



Perspectives on the Ethics of Antibiotic Overuse and on the Implementation of (New) Antibiotics

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ABSTRACT

The continuing rise in global antimicrobial resistance is seen by many governments and international organizations as a major threat to worldwide health. This means that many publications have already described the problems concerning the overuse of currently available antibiotics and potential solutions to this crisis, including the development of new alternatives to antibiotics. However, in this manuscript, the

authors approach the subject of increasing global antimicrobial resistance from two perspectives not normally covered by previous publications, namely the ethical use of antibiotics and potential issues relating to the implementation of new antibiotics.

Keywords: Antibiotic overuse; Ethics; Implementation; New antibiotics

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Key Summary Points

Ethics should be a major consideration in the global fight against antimicrobial-resistant pathogens.

The overuse of antibiotics has ethical dimensions with respect to human, food and environmental aspects, which need to be addressed.

Paying attention to the implementation of new antibiotics is an important process in ensuring their maximum use and efficacy against antimicrobial-resistant pathogens.

Healthcare economics, being AWaRe, forgotten and repurposed drugs, clinical and One Health perspectives all play a role in the successful implementation of new antibiotics.

ETHICAL PERSPECTIVES ON THE OVERUSE OF ANTIBIOTICS

The etymology of the word ‘ethics’ comes from the Greek *etos* meaning the place to live, the Greek *etikòs* meaning theory of living and the Latin *ethos* meaning customs/character, with ethical behaviour involving ‘the aggregation of actions, bound by a systematic code of actions and principles, which benefits both humans and the environment’ [1]. If anything, the COVID-19 pandemic situation has shown the effect that infectious diseases can have on global populations, their healthcare services and national economies. In such global health crises, individuals should consider prioritizing the long-term collective interest over their short-term individual interest and, in many cases, to prioritize the collective over the individual benefit is an ethical choice (‘tragedy of the commons’/‘principle of autonomy’) [2]. Under this aspect, citizens should understand that the overuse of antibiotics is a collective priority.

Overuse of Antibiotics in Humans

The irrational overuse of antibiotics has been attributed to increased morbidity and mortality [3–5]. Although access to antibiotics may be a potential problem for many poorer citizens of the world, paradoxically the overuse of antibiotics also represents an ethical challenge. Ethically speaking, the overuse of antibiotics is one of the major factors driving the current increase in antimicrobial resistance (AMR), with such overuse threatening not only the health of individuals, but also the financial wellbeing of national healthcare systems [6]. One of the major factors facilitating the overuse of antibiotics in human healthcare systems is the unethical over-the-counter selling of antibiotics by pharmacists and other vendors without a relevant prescription from a registered physician, or confirmatory results from a diagnostic test [7, 8]. Further, it has been reported that people who undergo self-medication without a prescription often do not follow instructions

and do not complete the course of antibiotics they have bought (possibly as a result of poverty), choosing instead to keep some antibiotics for use in the future when they again feel ill. Such behaviour may promote resistance development due to suboptimal antibiotic dosing [9]. Drivers of such behaviour include the economic benefit obtained by vendors from the promotion and sales of antibiotics, which means that altering such behaviour is a difficult task to achieve, as such changes may (seriously) impact on the standard of living of the vendor. Ideally, antibiotic use should be strictly controlled through legislation based on rational antibiotic stewardship policies, including policies that focus on proper record keeping of antibiotic dispensing by vendors. Such records may then be audited and monitored later by professionals at appropriate periods of time [10]. For example, China implemented a policy to promote the rational use of antibiotics, which ended up substantially reducing antibiotics sales and antibiotic prescribing both in hospitalized patients and outpatients [11]. One way to potentially change individual ethical behaviour is through targeted prescriber and general public education campaigns so that doctors and the general public are continuously made aware of the deleterious effect and risk associated with the irrational use of antibiotics to treat unconfirmed bacterial infections [11]. Ethically speaking, however, one of the possible ethical consequences of such policy implementations may be a reduction in the standard of living of vendors via the profits made by selling antibiotics [12, 13]. Another ethical problem is that blocking access to antibiotics may unfairly target lower income groups who cannot afford to pay for a visit to a doctor, or a diagnostic test, on top of the cost of antibiotic treatment. Further, such policies may lead to a rise in the number and amount of counterfeit drugs available on the (black)market, requiring the further implementation of validated enforcement, inspection, good procurement and post-market surveillance practices [10]. It has also been reported that doctors sometimes feel obliged to prescribe antibiotics on the basis of the expectations and persistence of patients, creating an ethical dilemma regarding

preserving the efficacy of antibiotics versus the patient's own treatment expectations [14].

As a long-term (and perhaps more ethical) strategy, the actual prevention of infection could help reduce the overuse of antibiotics without additional ethical burdens on vulnerable populations. For example, investment in adequate water, sanitation, hygiene (WASH) and wastewater management facilities could prevent infections and be lifesaving with respect to reducing the spread of antimicrobial-resistant infections and use of antibiotics. Further, such investment would contribute to all five objectives of the World Health Organization (WHO) One Health AMR Global Action Plan (GAP) [15]. Therefore, access to safe and clean water, improved sanitation, and hygiene may be more acceptable and ethical options to mitigating antibiotic use in a range of community and healthcare settings.

Another potentially alternative ethical approach to reduce antibiotic use is to invest in (new) vaccines and vaccination strategies against global pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenza*, *Klebsiella pneumoniae*, *Mycobacterium tuberculosis* etc. [16]. However, as can be seen by the controversy over COVID-19 vaccination, imposing vaccination strategies on populations (even during a global pandemic) may not be totally successful in the face of (unfounded) widespread mistrust of vaccines [17]. Basically, when vaccinating large populations, ethical issues relating to the protection of society versus the free will of an individual need to be considered [18]. Further, the actual emphasis of societal rights versus individual rights may vary dependent on individual countries, societies and governments [19]. This phenomenon ultimately leads to situations where governmental and non-governmental organisations may need to impartially educate the general public, patients and healthcare workers on how to recognise and avoid the spread of fake news and misinformation on the use of antibiotics. In this context, generating and distributing clear, concise and truthful communication should be tailored to particular populations, with the importance of involving representatives of target populations necessary in order to develop impactful vaccine

information without the possible introduction of (inter)national biases relating to religious background, gender, sexual orientation or ethnic group.

Overuse of Antibiotics in Animals

In the veterinary and animal food production sectors (cattle, pigs, poultry, seafood etc.), antibiotics may not only be prescribed for (potential) infections but may also be used as growth promoters. This practice has potential consequences for human health, animal health and animal welfare [20–22]. Ideally, the moral obligation to administer antibiotics should be limited to therapeutic purposes only, i.e. to cure sick animals (whether these animals are food animals or pets). However, it is interesting to note that humans will happily eat one species of animal (cow, pig, chicken, fish etc.), while being revolted at the thought of eating another species (e.g. dog, cat, snake etc.). The ethics of this situation are further confused by the knowledge that such revulsion may be related to cultural, religious or national perspectives. In any case, the overuse of antibiotics in animals is not restricted to one particular species and it could be argued that food animals should be bred and raised in humane, biosecure habitats with adequate hygienic conditions that are actually designed to prevent or hinder the spread of disease rather than for maximum profit [23]. Importantly, as is the case with the availability of antibiotics for human consumption without prescription, financial incentives may play a large part in the use of antibiotics in the food industry, especially their use as growth promoters [24]. However, alternatives to antibiotic growth promoters do exist, and include antimicrobial peptides, prebiotics, probiotics, enzyme, organic acids, phytogenics, bacteriophage, and hyperimmune egg yolk antibody, which has been administered to enhance growth and feed efficiency in poultry [25]. In addition, inactivated pathogens used as vaccines in aquaculture have shown efficacy in reducing disease and mitigating the requirement for antibiotics in controlling diseases and superbug development in water [26]. Another

study conducted on a Danish pig farm demonstrated that immunization reduced oxytetracycline consumption by 80% and the widespread administration of vaccines against *Aeromonas salmonicida* reduces antibiotic use in the salmon industry [27]. Veterinarians may also be encouraged to promote the ethical use of antibiotics to food animal producers and pet lovers [28, 29]. In 2022 a World Organization for Animal Health (OIE) report noted that only 71% of 95 countries published online reports providing information on the use of antimicrobial agents in animals [30]. In any case, the study and implementation of such non-antibiotic growth promoters should be further encouraged, with an emphasis on ethical animal welfare and productive farming without extra welfare burdens on food animals. There has, luckily, been some progress in this area. For example, antimicrobial growth promoters have been banned in the European Union, since 2006, and the USA decided to take similar action and restrict the use of antibiotics for clinical use in 2017 [31, 32]. In 2017, China banned the use of colistin as a growth promoter. However, China remains one of the world's largest hotspots for AMR bacteria, mainly due to the overuse of antibiotics in the agricultural sector. In 2018, it was estimated that approximately 29,774 tons of antimicrobials were consumed in China, of which 53.20% was destined for use as animal growth promoters [33, 34]

Overuse in the Environment

We should not only consider the ethical use of antibiotics in humans and animals but also the ethical (ab)use of our environment [35]. Our environment may act as a reservoir for antibiotic residues, as well as for the antibiotic resistance genes and pathogens that are generated by the overuse of antibiotics by human and animal farming practices. For example, food animals fed antibiotics may contaminate the environment via the dispersal of contaminated manure, bedding or water ponds (e.g., shellfish) into oceans, river waters and soils [36]. Human faeces may also be a problem, with a study finding a higher diversity in antibiotic

resistance in human waste from municipal treatment plants than in livestock waste [37]. Perhaps not surprisingly, another study reported on the higher presence of antibiotic resistance genes in sewage treatment plants compared to the discharge from antibiotic manufacturing plants [38]. These harmful AMR pathogens, antibiotics and antibiotic resistance genes cause ecological imbalance by replacing susceptible microbes and/or disrupting primary producers and decomposer of natural ecosystems. For example, *Cyanobacteria* spp. form 70% of total phytoplankton mass (a key part of ocean and freshwater ecosystems), producing more than 25% of total free oxygen production and fixing an approximately equivalent proportion of carbon dioxide. Importantly, *Cyanobacteria* spp. may be sensitive to a range of antibiotics in current use [39]. Therefore, a reduction of antibiotic use in humans and animals, as well as the proper management of the disposal of manure, bedding and wastewater would be a large step in successfully reducing antibiotic residues, antibiotic resistance genes and pathogens from entering the environment [40].

The overuse of antibiotics is a worldwide problem, occurring in human, farming and environmental domains. This fact has not gone unnoticed and in the last few years global organizations have started to inform stakeholders about the problems associated with the misuse of antibiotics [41]. However, the factors associated with the overuse of antibiotics are broad and may involve conflicting ethical priorities (e.g. personal versus societal health and welfare—where individual interest in treating infections conflicts with the collective interest in preserving antibiotic effectiveness). To help prevent this ‘tragedy of the commons/principle of autonomy’ effective policymaking and education are vital [2, 42, 43]. Therefore, for AMR policy development, clinicians, healthcare researchers, commercial AMR-related businesses, social scientists, patients, farmers, environment representatives and ethicists need to work together to ensure that strategies to address global AMR take note of ethical issues in order to ensure maximum efficacy in current and future target populations [42, 44–46]. For

educational purposes, the same group of stakeholders need to address customized aspects of political, socio-economic, commercial and cultural ethics if the different stakeholders in antibiotic overuse are to be persuaded to change their current practices [45, 47]. In this way, ethical considerations should be balanced between the conservation of existing antibiotics, the acceleration of new antibiotic development, potential regulatory hurdles and the conservation of antibiotic safety and efficacy [48, 49].

PERSPECTIVES ON THE IMPLEMENTATION OF NEW ANTIBIOTICS

Tackling antibiotic resistance is a global imperative and, as previously mentioned, defining ‘antibiotic use’ policies and educating stakeholders to take into account ethical choices may be a valued method in achieving a reduction in the overuse of antibiotics. However, even if such AMR policies and education programmes are successful, antibiotic resistance will still exist and the need for novel antibiotics will remain (albeit at a lower level of urgency). In this case, it is important to take a perspective of the situation in order to understand potential problems associated with the development and implementation of developing and bringing novel antibiotics onto the healthcare market. Such issues should be seriously considered by antibiotic innovators, as part of the ‘due diligence’ process before investing large amounts of money into the development (including clinical trials and scale-up) and implementation (including marketing strategies) of that particular drug.

Healthcare Economics

The development and implementation of novel antibiotics may not only rely on ‘bottom-up’ approaches involving academic and industrial partners but also on ‘top-down’ approaches from national governments, including the use of ‘pull’ incentives. Indeed, there appears to be

high-level support for such approaches, even if some countries are sceptical about the health value of novel antibiotics and an apparent mismatch between antibiotic developers and (inter)national policymakers. In this respect, Årdal et al. recently proposed a multinational model that could “match the needs of both countries and innovators”. Such research is necessary as countries may be sceptical about the actual public health value of recently approved antibiotics, resulting in mismatched revenue expectations between policymakers and antibiotic innovators [50]. In a systematic review, Dutescu and Hillier applied an incentive analysis to understand which incentives are most likely to “sustainably revitalize” the antibiotic development pipeline. The authors proposed the implementation of a “fully delinked subscription-based market entry system” [51]. Okhravi used a Monte Carlo simulation comparing the cost of investment-go decisions to the cost of directly funding the same antibiotics and concluded that “while indirect funding may be necessary... we may want to prefer direct funding as a cost effective long-term solution for future antibiotics” [52].

Different national institutions may be involved in advising on healthcare economics issues for new drugs. For example, the National Institute for Health and Care Excellence (NICE) of the UK uses independent committees (including professionals and lay members) to provide evidence-based guidelines on disease treatments and technologies [<https://www.nice.org.uk/>]. As part of the UK’s 5-year national action plan for AMR (published in 2019) NICE began to evaluate a model for the purchase of antimicrobials involving a competitive procurement exercise, whereby reimbursement to companies is based “primarily on their value to the NHS [the National Health Service of the UK] as opposed to volumes used”. In this project, payments are to be made on the basis of ‘benefits to patients’ rather than actual ‘quantities of antibiotics used’ and is currently comparing an existing antibiotic combination (ceftazidime with avibactam—Pfizer) to a new-to-market antibiotic (cefiderocol—Shionogi) [53]. The healthcare costs of novel antibiotics are also a major concern for private healthcare systems. In

1983 in the USA, the Inpatient Prospective Payment System (IPPS) generally replaced the existing cost-based reimbursement system for hospitals. However, this system ultimately generated the unintended consequence of financially penalizing the use of novel antibiotics. Recent proposed changes to this system include a new technology add-on payment and the recognition that drug-resistant infections should be automatically recognized as comorbidities/complications, factors that should help incentivize the development and implementation of novel antibiotics [54].

Although novel approved antibiotics could be a lifeline for many patients suffering from multidrug-resistant (MDR) infections, extensive knowledge on the drug's efficacy in treating large numbers of infections is limited as compared to the information available for existing antibiotics. This lack of information could influence the uptake of novel antibiotics if extensive studies on cost-benefit analyses are incomplete. In this respect, Yahav, Shepshelovich and Tau recently published a cost analysis of new and old antibiotics evaluating treatment cost, 14-day treatment course cost and estimated annual costs, using data provided by the Centers for Disease Control and Prevention's report on MDR bacteria prevalence in US hospitalized patients. Annual additional costs in their comparisons were 6–60-fold those of existing drugs, with an extra 30 million to 500 million USD for treating difficult-to-treat Gram-negative infections. It was concluded that the implementation of novel (newly approved) antibiotics carries with it a large incremental cost, with the need for survival benefit data being required in order to substantiate potential price differences between novel and existing antibiotics [55]. Interestingly, a recent publication indicated that (novel) antibiotic strategies that actually decolonize carriers of antibiotic-resistant bacteria could actually be "highly cost effective" when the indirect benefits of decolonization were considered for outbreak-vulnerable populations [56].

Not to be forgotten is the current emphasis on reducing antibiotic consumption with the goal to use antibiotics wisely (e.g. via public educational awareness campaigns or by using

financial disincentives such as co-payment for antibiotic prescriptions). The impact of such practices on the short- and long-term development and implementation (including any potential social impact) of novel antibiotics may need to be taken into consideration and applied to the long-term economics of antibiotic development and implementation [57].

Be 'AWaRe'

(Inter)national recognition and authorization of antimicrobials is an important step in the implementation of novel antibiotics into clinical practice. This recognition includes the potential naming of specific antimicrobials in (inter)national essential medicines lists. For example, the most recent revision of the Indian national essential medicines list being evaluated includes amikacin, mupirocin and new generation tuberculosis medications (e.g. bedaquiline, delamanid), but excludes erythromycin and the anti-TB drug rifabutin [58]. Globally, the WHO publishes its own model lists of 'Essential Medicines' and 'Essential Medicines for Children', where the term essential medicines relates to "medicines that satisfy the priority healthcare needs of a population..., are selected with due regard to disease prevalence and public health relevance, evidence of efficacy and safety and comparative cost-effectiveness..." and "are intended to be available in functioning health systems at all times, in appropriate dosage forms, of assured quality and at prices individuals and health systems can afford." These WHO lists are updated every 2 years in order to provide guidance to countries and regional authorities regarding medicines, including antibiotics [59]. However, not all antibiotics can (or should) be treated equally, as potential 'drugs of last resort' may be so valuable that they may be highly restricted to the treatment of 'Critical Priority' or 'High Priority' infections, where all other alternatives are unsuitable or have failed. In this respect, the WHO publishes the 'WHO Access, Watch, Reserve (AWaRe) classification of antibiotics for evaluation and monitoring'. This document includes lists of antibiotics that (1) are

recommended as essential first or second choice empiric therapy ('Access'); (2) are recommended as essential for a limited number of specific infectious syndromes ('Watch'); (3) should be reserved for confirmed or suspected MDR infections ('Reserve') or (4) are not recommended for use in clinical practice ('Not recommended') [60]. Antibiotics may be added to or removed from the list as it is revised. Inclusion of novel antibiotics in the 'Access' and 'Watch' categories is likely to generate more financial income for developers than if the antibiotic is placed in the 'Reserve' or 'Not Recommended' categories.

Competition with 'Forgotten' and 'Repurposed' Drugs

The relatively rapid development and clinical use of 'forgotten' (and now rediscovered) antibiotics, as well as 'repurposed drugs' (i.e. non-antimicrobial drugs that may be used to combat infections), could also impact on the implementation of novel antibiotics [61, 62]. Forgotten antibiotics may include older antibiotics that originally failed clinical trials or fell out of favour with clinicians, including antibiotics such as fosfomycin and polymyxins. Indeed, one of the most famous examples of a previously 'forgotten' antibiotic is colistin, a polymyxin antibiotic that exhibits (reversible) nephrotoxicity and (rare) neurotoxicity, but may be useful for the treatment MDR bacteria (including carbapenem resistance). Repurposed drugs, on the other hand, are drugs that were not originally conceived as antibiotics per se, with their antibiotic activity being determined at a later date (possibly as an additive or synergistic combination with existing antibiotics) [63]. Recent examples include the non-steroidal anti-inflammatory drugs (NSAIDs) piroxicam (PXC), diclofenac sodium (DCF), acetylsalicylic acid (ASA) and naproxen sodium (NPX) [64]. Importantly, the fact that both of these types of drugs (forgotten and repurposed) have previously been/continue to remain in clinical use means that detailed information on their toxicity, pharmacology and molecular structures already exists, potentially resulting in (1)

accelerated development and implementation by regulatory bodies and policymakers and (2) increased clinical acceptance by clinicians, when compared to the development and implementation of novel antibiotic strategies.

Clinical Opinion

The prescription of (novel) antibiotics in primary, secondary and tertiary care by clinicians is dependent on multiple factors, including the clinical experience and antibiotic prescribing practices followed by the individual clinician and their institution. Such factors may include 'Loss of ownership', 'Tension between health concerns', 'Evidence-based versus bedside medicine' and the 'Diverse priorities between different clinical teams' [65]. Another clinician consideration is whether to actually prescribe antibiotics to a patient, particularly in cases of 'Diagnostic uncertainty'. In this case, the training and experience received by the clinician may be a crucial factor in determining the clinician's antibiotic prescribing decision [66]. For example, faced with the prospect of a patient dying from an untreatable MDR infection, a clinician may determine that the use of a novel antibiotic is essential (as a 'drug of last resort') simply because of the lack of an effective alternative [67, 68].

Another important factor is the potential role of novel antibiotics within antibiotic stewardship programs. Such programs best succeed through clinicians adhering to best practice prescribing guidelines, antibiotic use monitoring, continual surveillance of antibiotic resistant bacteria and transparent reporting and effective communication of the findings [69]. Novel antibiotics compatible with best practice prescribing guidelines (e.g., first/second choice empiric therapy, or for use in specific infectious syndromes) may be more likely to be prescribed than those antibiotics that are not compatible.

Interestingly, clinicians may increasingly have access to (inter)national computerized decision support systems (CDSS) for guiding antibiotic prescribing practices. These CDSS may help clinicians make informed decisions about whether and which antibiotic to

prescribe. The potential addition of novel antibiotics to (inter)national CDSS (such as ‘AntibioClic’) could be very valuable in the implementation of such antibiotics in clinical practice [70].

Finally, the potential role of (Point-of-Care) diagnostics in informing clinicians about the need for (evidence-based) antibiotic treatment should not be underestimated [71]. In this case, diagnostics would be regarded as ‘companion diagnostics’ providing information about the actual need to prescribe an antibiotic [<https://www.fda.gov/medical-devices/in-vitro-diagnostics/companion-diagnostics>].

The One Health Perspective

If a novel antibiotic is identical to (or has a chemical structure similar to) an antibiotic widely used in intensive farming practices, e.g. poultry farming, it may be unlikely to be considered a successful drug candidate for extensive use in human infections. This is because of the risk of resistant bacteria evolving in animals and making their way into human infections. Examples of such risks include the use of colistin [72], as well as the potential relationship between the use of the growth promoter avoparcin in animals and the risk of vancomycin resistance in humans [73, 74]. In fact, in January 2019 the European Union adopted Regulation (EU) 2019/6 relating to veterinary medicinal products (part of its commitment of reducing antibiotic use by 50% by 2030), which is based on the One Health perspective of AMR [75]. This regulation came into force in all EU Member States in January 2022. However, this policy is not without its opponents, with interest groups such as the Federation of Veterinarians of Europe stating that “Banning authorized antimicrobials for animals without any scientific argument and science-based reasons is contra-productive and will endanger animal health, welfare and human health” [76]. Essentially, the role of novel antibiotics in human and/or animal health is an issue that antibiotic developers should be aware of when deciding their ‘target market’, and in any case before investing substantial amounts of money

into clinical trials and drug development for markets governed by restrictive international legal limitations.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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