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PERSPECTIVE

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Using antibiotics responsibly: are we there yet?

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Problems of antibiotic access and excess coexist in the world today and are compounded by rising rates of antibiotic resistance. We introduce two dimensions of responsibility to this context: responsible individual practices and a broad societal obligation centered on sustainability. Acting on these responsibilities requires recognizing the potential tensions between an individual optimum for antibiotic use and the societal optimum. We relate the tragedy of the commons metaphor to this situation to illustrate the complexity involved, and we draw on real-world experiences in Uganda, India, China and France. We conclude that we must form a global stewardship of antibiotics that can link access, innovation and conservation efforts across countries to ensure sustainable access to effective antibiotics for all who need them.

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- antibiotic stewardship
- antimicrobial resistance
- complexity

Background

The world is full of paradox: we discover the existence of antibiotics, a remarkable class of drugs that add several years to the average human's lifespan and radically alter our expectations of normal life. Then, over the course of 70 years we fail to make the value of these drugs accessible to all [1,2]. At the same time, we knowingly overuse these drugs in both humans and animals, accelerating the rate at which their value is eroded, while failing to invest in ways to maintain and to renew this value [3]. This raises a crucial question that we must ask ourselves: are we using antibiotics responsibly?

In this perspective piece, we argue that we need to collectively agree on what constitutes responsibility in the context of use of antibiotics. We propose a holistic approach that places the major focus on sustainability at a global level, while acknowledging the importance of responsibility in individual uses of antibiotics. We discuss how the application of this approach now requires us to reflect on, reshape and realign the many systems that guide our individual interactions with antibiotics, and to consider tensions that emerge when balancing sustainability with optimal treatment for individuals. This entails a whole-of-society approach to antibiotic effectiveness, building on the many initiatives that have been advocating broader engagement, and truly moving beyond the biomedical framing of antibiotic resistance that still largely predominates on a global level. Substantial global resource

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commitments are needed over the coming years and could be supported by the emerging sustainable development goals agenda [4]. We focus our specific examples and illustrations in human health, although the underlying principles can and must be applied far more broadly.

What is responsible use?

The word 'responsible' has many connotations, and forming an overall consensual definition for responsible antibiotic use is part of the ongoing DRIVE-AB initiative [5]. Two dimensions described in the Oxford English Dictionary are particularly relevant [6]. First, a responsible practice or activity is one that is carried out in a morally principled or ethical way. Second, to be responsible is to be capable of fulfilling an obligation or duty. We contend that both of these dimensions, responsible practices and being responsible, are important: an individual use of antibiotics can be considered responsible but we can also be responsible in how we choose in general to use antibiotics.

• The first dimension: responsible practices

Over the past two decades, we have placed an emphasis on irresponsible individual uses of antibiotics: these are often termed unnecessary, inappropriate, inadequate, imprudent or irrational uses [7,8]. Antibiotic stewardship efforts have sought to identify and reduce such uses, based on the understanding that they result in very large aggregate volumes of excess use [9]; there is general agreement that at least a third of human antibiotic use in most settings falls into these categories.

Why do such uses exist, let alone persist? On a global basis, most antibiotics are acquired by end users either from prescribers or via over-the-counter sales at drugstores; the latter is more common in resource poor settings where limited access to prescribers can otherwise threaten access to effective antibiotics. Inadequate knowledge among prescribers and dispensers contributes to irresponsible use, but it certainly does not account for all [7]. External judgments of appropriateness are typically based on patient clinical factors combined with expected local patterns of microbiological etiology and antibiotic susceptibility. This is a relatively narrow viewpoint that tends to neglect the far broader range of factors that influence individual antibiotic use decisions in practice for humans and animals. These include unspoken prescribing etiquettes, financial incentives, patient and caregiver expectations or demands, and even society-wide cultural constructs, such as managing high levels of uncertainty avoidance [10–12]. Intentionally ignoring the existence of these factors when judging responsibility will inevitably lead to the detection of irresponsible use.

The existence of competing factors that influence individual practices reveals a deeper truth: there is no single agreed upon purpose to the use of antibiotics. Different types of value are capable of being created when antibiotics are used. Just as a physician uses antibiotics in the treatment of a patient with pneumonia (clinical value), the hospital that they work in may use antibiotics to generate income to cover its operating costs (economic value); a pharmaceutical company uses antibiotics to generate income to cover research and development costs and provide profit to their shareholders; a pharmacy or drugstore can use their rights to dispense antibiotics as a way to sell other over-the-counter symptom-relieving medications to patients at the same time; more broadly, a society may use antibiotics for nonlife-threatening illnesses so that its population can experience symptoms for shorter periods of time, return to productive work more quickly, or simply feel reassured. Some societies also use antibiotics to make up for underinvestment in public health and hygiene. Antibiotics are used in veterinary medicine to create clinical value, but they are also used in agriculture to increase yields and profits and to satisfy evolving societal demands. In abstract terms, it is difficult to justify calling any of these purposes or value-creating processes unethical.

Prescribers and dispensers must manage these multiple purposes when deciding to use antibiotics, some of which they may not be directly aware of, such as fulfilling deep-seated societal expectations. Insofar as these individuals are permitted or encouraged to respond to these different purposes, very little antibiotic use is completely irresponsible on this individual level – in other words, carried out in a wholly morally unprincipled way.

Antibiotic stewardship efforts ask us to prioritize among different purposes of using antibiotics, and decide to use them in a way that optimizes clinical outcomes and minimizes development of bacterial resistance and other adverse effects. Antibiotic uses that follow these principles can be considered responsible: they help preserve the most important and unique

value of antibiotics (their clinical value) for tomorrow's patients while providing optimal care for patients today [13]. These stewardship principles are relevant for both human and veterinary medicine.

• The second dimension: being responsible & forming a global stewardship of antibiotics

An extraordinary result of pharmaceutical research and development efforts in the mid-20th century was the discovery of antibiotics effective against every single known human bacterial pathogen. The second dimension of responsibility asks us to consider our obligation in how we collectively manage the potential clinical value contained in this broad collection of antibiotics.

We contend that we have dual obligations: to make this clinical value accessible to all who need it today, and to maintain this clinical value for future patients. This emphasizes the need for both inter and intragenerational justice [14], and parallels our broad obligations to preserve our environment and natural resources. Critically, the clinical value of antibiotics is not inherently self maintaining or self renewing. All uses of antibiotics have the potential to select for the development and spread of resistant bacteria in a time frame and manner that we recognize has detrimental clinical impacts. Thus, their use is intrinsically coupled to a loss of their potential clinical value.

We reformulate these dual obligations into a single obligation: to ensure sustainable access to effective antibiotics for all those who need them. This is closely aligned with the goal of the WHO global action plan on antimicrobial resistance: to ensure, for as long as possible, continuity of the ability to treat and prevent infectious diseases with effective and safe medicines that are quality assured, used in a responsible way and accessible to all who need them [15]. Importantly, we contend that this should not be portrayed as a goal, but rather as our obligation. The above phrasing of our obligation allows for contextual and time-based adjustments: what we classify as responsible individual practices today may not be considered responsible in the future if resistance rates rise rapidly, or if new antibiotic classes and alternative therapies do not become available.

This obligation currently lacks formal acknowledgment at the highest of political levels, and perhaps also lacks informal acknowledgment at the level of individuals in societies. The widespread existence (and at times encouragement) of irresponsible uses of antibiotics can be seen as a symptom of society-wide lack of commitment to this deeper obligation. To the extent that people are suffering today from lack of access to effective antibiotics, we are already failing in our responsibility. Recognizing this obligation would in a sense be committing to creating a 'global stewardship of antibiotics' to sustain the potential clinical value of antibiotics as a therapeutic concept. In practice, this will rely on efforts to promote access, innovation and conservation. These efforts are interrelated and so require global collaboration and coordination: enhanced access has the potential to speed up emergence of resistant bacteria and must be coupled with improved conservation; and improved conservation must not become a barrier to innovation efforts [16].

Combining responsibilities

We have described two dimensions of responsibility in the context of antibiotic use. The first dimension concerns the responsibility of individual uses of antibiotics, acknowledging that multiple purposes for using antibiotics exist, but that there is a strong ethical justification to prioritize clinical value above other potential values due to the negative externality of antibiotic resistance. The second dimension introduces our global obligation to ensure sustainable access to effective antibiotics for all those who need them. The types of coordinated cross-country efforts that are required to meet this obligation help form a global stewardship of antibiotics [15,16].

These two dimensions of responsibility are clearly inter-related: sustainable access to effective antibiotics is easier to achieve when individual uses of antibiotics have prioritized creating clinical value and accounted for the risks of resistance. However, this brings us to a critical gap in our existing knowledge: to what extent do individual antibiotic uses need to be adapted to create sustainable access to effective antibiotics? Is optimizing individual uses of antibiotics sufficient, or does a society optimum use of antibiotics need to be prioritized? And, if a society optimum requires suboptimal treatment at the individual level for humans or animals, are we prepared to commit to this at a global level?

We contend that the optimal use of antibiotics for individuals (the first dimension of responsibility) is likely to be different to the optimal level of antibiotic use for society (the second

dimension of responsibility), and that sustainable access will require prioritizing the society optimum; the extent to which the society optimum needs to be prioritized has important ethical implications, which are currently underexplored.

In practice, prescribers and dispensers face limitations that predispose their actions toward the individual optimum, or frequently a level even worse than this. These limitations include incomplete information on the consequences of a single use of antibiotics (creating bounded rationality), and complexity in contextualizing these consequences. For a single use of antibiotics, a prescriber does not know to what extent resistant bacteria will be selected, or if and how these resistant bacteria will spread; this is the case both in highly controlled clinical settings, and in population-wide uses of antibiotics in agriculture. Even if the prescriber were to have access to this information, the prescriber would struggle to comprehend how the consequences fit into the dynamically complex global picture of antibiotic use and resistance. Together, these limitations result in patterns of antibiotic use that tend to prioritize the individual patient at the expense of ensuring sustainable access for all, as can be illustrated in the classical social dilemma, the tragedy of the commons.

Revisiting the tragedy of the commons

The ecologist Garrett Hardin described the tragedy of the commons in 1968 [17]. He presented the classic example of a common field onto which a group of farmers place cows to graze. Each farmer can choose to add more cows, from which they will individually benefit; in doing so, they will also cause all farmers to suffer a small fractional cost because each additional cow reduces the overall quality of the commons. This situation becomes a tragedy when the carrying capacity of the commons starts to be eroded: the cows consume so much grass that the commons loses its ability to renew itself, and it eventually collapses. In general terms, each user in a commons system benefits directly from each additional use they make of the commons, but shares the cost of abuse with everyone else in an environment that is ultimately erodible.

Levin related the tragedy of the commons to antibiotic use in 2001 [18], and a few authors have since developed this analogy further [19,20]. Use of antibiotics leads to higher levels of antibiotic resistance, which lowers the efficacy of antibiotics and so erodes the clinical value of antibiotics; this process is accelerated by overuse of antibiotics, and the emergence of a tragedy has been demonstrated in mathematical modelling studies [21–23]. Baquero and Campos summarized the situation, writing that 'we have treated antibiotics as if they provide an immediate benefit for free and have been considered an inexhaustible common, both by prescribers and the general public' [24]. We believe that this consideration has been shared by our organizations and our societies, and this needs to be addressed in the context of sustainablity. The commons of the 'clinical value of antibiotics' is depicted in **Figure 1**.

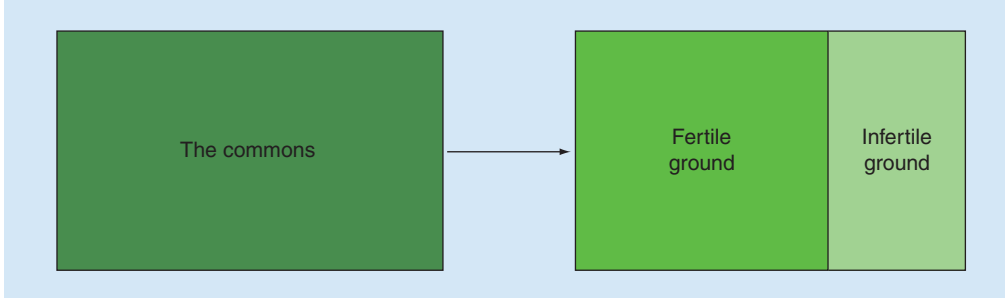


Figure 1. The commons of clinical value. The commons contains all the potential clinical value of existing antibiotics. At any point in time, it can be broadly divided into fertile ground, consisting of the proportion of bacteria that are susceptible to at least one antibiotic (i.e., representing the available clinical value of antibiotics), and infertile ground, consisting of the proportion of bacteria that are resistant to all existing antibiotics. After drug discovery in the mid-20th century, all the ground was fertile. Today, infertile ground remains an extremely small fraction of the total commons, since the vast majority of bacteria still retain susceptibility to at least one class of antibiotics. Discoveries of new antibiotic classes can convert previously infertile ground back into fertile ground.

Traditional approaches to the tragedy of the commons

There are three traditional ways to prevent commons situations developing into tragedies, and to ensure the sustainability of the commons as a valuable shared resource [25]:

- Educate the users of the commons
- Regulate the commons
- Privatize the commons

The first approach involves helping the farmers to recognize and understand the consequences of their actions (adding cows to the commons) with the intention that enhanced knowledge will translate into more responsible actions. The second approach involves collective agreements between farmers, in the forms of permits, incentives, quotas and outright bans on certain behaviors. These agreements are typically regulated by an external body, to whom all farmers are ultimately accountable. The third approach involves dividing up the commons, such that each farmer has an area of the field with its own carrying capacity and directly reaps the consequences of his or her own actions.

These approaches have relevance to antibiotic use. Education efforts for prescribers and dispensers are frequently used and have evidence of effectiveness [26]. Regulation is common at many points in healthcare systems: restricting over-the-counter availability of antibiotics, specifying valid indications for antibiotics during the licensing process and setting target prescribing rates for different institutions. Parallels exist in agriculture, such as bans on the use of antibiotics as growth promoters [27]. Sovereignty and domestic autonomy could be viewed as passive forms of commons privatization, and domestic antibiotic use is correlated with resistance rates in clinical isolates [28]. In reality, true privatization is not possible because antibiotic effectiveness cannot be divided in this way [19]: bacteria, resistance genes and antibiotic residues do not respect such artificial boundaries, especially in our increasingly interconnected world [29]. Indeed today, we are working from a single global commons of antibiotic clinical value, rather than a large number of geographically distinct commons. This limits the effectiveness of incompletely applied solutions: education efforts that improve antibiotic use in one sector but not in another, or regulation that is enforced in some countries but not in others.

Foster and Grundmann boldly suggested that solving the tragedy of the commons for antibiotic resistance may ultimately lie in regulation resulting from a collective agreement to place societal needs before patient needs, and that this may only be achievable by letting some patients go untreated [19]. This recognizes that the individual optimum for antibiotic therapy involves at least as high, but most likely higher, use of antibiotics than the societal optimum requires. This establishes a tragedy of the commons when combined with the negative externality of resistance **(Figure 2)**. We suggest that this societal optimum point represents the target of a global stewardship of antibiotics: a point at which sustainable access to effective antibiotics is available for all those who need them.

Additional data are still needed to understand where the societal and individual optima lie. For individuals (humans and animals), this includes a better understanding of the benefits of leaving different infections untreated: for instance, fewer immediate side effects, leaving the microbiome unaffected [31] and a lower likelihood of resistant bacteria in the future [32]. For society, our understanding is still poor concerning the costs and benefits of treating and not treating specific infections in humans, veterinary medicine and agriculture. Even more unclear are the consequences in terms of resistance, particularly in poor resource settings [19]. This lack of information contributes to the bounded rationality that characterizes each individual decision to use an antibiotic, and reinforces the tendency toward decisions that favor the individual optimum rather than the societal optimum. Even if these data were available, an important ethical challenge remains: defining the extent to which individual care in human and animal medicine can be deprioritized in order to target a society optimum. This requires global debate with participation from across society, and eventually consensus decisions and coordinated actions.

Complexity within the commons

We have been examining a single commons **(Figure 1)** that represents the total potential and available clinical value of all existing antibiotics. This simplification is helpful for demonstrating the possibility of a tragedy scenario. However, it also conceals the complexity inherent in linking an individual decision to use antibiotics to the total global context of sustainable antibiotic use. Examining the contents of the commons in more

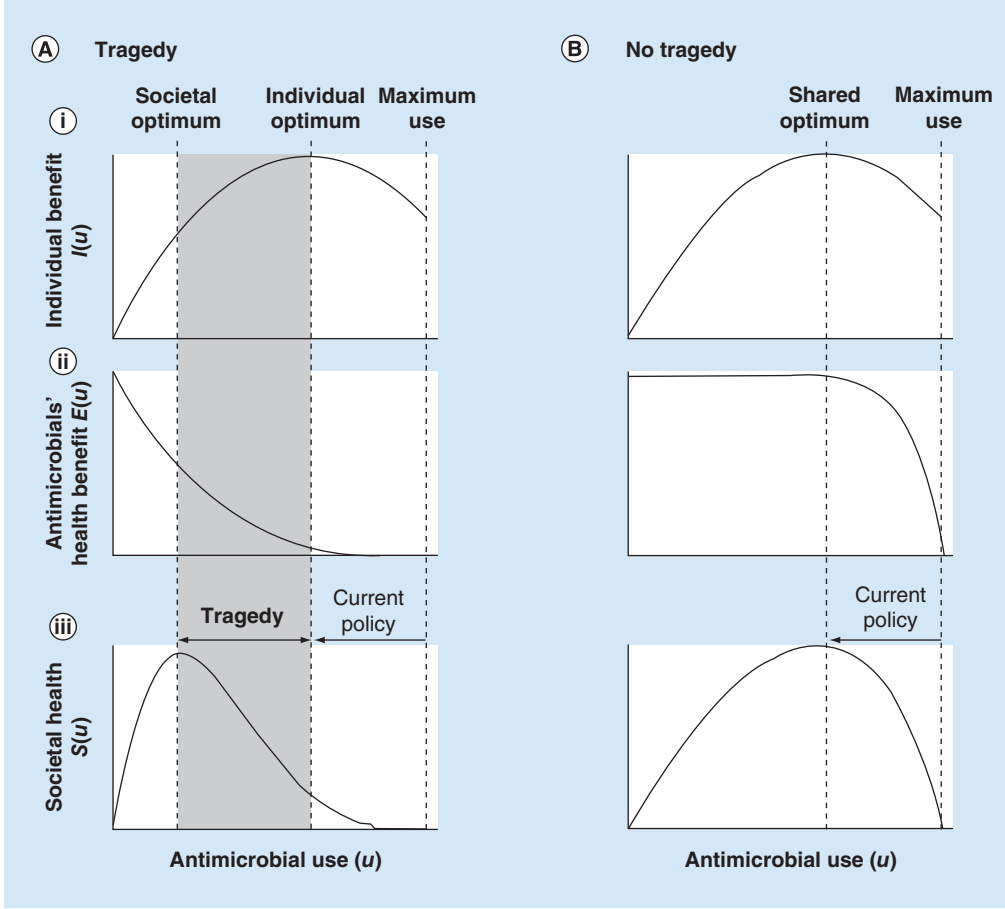


Figure 2. Tragedy scenario for antibiotic resistance. **(A)** Tragedy scenario. **(i)** Individual health benefit from antibiotic use *I(u)*. **(ii)** Cost to societal health from decreased effectiveness of antibiotics *E(u)* as a result of the evolution of antibiotic-resistant pathogens. **(iii)** Overall effect of antibiotic use on societal health $S(u) = I(u)E(u)$. **(B)** Best-case scenario. Low-to-moderate antibiotic use has little impact on our ability to treat later infections and is only weakly costly to societal health *E(u)*. This means there is no tragedy. The true nature of *E(u)* is unknown but it is a function of investment in innovation in new antibiotics and conservation efforts including antibiotic stewardship, public health and infection control, which may be able to shift us from scenario **(A)** to scenario **(B)**. (legend abbreviated from original description in [19]).
Modified with permission from [30].

detail reveals some of this complexity. The main commons **(Figure 1)** consists of multiple overlapping subcommons, each representing the clinical value for specific combinations of antibiotic classes and bacteria **(Figure 3)**. In practice, each of these individual subcommons is also subject to a tragedy situation.

Using the commons metaphor, **Table 1** describes many of the challenges involved in contextualizing individual antibiotic use into a total aggregate use and indicates where large gaps in our knowledge and understanding currently exist. This complexity results in uncertainty at the level of individual prescribing decisions and predisposes them toward the individual optimum, rather than the societal optimum. This is particularly the case in human medicine, where there is also a more widely accepted ethical duty to provide optimum treatment for the individual.

In summary, a very large number of individual components are involved (users, subcommons, rules and factors influencing access), and these have multiple, dynamic interconnections. Individual uses of the subcommons result in unpredictable effects on the state of many different subcommons. The bounded rationality and complexity that characterize

individual antibiotic use decisions will predispose prescribers and dispensers to making choices that are close to the individual optimum, or worse than this, at the expense of sustainability. Committing to a global stewardship of antibiotics is an essential step toward initiating debate on how to balance individual and society optima, and toward designing, developing and implementing education and regulation efforts that could translate the societal optimum into individual decision-making to avert a tragedy of the commons scenario.

How are we using the commons around the world today?

In the next section, we will explore how the antibiotic commons are being used today in human healthcare in four countries: Uganda, India, China and France. These are, respectively, low income, low-middle income, high-middle income and high-income countries. **Table 2** summarizes key national socioeconomic and health indicators data for each country, as well as national activities related to responsible antibiotic use in human medicine.

• Who are the users of the commons?

Outpatient antibiotic use accounts for the majority of antibiotic consumption worldwide. In both France and China, pharmacy dispensing of antibiotics requires a prescription issued by a doctor: over-the-counter sales are illegal. In practice, over-the-counter sales of antibiotics are rare in France [34], and increasingly rare in some urban centers in China, but do still occur. In this respect, doctors in France and China can be seen as the major gatekeepers to antibiotics, and access to doctors is not a challenge for most people. Most outpatient prescriptions in France are written by general practitioners. In China, most outpatient prescriptions in urban and semiurban areas are written by

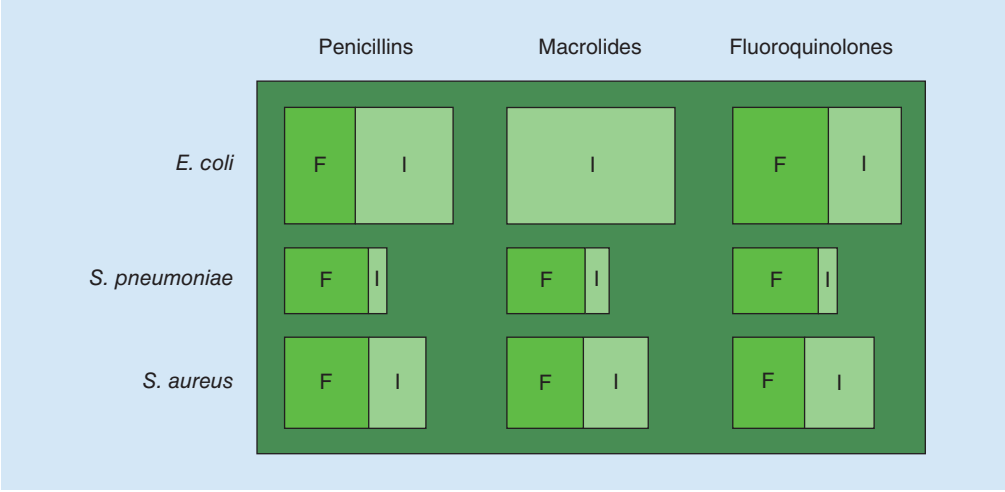


Figure 3. Multiple subcommons of clinical value. The number of subcommons is determined by the number of classes of antibiotics and species of bacteria. The size of individual subcommons is equal to the total number of bacteria within a species. Within a subcommons, ground can be fertile or infertile. Fertile ground (F) represents the bacteria in the species that are clinically susceptible (full or intermediate, for simplicity) to the specific antibiotic class, and infertile ground (I) represents the bacteria that are clinically resistant. The creation of a new class of antibiotics leads to the establishment of a new set of subcommons. A use of the subcommons is defined as a single course of antibiotics and has the potential to convert fertile ground into infertile ground. This includes many simplifications: all antibiotic use within the same class is considered equivalent; all routes of antibiotic use are considered equivalent; all course durations are considered to generally have the same effects on ground fertility. The main commons **(Figure 1)** is formed by combining together the individual subcommons for different bacterial species and identifying which individual bacteria are resistant to all classes of antibiotics (forming infertile ground) and which are susceptible to at least one class of antibiotics (forming fertile ground).
F: Fertile ground; I: Infertile ground.

doctors at general hospital outpatient clinics due to perceived lower quality of care in primary care facilities; in rural areas, prescriptions are commonly written by doctors working in small village clinics.

In both India and Uganda, antibiotics are commonly available through private pharmacies and drug stores (with or without a prescription), in addition to public health facilities staffed by doctors. There is frequently inadequate

Table 1. Challenges to responsible use illustrated by the subcommons.

Structure of the subcommons	
Number of subcommons and users	Large numbers of subcommons exist. There are also large numbers of potential users, from qualified antibiotic prescribers to individuals who self-medicate
Size of the subcommons	Many individual subcommons are vast, including the large reservoirs of bacteria that exist as commensals. Only a very small proportion of a total bacterial species are being exposed to antibiotics at any time point, representing the tiny fraction of the subcommons in active use
Renewability of the subcommons	The intrinsic renewability of a single subcommons represents the natural change of infertile ground to fertile ground. The rate at which this occurs is largely unknown but will vary between subcommons depending upon the evolutionary cost of maintaining different resistance mechanisms for different antibiotics and for different species of bacteria. Renewability rates may be very low in practice
Decisions to use the subcommons	
Multiple factors influence use of the subcommons	Clinical value should be the main reason to use a subcommons, but other factors, such as financial incentives and societal expectations, may affect how users select which subcommons to use. The needs and abilities of different users to respond to these factors change over time
Not all uses of the subcommons create the same clinical value	The same single course of antibiotics that saves the life of a patient with severe sepsis may on other occasions be used to treat a minor skin infection
Accessibility of different subcommons	The access of individual users to each subcommons is variable. It may be affected by stock availability, as well as local and national regulations
The need to use the subcommons can be reduced	Improvements in public health, sanitation and infection control can all reduce the incidence of infections, as can biosecurity measures in agriculture
Effects of using the subcommons	
Multiple subcommons are always used at the same time	Any antibiotic use will result in exposure of commensal bacteria (located on other subcommons) to the same antibiotic
False independence of individual subcommons	The states of subcommons are interconnected due to mechanisms of cross-resistance and the possibility of coselection of multiple resistance mechanisms. Changes in the fertility state of one subcommons can simultaneously affect other subcommons
The effects of using subcommons are unpredictable	The impact of a single use of antibiotics on the fertility of a subcommons is not constant (i.e., varies with each antibiotic class and bacteria species, and even varies within a single subcommons)
Individual uses of a subcommons have small effects	Even when a use of antibiotics leads to an increase in the number of bacteria resistant to that antibiotic, this number is still an extremely small fraction of the total number of bacteria on the subcommons
Timescale differences in effects	It takes a matter of a few seconds to commit to using a subcommons, and a few days to see clinical value. By contrast, significant changes in the state of the subcommons take place over many years
Information flows and feedback	
Monitoring of the subcommons is highly selective	Surveillance sampling of individual subcommons is typically from the small fraction of the subcommons that is causing infections at any time point
Users do not know which subcommons they are using	Most antibiotic use is empirical, in other words, given without knowledge of the specific (bacterial) cause, for the entire duration of the therapy
Users receive minimal feedback	Users may observe the clinical value of using a subcommons, but they rarely receive feedback on the direct effects that an individual use of the subcommons has on the overall state of the subcommons
The feedback users receive has limitations in interpretability	The feedback is normally based on the aggregate effects of large numbers of users and large numbers of uses of different subcommons, and will inevitably be time delayed

Table 2. Socioeconomic and health indicator data in Uganda, India, China and France with a summary of national activities related to responsible antibiotic use.

	Uganda	India	China	France
Population (millions)	39	1311	1371	67
Population living in rural areas (% of total)	84	67	44	20
GDP per capita (current US$)	676	1582	7924	36,248
Total health expenditure as (% of GDP)	7.2	4.7	5.5	11.5
Life expectancy at birth (years)	58	68	76	82
Under five mortality rate (per 1000 births)	55	48	11	4
Doctors (per 1000 people)	0.1	0.7	1.9	3.2
Pharmacists (per 1000 people)	0.01	0.6	0.3	1.1
National activities related to responsible antibiotic use				
Is there national surveillance of inpatient and outpatient antibiotic use?	No	No	Yes	Yes
Is there national surveillance of antibiotic resistance with samples from representative regions within the country?	No	No	Yes	Yes
Is there a formal national program or committee responsible for improving antibiotic use?	No	Yes, since 2011	Yes, since 2009	Yes, since 2001
Are there national guidelines on antibiotic use for common infections?	Yes	Yes, in draft format	Yes	Yes
Is continuing medical education on antibiotic prescribing mandatory for all prescribers?	No	No	Yes	No
Has there been a nationwide public education campaign on antibiotic use in the past 5 years?	No	No	No	Yes

Socioeconomic and health indicator data are primarily sourced from the World Development Indicators database of the World Bank [33].
GDP: Gross domestic product.

diagnostic support at health facilities, which has been used as a justification for prescribing antibiotics [35]. In both countries, problems with infrastructure and resources often drive large proportions of the population to private health facilities, and particularly in rural areas, many may have limited access to effective antibiotics [36]. In India, 46 antibiotics were recently subcategorized in Schedule H1 by the national drug regulatory body, and so should only sold on prescription [37]; in practice, these antibiotics may be prescribed by unqualified practitioners and practitioners from Indian Systems of Medicine. In Uganda, drug shops can be operated by any qualified health personnel, but their presence is not required at the counter; this has led to many drug shops being staffed by individuals with no healthcare qualifications. Self medication is also widespread in Uganda: in one study in Northern Uganda, nearly 75% of the community practiced self medication with antimicrobial drugs [38]. In aggregate, a large proportion of antibiotic use in both Uganda and India occurs without any contact from individuals who have had training in appropriate antibiotic use.

Inpatient antibiotic use is led by doctors in all four countries. Although inpatient use accounts for only a small fraction of total antibiotic consumption, it is where newer and broader-spectrum agents are most frequently used, and is an important setting for spread of multidrug-resistant organisms. Nonclinical factors can influence antibiotic use in hospitals: for example, in China most hospitals are reliant on income from selling drugs in order to cover operating costs [39,40].

Gatekeepers to the commons exist to some extent in all four countries. However, their large numbers (e.g., 2.5 million doctors in China, over 700,000 pharmacists in India) mean that it is difficult to monitor their activities and assess to what extent their uses of antibiotics are in keeping with an individual or society optimum. Furthermore, there is often little restriction placed on their ability to choose which antibiotics to prescribe or dispense, and their choices may be influenced by a wide variety of factors beyond clinical need.

• How is use of the commons regulated?

All countries have national drug agencies or equivalent organizations, whose role is to regulate the licensing and imports of drugs into the country. Implementation varies between countries with lower income countries having less capacity to ascertain and control the quality of all drugs in the drug market. Uganda has a fledgling under-resourced pharmaceutical industry

that produces a very limited range and quantity of drugs, exposing the drug market to more powerful international producers; most available drugs are imports from other countries, especially Asia. Uganda also has porous borders that lead to movements of drugs that are difficult to control.

National essential drug lists indicate which drugs should be available at public healthcare institutions and are used in Uganda, India and China [41–43]. In practice, however, drugs on these lists are often not available. In India, one study found that the availability of essential medicines in public sector facilities ranged from 0 to 30% [44], a situation that is often caused by stock-outs. The government in Uganda has responded to stock-outs by passing the National Medical Stores Vote 116, which centralized the funding, procurement and distribution of medical supplies, but reports of drug shortages and stock-outs still abound. Shortages are also a problem in France and other European countries due to the limited number of drug producers for old antibiotics. For example, IV fosfomycin, ticarcillin-clavulanate acid, IV cloxacillin and IV oxacillin are currently out of stock in France with very limited availability to prescribers. These 'forgotten antibiotics' still have important clinical value, but this is often unavailable to patients and prescribers [45].

In 2011, the government in China began a nationwide 3-year special campaign for rational antibiotic use. The campaign was primarily focused on hospitals in urban areas and introduced many new targets and regulations, including an outlining of the roles, responsibilities and liabilities of health administrative authorities, medical institutions, hospital task forces and all categories of healthcare professionals. Supervisors were assigned to hospitals to enforce the actions during the campaign [46]. Rapid and sustained reductions in antibiotic use across many levels of the healthcare system have been observed following the campaign [47,48].

In France, a national antibiotic plan led by the Ministry of Health has been in place since 2001, and a dedicated task force was set up in 2015 to suggest priority actions [49,50]. An antibiotic stewardship program certification is required in hospitals and has been a trigger for change. In contrast, there is currently little national regulation on use of antibiotics in outpatient settings.

Regulation is used in all four countries to improve how antibiotics are used; however, this is largely directed at reducing misuse and overuse at an individual level, rather than purposefully targeting a level of antibiotic use that is sustainable for society. Regulation can also be used to support access to effective treatment, but additional challenges remain in all four countries, from lack of licensing to stock-outs.

• What efforts exist to educate users of the commons?

Doctors who acquire the right to prescribe antibiotics receive education on antibiotic use during their training in all four countries, but this does not always include a component on responsible use. In China and France, and to a lesser extent in India, programs of continuing medical education are available to doctors; these can include sessions on responsible antibiotic use. The 3-year national campaign in China included mandatory education sessions for doctors on antibiotic use. India has made several efforts to educate on the importance of responsible antibiotic use, including the Antibiotic Stewardship, Prevention of Infection and Control program initiated throughout the country by the Indian Council of Medical Research, and the signing of the Chennai Declaration [51,52]. Education for pharmacists and drug store owners in Uganda and India are comparatively less developed, particularly in rural areas.

A mixture of national and regional clinical antibiotic guidelines exist in all four countries [53–55]; these typically indicate appropriate selection of agent, dose, route of administration and duration for specific infections. These guidelines are at different stages of maturation and connection with surveillance data on bacterial resistance rates. The use of guidelines is currently not enforced in any of the four countries. France has implemented some regional networks coordinating antibiotic stewardship in outpatient settings with expert advice available for all prescribers [56].

In summary, many of the prescribers and dispensers using the commons today have received little education on how to use the commons responsibly and may have limited access to up-to-date guidance on which commons should be used.

• What systems exist to monitor & inform users about the state of the commons?

Two types of information about the state of the commons may be relevant to its users: first,

information relating to a single use of antibiotics; second, a more general knowledge of the overall state of the commons. Cultures and susceptibility testing can provide prescribers with precise information on the type of bacteria causing an infection and its susceptibility to different antibiotics. The use of culture investigations varies significantly between countries, due to resource availability, cost and quality standards: whereas blood cultures are routine for all patients admitted to a hospital with sepsis in France, they are often used in China and India only when a patient fails to respond to initial therapy (especially in rural areas), and in many parts of Uganda the investigation may not be available at all. A consequence of this is use of unnecessarily broad spectrum antibiotics, as well as antibiotic use for nonbacterial infections, both of which are far from the individual and society optimum points; as resistance rates rise there is also the serious risk of undertreatment due to an inappropriate choice of antibiotics.

Knowledge of the overall state of the commons requires continuous surveillance of antibiotic susceptibility patterns in clinical and community bacterial isolates. Developing and implementing surveillance systems for antibiotic resistance and antibiotic use form part of the WHO global action plan [15]. In France, microbiology services and monitoring of antibiotic use and resistance are of excellent quality, and national policies with regional coordination are usual practice. High-quality data are quite easily available on quantity of antibiotics prescribed in hospitals and in the outpatient setting [57]; however, almost no mandatory monitoring of quality indicators of antibiotic use is currently in place. The French infectious diseases society has been conducting yearly national surveys assessing antibiotic prescriptions and antibiotic stewardship programs in hospitals for many years, but participation is voluntary [58]. In hospitals, regular audits of antibiotic prescriptions are recommended and are one of the hospitals' certification indicators [59], but the results are not publicly reported.

In China, a national antibiotic consumption surveillance (MOHCAS) and antibacterial resistant surveillance network (MOHNARIN) was set up in 2005, in which more than 1300 hospitals are included. The majority of hospitals participating in the network are located in urban areas. The yearly surveillance data are submitted to local healthcare authorities and have also informed national policy developments [55].

The WHO attempted to develop model surveillance sites for antibiotic use at three centers in India [60]. Sustainability and funding issues meant that the monitoring could not continue beyond 2 years. Surveillance of antibiotic resistance has also occurred at different timepoints through a few networks (SENTRY, INSAR, NCDC), but this has been fragmented, often focusing on particular microorganisms, and still remains far from comprehensive or sustainable. In Uganda, a baseline situation analysis led by the Uganda National Academy of Sciences is currently ongoing, which hopes to inform development of a national surveillance system for antibiotic resistance [61].

Overall, knowledge on the state of the commons is limited both by resource availability and the representativeness of sampling strategies. There is little linking between the state of the commons and antibiotic use, and the information flows back to prescribers and dispensers that could inform future antibiotics uses are poor.

• Is use of the commons directly linked to mechanisms that help maintain, renew or improve access to the commons?

The clinical value of the commons can be partly maintained through antibiotic stewardship efforts and renewed through the development of new classes of antibiotics. There is no direct mechanism in any of these countries that directly links use of the commons with an investment in resources to maintain, renew or improve access to the commons. Although financial profit is made from the use of antibiotics by many different stakeholders, there is currently no direct link to this profit being used to create sustainable access to effective antibiotics.

Conclusion: toward a global stewardship of antibiotics

We have described two dimensions of responsibility: responsible practices, and being responsible with how we decide to use, maintain and renew the unique clinical value of antibiotics. We portray this second dimension as an obligation to provide sustainable access to effective antibiotics for humans and animals. Fulfilling this obligation moves us toward a global stewardship of antibiotics. Individual and society optimal levels of antibiotic use are likely to be different, and this difference creates the potential for a tragedy of the commons scenario. In practice, our efforts to improve antibiotic use are

largely targeted at an individual optimum, but we frequently fail to reach even this.

First, we need to acknowledge our responsibility to create sustainable access to effective antibiotics at the highest of global political levels. The upcoming United Nations general assembly could be the most appropriate opportunity for this.

Second, this acknowledgment must be accompanied by greater resource commitments and coordinated efforts across all levels of societies. The tragedy of the commons analogy highlights many challenges to responsible antibiotic use at the level of the individual prescriber or dispenser, and at the level of society. We must appreciate and act on the great differences that exist today between countries of different socioeconomic levels in their abilities to promote responsible use of antibiotics. Many low- and middle-income countries need to find ways to improve both access and conservation simultaneously. An example of a possible development would be the creation of a global fund for antibiotic stewardship. Antibiotic stewardship has continuously suffered from a lack of funding, despite the gains it brings likely being quite cost effective compared with the development of new classes of antibiotics [3]

Third, we need to discuss the ethical implications of a difference between a society optimum and individual optimum level of antibiotic use. This may mean accepting on a society-wide basis that not all bacterial infections need antibiotics, with the consequence that less antibiotic use, for the common good, will likely cause a slight increase in the rate of some bacterial complications, in some patients. Attempts to prioritize the society optimum over the individual optimum will need to be supported by regulation and education that empowers individual prescribers and dispensers, as well as broader education efforts that enhance public understanding. A key barrier to effective regulation in poor resource countries will be existing weaknesses in the health system: creative solutions are needed to address these.

Fourth, we have to recognize how our existing systems and subsystems often contribute to usage that is worse than even the individual optimum. These systems may need radical redesigning or repurposing in some instances. A lot of our efforts so far have involved tinkering with individual components in the system, but we should think more generally about how our regulations, information flows and purposes influence our behaviors [25]. Each country developed its own subsystems, largely inspired by subsystems for other medications which do not generate the negative externalities that antibiotics do, and so are not adapted to the specificities of antibiotics.

We end by asking: what would you like to tell your grandchildren? The direction we are heading in at the moment: we were responsible for depleting the world of clinically valuable antibiotics over the course of a handful of generations. Or: we were collectively responsible for establishing the means to ensure sustainable access to effective antibiotic access for all who need them.

Future perspective

We believe that a global multisector consensus will soon be reached on actions needed to preserve the clinical value of antibiotics, and this will involve a recognition that the individual optimum and societal optimum can differ. This should lead to an increased availability of resources, assisted by the WHO global action plan and the development of national action plans. As a result, a shift will occur in the conceptualization of antibiotic resistance to a broader societal issue centered on sustainable access to effective antibiotics. This global consensus will allow a gradual migration toward the concept of global stewardship of antibiotics, in addition to and in collaboration with antibiotic stewardship at the level of individual clinical decision-making. In the coming years, transnational policies will be formed across human and animal healthcare and will be particularly valuable for conservation efforts.

The large implementation gap that currently exists for conservation efforts will start to be addressed, partly through dedicated funding for antibiotic stewardship activities. These interventions will increasingly draw on lessons from behavior change theories, which will increase their effectiveness. Health systems strengthening efforts will help improve access to existing effective antibiotics in poor resource settings. Comprehensive attempts will be made at improving the education of prescribers on clinical diagnosis of infection and responsible individual prescribing, throughout their clinical careers; regulation at different levels in human healthcare and agriculture will guide individual prescribers and dispensers toward more sustainable patterns of antibiotic usage that recognize differences between society and individual

optima. Hospitals will continue to act as role models in many settings, with effective interventions trickling down through the health system.

A point of resilience in our current systems has been the availability (existence, stocking and affordability) of multiple antibiotic classes for a single bacterial infection. Due to rising rates of resistance, the extent of this resilience has eroded, driving increases in healthcare costs, morbidity and mortality. As we become more aware of the extent of these costs, particularly as a result of better data gathering in low- and middle-income countries, more resources must be mobilized at a global level. At the same time,

EXECUTIVE SUMMARY

What is responsible use?

- Problems of antibiotic access and excess coexist in the world today and are compounded by rising rates of antibiotic resistance. We introduce two dimensions of responsibility to this context.
- The first dimension is responsible practices. A wide range of clinical and nonclinical factors influence how antibiotics are used. In aggregate, these lead to large volumes of overuse and misuse, from a purely clinical viewpoint. An aim of antibiotic stewardship efforts is to minimize these unnecessary and inappropriate uses.
- The second dimension is being responsible. The clinical value of individual antibiotics erodes with their use: active efforts are required to preserve, maintain and renew this value. We contend that the discovery of antibiotics has created a broad global obligation: to ensure sustainable access to effective old and new antibiotics for all those who need them. This requires linking conservation, innovation and access efforts.
- Enacting this obligation will result in a global stewardship of antibiotics.

How do we combine our responsibilities?

- The two dimensions of responsibility are inter-related; efforts to achieve both should be coordinated.
- A critical knowledge gap exists: to what extent does individual antibiotic use need to be adapted in order to provide sustainable access to effective antibiotics? This in turn raises an ethical challenge that must be debated: are we prepared to on occasion provide less than optimal treatment for individuals to sustain the effectiveness of antibiotics for society as a whole?
- In practice, the ability of individual prescribers and dispensers to account for the broad consequences of a single use of antibiotics is limited by two factors: incomplete information on consequences, and complexity in contextualizing these consequences.
- These limitations result in patterns of antibiotic use that tend to prioritize the individual patient at the expense of providing sustainable access for all.

The tragedy of the commons

- Applying the metaphor of the tragedy of the commons to antibiotics highlights the negative consequences of differences between a society optimum and an individual optimum for antibiotic use.
- The commons metaphor also reveals the complexity in linking an individual decision to use antibiotics to the total global context of sustainable antibiotic use.
- Examples from Uganda, India, China and France illustrate the challenges and successes we face in managing the real-world commons of antibiotics.

Toward a global stewardship of antibiotics

- Recent developments, such as the adoption of the WHO global action plan on antimicrobial resistance, support a move toward a global stewardship of antibiotics, although this obligation toward sustainability has yet to be acknowledged at the highest of global political levels.
- To create sustainable access to effective antibiotics will require a whole-of-society approach to responsibility. We will need to address the widespread implementation gaps in antibiotic stewardship, while acknowledging the limitations of individual prescribers.
- We must recognize how our existing systems and subsystems produce antibiotic usage that is often worse than even an individual optimum, and find ways to target a societal optimum that is compatible with sustainability.

there will be a greater need to ensure stocks of a broader range of antibiotics, even to which widespread resistance exists, since these will often be the options needed in individual cases. Improved diagnostics, including susceptibility testing, will also change how antibiotics are used in many settings: empirical broad-spectrum therapy will gradually become less necessary as targeted therapy can start earlier and unnecessary treatments can be avoided.

New classes of antibiotics are likely to become available, and potentially as a result of new models for research and development. This will provide important opportunities to collectively agree on the most responsible ways in which to implement their usage into our existing systems: financial incentives, marketing permissions, licensing strategies and dispensing rights are all important considerations. Innovation of alternatives to antibiotics, such as improved symptomatic treatments, may have an important role to play in reducing the perceived need for antibiotics for conditions that are not life threatening.

Finally, improved health education for the general public combined with a rising public awareness that antibiotics are a unique and precious class of drugs may help lower patient expectations for antibiotics for minor conditions, and increase their end adherence to antibiotic regimens.

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