

HTA AND PAYMENTS METHODS FOR NEW DRUGS TO TACKLE AMR

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This briefing summarises the main findings of an OHE research paper published in September 2019 on innovative HTA methods and contracting for antibiotics (Neri, 2019). The paper provides an overview of HTA and contracting for antibiotics in five European countries and of recent proposals for revising them. It includes recommendations developed following a Forum on 'Value Assessment and Contracting for Antibiotics', held in February 2019, involving various stakeholders from the countries included in this study.

The main findings of this work are that:

- **Governments and funding institutions should continue to advocate for changes to HTA and to contracting for antibiotics around the world**, and particularly within Europe. The European Network for Health Technology Assessment (EUnetHTA) or successor bodies, could be tasked with a role in developing a joint assessment of a new antibiotic, thus hopefully stimulating independent action. Countries gaining first-hand experience with innovative HTA and contracting for antibiotics, like the UK, should share the learnings with other countries, to contribute to the common understanding of the most effective policy interventions.
- **HTA approaches to assessing antibiotics need to reflect the public health elements of value that new antibiotics bring to patients and to the health care system.** RCT evidence from registration trials will not provide evidence of superiority, which will need to be estimated using other sources of evidence. The elements of value that are most relevant for particular types of antibiotics and usage scenarios should be identified and expert elicitation should be used to inform modelling. The advanced modelling approaches that are used for vaccines could be transferred to antibiotics to model the patterns of transmission and herd immunity.
- **Contracting for new antibiotics needs to move away from 'price x volume' agreements to delinking payments from volumes sold.** In the short term, new antibiotics should be excluded from DRG-bundled payments to disincentivise the use of cheaper drugs when more expensive ones may be appropriate. 'Volume-delinked' payments will provide a longer-term solution because they will encourage better adherence to stewardship.

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1. 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 proposed 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.

In this context, health technology assessment (HTA) and contracting have equally important and intertwined roles:

- HTA should appropriately recognise the value of antibiotics to ensure that the price paid (i.e. the pull incentive) is commensurate to their value to the health system.
- Contracting should be aligned with stewardship, with payments not linked to volume.

This will optimise expected health gains over the useful life of the antibiotic whilst incentivising R&D for new antibiotics.

This project aimed to:

- provide an overview of the current state of both HTA and contracting for antibiotics. We looked at France, Germany, Italy, Sweden, and the UK (England and Scotland);
- explore recent proposals in the literature for revising HTA and contracting for antibiotics to better capture value and more efficiently pay for new antibiotics;
- set out recommendations for future action, developed following a programme of interviews and a Forum held on 'Value Assessment and Contracting for Antibiotics'.

2. What constitutes value for antibiotics?

The challenge with antibiotics assessment is that a considerable part of their value arises from 'externalities', namely the benefits and costs to the health system beyond those attributable to the treated patient. Examples of these 'public health effects' include preventing the transmission of infections to other patients and slowing down the development of AMR. However, conventional HTA methods only include the effects associated with treating the immediate patient. A literature review of the methods of assessing antibiotics revealed that efforts have been made to capture the additional

benefits of antibiotics and to include them in deliberative decision making (e.g. France) (Charafi and Chen, 2017; Morton et al., Forthcoming), but there are no formal frameworks to conduct an AMR-related HTA assessment systematically. In Germany, recent legislation has established that antimicrobial resistance can be considered as an additional value element when assessing antibiotics, but it is not clear how this will be applied in practice.

Previous work by The Office of Health Economics (Karlsberg Schaffer et al., 2017) has 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. This work makes the case for going beyond the benefits of antibiotics typically considered in HTA (i.e. health gains and health system cost offsets, and, in some systems, unmet need, and productivity benefits) and identified public health benefits that are relevant to the health system and wider society but are not considered in the traditional assessments. These are: transmission value, insurance value, diversity value, novel action value, enablement value and spectrum value.

All the 'typically not included' elements of the antibiotics value framework appear to be important, but more research efforts are necessary to avoid double counting and to overcome the measurement challenges of using conventional approaches to evidence assessment. A helpful start to progress the practical adoption of the expanded value framework may be to concentrate efforts on the value dimensions that are expected to have the greatest impact on overall value, and for which it is possible to generate evidence of value.

3. Modelling antibiotic value

Morton et al. (Forthcoming) and Rothery et al. (2018) have proposed methods to include some of the public health benefits of antibiotics in HTA using quality adjusted life years (QALYs) and estimates of cost-effectiveness. Morton et al. (forthcoming) provided 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) set out an approach for a comprehensive assessment of antibiotics relevant for a health system, including consideration of the optimal strategy for use of a new antibiotic, and estimation of population benefits. The authors propose 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.

These proposals rely on complex modelling exercises that require expert capabilities for their implementation. Adequate expert capacity may be available in the UK, but progress is needed to build it up in other countries. Another barrier for implementing these approaches is the scarcity of data on AMR transmission and development to populate the models. However, given the public health threat posed by antimicrobial resistance, infectious disease clinicians, epidemiologists and other experts could have a role in supplying expert judgement where data are missing or to simplify the estimation of resistance trends and other key parameters.

These proposals on value modelling highlight the importance of using a perspective of analysis that is broad enough to capture appropriately the public health benefits of antibiotics. Furthermore, they stress the need to move away from strong reliance of standard HTA methods on evidence from randomised controlled trials (RCTs). This is

because new antibiotics are usually licensed on the basis of non-inferiority trials. Alternative sources of evidence are therefore proposed to estimate health gain using PK/PD data and in-vitro microbiological data, together with expert elicitation. Antibiotic value has then to be modelled using clinically relevant strategies of use.

An alternative strategy worth exploring for the modelling of antibiotic value is to draw on the use of vaccines modelling methods. Some elements of value that are relevant to antibiotics, such as transmission value, are already being applied in vaccines assessment when modelling herd immunity. The existing modelling capabilities of certain member state agencies in charge of assessing vaccines (e.g. France, Germany and England) could be used to assess the value of beneficial characteristics that are shared by vaccines and antibiotics.

4. Innovative payment models

With traditional pricing arrangements, companies rely on volumes sold to generate revenues, particularly in the period of patent protection. In the case of antibiotics, stewardship will limit the use of the drug during this period depending on the pathogen-specific rate of AMR and related clinical strategies for use of the product. Use will increase in the long-term, when the build-up of resistance means that the antibiotic is used as a first line treatment. Hence, even if HTA methods can capture the public health value of antibiotics, it will be of limited benefit to the innovator to get a high price as volumes are likely to be very low initially. Larger volumes will be sold after patent expiry when the product is priced as a generic.

Given these challenges, proposals for antibiotic contracting have been formulated in terms of models that delink payments from volume sales. Daniel et al. (2017) for example propose a Priority Antimicrobial Value Entry (PAVE) award, a largely delinked payment model aiming to provide appropriate returns whilst promoting stewardship. The PAVE award consists of two components: (1) 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 (2) a progressive shift towards value-based contracts to stimulate continuous stewardship over the useful life of the antibiotic.

'Volume-delinked' payment models can in theory incentivise stewardship programmes that optimise expected health gains over the useful life of the drug while also providing payments to innovators that reflect the value of the drug to the health system. With the exception of the UK, where the National Institute for Health and Care Excellence (NICE) and NHS England have recently announced a pilot programme of a delinked payment-based system, there has been little discussion to date on novel contracting approaches for antibiotics. In Sweden, a lump sum payment model covering the cost of supplying an antibiotic to the Swedish market is being piloted, but this initiative seems to address ensuring the continued availability of existing antibiotics, rather than providing appropriate R&D incentives for new antibiotics. Overall, delinked payment models will be challenging for many countries to implement as they represent a major departure from existing contracting approaches.

5. Recommendations

Awareness of the need to tackle AMR in the European countries of this study is high, as demonstrated by a number of important policy measures that have been put in place to address AMR. However, the focus has been mainly on guidelines for stewardship, surveillance and prevention, and on funding and co-ordinating early stage research for new antibiotics. Reforms to processes for rewarding and paying for new antibiotics are not high on the priority list. The effectiveness of measures that have been proposed is not clear, due to their recent implementation.

Our recommendations for encouraging further progress in antibiotic assessment and contracting are:

- HTA approaches to assessing antibiotics need to reflect the public health elements of value that new antibiotics bring to patients and to the health care system. Contracting for new antibiotics needs to move away from price x volume to “de-linking” payments from volumes sold.
- Governments and funding institutions should continue to advocate for changes to HTA and to contracting for antibiotics around the world, and particularly within Europe.
- Countries gaining first-hand experience with innovative HTA and contracting for antibiotics, like the UK, should share the learnings with other countries, to contribute to the common understanding of the most effective policy interventions.
- Awareness of the need for, and approaches to, change of antibiotics assessment and contracting should be encouraged through existing internationally coordinated initiatives. The European Network for Health Technology Assessment (EUnetHTA) for example, or successor bodies, could be tasked with a role in developing a joint assessment of a new antibiotic, thus hopefully stimulating independent action.
- To facilitate the adoption of the proposed approaches for measuring the public health value of antibiotics, which rely on complex modelling techniques, the elements of value that are most relevant for particular types of antibiotics and usage scenarios should be identified and expert elicitation should be used to inform modelling.
- RCT evidence from registration trials will not provide evidence of superiority, which will need to be estimated using other sources of evidence. Antibiotic value should be estimated using planned strategies of usage and begin with informed estimates of clinical value.
- There is an overlap between the elements of value that are relevant for vaccines and antibiotics. The advanced modelling approaches that are used for vaccines could be transferred to antibiotics to model the patterns of transmission and herd immunity.
- In the short-term, new antibiotics should be excluded from DRG-bundled payments to disincentivise the use of cheaper drugs when more expensive ones may be appropriate. ‘Volume-delinked’ payments will provide a longer-term solution because they will encourage better adherence to stewardship.



6. References

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