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Volume 5

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Ethics and Drug Resistance: Collective Responsibility for Global Public Health

Springer

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ISSN 2211-6680 ISSN 2211-6699 (electronic)
Public Health Ethics Analysis
ISBN 978-3-030-27873-1 ISBN 978-3-030-27874-8 (eBook)
https://doi.org/10.1007/978-3-030-27874-8

This Springer imprint is published by the registered company Springer Nature Switzerland AG.
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Introduction: Ethics and Drug Resistance

Background

Drug resistance is widely acknowledged to be one of the greatest threats to global public health in the coming decades. Tedros Adhanom Ghebreyesus, Director General of the World Health Organization, describes antimicrobial resistance (AMR) as 'a global crisis' and 'the perfect example of the complex, multi-sectoral, multi-stakeholder challenges we will increasingly face in the future'.[1] In addition to scientific research, addressing the challenge of drug resistance requires coming to grips with numerous difficult ethical questions. This book thus provides up-to-date ethical analyses, from multiple perspectives, of many aspects of this crucial public health problem.

Infectious diseases cause significant morbidity and mortality worldwide, with a disproportionately high disease burden among disadvantaged populations. Resistance to drugs for important pathogens also frequently tracks disadvantage, meaning that increasing rates of drug-resistant infections threaten to widen global health inequalities. Meanwhile, rising levels of resistance make it harder, or in some cases impossible, to effectively treat common bacterial (and other) infections. This has significant implications for healthcare and seriously jeopardises many of the gains of twentieth century clinical medicine, even in well-resourced settings. Successful surgery, transplantation, care of newborn children, and chemotherapy for cancer, for example, all depend upon effective antibiotics to treat infections that could otherwise be fatal.

AMR occurs when pathogens evolve resistance mechanisms in response to antimicrobial exposure and/or when resistance is spread from one microbe to another. Resistant pathogens arise in both humans and animals, and they can spread between individuals and between species. Antimicrobial treatment, infection control practices, and agricultural policies directly affect resistance patterns. This in turn raises

[1] https://www.who.int/antimicrobial-resistance/news/WHO-GAP-AMR-Newsletter-may-2017.pdf?ua=1

inescapable ethical questions about how to make trade-offs between different kinds of risks and benefits.

Increasing rates of increasingly drug-resistant infections might be driving humanity towards a 'post-antibiotic era' – i.e. a future situation analogous to the situation before effective antibiotics were discovered and/or became widely available. This would involve a dramatic increase in harms to patients and the costs of treatment. It could also have significant effects on public health policy and potentially dramatic effects on social life.

At this critical moment in the history of medicine, public health ethics has a key role to play in the shaping of practice and policy. This book provides unprecedented, comprehensive, in-depth analysis of ethical issues associated with drug resistance.

Part I: Ethics and Drug-Resistance in Context

Part I provides an overview of drug resistance in multiple contexts. Chapter 1 begins with a broad survey of the causes and consequences of drug resistance as well as potential policy responses to this problem. Chapters 2, 3, and 4 focus on analyses of drug resistance in the contexts of tuberculosis (TB), HIV/AIDS, and malaria – which cause especially high disease burdens among the worst off, predominantly in low- and middle-income countries (LMICs). Drug resistance threatens to undermine public health programmes to treat and control these diseases and could thereby stall progress in global health and socioeconomic development. Chapters 5, 6, and 7 explore the involvement of different sectors in the development of, and response to, drug resistance. These chapters focus (respectively) on private healthcare providers, the hospital as a nidus of drug resistance, and drug-resistant infections in non-human animals.

Chapter 2 focuses on drug-resistant (TB). In the most severe cases, patients with active multi- and extensively-drug-resistant tuberculosis (MDR- and XDRTB) have few (if any) effective treatment options and face high mortality rates. One TB control strategy involves treating individuals with latent (i.e. asymptomatic) TB infection (LTBI) before they develop active disease, but the treatment of *resistant* LTBI has until recently been a neglected topic in clinical research. Nguyen et al. focus on practical ethical challenges arising in the design and conduct of clinical research on MDR LTBI treatment in Vietnam, including community understanding of LTBI and the acceptance of such research in low-income settings. Such analyses arguably have wider implications, since asymptomatic carriage by otherwise healthy individuals is a significant feature of many other (drug-resistant) pathogens, and these phenomena are often poorly understood and/or neglected by researchers, despite having significant implications for research and public health.

In Chapter 3, Bridget Haire explores ethical issues related to drug-resistant HIV/AIDS. Highly active anti-retroviral therapy (HAART) can be highly effective in suppressing (but not curing) HIV/AIDS, thus significantly reducing rates of disease and/or transmission. Unfortunately, resistance to HAART sometimes develops,

particularly where HIV/AIDS patients have difficulty accessing a continuous (lifelong) supply of antivirals and/or where patients are (for other reasons) not able to take medicines reliably. As Haire points out, since the development of resistance can lead to treatment failure and higher risks of disease and transmission, and since diagnostic testing for resistance and second line HAART involves significantly increased costs, policymakers face difficult trade-offs. Haire highlights the ethical aspects of priority setting and cost-effectiveness assessments in the context of HIV/AIDS control policy, which can be particularly challenging in low-income settings where HIV/AIDS is most prevalent and public health resources are most constrained.

In Chap. 4, Cheah et al. focus on malaria, a pathogen for which a mid-twentieth century global eradication effort failed, in part due to the evolution of antimalarial resistance. An especially problematic recent development is the rapid emergence of resistance to newer anti-malarials, particularly in South-East Asia (SEA). Though there are strong moral reasons to prevent the spread of resistant malaria, relevant public health interventions pose numerous ethical and practical challenges. *Inter alia*, several strategies would necessarily involve treating, and thereby imposing risks upon, apparently healthy individuals (including some who are asymptomatically infected with malaria) – just as tuberculosis interventions sometimes target those with latent infection – raising questions regarding whether, or when, such treatment would be justifiable. Furthermore, preventing the spread of resistant malaria parasites to communities with the highest malaria-related mortality (e.g. in Sub-Saharan Africa) may require intensifying intervention in other communities (e.g. in SEA), thus involving burdens for one group in order to prevent even greater burdens for others.

Despite progress towards increasing access to healthcare in SEA, many individuals in this region, as in others, rely on private decentralised health providers for access to antimicrobial drugs. Chapter 5, by Liverani and colleagues, provides a rich analysis of the links between under-regulation of the private healthcare sector and the emergence of drug resistance in SEA. Gaps in surveillance systems, high rates of overprescription, and the dispensing of low quality (and/or counterfeit) antimicrobials are among several causes of increased risks of drug-resistant infections. Liverani et al. demonstrate the complexities of drug resistance as a public health problem across multiple pathogens highlighting tensions between access to antimicrobials and the excesses of profligate use. These tensions, and the associated challenges in the ethical governance of multiple sectors and countries, are recurring themes in the book.

In Chap. 6, Gilbert and Kerridge consider how and why hospitals have often become epicentres of antibiotic resistant bacteria – and why in-hospital strategies, such as antimicrobial stewardship and infection prevention/control, have often been only partially effective. Part of the problem is that even ‘appropriate’ (i.e. not just ‘inappropriate’ and/or ‘excessive’) use of antibiotics inevitably contributes to the emergence and persistence of resistant strains of bacteria. Ethically salient consequences of antibiotic use in hospitals include direct harms related to resistant bacterial infections (in patients, staff, and – through transmission – the wider

community), stigma and other burdens endured by carriers of drug-resistant strains and those who care for them, and the significant costs of reactive (as compared to preventive) infection control interventions. They conclude by outlining moral obligations of individuals and organizations to contribute to reduction of hospital-acquired drug-resistant infections.

Boden and Mellor, in Chap. 7, consider links between drug-resistance in animals and in humans. Although controversy continues to surround questions regarding the degree to which drug resistance in animals contribute to infections in humans, they characterise antibiotic resistance as a typical 'One Health' problem. As such, coherent policy responses are needed across multiple sectors (e.g. human health, animal health, food production, and environmental management). Boden and Mellor argue that international policy-making in particular should take existing socioeconomic inequities in to account, being careful to avoid unnecessarily punitive measures in LMICs which could compromise animal health as well as food production, while still attempting to reduce the incidence and spread of drug-resistant infections (across multiple species).

Part II: Theoretical Approaches to Ethics and Drug Resistance

In Part II, ethical issues associated with drug resistance are analysed via diverse theoretical lenses, appealing to a variety of philosophical and economic concepts including virtue, duty, rights, capabilities, justice, and public goods.

In Chap. 8, Justin Oakley approaches ethical dilemmas in antimicrobial prescription from a virtue ethics perspective. Oakley argues that prescribers should be guided not only by patient-centred virtues, but also by community-centred virtues, including the virtue of justice, in order to strike the right balance between the benefits of antimicrobials for patients and the societal harms of promoting resistant infections. He argues that this is especially important where the expected benefits to the patient from antimicrobial treatment would be low and the wider societal harms are potentially significant. Oakley notes that physicians' decisions are also influenced by a number of cognitive biases and situational factors. A virtuous physician would thus need to cultivate practical wisdom and meticulousness in addressing her own biases. In addition, individual prescribers need the support of healthcare policymakers and institutions to situate them in systems that foster and support virtuous prescribing practices.

In Chap. 9, Giubilini and Savulescu focus on cases where restricting one person's use of antibiotics could be plausibly described as an 'easy rescue'. These are situations in which, at little or no cost, one can consume less antibiotics and thus reduce imposition of risk on others (as well as, perhaps, reducing one's own risk of future resistant infections). The authors argue that individuals have moral obligations to avoid imposing risks on others, including by avoiding profligate use of antibiotics. Thus, policies restricting antibiotic use would have particularly strong ethical justification in situations of 'easy rescue' since (other things being

equal) there would be few important countervailing moral considerations. They note that such cases are particularly likely in high-income countries, where individuals have a reliable health system to support them in the event that the cost of not taking antibiotics (which is *ex ante* uncertain) turns out to be more significant (i.e. that the 'rescue' turns out to be less easy than expected). Furthermore, they argue that states have reciprocal duties to individuals whose antimicrobial use is restricted (e.g. by more stringent prescribing policies), which may plausibly include duties to provide various forms of compensation and/or healthcare. Finally, the authors situate their claims in broader notions of collective obligations to contribute to common goods and argue that antimicrobial effectiveness can be conceived of as such a common good – one that is undermined by overuse (as well as therapeutically justified use) of relevant drugs.

In Chap. 10, Shawa and colleagues apply a human rights approach to the problem of highly resistant strains of TB, for which the development of new drugs and wider access to existing treatments are urgently needed – especially in LMICs. In addition to the right to health, the authors argue that there is a right to enjoy the benefits of scientific progress and that states and international agencies have duties to respect, protect, and fulfil both of these rights (among others). Inadequate access to effective TB drugs and the longstanding relative neglect of resistant TB by funders, researchers, and diagnostics/drug developers are therefore framed as failures to fulfil (at least) these two human rights. Shawa and colleagues argue that duties to fulfil the right to enjoy the benefits of scientific progress in particular entail wide-ranging responsibilities, for example, to pursue legislation to promote TB research and expand access to newer TB drugs (even where this would involve overriding or reducing the scope of intellectual property rights such as those implicit in patents that often make such drugs unaffordable). Noting that there has not yet been international agreement on the minimum core obligations entailed by this right, they outline potentially useful ways of specifying these in order to provide more explicit guidance for states to respond appropriately to this urgent public health problem.

Carl Coleman, in Chap. 11, looks specifically at the right to refuse treatment and the conditions under which legislation and policy should endorse isolation and/or non-consensual treatment. He argues that although laws in some jurisdictions permit mandatory treatment for infectious diseases such as tuberculosis, such compulsion is ethically justifiable only in rare cases in which certain conditions are met, for example, where (i) treatment refusal poses grave risk to others, (ii) the imposed treatment is safe, effective, and not overly burdensome, and (iii) less restrictive measures are infeasible. Coleman surveys international human rights documents and laws in multiple jurisdictions regarding non-consensual treatment and/or TB, noting that provisions for compelled (diagnostic testing and) treatment often exist, even if they are rarely invoked. Even in high-risk cases, such as XDR-TB, the public can usually be protected from harm by isolating the patient (whether or not the patient accepts treatment in isolation). Coleman thus argues that there would rarely be adequate justification for enforcing treatment on the isolated individual. In cases where, for example, isolation facilities are overwhelmed (e.g. during a large outbreak) and large numbers of people refuse effective treatment for infection, mandatory

treatment might be more justifiable. However, Coleman points out that – in practice, particularly with adequate community engagement from public health authorities – conditions sufficient to justify such non-consensual treatment will seldom, if ever, be met.

In Chap. 12, Jamrozik and Selgelid explore the public health ethics implications of asymptomatic carriage and transmission of drug-resistant bacteria by otherwise healthy people. This chapter first summarises current evidence regarding the widespread carriage of key drug-resistant bacteria, noting important gaps in current data. The authors then analyse potential public health interventions for carriers in light of existing public health ethics frameworks, arguing that the relative burdens imposed by public health measures on healthy carriers (as opposed to sick individuals) warrant careful consideration and should be proportionate to the expected public health benefits in terms of risks averted. Ultimately, more surveillance and research regarding community transmission will be needed in order to clarify relevant risks and design proportionate policies, although community surveillance itself also requires careful ethical consideration.

In Chap. 13, Byskov et al. introduce a capability framework to enrich analysis of the burdens of public health interventions among carriers of multi-drug-resistant organisms. They note that carriers can face stigma and other harms as well as restrictions on their particular opportunities for choices (e.g. regarding freedom to chose where to go, with whom to interact, or which occupation to pursue). Thus carriers are potentially subjected to a wide range of potential burdens and/or harms, depending on the policy in question. The authors argue that examining these adverse effects in terms of reductions in the capabilities and functionings of carriers helps to illuminate the ways public health policies aimed at controlling the spread of resistant pathogens can constrain the lives of those affected. Because adverse effects on carriers' capabilities will be highly context specific, the authors ultimately aim to identify a rich taxonomy of ethically relevant considerations to help policymakers (i) determine the likely burdens of being a carrier and of a given intervention and (ii) weigh these burdens against the public health benefits (and costs) of potential interventions.

In Chap. 14, Michael Millar likewise draws on 'the capabilities approach' to illustrate the ways in which access to effective antibiotics among children is critical to secure normal childhood development and fully flourishing adult capabilities. He notes that there is significant inequality in the distribution of risk of (resistant) infectious disease and access to treatment. Millar argues that this is especially concerning where lifelong capabilities are adversely affected. Uncontrolled (or effectively untreatable) resistant infectious diseases can, furthermore, lead to a clustering of disadvantage in a particular individual or community, amplifying existing health injustices. Millar raises the compelling example of growth stunting among LMIC children. Often caused in part by early childhood infections, stunting results in poor long-term physical and cognitive outcomes. However, proposals for the mass treatment of children with antibiotics raise familiar tensions between assuring good health and promoting the rise of drug resistant infections. Given the global inequalities in the distribution of relevant risks and the potential for resistant pathogens to

spread across national borders, international co-operation is required (but can itself be threatened by persistent injustice).

In Chap. 15, Francis and Francis examine the collection and use of information in the measurement of, and response to, infectious diseases with a particular focus on the value of fairness in the context of public health surveillance. Relevant types of information, broadly conceived, include data regarding infected individuals and disease transmission as well as knowledge arising from research. Francis and Francis analyse the use of such information from the interconnected perspectives regarding 'vectors' (those who transmit infection) and 'victims' (those harmed by infection), noting that people may experience both of these states (often simultaneously). The authors emphasize that excessive focus on the vector perspective may lead to unnecessary stigmatization of individuals and punitive policies that can become counterproductive since infected individuals will have strong incentives to conceal their diagnoses. In contrast (simultaneous) concern for individuals as victims may help to foster less burdensome interventions and more support for those infected, but overemphasizing such concerns may lead to, for example, overuse of antibiotics and thus more drug resistance. Francis and Francis argue that the ethical principles of fairness and reciprocity should guide infectious disease policy formation to an appropriate balance of each perspective, especially where difficult trade-offs are required.

In Chap. 16, Lynette Reid examines the links between drug resistance and health inequalities, illustrated by cases such as the rising resistance of many sexually transmitted infections (including among sex workers) and the risks of resistant intestinal parasitic infections. Reid argues that drug resistance undermines global health development narratives because worsening drug resistance may make it impossible to mitigate the persistent large infectious disease burden associated with poverty. Thus, drug resistance is predicted to increase inequality, and a focus on improvements in infectious disease *prevention* (e.g. by addressing the social and economic inequalities that predispose people to infection) would arguably do more to reduce long-term health injustice than expanding access to increasingly ineffective treatments. On the other hand, Reid points out that drug resistance in high-income countries could lead to a 'levelling down' in health equality by undercutting the safety of high-cost interventions (such as complex surgery and immunosuppression). However, as effective antimicrobials become a scarce resource, their use could also be unjustly monopolized by the well-off (in both HICs and LMICs). In any case, Reid argues that policy should go well beyond assuring minimally sufficient access to water, sanitation, and antimicrobials – and address the underlying political and economic forces that result in the persistence of unjust risks of disease among underprivileged individuals.

In Chap. 17, Coast and Smith focus on intersections between economic and ethical analyses of antibiotic resistance. This chapter conceptualizes problems associated with AMR in terms of 'public goods' (a concept related to the idea of common goods invoked above). In economics, public goods are said to be non-rival (i.e. one individual's use/enjoyment of a good does not limit its use/enjoyment by others) and non-excludable (i.e. it is difficult or impossible to prevent access to the good).

Coast and Smith note that the lack of new antibiotics is a predictable consequence of economic forces leading to market failure. They also highlight alternative systems that have been proposed to stimulate useful research and development. At the level of consumers of antibiotics, they note that although many of the benefits of antibiotic use accrue locally and in the present, the harms and costs are (sometimes unfairly) distributed across space and time. Current consumption of antibiotics, for instance, may compromise interests of future people. Ultimately, they argue that economic and ethical considerations will often converge on similar policy recommendations. For example, they note that infection prevention (which is often more cost-effective than providing treatment once an infection becomes clinically apparent) and research into non-antibiotic treatments may be part of solutions aiming to achieve (economically and ethically) optimal improvements in health via a reduction in the burden of infectious diseases.

Part III: Ethics, Regulation, Governance, and Drug Resistance

The chapters in Part III provide unique perspectives on ethical issues associated with policy regarding drug resistance. These analyses draw on concepts related to game theory, collective action, risk limits in research, solidarity, environmental ethics, law, and social policy.

In Chap. 18, Jonathan Anomaly gives an account of the international co-operation urgently needed to regulate the use of antibiotics in animal agriculture. Anomaly starts by asserting that the situation of farmers deciding whether to use antibiotics as a means to sustain animals in crowded conditions is akin to the game theoretical model of a many person prisoners' dilemma. In short, those who opt not to use antibiotics are predicted to lose out economically as factory farmers heavily using antibiotics drive down the price of meat. In the long term, resistance becomes rampant and all are worse off. This predictable 'market failure' to secure the public good of antibiotic effectiveness is one reason in favour of regulating antibiotic use. Regulation needs to reduce the negative effect of 'free riders' (i.e. profligate antibiotic users) and provide assurance for individuals who use antibiotics carefully (i.e. in line with the social optimum) that others will do the same. Anomaly argues in favour of an international treaty and outlines how such a treaty might be designed and implemented.

In Chap. 19, Nichols King analyses an issue raised in many other chapters in this volume in more detail. Given what is known about the complexity of the causal and perpetuating factors involved in the problem of antimicrobial resistance, will 'technological fixes' (e.g. new diagnostics, drugs, vaccines) alone provide an adequate response, or are broader social, behavioural, political, and economic changes more likely to achieve sustainable improvements in public health? Noting that multiple co-ordinated policy responses are likely required, King traces the history of 'technological fixes' and examines the ways in which over-reliance on such approaches has implications for distributive justice.

In Chap. 20, Littmann, Rid, and Buyx explore the concept of 'rational use' of antibiotics. They note that, in some cases, there will be ethical conflicts between patients' interests and the need to preserve effective antibiotics for the future. Littmann et al. draw an analogy from research ethics regarding the acceptable limits to risks to which participants in research may be exposed and provide a framework for policymakers to evaluate potential antibiotic use policies ethically, particularly with respect to the degree of risk to which current patients are exposed due to potential reductions in antibiotic use.

In Chap. 21, Holm and Ploug also approach the problem of the ethical justification for restricting the use of antibiotics in cases where they will provide patients some benefit (but also entail risks of antibiotic resistance). They argue that the concept of solidarity can help to guide physicians and policymakers in such contexts, and also that it can help to promote the support of such policies among the general public. Once persons realize that each could (or anyone could) easily be affected by a drug-resistant infection, it should arguably lead them to act in solidarity with others by giving appropriate weight to the risks related to potential increases in drug resistance. Thus, such individuals would be more inclined to avoid the use of (or prescription of) antibiotics for self-limiting conditions. Furthermore, the authors give an account of how solidarity can inform public health policy, and the ways in which it might be expanded to the global level in the context of the international spread of drug-resistant infections.

In Chap. 22, Nijsingh et al. examine the ethical and evidentiary justification for public health policy responses to drug-resistant infections. Evidentiary justification can be challenging where little high-quality evidence is available and where the underlying causal pathways driving drug resistance are complex and/or poorly understood. In turn, ethical analysis of current policy must often be sensitive to the (sometimes limited) degree of evidence regarding the (cost-)effectiveness of an intervention (or package of interventions). With these complexities in mind, the authors give a thorough analysis of the application and limitations of the Precautionary Principle in the context of antibiotic resistance, as well as a number of other ethical and evidentiary challenges facing policymakers.

In Chap. 23, Anne Schwenkenbecher gives an account of how prospective moral responsibility for one's contribution to antimicrobial resistance – one's 'antimicrobial footprint' – can help to support collective action to reduce the problem. Shwenkenbecher considers arguments that failing to reduce one's use of antimicrobials (where it is possible to do so at acceptable costs) can contribute to unfairness and/or lead to collective harm, concluding that moral reasons to avoid contributing to collective harm (e.g. from drug resistant infection) should support individual action to reduce one's antimicrobial footprint.

The next two chapters address issues related to global health governance in the context of antimicrobial resistance. In Chap. 24, Bennett and Iredell explore the challenges of using existing governance frameworks. They begin by giving an account of the WHO/World Health Assembly 2015 Global Action Plan for Antimicrobial Resistance and the United Nations resolutions that closely followed. The complex problem(s) of antimicrobial resistance have been framed in a number

of different ways in different policies, and the authors argue that policymakers will need to overcome conceptual, practical, and political challenges in order to implement coherent and effective policy in this complex area. A key conceptual challenge is the need to define (and achieve international agreement on) what constitutes 'appropriate' antimicrobial use in order to implement effective regulation and accountability measures.

In Chap. 25, Lee and Ho also take the Global Action Plan as a starting point and complement the above analysis by offering a legal and regulatory toolkit to support effective health governance related to drug-resistant infections. The authors argue that an equitable regulatory 'lever' should be one key part of co-ordinated policy responses and will often be required in order to enable other policies. Lee and Ho give a detailed account of how regulation should be used to support (among other important priorities) quality assurance in antimicrobial production, optimum prescribing and dispensing practices, and the assurance of equitable access to antimicrobials.

Finally, in Chap. 26, Littmann, Viens, and Silva describe antimicrobial resistance as a 'super-wicked' problem. As noted in many other chapters, drug resistance is a complex policy area: there are huge numbers of contributors, stakeholders, and causal pathways involved in creating, perpetuating, and responding to the level of drug resistance across a wide range of pathogens, sectors, and settings around the globe. Littmann et al. conclude the volume by highlighting the many distinctive ethical issues arising in relation to drug-resistant infections and the ways in which ethical analysis should inform policy and response activities.

Acknowledgments

Dr Jamrozik worked on this volume during a residency at the Brocher Foundation. His fellowship at the University of Oxford is supported by the Wellcome Trust [216355/Z/19/Z], [203132/Z/16/Z].

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