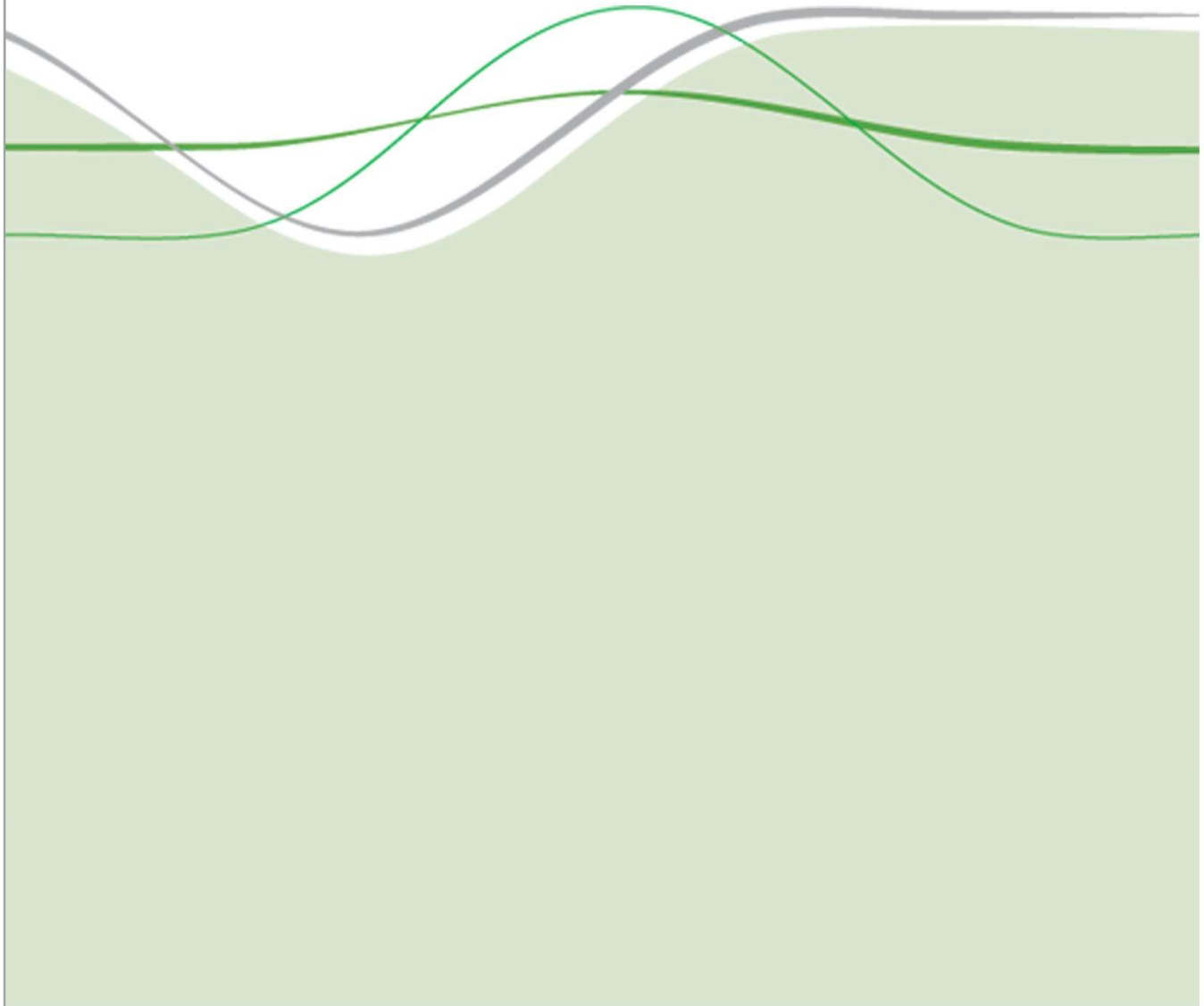


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The opinions expressed within this document do not necessarily reflect the views of any one of the organisations mentioned above.

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The Office of Health Economics (OHE) has over 50 years' experience of conducting high quality research on the economics of innovation and the life sciences industry, the organisation and financing of health care, and the role for outcomes research and health technology assessment. The OHE's current work programme is supported by research grants and consultancy revenues from a wide range of UK and international sources.

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The Academy of Infection Management (AIM) is a not-for-profit organisation, limited by guarantee, registered in the United Kingdom, under company number 07766910, with a registered office at the BioHub Science Park, at Alderley Edge, Cheshire. It is classified as an Infectious Disease society whose purpose is providing education for healthcare professionals. AIM engages with a global Faculty of clinicians with an interest in infectious disease (ID) in order to develop educational assets with the objective of improving outcomes through education. These are delivered via international congress or online via the AIM website at www.aiminfection.org

AIM works with government and academic institutions, other ID societies and industry in order to develop its programmes. AIM receives funding on a project by project basis through sponsorship/grants.

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Executive summary

Introduction

Antimicrobial resistance (AMR) occurs when microorganisms such as bacteria, viruses, fungi and parasites change in ways that render the medications used to cure the infections they cause ineffective.¹ Due to the development and rise of AMR, treatment options for multi-drug resistant (MDR) bacterial infections are decreasing and in some cases, only last resort therapies are available. Without new antibiotics, more patients will die from previously treatable infections.

The development of novel antimicrobials faces significant scientific, regulatory, clinical and economic challenges, and several organisations are currently working towards addressing them. However, a remaining issue is how antibiotics can be appropriately assessed, particularly by payers and/or health technology assessment (HTA) bodies, to take account of AMR and reflect the full benefit they provide to patients and society.

In the countries discussed in this paper², there are currently no specific HTA guidelines for the assessment of novel antibiotics; they are presumably therefore viewed and assessed similarly to other drugs in terms of how they are expected to demonstrate health gain (superiority trials with patients for whom reimbursement is sought) and may relevant wider societal benefits that are considered when making reimbursement decisions.

The purposes of this Briefing are: 1) to highlight the key challenges with the current approaches to assessing the clinical, economic and health system value of antibiotics; 2) propose additional elements of value that address these challenges from all relevant perspectives; and (3) suggest the next steps needed to refine and implement the additional concepts proposed. The Briefing reports on a multi-disciplinary, multi-stakeholder Value Forum, which focussed on how best to identify and assess the relevant elements of the value of new antibiotics to patients, health systems and society. This paper was developed by a project team, which included partners from the pharmaceutical industry (see 'Funding and acknowledgements').

Why do we need additional elements of value for antibiotics?

- 1. AMR is a public health priority.** The rise of AMR is recognised as a serious global and urgent threat, and tackling this threat is a priority for leading national and international organisations. Current HTA methods, in general, do not explicitly account for the value of reducing this public health threat, for example of the "insurance" value of having a treatment available in case of a future major or rapidly escalating problem of resistance.
- 2. A diverse set of non-inferior antibiotics are valuable to society.** Because of the rise of AMR, there is value in developing a new antibiotic for *MDR pathogens*, even if it is no more effective than existing antibiotics in treating susceptible (non-resistant) pathogens, since it enables diverse prescribing patterns. This concept is unique to antibiotics and is not explicitly considered by HTA bodies.
- 3. Non-clinical and microbiology data are important for demonstrating the value of antibiotics.** For antibiotics, non-clinical and microbiology data can be

¹ <http://www.who.int/features/qa/75/en/> [Accessed 23rd January 2017]

² France, Germany, Italy, Spain, Sweden and UK.

important predictors of outcomes. Difficulties in conducting clinical trials for antibiotics for MDR pathogens has led regulators to accept these alternative types of evidence as part of the approval process in areas of high unmet need

4. **Antibiotics have benefits that go beyond the patient treated.** When one patient is treated with an antibiotic, this reduces the spread of the infectious disease, leading to population-wide benefits.
5. **Antibiotics enable other types of treatment and procedures.** As well as treating infections, antibiotics reduce the risk associated with other types of treatment such as surgery and chemotherapy.

Additional Elements of Value Relevant to Antibiotics

We discuss 10 elements of value in this Briefing which can be split into two groups: relevant benefits typically included in HTA, and other types of benefits not traditionally included. We consider possible ways we can measure each element of value; the evidence that would need to be provided by the manufacturer to demonstrate value; whether the element/evidence is typically accepted by HTA bodies; and whether the issue is particularly relevant to antibiotics.

Focussing on the elements not typically included in HTA:

- **Transmission value** includes all benefits of avoiding the spread of infection to the wider population.
- **Insurance value** refers to the value of having a treatment available in case of a future major or rapidly escalating health problem.
- **Diversity value** refers to the benefits of reducing “selection pressure” (i.e. when an antibiotic fails to eradicate resistant strains, which then survive and multiply to create a resistance problem) and thus preserving the efficacy of existing antibiotics.
- **Novel action value** refers to the potential value associated with an antibiotic having a new or unique mechanism of action (MOA) or representing a new chemical structure i.e. first in class, which will provide “spillover” benefits.
- **Enablement value** is the value associated with enabling other treatments or procedures, e.g. surgery and chemotherapy.
- **Spectrum value** refers to the value associated with narrow spectrum antibiotics, which may be more valuable than broad spectrum antibiotics because they could reduce the spread of AMR by preventing ‘collateral damage’ to the microbiome.³

Discussion and next steps

Overall, there was broad agreement at the Forum that the additional elements of value were potentially relevant for HTA of new antibiotics. Participants offered a number of valuable insights into how further work could be approached in order to maximise both its practicality and its potential policy impact. In summary:

³ Williams and Wain (2014). Resurrection of a therapeutic area - problems and solutions in the discovery of new antibiotic drugs. *Pharmacology matters*.

- There is a need to refine and finalise the additional elements of value for consideration in HTA processes. This might focus (at least initially) on those most important/relevant to antibiotics and/or those that can be most feasibly measured or modelled, though there is a risk that excluding elements on this basis may be over-deterministic and therefore not achieve the necessary reform to ensure that new antibiotics are appropriately valued by health care systems.
- There is further work required to understand how these additional elements of value can be used to make HTA decisions. One option is multi-criteria decision analysis (MCDA), designed to introduce more structure into HTA decision making. Further research would be necessary, however, to explore how the elements of value could be presented, weighted and aggregated to make a decision. There are several MCDA models that could be used for this purpose, including those that are more algorithmic (involving development of common scale and weights) and those that support a more deliberative approach. Given that most HTA decision making is deliberative, then an MCDA approach that introduces more structure into a deliberative process is likely to be more attractive to HTA bodies.
- Further discussion is needed as to which elements of value could usefully be assessed at the product level, and so potentially by an HTA body, and which elements require a broader public health perspective. Whilst HTA bodies could help assess evidence of such broader elements, it might not be appropriate to reflect these in a higher per unit price for the product. Rewarding stewardship, or recognising the insurance value of having treatments available but not used, for example, may keep volumes low and require different types of contractual relationship between Health Ministries, hospitals and antibiotic manufacturers to provide, for example, top-up payments for making new antibiotics available.
- There is a clear need for further education in order to expand awareness among HTA bodies and health care payers of the particular characteristics of antibiotics and infectious diseases as a therapy area and the associated HTA challenges. It may be that experience from vaccine HTA, where transmission modelling is widely used, and there is emerging recognition of the "peace of mind" benefits provided by vaccination, can be used in HTA of antibiotics.
- Further discussions between regulators and HTA bodies are needed, particularly since many of the reforms to regulatory processes to facilitate development of novel antibiotics have significant impacts on the availability of data for reimbursement decisions. In particular, clinical trial design needs to change so that sufficient data on MDR pathogens in a relevant patient population is captured and forms part of the value assessment at HTA level. Ongoing collection of such data through post-marketing surveillance studies and registries, linking microbiological data and clinical outcomes is needed.
- Further education is needed to inform on the relevance and predictive value of antibiotic PK/PD and microbiology data in clinical decision making.
- The Forum was not able to recruit participants currently working at payer/HTA bodies in France, Germany, Spain and Italy. It is important that future activities in this area include these stakeholders.

1. Introduction

1.1. The growing issue of antimicrobial resistance (AMR)

Antimicrobial resistance (AMR) occurs when microorganisms such as bacteria, viruses, fungi and parasites change in ways that render the medications used to cure the infections they cause ineffective.⁴ The World Health Organisation (WHO) regards the growth of AMR as “so serious that it threatens the achievements of modern medicine”.⁵ Due to the development and rise of AMR, treatment options for multi-drug resistant (MDR) bacterial infections are decreasing, and in some cases, only last resort therapies are available. Without new antibiotics, many patients will die from previously treatable infections and minor injuries. Additionally, availability of effective antibiotics underpins both common surgical procedures (including hip and knee replacement surgery, organ repairs and transplants), and chronic treatments (such as chemotherapy for cancer patients and HIV medicines). The fight against AMR is long term: the development of resistance is inevitable and new antibiotics will always be needed. Therefore, continued research and development (R&D) in this area is required.

The UK’s O’Neill Review on AMR⁶ estimates that if no action is taken to increase stewardship and accelerate R&D, then by 2050 AMR would result globally in 10 million additional deaths per year and cost at least \$100 trillion in hospital costs and productivity losses over the total time period. On the other hand, O’Neill estimates that the global cost of preventing such an outcome would be of the order of \$40 billion over a 10 year period. Note that there is some dispute over these estimates.⁷

Tackling the problem of resistance requires a multi-sectoral, collaborative global effort to reduce infection rates, ensure the availability of effective treatments, rapidly diagnose and treat infections, and foster responsible antimicrobial stewardship.

1.2. Research and development (R&D) challenges in antibiotics

Ensuring effective treatment options for bacterial infections requires not only to slow the rate of AMR but also to accelerate the R&D of new antibiotics, ideally with novel mechanisms of action. But in reality a ‘perfect storm’ is brewing: AMR is increasing, but R&D investment in this area is falling (Cooper and Shlaes, 2011⁸, Shlaes, 2010⁹).

A number of antibiotics are currently in development (see Figure 1), but a sizeable majority of these are unlikely to progress to licensing due to R&D attrition, which appears to be higher for antibiotics than other therapeutic areas (see below). Further, as resistance develops against a certain antibiotic, it eventually loses efficacy and is no

⁴ <http://www.who.int/features/qa/75/en/> [Accessed 23rd January 2017]

⁵ World Health Organization, 2014. Antimicrobial resistance global report on surveillance: 2014 summary.

⁶ The Review on Antimicrobial Resistance was commissioned in July 2014 by the UK Prime Minister, who asked economist Jim O’Neill to analyse the global problem of rising drug resistance and propose concrete actions to tackle it internationally. It was established an independent, two-year, time-limited process, and the Review engaged widely with international stakeholders to understand and propose global solutions to the problem of drug-resistant infections from an economic and social perspective, and produced its final report and recommendations in the summer of 2016. O’Neill, 2016. Tackling drug-resistant infections globally: Final report and recommendations. Available here <https://amr-review.org/> [Accessed 23rd January 2017]

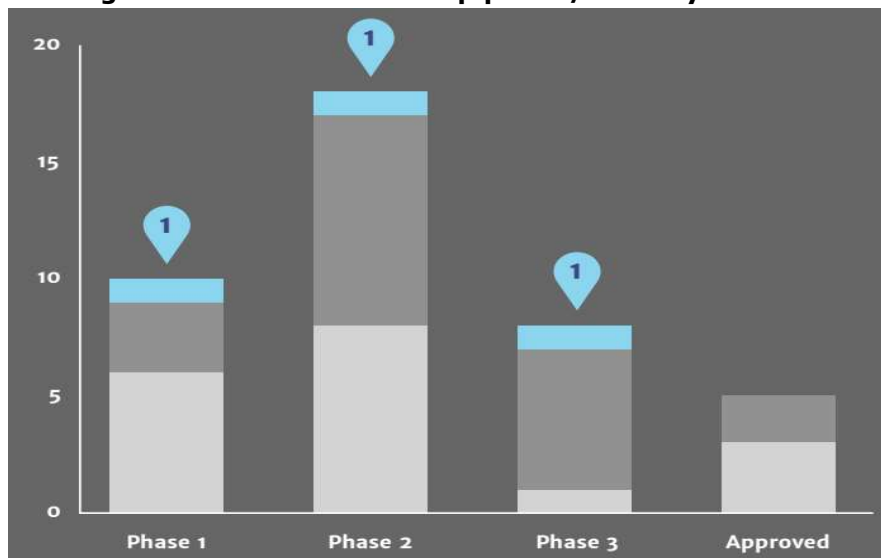
⁷ See de Kraker, Stewardson and Harbarth (2016) *Will 10 Million People Die a Year due to Antimicrobial Resistance by 2050?* Available at <http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002184> [Accessed 7th May 2017]

⁸ Cooper and Shlaes, 2011. Fix the antibiotics pipeline. *Nature*, 472, 32

⁹ Shlaes, 2010. *Antibiotics: The Perfect Storm*. Springer.

longer medically useful. The number of antibiotics becoming obsolete now exceeds the number of new therapies being approved (see Figure 2).

Figure 1: Antibiotics in the pipeline/recently licensed



Source: O'Neill Review, 2015¹⁰. Data from 2014. Notes: Blue: high priority - Potential for activity against at least 90% of carbapenemase-producing bacteria in the UK; Dark grey: medium priority - Targets at least one CDC 'Urgent' threat (Clostridium difficile, carbapenem-resistant Enterobacteriaceae or drug-resistant Neisseria gonorrhoea, but is not classed as a potential break through); Light grey: Low priority - Does not meet the criteria for "clinically useful".

Figure 2. Average new antibiotic molecules per year



Source: IFPMA, 2015¹¹

¹⁰ O'Neill Review, 2015. Securing new drugs for future generations: the pipeline of antibiotics. Available at: <https://amr-review.org/> [Accessed 7th May 2017]

¹¹ IFPMA, 2015. Rethinking the way we fight bacteria. Available at: http://www.ifpma.org/wp-content/uploads/2016/02/IFPMA_Rethinking_the_way_we_fight_bacteria_April2015_FINAL.pdf [Accessed 7th May 2017]

The development of novel antimicrobials faces significant challenges in three key areas:

1. **Scientific** – Major scientific challenges are associated with antibacterial discovery research – see for instance, Payne et al. (2007)¹². The authors report that a pharmaceutical company's success rate for antibacterial high throughput screening (HTS) was four to five-fold lower than for targets in other therapy areas.
2. **Regulatory and clinical** – Difficulties with trial design, especially around the evidence that can be generated pre-launch e.g. the challenges of obtaining superiority data and data for clinicians to make decisions for individual patients. Some of the regulatory challenges have been addressed in recent years. These issues are discussed in Section 2.
3. **Economic** – There are limited returns to investment in novel antibiotics. When safe and effective novel antibiotics are introduced, good antibiotic stewardship typically calls for reserving their use for bacteria that are resistant to existing antibiotics. Such resistant infections are initially rare, limiting demand for a novel antibiotic. Additionally, there is currently a lack at the local level of both rapid diagnostics and of good quality surveillance data on resistance to guide appropriate clinical use of new treatments, reinforcing reluctance to use a new drug. Current approaches to health technology assessment (HTA) and reimbursement can undervalue the current and future public health benefit of novel antibiotics in curtailing the development and rise of resistance (see Section 3.2). Reimbursement is often based on the prices of older, generic medicines available at low prices. These multiple factors result in low financial returns from antibiotic R&D relative to R&D in other therapeutic areas (see for instance Sharma and Towse, 2011¹³).

Global action to address these three challenges has been recommended by the United Nations (UN), the World Health Organisation (WHO) and the European Union (EU). On Challenge 1, the O'Neill Review recommended that more research funding is needed to kick-start early research into new antimicrobials and diagnostics (O'Neill, 2016⁶). Pre-competitive/open innovation research programmes are bringing companies and academics together to reduce the risks associated with antibiotic R&D (e.g. the Innovative Medicines Initiative's (IMI) TRANSLOCATION¹⁴ and ENABLE¹⁵ projects). The

¹² Payne DJ, Gwynn MN, Holmes DJ, Pompliano DL (2007). Drugs for bad bugs: confronting the challenges of antibacterial discovery. *Nature Reviews Drug Discovery* 6: 29-40

¹³ Sharma and Towse, 2011, New drugs to tackle AMR. Analysis of EU policy options. Office of Health Economics. London.

¹⁴ The Innovative Medicines Initiative's (IMI) TRANSLOCATION is a consortium made up of more than 19 academics/biotechs and five large pharma companies working together to improve the success of antibacterial discovery by understanding how drugs enter bacterial cells. See more at: <http://www.imi.europa.eu/content/translocation> [Accessed 23rd January 2017]

¹⁵ The Innovative Medicines Initiative's (IMI) ENABLE project consists of 32 initial partners, 18 academic groups, 10 SMEs and four large pharma companies, aiming to create a shared drug discovery platform to advance the development of potential antibiotics against Gram-negative bacteria. See more at: <http://nd4bb-enable.eu/> [Accessed 23rd January 2017]

Trans-Atlantic CARB-X initiative has been set up to provide funding and expertise to help research lead to products entering clinical development¹⁶.

On Challenge 2, and as highlighted in Section 2 of this report, regulators are working on adapting regulatory pathways and streamlining development of novel antibiotics. On Challenge 3, discussed further in Section 3, there is work under way by national authorities and other relevant stakeholders to address the economic challenges through novel incentive mechanisms and new commercial models, while ensuring stewardship and access strategies are in place. Efforts include the IMI DRIVE-AB project¹⁷.

However, there is a remaining issue: how antibiotics can be appropriately assessed, particularly by payers and/or HTA bodies, to take account of AMR and reflect the full benefit they provide to patients and society. Current HTA and reimbursement frameworks typically rely on evidence of superiority in clinical, health economic and patient-reported outcomes generated via randomised controlled trials (RCTs). While these frameworks are both appropriate and have been applied successfully in multiple therapeutic areas, more sophisticated approaches (detailed in Section 4) to evidence and elements of value may be needed for new antibiotics. Similarly, clinicians will need to consider a wider range of data in addition to that derived from conventional registration studies to guide treatment choice.

1.3. Developing this OHE Briefing

The purposes of this Briefing are: 1) to highlight the key challenges with the current approaches to assessing the clinical and health system value of antibiotics; 2) propose additional elements of value for antibiotics which address these challenges from all relevant perspectives and (3) suggest next steps to refine and implement an agreed approach to assessing the value of antibiotics.

The Briefing was developed in two stages. In the first stage, the authors, in collaboration with a project team (including partners from the pharmaceutical industry; see 'Funding and acknowledgements')¹⁸, developed a paper that explored the challenges of assessing new antibiotics from the clinical, regulatory and HTA perspectives using a combination of literature reviews and discussions with experts. The paper also proposed a Value Framework for antibiotics, highlighting the elements that are included in traditional HTA and those generally not considered in the HTA process but of particular relevance to antibiotics.

In the second stage, a multi-disciplinary, multi-stakeholder Value Forum was held, focusing on how best to identify and assess the relevant elements of the value of new antibiotics to patients, health systems and society, including the value related to

¹⁶ CARB-X describes itself as "possible the largest public-private partnership in the world dedicated to preclinical antibiotic development." It has seven partners in the United States and the United Kingdom backed with half a billion dollars in funding. CARB-X partners are working together to set up a diverse portfolio with more than 20 high-quality antibacterial products. See more at <https://www.phe.gov/about/barda/CARB-X/Pages/default.aspx> [Accessed 7th May 2017]

¹⁷ The Innovative Medicines Initiative's (IMI) DRIVE-AB is a consortium composed of 16 public and 7 private partners from 12 countries, tasked with the development of novel economic models that can create incentives for the discovery of novel antibiotics while ensuring responsible use. See more at: <http://drive-ab.eu/http://drive-ab.eu/> [Accessed 23rd January 2017]

¹⁸ The role of the project team was to discuss with and advise OHE and AIM on the development of the Forum programme, invitees, background papers and publications. In addition, there was a Steering Committee which was responsible for the governance of the project.

addressing the challenges of AMR. The paper developed in the first stage of the project was circulated to all participants as a pre-meeting read.

The forum took place over two days in February 2017 and was held under the Chatham House Rule – which means that all those attending may report freely what was said during the discussion, but not who said it. It involved 33 participants representing regulators, payers/HTA bodies, government, clinicians and industry from a number of EU countries. A list of participants is available in Appendix B. It should be noted that payer/HTA representatives from France or Germany were not present, and the representatives from Italy and Spain did not currently work at their country's payer/HTA organisations.

A key purpose of the Value Forum was to encourage open discussion in order for all stakeholders to understand the issues from each other's perspectives. A specific objective was to scrutinise the additional elements of value proposed for antibiotics and provide insights as to whether and how the concepts and proposals can be further developed with the aim of being relevant to HTA/payer policy in this area.

Following the Forum, key discussion points from the meeting were integrated into the pre-reading document to produce this Briefing. In particular, the Briefing includes feedback from participants on the additional elements of value proposed for antibiotics, and suggestions for further work.

The structure of the remainder of this Briefing is as follows:

- The regulatory and clinical issues associated with antibiotic trial design are outlined in Section 2. This includes a discussion of alternative sources of clinical data that could inform clinician and payer decisions.
- The role of HTA bodies is outlined in Section 3.
- In Section 4, we outline the different types of benefits that could be considered to comprise 'value' in health care and society more widely, with particular attention paid to the types of benefits offered by antibiotics. We also make suggestions as to how this thinking could be used to guide HTA and reimbursement decisions.
- In Section 5 we highlight the key insights gained from the Value Forum, focusing on how the framework could be revised in order to maximise both its practicality and its potential policy impact.
- In Section 6 we outline next steps for the project, including prioritising work on the elements of value presented in Section 4, modelling and evidence generation and suggestions on how to put the new elements of value relevant to antibiotics into practice. We then make some concluding remarks.
- Appendix A lists the acronyms, and Appendix B provides the list of participants of the Value Forum.

2. Regulatory and clinical issues

2.1. Clinical trial challenges

There are significant challenges in demonstrating superiority in clinical registration trials for new antibiotics whose main utility is likely to be activity against MDR pathogens.

These include:

- The choice of comparator.
- The patient population under study.
- The end points to be studied.

Choice of comparator

There is an ethical requirement to select a comparator which has activity against the likely causative pathogens. Antibiotics must be compared to an active comparator that is considered best available therapy (BAT) for the indication being studied. The trial cannot be designed to deliberately seek superiority in a way that puts patients at risk: it would be unethical to assign a patient to an arm of a study if they were at risk of being infected with a resistant organism against which the antibiotic that was the active comparator was known to be ineffective.

Given the lack of currently available antibiotics with activity against some MDR pathogens, this makes comparator selection difficult. SOC varies by geography, depending on local resistance patterns, among other factors, making it difficult to find a comparator that is SOC across different clinical trial locations.

Combination therapy may be employed in order to broaden the pathogen coverage however, this may result in a spectrum of activity that overlaps with the antibiotic under study, making it difficult to measure the safety profile and effectiveness of either agent.

Patient population

The complex nature of the conditions experienced by hospitalised patients with serious infections presents a significant challenge to demonstrating superiority in terms of outcomes. Several factors contribute to this:

- Patients with serious bacterial infections need urgent intervention with empiric¹⁹ antibiotic treatment.
- There may be diagnostic uncertainty about the aetiology of the patients' underlying disease, or difficulties in obtaining patient samples to identify the bacterial aetiology.
- Approvable indications in registration trials are usually based on infection site/type, rather than pathogen, and not all infection sites yield sufficient numbers of patients with resistant pathogens to support a meaningful statistical analysis of the antibiotic efficacy.

¹⁹ The definition of "empiric" therapy is treatment with an antibiotic when the causative bacteria is unknown

- Patients recruited to clinical trials are often only moderately ill compared to the real-life population (of severely ill patients) in which the antibiotic will have greatest utility.

Endpoints

The most widely accepted outcome measure in antibiotic trials is resolution of infection, usually expressed as “Test of Cure” (TOC). This may be a microbiological evaluation (ME) or a clinical evaluation of patient improvement (CE) based on the clinician’s opinion, or a composite of both. In some cases mortality is the expected regulatory endpoint. The endpoints used vary depending on regulatory authorities’ expectations and the infection and site under assessment.

Due to the high overall bacterial clearance rates for existing antibiotics, especially for susceptible organisms, there is little room for improvement in demonstrating superiority of a novel antibiotic against BAT using this outcome. Given this further challenge to demonstrating superiority, the inclusion of composite endpoints incorporating patient-related and societal factors, or the inclusion of novel biomarkers, should be considered in future clinical trials.

Non-Inferiority v Superiority trials

For the reasons explained, non-inferiority studies tend to be the norm for antibiotics in drug development.

The area of greatest unmet need, and therefore the development focus for new antibiotics, is the treatment of multi-drug resistant (MDR) organisms. Whilst, in theory, a superiority trial design may be possible, the numbers required to demonstrate this would be beyond the ability of most research groups to enrol. Recruitment into clinical trials for MDR antibiotics is particularly difficult because the patients that would be given the antibiotic in practice are severely ill and therefore often unable to provide written informed consent. Moreover, the number of patients with MDR can be very low.

For example, based on an infection with an expected mortality rate of 18% (e.g. hospital acquired pneumonia), a non-inferiority study, powered sufficiently to detect a statistically meaningful difference at a margin of 12.5%, would require around 400 patients to be recruited. For a similarly powered superiority study, aiming to show a 5% reduction in mortality, over 2000 patients would need to be recruited. As seen in some other therapy areas, in addition to increasing costs, the primary challenge is that recruiting these patients would extend timelines well beyond what may be practical or desirable, considering the urgent need for new antibiotics to treat those patients who are ill with an MDR infection.

Non-inferiority trials aim to provide evidence that a new antibiotic is not inferior to BAT in terms of efficacy in a given patient population²⁰. In a world where antibiotic resistance is reducing the number of treatment options available, these trials, by themselves, provide evidence that a new drug is effective and facilitates the availability of alternative treatment options that may have the potential to reduce *selection*

²⁰ For the FDA’s Guidance on Non-Inferiority Trials, see: <https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf> [Accessed 7th May 2017]

*pressure*²¹ on other agents. However, given that the major unmet need is for new agents to treat MDR infections, and that numbers of patients with MDR infections in clinical registration trials are likely to be few in number, non-inferiority trials do not necessarily provide sufficient data on which to make a confident clinical, or economic, decision.²² For this reason, further data are required.

Recent developments in antibiotic clinical trials

Pathogen specific-based studies

To address the increasing threat of MDR pathogens and incentivise greater investment in antibiotic development, regulators have recognised the importance of pathogen-based studies²³. Whilst these remain operationally challenging to recruit for, and more agreement is needed as to how data collected across body sites can be pooled and analysed, they do offer an opportunity to better study an antibiotic in a way closer to the way it will be used post-approval.

Greater emphasis on PK/PD and microbiology surveillance data

For antibiotic studies to inform decision-making, greater consideration of non-clinical endpoints is needed. Non-clinical end points are increasingly important in antibiotic trials. These include Pharmacokinetics (PK) and Pharmacodynamics (PD), and in-vitro microbiological susceptibilities.

Pharmacokinetics describes the drug concentration-time course in body fluids resulting from administration of a certain drug dose. Pharmacodynamics describes the observed effect resulting from a certain drug concentration.

Microbiology surveillance data provide a valuable source of information on the incidence and spread of MDR infections at a global, regional, and national level. Most importantly, at the local level, given the significant variance of resistance patterns (even within the same institution) it informs on local susceptibilities. It therefore forms a key part of the prescriber decision-making process and complements clinical information.

Traditionally, PK/PD studies for antibiotics have focused on defining dosage regimens for specific indications and drug exposure profiles to target pathogens. More recently they have been used for predicting therapeutic outcomes in different patient populations and for developing strategies to minimise the development of bacterial resistance.

Further application of PK/PD knowledge is being studied to help better define duration of treatment, which in turn may reduce the number of clinical studies needed to demonstrate efficacy. Understanding the PK/PD in specific patient populations may lend itself to supporting conditional approval of new antibiotics for specific indications, e.g. hospital acquired pneumonia (see Section 2.1).

²¹ "Selection Pressure" is when an antibiotic fails to eradicate resistant strains, which then survive and multiply to create a resistance problem

²² Note that although non-inferiority trials are informative for assessing alternative treatment options, they cannot be used to determine treatment pathways, e.g. for escalation of therapy.

²³ Pathogen-based studies contrast to indication specific studies, which focus on the site of the infection as opposed to the pathogen across different sites of infection.

Clinical trial networks

Experts have argued²⁴ that clinical trial networks could be a potential solution to the challenges of recruiting sufficient numbers of specific patient types in a single clinical trial. Networks of centres recruiting patients with serious infections could help address recruitment problems, as well as helping to streamline the process of setting up and running trials. In addition, they could improve trial quality through increased experience and use of a consistent, gold-standard comparator. Discussions at the Forum confirmed the importance of clinical trial networks as a potential mechanism to address the regulatory challenges of antibiotic development.

Post-approval evidence commitments

Recently a shift towards approving some antibiotics on the basis of smaller data packages (see Section 2.2), e.g. Phase I and II data, has taken place, and observational evidence is now seen by some as a viable complement to clinical trial data where large-scale RCTs are not feasible. For this to be realised, it would require a commitment, on behalf of the manufacturer, to collect real-world data post-approval, in order to further understand the safety and efficacy of the antibiotic and lead to better understanding of its utility, and therefore, value. In many cases companies are already doing this. Expanded microbiological surveillance programmes and other real-world evidence bases, such as clinical registries, are needed. Clinical registries which document experience in the real world across multiple geographies, patient types, infection sites and types of bacteria provide a valuable source for this information, but also require a substantial, ongoing financial commitment. Clinical trial networks, discussed above, could form an important basis for coordinated and reliable collection of data beyond trials at centres of expertise. For this to be possible, more detailed surveillance studies, linking microbiological and clinical outcomes would be required.

2.2. Streamlined regulatory process

The European Medicines Agency (EMA), the US Food and Drugs Administration (FDA) and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) consider that a robust response to the problem of AMR must be multifaceted and that the regulatory approach for the evaluation of antibacterial agents is an important element of the total response that is required to encourage and accelerate new antibacterial drug development to meet patient needs. Further, these agencies have made commitments to harmonise requirements and taken steps to streamline development.

The EMA in particular has taken steps to streamline the approval of new antibiotics that treat resistant infections and address areas of high unmet need. In 2011, it revised the EU regulatory standards for the approval of new antibiotics in relation to endpoints, non-inferiority margins and analysis populations.²⁵ The guidelines were further revised in 2013 to incorporate additional detail relating to study design and areas of unmet clinical need.²⁶ In addition, in 2016, comprehensive new guidelines were issued on PK/PD investigations in the development of antibiotics, encouraging collection of PK/PD data

²⁴ McDonnell A, et al. Clin. Infect. Dis. 2016;63:S57-9

²⁵ EMA (2011) *Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections*

²⁶ EMA (2013) *Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections*

from patients, use of in-vitro models to evaluate resistance selection, and determination of PK/PD targets and the probability of target attainment.²⁷

Specifically, EMA guidance now stipulates that non-inferiority trials are acceptable for five major indications: acute bacterial skin and skin structure infection (ABSSSI), community-acquired pneumonia (CAP), hospital-acquired/ventilator-associated pneumonia (HAP/VAP), intra-abdominal infection (IAI) and complicated urinary tract infection (cUTI). Ideally, the comparator would be one deemed to be sufficiently 'robust' to enable thorough assessment of the test antibiotic's value. Superiority studies are required, however, for other infections, such as acute exacerbations of chronic bronchitis and acute sinusitis.

In addition, the EMA can accept limited data packages in areas of high unmet need, including infections caused by MDR pathogens. In this case, data would be required to support understanding of the impact of resistance mechanisms on the new antibiotic's activity and extensive microbiological and PK/PD data are essential. PK/PD data are expected to become increasingly important, therefore comprehensive new guidelines have been issued on PK/PD investigations in the development of antibiotics. Further efficacy and safety findings could be derived from studies of site-specific infections, prospective uncontrolled studies, and observational data from registries.

In a recent, 2016, example, a new antibiotic was approved by the EMA for three major indications. One indication, in ventilator/hospital-acquired pneumonia patients, was supported by lung exposure data based on phase I data from healthy volunteers, efficacy and safety data from phase II/III trials in complicated urinary tract and intra-abdominal infections and PK/PD data from an ongoing phase III trial in ventilator/hospital acquired pneumonia patients. These data were supplemented with in-vitro microbiological susceptibility data that demonstrated which microbes are susceptible to the agent. The EMA justified the approval with the following statement:

The Agency's Committee for Medicinal Products for Human Use (CHMP) decided that [new antibiotic] benefits are greater than its risks and recommended that it be approved for use in the EU. The CHMP considered that the studies on [new antibiotic] show that it is effective at treating complicated intra-abdominal and urinary tract infections. A study of [new antibiotic] in patients with hospital-acquired pneumonia has not yet been completed. However, the CHMP considered that the data already available supported [new antibiotic's] activity in hospital-acquired pneumonia and for the treatment of infections due to aerobic Gram-negative organisms in adult patients when other treatments might not work.

2.3. Implications of streamlined regulatory processes

As a result of these new regulatory paradigms, new antibiotics are now reaching market authorisation with a smaller base of evidence than before. Therefore, it becomes even harder to use evidence collected in registration trials to provide the degree of certainty about the economic or clinical benefits typically expected for clinical and reimbursement decisions at-launch. Combining traditional clinical trial endpoints with non-clinical endpoints, such as pathogen susceptibility and patient PK/PD data, may, however, provide meaningful information to inform decision-making from a clinical, economic and regulatory perspective. A further consequence of such a paradigm shift in the type of

²⁷ EMA (2016) *Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products*

evidence used for regulatory approval of new antibiotics will be an increased need to build a post-launch database to generate observational evidence in post-marketing surveillance of effectiveness as well as safety. These issues are discussed further in Sections 3 and 4.

2.4. How clinicians make prescribing decisions for antibiotics

At the reimbursement approval stage, some assessment of therapeutic added value, or cost-effectiveness, is made at a national or regional level by HTA authorities. This is discussed in more detail in Section 3. National or regional level decisions will influence the choice of antibiotics available to the clinician at the local level. In some cases a decision may be taken at the national or regional level that an antibiotic is not to be made available in that geographical area.

At the hospital level, usage of antibiotics is routinely controlled – in many cases, strictly controlled – and it is unusual for antibiotics to be prescribed unless they are approved for inclusion on the hospital formulary. Choice of antibiotic prescription in hospitals is protocol driven, and approval for inclusion on the hospital formulary is generally based on cost, as well as clinical, factors. At the Forum, however, the point was made that clinical trial and other data are not always at the forefront of clinicians' minds when selecting an antibiotic to administer; in practice, prescribing decisions were often described as highly subjective or simply based on habit. Clinical efficacy data are often lacking and the decision to include an antibiotic on formulary will often be based on its microbiological activity and ability to solve specific pathogen problems occurring at that institution. As a result, use will be heavily restricted to tackling those specific pathogens. It is important also to note that an unintended consequence of protocol-driven clinical decision-making can be to produce homogeneous prescribing patterns which contribute to the rise of AMR²⁸.

There are significant variations in bacterial resistance patterns from one region to another, from one hospital to another and even from one ward to another in the same hospital, in addition to significant inter-patient variability. In choosing which antibiotic to prescribe for a seriously ill patient, the clinician will consider several criteria, based not only on the properties of different antibiotics, but a range of other factors:

- Patient factors, including: past medical history, previous antibiotic treatment, site of infection, clinical symptoms, any recent travel to areas where resistant pathogens are prevalent, and the general severity or fragility of the patient due to other co-morbidities.
- Environmental factors, including: the prevalence of known resistant pathogens both in the host institution and the institution from where the patient was admitted.
- Personal clinician preference: antibiotic prescribing decisions are influenced to some degree by the extent to which a doctor may be familiar with a certain antibiotic, providing the doctor feels that antibiotic is likely to cover the causative bacteria. In MDR infections, the lack of available treatment options may lead to over-selection of certain antibiotics, sometimes based on

²⁸ Use of the same drug to tackle an infection in an institution increases selection pressure, and will speed up the build-up of resistance. Ideally, the use of antibiotics is varied over time.

familiarity. The resultant homogenous prescribing, increases selection pressure and drives resistance.

- Diagnostic results: However, while rapid molecular tests may eventually supplant culture-based methods, currently microbiology testing may take between 48 and 72 hours to yield a result. Even then, the result could be inconclusive. In the meantime, treatment needs to be initiated empirically with an antibiotic that will cover the most likely cause/s of the infection.

The bacterial spectrum of the antibiotic is therefore a very important consideration. Activity against difficult-to-treat pathogens, such as resistant strains, is of very high importance, especially in institutions where those strains are known to be prevalent or in patients thought or known to be at higher risk of infection by them.

In summary, the way that clinicians choose antibiotics is based upon the local bacterial resistance environment, patient type, personal clinical preference, and the properties of the antibiotics available to them, of which the ability to cover the likely causative pathogens is key.

3. Payers and health technology assessment (HTA)

3.1 Health technology assessment (HTA) challenges for antibiotics

As mentioned above, there are concerns that the methods currently used by HTA and payer bodies may not capture the full range of benefits that antibiotics offer to patients and society, including the value of addressing AMR. Two main challenges are described below and discussed in the following sections of this report:

- First, for the reasons discussed in Section 2, registration trials of new antibiotics are typically designed to demonstrate non-inferiority, not clinical superiority. HTA bodies generally expect superiority data to demonstrate value. Furthermore, decisions by regulators to approve new antibiotics, and, subsequently, by clinicians to prescribe them to patients with potentially resistant infections, may reflect a wider range of data than that provided by the principal outcome measures in the pivotal trial, and HTA and payer bodies probably do not currently understand the relevance and significance of this additional data.
- Second, in the formal assessment process, the methods used by most HTA and payer bodies do not provide the opportunity to consider the public health related benefits that new antibiotics offer, particularly in the context of the rise in AMR. This can in principle be met by identifying and including these benefits as additional elements of value. It may be necessary to match this with more complex payment mechanisms, as an adjustment in reimbursed price may not be able to reflect these benefits.

We noted earlier that a new antibiotic was recently given regulatory approval by the EMA on the basis of pre-clinical PK/PD data, Phase II data, together with a requirement to collect additional post-marketing data. The regulator's decision reflected its view of the potential public health value of the new antibiotic to address an urgent unmet medical need. But the regulator's acceptance of a limited data package provides challenges for HTA bodies and payers who have less evidence of individual patient benefit than they

would normally expect, and who may have no means of factoring the wider public health value, which motivated regulatory approval, into their formal assessments.

Paradoxically, the possibility exists that while a new antibiotic may be licensed earlier in response to public health imperatives to expand patient access to effective antibiotics, it may take longer for it to be reimbursed by payers at the national level if the evidence base is limited, and indeed it may never be reimbursed, because of lack of HTA-relevant evidence. For this reason, it is imperative to reach agreement on how the two challenges above can be addressed.

The remainder of Section 3 discusses these issues in more detail in the context of current and evolving practice amongst HTA bodies and payers:

- Section 3.2 summarises approaches to reimbursing hospital-based medicines.
- Section 3.3 analyses in more detail the challenges that new antibiotics present for current HTA methods.
- Section 3.4 summarises HTA current practice in relation to antibiotics.
- Section 3.5 describes recent developments in their assessment.

3.2 Reimbursement of hospital-based medicines

Most antibiotics used in hospitals in most European countries are funded via a tariff-based system of reimbursement which sees hospital providers paid a lump sum for a patient episode, depending upon that individual's diagnosis. All inpatient costs, including diagnostics, provider care and medications, are bundled into a single tariff price for a given 'diagnosis-related group' (DRG). This creates pressure to minimise costs and so a disincentive for hospitals to authorise use of higher priced novel antibiotics, even when clinically justified. Such systems can, however, allow for exemptions/exclusion from the tariff for 'high cost' drugs (i.e. 'unbundling' from the DRG and reimbursing providers separately for their use). However, there is only one recent example we are aware of where a novel antibiotic was successful in achieving additional funding via listing on a 'high cost' drugs formulary, which was a T2A exclusion in France.

Although DRGs and additional funding mechanisms that enable the reimbursement of expensive inpatient drugs is not a focus of this Briefing, it is important to highlight two relevant points. First, DRG payments for a diagnosis-treatment pair are reset infrequently, other than for increases reflecting general inflation. It can take some time (even years) for them to reflect the cost of new drugs. Second, the criteria used to decide which novel drugs (including antibiotics) receive (or not) additional funding at the hospital level could be made clearer. If not, then HTA recommendations about use or non-use of a new antibiotic may not be implemented at the hospital level. For a discussion of the challenges involved in adapting DRGs to take account of treatment innovation see Sorenson et al., (2015).²⁹

²⁹ Sorenson et al., (2015). *Health Economics, Policy and Law*, 10:2, 133-159.
Doi:10.1017/S1744133114000358.

3.3 The challenge of antibiotic assessment for current HTA methods

In terms of the challenges for antibiotics in demonstrating benefit and value within the confines of the current HTA frameworks, it is useful to distinguish between patient-level benefits and benefits beyond the immediate health gain to the patients treated.

Patient-level benefits of antibiotics

As described above, HTA bodies in Europe make decisions based on an assessment of patient-level health gain using, as a starting point, clinical effectiveness data. In order to demonstrate health gain, HTA bodies typically require manufacturers to provide evidence of statistical superiority (relative to an active comparator) via some health outcomes included in RCTs. However, as discussed in Section 2.1, non-inferiority trials are the norm for antibiotics and there are generally few patients with resistant infections in clinical trials.

Demonstrating the benefit of new antibiotics against these resistant infections may instead require clinical evidence involving PK/PD data, non-clinical evidence such as in vitro microbiology susceptibility testing and/or post-launch data collection. Surveillance processes (see Section 2.1) will help collect post-launch data in a wider population, although currently it is unclear what form of post-launch data collection will be feasible, given the small number of multi-drug resistant cases likely to be treated with the new drug.

The need to consider additional types of evidence in the assessment of antibiotics is augmented by a further challenge. As patients infected with serious hospital-acquired infections are likely to remain in hospital for reasons other than the infection, and may have high mortality rates, demonstrating a significant benefit in terms of reduced length of hospital stay, overall survival and/or improved patient quality of life is difficult.

The final patient-level challenge is that antibiotics are generally licensed by indication as opposed to by pathogen. As many antibiotics are used to treat infections beyond their licensed indications, their value may be underestimated in the HTA process and/or they may not be reimbursed for off-label use in patients where much of their real value would be realised.

Benefits beyond the health gains for patients treated by antibiotics

A second challenge arises because antibiotics can provide benefits over and above the health benefits to individual patients – and beyond those currently considered by most HTA bodies. These benefits can be grouped under two general categories.

First, the societal benefits resulting from patients feeling well again. For example, the economic benefits of patients and their carers returning to work. Sweden takes the widest (societal) perspective to HTA of the relevant countries: the Swedish HTA authority, TLV, considers costs and benefits to worker productivity as well as to the wider public sector. These types of benefits are not unique to antibiotics.

Second, there are wider public health benefits from using antibiotics appropriately, and thus managing the build-up of AMR (e.g. the value of delaying the build-up of resistance by treating appropriately with an effective antibiotic). These aspects of value are discussed further in Section 4 and are key to a discussion of whether, and if so, in what ways current HTA methods may need to be developed to address the particular attributes of antibiotics.

3.4 HTA current practice in relation to antibiotics

To explore why additional elements of value for new antibiotics are needed, it is useful to review how antibiotics are currently assessed by HTA bodies. Although, as we indicated, the numbers of new antibiotics has been relatively small, Colson et al. (2016)³⁰ report on the available assessments of five antibiotics based on a review of HTA reports from the past 10 years in 11 European countries. The key finding from this paper is that there are currently no specific HTA guidelines for the assessment of novel antibiotics. This suggests that antibiotics are viewed and assessed similarly to other drugs in terms of how they are expected to demonstrate health gain (superiority trials with patients for whom reimbursement is sought) and the wider societal benefits that are considered when making reimbursement decisions. This is perhaps not surprising, given that concern and awareness of the challenge of AMR is relatively new. Some HTA reports used in Colson et al. do mention AMR as a public health threat, but it is unclear how they considered the value of containing AMR in their assessment or recommendation.³¹

For example, for one antibiotic, the evidence presented to payers was two double-blind, randomised controlled non-inferiority studies for each of its two indications (complicated skin and soft-tissue infection (cSSTI) and community-acquired pneumonia (CAP)). The primary objective for both pairs of trials was non-inferiority in clinical cure rate versus the comparator, and both excluded severely ill patients. Although non-inferiority was proven for both indications, the antibiotic was not given HTA approval for CAP in several European markets, and it was given heavy restrictions for use in the cSSTI indication. No non-clinical or pre-clinical data were considered in the assessment. While HTA bodies may be willing, in principle, to consider the wider public health related societal benefits from tackling AMR, it is not straightforward for them to do this in practice within their current procedures.

3.5 Recent developments in assessment of antibiotics

It is important to note that there are some interesting signs of a change in the way that antibiotics may be viewed by some HTA and payer bodies for reimbursement decisions. In France, in December 2015, an agreement was signed between the French pricing committee and the pharmaceutical industry ensuring that antibiotics are reimbursed using criteria that recognise the important benefits antibiotics bring to public health. Specifically, a five-year EU price guarantee is given even if the new antibiotic achieves an ASMR rating of IV (minor benefit), in comparison to other drug classes which must achieve ASMR rating I, II or III (major, important, and moderate benefit, respectively). This is important because ASMR IV is the most likely benefit rating that a new antibiotic, covering resistant organisms is likely to achieve, as superiority cannot be demonstrated in a feasible clinical study for reasons mentioned previously.³²

In Germany, in April 2016 the government and the pharmaceutical industry reached an agreement on changes to be made to foster an innovative pharmaceutical environment in Germany. As part of this agreement, the Ministry of Health was to introduce new

³⁰ Colson, A. 2016. Review of the health technology assessment (HTA) process for antibiotics in Europe. Available at: <http://drive-ab.eu/wp-content/uploads/2014/09/Colson-SMDM-slides-2016-06.pdf> [Accessed 23rd January 2017]

³¹ It should be noted that the governments of France and Germany have made very recent commitments to make changes to their reimbursement systems specifically for antibiotics (discussed in Section 3.5)

³² http://social-sante.gouv.fr/IMG/pdf/accord_cadre_version_definitive_20151231.pdf [Accessed 23rd January 2017]

regulation to specifically address AMR as part of the additional benefit assessment in the HTA process³³. Note that, at the time of writing this document, this legislation had not yet been passed.

To the best of our knowledge, there are no examples to date of assessments based on these proposed reforms.

The UK, Norwegian and Swedish Governments are separately each engaged in discussions with their respective pharmaceutical industry associations and HTA bodies around new models for assessing and reimbursing antibiotics. There is, at the moment, no public domain information about the content of these discussions.

4. Enhanced Value Assessment for antibiotics

4.1 Why do we need to consider additional elements of value to assess new antibiotics?

It is useful to review the most important reasons why the particular characteristics of antibiotics that mean that their value cannot adequately be accounted for using traditional HTA methods. These factors are separate from (but similar to) those that affect R&D incentives and suitability of pricing models (discussed in Section 1.2).

Why do we need additional elements of value for new antibiotics?

1. **AMR is a public health priority.** As discussed in Section 1.1, the rise of AMR is recognised as a serious global threat, and tackling this threat is a priority for many national governments and for leading national and international organisations. Current HTA methods, in general, do not explicitly account for the value of reducing this public health threat, for example of the “insurance” value of having a treatment available in case of a future major or rapidly escalating problem of resistance.
2. **A diverse set of non-inferior antibiotics are valuable to society.** Because of the rise of AMR, there is value in developing a new antibiotic for an MDR pathogen, even if it is no more effective than existing antibiotics in treating susceptible (non-resistant) pathogens, since it enables diverse prescribing patterns. According to the US FDA, “mechanistic diversity, even without a documented efficacy or safety advantage, is advantageous because antimicrobials become less effective over time.”³⁴ The need for prescribing heterogeneity and non-inferiority data are concepts unique to antibiotics, however they are not explicitly considered by HTA bodies (most of which are willing to accept only superiority data).
3. **Non-clinical and microbiology data are important for demonstrating the value of antibiotics.** For antibiotics, non-clinical and microbiology data can be important predictors of outcomes. As discussed in Section 2, difficulties in conducting clinical trials for antibiotics for MDR pathogens has led regulators to

³³ <http://www.bundesgesundheitsministerium.de/ministerium/meldungen/2016/pharmadialog.html> [Accessed 23rd January 2017]

³⁴ <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>

accept these alternative types of evidence as part of the approval process in areas of high unmet need.

- 4. Antibiotics have benefits that go beyond the patient treated.** When one patient is treated with an antibiotic, this can reduce the spread of the infectious disease, leading to population-wide benefits. We note that this also applies to vaccines, which are sometimes assessed differently to other drugs, e.g. in England and Wales they are assessed by the Joint Committee on Vaccination and Immunisation instead of NICE.
- 5. Antibiotics enable other types of treatment and procedures.** As well as treating infections, antibiotics reduce the risk associated with other types of treatment such as surgery and chemotherapy. We note that anaesthetics are another example of a procedure that enables another treatment.

These points are discussed in further detail in Section 4.2. To our knowledge, the additional elements of value for antibiotics we present below are published for the first time,³⁵ although we are aware that an assessment framework is being developed by IMI's DRIVE-AB initiative from which a publication is expected in 2017. A key difference between our approach and that currently expected from DRIVE-AB is that we focus here not only on the elements of value relevant to antibiotics but also on the evidence required to demonstrate value.

4.2 Elements and evidence of value

We have grouped the specific elements of value of antibiotics according to whether they are usually included in HTA or not. These are summarised in Table 1 and discussed individually in the following section, starting with the benefits included in traditional HTA.

Table 1. Summary of Elements of Value of Relevance to Antibiotics

Benefits typically included in traditional HTA	Benefits not typically included in traditional HTA
<ul style="list-style-type: none"> • Health gain • Unmet need • Cost offsets • Productivity benefits 	<ul style="list-style-type: none"> • Transmission value • Insurance value • Diversity value • Novel action value • Enablement value • Spectrum value

Relevant benefits typically included in traditional HTA

Health gain (measured as both life extension and quality of life gains) is generally accepted as the key criterion for positive recommendations by HTA bodies. The challenge for antibiotics is that the *evidence* typically required by HTA bodies to demonstrate health gain is often unachievable for reasons discussed in Section 2. Note that indicators of value for health gain should include both measures of short-term clinical efficacy, e.g. cure of infection, and long-term clinical efficacy, e.g. reduced recurrent infections or

³⁵ Note that several organisations have produced generic Value Frameworks and frameworks for other diseases, most notably for oncology. Examples include European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), Memorial Sloan Kettering Cancer Centre (MSKCC) and the National Comprehensive Cancer Network (NCCN).

reduced long-term mortality. Time to clinical response is also an important factor in determining value. The availability and use of rapid molecular diagnostics are a further contributor to health gain: diagnostic tests are important for antibiotics because if an infection can be accurately and speedily diagnosed, appropriate antibiotic therapy can be started earlier. Moreover, with better targeting, antibiotics could be used more appropriately, reducing AMR.

Another indicator of value that could be considered is addressing an **unmet need**. This could refer to a) severity of disease, in terms of the length and quality of life of patients treated with the standard of care (SOC); or b) the availability of alternative treatments for that condition. This second measure is particularly relevant for antibiotics because if there are no or limited remaining antibiotics available to treat an infection caused by a MDR bacteria, a new antibiotic with activity against this bacteria is extremely valuable. This could be considered by HTA bodies in their evaluations. A simple way of recognising unmet need could be using the CDC or WHO priority pathogen lists.

Cost offsets refer to the reduction of costs in other areas that come from the use of a new medicine. For example, this could relate to reduced use of the current standard of care or reductions in the length of hospital stay required by avoiding treatment failure due to AMR as a result of a new drug with therapeutic activity against resistant bacteria. Costs offsets could also be felt outside the health system, in social care, for example.

Productivity benefits refer to gains and losses related to the value of the patient's time, either when receiving medical care or related to the impact of absenteeism or presenteeism due to illness. Individuals who are cured at an early enough age can return to the workforce. Methods currently exist to include these benefits in HTA though few HTA bodies currently do so.

Other types of benefit of relevance to antibiotics

Transmission value: For a patient with an infectious disease, (successful) treatment using an antibiotic brings benefits not only for that patient but for all other individuals to whom the patient could have spread the disease if they had not been treated. In other words, treatment of an individual patient reduces the overall incidence of infection (spill-over/externality effects). Reductions in transmission (transmission value) can include all benefits of avoiding the spread of infection to the wider population: health/quality of life gain, cost offsets and productivity benefits. As noted above, similar benefits exist for vaccines (in that case through herd immunity) and there is experience in the assessment of vaccines of use of transmission value.

Insurance value refers to the value of having a treatment available in case of some catastrophic (or non-catastrophic) health situation, such as a sudden or major increase in MDR infections that kill patients and which cannot be contained by existing 'last line' antibiotics. As argued by Lakdawalla et al. (undated)³⁶, "(traditional cost effectiveness analysis) does not attempt to determine whether the new treatment also makes it less costly to face the risk of acquiring that illness in the future for patients without the illness. The reason is that cost-effectiveness analysis seeks to determine whether a new treatment makes it less costly to live with an illness for patients currently with that illness". Although insurance value is, in theory, important for other types of treatments, it is particularly relevant to antibiotics because AMR is internationally agreed to be highly

³⁶ <http://petriefflom.law.harvard.edu/assets/publications/Malani.pdf> [Accessed 23rd January 2017]

likely to give rise to a situation of this nature. The insurance value has been described by Rex and Outterson (Rex and Outterson, 2016)³⁷ as analogous to having a “fire engine” available and on duty: “antibiotics and infection control bear a striking resemblance to the fire-fighting infrastructure, the microbiology laboratory serves as the smoke detector, medical personnel are the fire fighters, and antibiotics are the water supply. All of these elements have to be established before the fire (infection), since buildings burn (and patients die) far more quickly than infrastructure can be built (or new drugs developed)”. While this is challenging to model and evaluate quantitatively, especially as the spread of resistance is difficult to ascertain, the value of delayed resistance is an important benefit that should be considered in the HTA process. There are however, two different components to the insurance element of value:

1. One is to model the expected rate of growth in resistance, and thus of the use of the “new” antibiotic over time, though this is challenging as rates will vary by type of pathogen and by geographical region. Thus, there is a high uncertainty as to how much the antibiotic would actually be used. Of course much of the value may come after patent protection has expired (possibly 8-10 years after launch), because the antibiotic is not needed until then. This expected value can be brought forward as a benefit for consideration when the new antibiotic is evaluated, although how it can be appropriately reflected in reimbursement decisions is unclear.
2. There is a small but important risk of the extent and speed of the build-up of AMR being substantially worse than we expect. If governments want to avoid such a catastrophe, then they should be prepared to pay for more insurance than the consideration in the first bullet point above would give us. This is the precautionary principle³⁸. In our “fire engine” analogy, although we expect one engine to be enough, the consequences of multiple simultaneous fires are such that we might want more than one fire engine permanently on standby. Quantification, valuation and contracting for this effect could be challenging but it could be considered, at least qualitatively, when making reimbursement decisions.

Diversity value: Overuse of some antimicrobial agents has been associated with the development of resistance. This may be due to “selection pressure” where an antibiotic is able to eradicate susceptible species of bacteria, but not able to eradicate other resistant pathogens that are present. Consequently, the resistant pathogens are able to survive and multiply and the antibiotic becomes ineffective. There is evidence that reducing this selection pressure, by withdrawing the antibiotic for a period of time, may lead to the restoration of susceptibilities. Strategies to reduce, or even withdraw, the usage of specific antibiotics, or entire classes of antibiotics, in hospital, have been practiced, with varying degrees of success. There is also evidence that using two antibiotics simultaneously (combination therapy) can be effective in treating MDR infections.

In an attempt to reduce the spread of AMR, ‘Antimicrobial stewardship’ programmes have been introduced that are designed to improve and measure the appropriate use of

³⁷ Rex and Outterson. (2016). Antibiotic reimbursement in a model delinked from sales: a benchmark-based worldwide approach. *Lancet Infect Dis*; 16: 500–05

³⁸ For a discussion of the precautionary principle and its relevance to HTA see Fischer A., and Ghelardi G. (2016) <http://journal.frontiersin.org/article/10.3389/fpubh.2016.00107/full> [Accessed 7th May 2017]

antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration.

The availability of new antimicrobial agents, incorporated into Antimicrobial Stewardship programmes, offer potential benefits at, and beyond, the individual patient level, in terms of efficacy, safety and the potential to reduce selection pressure and preserve the efficacy of existing agents.

Novel action value: This refers to the potential value associated with a medicine having a new or unique mechanism of action (MOA) or a new chemical structure i.e. first in class. This is seen by some as important in the evaluation of all medicines (to encourage innovation), but frequently not accepted by payers as relevant independently of health gain. There is however a specific case for recognising novel action per se for antibiotics because new antibiotics, with novel modes of action, may avoid problems of cross-resistance seen amongst existing classes.³⁹ That is, antibiotics with new mechanisms of action will have potentially higher value than antibiotics that have similar action to existing antibiotics, where those existing antibiotics exhibit the effects of resistance. Moreover, discovery of a new MOA will make it easier for “follow on” products to enter the market with the same mode of action but with different resistance effects.

Enablement value: Availability of effective antibiotics underpins many surgical procedures such as hip and knee replacement or heart bypass, as well as treatments for people whose immune systems have been compromised. Smith and Coast (2013)⁴⁰ argue that if no antibiotics were available to prevent or treat surgical site infections for patients undergoing total hip replacements, the post-operative infection rate would be approximately 40–50%, as compared with the current rate of 0.5–2% with effective antibiotic use. Of the 40–50% of patients who would have post-operative infections, 30% would die. This is an important value indicator for new antibiotics but it is not one readily assessed by HTA bodies.

Spectrum value: The final element that should be considered is the spectrum of the antibiotic. Narrow spectrum antibiotics may be more valuable than broad spectrum antibiotics because they could reduce the spread of AMR by preventing ‘collateral damage’ to the microbiome.⁴¹ For example, an antibiotic that covers pseudomonas only (i.e. pathogen specific), should be valued proportionally higher than one that covers multiple pathogens (i.e. broad spectrum).

Table 2 summarises this analysis and shows: (1) the indicators of value that we propose for inclusion in the assessment of antibiotics; (2) the evidence that should be provided to demonstrate value; (3) whether the element/evidence is typically accepted by the HTA bodies of all countries discussed at the Forum; and (4) whether the issue is particularly relevant to antibiotics.

Table 2. Elements of Value Relevant for Antibiotics

³⁹ Cross-resistance – a single resistance mechanism confers resistance to an entire class of antibiotics. Cross resistance can also occur across different classes of agents - a result of either overlapping drug targets or the presence of efflux pumps, which are capable of exporting different classes of drugs.

⁴⁰ Smith and Coast. (2013). The true cost of antimicrobial resistance. *BMJ*;346:f1493 doi: 10.1136/bmj.f1493

⁴¹ Williams and Wain (2014). Resurrection of a therapeutic area - problems and solutions in the discovery of new antibiotic drugs. *Pharmacology matters*.

Element of value	Indicator of value	Evidence of value	Is the indicator of value and evidence of Value typically accepted by HTA bodies?	Issue particularly relevant to antibiotics?
Relevant benefits typically included in traditional HTA				
Health gain	Short-term clinical efficacy: cure of infection	Non-inferiority trials	X	✓
	Long-term clinical efficacy: reduced recurrent infections, reduced long-term mortality	Superiority trials	✓	X
		Non-RCT evidence of superiority, e.g. RWE	X	✓
	Microbiological efficacy	Non-RCT evidence of superiority e.g. microbiology, PK/PD data	X	✓
	Quality of life improvement (short term and long term)	Non-inferiority trials	X	X
Superiority trials		✓	X	
Availability of rapid molecular diagnostic	Evidence of test accuracy	X	✓	
Unmet need	Severity of disease	Evidence of length/quality of life with SOC	X	X
		Priority pathogen lists	X	✓
	Availability of alternative treatments, e.g. other effective antibiotics	Epidemiology studies (AMR rates for particular pathogens)	X	✓
Cost offsets	Reduction in use of other treatments/ services or length of hospital stays	Modelling studies/clinical trials	✓	X
Productivity benefits	Presenteeism/ absenteeism	Modelling studies	X	X
Other types of benefit of relevance to antibiotics (not included in traditional HTA)				
Transmission value	Reducing overall incidence of an infection	Epidemiology studies	X*	✓
Insurance value	Protection from (non-) catastrophic event	Modelling studies	X	✓
Diversity value	Reduced AMR due to 'rest period'	Modelling studies	X	✓
Novel action value	New mechanism of action	Evidence of new or unique mechanism of action	X	✓
Enablement value	Enablement of treatment, e.g. prophylactic use in surgery or chemotherapy	Modelling studies	X	✓
Spectrum value	Narrow vs broad spectrum	Depends on AB	X	✓

Key: '✓' means that the answer to the questions posed in columns 4 and 5 is 'yes'. 'X' means that the answer to the questions posed in columns 4 and 5 is 'no'. *Note that transmission value is considered in vaccine assessment and decision making. However, many HTA bodies assessing drugs do not assess vaccines.

5. Insights gained from the Value Forum

Overall, there was broad agreement that all the additional elements of value included in the proposed enhanced assessment of value were potentially relevant for HTA of new antibiotics. However, the Forum participants offered a number of valuable insights into how the approach could be revised in order to maximise both its practicality and its potential policy impact. These insights can be grouped into the following five headings:

Focusing on the most important/relevant elements for antibiotics

Several participants at the Forum raised the issue that some of the additional elements of value not typically considered in traditional HTA are not unique to antibiotics. For example, novel action value is seen to be important for some other types of products. Transmission value is important in assessing the value of a vaccine – although many HTA bodies do not assess vaccines and so may not understand the arguments or methods involved. Surrogate end-points are used in a number of disease areas⁴². Whilst some participants believed that there are aspects of these elements that *are* specific to antibiotics,⁴³ it was acknowledged that these distinctions are perhaps more subtle than for other elements. Therefore, it was felt that the policy impact would be increased if the emphasis was on the elements that are the most important for/specific to antibiotics. It was suggested by participants that insurance value was one of the most important elements.

Measuring the elements of value

Another issue discussed at the Forum was that even if the HTA and payer communities were to agree that all the elements of value are important and should be considered in decision-making, this is more likely to happen if they can feasibly be quantified, measured and/or modelled – or some approach can be developed for factoring them into decisions qualitatively.

For some elements of value, e.g. novel action value, measurement is relatively straightforward: either the criterion is met (the antibiotic has a new MOA) or it is not (the antibiotic does not have a new MOA). Note that although measuring these elements is simple, quantifying their *importance relative to all other elements and the value that should attributed to them* in the framework is a separate and challenging issue (see next sub-section on “Combining value elements to make HTA/reimbursement decisions”).

For other elements, including transmission value and insurance value, measurement is likely to require modelling studies. For example, for transmission value, HTA bodies may require development of indication-level epidemiology evidence on the spread of AMR over time. It should be possible to draw on experience of vaccine review where modelling reduced transmission is a key element of establishing value. For insurance value, evidence on decision-makers and/or the public’s attitudes towards risk, to inform a decision on the appropriate degree of risk aversion, may be valuable.

⁴² Ciani et al., (2016). Time to Review the Role of Surrogate End Points in Health Policy: State of the Art and the Way Forward. *Value in Health* 20 (3), 487-495.

⁴³ For example, novel action value is particularly important for antibiotics because antibiotics with novel modes of action may avoid problems of cross-resistance seen amongst existing classes.

Combining value elements to make HTA/reimbursement decisions

It was suggested at the Forum that at the stage when the additional elements of value relevant to antibiotics are finalised and it is clear how each can be measured, further work is required to explore how they can be combined to make HTA/reimbursement decisions.

One set of methods for decision-making discussed at the Forum was multi-criteria decision analysis (MCDA), which uses structured, explicit approaches to decisions involving multiple criteria (see Section 6.3). In addition, participants discussed the potential for those HTA agencies that use cost-effectiveness thresholds to apply a more generous threshold for antibiotics to reflect the additional elements of value, similar to the way NICE gives a 'threshold premium' to drugs that meet its end-of-life criteria. This however, assumes that a higher price will be reflected in higher revenues for the product which may not be the case if stewardship requirements mean the drug is held largely in reserve.

There was also a discussion as to which elements of value could usefully be assessed at the product level, and so potentially by an HTA body, and which elements require a broader public health perspective. Whilst HTA bodies could help assess evidence of such broader elements, it might not be appropriate to reflect these in a higher price per unit for the product. They may require some other form of reimbursement arrangement, e.g. a fully de-linked market entry reward scheme, which was recommended by the O'Neill AMR Review, and is currently being assessed by other groups (such as DRIVE-AB). Such an arrangement might require the direct involvement of the Health Ministry.

Positioning of the elements within current HTA frameworks

The fourth key issue that arose in discussion at the Forum was that HTA organisations may be more likely to consider the elements of value as part of the decision-making process if they were able to be presented as additional elements within current HTA frameworks rather than requiring a completely new assessment framework for antibiotics. There are already examples of where HTA bodies have needed to adapt their approaches – for example for medical devices; orphan drugs; and public health interventions including vaccines. If additional new elements of value particularly relevant to antibiotics could be 'packaged' in this way, HTA bodies may be more able and willing to consider them. Put another way, HTA bodies are unlikely to be willing to change their basic methodologies when reviewing antibiotics and it would therefore be best to present the changes needed for assessments of antibiotics as developments of existing assessment frameworks. For example, many HTA bodies already consider addressing unmet need as an important potential benefit of a new technology. The 'unmet need' in the case of antibiotics is severely ill patients with MDR infections. Similarly, several HTA agencies consider 'meeting health system policy priorities' to be a relevant factor in decision-making, and tackling the rise in AMR is clearly a health system priority in many European countries.

It was also suggested that the issues set out are more likely to be recognised and acted upon by HTA agencies if they are couched in the 'language of HTA' that agencies are used to. For example, for countries that use QALYs (for example the UK and Sweden), it was suggested that where possible, the elements of value should be presented in quality adjusted life years (QALYs), although this may be challenging to do so for some of the elements.

Engagement and education

Finally, it was agreed at the Forum that improving awareness and education for HTA and payer bodies on AMR, the value of new antibiotics and the need for appropriate frameworks to capture this value would be a critical next step to bring about change in the way antibiotics are valued. Participants recommended collaboration and/or engagement with international and global organisations such as the European Commission, the Organisation for Economic Co-operation and Development (OECD) and/or the European network for Health Technology Assessment (EUnetHTA).

It was also suggested at the Forum that there is a need for more work to be done with patient groups as to the need for new antibiotics as well as the need to conserve existing ones, and for more work to be done to alter clinicians' prescribing behaviour. The latter could include education of, and engagement with, clinicians on the relevance and predictive value of antibiotic PK/PD and microbiology data in clinical decision making, and on the value of heterogeneous prescribing. These could be the subject of future work.

6. Discussion and next steps

In this section, we outline a series of potential next steps for the development of enhanced value assessment for antibiotics, and offer some concluding remarks.

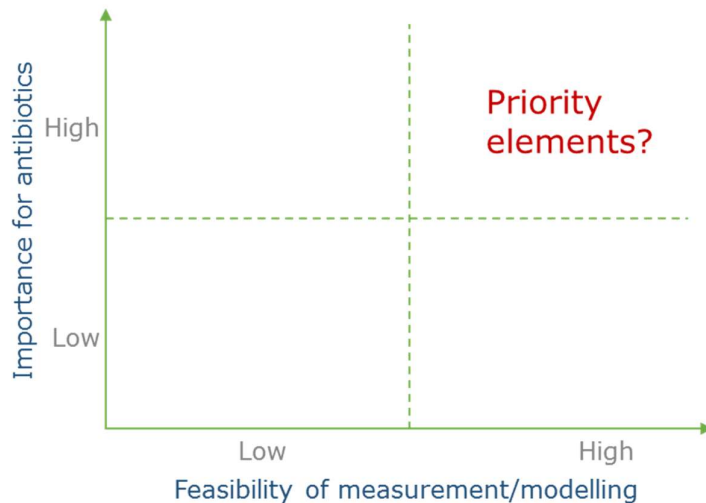
6.1 Towards prioritising elements of value

In Section 5, we note that a key point of discussion at the Forum was that greater policy impact would be achieved if the focus was on the elements that are most important for antibiotics. Furthermore, it was suggested that any enhanced framework for assessment can be operationalised only if the elements can feasibly be measured and/or modelled, or presented in a way that allows them to be factored into decisions qualitatively.

Therefore, one possibility for the first step towards prioritising the elements, focusing on those not typically considered in traditional HTA, is to consider (1) each element's importance for antibiotics; and (2) the feasibility of demonstrating value based on measurement or modelling. For example, in the simplest case, each element could be given a binary ('high/low') categorisation for the two criteria ('importance' and 'feasibility'), as shown in Figure 3. Where an element is 'high' for both criteria, it could be considered a priority for inclusion in the framework.

In practice, however, we may not want to limit research attention to elements in the north-east quadrant (e.g. focussing also on the north-west or south-east). The argument that research into reforming HTA for antibiotics should focus only on the elements that can be measured or modelled may be over-deterministic. HTA and decision-making are, in practice, quite pragmatic in many settings, and decisions often factor in 'wider' and unquantified dimensions. Although there are always good reasons to focus on the 'low hanging fruit' in order to make early progress, this should not be to the exclusion of the other elements, particularly when there is little agreement about which elements are easy to implement.

Figure 3. Prioritising elements of value



6.2 Modelling and evidence generation

One next step is to explore the feasibility of modelling these additional elements of value, as well as mapping future global AMR patterns. Specifications for these modelling studies could be developed at EU level, involving EUnetHTA, for example, as an extension or application of the EUnetHTA Core Model for Value Assessment. It may also be helpful for researchers to explore the literature on evaluating vaccines, particularly that relating to modelling transmission value.

There could be benefit in developing evidence on societal/public preferences towards funding antibiotics, relative to other types of drugs, although it would be important to raise awareness of the significance of AMR and the need to increase the number of antibiotics available. This may help convey the importance of the additional elements of value to relevant stakeholders. Finally, and importantly, the collection of observational data, e.g. through registries, could help strengthen the evidence base for some of the elements of value.⁴⁴

6.3 Aggregating elements of value in practice

As noted in Section 5, participants discussed MCDA as a technique for combining value elements to make HTA decisions. MCDA in any setting generally involves the following four steps: (1) selecting the appropriate criteria; (2) measuring the performance of the technology against the criteria and assigning a score for each criterion; (3) weighting the criteria and (4) aggregating the scores to produce an overall evaluation.

The work set out in this Briefing goes some way towards designing an MCDA framework for antibiotics (partially addressing steps 1 and 2). Exploring how the elements of value could be measured, weighted and aggregated could be a direction for future research.

⁴⁴ Note that there was no consensus at the Forum on whether routine, clinical practice data would be sufficient for making HTA decisions. There was no discussion about whether responsibility from data collection would rest with the health system or the antibiotic manufacturer.

It is important to note, however, that the countries discussed in this Briefing use deliberative committee processes to make HTA or reimbursement decisions. Adoption of additional elements of value in an algorithmic manner would therefore represent a policy challenge as well as a scientific challenge. Incorporation of the relevant elements in a more deliberative form of structured decision making may therefore be more appropriate.

Technical challenges will remain. For example, given that most trials are designed to demonstrate non-inferiority (not superiority), estimating the cost per QALY gained from these clinical trial data is not feasible for many antibiotics (though may, in theory, be possible using other types of data, e.g. PK/PD and only for drug-resistant patients). In addition, measuring the QALYs gained within elements of value other than 'health gain' (e.g. insurance value or diversity value) could be difficult.

Whichever approach to combining elements and operationalising the framework is taken forward, it would be highly valuable as part of the development process to test/validate options using case studies or pilots and discussion with staff in actual HTA agencies. This could involve a real (historical) product or a new hypothetical antibiotic.

6.4 Concluding remarks

AMR is a severe and urgent public health threat that requires global and multi-sectoral collaboration. One part of addressing this threat is ensuring HTA systems and payers are able to value new, effective antibiotics adequately and therefore make them available, when appropriate, to treat MDR infections. The discussion at the Forum involving clinicians, payers, HTA experts, regulators and economists, provided invaluable feedback and recommendations.

There are two key aspects. The first aspect is taking a different approach to the way in which the core element of value – health gain – is evidenced in antibiotics. The threat of AMR is driven by MDR pathogens that may not be present in such large numbers in current RCT's. Therefore, current RCT trial design cannot fully inform on the true clinical and economic value of antibiotics. Greater emphasis on the predictive value of microbiological factors and PK/PD and the inclusion of patients that are more representative of the population who are most likely to receive and benefit from such antibiotics is key. Smaller studies focused specifically on MDR pathogens, perhaps of an open-label design, would be valuable, as would post-marketing surveillance data, linking microbiological data and clinical outcomes in the MDR patient population.

The second aspect is exploring the inclusion of additional elements of value in the assessment of new antibiotics. The discussion at the Forum indicated that substantial work is required before these additional elements of value can be used as part of decision-making by HTA bodies in Europe and the rest of the world. In summary:

- There is a need to refine and finalise the additional elements of value within the framework. This might focus (at least initially) on those most important/relevant to antibiotics and/or those that can be most feasibly measured or modelled, though there is a risk that excluding elements on this basis may be over-deterministic and therefore not achieve the reform needed to ensure that new antibiotics are adequately valued by health care systems.
- There is further work required to understand how additional elements of value can be used to make HTA decisions. One option is multi-criteria decision analysis

(MCDA), where further research would be necessary to explore how the elements of value could be presented and aggregated. There are several models that could be used for this purpose, including those that are more algorithmic (involving development of common scale and weights) and those that support a more deliberative approach. The latter are likely to be more relevant to HTA and reimbursement bodies.

- Further discussion is needed as to which elements of value could usefully be assessed at the product level, and so potentially by an HTA body, and which elements require a broader public health perspective. Whilst HTA bodies could help assess evidence of such broader elements, it might not be appropriate to reflect these in a higher per unit price for the product. They may require some other form of reimbursement arrangement, which might require the direct involvement of the Health Ministry.
- There is a clear need for further education in order to expand awareness among HTA bodies and health care payers of the particular characteristics of antibiotics and infectious diseases as a therapy area. The Forum was not able to recruit participants currently working at payer/HTA bodies in France, Germany, Spain and Italy. It is important that future activities in this area include these stakeholders.

Appendix A: List of acronyms

AMR – antimicrobial resistance
ASMR - Improvement of Medical Benefit (France)
BAT – best available therapy
CAP – community-acquired pneumonia
CDC – Centres for Disease Control and Prevention
CHMP – Committee for Medicinal Products for Human Use (EMA)
cSSTI – complicated skin and soft-tissue infection
DRG – diagnosis-related group
EMA – European Medicines Agency
EU – European Union
EUnetHTA – European network for Health Technology Assessment
FDA – Food and Drugs Administration
G-BA - Gemeinsamer Bundesausschuss (Joint Federal Committee)
HAS – Haute Autorité de Santé
HTA – health technology assessment
HTS – high throughput screening
IMI – Innovative Medicines Initiative
IQWiG – Institute for Quality and Efficiency in Health Care
MCDA – multi-criteria decision analysis
MDR – multi-drug resistant
NICE – National Institute for Health and Care Excellence
OECD – Organisation for Economic Co-operation and Development
PMDA – Pharmaceuticals and Medical Devices Agency
PK/PD – Pharmacokinetics/Pharmacodynamics
R&D – research and development
RCT – Randomised Controlled Trial
RWE/D – Real World Evidence/Data
QALY – quality adjusted life year
SMC – Scottish Medicines Consortium
SOC – standard of care
TLV – Dental and Pharmaceutical Benefits Agency (Sweden)
UN – United Nations
WHO – World Health Organisation

Appendix B: List of participants of Value Forum

Name	Affiliation
Prof Adrian Towse	Office of Health Economics (OHE), UK
Dr Alan MacDonald	Scottish Medicines Consortium, UK
Dr Alastair Fischer	Office of Health Economics (OHE), UK
Prof Alec Morton	University of Strathclyde, UK
Dr Andrew Seaton	Scottish Medicines Consortium, UK
Dr Ben Porter-Brown	Roche
Prof Bob Masterton	Academy of Infection Management (AIM) Ltd., UK
Dr Chris Henshall	Independent consultant; Chair of Value Forum
David Findlay	GlaxoSmithKline
Mr Douglas Lundin	Dental and Pharmaceutical Benefits Agency (TLV), Sweden
Ms Emilie Taymor	MSD
Dr Hillar Kangro	GlaxoSmithKline
Prof Jordi Rello	Vall d'Hebron University Hospital, Spain
Dr Jorge Mestre-Ferrandiz	Office of Health Economics (OHE), UK
Prof Keith Abrams	University of Leicester, UK
Dr Marco Cavaleri	European Medicines Agency, UK
Prof Mark Wilcox	Leeds Teaching Hospitals, UK
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Dr Nick Crabb	National Institute for Health and Care Excellence, UK
Dr Oriol Sola-Morales	Health Innovation Technology Transfer, Spain
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Prof Pieter van Baal	Erasmus University Rotterdam, Netherlands
Dr Rhian Harper-Owen	Academy of Infection Management (AIM) Ltd., UK
Mr Rory Constable	UK Department of Health
Prof Dame Sally Davies	UK Government
Ms Sarah Karlsberg Schaffer	Office of Health Economics (OHE), UK
Mr Silas Holland	MSD
Dr Sofie Larsson	Public Health Agency, Sweden
Mr Stefan Frenning	GlaxoSmithKline
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Prof Vincenzo Atella	Università Tor Vergata, Italy
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