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Hot Topic

Valuing antibiotics: The role of the hospital clinician

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ABSTRACT

The global public health threat of antibiotic-resistant infections as well as the lack of new treatments in clinical development is a critical issue. Reasons for this include diminished commercial incentives for pharmaceutical companies to develop new antibiotics, which part-reflects a shift in antibiotic marketing paradigm from broad deployment to targeted therapy in relatively small patient populations. Such changes are encouraged by antimicrobial stewardship (AMS). Other factors include a lack of recognition in the traditional assessment of new antibiotics by regulators, health technology assessors and payers of the broad range of benefits of new agents, particularly their value to health care, economies and society. Recognising the seriousness of the situation, there have been recent changes and proposals by regulators for modification of the assessment process to accommodate a broader range of acceptable data supporting new drug applications. There is also increasing recognition by some payers of the societal benefit of new antibiotics and the need for financial incentives for those developing high-priority antibiotics. However, progress is slow, with recent publications focusing on industry and strategic perspectives rather than clinical implications. In this opinion piece, we therefore focus on clinicians and the practical steps they can take to drive and contribute to increasing awareness and understanding of the value of antibiotics. This includes identifying and gathering appropriate alternative data sources, educating on AMS and prescribing habits, and contributing to international antibiotic susceptibility surveillance models.

1. Introduction

Antibiotic-resistant infections and the lack of new treatments are widely accepted to be critical issues [1], with antibiotic resistance a global public health threat [2] driving concerns of a post-antibiotic era [3]. Moreover, the appropriate treatment of serious life-threatening infections, such as those requiring intensive care unit admission, is also hampered by an emerging lack of effective treatments owing to antibiotic resistance [4,5]. Most recently in the UK, the Government Health and Social Care Committee published a report in October 2018 that called for the subject of antimicrobial resistance to be included in the top five policy areas nationally [6]. The report called for political and industry leadership to take urgent action. Notwithstanding these important political statements, the real impact of the continued decline in the number of new antibiotics in development is, essentially, a clinical matter occurring at the individual patient interface where our present approaches are compounding the severity of this challenge [7]. The result is a future lack of essential new antibiotics to combat the rising tide of resistance and the formation of a new antibiotic paradigm (Table 1).

In January 2018, a report was published that reviewed and made recommendations on ways to incentivise new antimicrobial drug development [8]. Notably, there was a lack of unanimous agreement on these recommendations among the report's authors, with areas of contention even within the core concepts being raised. This demonstrates dramatically the current uncertainties and outstanding debates in finding the best way forward to deal with what is a universally agreed critical patient matter.

More recently, in January 2019, two authoritative groups called for re-energised action to deal with the challenges being faced.

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Table 1
Factors constituting the new antibiotic paradigm.

- A shift in the antibiotic marketing paradigm from broad deployment to targeted therapy in relatively small patient populations with specific infection needs and/or resistance challenges.
- A lack of new antibiotics in clinical development leading to a diminishing choice of antibiotic therapies.
- An increase in the incidence of bacterial infections caused by multidrug- and pandrug-resistant pathogens.
- Incorporation of a 'societal' value of antibiotics, e.g. a greater value assigned to antibiotics associated with a delayed propensity for resistance development and transmission.
- New indications for existing, marketed antibiotics.

First, a UK 5-year action plan was published, which emphasised the need for the avid application of the principles of antimicrobial stewardship (AMS) [9]. It also included a substantial section calling for broader efforts to invest in innovation, supply and access in order to further support antimicrobial stewardship programmes (ASPs) into the future. Second, a public discussion document was released on the draft recommendations of the Ad hoc Interagency Coordination Group (IACG) on Antimicrobial Resistance, which identified five action areas [10]. Key amongst these is the need to innovate and invest to secure the future of antimicrobials whilst collaborating internationally and across disciplines to maximise the effectiveness of the interventions being delivered.

In 2017, the Office of Health Economics (OHE) and the Academy of Infection Management (AIM) held a cross-disciplinary forum on the value of antibiotics, attended by invited representative clinicians, regulators, payers/health technology assessment (HTA) bodies, government and the pharmaceutical industry from European Union (EU) countries. An earlier publication [11] arising from this meeting concentrated on the economic aspects of the issue, and other recent papers have focused on industry and strategic perspectives [12,13]. The following commentary focuses alternatively and importantly on the practical aspects that are particularly pertinent to clinicians who are leaders and/or are interested in this field. We believe that this contribution, which is written as an opinion piece by the clinicians who attended the OHE/AIM forum, will help to address the current challenge of the diminishing pool of new antibiotics. The main recommendations are summarised in Table 2.

2. Antibiotics are 'special' medicines

In 2016, a Review on Antimicrobial Resistance report commissioned by the UK Government and the Wellcome Trust advised that antibiotics are a 'special category' of drugs, underpinning general medicine and enabling medical and surgical procedures to be performed [14]. Used routinely both as prophylaxis and treatment across multiple specialties, antibiotics are unique medicines. Furthermore, in contrast to other medicines, appropriate use of an antibiotic encompasses more than just its safety and effectiveness in clinical trials [15]: the collateral damage impact of antibiotic resistance bolsters the case for the uniqueness of these agents. Unlike non-curative medicines for managing chronic, non-infectious conditions (e.g. antihypertensive medication), a systemically-administered antibiotic treatment course typically lasts around 7 days, making them less desirable as an investment for pharmaceutical companies [16]. In essence, antibiotics (and antimicrobials in the broadest sense) are not the same as other medicines.

The OHE estimates that the average net present value of an antibiotic project (the sum of all development costs and the present value of expected future revenues) from an antibiotic is –US$50 million (i.e. development costs exceed revenues), compared with +US$1.15 billion for musculoskeletal drugs and +US$720 million for neurological drugs [17].

The previously accepted industry model for marketing antibiotics was, essentially, based on maximising sales, and the medical profession (passively) allowed their introduction into practice on this basis. However, an evolving awareness of the impact of this approach, which encouraged overuse of new antibiotics and the rise of resistance [18], led (alongside other promoters such as cost-effectiveness programmes) to the development of AMS strategies. Additionally, concerns over the increased risk of *Clostridioides difficile* infection through overuse of especially broad-spectrum antibiotics (including fluoroquinolones and cephalosporins) led to marked changes in their use [19]. The current emphasis is on using all antibiotics appropriately and to only deploy new agents if/when there is a specific clinical need, thereby aspiring to safeguard their future utility. An indirect effect of AMS has therefore been to reduce potential revenues from many new antibiotics.

Thus, the antibiotic marketing paradigm has shifted from maximising sales and achieving broad deployment of a new medicine to a targeted approach with use expected in a relatively small patient population with specific infection needs and/or resistance challenges. This targeted approach also relies on rapidly identifying patients infected (or colonised) with multidrug-resistant (MDR) pathogens. However, society, the pharmaceutical industry, infectious diseases (ID) clinicians and clinical researchers are yet to find a solution that makes such developments commercially viable, although various approaches have been suggested [18]. Failure to tackle the crisis of antibiotic-resistant infections, including the shortage of new treatments, is projected to cost US$100 trillion and result in approximately 10 million MDR-related deaths by 2050 [14].

3. Factors influencing the assessment of antibiotics

3.1. Regulatory issues

Recognising the importance of antibiotics and the scarcity of new agents in the development pipeline, regulatory bodies have taken steps towards modifying the approval process for new antibiotics, particularly in areas where there is a need for alternative medicines (Table 3).

Despite these encouraging changes, progress is slow and it remains to be seen whether a global objective of developing 15 new antibiotics in 10 years to combat antibiotic resistance [14] will be achieved, and whether the key priority pathogens will be addressed [25].

3.2. Payer issues

Historically, payer organisations as opposed to healthcare providers of antibiotics have discouraged the development of new analogue ('me too') antibiotics [18], and they have been reluctant to consider new agents with proven non-inferiority to current standard antibiotics as having greater value than generic antibiotics, thus reducing the price of new agents below what is deemed their true societal (and therefore true economic) value [17]. Social or public health-related value has been highlighted as a key element missing from payer evaluations of new antibiotics, although this omission is now being addressed in some countries [11].

Table 2
Recommendations on how clinicians can assist in, and contribute to, improving the assessment of antibiotics and in enhancing recognition of the broader benefits of antibiotics.

Recommendation
Generation of new intelligent data to support decision-making
• Influence the modification of (registration) clinical trial designs to enable demonstration of the broad range of benefits of an antibiotic in a quantifiable format: ○ Conduct clinical trials that would generate data sets of sufficient size and quality for HTA evaluation of novel agents against antibiotic-resistant pathogens in relevant patient populations; ○ Incorporate multiple or composite endpoints into clinical trials that measure non-clinical outcomes appropriate to the antibiotic's prospective indication, such as patient-reported outcomes, time to clinical response, length of stay, in vitro susceptibility data, novel biomarker data and other societal factors; ○ Generate supplemental data from post-marketing surveillance studies and registries to complement microbiological, economic and clinical evaluations of novel agents; ○ For difficult-to-treat infections, create clinical trial networks split by serious infection type to generate and collate reliable, high-quality and comparative data for standard phase II and III non-inferiority trials; ○ Create master protocols for umbrella, basket and platform trials suitable for use in clinical trial networks and for generating comparative data for multiple treatments in several infection and patient types. These trials could also help identify new indications for older agents ○ Create appropriate mathematical models capable of estimating future antibiotic resistance patterns associated with a novel antibiotic to evaluate the propensity for resistance development and ease of transmission.
Reconsider available data
• Where there is a paucity of clinical trial data for specific (including antibiotic-resistant) infections, consider preclinical, observational/non-observational PK/PD, observational/non-observational antibiotic surveillance, other observational data and real-world data from clinical practice. • Extrapolate published economic and other evaluations to the geographical region of interest.
Influence HTA processes
• Ensure that the value aspects of antibiotics other than the traditional efficacy and safety properties are appreciated and understood by assessors by informing MCDA and other models that are recognised by HTA bodies: ○ Where necessary, advocate for greater flexibility within the HTA of antibiotics to enable appreciation of the broad range of relevant benefits of a new agent.
Education and collaboration
• Create and conduct educational programmes to teach clinicians of all levels and, where appropriate, pharmacists and nurses in multidisciplinary teams on the appropriate use of antibiotics, AMS and antibiotic surveillance. Programmes should raise awareness of the issues in the HTA of antibiotics and the scope for ascribing a broader of range of values to agents. • Develop local AMS programmes. • Improve on existing local, national and international collaborative efforts and create new ones where necessary for sharing experiences of AMS.

HTA, health technology assessment; PK/PD, pharmacokinetic/pharmacodynamic; MCDA, multiple-criteria decision analysis; AMS, antimicrobial stewardship.

Table 3
Overview of steps being taken by regulatory bodies towards modifying the approval process for new antibiotics.

Regulatory body	Key changes made or proposed
European Medicines Agency (EMA)	• Modification of guidelines on antibiotic clinical trials, particularly for agents targeting infections lacking treatment options, such as those caused by MDR pathogens [20]. Changes include [18,20]: ○ Alterations to patient eligibility criteria (e.g. patients can be enrolled even if they have received a dose of a previous antibiotic treatment), types of clinical trials undertaken (e.g. organism-specific rather than disease-specific trials), clinical trial endpoints (e.g. time to resolution of infection-specific features) and non-inferiority margins (e.g. for certain infections, these margins could differentiate between the treatment effect of a test agent and no antibacterial treatment while also being able to reflect clinically acceptable differences between test agent and appropriate active comparator); ○ Option both of gathering additional supporting data after regulatory approval and on using PK/PD aspects of the antibiotic.
US Food and Drug Administration (FDA)	• For unique antibiotic molecules, permit priority review, fast-track designation and an additional 5 years of market exclusivity [21,22]. • Proposal (in 21st Century Cures Act) to permit trials in smaller patient populations than usual for drugs targeting serious or life-threatening infections, provided that the labels of such approved antibiotics stipulate their use in specific patient populations only [21,23,24].

MDR, multidrug-resistant, PK/PD, pharmacokinetic/pharmacodynamic.

Payers need to consider evidence beyond the preclinical and clinical data traditionally accepted as verification of an antibiotic's value. These additional value elements are described in the OHE/AIM forum publication [11].

Inappropriate budgetary approaches frequently restrict the true appreciation of the cost of using an antibiotic, whether at payer or departmental budget level [11]. Because of the ease with which antimicrobials are accessed, there can frequently be an overemphasis on drug acquisition costs rather than their true societal impact. Such simple acquisition cost approaches can result in the use of drugs to which pathogens already show clinically important levels of resistance, so further driving such trends. These approaches ignore consideration of related costs, such as administration expenditure, compliance issues, adverse reactions, lengths of hospital stay, etc., all of which can have a marked impact on the overall cost of using an antimicrobial. A new level of maturity and sophistication amongst payers in terms of appreciating the overall cost of an antimicrobial is necessary in order to truly assess the value of a novel drug under consideration. There is clear evidence that such appropriate holistic assessments are now being understood and adopted at higher payer levels [8–10,12,13], although there is less proof of their adoption amongst front-facing clinical services.

3.3. Industry issues

Pressures dictating a pharmaceutical company's involvement in antibiotic research and development include a lack of return on investment [5], the HTA requirement for data from superiority rather than non-inferiority trials [18], the absence of appropriate, especially financial, incentives to develop restricted-use antibiotics [18], and the perceived undervaluation of new antibiotics [18]. The present approaches to preclinical and clinical development programmes have led to a need for greater post-marketing surveillance and a presumed increase in post-marketing costs. Furthermore, some regulatory restrictions, including the standards for demonstrating non-inferiority, and disparities between countries in terms of regulatory and clinical trial requirements appear to cause difficulties for pharmaceutical companies [17]. Joint initiatives between industry and public bodies have been instigated to find solutions [23,26]. To date, there have been no breakthroughs, although proposals have been suggested for financial and market-related rewards, including cash awards for drugs achieving regulatory approval to address public-health high-priority infections, such as those caused by carbapenem-resistant Enterobacteriaceae, or a defined extension to the duration of market exclusivity for an existing antibiotic with activity against a high-priority infection [12,13].

3.4. Clinician and patient issues

Whilst the above describes the responses of other stakeholders on this issue, hospital clinicians as a whole, but in particular those with specialist insights such as ID clinicians, clinical microbiologists, antimicrobial pharmacists and some infection specialist nurses, as the champions for the patient and prescribers of the drugs have not, to date, been at the forefront of directing the required changes. However, they are key in implementing and driving AMS strategies and educating about appropriate antibiotic use [27], a particularly important role in increasingly overburdened and under-resourced national healthcare systems.

One of the fundamental difficulties that undermines the clinically correct utilisation of antibiotics is the ability of prescribers to be confident that they are administering an antibiotic in a case of infection and not inflammation. Whilst the clinical appropriateness of the definition of sepsis has improved significantly with the establishment of the 'Sepsis-3' criteria [28], a recent study has demonstrated that even with these modern approaches there remains considerable uncertainty surrounding the differential diagnosis of sepsis versus systemic inflammatory response syndrome [29]. This is especially so in the critical phase before organ damage has become obvious. More effort is needed to progress this persisting conundrum that is so perplexing for clinicians. A promising but as yet unproven approach to this has been to explore a pathobiology-driven understanding of the host response to sepsis. It is hoped that by better understanding the heterogeneity of distinct host response subgroups, so the diagnosis and outcome prediction of sepsis might be greatly improved [30]. There remains a pressing and unresolved need to provide physicians with ways to make an accurate clinical diagnosis of sepsis in a timely manner.

Although there are enormous variations in global prescribing practices, in general, initial (often clinical rather than laboratory) diagnostic accuracy dictates antibiotic treatment decisions [18]. A central role of hospital-based ASPs—now a worldwide approach—is to monitor antibiotic use, directed and driven by guidelines, and is largely limited to the hospital formulary list. ASPs have been proven to reduce unnecessary use of antibiotics in hospitals without having a detrimental impact on safety [31]. Inclusion on the hospital formulary is based not only on clinical factors and local susceptibility data but also on acquisition cost. Potential usage (by frequency of indication) rather than purchase cost is a more accurate basis for antibiotic expenditure measurements [27,32]. In clinical practice, the choice, dose and duration of antibiotic will also be determined by patient characteristics, potential adverse events, drug–drug interactions and, once treatment has begun, clinical response and serum biomarkers etc. [33–35]. However, hospital clinicians may not always adhere to antibiotic prescribing policies and, in practice, their prescribing decisions and those of their colleagues may be highly subjective, following the local prescribing 'customs', or be based on habit or personal experience [36]. Increasingly, ASPs are recognising the importance of behavioural science studies on prescribing habits and the value of behaviour change on the delivery and impact of ASPs [31]. An additional challenge in the era of 'protected' antibiotics is delivering patient-centred care, including preserving an individual's right to receive the most appropriate antibiotic for their individual need. This potentially conflicts with the demands dictated by other factors in the decision-making process, such as cost, avoidance of unnecessary antibiotic prescribing, current antibiotic resistance and the threat to future patients from antibiotic-resistant pathogens [15,37,38]. Nevertheless, given that multiple antibiotic options exist in most prescribing scenarios, there is rarely a single best option, which adds complexity to the prescribing decision-making process and drives (both reasonable and less than reasonable) variation.

4. Improving the assessment of antibiotics

The starting position must be collection of the best possible data, where large, randomised controlled studies offer proven benefits. However, the patient populations examined in large, randomised controlled studies could be different to the patient population in whom the antibiotic may have the greatest clinical utility in the real world. In the new antibiotic paradigm of a lack of new antibiotics in clinical development, this may not always be possible. Despite the recent changes instigated by regulatory bodies, a key limitation in the HTA of new antibiotics lies in how their economic and clinical values are quantified.

In particular, there are constraints on how registration clinical trials are designed and conducted, which do not currently allow the demonstration of all benefits. For instance, the concept of developing pathogen-specific antibiotics, e.g. against antibiotic-resistant bacteria, is an attractive one and was suggested for aerosolised antibiotics in a recent European Society of Clinical Microbiology and Infectious Diseases (ESCMID) position paper [39]. However, as with broad-spectrum antibiotics, current clinical trial protocols may not yield sufficient numbers of resistant strains to generate adequate data to demonstrate clinical and economic benefits against current statistical analysis standards. Essentially, clinical trial designs should evolve to capture a data set of sufficient size, quality and fitness for a defined purpose on antibiotic-resistant pathogens in a relevant patient population, but these data must then form part of the value appraisal at the HTA level. Additionally, against these initial data constraints there is the need, through post-marketing surveillance studies and registries, to generate supplemental information, ensuring the link between microbiological data, economic value and clinical outcomes [11]. There is a need to reconsider the important contributions that preclinical, pharmacokinetic/pharmacodynamic (PK/PD) and real-world data can add to the pool of decision-making data for new antibiotics and value assessments. A key consideration when assessing studies is the transferability of data between regions and healthcare systems. A recent Spanish study determined that the costs of drug-related complications and bed-days were key drivers of overall treatment costs for methicillin-resistant *Staphylococcus aureus* (MRSA)-associated nosocomial pneumonia and were likely very different to the equivalent costs in the US healthcare system

[40]. It is evident that the cost implications of the various components of health economic evaluations differ substantially, particularly in lower- and middle-income countries [32].

The choice of endpoints is crucial to the analysis and appraisal of clinical trial data. There is a clear need to consider multiple or composite endpoints that are appropriate to the severity of the infection, and not just traditional data on infection resolution and/or microbiological eradication [41]. Time to clinical response is also important. Future endpoints should encompass appropriate non-clinical factors such as patient-reported outcomes, length of stay, in vitro antibiotic susceptibility data, novel biomarker data and other societal factors [11]. For antibiotic-resistant infections, the ability to model future resistance patterns may be important. Antibiotics associated with a tendency for delayed resistance development and transmission might arguably be more 'valuable' to society than others where resistance develops rapidly, and as such they could demand a higher market value.

In the envisioned future era of streamlined registration trials and comparatively smaller evidence bases to support new antibiotic deployments, there needs to be an agreement between the pharmaceutical industry, prescribing clinicians, clinical researchers, payers and regulatory bodies that the data collected are relevant and represent a measurable benefit that provides a level of certainty of an antibiotic's value. Furthermore, there should be agreement that these data will have the same influence on payers and regulators in different countries. Currently, there are recognised differences and uncertainties between the processes that the European Medicines Agency (EMA), the US Food and Drug Administration (FDA) and regulators in other countries have for antibiotic assessments [23,42]. Ensuring that an antibiotic meets the requirements for all such regulatory agencies is costly [23]. Agreeing, simplifying and rationalising such matters on an international basis, whilst remaining sensitive to local and national perspectives, would be a major step forward, particularly in establishing an explicit realm for industry to develop these much-needed new drugs. A more fit-for-purpose and targeted structure needs to be introduced into HTA decision-making on the value of antibiotics; a multiple-criteria decision analysis (MCDA) model could be a means of achieving this [11]. Such a model assigns a score to selected value elements of an antibiotic, with an aggregate score providing an overall calculation of value.

5. The role of the clinician

Against the above setting there is a strong argument that clinicians with a specialist interest in this field and their associated clinical researchers should influence this agenda for the benefit of future patients (Table 2). The previous gold-standard, 'traditional' data were derived from rigorously-designed superiority clinical trials, but such trials have become increasingly difficult to conduct and can pose ethical dilemmas [43] and so today, non-inferiority trials of antibiotics are acceptable for demonstrating clinical efficacy [44]. The challenge is therefore to identify how these issues can be overcome whilst maintaining the demand for high-quality data.

In the context of difficult-to-treat infections, clinical trial networks split by serious infection type (for which morbidity and mortality are predictable for usual drug resistance situations and high-quality study designs are available), have been proposed as a means of collating reliable, quality data [11,43]. Such networks would generate the comparative data for standard phase II and III non-inferiority trials, although additional phase I trials and those involving MDR pathogen infections would need to be conducted separately [43]. There have also been calls to create master protocols for umbrella, basket and platform trials, each constituting a collection of trials or substudies and capable of generating comparative data for multiple treatments in several infection and patient types [45]. Such a master protocol is being evaluated to investigate treatments for several MDR infections in a platform trial that would employ pre-existing trial networks [46]. These studies could also help identify new indications for older agents. Clinicians and their clinical researchers, through their recognised national and international, formal and informal networks and within multidisciplinary teams, are ideally placed to facilitate such trial networks and clinical research endeavours.

Whilst behaviours determining antimicrobial prescribing practices are influenced by psychosocial factors (e.g. attitudes, social norms and beliefs) [36], clinicians also need to consider different data from diverse studies. In this context, there is a need for educational programmes to teach all clinicians the prudent use of new agents against the backdrop of the dearth of treatment options. Such educational programmes will need to appreciate that clinicians prescribing antibiotics are, most likely, used to considering AMS and other interventions that aim to reduce resistance, but are likely not sighted upon the challenges of the new antibiotic paradigm (Table 1). For antibiotic-resistant infections, data from observational studies are helpful, particularly for pathogen-specific infections, as are PK/PD and antibiotic surveillance data for defining optimal doses and duration of treatment [11].

As well as leading educational programmes to raise awareness about assessing and valuing new-generation antibiotics, clinicians, in order to help break unwanted prescribing patterns, must teach on ASPs [18] and antibiotic resistance surveillance [3]. In addition to education, other techniques with which clinicians can assist to instigate a change in prescribing habits during the implementation of an ASP include the creation of rules to restrict unwanted prescribing behaviours, the production of reminders (e.g. on posters, laboratory test reports) to prompt appropriate prescribing, the design of new working practices (e.g. rapid reporting of test results) and to encourage the use of automated computerised systems and point-of-care digital apps that offer decision-making support in relation to antibiotic prescribing [31]. For multidisciplinary teams that regularly encounter infections, education is warranted for all team members who are influential in antibiotic use, such as pharmacists and nurses [36].

In an effort to tackle the global increase in antibiotic resistance, there have been calls to improve collaboration between different countries: AMS offers a modern, established, international platform to share such future progress, experiences and resources [3]. On a local level, an institution's ASP, whilst aligning to the evolving new antibiotic environment and practice guidelines, needs to allow for individual decision-making for specific patients [47]. ID clinicians therefore need to have a proactive role in the development of local ASPs with an intention to build relationships with those running other programmes in the same country and internationally.

ASPs have a proven track record but should not be viewed as a single, global panacea for delivering reduced antimicrobial resistance development through improved antibiotic usage. This is because they must be implemented in a manner that is sensitive to the local healthcare economy, where deep differences exist worldwide. In these various nations, unpredictable and inconsistent function gaps can exist between the front-line antibiotic prescribers, where the knowledge base can be at its lowest, and more senior clinical decision-makers with specific expertise. The critical success feature in such circumstances will be the delivery of local AMS oversight that is tailored to local needs and systems. This will be of particular importance and a challenge in the outpatient setting, which is where most antibiotic prescribing takes place and the chasms described above are likely to be at their greatest.

Rapid point-of-care diagnostics are anticipated to have a profound impact on antibiotic demands, although empirical treatment is still expected to remain widespread [48]. These diagnostics will

assist clinicians to prescribe more targeted therapies, thereby reducing the demand for broad-spectrum and/or new antibiotics. Whilst providing much promise, currently available rapid diagnostics are narrow in utility and slow to be adopted in routine clinical practice [49]. Moreover, there is the potential for rapid point-of-care diagnostics to reduce clinical trial running costs by better targeting the use of trial drugs on the specifically intended organism population, and this thinking must be included in future antibiotic evaluations [48].

The best recent evidence on rapid testing promotes a combination approach with AMS interventions [50,51]. However, overall, the recent developments in terms of mainly PCR-based microbiological rapid diagnosis are showing limited benefit. Leaving aside monetary, technical and logistical issues, the clinical uncertainties that arise from this methodology serve to pose new decision-making problems for clinicians. Whilst there is no doubt that PCR tests produce much more rapid results than conventional cultures, they also, because of their enormously enhanced sensitivity, significantly increase the number of pathogens identified, leaving the clinician with the challenge of establishing their relevance. This is often not possible and, in these circumstances, the clinical significance of the PCR results remains open, which can then drive further antibiotic overuse in a desire to cover all possible identified pathogens in a seriously ill patient, for example. This is of course exactly the opposite effect that the use of rapid testing is intended to achieve [52].

Clinicians and clinical researchers also have a role to play in informing models, such as MCDA, that are recognised by HTA bodies, by providing expert input on the clinical and other value aspects of antibiotics, ensuring that these are widely understood. This will broaden the measures used to assess antibiotics and so support transparent and consistent decisions [53]. Furthermore, and against a current dearth of such data, clinicians can both drive and contribute to internationally standardised antibiotic susceptibility surveillance models, particularly those that map local data, so maximising appropriate future performance [11]. Although arguably relevant, the value aspect of successfully treating one patient to reduce the overall incidence of the same infection in the wider population is not included in current antibiotic HTAs [11]. Clinicians' roles should extend to support policies that allow greater flexibility in the antibiotic HTA process so that access to new antibiotics is considered a priority. There is a need to construct appropriate epidemiological data, jointly identified and collected by clinicians and epidemiologists, to feed such models.

6. Conclusions

There is a recognised deficiency in current clinical trial designs to provide sufficient evidence on which to calculate the value of an antibiotic. Rather, comprehensive clinical and supporting data packages on new antibiotics need to be used by HTAs, according to an agreed list of key value drivers, so that they can determine the broader value of new-generation antimicrobial agents. Importantly, a considerable remaining challenge lies in the traditional industry model of revenue from unit-based sales. Appropriate assessment of antibiotics from clinical, economic and societal perspectives is essential not just for the successful introduction of new drugs, but also to provide a robust and common platform that forms a commercially attractive prospect for developers. The present situation poses a dilemma in the setting of the rising rate of antibiotic-resistant infections and the lack of novel antibiotics in development to deal with them: the full dimensions of this are presently neither fully understood nor addressed. Meeting the challenge of a declining portfolio of effective antibiotics requires the identification of new indications for older agents and the introduction of AMS in every hospital worldwide. As prescribers of antibiotics and subject experts, clinicians must play a central role in addressing this situation. Identifying and increasing awareness and understanding of the broad range of benefits and values—not just the acquisition cost—associated with antibiotics, as well as how to measure these, are crucial in this regard. Clinicians need to become fully involved leaders in this agenda.

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