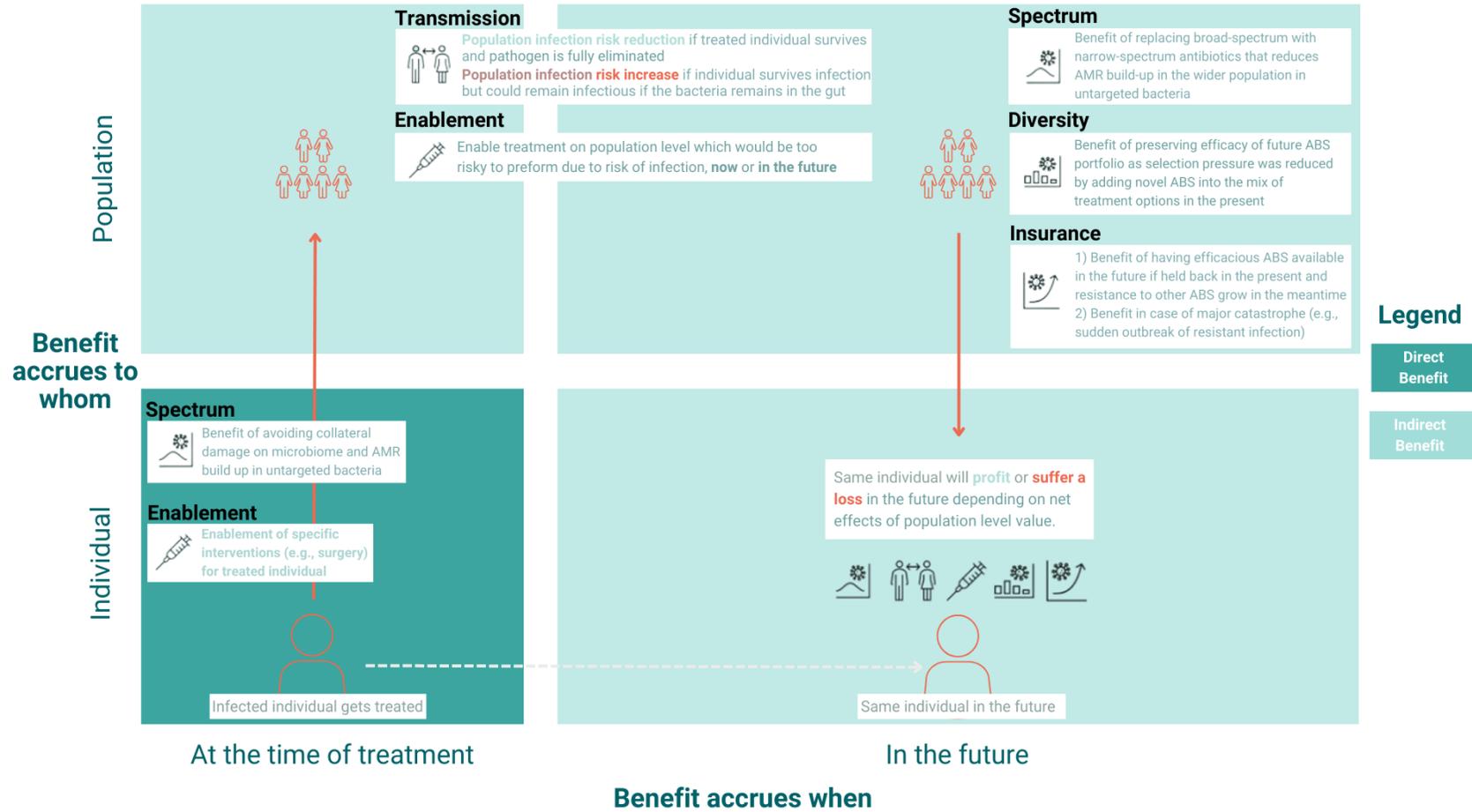|	Definition	Explanation
Spectrum	The benefit associated with the use of narrow(er)-spectrum antibiotics stemming from a reduction in collateral damage on the treated individuals' microbiome and the prevention of resistance selection in untargeted bacteria.	The overuse of broad-spectrum antibiotics causes collateral damage to the microbiome of the treated individuals. In addition, it can lead to a build-up of resistant bacteria across a wide spectrum. Therefore, spectrum value is generated by reducing the collateral damage on the microbiome and avoiding future resistant pathogens that could cause infections unrelated to the one for which the patient has been treated.
Transmission	The indirect benefit of reduced infection rates by avoiding the onward spread of pathogens to other individuals within a population using antibiotics.	Successfully treating an infection in person X reduces the risk of infection with the disease in person Y due to the reduced risk of transmitting the pathogen.
Enablement	The benefit associated with enabling or improving the outcomes of other treatments or procedures where antibiotics are also needed.	Antibiotics enable us to treat disease and ensure that surgery, chemotherapy, and a range of other treatments can proceed with a reduced risk of life-threatening infection.
Diversity	The indirect benefit stemming from preserving the activity of existing antibiotics for longer as they will be used less if the novel antibiotic is added to the treatment options.	Having a diversity of antibiotics at our disposal enables us to avoid overusing a limited number of antibiotics to which bacteria will build up resistance through selection pressure and which consequently would reduce the future value of the overused antibiotics. This value would apply to any new antibiotic.
Insurance	The indirect value associated with having an antibiotic treatment as a last line option for a patient if all other treatments fail, and for dealing better with (or completely avoiding) major catastrophic outbreaks of AMR in the future.	There are two potential elements of insurance value: 1) Not using a novel antibiotic will preserve the use of the new antibiotic as the last line until resistance to all other existing antibiotics worsens and the prevalence of resistant infections cannot be contained. This value might be much greater compared to using it now. 2) Having enough effective antibiotics in reserve in the event of a major outbreak of, or growth in, drug-resistant infection. As resistant infections can constrain health system capacity (e.g., through ward closures), this can have serious knock-on implications for the health of non-infected patients in need of other treatments and procedures.

Benefit accrues to whom

Population

Transmission
Population infection risk reduction if treated individual survives and pathogen is fully eliminated
Population infection risk increase if individual survives infection but could remain infectious if the bacteria remains in the gut

Enablement
Enable treatment on population level which would be too risky to preform due to risk of infection, now or in the future

Spectrum
Benefit of replacing broad-spectrum with narrow-spectrum antibiotics that reduces AMR build-up in the wider population in untargeted bacteria

Diversity
Benefit of preserving efficacy of future ABS portfolio as selection pressure was reduced by adding novel ABS into the mix of treatment options in the present

Insurance
1) Benefit of having efficacious ABS available in the future if held back in the present and resistance to other ABS grow in the meantime
2) Benefit in case of major catastrophe (e.g., sudden outbreak of resistant infection)

Individual

Spectrum
Benefit of avoiding collateral damage on microbiome and AMR build up in untargeted bacteria

Enablement
Enablement of specific interventions (e.g., surgery) for treated individual

Same individual will profit or suffer a loss in the future depending on net effects of population level value.

Infected individual gets treated

Same individual in the future

At the time of treatment

In the future

Benefit accrues when

Legend

Direct Benefit

Indirect Benefit

FIGURE 3: STEDI - DIRECT AND INDIRECT EFFECTS OPERATIONALISATION OF THE STEDI FRAMEWORK

Three other critical uncertainties underlying the theoretical concepts of individual STEDI elements exist. Firstly, there is a risk of overlaps or double-counting between STEDI elements (e.g., some insurance value might be counted as enablement) - or between STEDI elements and the standard NICE evaluation of direct patient-level health benefits (i.e., as usually measured by QALYs).

Secondly, it is impossible to maximise the value profile of an antibiotic across all STEDI value elements, as there are contextual trade-offs between individual value elements. For example, a broad-spectrum antibiotic has little spectrum value but might generate more considerable enablement or insurance value. More clarity is needed on how to deal with those trade-offs. This is particularly important in deciding between using or holding back antibiotics. It is also essential when considering how the different STEDI elements interact over time (e.g., spectrum vs diversity and enablement vs insurance) and how these trade-offs depend on the level at which the value is derived (e.g., patient or population).

Finally, the broader value of an antibiotic can accrue differently across varied (geographical) populations. Many contextual factors (e.g., local resistance rates, available existing antibiotic portfolio and real-world usage) impact the overall achievable STEDI value, partly through different AMR trajectories. It is unclear how the STEDI framework can capture these variations without its application becoming prohibitively complex.

2.1.2   Uncertainties concerning individual STEDI elements

SPECTRUM
The concept of spectrum value is a critical source of uncertainty. Spectrum value has two distinct components: i) It is generated by avoiding collateral damage on the microbiome at the individual level and ii) avoids resistance build-up in bacteria that are out of interest for the specific course of treatment on both the individual and population level now and in the future. However, the exploration of spectrum value does not always separate those two components.

Further, while broad-spectrum antibiotics generally have less or no spectrum value, the benefits and drawbacks of broad-spectrum antibiotics during different forms of prescribing (empirical vs guideline-driven) must be made more explicit.

Finally, there is also a lack of consensus on what the difference in value is between 'broad spectrum' and 'narrow spectrum' antibiotics. There is however general agreement that spectrum value should be measured on a continuous scale rather than a binary one.

TRANSMISSION
The main conceptual uncertainty underlying transmission value relates to its definition. Within the pilot, NICE defined transmission value as foregone resistant infections only rather than all foregone infections. This contrasts the definition of transmission value used to quantify the broader value of other health technologies targeting infectious disease (i.e., vaccines).

ENABLEMENT
The concept of enablement value must be separated more clearly from insurance value and clinical value or downstream effects usually considered by NICE. The latter might already include savings that stem from improved safety profiles of a health technology (e.g., reduced renal toxicity) that reduce the need for costly long-term therapies (e.g., renal dialysis, as explored in the pilot). There is also a lack of operational guidance on how to measure enablement value on a continuous scale.

DIVERSITY
The concept of diversity value is relatively clear. However, within the NICE-NHSE pilot, the diversity value of last-line therapies was assumed to be zero. As there is no agreement that this assumption is indeed correct, it requires further exploration and operational guidance.

INSURANCE

Similar to spectrum value, the concept of insurance value consists of two distinct components (see Figure 3). However, definitions, applications and debates about insurance value often fail to separate these concepts more clearly.

It is yet to be agreed upon how to present (part of the) insurance value alongside other STEDI elements. Modelling insurance value for a catastrophic event requires assuming a scenario in which the antibiotic would be actively held back, thus the other value elements may be less relevant in the short term. Then, there is confusion about whether insurance value would capture the value from the remaining STED elements in a modelled state of the world where the catastrophic event does occur. Other potential overlaps relate to the separation of insurance and enablement value. For example, the value of the risk reduction of a potential ward closure could be captured either by modelling the second element of insurance value or by modelling the enabled care on the ward.

2.2 Evidence uncertainties

Evidence uncertainty stems from a lack of robust, relevant, and standardised evidence or data required to estimate the broader value elements. Overcoming evidence uncertainty relies on first resolving the more foundational conceptual and scientific uncertainties: we need to define what we are trying to measure before we can define how we are going to measure them (methods) and what information we need to support that measurement (evidence). This said, we tackle evidence uncertainties next as it was considered to be one of the most important sources of uncertainty, along with conceptual (see Figure 2). Many of the evidence uncertainties are broad, covering all the STEDI value elements.

2.2.1 Uncertainties relevant for all STEDI value elements

A crucial problem with the current evidence base is the lack of historical, real-world evidence. Therefore, there is a need to collate and index the registries and data sources within the UK that could be used as the basis for STEDI estimation.

Another barrier is the structure of the historical real-world data available. The evidence that does exist in registries or clinical records does not enable the comparison of the effects of different treatment scenarios on relevant clinical endpoints. These barriers are problematic as real-world data is crucial to valuation efforts, as evidence from clinical trials will always be limited for antibiotics.

The kinds of data needed by those estimating STEDI can be grouped into two categories:

- evidence indicating the presence or absence of a STEDI element; and

- evidence of the magnitude of that value.

Currently, there is a lack of both, and both are important. Evidence to help evaluators rule out the STEDI elements that are likely to be insignificant to the value profile would make the evaluation process more feasible. The NICE-NHS England AMR pilot was extremely resource-intensive and would have benefited from robust evidence indicating which of the STEDI value elements to focus on. As explained above, defining the relevant evidence in this context requires clear and agreed definitions of the STEDI elements themselves. Poor evidence to support the estimation of the magnitude of the STEDI values within the pilot´s evaluation process was also one of the key limitations of the scheme, resulting in a ´descriptive analysis´ rather than the kind of quantification typically used to support decision making.

It has been suggested that in the short term, expert elicitation should be relied on to estimate key values for which empirical evidence is missing. However, we suggest caution here. Expert elicitation is valid when experts are asked to predict observable values. Many aspects of the STEDI quantification rely on evidence that the experts cannot observe and therefore have less knowledge and experience of - such as international resistance rates, rate of resistance build-up in the population or the rate of transmission from someone with gut colonisation of the organism of interest.

When considering novel data collection for STEDI estimation, evaluators must ensure the data is relevant to how antibiotics are used in real-world settings. Antibiotics are prescribed in prophylactic and infection treatment contexts. Treatment is further divided into empirical treatment, where doctors try antibiotics and monitor the response of the infection, and targeted treatment where specific antibiotics are selected supported by diagnostics based on the specific pathogen. The empirical and targeted approaches require different kinds of antibiotics suggesting that different profiles of STEDI values will be most valuable. For example, narrow spectrum antibiotics are of high value for targeted treatment where an antibiotic can be given for a specific organism of interest without the risk of generating ´collateral damage´ to the microbiome. However, effective broad-spectrum antibiotics are valuable for empirical treatment contexts to give the best chance of starting to control an infection where action is urgent. Both treatment contexts are required clinically, but rapid diagnostics to support targeted prescribing could shift the balance to enable more targeted prescribing. Therefore, collecting the right data to assess each treatment option is crucial.

2.2.2 Uncertainties relevant for individual STEDI elements

SPECTRUM

Clinical trials for antibiotics recruit based on indication (e.g., people with a severe UTI). However, the scope of an economic evaluation may be defined instead on the resistance mutation of the causative bacteria as happened in the NICE-NHS England pilot. Some resistance mutations are relatively rare so trials based on these mutations alone will be expensive and impractical to recruit for. It will be important to generate evidence of whether an antibiotic selects for the organism of interest (e.g., multi-drug resistance gram negative bacteria) and then link the clinical outcomes to the selection of that organism. There is no good proxy measure for the relationship between the microbiological features and the clinical outcomes in this context.

Spectrum value relies on the premise that reducing selection pressure on bacteria generates better clinical outcomes. Therefore, measuring spectrum value relies on measuring the link between the resistance of the causative bacteria and a meaningful clinical outcome. However, currently, resistance is measured using in vitro assays. Evidence is needed to validate the clinical value of resistance measured in vitro. Currently, proxies for the link between resistance and clinical outcomes are immature in two ways: 1) HTA agencies are not used to using in vitro susceptibility data to derive clinical value 2) There are no international standards for defining resistance, meaning in vitro data is not comparable across labs. In addition to the proxies for clinical value of narrow spectrum antibiotics being immature, there is also a lack of consensus on what type of evidence is needed to define an antibiotic as narrow spectrum in the first place.

There is also uncertainty about whether the resistance mutation itself impacts the infection's clinical outcomes. The key driver of the impact of resistance on clinical outcomes may be on the ´fitness´ of the resistant bacteria. Fitness is the ability of a bacteria to grow in a given environment. For example, whether or not a resistance mutation has an impact on the fitness of a bacteria may determine the severity of an infection. The NICE-NHS England pilot assumed that resistance had no impact on fitness, however it could have a clinically meaningful positive or negative impact on fitness. Evidence needs to be collected to understand the relationship between resistance, fitness and severity among key pathogens of interest.

A key component of spectrum value, when defined at the individual level, is the impact of the antibiotic on the microbiome. Collateral damage is also a poorly defined term scientifically and clinically. Standards of evidence to measure so called ´collateral damage´ are not agreed and there is no regulatory requirement for companies to measure this outcome. Furthermore, evidence is not collected on the link between microbiome damage and short/long-term health in the individual and the population. Given the growing scientific literature on the impact of the microbiome on overall health, there may be significant value in protecting the microbiome in terms of reducing risks of chronic diseases like obesity and diabetes and mental health issues like anxiety and depression. C. difficile infections have been used as a relevant clinical end point which indicates microbiome disruption.

TRANSMISSION
The key evidence barrier for transmission value is how better evidence can be generated on the spread of different resistant mutations within the population. Once the epidemiology of resistance mutations can be tracked, there will be scope to model the impact of interrupting transmission and reducing resistance spread in the population on clinical outcomes relevant to modelling transmission value. Overall, there is disagreement whether empirical evidence can be generated for transmission value at a population level at all, or whether evidence needs to be for proxies that can be used in modelling efforts.

INSURANCE
Insurance value relies on the assumption that the payer is willing to pay to avoid an outbreak (i.e., through insurance). However, there is no established willingness to pay to avoid outbreaks, as was noted as a barrier in the NICE-NHS England pilot. In addition, evidence on how resistance moves internationally to ´seed´ local outbreaks is needed.

2.3   Scientific uncertainties

Scientific uncertainty stems from a lack of scientific understanding of the relevant microbiological processes, physiological and epidemiological phenomena, or clinical contexts determining the presence or magnitude of the STEDI value elements. Resolving scientific uncertainties helps define what we are trying to measure (i.e., conceptual issues) and how we measure it (i.e., evidence and methodological uncertainties).

2.3.1   Uncertainties relevant for all STEDI value elements

In general, defining scientific uncertainty is complicated by ´unknown unknowns´, which prevent experts from articulating the impact of certain uncertainties on the broader value of an antibiotic or how to resolve them. In addition, the requirement for interdisciplinarity is particularly challenging when discussing scientific uncertainty: clinical and microbiological experts speak a different technical language to health economists and those involved in determining evaluation criteria for antibiotics. The result is that it is hard for non-specialists to understand the significance of particular scientific uncertainty to the wider valuation problem.

2.3.2   Uncertainties relevant for individual STEDI elements

SPECTRUM
There is significant scientific uncertainty around spectrum value, which stems from limitations in understanding the drivers, epidemiology and clinical implications of resistance build-up at the individual and population level. For example, whether the value of a narrow-spectrum antibiotic is specific to a particular bacterial species or strain and how narrowly that value should be defined. A broader source of uncertainty is that it is not known how species, strains, or bacteria-specific phenomena are linked to resistance build up. For example, how different species generate resistance

to antibiotics is often assumed to be a generalisable problem, drawing on the Darwinian model of evolution to overcome the presence of antibiotics as the key driver of resistance. In this model, exposure to the antibiotic drives resistance and therefore limiting usage should slow resistance build-up at the population level. However, the other mechanisms for generating resistance may not be adequately explained by this mechanism, and these other mechanisms may be strain or species-specific. For example, gram-negative bacteria acquire resistance through horizontal gene transfer of small amounts of genetic information between bacteria which are not directly selected through the kind of natural selection mechanism that underpins an assumed link between resistance and usage of an antibiotic. Understanding resistance and how it relates to exposure to an antibiotic is a crucial uncertainty that underpins many aspects of STEDI valuation.

TRANSMISSION

The fundamental dynamics underpinning transmission value were shown to be uncertain during the NICE-NHS England pilot, where the uncertainty around the link between treatment, gut colonisation and onward infection prevented quantification. This scientific uncertainty led the NICE committee to assume that the antibiotics assessed within the pilot did not have transmission value or may have ´negative´ transmission value. The suggestion of a negative transmission value explains a situation where treatment of very serious infections keeps someone alive longer, the treatment does not lead to eradication of the microbe from the body as it remains in the gut, and if that gut colonisation means people remain infectious. The assumption of negative transmission value is based on the idea that if treatment resulting in gut colonisation means people are infectious for longer that they would otherwise be and therefore they spread the bacteria to more people.

There is also poor understanding of bacterial transmission and infection dynamics at a population level. For example, how different bacteria spread between people, how treatment with antibiotics moderates these dynamics and whether patient and environmental factors modulate these transmission dynamics. This fundamental knowledge gap prevents meaningful modelling or quantification of transmission value.

DIVERSITY

Similar to spectrum value, quantification of diversity value suffers from scientific uncertainty that stems from limitations in our understanding of the epidemiology and clinical implications of resistance build-up. In particular, diversity value relies on the assumption that reducing exposure to one antibiotic, though mixing in additional antibiotics, reduces resistance build-up to any one of the antibiotics in circulation. The current understanding of the relationship is based on assumptions that resistance develops through selection of advantageous mutations through antibiotic exposure. However, most of the high-priority gram-negative pathogens mainly acquire resistance through a different mechanism (horizontal gene transfer) that is not dependent on exposure to the antibiotic in question. Instead, bacterial species can acquire resistance stochastically without antibiotic exposure and retain resistance for long periods because the resistance mutation is co-selected with other genes. The existing assumptions that a diverse mix of antibiotics reduces the selection pressure on resistance may be irrelevant when resistance is acquired through horizontal gene transfer. Therefore, the relationship between the antibiotic usage scenario (i.e., mixing different antibiotics) and resistance generation and accumulation in the population is a vital missing link for STEDI evaluation.

The impact of the international context on local resistance rates is another key uncertainty in estimating diversity value which relies implicitly on the assumption that local stewardship through antibiotic mixing has a meaningful impact on resistance rates and clinical outcomes as a result. However, there is not a good scientific understanding of the relationship between local stewardship and international usage on local resistance trends and trajectory. While relevant for all the STEDI elements, this uncertainty is particularly important for diversity value and insurance value that rely on long-term resistance dynamics and a chance of outbreaks (seeded from an international pool).

Within the NICE-NHSE pilot, there was a lot of discussion about the scientific basis of the relationship between antibiotic usage and resistance. The link between usage and resistance (therefore, the basis of diversity value) is further complicated because it varies between clinical contexts and the microbes with very different ecological niches and epidemiology. It is not straightforward to predict the impact of these factors, and the understanding is poor across pathogens. Furthermore, it is often not known whether the resistant mutation affects relevant clinical outcomes.

2.4   Methods uncertainties

Methods uncertainty relates to the toolkit necessary to estimate STEDI value. While some STEDI elements can be theoretically quantified with existing methods (e.g., dynamic transmission modelling), others require novel methods or less common assumptions (e.g., incorporating risk preference into modelling). The complexity of infection and transmission patterns adds to this challenge.

2.4.1   Uncertainties relevant for all STEDI value elements

A key source of methods uncertainty affecting all STEDI elements relates to estimating annual patient numbers eligible for treatment with the antibiotic under consideration. The debate within the NICE-NHSE pilot revealed that providing a reasonable estimate for annual patient numbers eligible in the first year is difficult as different assumptions can lead to a wide range of patient numbers. Further, projecting the eligible population over time is challenging as resistance patterns change. As the number of patients treated within the model is a primary driver behind the estimated value, these uncertainties can strongly impact the overall evaluation results.

Another complexity with patient numbers is that new antibiotics may undergo multiple trials in different indications at different timepoints, resulting in the indication of the therapy expanding over time. An agreed approach on how to translate potential increases in patient numbers over time due to potential label expansions is important to ensure the valuation is fair and accurate over the lifecycle of the product.

There is also uncertainty surrounding modelling methods, as there is general agreement that estimating STEDI value requires a different approach than most other therapeutics, for example via advanced health economic modelling that allows incorporation of infectious disease dynamics and different AMR trajectories. There is, however, still a lack of practical methodological guidance beyond the original framework from Rothery et al. (2018a). Within the NICE-NHSE pilot, this resulted in unclarity regarding the combination of patient and population-level models (e.g., the alignment of eligible patient populations and timelines).

Another critical method surrounded by uncertainty is expert elicitation, in particular how and when to use it. This is especially important in the short term, until more high-quality empirical evidence is available. Critics found the expert group size within the NICE-NHSE pilot to be too small, and suggested there may have been an overreliance on expert opinion.

Finally, there is uncertainty about how the methodological toolkit will need to evolve. As noted in Chapter 1, NICE are proposing a more pragmatic scoring system for implementation in the near term. To date, there is no clear plan for how or whether these arrangements will evolve into a more comprehensive evaluation in the long run.

2.4.2   Uncertainties relevant for individual STEDI elements

TRANSMISSION

Similar to vaccines, modelling antibiotics requires the application of dynamic transmission models to capture the externalities beyond the individual. While these methods exist, modelling transmission dynamics in combination with resistance patterns is complex. The model applied within the NICE-NHSE pilot failed to capture the externalities characteristic of infectious diseases. Further standardisation and consolidation of methods is required to capture transmission value.

ENABLEMENT

Enablement value is a novel value element for which no agreed methods exist, thus methods uncertainty is significant. Parts of enablement value might already be captured, or at least be capturable, within NICE's downstream effects of regular technology appraisals, e.g., as is currently done for diagnostics. Other parts might overlap with potential insurance value, especially when considered on a ward level. The NICE-NHSE pilot failed to estimate enablement value from population-level data. Finally, it is unclear whether enablement value should be modelled ´bottom-up´ (i.e., in a decision tree format used in traditional economic evaluations) or empirically estimate it from population-level data.

DIVERSITY

To date, how to model a new antibiotic's impact on existing antibiotic portfolio usage and consequential resistance patterns is unclear. Methodological challenges are also interlinked with conceptual ones as diversity value faces a trade-off with insurance value as the antibiotic is either held back or used daily. Finally, models should capture that diversity value can be driven by 'better' antibiotics and simply by having 'more' antibiotics at our disposal.

INSURANCE

There is a general notion that estimating insurance value relies too much on expert opinion and that it is generally difficult to predict future outbreaks. However, modelling low probability, high impact events is more common in other disciplines (e.g., climate economics). Risk preference modelling is not well established within health economics, but necessary as modelling insurance value requires taking a risk-averse perspective.

TABLE 2: SUMMARY OF UNCERTAINTIES

	PAN-STEDI Uncertainties	Spectrum Uncertainties	Transmission Uncertainties	Enablement Uncertainties	Diversity Uncertainties	Insurance Uncertainties
Conceptual	• Definitions are unclear, with the boundaries of value elements not explicitly defined. • Lack of separation between patient and population benefits and valuation of these. • Risk of double counting due to the overlap in definitions of some elements. • Complexity of dealing with trade-offs between STEDI elements for antibiotic implementation and interaction of elements over time. • Complexity of estimating the broader value of an antibiotic in different geographical settings.	• No consensus on whether spectrum value includes both individual- and population-level benefits. • The concept of spectrum value does not take into account that there are both benefits and drawbacks of broad-spectrum antibiotics in different treatment scenarios. • There is no clear and agreed way to classify broad and narrow-spectrum antibiotics.	• Unclear on if value relates to forgone resistant infections or all forgone infections.	• Unclear delineation from parts of insurance value. • Unclear distinction between enablement and clinical value/downstream effects already included in the NICE standard TA process. • Operational guidance is missing for measurement on a continuous scale.	• Not clear whether there is zero diversity value of last-line therapies.	• Lack of separation of individual and population-level definitions. • No consensus on incorporation of other STEDI value elements in catastrophe scenario. • Unclear separation of insurance and enablement value.

	PAN-STEDI Uncertainties	Spectrum Uncertainties	Transmission Uncertainties	Enablement Uncertainties	Diversity Uncertainties	Insurance Uncertainties
Evidence	▪ No repository of registries for relevant RWE for STEDI valuation. ▪ The current structure of RWE collected in registries is not for estimating STEDI values. ▪ Poor evidence indicating both the presence and magnitude of STEDI elements. ▪ Expert elicitation is limited without observational data or historical reference cases to inform estimates. ▪ Real world data needs to include the context of the AB use (i.e., prophylactic, empirical or targeted). ▪ Mathematical models need to be developed to combine multiple sources of evidence.	▪ The rarity of recruiting specific resistance mutations into clinical trials means relevant trial population sizes will be small. ▪ Measurement of resistance is not standardised and relevance to clinical outcomes is poorly understood. ▪ Poor understanding of effect of resistance mutation on bacterial fitness and clinical outcomes. ▪ Measurement of collateral damage to the microbiome is not standardised or widely done as well as the links to clinical outcomes.	▪ Better evidence is needed for transmission of different resistance mutations within a population (or proxy needed).			▪ No willingness-to-pay evidence for avoiding a catastrophic outbreak of a disease.

	PAN-STEDI Uncertainties	Spectrum Uncertainties	Transmission Uncertainties	Enablement Uncertainties	Diversity Uncertainties	Insurance Uncertainties
Scientific	▪ Scientific understanding of microbiological processes is not strong enough to estimate STEDI values. ▪ Interdisciplinary collaboration is needed to overcome the challenges to STEDI valuation but there are communication barriers between the experts within different fields.	▪ Understanding of the drivers, epidemiology and clinical implications of resistance build-up at both the patient- and population-levels is limited.	▪ Dynamics between treatment and gut colonisation leading to possible onwards infection are not well understood. ▪ Differences between bacterial transmission mechanisms and infections, and patient/environmental factors that may affect these are not well understood.		▪ The presence of horizontal gene transfer mechanisms spreading resistance delinks resistance development from usage. This is not well understood. ▪ The impact of international usage of antibiotics on local stewardship and resistance trends is not well understood. ▪ Poor understanding of the link and variation between antibiotic usage and resistance for different microbes.	

	PAN-STEDI Uncertainties	Spectrum Uncertainties	Transmission Uncertainties	Enablement Uncertainties	Diversity Uncertainties	Insurance Uncertainties
Methodological	▪ Robust methods and data for estimating annual patient numbers are not well established. Different assumptions lead to wide range of values. ▪ Lack of robust methodology for incorporating infectious disease dynamic models within patient and population level models. ▪ Robust and validated methods for incorporating expert opinion are needed as well as larger/cross-industry panels.		▪ Modelling transmission dynamics with resistance patterns is complex and there is still no standardised methodology.	▪ No standardised methodology in place, separating enablement value from insurance and clinical effects already captured in a TA. ▪ Unclear whether this should be modelled via a bottom-up approach or top-down approach.	▪ Unclear methodology and overlap with other value elements	▪ Lack of agreement on methods despite availability and use in other areas of economics.

3 How to operationalise full value assessment of future antibiotics

A research roadmap to ensure future estimation of STEDI value elements within the HTA of antibiotics must address the uncertainty across conceptual, science, evidence and methods domains within an appropriate time frame. We give an overview of the roadmap in Figure 4 and lay the path forward within the short-, medium- and long-term in the remaining chapter. For each of the key research areas we indicate which stakeholders should lead the research and which of the following stakeholders need to provide support: industry, HTA bodies and health economists, clinicians and microbiologists.

At the end of this chapter (section 3.4) we also provide a comparison to the World Health Organisation's recently published research agenda for antimicrobial resistance, which had a different scope but contains some overlapping themes.

3.1 Short term (0-1 year)

CONCEPTUAL: REFINE CONCEPTS AND DEFINITIONS
LEAD STAKEHOLDER: HTA BODIES, CLINICIANS, MICROBIOLOGISTS AND HEALTH ECONOMISTS
SUPPORTING STAKEHOLDERS: INDUSTRY

The first step must be to address the uncertainties underlying the concepts and definitions of each STEDI value element. We suggest setting up an interdisciplinary task force of experts to publish a consensus report within one year. Must-have disciplines represented within the task force are health economics, medicine, microbiology and representatives from NICE.

The report should draw clear boundaries between individual STEDI elements, the STEDI framework, and NICE's standard technology appraisal. Potential pitfalls (e.g., risk of double counting) should also be explained and addressed through operational guidance in the medium term. Once the STEDI elements are clearly defined then it may be worth validating with experts whether they believe all of the elements as defined in this exercise fully capture the value of antibiotics or if there are elements of value that are missing and should be captured within, or separately to STEDI.

SCIENTIFIC: IDENTIFY HISTORICAL REFERENCE CASES THAT CAN HELP TO ADDRESS TODAY'S SCIENTIFIC UNCERTAINTY
LEAD STAKEHOLDER: CLINICIANS AND MICROBIOLOGISTS
SUPPORTING STAKEHOLDERS: INDUSTRY, HTA BODIES AND HEALTH ECONOMISTS

Historical cases could be used to fill in evidence gaps to support economic evaluation, including in support of expert elicitation (i.e., by giving experts a range of plausible values to frame their estimations). A multidisciplinary panel is needed to identify the historical cases for which 1) the most pathogen-treatment-outcome information is known and 2) evidence is the most transferable to other novel antibiotics joining the market. For the correct cases to be identified, health economists must articulate what needs to be measured (i.e., through providing clearer concepts and definitions of the STEDI elements). Microbiologists, clinicians and scientific experts on AMR then need to assess which historical cases have useful data and the ways in which these cases could be extrapolated for different uses.

OHE

Long term (>3yr)

Update operational guideance
Expand exisiting and build new data sources
Formalise comprehensive methodological framework

03

Short term (0-1 yr)

Refine concepts and definitions
Identify historical reference cases
Assess existing data resources
Specfiy the methodological toolkit

01

Medium term (1-3 yr)

Provide guidance on the operationalisation of STEDI
Use historical data to investigate key drivers of resistance and outcomes
Define data strategy
Develop methods to quantify individual value elements

02

KEY
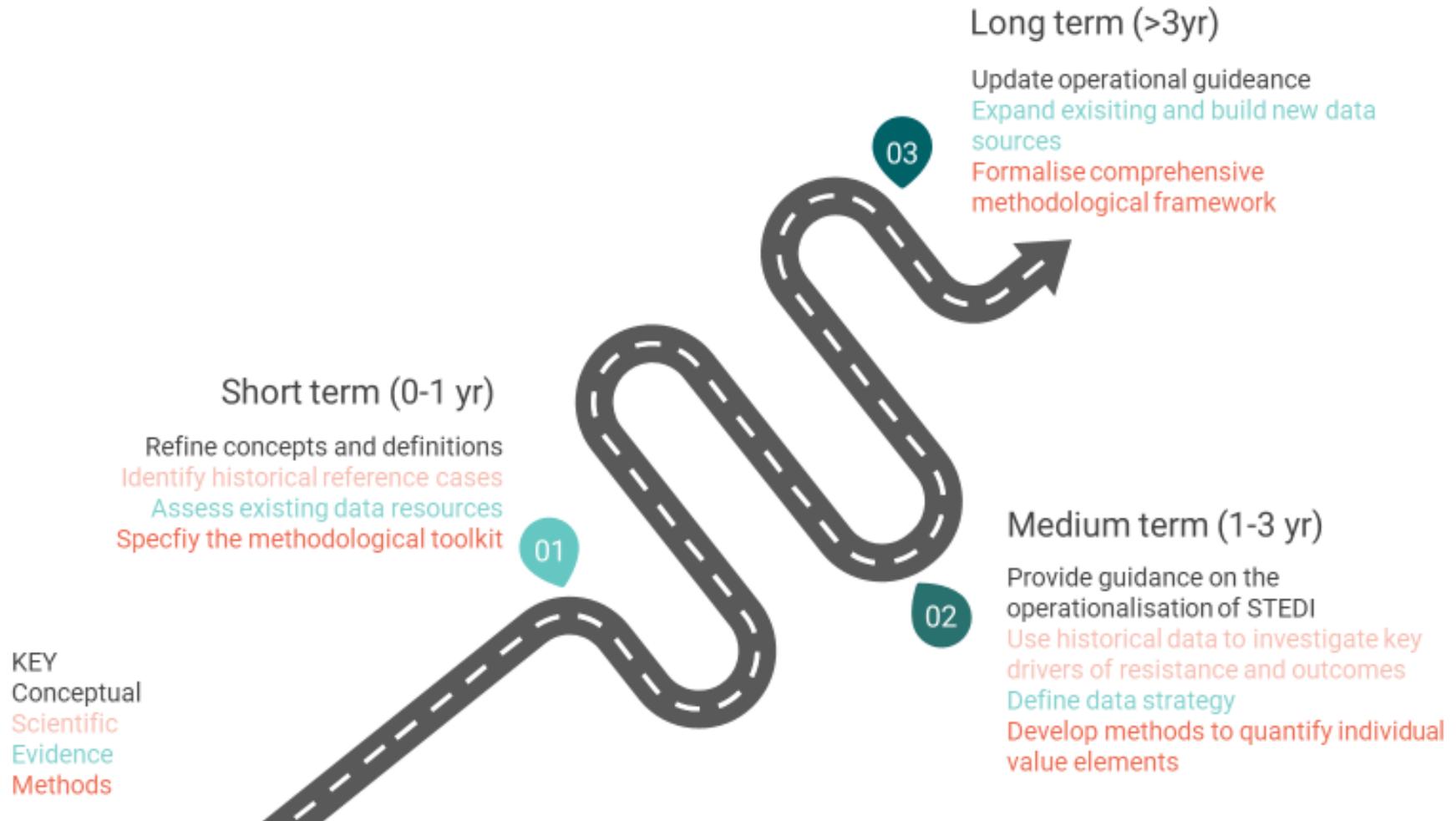Conceptual
Scientific
Evidence
Methods

FIGURE 4: ROADMAP TO RESOLVE UNCERTAINTIES IN ESTIMATING STEDI VALUE. SOURCE OHE.

EVIDENCE: PERFORM A THOROUGH ASSESSMENT OF EXISTING DATA RESOURCES AND NEEDS
LEAD STAKEHOLDER: HTA BODIES AND HEALTH ECONOMISTS
SUPPORTING STAKEHOLDERS: INDUSTRY, CLINICIANS AND MICROBIOLOGISTS

Before any additional investment in data infrastructure is made, those involved in STEDI estimation need to understand what information is available, how it may link together and for which areas of uncertainty existing data could be leveraged. Improving the use of real-world data in HTA is relevant more broadly than the AMR context and therefore the exercise of identifying these databases and repositories is likely to generate valuable learnings for other clinical settings. As part of this exercise, development of a repository of relevant clinical registries would be useful.

METHODS: SPECIFY THE FUTURE METHODOLOGICAL TOOLKIT TO ESTIMATE STEDI VALUE
LEAD STAKEHOLDER: HTA BODIES AND HEALTH ECONOMISTS
SUPPORTING STAKEHOLDERS: INDUSTRY

Based on revised definitions and more clearly defined concepts, a thorough assessment of the methodological status quo and future opportunities to inform the specification of a methodological toolkit is required.

Some methods will be STEDI element agnostic. For example, methods to estimate the patient numbers that might profit from the antibiotic in question will drive the value estimate from all STEDI elements incorporated in the assessment, or mathematic models to combine the multiple evidence sources that will be needed to support STEDI quantification. Others will be element specific—for example, methods to quantify enablement value on an individual and population level. In addition, models themselves could help to define where to focus the evidence-generation efforts by highlighting areas of impact where uncertainties exist (e.g., through value of information analysis). Such techniques, including consideration of how and when each could be considered for use, should be considered as part of this methodological toolkit.

The methodological assessment should consider existing methods within the health economics space (e.g., dynamic transmission modelling) and may also profit from looking into other areas (e.g., climate change economics or actuarial science to inform catastrophe modelling). The STEDI methods toolkit must consider any methods needed to support evaluation via a pragmatic scoring mechanism in the short-medium term, and full QALY estimation in the long term.

3.2   Medium term (1-3 years)

CONCEPTUAL: PROVIDE GUIDANCE ON THE OPERATIONALISATION OF THE STEDI VALUE FRAMEWORK
LEAD STAKEHOLDER: HTA BODIES AND HEALTH ECONOMISTS
SUPPORTING STAKEHOLDERS: INDUSTRY, CLINICIANS AND MICROBIOLOGISTS

Successful and standardised STEDI value estimation requires a detailed operational guidance document (or 'manual') to allow analysts and HTA bodies to produce standardised and comparable assessments. The same task force responsible for refining concepts and definitions could be utilised to produce this operational guidance.

The guidance could be used as a supplement to NICE's existing manual for TAs, to highlight methods and processes where evaluation of antibiotics differs from that within the usual TA process. It could be considered interim guidance at this stage, whilst methods and processes continue to develop. Amongst other things, it should include emerging practices for:

- an antibiotics reference case.

- details of the recommended methods for estimating patient numbers and each value element (as per the methodological toolkit), and any acceptable alternatives. This is likely to develop over time as methods evolve in sophistication.

- how to deal with trade-offs between individual value elements. It is not possible to maximise each value element within the same scenario, thus research to identify high-value scenarios for different pathogens and populations and the most relevant value elements could significantly increase the efficiency of the evaluation process. This could be explored (for example) through a case study exercise that maps the most critical pathogens against the current antibiotic pipeline and most likely usage scenarios. The essential value element combinations that are likely to deliver the most value could be identified for each case, while value elements that produce little or no value could be actively excluded.

- the aggregation of value elements to avoid double counting within the framework and concerning NICE's standard reference case. Experts from NICE and other health economists could perform a joint risk assessment and provide mitigation strategies.

In the short term, the guidance should be aligned with NICE's suggestion for a score-based estimation mechanism.

SCIENTIFIC: USE HISTORICAL DATA TO INVESTIGATE KEY DRIVERS OF RESISTANCE AND OUTCOMES
LEAD STAKEHOLDER: CLINICIANS AND MICROBIOLOGISTS
SUPPORTING STAKEHOLDERS: INDUSTRY, HTA BODIES AND HEALTH ECONOMISTS

When a multidisciplinary process has defined the historical cases, they should be investigated to identify key parameters for STEDI estimation. For example, historical cases could be used to estimate the key drivers of resistance, the link between resistance and clinical outcomes, and the impact of antibiotic mixing or other stewardship processes on resistance and outcomes. The work could be co-produced by national funding bodies, NICE, and industry to ensure joint buy-in.

EVIDENCE: DEFINE DATA STRATEGY
LEAD STAKEHOLDER: HTA BODIES AND HEALTH ECONOMISTS
SUPPORTING STAKEHOLDERS: INDUSTRY, CLINICIANS AND MICROBIOLOGISTS

In light of the historical use cases and the progress made with conceptual uncertainty in the short term, a new data strategy for STEDI needs to be defined. The data strategy should include three components:

1. Recommended requirements from regulators on data collected during product development. For example, this may include a requirement to measure the impact of an antibiotic on the microbiome, or guidelines on in vitro methods and standards.

2. Strategy for using clinical data, including how clinical data should be captured and stored to be most helpful for evaluating novel antibiotics.

3. Requirements for novel repositories to fill the gaps in historical and real-world data.

METHODS: DEVELOPMENT OF SELECTED METHODS TO QUANTIFY INDIVIDUAL VALUE ELEMENTS
LEAD STAKEHOLDER: HTA BODIES AND HEALTH ECONOMISTS
SUPPORTING STAKEHOLDERS: INDUSTRY

While NICE is expected to apply a pragmatic scoring mechanism to estimate STEDI value in the short term, methods to quantify individual STEDI elements should be further developed in parallel to enable full QALY assessment in the long term.

This could be achieved by designing grants on a national or international level with the objective to develop and test sophisticated quantification methods for individual value elements. Value elements with high methodological uncertainty, like insurance or enablement value should be given priority.

3.3   Long term (>3 years)

CONCEPTUAL: UPDATE OPERATIONAL GUIDANCE
LEAD STAKEHOLDER: HTA BODIES AND HEALTH ECONOMISTS
SUPPORTING STAKEHOLDERS: INDUSTRY

As evidence, science, and methods behind STEDI value estimation evolve, so should the operational guidance. Regular updates in the long term are necessary to achieve the long-term objective of a full QALY-based STEDI value estimation that is fully aligned with NICE's regular technology appraisal process. The operational guidance must therefore explicitly consider future progress, especially concerning data collection, evidence generation and methodological advancements and be updated accordingly in regular cycles.

EVIDENCE: EXPAND EXISTING AND BUILD NEW DATA SOURCES TO TRACK RESISTANCE AND CLINICAL OUTCOMES
LEAD STAKEHOLDER: CLINICIANS AND MICROBIOLOGISTS
SUPPORTING STAKEHOLDERS: INDUSTRY, HTA BODIES AND HEALTH ECONOMISTS

With previous advancements in knowledge, the next step for overcoming evidence uncertainties would be to expand existing and to build new data sources to track key variables of interest in real time. For example, the global scale of resistance generation and spread is one that is currently poorly understood. A global observatory would increase data quality and allow real-time estimation of resistance spreading as well as provide data for research to understand the dynamics of the spread of resistance. The observatory could be an expansion of that WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS). Currently GLASS has data with lots of gaps. In addition, through further research it may become clear that some countries are global sources of resistance more than others, similar to global spread of influenza, which would enable prioritisation of data infrastructure.

METHODS: FORMALISATION OF A COMPREHENSIVE METHODOLOGICAL FRAMEWORK TO FULLY CAPTURE STEDI VALUE WITHIN ECONOMIC EVALUATION
LEAD STAKEHOLDER: HTA BODIES AND HEALTH ECONOMISTS
SUPPORTING STAKEHOLDERS: INDUSTRY

In the long run, the objective should be to enable a full QALY-based evaluation. This does not mean that each antibiotic must be assessed against each STEDI element, but that the most likely value drivers can be quantified using QALYs. In this way, the opportunity costs of introducing a novel

antibiotic compared to other health technologies can be assessed, done so via comparable methods to other health technologies.

The objective should be to have a fully integrated value assessment framework between NICE's standard TA and the STEDI value framework. Methods must avoid double counting and results must be comparable with other health technologies to allow for an accurate assessment of opportunity costs. This can only be achieved if concepts are clear, scientific uncertainties are resolved, and a fully implemented data strategy allows for the generation of high-quality evidence. A validation exercise might be worthwhile to ensure that the outputs of the fully integrated value assessment have face validity.

Given the overall complexity of the value quantification of antibiotics, the potential to reduce complexity and increase efficiency needs to be identified. Hence, the progression of artificial intelligence or other technological advancements is likely to play an enabling role.

3.4   Comparisons with WHO research priorities for AMR

The WHO recently published a research agenda for antimicrobial resistance (WHO 2023), with the aim of identifying and prioritising research topics with the greatest impact on mitigating AMR in human health. They reviewed evidence gaps for anti-bacterial, anti-fungal resistance, and *Mycobacterium tuberculosis*, the causative agent of Tuberculosis (TB). They undertook an extensive systematic literature review to identify research gaps and then an expert committee on AMR grouped and prioritised the research gaps identified based on five criteria: 1) filling critical knowledge gaps, 2) answerability and feasibility by 2030, 3) potential for translation into policy 4) impact to mitigate AMR 5) promoting health equity. The committee also had a global remit which included specifying the relevance of the research topics to different resource settings including low-income settings. The outcome was forty research priorities split into four categories for bacterial and fungal resistance and one focussed on TB (prevention, diagnosis, treatment and care, cross-cutting and drug-resistant TB). As such, the scope of the WHO research priorities was different to the scope of this research roadmap. By design, their roadmap focuses on (what we classify as) evidence and scientific uncertainty only and does not consider other domains relevant to valuation.
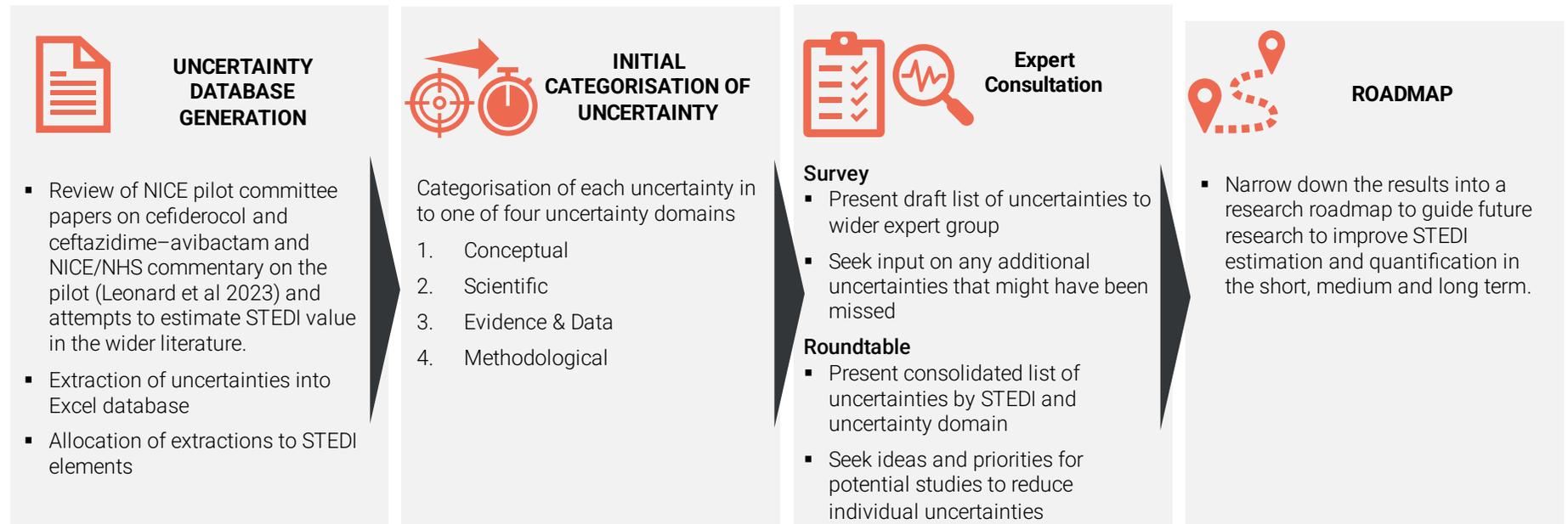
Despite these differences in scope, there are some overlaps in suggested research priorities which validate the importance of the uncertainties presented in Chapter 2 of this report and outlined in our research roadmap (Chapter 3). For example, WHO also recommend efforts to investigate strategies to improve empirical prescribing as well as diagnostics to support targeted therapy (see section 2.2.1 of our report). They also recommend research into the global epidemiology, mortality, morbidity and impact of infections by priority pathogens as well as the development of surveillance methods to generate accurate and reliable data (closely related to our suggestion of a global observatory). Similarly, they suggest research into the relationship between mass administration of antibiotics and the burden of resistance (i.e., the link between usage and resistance). In addition, they recognise the importance of further research into the factors driving colonisation with resistant pathogens. More generally, they recommend further investigations into how regulatory frameworks, marketing incentives and financing models affect the sustainable development, availability, equitable access and use of new antibiotic medicines. The consensus developing in the AMR world on the research needed to address important usage, policy and financing problems that contribute to the problem of AMR is encouraging and should be a catalyst for action in the research roadmap outlined here.

4 Conclusion

The threat of AMR requires concerted efforts to fight back. The NICE-NHSE pilot revealed, however, that current science, evidence base and methodological capability are insufficient for a full, QALY-based quantification of an antibiotic's value. The status quo of value assessment of antibiotics therefore compromises attempts (via pull incentives) to overcome the prevailing market failures that hinder antibiotic innovation.

The suggested roadmap provides a route to appropriate quantitative value assessment of antibiotics in the long run, via progression through three phases. The proposed actions require collective, interdisciplinary action. While the path towards a comprehensive value assessment of antibiotics will not be easy, we have identified various ways forwards and suggest that with meaningful stakeholder collaboration, significant progress can be made.

Appendix: Project overview

UNCERTAINTY DATABASE GENERATION

- Review of NICE pilot committee papers on cefiderocol and ceftazidime–avibactam and NICE/NHS commentary on the pilot (Leonard et al 2023) and attempts to estimate STEDI value in the wider literature.
- Extraction of uncertainties into Excel database
- Allocation of extractions to STEDI elements

INITIAL CATEGORISATION OF UNCERTAINTY

Categorisation of each uncertainty in to one of four uncertainty domains

1. Conceptual
2. Scientific
3. Evidence & Data
4. Methodological

Expert Consultation

Survey
- Present draft list of uncertainties to wider expert group
- Seek input on any additional uncertainties that might have been missed

Roundtable
- Present consolidated list of uncertainties by STEDI and uncertainty domain
- Seek ideas and priorities for potential studies to reduce individual uncertainties

ROADMAP

- Narrow down the results into a research roadmap to guide future research to improve STEDI estimation and quantification in the short, medium and long term.

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