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Colson, Abigail, Morton, Alec, Ardal, Christine et al. (14 more authors) (2021) Antimicrobial Resistance: Is Health Technology Assessment Part of the Solution or Part of the Problem? Value in Health. pp. 1828-1834. ISSN 1524-4733

https://doi.org/10.1016/j.jval.2021.06.002


ScienceDirect

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Journal homepage: **www.elsevier.com/locate/jval**

Policy Perspective

Antimicrobial Resistance: Is Health Technology Assessment Part of the Solution or Part of the Problem?

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ABSTRACT

Antimicrobial resistance is a serious challenge to the success and sustainability of our healthcare systems. There has been increasing policy attention given to antimicrobial resistance in the last few years, and increased amounts of funding have been channeled into funding for research and development of antimicrobial agents. Nevertheless, manufacturers doubt whether there will be a market for new antimicrobial technologies sufficient to enable them to recoup their investment. Health technology assessment (HTA) has a critical role in creating confidence that if valuable technologies can be developed they will be reimbursed at a level that captures their true value. We identify 3 deficiencies of current HTA processes for appraising antimicrobial agents: a methods-centric approach rather than problem-centric approach for dealing with new challenges, a lack of tools for thinking about changing patterns of infection, and the absence of an approach to epidemiological risks. We argue that, to play their role more effectively, HTA agencies need to broaden their methodological tool kit, design and communicate their analysis to a wider set of users, and incorporate long-term policy goals, such as containing resistance, as part of their evaluation criteria alongside immediate health gains.

Keywords: antibiotic agents, antimicrobial resistance, economic evaluation, health technology assessment.

VALUE HEALTH. 2021; 24(12):1828–1834

Introduction: The Growing Threat of Antimicrobial Resistance

The spread of antimicrobial resistance (AMR) is a key challenge for healthcare systems. Modern medicine depends on antimicrobial agents to treat disease and ensure that surgery, chemotherapy, and a range of other treatments can proceed without the risk of life-threatening infection.[1] Nevertheless, using antimicrobial agents promotes resistance, opening up an ecological niche in which resistant pathogens can thrive. Almost 80 years of history of antibiotic use shows that within a few years of introducing an antibiotic, resistant pathogens emerge. In recent years, resistance to both colistin, the last line of treatment for many bacterial infections,[2,3] and artemisinin, the core element of effective combination therapy for malaria,[4] has been detected.[5–7]

The World Health Organization (WHO) estimates that, in 2016, a total of 490 000 people worldwide developed multidrug-resistant tuberculosis.[8] The European Centre for Disease Prevention and Control estimates that drug-resistant infections killed 33 000 people in Europe in 2015,[9] and in 2019 the US Centers for Disease Control and Prevention estimate they kill 35 000 patients in the United States annually.[10] Forecasts suggest that, without action, drug-resistant infections could cause millions of deaths annually and significantly reduce global gross domestic product by 2050.[11,12] AMR is a public health emergency, damaging human (and nonhuman) health worldwide. It is likely to have considerably greater impact on health and well-being in the future, with the greatest health and economic impact occurring in low-income settings.[11] This threat may worsen in the coronavirus disease 2019 era, because of the use of antibiotic agents to control infections in hospitalized patients with COVID-19.

Several vital steps have been suggested to combat AMR. These include controlling the use of antibiotic agents in farming and reducing levels of antibiotic agents in wastewater. In many countries with poor access to healthcare, widespread inappropriate consumption of antimicrobial agents coexists with a lack of access for patients in genuine need.[13] Hospitals and other healthcare facilities need to improve their antimicrobial stewardship and infection prevention and control practices, and patients need to moderate their expectations about the availability of antimicrobial agents. Tackling these issues can reduce resistance rates and preserve antimicrobial efficacy, but the struggle against AMR also requires new technologies, such as innovative antimicrobial agents and improved diagnostics that can

help target antimicrobial agents, ensuring they are only used when necessary. New and existing vaccines can also help, through tackling the spread of microbial diseases generally or resistant strains specifically.[14]

Despite the need for new technologies, the WHO has said the clinical antibacterial pipeline is not sufficient.[15-17] Large pharmaceutical companies such as Sanofi, Novartis, and AstraZeneca have stopped their antimicrobial development programs.[18] High development costs, the availability of cheap alternatives, and the small potential market for new antimicrobial agents (in part because of the necessity of ensuring appropriate stewardship of novel therapies) reduce the economic incentives for research and development (R&D) of new antimicrobial agents, creating a need for innovative policy and thinking to support R&D efforts.

Why Does This Matter for Health Technology Assessment?

AMR has ascended the international policy agenda (Table 1), and this political attention has been matched with increased funding to support R&D of antibiotic agents: the international nonprofit funding vehicle CARB-X is supporting more than 80 new antibiotic R&D projects with funding up to $500 million over 2016 to 2021[29,30]; the REPAIR Impact Fund will spend $165 million over the next 5 years as an investor in antibiotic R&D[31]; and Global Antibiotic Research and Development Partnership, a nonprofit cofounded by WHO, and the Drugs for Neglected Diseases Initiative focusing on health needs in low- and mid-income countries (LMICs) have cofunded phase III trials for a new drug for gonorrhea.[32,33]

These initiatives are an important step, but new technologies, however clinically promising, will not be available on the market unless investors have a clear path to secure an adequate return. Currently, potential investors doubt whether these technologies represent a viable business proposition. The recent failure of Achaogen, a biopharmaceutical company that brought plazomicin—a new antibiotic capable of treating multidrug-resistant infections—to market in 2018 but filed for bankruptcy in April 2019,[34] demonstrates the validity of these concerns. The application for market authorization in Europe for plazomicin was withdrawn in June 2020,[35] and omadacycline had a similar fate the previous October,[36,37] with both withdrawals substantially driven by economic infeasibility.

One way to match demand for a new technology to clinical need is through the use of health technology assessment (HTA), which estimates the cost-effectiveness of a new medical technology and suggests to payers whether or not the product should be reimbursed. HTA bodies in some countries go a step further and use cost-effectiveness analysis to also establish the price to be paid, which is called value-based pricing. HTA—which is not limited to formal cost-effectiveness analysis—informally or indirectly supports decisions about eligibility and/or price negotiations in other countries and is increasingly being recognized as an important tool for priority setting in LMICs.[38,39] Many smaller countries follow the lead of larger countries in matters of access, pricing, and reimbursement through external reference pricing. Thus, HTA plays a critical role, through both HTA agencies' recommendations about technologies and the perception of how they arrive at their recommendations, which has a direct impact on investments and which technologies are profitable.

Given this central role of HTA agencies, the way in which they assess whether new technologies offer value for money is very important. An inappropriate assessment of value could mean that manufacturers are unable to earn a return on their investments, signaling that a given product should not be brought to market. Here, we argue that in the case of antibiotic agents agencies are not routinely using appropriate evaluation methods, and they are approaching their assessment from a perspective that blinds them to many of the elements of value provided by new antimicrobial agents.[40]

Clinical and Public Health Value of Antimicrobial Agents

Critical to understanding the value of new antimicrobial agents is the notion of disease transmission. When a patient hosts a pathogen that has evolved to be resistant to standard treatment, this patient may transmit this pathogen to others, potentially leading to a costly and damaging outbreak of resistant infections. If an innovative technology exists to treat a patient with the resistant pathogen, the spread of resistance can be reduced. In this sense, antibiotic agents are like a fire extinguisher that, at a modest cost, prevents the whole house from burning down.[41] Most therapeutic medical technologies only benefit the individual patient, whereas antimicrobial agents (as well as diagnostics and vaccines) indirectly benefit the wider society. Nevertheless, unlike diagnostics and vaccines, if treating someone reduces the demand for treatment from other patients, the antimicrobial manufacturer makes a lower return if they are paid per dose. Ignoring this "positive economic externality" is one market failure at the heart of the mispricing of innovative antimicrobial agents, and HTA needs methods to incorporate this additional value in their assessments.

A further complication is that, for reimbursement purposes, we need to put a value on having antimicrobial agents available now for the resistant pathogens that will cause outbreaks in the future, so that they are available when needed.[42] We hope, though, that health systems will not actually use these doses for many years. New antimicrobial agents may also provide value by enabling surgical procedures and cancer chemotherapy to take place, providing a more diverse portfolio of options to treat infectious disease, or through other characteristics that are unique compared with other types of medical technologies,[43-46] sometimes referred to with the acronym "STEDI"—spectrum, transmission, enablement, diversity, and insurance (Table 2). The use of antimicrobial agents also results in a negative externality, because increasing consumption results in increasing selection pressure for resistance.[47,48] Ignoring this negative externality leads to the overconsumption of currently available antimicrobial agents, which increases the problem of resistance and thus the need for additional novel treatments.

The default framework for thinking about disease in HTA agencies has been a noncommunicable disease (NCD) paradigm, focused on benefits accrued to an individual patient, which misses these broader benefits of antibiotic agents. This is reflected in the orientation of the core HTA methodology texts and United Kingdom National Institute for Health and Care Excellence (NICE) methods guidance, which have no or sparse mention of antibiotic agents, antimicrobial agents, communicable disease, and infectious disease.[49-52] Furthermore, the NICE Guide section on "time horizon" focuses on whether the time horizon of modeling should be the lifetime of the patient receiving treatment or shorter, but, from an infectious disease point of view, the time horizon may be longer than the patient's life. Nevertheless, the National Immunization Technical Advisory Groups such as the UK's Joint Committee on Vaccination and Immunisation and

Table 1. High-level political action on antimicrobial resistance.

Year	Action
2015	World Health Assembly (the governing body of the WHO) agrees to a resolution on AMR and adopts a Global Action Plan on AMR.[19]
2015	The G7 health ministers agree to a declaration on AMR.[20]
2016	World leaders commit to the struggle against AMR at the UN General Assembly (1 of only 4 occasions on which a health issue has been addressed in this forum).[21]
2017	The G20 health ministers, meeting for the first time, address the importance of international cooperation on AMR.[22]
2017-2020	G20 leaders consider AMR for 4 consecutive years.[23-26] In 2019, G20 leaders specifically highlight the need for push and pull incentives to promote R&D in antimicrobial agents.
2019	G20 health and finance ministers meet together for the first time, discussing AMR.[27]
2020	Launch of the One Health Global Leaders Group on Antimicrobial Resistance by the WHO, the FAO of the UN, and OIE[28]

AMR indicates antimicrobial resistance; FAO, Food and Agriculture Organization; OIE, World Organisation for Animal Health; R&D, research and development; UN, United Nations; WHO, World Health Organization

the US Preventive Services Task Force do often incorporate economic evaluations that capture community-wide externalities in developing their recommendations, demonstrating that it is feasible to adapt economic evaluation methods to the special characteristics of infectious diseases.[53,54] A recent discussion around expanding the concept of what constitutes "value" in HTAs more broadly[55] also captures some of the elements that are important for antibiotic agents (risk of contagion and insurance), but not all.

There is some appreciation at policy levels of the importance of taking into account transmission benefits and the other unique benefits of antimicrobial agents alongside the negative externality associated with consumption. In the United Kingdom, for example, the government has committed to developing and testing a new antibiotic "subscription" purchasing model for 2 products based on revised assessment methods.[56,57] The model will consist primarily of annual lump-sum payments based on a product's value to the National Health Service rather than the number of doses sold, rewarding companies based on the full range of benefits provided by the product and recognizing that basing pharmaceutical companies' revenue for antimicrobial products on the number of doses sold does not provide appropriate incentives for stewardship. Nevertheless, although similar subscription models have been proposed in the United States[58,59] and some national HTA agencies show an awareness of the issues surrounding antimicrobial agents, there are fewer signs of practical actions and less consideration being given to how these issues might impact payment models,[40,60] although Norway has taken a first step in allowing the societal value of AMR to be included in HTA.[61] In the United Kingdom, the evaluation framework is under active development with NICE for the critical question of how a reasonable fixed price can be determined.[45,62] Such a price must be sufficient to incentivize innovation, but also, in keeping with value-based pricing philosophy, represent good value for the taxpayer who is the ultimate payer in a single-payer healthcare system.

Deficiencies of Current HTA Processes for Appraising New Antimicrobial Technologies

In our view, there are 3 main shortcomings in current HTA process: a methods-centric rather than problem-centric approach to dealing with new challenges, a lack of tools for thinking about the changing pattern of infection and resistance, and the absence of an approach to epidemiological risks. We expand on each in turn:

Methods-Centric Rather Than Problem-Centric Approach to Dealing With New Challenges

HTA has developed its methodological armory over recent decades, but a danger with proficiency in a fixed armory is that elements of the problem are ignored because they are not easily handled with that armory. We argue this is the case for AMR. Challenges designing randomized control trials for antimicrobial agents make determining the patient-level clinical effectiveness of a new antimicrobial for resistant infections difficult,[63-65] and gauging an antimicrobial's population-level effectiveness cannot easily be done with trial data. Indeed, even assessing the baseline risk of a resistant outbreak is far from trivial: this risk cannot be readily read off or extrapolated from available epidemiological data. Furthermore, trials designed for registration of a new product may not reflect the variety of ways clinicians will use the technology in practice, so HTA bodies may need to think more broadly about a product's use and consider additional data sources, such as pharmacokinetic/pharmacodynamic data and pragmatic trials, cluster randomized trials, observational data, and other studies that capture the real-world effects of treatment, where applicable.[44]

Lack of Tools for Thinking About the Changing Pattern of Infection

As noted earlier, HTA agencies' methods expertise tends to focus on NCDs. Nevertheless, most infectious disease models are population level, making them different from the models used for NCDs. For example, infectious disease models (1) generally have more parameters because they include contacts and transmission between individuals in addition to disease progression within the individual, (2) are difficult to validate because the unit of analysis is the population, and (3) have nonlinear model dynamics. Modeling the spread of resistant pathogens is particularly challenging because a critical determinant of the spread of resistance is the "fitness cost" associated with the resistance mechanism, and for many resistance mechanisms, this is not well understood. The expertise to interpret models of infectious diseases may lie not with HTA agencies but with other government agencies such as public health agencies and their advisory committees (such as the Joint Committee on Vaccination and Immunisation and the Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection in the United Kingdom). Hence, HTA agencies should build their capacity in this area but also partner with research and policy institutes and programs who can generate and interpret the fundamental scientific knowledge on which such modeling depends.

Table 2. The "STEDI" values of antimicrobial agents.

Values	Description
Spectrum	Reducing unintended impacts on the microbiome through moving from broad- to narrow-spectrum antimicrobial agents
Transmission	Reducing spread to other individuals through effective treatment
Enablement	Providing access to medical treatments and procedures through effective prophylaxis
Diversity	Reducing selection pressure on pathogens by increasing the range of treatment options available
Insurance	Preparing for future increases in the prevalence of resistant infections by developing new antimicrobial agents now

Note. Adapted from Rothery et al[45] and Outterson and Rex.[46]
STEDI indicates spectrum, transmission, enablement, diversity, and insurance.

Absence of an Approach to Epidemiological Risks

A persistent theme in health economics is the difficulty of assessing the quality of medical care. This expresses itself in HTA through a heightened awareness of the high cost of obtaining information about the effectiveness of a medical technology. Hence, as the field has matured, we have seen an emphasis on characterizing the uncertainty in the evidence base and making provisional decisions which get promising technologies into the hands of patients, while simultaneously generating additional evidence. Nevertheless, the risks in the area of antimicrobial agents are different in nature from the risk that, say, an antihypertensive may perform worse in the clinical setting than the trial setting: they are what could be called "epidemiological risks." The risks of poor clinical performance can, in principle, be reduced with larger, better designed, more representative trials and observational studies; epidemiological risks (eg, the risk of a new resistance mechanism evolving and spreading) cannot be reduced in this way, although relevant information may become available over time via surveillance systems collating data on resistant infections. As highlighted earlier, a key reason is that understanding and modeling the spread of resistance could be called "frontier science." Even if we could have perfect data about resistance patterns up to the present and perfect trial data about the performance of a new technology (and currently we are far from having either), we would not know how to extrapolate this information to predict future resistance trends if the technology were to be deployed. Nevertheless, despite this uncertainty, we need antimicrobial agents to provide protection against a potential future pandemic or rapid change in epidemiology, much as we need the protection that fire departments and the military provide, even if future demand for the new technologies proves to be lower than predicted.[41]

What Can Be Done?

The shortcomings of HTA agencies identified in the previous section relate to their capacity to make assessments of new technologies to combat AMR in particular. HTA agencies perform an important role in our health systems, and for most of the technologies they consider (ie, those that apply to NCDs with no important externalities), their methods are, in our view, fit for purpose. Furthermore, some of the challenges mentioned, such as the difficulty developing predictive models that describe the emergence and transmission of resistant pathogens, are not the exclusive problem of HTA. Nevertheless, we believe HTA agencies (including related bodies applying HTA methods to priority setting in the health sector) could do more to address the shortcomings identified earlier with respect to the assessment of technologies to combat AMR. As LMICs increasingly embrace HTA, expanding the HTA tool kit and broadening the HTA role to appropriately assess value for technologies addressing both NCDs and infectious diseases are increasingly important.

We make the following 3 recommendations.

Recognize a Greater Role for Epidemiological Modeling and Structured Expert Judgment

Recognizing that methods for extracting more information from clinical trials and other studies cannot address major residual uncertainties (eg, surrounding the emergence and spread of resistance), we suggest that there is a greater role for formal epidemiological modeling and institutionalizing how expert judgment is used and quality controlled. For example, some of us have used Cooke's Classical Model, which incorporates a method for weighting experts based on their performance on test questions,[66-68] to elicit expert projections and uncertainty bounds for resistance rates.[69] Of course, relying on expert judgment is a transitional solution. As science advances, epidemiological models will be developed that allow us to understand the spread of resistance with greater confidence than is currently possible. This requires trials and other studies to collect the endpoints needed in such models, such as resistance levels and antimicrobial use in the community. HTA agencies should both express this need to their sponsoring ministries and also engage with the scientific community to ensure that science, including the data that manufacturers are expected to submit in support of their technologies, evolves to align with the needs of decision makers.

Recognize the Needs of Diverse Stakeholders and Decision Makers

Challenges such as AMR also raise the question of who is the customer for HTA. For most technologies, the primary customer will be healthcare providers or purchasers: they will change their procedures or purchasing. Nevertheless, AMR poses a long-term threat that falls under the purview of different system actors who control additional funding levers: national leaders outside the Ministry of Health, international organizations, and charitable foundations. Addressing these stakeholders in a way that ensures that messages are given a sympathetic hearing requires changes in presentation and building new relationships, and, possibly, institutions. An example of the lateral thinking this sort of challenge requires is the blueprint developed by the Center for Global Development to support an advance market commitment for a new tuberculosis regimen.[70]

Recognize the Role and Value of Supporting Policies and Targets

Regarding epidemiological risks in the midrange future, we believe that government health agencies should play a role, because they can provide expectations of the national resistance profile. For example, the UK government has announced that it

aims to reduce specific drug-resistant infections in the population by 10% by 2025.[71] HTA agencies should recognize that when there are significant externalities, contributing to these targets is an important goal that should also be formally factored into prioritization. Simultaneously, HTA can contribute to an understanding of whether declared targets are indeed health and welfare maximizing; a feedback mechanism should exist so that targets can be adjusted as evidence and understanding advances. To incentivize appropriate research, HTA agencies should incorporate in their guidelines explicit recommendations to capture the community externalities of antimicrobial agents and other infectious disease interventions where data to inform such valuations exist.

Conclusion

HTA is based on the concept that there should be no "special pleading": that the rules should be applied without discrimination to all health technologies. This impartiality is core to HTA's conception of itself. Nevertheless, antimicrobial agents and AMR pose no challenge to the fundamental principles of HTA; the rules of HTA—developed primarily with technologies for NCDs in mind—do a poor job of addressing the particular scientific and policy challenges that arise in appraising technologies to combat infectious disease, similar to vaccines.[54,72] We believe that HTA being part of the solution in the struggle against AMR will require an expansion in the technical tool kit and a change in philosophy. Otherwise, HTA risks becoming part of the problem, destroying value and destroying incentives to bring life-saving new technologies to future populations.

Article and Author Information

Accepted for Publication: June 7, 2021

Published Online: September 20, 2021

doi: https://doi.org/10.1016/j.jval.2021.06.002

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Administrative, technical, or logistic support: Colson, Morton, Laxminarayan, Sarker *Supervision:* Colson, Morton, Laxminarayan, Sarker
Other: Outterson

Conflict of Interest Disclosures: Dr Morton reported receiving personal fees from AstraZeneca and the Office of Health economics; and reported nonfinancial support from the European Federation of Pharmaceutical Industries and Associations (consortium of pharmaceutical firms) outside the submitted work. Dr Årdal reported receiving grants from the European Union Innovative Medicines Initiative and the European Commission for European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections during the conduct of the study. Dr Chalkidou is an editor for *Value in Health* and had no role in the peer-review process of this article. Dr Outterson reported receiving grants from the US Department of Health and Human Services Biomedical Advanced Research and Development Authority, the UK Global Antimicrobial Resistance Innovation Fund, Germany, BMBF, the Gates Foundation, and the Wellcome Trust outside the submitted work. Dr Rex reported being Chief Medical Officer and Director, F2G, Ltd; reported being Editor-in-Chief of *Antimicrobial Resistance Solutions*; reported being Operating Partner and Consultant, Advent Life Sciences, and Adjunct Professor of Medicine, McGovern Medical School, Houston, TX; reported serving on the scientific advisory boards of Bugworks Research, Inc, Basilea Pharmaceutica, Forge Therapeutics, Inc, Novo Holdings, and Roche Pharma Research and Early Development; reported receiving consulting fees from Phico Therapeutics, ABAC Therapeutics, Polyphor, Ltd, Heptares Therapeutics, Ltd, Gangagen, Ltd, Meiji Seika Pharma, Basilea Pharmaceutica International Ltd, Allecra Therapeutics GmbH, Forge Therapeutics, Inc, SinSa Labs, AtoxBio, Peptilogics, F. Hoffmann-LaRoche, Ltd, Novo Holdings, Innocoll, Vedanta, Progenity, Nosopharm SA, Roivant Sciences, Shionogi Inc, GlaxoSmithKline, and Pfizer Pharmaceuticals outside the submitted work; reported stock ownership in AstraZeneca Pharmaceuticals, F2G, Ltd, Advent Life Sciences, Zikani Therapeutis, and Bugworks Research, Inc outside the submitted work. Dr Sculpher reported receiving grants from the National Institute of Health Research Policy Research Program during the conduct of the study; and reported receiving personal fees from various life science companies outside the submitted work. No other disclosures were reported.

Funding/Support: The authors received no financial support for this work.

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