

# OHE



## HTA and payment mechanisms for new drugs to tackle AMR

Margherita Neri  
Grace Hampson  
Christopher Henshall  
Adrian Towse

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**Margherita Neri**

Office of Health Economics, London

**Grace Hampson**

Office of Health Economics, London

**Christopher Henshall**

Office of Health Economics, London

**Adrian Towse**

Office of Health Economics, London

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**Corresponding Author:**

Margherita Neri

[mneri@ohe.org](mailto:mneri@ohe.org)

For further information please contact:

**Professor Graham Cookson**

Chief Executive, OHE

Honorary Visiting Professor in Economics at City, University of London

**Tel** +44 (0)207 747 1408

**Email** [gcookson@ohe.org](mailto:gcookson@ohe.org)



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# Executive summary

## THE NEED TO UNDERSTAND THE VALUE OF ANTIBIOTICS

Antimicrobial resistance (AMR) is a growing public health threat, limiting the ability of health care systems to prevent and treat infections. This leads to greater morbidity, rising cost to the health care system, and increased mortality. If significant action is not taken, by the year 2050 10 million lives will be lost globally each year due to AMR, and global economic output will be reduced cumulatively by \$100 trillion (O'Neill, 2014).

The antibiotics available today are becoming obsolete at a fast pace, and industry development pipelines of antibiotics are weak. A number of interventions have been designed to address the scientific, regulatory and economic challenges associated to bringing new antibiotics to market. These can be classified as: 'push' incentives, focusing on providing financial and scientific support to the development of antibiotics, and 'pull' incentives, including market entry rewards, to provide rewards to manufacturers for bringing to market a product of clinical and public health value. It has been argued that the current set of 'push' incentives to support the R&D stages will not be sufficient to stimulate the required private sector investment in antibiotic innovation (Ferraro, 2017; Towse et al., 2017), and that the size of the 'pull' incentive necessary to bring the desired number of antibiotics to the market would be large (O'Neill, 2016; Towse et al., 2017). In this context, health technology assessment (HTA) is an obvious tool to assess whether the size of the required payment is commensurate with the value of the new antibiotic. However, it will be important that HTA processes assess the full benefit that antibiotics provide to health systems including the broader public health benefits of tackling resistance.

## THE AIM OF THIS PROJECT

The work of this project addresses the challenges and potential solutions for adapting HTA, and its use alongside new contractual arrangements for antimicrobials. The key challenges are (1) the need to capture the 'externalities' of the public health benefits that are not reflected in the health gain to the treated patient and (2) the need to separate volume use from revenues, so that appropriate stewardship plans can be put in place to conserve new antibiotics. The aim of this project is to develop recommendations for approaches to modifying HTA and contracting for antibiotics that can be taken up in practice by HTA and reimbursement bodies.

This report was developed in two stages. In the first stage, the authors developed a draft report summarising the current state of HTA and contracting for antibiotics and the recent proposals that have been advanced for revising both. This research focussed on five countries which have been taking initiatives in the area of AMR: France, Germany, Italy, Sweden, and the UK (England and Scotland). It was based on a literature review and two rounds of interviews with experts with detailed knowledge of their country's HTA and contracting system, who discussed the opportunities for and challenges of implementing these proposals. The resulting report formed the background reading for a forum on 'Value Assessment and Contracting for Antibiotics', which was held in February 2019 and involved 26 participants from HTA and payer bodies, government, academia and industry from the countries included in this study. The report was then revised to include the key discussion points and learnings from the Forum and sets out our conclusions and recommendations.

## PROPOSALS FOR MODIFYING HTA AND CONTRACTING OF ANTIBIOTICS

Antibiotics give rise to what is known in economics as an externality, namely spill over benefits and/or costs of a product's activity, beyond the impact on the immediate consumer which are not accounted for in market transactions. In the context of health care, these are benefits and costs to the health system beyond those attributable to the treated patient. Estimates suggest that a considerable part of the value of new antibiotics will come over time from these types of benefits, such as preventing the transmission of infections to other patients and slowing down the development of resistance to other drugs. We call these 'public health effects' as they accrue to the payer in the future and to future patients. Good policy design should 'internalise' these public health effects into the payer's assessment of value, but conventional HTA methods only include benefits and costs associated with treating the immediate patient, thus reinforcing the low returns for new antibiotics and hitting at incentives for innovation.

A number of proposals for the revision of HTA and contracting methods for antibiotics have been advanced by Karlsberg Schaffer et al. (2017), Morton et al. (forthcoming), Rothery et al. (2018) and Daniel et al. (2017).

Karlsberg Schaffer et al. (2017) made the case for going beyond the benefits typically considered in HTA (i.e. health gains, unmet need, cost offsets and productivity benefits) when assessing antibiotics. Among the public health benefits of antibiotics that are relevant to payers and the health system, but not considered in the traditional assessments, this work identified: transmission value, insurance value, diversity value, novel action value, enablement value and spectrum value.

Morton et al. (forthcoming) and Rothery et al. (2018) considered methods to include some of these elements of value in an HTA assessment using quality adjusted life years (QALY) and estimates of cost-effectiveness. Morton et al. (forthcoming) provides a number of recommendations to modify incremental cost-effectiveness ratios (ICERs) in order to capture the public health effects of antibiotics. Rothery et al. (2018) advanced a modified approach for a comprehensive assessment of antibiotics that is relevant for a health system, including consideration of relevant strategies for its use, and estimation of population benefits. It does this by modelling the dynamics of resistance transmission and development. More specifically, mechanistic dynamic models are simulated to demonstrate how the multiple mechanisms of infection and resistance transmission can be considered.

Most HTA and pricing and reimbursement arrangements agree a price for a new drug. Once the price has been set, companies have an incentive to sell more volume of the drug in order to get more revenue. However, in the case of new antibiotics, the norm will be stewardship arrangements that limit use of the drug, depending on the current rate of AMR for the pathogen the new antibiotic is targeting, and its rate of growth. Most of the use of the drug is likely to occur after patent expiry, when the build-up of resistance to existing drugs means that the new drug is now routinely used as a first line treatment. This value can be captured by HTA methods, providing that the right time horizon is used, and public health benefits are accounted for, but it will be of no benefit to the innovator as the product will be off-patent and priced as a generic. Hence the proposals for delinking payments from volume sales to (1) support stewardship to optimise expected health gains over the useful life of the drug and (2) find a way of providing payments to innovators that reflect the value of the drug to the health system.

Daniel et al. (2017) propose a Priority Antimicrobial Value Entry award, a largely delinked payment model aiming to provide appropriate returns whilst promoting stewardship. Their volume delinked payment scheme consists of two components: a pre-set market entry reward available for five years from the time of launching the new antibiotic, to provide a form of predictable revenue; and a

progressive shift towards value-based contracts for example on a per-member-per-month payment basis for each health plan, to stimulate continuous stewardship over the useful life of the antibiotic.

#### **CURRENT HTA AND CONTRACTING METHODS FOR ANTIBIOTICS**

A literature review of the methods of assessing antibiotics in the four countries studied revealed that while some have made efforts to capture additional benefits of antibiotics (e.g. France), and there is some inclusion of additional factors in deliberative decision making (Charafi and Chen, 2017; Morton et al., Forthcoming), there are no formal frameworks to conduct an AMR-related HTA assessment systematically (Morton et al., forthcoming).

A few countries have made steps towards changing the HTA and contracting of antibiotics, but the effectiveness of these initiatives is still uncertain due to their recent introduction. At present, special allowances for antibiotics in HTA are made in:

- France, where a reform is underway to create a new 'AMR committee' within the main HTA body, to provide advice on antibiotics and look at other AMR related issues. Furthermore, new antibiotics with 'minor' incremental benefit can receive a price guarantee, similarly to drugs with higher degrees of incremental benefit;
- England, where the National Institute for Health and Care Excellence (NICE) and NHS England will pilot a de-linked payment system based on a 'pragmatic HTA framework' for antibiotics combining elements of health economic modelling and qualitative information;
- Sweden, where a lump sum payment model covering the cost of supplying an antibiotic to the Swedish market is being piloted to address challenges around the availability of antibiotics.

In Germany, recent legislation established that antimicrobial resistance can be considered as an additional value element when assessing antibiotics, but the overall policy interest seems to remain focused on 'push' incentives. Similarly, the current national plan on AMR in Italy includes guidelines for stewardship, surveillance and prevention but no provision for changes to HTA processes.

The contracting of antibiotics used in hospital settings is usually regulated through tariff-based payments, often based on diagnosis related groups (DRGs), consisting of a single lump sum payment for the whole illness episode (i.e. diagnostic, provider care and medications). This system creates a disincentive to the appropriate use of new antibiotics, if their value is reflected in a high price.

#### **FINDINGS FROM EXPERT INTERVIEWS AND A STAKEHOLDER FORUM**

The experts interviewed broadly supported the importance of all the 'typically not included' elements of value of the expanded value framework of Karlsberg Schaffer et al. (2017) but highlighted the potential risk of overlaps across value attributes and the challenges of measuring these elements of value using conventional approaches to evidence assessment. The forum participants shared similar concerns and recommended that, in order to progress the practical adoption of the expanded value framework, effort should concentrate on the value dimensions that (1) have the greatest impact on overall value and for which (2) it is possible to generate evidence of value on.

On the modelling methods for antibiotics, the experts interviewed felt that some elements of value that are relevant to antibiotics are already being applied in their countries to vaccines. The existing modelling capabilities of certain European state agencies in charge of assessing vaccines, such as in France, Germany and England, could be used to assess the value of beneficial characteristics that are shared by vaccines and antibiotics (e.g. transmission value). The Forum participants agreed that

this is a strategy worth exploring starting with those countries where vaccines assessment based on advanced modelling is more firmly established.

The modelling methodology of Rothery et al. (2018) relies on advanced and complex modelling exercises. The Forum participants expressed the view that the necessary expertise to implement this approach is available in the UK, but progress has to be made to build it up in other countries. Other key learnings from Rothery et al. (2018) supported by the Forum were the need: (1) to adopt a public health perspective, to measure all the elements of value of antibiotics in terms of expected health gains/ losses (QALYs or others), and (2) to focus the modelling on the strategies of antibiotic use that are likely to be adopted in clinical practice, even though these may be different from those analysed in registration trials. This may be challenging for countries like Italy and Germany that focus assessments on the usage and evidence from registration clinical trials. Additional remarks from the Forum included the need to allow for some degree of expert judgement or elicitation where the quality of the data is insufficient to generate reliable estimates.

Both interviewees and forum participants were unclear about the extent to which de-linked payment models will be considered by countries other than the UK, given it represents a major departure from existing contracting approaches (notably in countries like Italy, Germany and France where there has been little discussion to date on novel contracting approaches for antibiotics). It is hoped that the experience in the UK and elsewhere with delinked payment approaches to contracting for antibiotics, supported by a period of ongoing discussion between industry, payers and HTA bodies, will work as an example for other countries to build on in the future.

The forum proposed both solutions that can be operated in the short term, and longer-term ones, and for more coordination between domestic and global initiatives. For example, at the European level the European Network for Health Technology Assessment (EUnetHTA) (or its successor arrangements) could be tasked with a new programme of action on adapting HTA to AMR, raising the profile of the issue amongst individual EU member states, or through the existing Joint Scientific Advice workstream to promote better understanding and coordination of work on antibiotics by HTA and regulatory bodies. In the context of promoting educational initiatives, HTA and regulatory bodies should be brought together to discuss which evidence from non-randomised clinical trials is acceptable (e.g. to define how pharmacokinetic/pharmacodynamic (PK/PD) data or in-vitro microbiological data can be used as a surrogate for relative efficacy).

#### **AUTHORS' CONCLUSIONS AND RECOMMENDATIONS**

'Push' incentives will not be sufficient alone to stimulate enough investment in antibiotics R&D. While it is crucial and urgent to get the right market 'pull', there is a need to expect that new antibiotics offer value that is commensurate with the level of funding being proposed. While value assessment of antibiotics will be key in this process, the HTA methods currently applied in most health systems do not capture adequately the value that new antibiotics offer to whole health systems.

The full implementation of the proposed value assessment methods calls for consideration of a number of additional value elements. The underlying logic is grounded in the economic concept of externalities, in this case the benefits to the payer that fall outside of the patient treated with the new antibiotic. While complex modelling may be required for 'internalising' them in the estimation of antibiotic value, we suggest two ways in which adoption of the proposed methods could be facilitated: (1) identify the elements of value that are most important for particular types of antibiotics and usage scenarios, so that efforts can be focussed on these; (2) use expert elicitation as a tool to inform modelling where the quality of the data is poor, or directly, as a proxy to detailed modelling, at least until greater expertise has been developed.



Even when simplified, the proposed value assessment methods for new antibiotics call for some rethinking of the basic HTA approaches. In particular, the proposed approaches seek to measure the benefits that an antibiotic offers as part of the actual strategies of usage which may differ markedly from that tested in registration trials. This may represent a significant challenge for many existing HTA systems which rely on this evidence for generating their recommendations.

Countries where the assessment of vaccines relies on advanced modelling approaches and expertise (e.g. England, France) could however try to transfer this skillset to antibiotics. This will be particularly valuable for antibiotics with a large public health impact, as the patterns of transmission and herd immunity could be modelled using vaccines assessment techniques. Vaccines assessment methods for antibiotics may also give an opportunity to consider contracting strategies that are similar to vaccines procurement and allow for some de-linkage between payments and volumes sold.

Regarding contracting, in the short term, new antibiotics should ideally be excluded from DRG bundled payments to disincentivise the use of cheaper antibiotics when more expensive ones may be appropriate. There is increasing support to the idea that payments delinking value from volumes prescribed may represent a longer-term solution, since the overall value of a new antibiotic to the whole population is likely to be enhanced by restricting its use within a stewardship programme.

Given the observed degree of heterogeneity in addressing assessment and contracting methods of antibiotics among the countries studied, a better understanding of why change is needed and how it can be implemented in practice is needed. Our recommendations to encourage further progress in the study countries are:

1. The Wellcome Trust and other major institutions supporting R&D and policy analysis to promote the development of new antibiotics, and the UK Government, should continue to advocate urgent changes to approaches to HTA and contracting for antibiotics, starting with practical, implementable solutions that have political support and can be put in place quickly, while some adjustment over time may be required.
2. The Department of Health and Social Care (DHSC), NHS England and NICE should share the learnings from the England pilots with other countries and promote further pilots of innovative HTA and contracting approaches in other jurisdictions.
3. The Wellcome Trust and other funders should promote the findings of this project with officials working for assessment and contracting systems in key European countries. The three most important policy messages from this project in relation to methods for value assessment are:
  - a. Value assessments of antibiotics should consider the benefits that antibiotics offer to the wider society in addition to the patients actually treated.
  - b. Value assessments should consider the benefits that antibiotics offer when as part of actual clinical strategies, even if these strategies differ markedly from those tested in registration trials.
  - c. A combination of modelling and expert elicitation methods should be used to estimate key parameters and outcomes in the value assessments of antibiotics.
4. Make progress in identifying the elements of the value frameworks which contribute most to antibiotic value and should be the main focus of the assessments, as well as in how they can be measured in practice.

5. Learn from the methodologies of appraisal of vaccines, particularly in those countries that already use advanced vaccines modelling methods. Promoting vaccines approaches for antibiotics may also foster the adoption of elements of vaccines procurement that rely on delinking volumes from payments.
6. The DHSC, NICE and the ministries of health of other jurisdictions should advocate for EUnetHTA (or its successor) to be tasked with promoting changes in antibiotics HTA, including developing a joint assessment of a new antibiotic to test in a number of EUnetHTA countries. Such a project could help to raise awareness in EUnetHTA countries, thus hopefully stimulating independent action.
7. Undertake further policy work to determine the mix of 'pull' incentives that would be best suited to the current policies and systems in different countries in Europe.

Formulate clear messages about the pull incentives that manufacturers would like to see, that are likely to be acceptable to governments and health system.

# 1 Introduction

## 1.1 Antimicrobial resistance

Antimicrobial resistance (AMR) occurs when microorganisms such as bacteria, fungi and parasites develop resistance mechanisms to antimicrobial drugs, which then become ineffective against these resistant organisms (WHO, 2018). AMR is a growing public health threat, limiting the ability of health care systems to prevent and treat some infections, which in turn may lead to further illness, increased cost (due to additional tests, more expensive treatments, and longer hospital stays) and increased mortality. Furthermore, AMR threatens the ability of health care providers to deliver interventions that carry a risk of infection such as caesarean sections, surgical joint replacements, cancer chemotherapy and immunotherapies. It has been estimated that, if significant action is not taken, by the year 2050 10 million lives will be lost each year due to AMR, and global economic output will be reduced annually by \$100 trillion (O'Neill, 2014).

AMR tends to occur naturally over time, but the misuse and overuse of antimicrobial drugs is accelerating this process (WHO, 2018). And, while the number of effective treatment options is decreasing, industry development pipelines for new antimicrobial drugs are weak. The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA, 2015) has estimated that the number of antibiotics becoming obsolete exceeds the number of innovative antibiotics being approved. This suggests that the number of effective antibiotics available to clinicians to treat infection is falling.

The development of antibiotics faces a threefold challenge (Karlsberg Schaffer et al., 2017):

- **scientific**, due to the low success rates in finding antibiotics that are likely to be effective against target pathogens. Success rates are four to five times lower than for other therapy areas (Payne et al., 2007);
- **regulatory and clinical**, due to the challenges of generating randomised controlled trial (RCT) evidence of efficacy in relation to clinically relevant usage pre-launch. For ethical and practical reasons, registration trials are typically designed to demonstrate non-inferiority; and
- **economic**, due to the low expected returns on investments (ROI) from antibiotic sales. Low expected ROI are the consequence of several factors exerting a cumulative impact on volumes sold, price, or both. These include:
  - infection control and stewardship programmes aiming to ensure appropriate prescription of new antibiotics in order to preserve their effectiveness over time against resistant infections. This frequently involves restricting use during the patent life of the product.
  - The value of new antibiotics is likely to be underestimated by current health technology assessment (HTA) approaches because the value to the health system of preventing the transmission of infection and slowing the development of resistance is not taken into account.
  - RCT evidence of non-inferiority rather than of superiority, which in many pricing systems limits price to that of existing treatments, many of which are low price generics.

## 1.2 Ongoing initiatives to stimulate antibiotic R&D

A number of interventions have been proposed to address various aspects of getting new antibiotics to market:

- 'Push' incentives, in the form of financial and infrastructure support for basic research to incentivise manufacturers' investment in R&D. The CARB-X initiative in the US and the UK, for example, provides financial and scientific support to the development of antibiotics entering clinical development (CARB-X, 2018).
- 'Pull' incentives, in the form of rewards for bringing to market a product of clinical and public health value. For a normal drug, the appropriate pull incentive is in place if the price paid for the drug reflects its value to the health system, and volumes are clinically appropriate for use at that price. In the case of antibiotics, low prices (below value) and low volumes (in order to preserve the long-term value of the drug) depress revenues. Two main types of proposals have been made to address the economic challenges of the market for new antibiotics:
  - New contractual arrangements that 'delink' payment for a new drug from the volumes sold of the drug, in order to provide appropriate returns whilst promoting stewardship. This usually involves some form of 'up front' one-off or multi-year payments on obtaining a product licence, subject to some form of value assessment. These are designed to ensure that manufacturers gain an early return on their R&D investment given low expected returns from regular sales of a new antibiotic. These payments are often termed a 'market entry reward' (MER), following their proposal by O'Neill (2016).
  - Modifications to normal approaches to the HTA assessment of the value of drugs to ensure that the public health benefits that arise to the health system in the context of AMR, in addition to the immediate health gain for the patients directly treated with the drug, is taken into account. This is important for determining the value that it is appropriate to recognise whatever payment mechanisms are adopted.

It is increasingly recognised that the current set of 'push' incentives to support the R&D stages will, of themselves, not be sufficient to stimulate investments in antibiotic innovation (Ferraro, 2017; Towse et al., 2017). Various studies have focussed on determining the size of the 'pull' incentive which would be necessary to bring the desired number of antibiotics to the market. Estimates of the required pull incentive range from \$1 billion to \$1.9-\$2 billion (Towse et al., 2017; O'Neill, 2016; DRIVE-AB, 2018) per antibiotic. Note that these estimates are based on the expected cost of bringing a new antimicrobial to market, and further resources may be required to incentivise commercialisation. But governments and payers are likely to want to be reassured that any rewards offered to manufacturers are commensurate with the value of the products on offer, in line with general policies for agreeing prices for drugs. It is therefore important that new antibiotics are assessed with HTA processes and value frameworks that recognise expected benefits that new antibiotics will provide to patients and the health care system. We note that these considerations are also relevant in settings where formal HTA processes are not used. For example, if some sort of delinked payment was to be triggered by the licensing of a new antibiotic that met a target profile against a drug resistant pathogen, then some sort of assessment of the likely value of that drug would underpin the case for public intervention to provide the funding payments.

### 1.3 HTA and contracting for antibiotics

HTA has a central role in many health systems in recognising the value of technologies and supporting pricing and reimbursement arrangements to ensure that the price paid is commensurate to their value. HTA approaches typically rely on evidence from RCTs to show clinical superiority against a comparator treatment. In the case of antibiotics, it is challenging to prove clinical superiority for reasons we discuss below. Antibiotics also give rise to what is known in economics as an externality, namely spill over benefits and / or costs of a product's activity, beyond the impact on the immediate consumer, to other consumers, which are not accounted for in market transactions (Donaldson and Gerard, 1993). In the context of health care, these are benefits and costs to the health system beyond those attributable to the treated patient. Estimates suggest a considerable part of the value of new antibiotics will come over time from these types of benefits, such as preventing the transmission of infections to other patients and slowing down the development of resistance to other drugs enabling them to be used to treat other patients effectively for longer. We call these effects 'public health benefits' as they accrue to the payer in the future and to future patients. Good policy design should 'internalise' these public health effects of antibiotics into the payer's assessment of value. The use of conventional HTA methods, which only include benefits and costs associated with treating the immediate patient, will reinforce the low returns for new antibiotics, hitting at incentives for innovation and ultimately risking harm to patients.

Most HTA and pricing and reimbursement arrangements agree a price for a new drug. This may be accompanied with an expectation about volumes sold, with a few countries operating forms of price-volume contracts or revenue caps for certain new drugs. However, in most cases, once the price is set, companies have an incentive to sell more volume of the drug in order to increase their revenue. Nonetheless, in the case of new antibiotics, the norm will be stewardship arrangements that limit use of the drug. The exact use will depend on the current rate of AMR for the pathogen the new antibiotic is targeting, and its rate of growth. However, it is likely that most of the use of the drug occurs after patent expiry, when the build-up of resistance to existing drugs means that the new drug is now routinely used as a first line treatment for certain types of infection. Whilst this value can be captured by HTA methods, providing that the right time horizon is used, it will be of no benefit to the innovator as the product will be off-patent and priced as a generic.

Thus, using HTA methods that account for public health benefits, and setting a price to reflect this, will still not be sufficient to provide incentives to innovators, because the use of the product and the associated revenues to the manufacturers will be limited prior to patent expiry. Hence the proposals for delinking payments from volume sales to (1) support stewardship to optimise expected health gains over the useful life of the drug and (2) find a way of providing payments to innovators that reflect the value of the drug to the health system.

A further complication in a number of health systems is the use of DRGs to pay hospitals for treating patients. A new antibiotic may be used even less than recommended under stewardship arrangements if the DRG payment is not adjusted to take account of the (higher) price of the new antibiotic. Treatment may persist with older cheaper antibiotics which are less effective for the patient, contributing to the build-up of antibiotic resistance. De-linkage of some or all payments from volumes sold should also tackle this problem. Other interim measures, such as top up payments for the use of new antibiotics in line with recommended stewardship arrangements would also help.

### 1.4 This report

Previous work by the Office of Health Economics (OHE) on HTA for antibiotics includes a program of research leading up to a meeting in London in February 2017 with HTA bodies and infectious disease

clinicians from a number of European countries. One of the key findings of this project was that further work is required to develop and explore potential changes in the way HTA agencies and governments assess and reward the value of antibiotics (Karlsberg Schaffer et al., 2017).

The programme of work set out in this report builds on these findings and addresses the challenges and potential solutions to modifying HTA for, and payment methods for, antibiotics. As explained in the previous sections, the two go hand in hand. Rewards need to reflect value delivered in the case of antibiotics as in the case of other drugs. This requires both new contractual arrangements for antibiotics and improved HTA models that are able to capture public health benefits beyond the immediate health gain to the treated patient.

The aim of this report is to:

- provide a comprehensive overview of recent proposals for modifying HTA arrangements and contracting for antibiotics;
- consider the attractiveness and feasibility of these options in a number of European countries;
- outline recommendations for further research and policy action around the most promising proposals.

## 2 Methods

This report was developed in two stages. In the first stage, the authors developed a draft report summarising the current state of HTA and contracting for antibiotics, recent proposals that have been advanced for revising these methods, as well as the potential for implementing them. The geographical scope of this research was France, Germany, Italy, Sweden and the UK (England and Scotland). All five countries have been involved in European dialogue on the need for new drugs and have taken national policy action to start to address the need for additional incentives.

The draft report was circulated to participants in a Forum on 'Value Assessment and Contracting for Antibiotics' organised by the authors. The Forum took place over two days in February 2019 and involved 26 participants from HTA/ payer bodies, government, academia and industry from the countries of interest for this study. The draft report was then revised to include key discussion points from the Forum.

This report is structured as follows:

- Section 3.1 comprises the results of a literature review of recent proposals for revisions to HTA and payment mechanisms for drugs tackling AMR. Specifically, we reviewed the work by Karlsberg Schaffer et al. (2017), Rothery et al. (2018), Daniel et al. (2017) and Morton et al. (Forthcoming). In addition, we conducted a round of interviews with the authors of these studies to discuss how their proposals could be implemented, and the associated challenges addressed;
- Section 3.2 describes the current arrangements for the assessment and contracting of antibiotics in the study countries, and how these methods differ, if at all, from those of other health technologies. We conducted a literature review, following the methodology described in Appendix B, and looked for any further HTA reports written in English, German and Italian<sup>1</sup> on antibiotics that may have been published since April 2016. We also interviewed experts with detailed knowledge of their country's HTA and contracting system. We secured five interviews with experts: England (2), Germany (1), France (1) and Sweden (1). All the interviews lasted approximately one hour and were conducted over the phone. Discussions were semi-structured, based on interview guides that were sent to participants in advance. Additional relevant information collected in the Forum is also included in this section.
- The interviews also explored the experts' perspectives on the proposals for revision of HTA and contracting (identified in Part 1) and discussed the opportunities and challenges of adoption for a country's health system. The related findings are summarised in Section 3.3 of this report, again including further information collected at the Forum.
- Section 4 attempts to capture key points from the discussions at the Forum on the extent to which systems are currently aware of and able to respond to the challenges posed by antibiotics. Recommendations are made as to how raise awareness and adapt existing methods.

The draft version of this report, circulated to the Forum participants as the meeting pre-read, included a literature review of the current HTA and contracting approaches in the study countries. The results of this exercise are in Appendix A of this, final, report. A list of the discussion questions that were discussed during the Forum is available in Appendix E.

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<sup>1</sup> Based on the language skills of the review team.

## 3 Findings

### 3.1 Proposals to revise HTA and contracting of antibiotics

We identified four publications addressing the revision of HTA and contracting of antibiotics:

- Karlsberg Schaffer et al. (2017) is the earlier OHE report referred to above. It summarises the key messages of a Value Forum with European stakeholders to identify value attributes of antimicrobial treatments and to suggest potential ways to include them in HTA. The Value Forum was held in February 2017 and was organised by the OHE in partnership with the Academy of Infection Management (AIM).
- Morton et al. (Forthcoming) is one of the publications of the DRIVE-AB project, funded by the Innovative Medicines Initiative, on proposals to modify the HTA of antibiotics in countries using 'quality adjusted life year (QALY)-based' approaches.
- Rothery et al. (2018) is a publication by the EEP RU on the methodology and the evidence required for the evaluation of antibiotics when volume delinked payments are in place.
- Daniel et al. (2017) is a work by the Duke-Margolis Center for Health Policy on an alternative payment system, called the Priority Antimicrobial Value and Entry (PAVE) award, incentivising antibiotics R&D and stewardship.

In the following sections, we summarise the main proposals of these works under four leading issues for antibiotics: (1) the identification of value elements relevant to antibiotics, (2) HTA methods for antibiotics, (3) HTA processes for antibiotics and (4) contracting for antibiotics. Finally, we comment briefly on their methodological and practical applicability.

#### 3.1.1 What constitutes value for antibiotics?

Among the multiple challenges of bringing new antibiotics to the market, Karlsberg Schaffer et al. (2017) addressed the scarcity of opportunities to consider public health benefits in the majority of the HTA systems, particularly in the context of the rise of AMR. To fill this gap in value assessment, they identified 10 elements of value of antibiotics, categorised as either included or not included in traditional HTA methods of new drugs (Table 1).



**TABLE 1. ELEMENTS OF VALUE OF RELEVANCE TO ANTIBIOTICS**

<b>Benefits typically included in traditional HTA of new drugs</b>	<b>Benefits not typically included in traditional HTA of new drugs</b>
<ul style="list-style-type: none"> <li>▪ Health gains for patients treated</li> <li>▪ Unmet need</li> <li>▪ Cost offsets</li> <li>▪ Productivity benefits</li> </ul>	<ul style="list-style-type: none"> <li>▪ Transmission value</li> <li>▪ Insurance value</li> <li>▪ Diversity value</li> <li>▪ Enablement value</li> <li>▪ Novel action value</li> <li>▪ Spectrum value</li> </ul>

Source: Karlsberg Schaffer et al. (2017)

The benefits traditionally included in HTA are set out below. Different HTA systems include different effects, depending on the perspective being taken:

1. **Health gains for patients treated** (i.e. extended life expectancy and improved quality of life of the patients treated), acting as the main element of value for successful HTA recommendations. New antibiotics typically struggle to demonstrate appreciable health gains for patients because clinical trials are typically designed to demonstrate non-inferiority using populations and comparators that may not reflect the setting in which the antibiotics are expected to be used.
2. **Unmet need**, is, in effect, a weighting factor, giving greater value to a given amount of health gain delivered where the condition is severe. If thought applicable, it can be defined jointly by disease severity and the availability of alternative treatments. Unmet need could potentially be identified for antibiotics using the priority pathogen lists from the WHO or the Centre for Disease Control (CDC).
3. **Cost offsets**, referring to the reduction of costs in other areas of the health system when a new medicine is made available.
4. **Productivity benefits**, corresponding to gains/ losses from the time spent receiving medical care, being unable to work, or working less productively, due to the disease. This value element is considered by some HTA systems but not others.

The potential benefits of antibiotics not typically included in HTAs for drugs are:

5. **Transmission value** which arises from preventing the spread of the disease among the wider population by treating individual patients. This is usually captured in vaccine appraisal, where there are herd immunity effects. As we noted, economists term these externalities. Experience with vaccines evaluation demonstrate that modelling techniques can be used to assess this element quantitatively. This type of modelling may be more challenging in the AMR setting due to the need to track the emergence and spread of both resistant and susceptible infections.

6. **Insurance value** which arises from having an effective treatment available in case of a catastrophic event, such as an outbreak of a multi-drug resistant pathogen that cannot be contained with existing drugs. There are two elements to this. The first arises in an expected value calculation, whereby the potential disruption to the health care system can be estimated along with the probability of it occurring. There may already be experience of this as it may be factored into the assessment of a vaccine which could avoid a pandemic. In addition to this basic insurance concept, decision makers may adopt the 'precautionary principle', and be risk averse to a catastrophic outcome. This would indicate a willingness to pay to address the problem over and above expected value. This would be a matter for policy makers, but could be informed by collecting evidence of decision maker and public attitudes towards the consequences of specific AMR events.
7. **Diversity value** which arises where new treatment options attenuate 'selection pressure' on existing antibiotics and preserve the efficacy of these existing treatments against resistant pathogens. If antimicrobial stewardship programmes are well implemented and old antibiotics can be replaced for certain periods of time with alternatives, bacterial susceptibilities may be restored. This is another form of externality.
8. **Enablement value** which arises if a new treatment increases the ability to successfully prevent and treat serious infections that may be acquired following surgical procedures or treatments that leave patients with compromised immune systems.
9. **Novel action value** which arises where a new mechanism of action helps to prevent the cross-resistance that develops among classes of antibiotics. A novel mechanism of action may also pave the way for 'follow-on' products with the same mechanism of action.
10. **Spectrum value.** Antibiotics that cover a narrower spectrum of pathogens may be more valuable than those targeting a broader spectrum because they prevent the 'collateral damage' to the microbiome and reduce the build-up of AMR.

We can note that there are some trade-offs between elements (5), (6), and (7). To the extent the product is used, then there may be transmission and diversity effects, but the insurance value will be diminished. Any HTA assessment will need to begin with a clear understanding of the optimal strategy for using the new drug. Elements (8), (9), and (10), can in principle also be modelled, i.e. taken into account, based on the planned use of the drug. In practice this is unlikely to be feasible, as we discuss later.

Of note, the same expanded definition of value paradigm for antibiotics is shared by Rothery et al. (2018). Morton et al. (Forthcoming) does not discuss the optimal antibiotics value framework but focuses on modelling a subset of the antibiotic benefits (transmission value and diversity value).

### 3.1.2 HTA methods for antibiotics

Karlsberg Schaffer et al. (2017) note that participants at the 2017 OHE-AIM Value Forum expressed broad support for expanding the antibiotics value paradigm to address the wider value elements not typically included in HTA for drugs. One of the main recommendations was that the inclusion of additional value elements in HTA frameworks will have greater chances of success if these fit within existing HTA approaches. For example, agencies using QALYs as the main outcome are likely to expect any additional value elements to feed into this measure. To facilitate the practical adoption of a broader antibiotic value paradigm, the value elements could be prioritised according to their relative importance and the feasibility of measuring or modelling them.

Morton et al. (Forthcoming) and Rothery et al. (2018) propose approaches to formally include additional value dimensions in the HTA methods of countries using QALY-based approaches<sup>2</sup>.

**MORTON ET AL. (FORTHCOMING)**

Morton et al. (Forthcoming) developed three recommendations to modify the ICER calculation for antibiotics. These are:

1. To include the benefits of avoided transmission and preserved efficacy of existing antibiotics (i.e. transmission and diversity value) in an HTA assessment for an antibiotic. The authors regard modelling these effects as a difficult exercise, but dynamic disease models could incorporate the benefits of avoided transmission, whilst expert elicitation may be appropriate to estimate the potential impact of preserving the efficacy of existing antibiotics. Morton and colleagues suggest that the enablement value of antibiotics (i.e. being able to perform surgery and other procedures more safely), should be included in a separate cost-effectiveness analysis. Although health effects are at stake, they argue that this represents a different mode of use of antibiotics.
2. To perform sensitivity analyses of the impact of resistance to the new antibiotic as the effect of antibiotic use on the transmission of infections and the development of resistance (i.e. selection pressure) is difficult to predict with accuracy.
3. To perform the analysis at population level in order to capture all the externalities from antibiotic use.

Based on their assumptions, Morton et al. propose the ICER for antibiotics is calculated as follows:

$$ICER = \frac{C - S - S_t - S_d}{V + V_t + V_d}$$

Where:

- C is the direct cost of the new antibiotic
- S are the direct savings from treating resistant infections
- V is the direct benefit of the new antibiotic measured in QALYs
- $S_t$  and  $V_t$  are, respectively, the cost savings and the health benefits from preventing the transmission of resistant infections
- $S_d$  and  $V_d$  are, respectively, the cost savings and health benefits generated by preserving the efficacy of the old antibiotic, as a result of reducing the selection pressure

All the costs and benefits are calculated incorporating a hypothetical effect of reduced resistance transmission rates. The sensitivity analysis performed by the authors shows that the greatest uncertainty for the cost/benefit ratio comes from varying the parameters of the direct effects (V and C), followed by transmission ( $S_t$  and  $V_t$ ) and then diversity effects ( $S_d$  and  $V_d$ ).

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<sup>2</sup> For an explanation of the difference between the 'therapeutic added value-based' and 'QALY-based' approaches refer to Appendix A

**ROTHERY ET AL. (2018)**

Rothery et al. (2018) have proposed a modified framework for assessing antibiotics when 'insurance-based delinked payment models' are to be used.

According to the framework, the first step should be defining all relevant potential strategies for use of the new and existing antibiotics (e.g. mixed strategies, combination therapy, antibiotics rotation). Secondly, all the relevant population benefits and costs should be assessed for each strategy over an appropriate time horizon. This step involves modelling the long-term impact of each strategy on infection rates, resistance emergence, and individual patients cost, morbidity and mortality outcomes. Of note, given that the antibiotic is not to be rewarded by means of a per-pill price, they suggest that the acquisition costs of the antibiotic should not be an input to the value assessment. In this way, the framework should identify the value that would result in optimum use of new antibiotic regardless of price, and therefore help inform a contracting process that delinks payments from usage. The value of each alternative use strategy for the antibiotic is assessed and compared using net health benefit. This is a measure of value, typically quantified in terms of net QALYs. To determine the value of the net health benefit, a measure of opportunity cost (e.g. the cost-effectiveness threshold [CET]) is used to convert costs into a number of QALYs). In addition to the health benefits measured in terms of QALYs, cost savings are therefore assumed to produce additional QALYs at the CET conversion rate and additional costs likewise to reduce the QALYs gained in the same way. The net health benefit, using these assumptions, can be used to estimate the maximum value-based payment that would not result in a negative impact on population health. This is the difference between the net health benefit of the new and comparator strategies, multiplied by the opportunity cost. Additionally, the net health benefit can be used to generate a ranking as between alternative strategies of use for the new antibiotic.

They argue that this framework can be used to model the value attributes of antibiotics referred to in Karlsberg Schaffer et al. (2017): the *diversity value* will be included by evaluating strategies including diverse prescribing (e.g. antibiotic rotation); dynamic models or other ways to predict long-term infection rates could be used to estimate the health benefits and cost savings of reduced infection rates (*transmission value*) and dynamic, or more standard, models could be used to capture the effects on treatment procedures that will continue to take place as a result of the availability of antibiotics (*enablement value*). *Insurance value* can be used to capture two components: the value of pursuing a strategy of preserving the efficacy of the antibiotic for use in case of catastrophic events in the future by holding it back from widespread use, and the benefit of insurance against catastrophic health events. The former element could be reflected by comparing the value of alternative use strategies. The latter can be estimated by assessing the impact of different strategies on the likelihood and/or consequences of extreme catastrophic events. The likelihood of catastrophic events and their consequences can be quantified using standard probabilistic modelling methods, with or without additional weighting for the health outcomes achieved, depending as to whether the decision maker is risk neutral or risk averse. Reflecting *spectrum value* quantitatively is likely to be very challenging as it requires predicting how alternative strategies might impact on the microbiome and how changes in the microbiome might impact future infections. Instead a qualitative assessment of these potential effects of different strategies on the microbiota is proposed. *Novel action value* is not considered on the grounds that it is not an additional element of value. They argue that the benefits of novel action value should be captured when modelling the other elements of value.

A case study is presented by Rothery et al. (2018) to illustrate how the proposed value assessment framework can be applied. Two models were developed. A mechanistic dynamic transmission model is simulated to model the dynamics of infection transmission and resistance emergence. A Markov model is used to assess any additional impacts of infection on patients in the three months after they are discharged from the intensive care unit (ICU). The term *dynamic* means that the probability

of acquiring infections over time evolves based on the number of infections in the population. Therefore, the infection rates of susceptible and resistant infections are re-estimated by the model at each point in time given the proportion of uninfected, infected and colonised individuals in the population. The term *mechanistic* implies that the underlying mechanisms of resistance and transmission are also modelled. The case study model captures both primary resistance (resistant infection transmitted from one individual to another) and resistance acquired during treatment (selection pressure favours the development of bacterial resistance during treatment). This is an attempt to reflect the various biological processes of resistance emergence and transmission<sup>3</sup>. In addition, the model distinguishes between the infected state, where susceptible or resistant bacterial presence is accompanied by clinical symptoms, and the colonised state, where bacterial presence endures without clinical symptoms. Appendix C of this report includes an explanation of how non-clinical endpoints (pharmacokinetic, pharmacodynamic and in-vitro microbiological data) could help distinguish between bacterial infections and colonisations. Appendix D contains a representation of the model resistance emergence dynamics. The added value of the mechanistic dynamic model is to provide projections of how alternative strategies for using new and existing antibiotics alter overall infection rates and resistance rates. By distinguishing between colonised and infected individuals the model can reflect the effect of infections which, although clear from clinical symptoms, are not eradicated, and thus continue to fuel the transmission of resistant bacteria.

The model was populated using data from the literature to inform parameters describing: the transmission dynamics in the ICU setting (e.g. number of beds and admission rates, fraction of admitted patients colonised, daily discharge rate, daily rate of spontaneous recovery), treatment efficacy (e.g. clinical success, probability of acquiring resistance, microbiological success), costs and Health-related quality of life (HRQoL) (e.g. comparator treatment costs, susceptibility testing cost, daily cost of stay in ICU, baseline HRQoL for ICU patients and impact of infection on HRQoL).

The authors discuss the challenges likely to be faced when parameterising models to evaluate antibiotics. Information on the model parameters are often retrieved from routine observational and surveillance data (e.g. antimicrobial surveillance programmes). Where data are unavailable or sparse, model outputs can be calibrated using empirical data to infer estimates of the unobserved (and possibly unobservable) parameters. Formal expert elicitation based on advanced techniques, such as probabilistic belief statements, can also be used to infer such estimates and collect judgements on uncertain quantities. Experts, for example, are able to directly incorporate their expectations about changes in antibiotic use and infection control measures.

Rothery et al. (2018) discuss the relative merits of dynamic models which aim to model the process by which resistant infections emerge and spread amongst populations, and static statistical forecasting models which aim to predict infection and resistant rates directly based on historic data and expert judgements. Dynamic models are more challenging to develop due to uncertainties about the way in which resistant infections arise and spread. These lead to uncertainties about how the model should be structured. In addition, the size of the uncertainty associated to the model parameters may be large and individual effects will be hard to disentangle due to the complexity of the models. They may also become more complex in settings where multiple antibiotics are used as the models may need to track different forms of multi-drug resistance, and when complex processes underpin the spread of infections through populations. In comparison, static models are simpler to handle and more transparent: the risk of infection is estimated directly, and alternative scenarios are used to explore the impact of uncertainty and resistance development. Neither dynamic nor static models have proved superior in providing credible forecasts of historical infection and resistance

<sup>3</sup> *The mechanisms of transmission of resistant infections include: transmission of new infection to previously uninfected individuals (primary resistance) and acquired resistance during treatment, either of infected individuals receiving treatment (target selection) or of colonised individuals (carriers of the bacteria but not yet infected) who do not show symptoms (collateral selection). 'Competition' dynamics between sensitive and resistant bacteria can lead to replacement infections (existing bacterium to be replaced by a novel one) strain conversion (conversion from sensitive to resistant strain, or vice-versa) and superinfections (individuals infected with both susceptible and resistant bacteria).*

rates. Colson et al. (Forthcoming) have argued that judgements obtained through expert elicitation can be an effective instrument to quantify uncertainty about future resistance.

### 3.1.3 Modifying HTA processes to address antibiotics

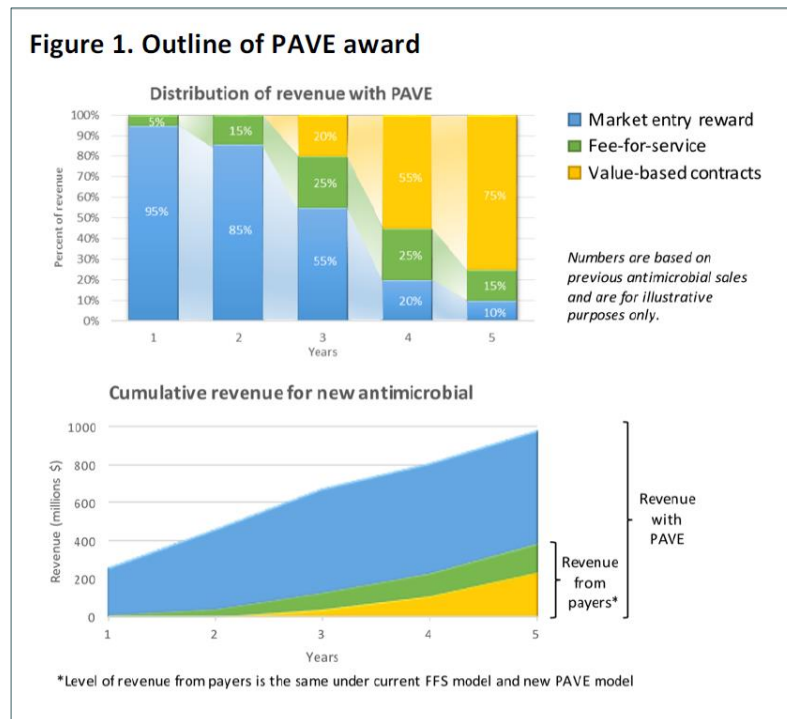
The possible need to adapt HTA processes for antibiotics was discussed by Rothery et al. (2018). Although this was in the specific context of the UK National Institute for Health and Care Excellence (NICE) assessment and appraisal processes, their proposals have more general applicability. They argue that:

- *Topic selection* (i.e. identification of technologies to include in the appraisal programme) should involve two elements: first, considering which antibiotics are potential candidates to be eligible for NHS funding using contract delinked payments, and second, prioritising among them, i.e. in which order they should be appraised.
- The *scoping* process (i.e. definition of indication, population, comparator, perspective, time horizon and discount rate) would become of central importance due to the HTA challenges of defining all the alternative strategies of use of the antibiotic and the eligible populations (see Appendix C for a summary).
- *Identification, modelling and synthesis* of the evidence relating to the technology is currently carried out by manufacturers under the single technology appraisal (STA) programme. However, the manufacturers' modelling expertise and the timelines between the referral and final appraisal may be too limited to accommodate the modified conceptual framework proposed by Rothery et al. (2018). The authors argue that the approach used by NICE for multiple technology appraisals or diagnostic assessment programmes, where assessments are undertaken primarily by academic groups with greater expertise in modelling, may be more suitable for antibiotics. In the interviews, experts felt that the proposed HTA methods differed significantly from those routinely used by NICE. It was suggested that the Joint Committee on Vaccination and Immunisation (JCVI) in the UK has strong experience with modelling the transmission dynamics of infections and may be better suited than NICE to assess the population health benefits of antibiotics.
- Finally, the *appraisal* phase, where the advisory committee produces guidance for NHS England and the NHS, will have to engage more frequently with the assessment group in order to agree the key factors to be explored in order to understand the uncertainty around antibiotic health benefit.

### 3.1.4 De-linked payment models

Both the UK and Swedish governments have been considering delinked payment models as we discuss later in the paper. Two papers set out how elements of a delinked payment scheme might work.

The PAVE award proposed by the Duke-Margolis group (Daniel et al., 2017) is a contractual scheme that partially delinks payments from the volumes of antibiotic sold, while also aiming to provide incentives for the development and appropriate use of antibiotics. As we have noted, contractual designs of this kind are desirable in the case of antibiotics in order to reward manufacturers appropriately for their R&D and commercialisation efforts (typically difficult to achieve with low prices for antibiotics) whilst removing the incentive to sell volumes of antibiotics above the levels recommended by stewardship plans. Figure 1 illustrates how the PAVE award could work over a five-year timeline from the introduction of the antibiotic.



**FIGURE 1. PAVE AWARD. SOURCE: DANIEL ET AL. (2017)**

Component (1) of the PAVE award is a MER to provide a form of predictable revenue to manufacturers. In the model of Daniel et al. (Figure 1), MERs are available over the first five years after launch as a yearly payment of decreasing size over time. A MER multi-year payment schedule is proposed to ensure that manufacturers meet stewardship requirements in the years following launch. Another proposed feature of MERs component is that it can be targeted at drugs expected to be of value. The eligibility criteria can be set to incentivise the development of high priority antimicrobials (e.g. antibiotics targeting pathogens in the WHO and CDC priority lists). Focusing on the USA, Daniel et al. propose that the MERs should be publicly funded, and their size should be large enough to stimulate R&D. Funding for MERs could come from general government revenues or other dedicated funding sources such as: charges on companies that do not contribute to antibiotics development ('pay or play' fees, charges to discourage inappropriate antibiotic use, yearly per member fees for healthcare plans or awarding of transferable exclusivity vouchers.

Component (2) of the MER would combine payments for use (e.g. fee-for-service model) with value-based contracts. The latter are assumed to increase in size over time to gradually replace the MER (Figure 1). Value-based contracts would consist of yearly payments of size proportional to the value of the new antibiotic and delinked from volumes sold, in order to preserve the stewardship incentives. For example, these could be calculated on a per capita basis for the population covered (i.e. some sort of availability award). Value-based contracts would potentially be linked to an assessment of value that would take account of (1) the incidence of the infections that the drug is indicated for and (2) the different types of costs that would be avoided if the drug was available (e.g. hospital avoided readmissions, diminished length of stay). This type of payment will necessarily be linked to continued data collection on performance (appropriate use, continued effectiveness, better evidence on benefits), as antibiotics are approved with evidence on limited populations and usually with only evidence of non-inferiority. Further work by the Duke-Margolis group is looking to understand how the

MER and value-based contracts could be implemented, funded and fit within the health system in the USA.

Rothery et al. (2018), as we noted above, model net value, excluding the price of the drug, to come up with an estimate of the total additional value of the product to the health system. This estimate can then be used as a basis for negotiation of a delinked contract of payments to the innovator that are independent of volumes sold. Rothery et al. (2018), also reflect on the relationship between uncertain estimates of population health benefits and the reimbursement arrangements of antibiotics. There may be evidential uncertainty on epidemiology (patterns and time of resistance development to existing and new antibiotics), and the success of stewardship policies. Uncertainty can have implications for the optimal timing of reimbursement and how to share value between manufacturers and payers. While more evidence is collected to address the evidence gaps, risk can be shared through the price paid and the cost of generating additional evidence<sup>4</sup>. There is also a strong case for periodic reconsideration of the rate of delinked payment for new antibiotics as additional evidence emerges.

### 3.1.5 Where these proposals get us to on HTA and on delinked contracting

The papers we have reviewed in section 3.1 indicate that the ‘public health’ elements of value are important and can be estimated. The degree of complexity of the modelling required depends, to some extent, on the willingness of payers to accept the use of expert opinion (expert elicitation) for some of the parameters that will drive the likely value of a new antibiotic. Reaching agreement on the likely options for optimal use of a new antibiotic will also be critical. There is a limit to the number of scenarios that can be modelled. Whilst it is important to avoid double counting of elements of value, it may not be possible to take account of all of the interrelated elements of value in the modelling exercise – which again may require the use of expert elicitation.

Delinking payments to innovators from the volume of antibiotics sold is also needed, although the papers do not set out the precise legal and contractual mechanisms that may be required. However, two alternative approaches are set out. A MER needs to be linked to an assessment of expected value based on the type of drug resistant pathogens the new antibiotic is expected to address. The other route is to tie payments more directly to the results of the HTA assessment in order to arrive at a value for the new antibiotic that will then be paid to the innovator in a contract that delinks payments from the volumes of the drug sold. These are not mutually exclusive – the PAVE proposal includes one (MERs) being used initially to be replaced by a per capita population value-based contract.

Rothery et al. (2018) term the delinked value-based contract an ‘insurance-based delinked payment model’. Daniel et al., 2017 term it a ‘value-based contract’ which the paper expects to be calculated on a per capita basis for making the drug available to the population covered. Both papers are describing the same thing, whether the term insurance or availability is used. The point is that innovators are being rewarded for the drug having been developed so it can be used when it is needed – in line with the stewardship arrangements agreed when the contract was put in place. The period of the contract is a matter for future discussion. As Rothery et al. (2018) note, understanding of the value of a new antibiotic will change over time. On the other hand, developers need some understanding of expected returns so they can decide whether or not to invest in R&D.

Daniel et al., 2017 assume that there will also be a price per unit (fee for service in their terminology) paid for the antibiotic. Under a delinked contract it will make sense for some price to be agreed for

<sup>4</sup> The authors note that in principle it may be optimal to delay adoption until additional evidence is collected. In the case of new antibiotics, postponing reimbursement may be suboptimal because the characteristics of the decision problem (i.e. the resistance environment) change over time and collecting evidence is difficult other than in routine use of the product.



use of the product, otherwise, if it is effectively free to hospitals, there is a risk of overuse. Such price volume payments could be viewed as an additional part of remuneration for the innovator (as envisaged in the Daniel et al., 2017 paper), or deducted from the delinked contractual payments, i.e. 'clawed back' from the antibiotic supplier. If payments for use of the antibiotic are to be received by the innovator over and above those included in the delinked contract, then we can use the term 'partially delinked' to describe this.

### 3.2 Current methods for HTA and contracting of antibiotics

Our literature search identified only two studies describing how HTA bodies approach new antibiotics in practice (Charafi and Chen, 2017; Morton et al., Forthcoming). Charafi and Chen (2017) observed the influence of tackling multi-drug resistance (MDR) in the assessment of new antibiotics in the period 2012-June 2017 in France, Germany and the UK. They found that in France, antibiotics tackling MDR could be awarded the status of 'substantial clinical benefit' because of their impact on public health. This would have a positive impact on the price that could be charged. MDR also impacted the benefit assessment of antibiotics in Germany and was recognised in England. We note that, in France, public health benefit constitutes a separate value element. Experts interviewed and present at the Forum indicated that the meaning of public health benefit has been redefined in recent years to include the impact on the healthcare system as well as other factors (HAS, 2018). They suggested that these considerations are addressed through a deliberative process, rather than a formal multi-criteria decision analysis tool where the evaluation criteria have preassigned weights reflecting their relative importance within the framework. In Germany, the independent Institute for Quality and Efficiency in Health Care (IQWiG) conducts assessments of new drugs, and the Federal Joint Committee (G-BA) makes decisions on access and price, based on technical advice from IQWiG and other factors. Experts interviewed and present at the Forum noted that IQWiG has a strong preference for clinical evidence from RCTs in its assessments, while the approach to appraisal adopted by G-BA may allow for wider public health considerations to be factored in.

Morton et al. (Forthcoming) reviewed the HTA reports of five antibiotics assessed between 2000 and 2016 and found that some European countries had captured the public benefit of antibiotics qualitatively in their HTA processes. The French health technology assessment authority (HAS), for example, acknowledged the value of avoided transmission of resistance, the value of having a new mechanism of action, and the value of having a diversity of antibiotics to use. Resistance patterns were also considered using the percentage of drug-resistance isolates after 0-24 weeks of use. While we were unable to identify additional HTA reports on antibiotics published since April 2016, it would appear that no agencies are currently using formal frameworks that capture the specific value dimensions of antibiotics systematically.

Regarding future processes to assess antibiotics in the study countries, a reform of the assessment system of antibiotics is underway in France. The reform aims to create a new 'AMR committee' within HAS which would provide advice on antibiotics in the same way as the committee for vaccines assessment (CTV) currently does for vaccines, while also looking at other AMR related issues (COMITÉ INTERMINISTÉRIEL POUR LA SANTÉ, 2016). However, the degree of progress with this reform is unclear at this stage. More recently, the newly created Strategic Committee of the Health Industry and Technology Sector (CSF ITS) identified AMR as one of the four major areas of work for the forthcoming years. The committee is working on proposals for new economic models to incentivize antibiotic R&D (Conseil national de l'industrie, 2019).

In Germany, where the Government has taken the lead in establishing a Global AMR R&D Hub centred in Berlin (<https://www.gesundheitsforschung-bmbf.de/en/GlobalAMRHub.php>), interest seems to be focused on push incentives. However, a new federal law has been passed requiring G-BA to consider AMR when assessing antibiotics (Federal Ministry of Justice and Consumer

Protection, [https://www.gesetze-im-internet.de/am-nutzenv/\\_5.html](https://www.gesetze-im-internet.de/am-nutzenv/_5.html)). At the time of writing, it appears that no assessment considering AMR has been completed since this law was passed and it is not clear how it will be applied and, in particular, whether there is interest in approaches that acknowledge the specific public health attributes of antibiotics more explicitly<sup>5</sup>. In Italy, the Ministry of Health has recently launched a national plan on AMR, including guidelines for stewardship, surveillance and prevention (Ministero della Salute, 2017). However, this plan does not appear to include any explicit provision for revisions to the HTA processes.

In the context of the UK five-year national action plan for AMR (DHSC, 2019), NICE, in collaboration with NHS England and the Department of Health and Social Care (DHSC), are considering exploring an assessment model that could support delinked payment models for antimicrobials. The proposal builds on the learnings of the EEPUR report (Rothery et al. (2018), which demonstrated the complexity of estimating value and forecasting use of new antibiotics. As part of this project, NICE will adapt its existing processes into a 'pragmatic HTA framework' for antibiotics where health economic modelling is informed and supplemented by qualitative information. In other words, the pilot aims to test an approach that combines quantitative modelling with more deliberative methods, for dimensions where QALY values are difficult to quantify. The resulting evaluation framework will feed into a negotiation process, whose characteristics will also be developed as part of the pilot. The project will pilot two products: one antibiotic already in the market, for which there is experience of clinical use; and one yet to be launched product, although no specific antibiotics have yet been chosen.

A more general comment by the Forum participants in relation to the current HTA system of antibiotics in Europe was that companies may choose not to engage with the process. Specifically, where companies feel that a non-critical market is likely to provide a negative recommendation, they may prefer an outcome of 'not recommended by non-submission of evidence' to submitting evidence and getting a 'not recommended'. This implies that what gets assessed is determined jointly by the policy of a country for selecting the antibiotics to assess and the manufacturers' decision to launch in that country. Therefore, the absence of negative assessments for antibiotics should not be interpreted as a signal that current HTA approaches do not have problems.

From a rapid review of antibiotics contracting approaches in Europe, we found that antibiotics used in hospital settings are usually reimbursed through tariff-based payments, typically forms of diagnosis related groups (DRGs), consisting of a single lump sum payment for the whole illness episode (i.e. diagnostic, provider care and medications). This system may disincentivise the use of high-priced new antibiotics. Exemptions from the single tariff are available in theory in all systems, for example for high cost drugs, but in practice are not granted frequently. Karlsberg Schaffer et al. (2017) note that tariff-based payments are typically revised infrequently and there is often not enough clarity around the eligibility criteria for hospitals to receive additional funding.

In France, since December 2015, new antibiotics with at least minor incremental therapeutic benefit (ASMR IV) are granted a 'price guarantee' in the same way as drugs with moderate, important or major incremental benefit (ASMR III-II-I) (HAS, 2014). This 'price guarantee' ensures that the price is not inferior to lowest price used for that product among the four main European markets.

Efforts to change contracting for antibiotics are ongoing in Sweden, where the Public Health Agency and the Dental and Pharmaceutical Benefits Agency (TLV) have designed a compensation model to address the availability of antibiotics in the Swedish market (Folkhälsomyndigheten and TLV, 2017). The proposal targets new antibiotics to be covered by market protection when they are of special medical value and at risk of insufficient availability. Medical value is determined according to the criteria of: activity against resistant infections, available treatment options, and importance for

<sup>5</sup> A new antibiotic (*Bedaquiline*) is currently under assessment <https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/433/>

specific patient groups. Broadly, the proposal consists of negotiating with the manufacturer a minimum lump sum payment guaranteed at national level to cover the cost of keeping the antibiotic on the market if revenues are too low. In parallel, a value-based price will also be assessed and paid by counties/ regions as usual, without having to modify current HTA approaches. The government has recently agreed the piloting of this proposal. However, it is not clear whether the Swedish approach, consisting of a compensation model used alongside standard HTA value-based pricing, will be enough to incentivise the industry to intensify R&D in antibiotics as the objective is to keep products on the market, once they have been developed.

### 3.3 Experts' perspectives on the proposals to revise HTA and contracting of antibiotics

We explored the perspectives of experts from England, Germany, France and Sweden on the feasibility and the potential interest in the proposals in the literature on methods for valuing, HTA and contracting for antibiotics.

Overall, the expert interviewees reported that their countries' systems for value assessment do not address the specific public health elements of value of antibiotics (Column 2, Table 1). Among the challenges in broadening the value paradigm to address these elements they highlighted: possible overlaps within the proposed antibiotics value attributes and with existing considerations (e.g. enablement value and unmet need); and measurement problems using the available evidence and current methodologies (e.g. judging enablement requires not only estimates of the incidence of resistance with and without the antibiotic being assessed but also estimates of the impact of high resistance rates on death rates from routine procedures; judging insurance value requires information on societal preferences for insurance against catastrophic health events).

While existing frameworks do not address directly the public health value attributes of antibiotics, some interviewees suggested that similar aspects of value may currently be applied to vaccines. In England, France and Germany, vaccines are subject to separate assessment procedures which involve modelling exercises carried out by committees sitting within or outside the central HTA authority. In England, the JCVI is an independent advisory committee of the DHSC producing binding recommendations on new and existing immunisations programmes based on analysis of evidence on effectiveness and cost-effectiveness. In Germany, the Standing Committee on Vaccination (STIKO), conducts the appraisal of vaccines and makes recommendations. In France, the Technical Vaccination Committee (CTV) develops the immunisation strategy and conducts investigations on vaccines, although its recommendations are not binding. Of note is that while France and Germany undertake modelling exercises for vaccines, drugs in these countries are usually assessed using evidence from clinical trials and more deliberative methods, rather than modelling. Expertise and precedent therefore exist in these countries for using modelling techniques to estimate characteristics that are shared by vaccines and antibiotics, like transmission value.

The interviewees had mixed views about the likely policy acceptability and practical feasibility of using multi criteria decision analysis (MCDA) tools to expand the value assessment of antibiotics. On the one hand, systems that aim to quantify value using QALYs may struggle to find ways in which MCDA can be seen to deliver valid numerical adjustments to the QALY. On the other hand, in systems using more deliberative methods, MCDA could help to structure key value attributes for antibiotics more explicitly into assessments. In France, for example, multiple considerations contribute to determining the therapeutic benefit through the SMR score (e.g. efficacy, safety, disease severity, public health benefit). Hence, value elements specific to antibiotics could either be incorporated to existing dimensions or included as new ones.

The general feeling about the modelling work set out by Rothery et al. (2018) to tackle valuation of the additional public health benefits was that their methodology relies on advanced and complex modelling, which may not be achievable in countries where the expertise to undertake and interpret such modelling is not currently available to the HTA system. Given the urgency of assessing antibiotics more effectively due to the public health threat posed by antimicrobial resistance, experts felt it would be reasonable, at least initially, to make more use of infectious disease clinicians, epidemiologists and other experts to supply judgement where data are missing (e.g. on resistance progression) and to simplify the estimation of resistance trends and other key parameters. The skills to undertake complex modelling approaches could be developed over time, for example, by working with those involved in assessing vaccines, as noted above.

Overall, while interviewees acknowledged various limitations of their countries' systems for assessing antibiotics, their view was that changing the assessment of antibiotics was currently not be seen as a policy priority in their countries.

Thinking about alternative approaches to contracting for antibiotics seems to be at an even less advanced stage than thinking on assessment methods. Interviewees were sceptical about the extent to which delinked payment approaches to contracting such as the value-based contracting proposal being considered by the UK government, and the Duke-Margolis per-member-per-month proposal, were likely to be considered, due to the distance from existing approaches.

### 3.4 Where current methods and expert interviews get us to on HTA and on delinked contracting

It is apparent that awareness of the need to tackle AMR is high in the European countries reviewed. Indeed, we chose these countries in part because it was a priority. A number of important policy measures have been put in place in each of these countries. However, reforms to processes for rewarding and paying for new antibiotics are not on the priority list, with the exception of the UK. The literature and the experts indicate that willingness to adapt HTA and pricing and reimbursement processes to better reflect the public health value of new antibiotics seems to be at a relatively early stage, and, delinked contracting is not on the agenda for most countries.

# 4 Conclusions and Recommendations

## 4.1 Conclusions and Recommendations from the Forum

### **ACTION AND COORDINATION**

The Forum participants agreed that the public health threat posed by AMR requires urgent action, including reform to approaches to assessing the value of, and contracting for, antibiotics. Solutions that can be operated in the short term are necessary, even though these may differ from long-term solutions.

Further coordination between domestic and global initiatives on HTA and contracting for antibiotic is also needed. While more progress is expected on the global stage, action could be facilitated by regionally coordinated solutions. In Europe, for example, the European Commission could play a central role in steering coordinated action by the member states.

At the European level, a way to promote a common HTA process for antibiotics could be considered. While the European Network for Health Technology Assessment's (EUnetHTA) role is clearly relevant here, its work is typically at a technical level, and it would need an agreement at a policy level that it should work in this area. The HTA Council could be asked to agree to this and task EUnetHTA with a new programme of action on adapting HTA to AMR. This would be likely to take some years and its direct impact on practice in individual countries might be limited. However, if this could be agreed as a priority for EUnetHTA, this would raise the profile amongst individual EU member states. There might also be scope for some fast-track and potentially valuable work to promote better understanding and coordination of work on antibiotics by HTA and regulatory bodies, for example through existing EUnetHTA workstreams on Joint Scientific Advice.

At national level, policies to tackle AMR seem to have had little or no impact on the practical working of HTA agencies in many countries. One of the reasons for this impasse may be the paucity of new antibiotics being launched. Given the fact, noted earlier, that companies may choose not to launch if they fear a negative assessment, it was suggested that companies should take more risk in the HTA submissions to highlight the problems with current HTA approaches, though it was acknowledged that this could entail major commercial risks for manufacturers, particularly small companies. Further evidence on where companies choose to launch and/or submit to HTA agencies in Europe would be valuable.

### **EXPANDED VALUE FRAMEWORK FOR ANTIBIOTICS**

In line with the interviewees' concerns about the risk of overlapping value attributes, Forum participants expressed mixed views on the legitimacy of 'spectrum value' as a special consideration for antibiotics. On the one hand, it is true that the impact on cross-resistance (i.e. tolerance to antimicrobials as a result of exposure to similarly acting antimicrobials) and resistance development will differ depending on the spectrum of bacteria covered by the antibiotic (i.e. large vs narrow). However, the degree to which the corresponding 'spectrum value' may overlap with other dimensions of the expanded framework needs careful consideration, possibly on a case by case basis, to avoid double counting. In any case, it is important that the value assessment of antibiotics is based on

clear understanding of the different strategies of use and the expected benefits from each strategy over time.

It was also suggested that, in order to progress the practical adoption of the expanded value framework, the value dimensions that have the greatest impact on overall value should be identified empirically. A second step of this prioritisation exercise could involve identifying the attributes that it is possible to build evidence of value on. If there is an overlap, efforts can be devoted to collecting evidence on the elements of value that are likely to matter the most.

The Forum participants stressed the importance of rewarding new antibiotics that will tackle the most dangerous pathogens (e.g. as set out in the WHO priority pathogens list, for which new antibiotics were needed to tackle them).

### **MODELLING METHODS FOR ANTIBIOTICS**

The Forum discussion on modelling methods for antibiotics focussed on the opportunities offered by the EEPRU work (Rothery et al., 2018) and the analogies that can be drawn with the methods currently used for evaluating vaccines.

Despite the interviewees' concern that the modelling required to carry out the EEPRU modelling is complex, among the Forum participants there was some consensus that expertise is available in the UK, and progress could be made to build it up in other countries. At the same time, it was noted that the successful application of a modelling approach requires all the stakeholders and/or committee members involved in an assessment to understand it, at least in terms of its basic elements and linkages. This would need to be considered when developing arrangements.

The main perceived challenge for modelling was seen to be the quality of the data available to populate the models. Given the likely large amount of uncertainty, the Forum participants pointed to the need to: quantify the uncertainty generated by the quality of the data and identify the areas where bringing in the judgement of experts could be most useful to generate stronger estimates.

While the EEPRU model was built using NICE as a reference case, it was suggested that the recommendations of this work can also be relevant for countries using therapeutic added value approaches which do not rely on QALYs as the primary outcome. Key elements of the EEPRU model include the adoption of a public health perspective and the need to measure all the elements of value of antibiotics in terms of expected health gains/ losses. While some elements of value may be difficult to measure in terms of health (e.g. insurance value), the other benefits can be evaluated using measures other than QALYs.

Another key transferable learning from the EEPRU work is that the strategies of antibiotic use that need to be modelled are those likely to be adopted in clinical practice, and these will not be the same as those analysed in registration trials. Clinical practice tends to be pathogen based and take account of a range of other available antibiotics, whereas registration trials tend to be based on head to head non-inferiority comparisons for specific infection sites. It is important to explore the optimal use to be made of a new antibiotic in each health system, as this may depend on country-specific practices and rates of MDR to current antibiotics. An approach of this kind is currently far from the practice followed by countries like Italy and Germany that focus assessments clearly on the usage and evidence of registration clinical trials. The development noted earlier of a possible ad-hoc AMR Committee within HAS in France might be more supportive of an approach to assessment reflecting real world clinical usage and a public health value framework.

The Forum participants also saw value in exploring the parallels with the methodologies to assess vaccines, at least in some countries. In this regard, the approach of the JCVI in the UK was quoted as

exemplar in generating public health messages that hold relevance internationally. Two of the key elements for the success of the JCVI are: (1) advanced techniques to model the cost-effectiveness of vaccines; (2) a proactive and constructive approach towards manufacturers, aiming to build a clinical trial/ modelling strategy that can support the value proposition of new vaccines.

Developments and current practice in France made this approach seem promising there, but more political push is desirable in order to achieve tangible changes. In contrast, the current challenges with national vaccination policy in Italy mean that promoting the assessment of vaccines as a policy model for antibiotics was unlikely to be constructive. Given the currently scarce national expertise in modelling, Italy could consider investing in the development of capacity and expertise (probably in institutes, rather than in collaboration with in academia) and build a national network of experts.

As noted earlier, in Germany, despite the focus of IQWiG on clinical endpoints from RCTs, G-BA may be able to exercise a more flexible approach thanks to the new law that requires it to consider AMR as part of the assessment of antibiotics. G-BA may therefore be prepared to consider modelling of public health benefit or AMR transmission, given that evidence is scarce.

#### **EVIDENCE STANDARDS**

The Forum participants expressed a view that HTA bodies should be more open to considering evidence from non-RCTs for two reasons: first, as noted, RCTs address a different clinical scenario from that in which most antibiotics will be used; and second, most RCTs are designed as non-inferiority trials with the intention on the part of the regulators that the findings be considered alongside non-clinical data. In particular, regulators typically consider PK/PD data or in-vitro microbiological data when assessing antibiotics, but HTA agencies typically seem to lack the knowledge (and possibly the willingness) to understand it. Educational initiatives bringing together HTA and regulatory bodies could be highly valuable, as suggested earlier in the discussion of a possible role for EUnetHTA.

In discussion of the EEPRU model and UK pilot, it was noted that the collection of post-launch evidence could be helpful to manage the uncertainty around the value of antibiotics due to the scarcity of evidence on clinical superiority and resistance development patterns by pathogen. Initial approval might need to be conditional with a recommendation to collect more data, and data collection could be linked to the contracting between payer and pharmaceutical company. The exact specification of data requirements and timescale would depend on population, therapeutic indication and pathogens. It was suggested that a two-year review point might be appropriate for some new antibiotics.

#### **INNOVATIVE PAYMENT MODELS**

The interviewees' scepticism about the likelihood that delinked payment models will be considered for implementation was echoed in the Forum, at least with respect to the countries where there has been little or no discussion to date on novel contracting approaches for antibiotics (Italy, Germany, France). While a push from the relevant ministries of health may be needed in order to support innovative thinking on payment models, it is hoped that the experience in the UK and elsewhere with delinked payment models will work as an example to be imitated by other countries, and should be disseminated to promote bottom-up as well as top-down action. In the UK experience, ongoing discussions between manufacturers and payers/ HTA bodies have been key for the agreement of the pilot programme of delinked payment models. Whether such type of collaborations could lead to positive outcomes/ initiatives in other countries should also be considered.

In countries where alternative payment models are being considered, the optimal length and the design of contracts have not yet been agreed. It is difficult to establish the length of the contracting

period and, at least initially, timelines and criteria for the review should be agreed upfront. Contract designs may need to vary between countries to take account of the variations in payer structures. For example, in Sweden, there are 21 county councils with responsibility for health and, in England, payments come from a variety of budgets (including NHS England and NHS provider hospitals).

## 4.2 Our Conclusions and Recommendations

First of all, there appears to be agreement amongst all stakeholders that, despite progress with ‘push’ incentives, these will not be sufficient to stimulate manufacturers to continue to invest in developing new antibiotics and bring them to market. For this reason, it is crucial and urgent to get the right market ‘pull’. While views differ on the range of ‘pull’ incentives that are needed, it is important to demonstrate that antibiotics offer value that is commensurate with the level of funding being proposed since some, or all, of this money will come from healthcare and other budgets that are routinely subject to such scrutiny.

While value assessment of the public health benefits of antibiotics is needed, the methods currently applied in most health systems do not capture adequately some of these elements of the value that new antibiotics offer to health systems. Of the elements of value included in the expanded value framework for antibiotics (Karlsberg Schaffer et al., 2017), most HTA systems currently focus on assessing the health benefit to the individual patients treated and thus fail to capture much or all of the important benefits to the wider population. However, experts in value assessment and HTA in the study countries generally agree that existing methods and approaches could be modified to take much better account of the full range of value elements that new antibiotics offer to both patients and society.

The full implementation of the proposed value assessment methods calls for consideration of a number of additional value elements and, in some cases, complex modelling. But the logic underlying the proposed methods is relatively simple and easy to understand. As we noted, it is grounded in the economic concept of externalities – benefits to the payer that fall outside of the immediate ‘consumer’ i.e. the patient treated with the new antibiotic. The solution is to ‘internalise’ them, i.e. add them into the payer’s estimation of the value of the treatment. We suggest two ways in which adoption of the methods could be facilitated. The first is to identify those elements of the value framework that are most important for particular types of antibiotics and usage scenarios, so that efforts can be focussed on these. The second is the use of expert elicitation as a tool to inform modelling where the quality of the data is poor, or directly as a proxy to detailed modelling.

The proposed approaches to value assessment for new antibiotics call for some further rethinking of ‘traditional’ HTA approaches. In particular, the proposed approaches seek to measure the benefits that an antibiotic offers when used alongside other antibiotics, as part of a strategy developed by clinicians and infection control experts to target and reserve drugs for those infections and patients most able to benefit. Such a strategy of usage may differ markedly from that tested in registration trials, which are, in any case, based on non-inferiority trials. This presents a significant challenge to acceptance and adoption of the proposed new approaches to value assessment of antibiotics in many existing HTA systems.

When it comes to modelling benefits, however, countries where the assessment of vaccines relies on advanced modelling approaches and capabilities (e.g. England, France, and potentially Germany) could in principle transfer these methodologies and skills to antibiotics, even if they are not currently applied to the HTA of drugs. This will be particularly valuable where the public health impact of antibiotics is large, and the patterns of transmission, for example, can be modelled with the techniques currently accepted for vaccines assessment. A further advantage of introducing elements of the vaccines assessment methodology for antibiotics may be the opportunity to consider





contracting strategies that are similar to vaccines procurement, which may allow for some element of delinking payments from volumes sold.

We observed wide variations across HTA and value assessment systems in the study countries in the extent to which all these challenges are understood and progress has been made towards addressing them and the remaining steps that each country needs to achieve. These are summarised in Table 2 below, with a colour coding to show our assessment of the overall state of progress in each country with changing the HTA and contracting approaches of antibiotics, as well as recommendations on potential options to accomplish the remaining objectives.

Regarding contracting, an immediate challenge is the inclusion of hospital antibiotics in DRG bundled payment systems in many countries. This encourages the use of cheaper antibiotics when a targeted use of a more expensive antibiotic may be appropriate. Exemption of new antibiotics from inclusion in DRGs with separate remuneration may be an initial step forward. We found growing agreement that a longer-term solution would come from delinking payments to manufacturers from volumes prescribed, since the overall value of a new antibiotic to the whole population may be enhanced by restricting its use. The models discussed in Daniel et al. (2017) involve some kind of annual payment to the manufacturer depending on the population covered, possibly combined with a price per pill actually prescribed, both reflecting the value offered. Again, Table 2 shows variation across the study countries in the extent to which the case for delinked payments is understood and the need for change to current per-pill contracting approaches is accepted, and work is in hand to develop and test modified approaches.

Given the observed degree of heterogeneity, it is important that government officials working in all of these countries' systems understand why change is needed and how it can be implemented in practice. This calls for both top-down work with politicians and senior officials to encourage them to require systems to change, and bottom-up work with those operating the systems to help them to understand how to achieve practical change within the particular systems they operate. With this view, it is crucial that the work in England on reviewing HTA methods for new antibiotics is shared and the potential for adapting the principles of this approach to other systems are discussed. Similarly, the work in England and Sweden for change in contracting of antibiotics through new piloting approaches should be shared and discussed with those responsible for contracting in other systems.

**TABLE 2. STUDY COUNTRIES PROFILES**

	Progress to date	Remaining steps	Possible options to consider
England 	<b>Significant progress on building consensus between industry, government and health system, and on developing policies and methods</b> <ul style="list-style-type: none"> <li>▪ Joint industry-Government Steering Group</li> <li>▪ Detailed review of HTA and de-linked contracting approaches for antibiotics, and ongoing multi-stakeholder discussion of policy</li> <li>▪ Pilot being developed of pragmatic HTA framework and delinked payment models</li> </ul>	<ul style="list-style-type: none"> <li>▪ Identify the right antibiotics for the pilot of pragmatic HTA and delinked payment models</li> <li>▪ Define reimbursement approaches depending on antibiotic-specific pathogens, unmet need, settings etc.</li> </ul>	<ul style="list-style-type: none"> <li>▪ As part of the Pilot, explore/identify those elements of antibiotics expanded value framework that are most significant and tractable for the antibiotics/scenarios being considered</li> <li>▪ Build on vaccines modelling approaches and expertise of JCVI in undertaking assessments in the Pilot</li> </ul>
France 	<b>Interesting proposals but limited change so far</b> <ul style="list-style-type: none"> <li>▪ Thinking on economic models to incentivise antibiotics R&amp;D currently being promoted by CSF ITS</li> <li>▪ 5-year fixed-price guarantee for antibiotics and minimum price to prevent market exit of antibiotics</li> <li>▪ Proposal to introduce an AMR committee within HAS but progress not known</li> <li>▪ No discussion to date on innovative contracting approaches for antibiotics</li> </ul>	<ul style="list-style-type: none"> <li>▪ Adapt current processes for value assessment and pricing for antibiotics – through proposed HAS AMR Committee and/or other means</li> <li>▪ Develop contracting approach that provides appropriate rewards and incentives for value and stewardship</li> </ul>	<ul style="list-style-type: none"> <li>▪ Consider building on the existing vaccines modelling capabilities and systems to progress proposals and thinking around antibiotics value assessment and contracting</li> </ul>
Germany	<b>Some awareness of issues but limited progress</b>	<ul style="list-style-type: none"> <li>▪ Adapt current processes for value assessment and pricing for antibiotics.</li> </ul>	<ul style="list-style-type: none"> <li>▪ G-BA needs to consider how to incorporate a public health</li> </ul>

	<ul style="list-style-type: none"> <li>Government appears mainly focused on 'push' incentives</li> <li>New federal law requiring G-BA to consider AMR when assessing antibiotics does not appear to have had much practical impact to date, but officials appear interested in how it might be implemented</li> <li>No discussion to date on innovative contracting approaches for antibiotics</li> </ul>	<p>Important to note in the German context that this will require a public health perspective and consideration of scenarios and evidence beyond registration trials</p> <ul style="list-style-type: none"> <li>Develop contracting approaches that provide appropriate rewards and incentives for value and stewardship</li> </ul>	<p>perspective and full range of appropriate evidence in its consideration of antibiotics, and to consider where it might get technical help for that. Current systems for assessing vaccines may provide a model.</p>
<p>Italy</p>	<p><b>None apparent</b></p> <ul style="list-style-type: none"> <li>The new national plan on AMR stewardship and prevention does not include explicit provisions for revisions of HTA processes</li> <li>No discussion to date on innovative contracting approaches for antibiotics</li> </ul>	<ul style="list-style-type: none"> <li>Make politicians, health system leaders and AIFA aware of the need to change current approaches to HTA and contracting.</li> <li>Adapt current processes for value assessment and pricing for antibiotics, noting that this will require a public health perspective and consideration of scenarios and evidence beyond registration trials</li> <li>Develop contracting approaches that provide appropriate rewards and incentives for value and stewardship</li> </ul>	<ul style="list-style-type: none"> <li>Start a dialogue between AIFA and experts in infectious diseases, disease control and public health, and involving those with expertise in modelling health benefits of vaccines.</li> </ul>
<p>Sweden</p>	<p><b>Some work on contracting ongoing; TLV aware of issues around value assessment, but there do not seem to be plans at present to address these</b></p> <ul style="list-style-type: none"> <li>Pilot being developed for a contracting compensation model to address the availability of new antibiotics in the Swedish market</li> <li>TLV engaged in international discussions on HTA challenges and possible reforms</li> </ul>	<ul style="list-style-type: none"> <li>Make politicians and health system leaders aware of the need to change current approaches to HTA</li> <li>Make appropriate adaptations to current systems for value assessment and pricing</li> </ul>	<ul style="list-style-type: none"> <li>Given similarity in HTA approaches, consider that can be learned from UK work on methods and pilots</li> </ul>

We conclude with a number of recommendations to encourage further progress in the study countries:

1. The Wellcome Trust and other major institutions supporting R&D and policy analysis to promote the development of new antibiotics, and the UK Government, should continue to **advocate change** to approaches to HTA and contracting for antibiotics around the world, and particularly within Europe. Without HTA methods that recognise the full individual and public health value of antibiotics, and innovative payment models that reward that value whilst promoting stewardship, manufacturers and investors will not see sufficient incentives for developing new antibiotics, however strong ‘push’ incentives may be. These challenges should be addressed in the short-term through practical, implementable solutions which will likely require adjustment over time, but which have political support and can be put in place quickly.
2. The DHSC, NHS England and NICE should continue with their plans to **share the learnings from the England HTA and de-linked payment pilots** with other countries. In the meantime, **other jurisdictions should also promote pilots** in their countries and share their learnings, thus contributing to the overall understanding around antibiotics HTA and contracting policies. In this context, the Wellcome Trust and other independent funders of health research and policy should explore how they can contribute to the dissemination and discussion of the England pilots, along with any other similar work in other countries.
3. The Wellcome Trust and others advocating for policy change should also consider how they can promote awareness and **discussion of the findings of this project** with those responsible for the practical operation and development of assessment and contracting systems in other countries, and in particular in key European countries. The most important policy message from this project in relation to value assessment is that current methods for value assessment need to be modified in three important ways to capture the true value of new antibiotics:
  - Value assessments of antibiotics should consider the public health benefits that an antibiotic offers to payers, in addition to the patients actually treated (many HTA systems currently fail to consider these wider benefits when assessing new drugs);
  - Value assessments should consider the benefits that an antibiotic can offer when used alongside other antibiotics as part of a planned strategy, developed by clinicians and infection control experts, to target and reserve drugs for those infections and patients most able to benefit. Note this strategy of usage may differ markedly from that tested in registration trials;
  - To achieve the above, value assessments of antibiotics will need to use a combination of modelling and expert elicitation to estimate key parameters and outcomes.
4. The proposals in the literature around modelling approaches and the role of expert elicitation in value assessment have intellectual appeal but more work is needed (1) to **understand which elements of the proposed value frameworks contribute most to the value of different types of antibiotics** (and should therefore be the main focus of effort in assessments); and (2) to **understand how they can be put in practice**, with academic experts working in collaboration with those responsible for, or with first-hand experience in, relevant agencies in Europe.
5. The opportunities to **learn from the methodologies of appraisal of vaccines** should be actively explored, particularly in those countries that already have advanced modelling

expertise and capabilities in this area. Promoting the use of vaccines approaches for antibiotics may also help to foster the adoption of elements of vaccines procurement that include some delinking of volumes and payments.

6. The DHSC, NICE and the ministries of health of other jurisdictions should advocate for **EUnetHTA (or successor arrangements) to be tasked with a role in promoting awareness** of the need for, and approaches to, changes in the way HTA is conducted for antibiotics, including developing a joint assessment of a new antibiotic, ideally including England, Sweden, France, Germany and Italy. Such a project could help to raise awareness of the issues in EUnetHTA countries, thus hopefully stimulating independent action.
7. Further policy work is needed to **determine the mixes of 'pull' incentives that would be best suited to the current policies and systems in different countries**, particularly/starting in Europe.
8. Policy work on pull incentives would be helped by **clear messages from manufacturers** about the pull incentives they would like to see that are likely to be acceptable to governments and health systems.

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# Appendix A: current approaches to HTA and contracting

Our review of current HTA approaches covers: (1) evaluation criteria and (2) methods in the seven study countries. Relevant literature was identified through searches of peer-reviewed articles on PubMed and grey literature on Google. Searches were undertaken in August 2018 and were limited to the English Language. A description of the search strategy for PubMed is detailed in B. We built on the findings of Angelis, Lange and Kanavos (2017), Heintz et al. (2016), who reviewed HTA approaches and health economic evaluation guidelines of selected European countries. Other selected studies were used to expand the description of specific HTA aspects, such as patterns of acceptance of endpoints, real world data and non-comparative clinical studies among the study countries. We focused on describing the aspects of the HTA methods that may be of particular relevance to HTA of antibiotics, as identified in section 3.4 of the Policy Research Unit in Economic Evaluation of Health and care Interventions (EEPRU) report (Rothery et al., 2018). These aspects are: comparator, perspective, time horizon, clinical evidence and preferred sources of clinical evidence, resources and costs, health-related quality of life (HRQoL) measurement, discount rates and evidence and modelling uncertainty. An explanation of why these aspects have been highlighted by Rothery et al. is provided in Appendix .

The review of contracting approaches was based on recognised sources (known to the authors) describing general approaches to the pricing and reimbursement of pharmaceuticals and the way these relate to the assessment of value and price-setting in the study countries (Paris and Belloni (2013), OECD (2008) and Ruggeri and Nolte (2013)). Specifically, we focused on capturing the contractual arrangements of new medicines (i.e. new active ingredients or new indications or presentations for existing products) - contracting of generic or off-patent medicines was beyond the scope of this work.

## A.1 Current approaches to HTA

The literature review of current HTA approaches in the study countries was tailored to focus on the aspects that are potentially relevant to the review of antibiotics HTA. Specifically, we focussed on value criteria and methods of analysis, which are also the subject of proposals to review antibiotics HTA (Sections 3.1.1 and 3.1.2). Table 3 provides an overview of country profiles with respect to the type of approach, evaluation criteria and methods followed in HTA practice. Below the Table, we provide a more detailed description of each aspect across the study countries.



TABLE 3. HTA PROFILES BY COUNTRY

	England	France	Germany	Italy	Scotland	Sweden
	<b>Approach</b>					
	QALY-based	Therapeutic added value	Therapeutic added value	Therapeutic added value	QALY-based	QALY-based
	<b>Evaluation criteria</b>					
<b>Clinical effectiveness and incremental effectiveness outcomes</b>	QALYs	Clinical benefit is assessed on a 4-level SMR scale (important, moderate, low, insufficient) Incremental clinical benefit is assessed on 5-level ASMR scale (major, important, moderate, minor, negligible)	Probability of added benefit/ harm scored on a 6-level scale (major, considerable, minor, non-quantifiable, no added benefit, lesser benefit), based on patient relevant endpoints and certainty of evidence, classified in turn as proof, indication, hint.	2-level classification for therapeutic innovation recognition (full or potential/ conditional) based on therapeutic need, therapeutic added value and robustness of CTs. Therapeutic need and added value are scored on a 5-level scale (maximum, important, moderate, low, absent)	QALYs	QALYs
<b>Burden of disease (disease severity and availability of alternative treatment)</b>	Considered deliberately	Considered formally as part of SMR	Only disease severity, considered as part of incremental therapeutic value	Considered as part of the overall assessment of therapeutic innovation, specifically regarding the therapeutic added value	Considered formally	Considered formally



	England	France	Germany	Italy	Scotland	Sweden
<b>Public health benefit</b>	Yes, although unclear how it is done in practice	Considered as part of the SMR with the Interêt santé publique (ISP) indicator, although rarely used	No, but expected number of patients benefitting from the technology used as proxy indicator	Considered implicitly as part of other criteria	N/A	Considered indirectly through the elements of human dignity, need/solidarity (as part of societal perspective)
<b>Social productivity</b>	Caregiving cost, rarely submitted separately	Rarely considered	Productivity loss due to mortality and productivity loss due to incapacity	Only direct costs are considered, indirect costs can be taken into account in separate analysis	Effects on informal caregivers included in sensitivity analyses, if relevant	Indirect costs explicitly considered
<b>Cost-effectiveness</b>	Cost per QALY gained	Cost per QALY used when expected high budget impact and incremental therapeutic value (ASMR) is significant	Efficiency frontier approach	Cost per QALY considered if quality of life gain is significant	Cost per QALY gained	Cost per QALY gained
<b>Budget impact</b>	Budget impact test for products with annual net budget impact $\geq$ £20 million in the first 3 years of introduction	Recommended	Mandatory	Mandatory and used in price negotiations	Required	Not mandatory
<b>Methods</b>						
<b>Comparator</b>	Usually best SOC; most cost-effective, least expensive and routinely used treatments are also	Usually best SOC; most cost-effective, least expensive and routinely used	Usually best SOC; cost-effective, least expensive and routinely used treatments also	Usually best SOC; most cost-effective, least expensive and routinely used treatments are also	Usually best (SOC);	Usually best SOC; most cost-effective, least expensive and routinely used



	England	France	Germany	Italy	Scotland	Sweden
	allowed; unlicensed medicines can be considered if part of clinical practice	treatments are also allowed	allowed; relevant comparators for the indication when efficiency frontier approach is used in the CBA	allowed. Reported explicitly in therapeutic need		treatments are also allowed
<b>Perspective</b>	Health care system (payer) perspective; societal perspective used rarely	'Collective' perspective, to include all health system financing bodies	Usually perspective of the statutory health insurance and patients	Health care system (payer) perspective	Health care system; societal perspective can be explored in sensitivity analyses	Systematic use of societal perspective
<b>Time horizon</b>	Long enough to show differences between technologies	Long enough to include all treatment outcomes	At least the length of the trial; can vary by disease (e.g. longer for chronic conditions)	Length of the trial	Long enough to show differences between technologies	Long enough to cover main treatment outcomes and costs
<b>Accepted/preferred clinical evidence</b>	All clinically relevant outcomes; final outcomes and HRQoL preferred over intermediate and surrogate endpoints	All clinically relevant outcomes; clinically meaningful endpoints preferred over surrogate and composite endpoints	All clinically relevant outcomes; clinically meaningful endpoints preferred over surrogate and composite endpoints	Disease specific QoL and surrogate and composite endpoints	All clinically relevant outcomes; clinically meaningful endpoints preferred over surrogate and composite endpoints	All clinically relevant outcomes (final, surrogate, composite); generic QoL preferred over disease specific
<b>Preferred sources of clinical evidence</b>	Head-to-head RCTs, other studies accepted if RCT not available; manufacturer and regulator SR; extrapolation if effectiveness data from RCTs or long-term effects not available	Head-to-head RCTs, other studies accepted if not RCT available; manufacturer and regulator SR; qualitative extrapolation if effectiveness data from RCTs not available	Head-to-head RCTs, other studies accepted if not RCT available; manufacturer SR	Head-to-head RCTs, other studies accepted if not RCT available; manufacturer and regulator SR; meta-analysis; extrapolation if effectiveness data from RCTs not available	Head-to-head RCTs	Head-to-head RCTs, other studies accepted if RCT not available; quantitative extrapolation if effectiveness data from RCTs or if long-term effects not available



	<b>England</b>	<b>France</b>	<b>Germany</b>	<b>Italy</b>	<b>Scotland</b>	<b>Sweden</b>
<b>Resources/ costs</b>	Direct health system costs; patients cost can be presented separately, but rarely considered	Direct costs (medical and non-medical); indirect costs can be presented separately	Direct medical costs (health system and patient borne);	Direct costs; indirect costs can be presented separately	Direct costs to the health care system	Direct costs (medical and non-medical) and indirect costs (wider societal impacts)
<b>Measurement of health-related quality of life</b>	Indirect methods (EQ-5D)	EQ-5D and HUI3 questionnaires	Indirect methods accepted but instruments should be validated	Indirect methods (EQ-5D)	Indirect methods (EQ-5D preferred)	Direct methods are preferred (TTO, SG or, as a second choice, VAS)
<b>Discount rate (costs and outcomes)</b>	3.5%, fixed over time	4% (up to 20 years), 2% after	3%, fixed over time	N/A	3.5%	3%, fixed over time
<b>Evidence and model uncertainty</b>	Evidence uncertainty implicitly addressed through RCTs preference; uncertainty modelled with univariate and best- or worst-case sensitivity analysis; PSA for parameter uncertainty.	Evidence uncertainty implicitly addressed through RCTs preference; uncertainty modelled with univariate or multivariate SA; Scenario analysis for structural uncertainty; PSA for parameter uncertainty	Evidence quality ranked according to associated uncertainty level; Univariate and multivariate analyses; PSA; structural sensitivity analysis	Evidence uncertainty addressed with conditional reimbursement schemes supported by national registries on patient prescriptions/ dispensing including clinical eligibility data; model uncertainty addressed with sensitivity analyses and PSA	Evidence uncertainty on economic case tolerated for orphan medicines due to limited data on efficacy. Additional factors can also be considered in assessing both the level of uncertainty and cost per QALY which is acceptable; model uncertainty addressed with one- or two-way sensitivity analysis; PSA	Evidence uncertainty implicitly addressed through a preference for RCTs; model uncertainty addressed with sensitivity analyses

**HTA approaches** can be broadly categorised as TAV approaches or ‘QALY-based’ approaches. TAV and QALY-based approaches identify and measure the value of new technologies in different ways: the former focuses on the incremental therapeutic value, identified through clinical effects, compared to the other options already in the market. Prices are generally negotiated based on the added value identified in the assessment. The latter approach focuses on incremental health effects (measured in QALYs) and incremental costs relative to existing treatments, generally expressed in the form of incremental cost-effectiveness ratios (ICER)<sup>6</sup>.

Among the study countries, France, Germany and Italy use TAV approaches to assess the value of new technologies. Sweden, England and Scotland both consider cost-effectiveness as one of the most important formal evaluation criteria. Cost-effectiveness is assessed against an explicit ICER threshold in England and Scotland (£20,000-£30,000 per QALY gained), while in Sweden there is no official threshold, but the likelihood of approval is 50% if the ICER lies between €79,400 and €111,700 per QALY gained.

As for the **evaluation criteria**, HTA systems in the study countries rely on consideration of both clinical effectiveness and economic outcomes, in addition to other aspects such as innovation, burden of disease and wider societal impacts. Briefly:

- **Clinical effectiveness and incremental clinical effectiveness** are assessed, using health-related quality of life (QoL), clinically meaningful outcomes or surrogate endpoints. In England, Sweden and Scotland, QALYs are the preferred outcome to synthesise evidence on clinical effectiveness. The French system assesses the clinical benefit using the 4-level Service Médical Rendu (SMR) scale (important, moderate, low, insufficient), based on joint consideration of efficacy, side effects, illness severity and public health impact and the incremental benefit with the 5-level Amélioration du Service Médical Rendu (ASMR) (ASMR I = major, ASMR II = important, ASMR III = moderate, ASMR IV = minor, ASMR V = negligible). In Germany, the probability of added benefit/harm is scored using a 6-level classification (major, considerable, minor, non-quantifiable, no added benefit, lesser benefit), based on relevant endpoints and certainty of evidence. In Italy, a 2-level classification is used to determine the level of therapeutic innovation (full or potential/conditional) according to therapeutic need, therapeutic added value and robustness of CTs. Therapeutic need and added value are scored in turn on a 5-level scale (maximum, important, moderate, low, absent).
- **Burden of disease and unmet need** (disease severity considered alongside the availability of alternative treatment) is considered formally, Sweden and France. In England it is considered deliberately in committee deliberations. In Italy it is considered implicitly as part of the overall assessment of therapeutic benefit. In Germany, disease severity is considered as part of the assessment of added benefit/harm. In England and Scotland, a specific allowance, by way of a higher cost-effectiveness threshold, is made when technologies meet the criteria for ‘end-of-life care’. In Sweden, burden of disease is particularly important due to the leading role of ‘human dignity’ as a value criterion. In France, disease severity is very important and is considered, as part of the SMR, alongside the existence of alternative treatments under the concept of ‘need’ (Akehurst et al., 2016).
- **Public health benefit and social productivity** are factors determining the wider socioeconomic impact. In England, there is flexibility in the system to include some such wider benefits if they are deemed particularly relevant though the extent to which this is done in practice is unclear. The emphasis is on patient health gain and health system cost. In France these elements are rarely considered. In Germany, only social productivity (productivity loss due to mortality and

<sup>6</sup> The ICER is a measure summarising the additional cost incurred per additional unit of health (QALYs). It is calculated by dividing the difference in total costs between the new and old intervention by the difference in incremental benefits between the new and old intervention.

productivity loss due to incapacity) is explicitly considered; the number of patients who are expected to benefit from the new technology are used as a proxy for the public health benefit. In Italy, public health benefit enters the assessment implicitly and social productivity only in terms of direct costs. In Scotland the effects of the technology on informal caregivers may be included in sensitivity analyses, if relevant. In Sweden, public health value is considered through the elements of human dignity and solidarity entering the societal perspective. The indirect costs of societal productivity are also considered.

- Economic considerations include **cost-effectiveness** and **budget impact**:
  - Cost-effectiveness is routinely assessed and is of paramount importance in England, Scotland and Sweden. In France, cost-effectiveness is assessed when the expected budget impact is high, and the incremental therapeutic value is significant. In Italy cost-effectiveness considerations are used for price negotiations. In Germany, economic considerations are made through the efficiency frontier approach where costs and benefits of new technologies are compared to the ‘efficiency frontier’ for existing interventions within each therapeutic area.
  - Budget impact analysis is required in Italy and Germany and it is considered during price negotiations. In France, it is also used to strengthen the negotiating power of the pricing committee. In Sweden, it is not mandatory and does not constitute a decision criterion for reimbursement. In Scotland, an estimate of the budget impact over a five-year time horizon must be submitted with all applications. In England, the budget impact test (introduced in April 2017) looks at the net budget impact of new products to be replaced by new treatments. Negotiations with NHS England are required for products with an annual net budget impact of £20 million or more, in any of the first 3 years of its use in the NHS.

Our review indicates that the aspects of HTA **methodology** that may be particularly relevant to antibiotics (Rothery et al., 2018) are applied in each country as follows:

- All of the study countries tend to choose the best standard of care (SOC) as the **comparator**. SOC assumes a slightly different definition across countries, including most cost-effective, least expensive, most likely to be replaced or routinely used technology.
- The only country using a full societal **perspective** systematically is Sweden; in England it is used only in ad-hoc circumstances, and in Scotland in sensitivity analyses. Otherwise, the health system (payer) perspective is used. This is similar to Germany (which takes a statutory health insurance and patient perspective) and Italy (wider perspectives are possible or can be presented separately). In France, a ‘collective’ perspective including all the health system financing agents (including patients) is used.
- The **time horizon** of the analysis is generally defined as a long enough time frame to capture the differences between new and existing technologies. In some cases (Germany and Italy) it is attached to the length of the trial, but generally it is not defined within fixed boundaries.
- **Clinical evidence** based on surrogate and intermediate endpoints is typically accepted by all the study countries. However, clinically meaningful final endpoints are explicitly stated as preferred in France, Germany, England and Scotland. Research by Staab et al. (2016) showed inconsistent patterns of acceptance of primary endpoints in Germany. Their study found that mortality endpoints are generally considered ‘patient-relevant’ while morbidity endpoints are accepted inconsistently across disease areas. For example, asymptomatic endpoints (i.e. laboratory parameters or endpoints assessed with imaging techniques) seem more often accepted for infectious diseases (e.g. hepatitis C) than oncological or metabolic diseases. The authors conclude that this inconsistency will add uncertainty to the optimal clinical trial design given a

misalignment between EMA and HTA requirements. HRQoL can be measured using general or disease-specific endpoints, the former being explicitly preferred in Sweden.

- RCTs are the preferred **source of clinical evidence**. However, the policies on use and acceptance of other study designs and evidence sources vary across countries.
- In the European study countries, real world data (RWD) can be accepted for discussion in the initial reimbursement phase and are recommended for pharmacoeconomic analyses or conditional reimbursement schemes (Makady et al., 2017). This said, RWD are typically viewed on a lower level of the 'hierarchy of evidence' than data from RCTs, and are generally used to complement, rather than substitute for evidence on treatment effects from RCTs. With the exception of Germany, where reliance on RWD in isolation is not permissible, RWD can be accepted for demonstrating treatment effects in specific circumstances (e.g. when RCTs are not feasible; for orphan diseases). However, the assessment of the treatment effect will be regarded as 'circumspect' (Makady et al., 2017). The collection of RWD is recommended in all the European countries, excluding Germany, for pharmacoeconomic analyses purposes (i.e. epidemiology data, direct and indirect costs, resource use, adherence to treatment). Additionally, France and Italy request the collection of RWD in conditional reimbursement schemes to address evidential gaps on effectiveness or to answer questions raised during the initial assessment.
- In England and Germany, submissions based on non-comparative evidence only (i.e. single-arm trials, dose-ranging studies, registry studies, uncontrolled extension studies, compassionate use programmes) lead to negative decisions more often (40% of cases England, 85% of cases Germany) than submissions presenting non-comparative evidence in support of comparative data (31% of cases England, 65% of cases Germany) (Griffiths et al., 2017). Of note NICE (England) state they are willing to consider non-comparative evidence if no more robust evidence exists, while the Institute for Quality and Efficacy in Health Care (IQWiG, Germany) are less prepared to consider it. The reasons justifying the acceptance of non-comparative evidence are: lack of treatment alternatives or unmet clinical need for new technology (England and Germany), licence in a small patient population (England), unethical comparative trials due to high clinical effectiveness of new technology (England and Germany), unethical comparative trials due to life-threatening disease (England). Non-comparative studies can be used with post-marketing surveillance data to monitor product safety (Oyebode et al., 2015).
- The type of **resources and costs** included in HTA are dictated by the perspective adopted. Countries choosing the payer or insurer perspective (England, Scotland, Germany, Italy) prioritise direct medical costs, while indirect costs are presented separately. The 'collective' perspective, in France, allows for the inclusion of direct non-medical and indirect costs too, though the latter must be presented separately. In Sweden, where a societal perspective is used, all relevant direct and indirect costs and revenues, and wider societal impacts are incorporated into the QALY estimates.
- **HRQoL** can be elicited using either indirect or direct methods<sup>7</sup>. Indirect methods are preferred in England, Scotland, Italy and France and are based on using questionnaires (like the EQ-5D or the HUI3) with a pre-scored value set (utilities) derived, in turn, with one direct method (time trade off (TTO), standard gamble (SG) or visual analogue scale (VAS)). In Sweden, direct methods are preferred over indirect ones. In Germany, indirect methods are accepted but instruments and minimally important differences should be validated.

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<sup>7</sup> With direct methods, patients are asked to directly value their health using elicitation techniques like SG, TTO or VAS. With indirect methods, patients are asked to fill quality of life questionnaires which can convert the results to utilities using pre-populated values.

- In the study countries, the **discount rates** are generally fixed over time and range between 2% and 3.5%. The exception is France, where the discount rate is 4% up to 20 years and 2% afterwards.
- In Germany, **uncertainty in the evidence base** is judged according to the type of study (i.e. randomised vs non-randomised) and the level of 'bias risk'. Countries like France, Sweden and England implicitly deal with uncertainty through a preference for RCTs. In Italy, uncertainty of evidence at the time of decision making is in part addressed using national web-based registries monitoring prescriptions/ dispensing at patient level (including clinical data) and supporting the implementation of conditional reimbursement schemes. In Scotland, the Scottish Medicines Agency (SMC) is willing to tolerate more uncertainty in the economic case of orphan medicines, defined as licensed for treating or preventing life-threatening rare diseases affecting fewer than 5 in 10,000 people in the European Union. This is justified on the basis of limited data on efficacy (i.e. due to smaller clinical trial programmes). Additional factors, such as whether the drug: treats a life threatening disease; substantially increases life expectancy and/or quality of life; can reverse, rather than stabilise, the condition; or bridges a gap to a 'definitive' therapy, can also be considered in assessing both the level of uncertainty and cost per QALY which is acceptable. **Model uncertainty** is explored by means of deterministic or probabilistic sensitivity analyses of the incremental costs and health effects and of incremental cost-effectiveness ratios.

In Rothery et al. (2018), the choice of population and modelling approach are also highlighted as challenging for the HTA of antibiotics. However, our review could not identify any publications describing the country specific approaches with respect to these dimensions.

## A.2 Current approaches to contracting

From a theoretical perspective, the need for pharmaceutical price regulation arises because of the role played by health insurance (public or private) and third-party payers. Health insurance has a welfare improving function because it protects individuals from the risk of catastrophic health expenses (Arrow, 1963). However, unless demand is completely insensitive to price change, insurance will also move the demand for health care away from the optimal level (Pauly, 1968). In other words, even though individuals as a group bear the cost of health care with taxes or social or private health insurance premiums, individual's demand for health care will generally be insensitive to price changes, thus leading to excessive spending. The financial sustainability issue is a particular challenge in the context of on-patent drugs when direct competition is limited by intellectual property right protection in order to help provide the innovator with a return on their R&D investment.

The countries in our study tend to adopt a mix of regulatory techniques aiming to directly contain the level of prices and to reward the value of medicines at the same time.

External benchmarking or reference pricing, and internal reference pricing are examples of tools imposing direct limits on the level of reimbursement prices. External referencing (also called international reference pricing) is based on the idea that the prices of new drugs in a country should be fair in relation to what is paid by other countries, taking account of economic comparability and geographic proximity. A common practice to establish the externally benchmarked reference price is to take the average prices observed in the relevant group of reference countries (Paris and Belloni, 2013). Internal reference pricing uses therapeutic comparators and relevant incremental benefits to define differences in the price of drugs and is also called therapeutic reference pricing.

Some countries – such as Germany and the UK - have favoured free or market-based pricing approaches where manufacturers are not constrained when they choose their sales prices (at list level) at market entry (OECD, 2008). However, even in such countries, this approach is typically used



together with referencing and/or other direct or indirect tools (e.g. direct price cuts or price ‘freezes’) to impose price limits where the price is thought to be too high or unaffordable.

Most OECD countries also use pharmaco-economic analysis (economic evaluation) to support pricing and reimbursement decisions. Assessing the cost of new medicines in relation to their incremental benefit, compared to other options, supports value-based pricing approaches. When the evidence to demonstrate value is insufficient at the time of decision-making or there is uncertainty about utilisation and budget impact, Managed Entry Agreements including so-called ‘risk-sharing’ agreements may represent an attractive way forward. In these circumstances, reimbursement is typically conditional on pre-agreed outcomes (clinical or financial or both) to be demonstrated with evidence collected in the post-launch period or conditional on a defined budget impact not being exceeded.

In the UK, manufacturers are free to set the price of new medicines at launch, and they can subsequently apply for price changes only in a limited number of cases and should accept mandatory price cuts. However, the voluntary scheme for branded medicines and pricing and access (VPAS) seeks to regulate both overall branded medicines expenditure and its growth and the level of profits that companies can achieve. De facto, a form of indirect price control is exercised through the cost-effectiveness (cost-per-QALY) threshold, above which medicines are unlikely to be recommended. Willingness to pay for value elements which do not formally enter the QALY function is reflected by the willingness to accept higher cost-effectiveness thresholds when those value elements are demonstrated. NICE uses a cost-effectiveness threshold range of £20,000 per QALY, rising to £30,000 when other factors are deemed relevant, and to £50,000 when treatments meet ‘end of life’ criteria. Similarly, when the cost per QALY is relatively high, other factors may play a role in modifying SMC’s final decision. These ‘modifiers’ include factors similar to those allowing more uncertainty around the economic case.

In France, prices are negotiated between manufacturers and the Economic Committee for Health Products (CEPS). The level of added therapeutic value of new medicines, as measured through the ASMR five-level classification, works as one of the main criteria determining prices. Products that are awarded a high level of innovativeness (ASMR I-II) are priced according to external price benchmarking and can benefit from a five-year price guarantee, while products with a low level of innovativeness are priced using internal or therapeutic reference pricing.

A five-year agreement between the CESP and the industry sets the terms for multiple shared objectives including the growth of pharmaceutical spending. The pricing committee considers the expected volume of sales which, if above a certain ceiling, will result in ‘price per volume’ agreements. The rebates associated to price per volume agreements tend to be based on therapeutic class or innovation level to meet public health objectives (OECD, 2008).

Germany is among the countries using market-based techniques for pricing of pharmaceuticals at launch. Since 2011, the prices of innovative medicines are reviewed after one year. In preparation, new medicines are subject to benefit assessment within three months of launch to ensure prices represent an efficient use of resources. As we have noted, medicines are classified according to the additional therapeutic benefit and the quality of the evidence demonstrating that. Medicines providing low additional benefit are clustered for internal reference pricing in therapeutic reference groups and maximum reimbursement rates are imposed if there is no additional benefit. If the additional benefit is considered significant, the list price may be accepted or a lower price negotiated. In the absence of agreement, external price benchmarking can be used.

In Italy, price negotiations take place between pharmaceutical companies and the Italian Medicines Agency’s (AIFA) Pricing and Reimbursement Unit. The discussion at AIFA Technical Scientific Committee (CTS) on clinical considerations of therapeutic value, place in therapy are decisive criteria



in determining prices, accompanied by evidence on the degree of innovativeness recognition. External reference pricing is used only as supportive information for price negotiations, with reference countries chosen on an ad-hoc basis.

When the evidence on clinical effects is uncertain, Managed Entry Agreements are widely used to grant access and reimbursement to new medicines to evaluate the performance of the drug while collecting post-launch patient prescription data using AIFA web-based registries.

In Sweden, similarly to the UK, new medicines are approved for reimbursement if they are found to be cost-effective. This works as a form of de facto price regulation where manufacturers have an incentive to contain the price levels to meet the approval requirement. Once approved, the price of the product may not be raised again without approval. External reference pricing is not used.

## Appendix B: PubMed search strategy

For the review of HTA and contracting in the study countries, we performed a number of searches on PubMed as described in Table. Query #1 searched articles on HTA in the European study countries and query #3 searched articles on HTA methods for antibiotics in the study countries.

The time period for the inclusion of the articles was: after January 2014 for query #1 and from January 2000 for query #3. The year 2014 was chosen as the start date of the articles to include in query #1 because one of the main articles we used for the HTA review (Angelis et al., 2017) is a review of articles on HTA in Europe published between the years 2000 and 2014.

After a first screening of the query results, papers were selected for review if the title or the abstract was considered relevant and if in English language. Finally, information was extracted from the articles to be included in the review if the content was considered relevant for the topic of the review.

TABLE B.1 PUBMED SEARCH STRATEGY

#	Query	Number of results	Papers reviewed (1 <sup>st</sup> screening)	Relevant papers
1	(health technology assessment[Title/Abstract]) AND (methodologies[Title/Abstract] OR Europe [Title/Abstract] OR France [Title/Abstract] OR Germany [Title/Abstract] OR Italy [Title/Abstract] OR England [Title/Abstract] OR Sweden [Title/Abstract] OR Scotland [Title/Abstract])	346	10	7
2	(health technology assessment [Title/Abstract]) AND (methodologies [Title/Abstract] OR Europe [Title/Abstract] OR France [Title/Abstract] OR Germany [Title/Abstract] OR Italy [Title/Abstract] OR England [Title/Abstract] OR Sweden [Title/Abstract] OR Scotland [Title/Abstract]) AND (antibiotics [Title/Abstract] OR antimicrobial resistance [Title/Abstract] OR AMR [Title/Abstract])	7	0	0

## Appendix C: Challenges of antibiotics HTA

Section 3.4 of the EEPRU report (Rothery et al., 2018) describes the challenges associated with the HTA of antibiotics compared to standard NICE guidance. The HTA aspects picked up in the comparison are: population, comparator, perspective, clinical evidence, preferred sources of clinical evidence, resources/ costs, measurement of HRQoL, modelling approach, time horizon, discount rates and dealing with the uncertainty. The following paragraphs summarise the challenges of performing antibiotics HTA and recommendations to resolve them.

- Identifying the appropriate patient population can be challenging because certain benefits of antibiotics are reaped by the wider population in addition to the patients receiving treatment. For example, the use of the antibiotic will impact the emergence and the transmission of resistance. Additionally, the value assessment of antibiotics may struggle to reflect multiple indications of antibiotics at launch.
- There are multiple issues relating to the choice of the right comparators. Firstly, comparators are likely to differ across geographies depending on local clinical practice. Secondly, comparing existing and new antibiotics may be inappropriate because new antibiotics should be used in addition, not in replacement to existing standard of care (i.e. heterogeneous prescribing in the form of antibiotics rotation, mixing protocols, combination therapies). Additionally, in the case of multi-drug resistant (MDR) infections, no alternative comparators may be available.
- The perspective should include both direct and broader (indirect) health effects and costs. This is crucial in order to capture the transmission value of preventing the spread of resistant infections and that of performing other procedures (e.g. invasive surgeries) (enablement value). The perspective is likely to be influenced by the indication and the population.
- The time horizon should be long enough to reflect differences in outcomes between the new antibiotic and the comparator. There are three potential time horizons: (1) the model/ analytic time horizon, (2) the technology time horizon and (3) the contractual time horizon. (1) is the period when benefits and costs are compared to reflect all important differences. Usually, the model time horizon corresponds the lifetime horizon, but in the case of antibiotics it may be indefinite because of the evolution of transmission and resistance rates. In the case of immunisation programmes, the JCVI in England recommends using indefinite time horizons and carrying out appropriate sensitivity analyses to assess how cost-effectiveness is impacted by different timescales. (2) is the time horizon during which new and existing antimicrobials are used and depends on changes on treatment protocols and development of resistance over time (i.e. after the 'lag phase'). The technology time horizon could be estimated using historical trends, extrapolated data from similar antibiotics, expert opinions on resistance patterns and sensitivity analyses.
- Clinical evidence is hard to generate due to the lack of efficacy data for MDR pathogens. Patients with resistant infections are difficult to enrol into trials due to ethical reasons or the need to treat their infections without delay. Non-clinical endpoints such as PK/PD and in-vitro microbiological data may represent alternative sources of evidence to predict the antibiotic outcome on resistant pathogens. Microbiological data are used to identify the susceptibility of bacteria to antibiotic agents and to establish the minimum inhibitory concentration (MIC) (i.e. the lowest antibiotic agent concentration which inhibits bacterium growth). De facto, the MIC is a threshold for the

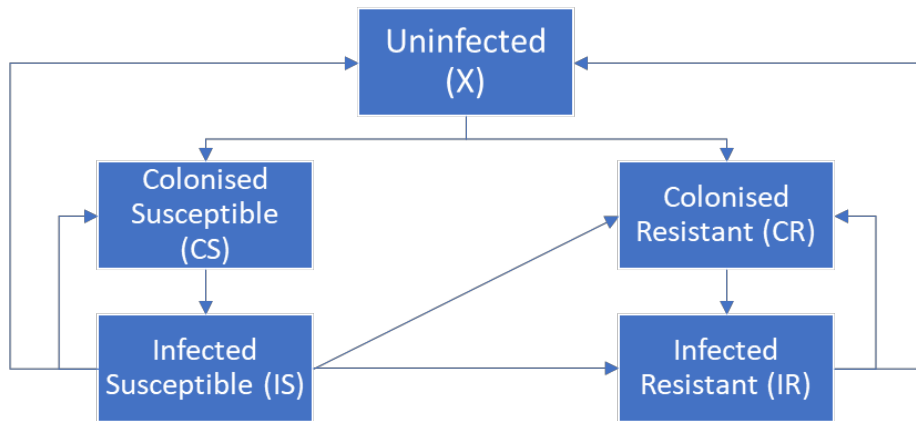
drug efficacy: the lower MIC values, the less antibiotic agent is required to inhibit the bacterium growth. The key distinction between clinical and microbiological data is that the former measures outcomes related to the indication, the latter to the pathogen. There is no perfect correlation between clinical and microbiological outcomes. For example, clinical success (i.e. cured infection) does not always imply bacterial eradication, as demonstrated by susceptibility testing with microbiological data.

- PK data provide information on the relationship between drug dosing and concentration in body fluids while PD data on the relationship between the drug concentration and the effect on the bacteria. PK/PD data can be used to inform the relationship between dose, exposure and response to treatment, all measures of antibiotic efficacy.
- All the health system and personal social services cost deriving from the transmission of infections in the wider population should be included. In line with the proposal to move to delinked payments, where volumes sold are delinked from payment, the acquisition cost of new antibiotics should be excluded when calculating the net health benefit of alternative strategies.
- Measuring HRQoL can be a challenging exercise in the short term. Generic, preference-based measures of HRQoL, like the EQ-5D, are not always collected in clinical trials.
- The modelling approach for antibiotics should reflect the transmission of sensitive and resistant bacteria through the population over time, as well as transmission dynamics. Models used to deal with non-communicable diseases may therefore be inappropriate for antibiotics.
- The optimal discount rate for antibiotics is uncertain. It is unclear, for example, whether health outcomes and costs should be discounted at the same rate. Furthermore, due to the evolution of resistance patterns over time, time-varying discount rates may be more appropriate. The health effects discount rate includes the risk premium for catastrophic expenses and the future time preferences components. However, it excludes the diminishing marginal utility of future consumption when per capita consumption increases over time (i.e. assuming GDP growth). Contrarily to costs, there is no consensus that the value of future health will be lower in the future as a consequence of increasing per capita consumption. The choice of the discount rate also influences the analytic time horizon with lower discount rates extending the time horizon.
- Deterministic and probabilistic sensitivity analyses should be performed to test parameter and structural uncertainty of the cost-effectiveness modelling. This is generally done in the study countries for health effects and costs over the modelled time horizon. The factors which are likely to increase the estimates variability are: uncertainty around the future prevalence infections and resistance rates and how these are modified by different strategies, future stock of effective antibiotics coming to market, lag period between introduction of new antibiotic and development of resistance.

# Appendix D: Resistance emergence model

Figure D.1 provides a simplified representation of the dynamics of resistance emergence modelled by Rothery et al. (2018). For ease of representation, we included only the dynamics originating from the use of one antibiotic. Rothery et al. (2018) perform the same exercise with two treatments, so the model includes dynamics of resistance emergence originating from the use of two treatments.

FIGURE D.1 RESISTANCE EMERGENCE MODEL



Source: Adapted from Rothery et al (2018)

The resistance emergence model is based on transitions across 6 health states: uninfected (X), colonised by susceptible bacteria (CS), colonised by resistant bacteria (CR), infected by susceptible bacteria (IS) and infected by resistant bacteria (IR).

Uninfected individuals can become infected with either susceptible or resistant bacteria. Infected individuals receiving treatment can clear the clinical symptoms or remain infected. A crucial assumption of the model is that, if the infection clinical symptoms are cleared, patients can transit to the uninfected state or, in case the bacteria have not been eradicated, to the colonised state. Failure to eradicate the bacteria means that the patient transits from infected to colonised susceptible or colonised resistant states. With this model, the typical assumption that resistance emergence always leads to clinical failure (remain infected) can be disregarded. This modelling improvement is possible because clinical and microbiological outcomes following treatment can be used to identify the transition between infected and colonised state.

Therefore, there are two mechanisms of resistance growth in this model: (1) infections transmission through primary resistance ( $X \rightarrow CR \rightarrow IR$ ) or as a result of treatment (when the infection symptoms are cleared but the bacteria is not eradicated ( $IS \rightarrow CR$ ), and (2) when the infection symptoms are not cleared ( $IS \rightarrow IR$ ).



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- Drivers of, and incentives for, the uptake of pharmaceuticals and prescription medicines
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- Incentives, disincentives, regulation and the costs of R&D for pharmaceuticals and innovation in medicine
- Capturing preferences using patient-reported outcomes measures (PROMs) and time trade-off (TTO) methodology
- Roles of the private and charity sectors in health care and research
- Health and health care statistics