



## Discussion

## Antibiotic resistance: An ethical challenge

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## ABSTRACT

In this paper, we argue that antibiotic resistance (ABR) raises a number of ethical problems that have not yet been sufficiently addressed. We outline four areas in which ethical issues that arise in relation to ABR are particularly pressing. First, the emergence of multidrug-resistant and extensively drug-resistant infections exacerbates traditional ethical challenges of infectious disease control, such as the restriction of individual liberty for the protection of the public's health. Second, ABR raises issues of global distributive justice, both with regard to the overuse and lack of access to antibiotics. Third, the use of antibiotics in veterinary medicine raises serious concerns for animal welfare and sustainable farming practices. Finally, the diminishing effectiveness of antibiotics leads to questions about intergenerational justice and our responsibility for the wellbeing of future generations. We suggest that current policy discussions should take ethical conflicts into account and engage openly with the challenges that we outline in this paper.

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## 1. Introduction

Antibiotic resistance (ABR) is now widely recognised as a grave threat to global health in the 21st century [1]. Increasing levels of ABR in many countries have sparked fears of a future 'post-antibiotic age' in which bacterial infections are no longer treatable [2,3]. At the same time, unequal access to healthcare resources has meant that many low-income settings never fully entered this antibiotic age to begin with.

The consequences of ABR are difficult to forecast, but a recent report for the UK government estimates the cost of drug resistance to be as high as US\$100 trillion worldwide by 2050, with a death toll of up to 10 million per year [4]. Whilst these figures also include the predicted consequences of resistance to other antimicrobial agents, they give an indication of the magnitude of the challenge that the world is currently facing.

Many of the consequences of increasingly drug-resistant bacterial infections are already affecting patients around the world; infections are becoming increasingly difficult to treat, have higher rates of complications and take much longer to cure [1]. Of special concern is the rapid global spread of bacteria with multiple resistances to antibiotics. The European Centre for Disease Prevention

and Control (ECDC) estimates that, today, ABR is already responsible for ca. 25 000 deaths and €1.5 billion in health expenditures per year in Europe alone [5]. Given the limitations of available data, the true cost of ABR is likely much higher.

The challenge of ABR is increasingly recognised by policy-makers. The World Health Assembly recently adopted a new global action plan, and a number of national and international projects are underway to incentivise the development of new antibiotics [6,7].

In addition, there is an increasingly vocal initiative for the development of a global treaty to combat ABR [8].

These on-going policy efforts seek, on the one hand, to revive and encourage the development of new antibiotics. On the other hand, they also include measures to improve surveillance and diagnostic tools for bacterial infections, to promote antibiotic stewardship and, crucially, to minimise the global uncontrolled sales of antibiotics. In countries with developed health and regulatory systems, a restrictive antibiotic prescribing policy is needed that limits the use of antibiotics for human and animal use to instances where their use is clearly indicated and offers a measurable therapeutic benefit. Similar policies need also to be implemented in low- and middle-income countries to the extent possible without reducing access to essential antibiotics [9].

As commendable as many of the current policy efforts to curb drug resistance are, they have so far failed to address sufficiently the ethical challenges that arise as a consequence of ABR. In this paper, we will describe these ethical challenges and outline their relevance for patients, physicians and policy-makers.

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## 2. The ethical dimensions of antibiotic resistance

Given the complexity and dimension of ABR, as well as the many ways in which it affects people, there are numerous ethical problems that arise in its wake. At the most fundamental level, these can be distinguished into four different sets of problems.

### (i) Ethical challenges in infectious disease control

These well-known challenges are exacerbated by ABR. For example, whether social distancing measures or mandatory reporting of patients with contagious bacterial infections is ethically acceptable has remained controversial (as illustrated by the problems surrounding the treatment of multidrug-resistant tuberculosis) [10]. With an increasing number of drug-resistant infections that are more difficult to treat or that no longer respond to treatment, such measures could be considered more frequently. Their inherent ethical conflict between patient autonomy and control, and the protection of others, will thus have to be addressed. Moreover, owing to increased healthcare costs and longer hospital stays, ABR will also further increase existing resource limitations in hospitals, leading to conflicts in the allocation of already scarce medical resources.

### (ii) Ethical challenges for the fair distribution of global resources

Since the burden of ABR disproportionately affects low- and middle-income countries, it has the potential to widen existing discrepancies in health outcomes between regions. Weak healthcare systems are less likely to be able to address the challenge of ABR by themselves, and whilst it is important to curb the use of antibiotics, it should also be noted that more people die from lack of access to high-quality antibiotics in low-income countries than die from ABR in high-income countries [11]. Since many healthcare systems are insufficiently equipped to deal with ABR themselves, an ethical policy response to ABR will have to be explicit about the degree of international assistance and capacity-building that resource-poor healthcare systems are entitled to.

### (iii) The ethical use of veterinary antibiotics

Whilst it is acknowledged that large savings in the use of antibiotics can be achieved in the veterinary sector, where more than one-half of the world's total production of antibiotics are used, the related ethical issue of animal welfare is rarely addressed. If entire classes of antibiotics are exclusively reserved for human use, certain treatable infections would no longer be curable in the veterinary sector. At the same time, a more restrictive use of antibiotics also necessitates a frank discussion of animal welfare standards in food production, especially where current modes of production are only attainable due to the widespread prophylactic use of antibiotics to compensate for overcrowded farming conditions [12].

### (iv) Ethical challenges of intragenerational and intergenerational justice

With decreasing antibiotic effectiveness, an ethical conflict emerges for the fair distribution both within and across generations. How should we allocate this increasingly scarce public good? Is it fair if we leave future generations without effective antibiotics? These are ethical challenges that exist because of the unique properties of antibiotics, as we will explain below. We believe that they are commonly overlooked in policy-making and clinical practice, but deserve more attention because they affect both patients and prescribers.

To date, what little discussion there has been about ethical implications of ABR has been focused on the first three challenges. The first falls into the traditional realm of public health ethics. At its heart lie concerns about the patient's autonomy and its trade-off against public interests, either due to limitations of individual liberty or as a lack of informed consent [10]. It is vital that the proper balance between patient and public interests is achieved at the international, national and regional levels. However, this issue as such is not unique to the case of ABR, but only exacerbated by it. An established literature exists on the trade-off between patient rights and public health that can and should be used to establish such balance in practice [13].

The same is true for categories (ii) and (iii), both of which constitute complex ethical and political challenges in themselves that also exist in the absence of ABR and are the subject of expansive and ongoing discussion.

Category (iv), on the other hand, is distinct from the other three categories because it constitutes a set of ethical challenges that are not merely exacerbated by ABR, but exist as a direct result of the properties of antibiotics. We will therefore focus on these properties and the ensuing challenges for the remainder of the paper.

## 3. Antibiotics: a class of drugs with inbuilt expiry?

Even careful use of antibiotics leads to the emergence of ABR, and thus eventually to the diminishing effectiveness of antibiotics [11]. Whilst this is broadly accepted among experts, it also implies that the use of antibiotics is inherently unsustainable. To be sure, the effectiveness of available drugs can be exhausted at varying rates and can temporarily be countered by the development of new drug classes. However, despite ongoing policy efforts to encourage their future development, the pipeline for new antibiotics, especially against Gram-negative pathogens, remains dangerously empty [2].

As a result, it appears more appropriate to currently consider antibiotics as a non-renewable resource that is currently being depleted at a worrying rate. This is made worse by the fact that we do not have any substitutes that could replace antibiotics more widely. Consequently, antibiotic prescribing should aim to preserve the effectiveness of antibiotics as far as possible, for example by implementing antibiotic stewardship programmes and rational prescribing guidelines. At the same time, rational prescribing must also involve the creation of access to antibiotics in regions where this is not yet the case. Given that effective antibiotics are already becoming scarce for some bacterial pathogens and that this is likely to worsen over the coming decades, the current trend towards rational prescribing of antibiotics must be welcomed. However, it also presents prescribers with an ethical dilemma because, as we shall outline next, the patient's individual interests and the preservation of antibiotic effectiveness are goals that may at times conflict.

## 4. Antibiotic resistance as a collective action problem

ABR has previously been described as a collective action problem. The individual's personal interests in using antibiotics may be misaligned with public interests, that is it can be rational for a self-interested individual to use antibiotics to an extent that is not compatible with rational-use criteria [14]. For the individual patient, the argument goes, the use of antibiotics is rational if the individual benefits of such a treatment outweigh the costs. In economic terms, this occurs when the benefits of antibiotic treatment are largely internalised by the patient (although there are some external benefits, e.g. by reducing the risk of contagion), whilst the majority of costs in the shape of ABR are externalities that

are borne by society as a whole. As a result, many people will be prone to consuming antibiotics even if the individual benefit is very small. Whilst this line of argument appears plausible, it likely underestimates the potential costs of antibiotic use to the individual. Antibiotic use leads to changes to the microbiome, which can make future endogenous infections more difficult to treat and it can also increase the risk of superinfections.

## 5. From collective action to individual prescribing

If individual and societal preferences for the use of a resource are not aligned, economic theory prescribes a price adjustment through taxation, which accounts for the externalities of the resource and incorporates the societal costs of such a good [14]. For some externalities-producing goods this appears to be a sound approach. However, in ABR this comes with ethical issues: in most high-income countries the cost of medication is borne by the already strained healthcare systems, and higher prices would push up costs. In low-income countries, a price hike would unfairly discriminate against those with limited financial means who are already more vulnerable and often have to pay for drugs out-of-pocket without reimbursement or co-financing through health insurance schemes. Partly because of these ethical complexities, attempts to limit antibiotic use—especially in countries where prescribers act as gatekeepers to access—focus not on price increases but on rational prescribing. This concept appears unproblematic in ethical terms as long as it merely focuses on the elimination of misuse of antibiotics, e.g. their prescription against viral infections. In such instances, the patient is not disadvantaged (in fact, they may be spared the risk of side effects) and antibiotic therapy can be safely avoided.

However, in many instances, rational use must also mean that antibiotic treatment is not indicated, even though a small benefit for the patient could be realised or a risk averted. This is, for instance, reflected by prescribing guidelines that place restrictions on the immediate and frequent use of antibiotics of last resort, such as carbapenems, to avoid a rapid progressive escalation of antibiotic therapy.

In these instances, prescribers may find themselves in a conflict of interest between the interests of the patient and the public's health. What is not made explicit in current proposals for antibiotic policy is whether and how such a trade-off should be made and what risks to the individual would be acceptable, should antibiotic prescribing be restricted.

This situation is further complicated by the fact that a given risk for the present patient would be accepted for an uncertain positive effect in the future. Since any one individual course of antibiotic treatment is neither necessary nor sufficient for the emergence of ABR, there is no demonstrable link between one patient's use of antibiotics and the future burden of ABR. On the other hand, the cost to the present patient will be immediate and can be predicted with some accuracy [15]. Prescribers who want to restrict antibiotic use therefore face a deep ethical dilemma between the interests of present and future patients, which current prescribing guidelines do not resolve. There is no obvious answer as to how the interest of future persons should be valued in policy decisions, and

different normative approaches come to vastly different conclusions about the duties we owe to future human beings. However, an important starting point for policies that combat ABR would be to explicitly acknowledge that future patients may have a right to effective antibiotics and to begin a discourse about the implications this will have for our current use of antibiotics.

## 6. Conclusion

The complexity of ABR as a policy challenge is reflected in the multitude of practical and ethical problems. However, more often than not, ethical issues of ABR are not explicitly addressed in policy development and discussion, even though they are becoming increasingly relevant for prescribing physicians, patients, pharmacists and policy-makers. This paper has highlighted a number of pressing ethical challenges that effective and credible future policy should address. In particular, if and when it is ethical to withhold antibiotics when this would constitute a risk to patients remains an open question. We believe that it must be answered with some urgency, in an open and transparent debate that includes clinicians and researchers as well as ethicists and policy-makers.

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