The tragedy of antimicrobial resistance: achieving a recognition of necessity

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When moderate benefits might accrue to individuals, the absence of incentive for a more valuable common good can lead to consequent societal catastrophe. Proposals for dealing with this type of problem have been examined within multiple, typically economic or ecological frameworks. Antimicrobial resistance is a global and growing anthropomorphic problem. Pathogen susceptibility to antimicrobial drugs is a resource, whose exploitation has been likened to a Prisoner's Dilemma game or a Hardin-type tragedy of the commons. As with actual commons, motivating altruism and enforcing favourable outcomes are potential strategies for preserving an antimicrobial susceptibility commons. However, unlike the prototypical tragedy of the commons example of an overgrazed pastureland, users of the antimicrobial susceptibility commons are often blind to virtually complete deterioration of the resource, precluding timely implementation of interventions for control. Collection and dissemination of information about the state of the susceptibility commons is essential for achieving a 'recognition of necessity' and for moderating the preservation of susceptibility. The most reliable information can only come from the dissemination of drug susceptibility data collected and compiled by laboratories. In developing countries, enhanced access to limited quantities of a smaller repertoire of antimicrobials is often coupled with a higher infectious disease burden, resulting in a considerably strained commons where the need to provide information to support and guide resistance containment is most pressing.

Keywords: Antimicrobial resistance, drug resistance surveillance, prisoners' dilemma, tragedy of the commons.

ANTIMICROBIAL resistance is compromising our ability to treat infection and currently represents a major roadblock for global disease control[1]. More than 60% of *Staphylococcus aureus* isolates recovered in some US and UK hospitals in recent times have been methicillin-resistant *S. aureus* (MRSA). Other multidrug-resistant pathogens such as vancomycin-resistant enterococci and multiply-resistant Gram-negative rods like *Acinetobacter baumanii* and *Pseudomonas aeruginosa* are emerging and spreading rapidly[2]. Community-acquired infections caused by organisms such as MRSA and *Mycobacterium tuberculosis* are becoming increasingly common in industrialized countries. In addition to these organisms, many developing countries are battling multidrug-resistant enteric bacteria and malaria parasites[3,4]. Extensively-resistant *M. tuberculosis*, quinolone-resistant Salmonellae and vancomycin-intermediate *S. aureus* represent recently emerged pathogens that can cause potentially untreatable infections; something that human-kind has not faced in almost three-quarters of a century.

Ehrlich[5] foretold an era of drugs that could destroy pathogens without harming their hosts but it was many years later before humans created a drug susceptibility 'resource', which is the foundation for Ehrlich's principle of chemotherapy. The semi-serendipitous discovery of penicillin by Alexander Fleming is a critical milestone because it spurred the discovery of similar agents produced by some micro-organisms, which could inhibit others[6]. These antibiotics became a mainstay of clinical care, revolutionizing treatment for patients with bacterial infections. Thus, humans created a chemotherapeutic sphere where infecting organisms could be eliminated, preserving the life of the host. In addition to antibiotics, which are natural products, other effective antimicrobials have been chemically synthesized. The term antimicrobial, being all-encompassing is employed here.

The age of antimicrobial chemotherapy began with a period of chemotherapeutic optimism during which it was thought that antibiotics would relegate infectious diseases to the pages of history and the 'book on infectious diseases' was described as being all but closed[7]. By the 1980s, it was clear that a significant proportion of this optimism was misplaced and that infectious diseases would continue to threaten human and animal welfare[8]. Infection continues to be the major cause of illness and death in most tropical countries. There and elsewhere, new pathogens were emerging, and HIV and medical science created susceptible hosts for opportunistic pathogens. At the same time, previously effective therapies were unexpectedly being overcome by microbial genetic innovation, assisted by selective pressure from excessive and indiscriminate antimicrobial use. A period of chemotherapeutic challenge has replaced that of optimism and there is now a pressing need to tackle infectious disease challenges in general, and resistance in particular, to stem the tide. If the current trajectory continues unabated, we could reach a third, post-antimicrobial period.

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Antimicrobials provide almost instant gratification in the form of infectious disease cure, where necessary, and in the many other instances they are administered unjustifiably, a placebo effect. Resistance, an unavoidable adverse consequence of antimicrobial use, is magnified when antimicrobials are used when not indicated, too little drug is used per infection, or when the duration of therapy is too short. Resistance is essentially a conservation problem arising from the natural tendency to prefer immediate to long-term rewards, even when the latter are of greater value[9]. The archetypical model for overcoming resistance is a disposable drug strategy – as resistance appears, older drugs are discarded and replaced with new drugs with novel mechanisms. A disposable system can only be sustained if the rate of new drug development exceeds that of resistance emergence. Presently, due to scientific, economic and political constraints, microbes develop resistance faster than humans develop antimicrobials. Even if the rate of antimicrobial development were to accelerate after the current dip[10], a significant lag period must be expected because new drug development takes almost two decades.

Antimicrobial resistance has most commonly been the concern of clinicians and biologists. Although a biological phenomenon, resistance is in fact a public health and socioeconomic problem and linked to behavioural patterns. As with similar problems, solutions are just as likely to come from the social as from the natural sciences. There is therefore a need for radical and interdisciplinary thinking about resistance control and antimicrobial conservation.

A resistance dilemma

The invention of antimicrobials created an exploitable and potentially finite microbial susceptibility resource[11,12]. The growing resistance paradigm that threatens this resource can be represented by the game theory scenario referred to as the 'Prisoner's Dilemma'[13]. In a simple Prisoner's Dilemma setting, two guilty individuals are accused of a collaborative crime for which their testimony will constitute evidence. Each prisoner must independently decide whether to cooperate with his colleague or defect. If both cooperate, neither can be convicted. If one defects, the other is convicted and the defector rewarded and if both defect, both loose[14]. The structure of payoffs in the Prisoner's Dilemma is such that the stable strategy for each player is to defect rather than cooperate. If the prisoners are permitted to communicate with each other, the stable outcome is changed: they will inevitably choose to cooperate. When information cannot be shared, each participant defects simply because there is a chance that the other will defect. Thus, if the resistance problem is to be viewed as a Prisoner's Dilemma, a solution might be transparency about the magnitude and consequences of antimicrobial use, that is surveillance. The outcome of communication in the antimicrobial resistance dilemma is even better than for the pure Prisoner's Dilemma in that there is the potential for the development of resistance to be slowed or even reversed (Figure 1).

A simple Prisoner's Dilemma game is convenient for highlighting the importance of surveillance in resistance control and compelling in other ways but is too simplistic to account for many of the nuances of the multiplayer, non-symmetric resistance problem. There are other public goods games which illustrate one of more aspects of the resistance problem but the closest parallel to the problem of resistance appears to be a more nuanced Prisoner's Dilemma known as the 'Tragedy of the Commons'.

The antimicrobial resistance tragedy of the commons

The most frequently referenced version of the tragedy of the commons was originally described by Hardin[15] as overexploitation of exhaustible collective property occasioned by population increase. The consequence is destruction and a loss to all users of the common resource. Hardin illustrates the tragedy with the example of a common grazing ground to which all herdsmen have access for the use of their cattle. The individual herdsman who adds to his herd maximizes his own gain to the detriment of the community. Were every user to do likewise, the commons would deteriorate until it ceases to be a resource for all. Hardin extended this scenario to many population-based resource problems including the erosion of public parks, the fishing of common seas and pollution. Others have included additional environmental and economic resource problems including firewood crises in developing countries, acid rain, traffic congestion, and even US Congress overspending problems (reviewed by Ostrom[16]).

As initially observed by Baquero and Campos[17], a number of features of the antimicrobial resistance problem make it almost a tragedy of the commons exemplar. There is a lag period before a commons becomes limited because hazards of the environment keep the population in tune with the resource capacity. In the same vein, in the years following the discovery of penicillin, the difficulty in obtaining sufficient amounts of the drug (the drug was extracted from the urine of the earliest patients for reuse) ensured that overuse did not occur. The idea of applying an antimicrobial without a precise indication was untenable in those days so that use of these drugs was kept below a threshold, analogous to under-grazing of Hardin's commons at a time when the numbers of users is kept below 'the carrying capacity of the land'. When we learned to produce antimicrobials in large fermentation vats, and through chemical synthesis, supply became, for all intents and purposes, unlimited and a

A. The Prisoner's Dilemma: In the absence of communication, it pays to defect

Prisoner 1 → Prisoner 2 ↓	Cooperates with the other prisoner	Defects and accuses Prisoner 2
Cooperates with the other prisoner	Both are released	Prisoner 1 is rewarded, 2 is punished
Defects and accuses Prisoner 1	Prisoner 2 is rewarded, 1 is punished	Both are punished

B. The antimicrobial resistance Prisoner's Dilemma: In the absence of surveillance, it pays to deliver health care in complete disregard to resistance emergence and spread

Locality 1 → Locality 2 ↓	Implements expensive interventions to combat resistance	Continues health care delivery in complete disregard to resistance
Implements expensive interventions to combat resistance	The emergence and spread of resistance is slowed	Resistance is unlikely to be contained, expense of (2) is wasted, (1) has conserved expenditure
Continues health care delivery in complete disregard to resistance	Resistance is unlikely to be contained, expense of (1) is wasted, (2) has conserved expenditure	The resistance problem grows unabated

Figure 1. In an antimicrobial resistance Prisoner's Dilemma game, it pays to use antimicrobials in complete disregard to their effect of resistance emergence and spread in the absence of surveillance.

tragedy set in. Using antimicrobials, even in the most remote chance of an infection, was perceived to be beneficial as it is in the short term. According to Hardin[15], the paradigm is best applied to those examples for which there is no technical solution. Developing new drugs has proved to be too slow to accommodate the escalating rate of resistance. Other technologies for fighting resistance such as resistance-proof drugs, alternatives to chemotherapeutics, or chemical agents that could reverse resistance are emerging at an even slower rate. Thus, although there may be changes with time, at present, the problem of resistance does not have a feasible technological solution now.

Previous models of the antimicrobial susceptibility commons have sketched the resource as is typical in industrialized countries where prescription laws are in operation and the burden from infectious disease is modest[17,18]. This article aims to produce a more global picture and is deliberately biased towards the problem in developing countries where there are often mitigating factors that are overlooked when resistance is examined, more commonly, from other points of view. Nonetheless, the antimicrobial susceptibility resource I attempt to describe is global and worldwide commitment is needed for conservation.

A global view of the antimicrobial susceptibility commons

Baquero and Campos[17] as well as Foster and Grundmann[18] have sketched an antimicrobial resistance tragedy along similar lines as put forward by Hardin. The parallels are striking but it is also important to emphasize features of the antimicrobial susceptibility commons that are distinct from a true Hardin 'commons'. The tragedy is global, but the precise nature of the commons varies from place to place and access is not the same for each potential user. In countries where antimicrobials can be obtained only by prescription, access is restricted by prescribers, who are analogous to gatekeepers in Hardin's public park example. Where antimicrobials are not regulated, it is tempting to view the commons as being freely open to all and thus more similar to a real commons, where, in the words of Hardin[15] free access 'brings ruin to all'[19]. In actual fact, access to the commons in those places is restricted in a less rational way. First, not everyone can afford antimicrobials and cost is a major factor to selection. Secondly, in some areas, availability of specific antimicrobials may be limited so that the commons cannot be exploited by all who would like to do so. These limitations offer an explanation for why, in developing countries, resistance tends to be more prevalent in urban areas than rural locations[20,21].

Until recently, there were distinct and almost non-overlapping bacterial 'Commons' in industrialized countries like the USA and developing countries like Nigeria. From the late 1980s, Americans had access to second- and third-generation cephalosporins, beta-lactamase inhibitors and quinolones for dealing with bacterial infections. In spite of an overall greater per-capita need for antibacterials, economic barriers restricted access to newer drugs for the majority of Nigerians. Thus, at the time, America was one generation of antibacterials ahead of Nigeria so that the effective 'commons' were actually different. By the time an antibacterial drug became universally available in Nigeria, it had been discarded or at least relegated to use in non-life threatening infections in America. This pattern of use has promoted accelerated clonal expansion of resistant strains or horizontal dis-

Table 1. Resistance containment strategies that require collective action

Goal	Action	Implementation level
Develop new drugs	Therapeutic development incentives	National/international
Drug use programmes	Antimicrobial mixing, combinations or cycling	National/international
	Antimicrobial quality assurance	National/international
Reducing antimicrobial use	Improved diagnostic precision	Health providers*
	Antimicrobial prescription control	Health providers
	Antimicrobial use disincentives	Health providers, patients/the public
Preventing dissemination of resistant organisms	Resistance surveillance, 'Search-and-destroy' programmes	National/international
	Accelerated access to diagnosis and treatment irrespective of ability to pay	National/international National
	Improved sewerage and sanitation systems	Health providers
	Infection control in hospitals	Health providers, patients/the public
	Hand-washing	

*Refers to sanctioned as well as unsanctioned providers.

semination of resistance genes from countries where they emerge to others where microbial transmission is efficacious[22,23]. More recently, drug development rates have slowed and resistance has continued to escalate worldwide, allowing the pools of available antimicrobials to all but unite. Nigerians have been forced by resistance to pay for newer, more expensive drugs and the Western world had come close to the end of the list of new drugs. Currently, the quinolones and second- and third-generation beta lactams are antibacterials of choice in Nigeria, the US and the world over. Our emerging data suggest that although the quinolones were introduced much more recently to West Africa than Western Europe and North America, resistance is already highly prevalent in Nigeria[24]. Once resistance has emerged somewhere, it spreads rapidly without regard for geographic or other boundaries[23]. At no time before the present has the need to come to a 'mutually agreed-upon'[25] solution to the resistance problem that is effective and global.

All bear the brunt of globally disseminated multi-drug resistant pathogens but like climate change, the worst sufferers from a resistance catastrophe will be the poor[4]. The originator of the tragedy of the common's paradigm, Hardin became infamous for stating the poor, if allowed into the boat of the rich would sink all[26]. Over time, patent laws, poor surveillance and weak health systems have essentially limited weight of the poor in the antimicrobial boat, without addressing the fundamental problem of resistance. Poor people are more likely to become infected, less likely to access appropriate antimicrobials and even less likely to do so if they have a resistant infection[4,27]. However, as the repertoire of available antimicrobials becomes smaller, a failure to grant the poor sufficient access to the commons consigns them to remaining infected, and therefore infectious, reservoirs. Thus, unless solutions are all-inclusive, everyone remains at risk. It would be overly naïve to speak of averting the tragedy, since it is already here[3,28,29].

Dealing with the tragedy: coercion or cooperation?

The World Health Organization (WHO) has compiled a global strategy for resistance containment[29], which aims to reduce selective pressure by curtailing irrational antimicrobial use, to prevent the spread of resistant organisms, and to encourage the development of new antimicrobials. The WHO report details recommendations that could be implemented at national, prescriber and consumer levels, many of which need to be enacted collectively (Table 1). There is no plan for implementation: countries are expected to prioritize implementation of the numerous interventions according to local needs and abilities but very little of the data on which the strategy is based was derived from developing countries[30]. Education of all stakeholders is one of the most commonly advocated resistance control strategies. Hardin states that education can 'counteract the natural tendency to do the wrong thing' but because evolution favours denial, it must be frequently refreshed. Educational interventions can produce a significant if modest change in risk behaviour associated with resistance[31] but must be repeated several times in each generation. Because the background, actions and response of each user cadre is different, tailored educational programmes are needed for prescribers, other health workers, health policy makers, agriculturists and consumers[32]. Education will always be an essential component of resistance control but only as means to implement structured interventions[29].

Hardin[15] suggested that all strategies for dealing with a tragedy of the commons are objectionable but that at least one must be selected. Early solutions to the tragedy of the commons have focused on coercive, state-managed solutions or incentive-driven privatization. A role for privatization in antimicrobial conservation has yet to be seriously exploited. Presently, innovators have a short period to market each new drug aggressively before patent expiration[33,34]. Patients only take an antimicrobial drug for a short period, limiting total sales. Development of antimicrobial resistance further reduces the profit potential for antimicrobials. Thus the current patent structure provides little incentive to develop much needed antimicrobials and no incentive to conserve them. The picture is worsened for antimicrobials for neglected diseases or infections that are most prevalent in developing countries, where a traditional exploitable market may not exist[35].

Foster and Grundmann have cautiously but courageously proposed withholding antimicrobials from some patients[18]. This solution may appear extreme but coercive solutions for tragedies of the commons are not pleasant. Hardin's idea of coercion was not brute force but rather pre-agreed coercive laws or taxes. For example, imposing an individual cost to access to the commons, such as an antimicrobial use levy could serve as a more effective means than outright prohibition[18]. In countries where antimicrobial use is regulated, National Health Services or Health Insurance could elect to reimburse the cost of diagnosis but not of antimicrobial chemotherapy, providing a disincentive for patients to demand unneeded antimicrobials[36].

Currently prescription drug legislation provides an inadequate shield for the susceptibility commons, even in countries where these laws are enforced. Further protection could potentially be gained by tightening prescriber access to antimicrobials, so that these drugs can only be ordered in very specific situations. This creates a '*Quis custodiet ipsos custodies?*' or 'Who shall watch the watchers themselves?'[15] quandary on one hand but does limit those who must be coerced to a smaller, well educated, if opinionated group, which prefers to police itself. Many hospitals have instituted extra gate-keeping on second- or third-line drugs. LaRosa *et al.*[37] found that prescription of restricted antimicrobials at an institution with one such antimicrobial stewardship programme occurred most frequently in the hour after 10 pm, when stewardship gate-keeping became inactive each night. Gatekeeper cheating is not the only barrier to curtailing use because in well-regulated countries, patients frequently go around the law – by pressurizing their prescribers or by seeking drugs from unofficial and unorthodox sources such as pet stores, illegal internet distributors or other countries[38–40]. Thus even though many studies report success with antimicrobial gate-keeping at many levels, this approach – as does any other coercive approach – requires highly effective policing for success. Effective policing must be paid for by owners of the common resource, who are in agreement on the coercive rules to be applied. Outside closed systems like hospitals, these criteria are difficult to meet, even where antimicrobial prescription is regulated. In countries where prescription laws are not enforced coercive containment strategies cannot be implemented. It is also unreasonable to enforce the prescription of antimicrobials by qualified professionals when there is a shortage of such professionals and a high burden of disease. Restricted access cannot be fairly implemented or properly enforced unless there are sufficient gate-keepers. There is currently no viable model for curtailing antimicrobial access from unregulated providers in developing countries save for the suggestion that such distributors should be proscribed, which in most cases has not occurred. The risk of a concerted rebellion in response to coercive attempts to salvage health-related commons is a real possibility in countries where governance unorganized, not trusted, or otherwise far from optimal, and policing weak[41].

McCay and Acheson[42] have observed that coercive strategies are the most commonly advocated for controlling the commons and although rules are yet to be enforced, this is the model favoured for resistance control. A preference for the hard-line coercive approach derives from a desire to propose a single solution to the tragedy and to unify different tragedies by proposing that they represent an identical cast from a single mold. More flexible analyses, which includes observations from case studies of different – typically small-scale – commons, have led others to propose cooperative preservation strategies[16]. It remains to be seen whether strategies that work in small-scale common resource problems can be scaled up to global problems, in part because the number and diversity of stakeholders is one of the variables predicting successful management of a shared resource[16].

There is experimental evidence for kin-cooperation in humans and non-human species[43]. Furthermore, in spite of the advantages that cheating proffers to the individual, human cooperative behaviour is highly developed and, even in non-kinship groups, humans cooperate better than economic theory predicts[44,45]. Because of the disconnect between action and consequence, indirect reciprocity would be more relevant to conserving antimicrobial susceptibility. Rewards for judicious antimicrobial consumers and prescribers, as well as those who reward them, could deter free-riders. Similarly, sanctioning non-cooperators might serve as a further disincentive for selfish action[46]. Finally, recent experiments suggest that if some groups are able to observe and appreciate success in resistance control in another group, they may be motivated to emulate them[47].

Recent experiments appear to suggest that group sanctioning may be more effective than incentives for appropriate use of the commons. This is true even when, as is usually the case, punishment can only be implemented at some cost[48]. In the absence of governing institutions, commoners can develop and maintain peer punishment systems. Fair punishment, such as that which could be 'mutually agreed upon' appears to increase cooperation at the start and to improve it over the long term[49]. The threat of sanction is not sufficient; defectors must be punished in order for the situation in the commons to evolve towards majority cooperation. In a sense, the experimental evidence demonstrates that 'mutual coercion, mutually agreed upon'[25] appears to work. Strategies for resistance control have however rarely considered incentives and have never explicitly included sanctions and it may be challenging to introduce them. The status quo is one in which majority of users and gate-keepers are defectors and therefore costs will be incurred to develop a sanctioning system from scratch, particularly one that will make sanctioning advantageous and therefore be sustainable[48,50].

Reputation might be one of the most straightforwardly invoked incentive, or sanction, to assist in resolving the tragedy[51]. Among health professionals, reputation is key to wealth and personal value and is the basis for many prescriber-targeted interventions[29]. Baquero and Campos[17] suggest that it would not be difficult to set up a sanctioning system where the irrational prescriber of antimicrobials would suffer from a loss of reputation among patients. Reputation can also be exploited at the institutional level, for example to encourage hospitals to mount costly infection-control interventions that could reduce the transmission of resistant organisms[52]. In medically pluralistic cultures, such as in many parts of Africa, reputation is key to provider success.

As with other common-resource problems[53,54] there is no simple or unified solution to the resistance problem. However, one-size fits-all solutions are likely to exclude developing countries, which at present are least likely to manage infections according to ideal standards of Western medicine. It is most likely that effective and appropriate incentives and sanctions will vary among different subgroups as well as in different parts of the world. Interventions therefore need to be developed, piloted and implemented more locally and in particular in developing countries. Presently, many of the recommended strategies for resistance containment have an expectation of vertical, top–down implementation[29]. Over-reliance on western-model international and national authorities has been a roadblock in the preservation of other common resources and does seem to be having very little impact on the problem of resistance[16,54]. In areas where the state is mistrusted, civil society groups may be better suited to carry the torch of antimicrobial conservation and innovative ideas for management of this and other common resources could emerge from other cultures[54]. It is possible that more grassroots approaches, though limited in reach, may have significant overall impact, particularly if they are coordinated and learned from.

A recognition of necessity

Coercive solutions break down if monitoring is incomplete or information is inaccurate[16]. For example, a plan to withhold antimicrobials from patients that might not need them requires a rigorous definition of who needs a drug and who does not in order to succeed. This in turn requires rapid, sensitive and specific diagnostics. Tests presently employed for this purpose in most health systems are reliable but generate results too slowly. In many parts of the developing world, even those tests are unavailable[36], presenting an ethical predicament for drug withholding. The present situation is that most ill people in Africa, and many other parts of the developing world, never receive a diagnosis confirming an infecting pathogen, irrespective of whether they receive antimicrobials from the official or unofficial sector[36,55].

Ostrom[56] cites communication capacity and transparent monitoring systems as essential for cooperative preservation of common resources by mutually agreed-upon rules. The better the information sharing, the easier it is to engage stakeholders[16,56]. She notes that leaders are persuaded to adopt rules in favour of long-term, relative to short term, gain when 'there are clear indicators of resource degradation, generally perceived to be accurate predictors of future harm, or when leaders are able to convince others that a "crisis" is pending'[16]. This builds upon Hardin's idea, that a 'recognition of necessity' is essential to start the process of 'mutual coercion, mutually agreed upon'[25]. Even though the problem of resistance was recognized by Fleming soon after the discovery of penicillin[57], and accepted in most clinical circles by the close of the 20th century, a true 'recognition of necessity', commensurate with the extent of the resistance problem, has not been achieved among all stakeholders and decision makers that could impact the crisis.

Recent outbreaks of hospital- and community-acquired MRSA and other multidrug-resistant hospital pathogens, including vancomycin-intermediate *S. aureus* have served as a warning for many industrialized countries. In developing countries with weaker surveillance systems, mortality from multidrug-resistant enteric pathogens like *Vibrio cholerae*, and more recently extensively-drug resistant *M. tuberculosis* should be seen as a similar admonition. However, most of these examples are often viewed as localized catastrophes[2] and, particularly where very few resistant outbreaks are documented, fail to illustrate that antimicrobial susceptibility is a shared resource belonging to all. Localities that do not have such outbreaks (or are unable to detect them) are more likely to view susceptibility as an open access resource, belonging to no one[16,58], and less likely to see how their own activities might affect future benefits. Thus, news of multiple outbreaks of resistant infections has so far been largely insufficient to motivate necessary action for change. For example, antimicrobial prophylaxis in *V. cholerae* epidemics in Africa was clearly associated with the emergence of resistant bacteria in the 1970s[59,61] but widespread antimicrobial prophylaxis was used in a cholera outbreak in Cameroon as recently as 2004[62].

Therapeutic failure can only provide clues about antimicrobial resistance that are riddled with confounding due to patient factors and variations in the quality of care or medicines[36]. The most specific and reliable information on resistance can only come from the dissemination of microbial suceptibility data collected by local laboratories. In the game theory context, near 'perfect' information: that is information about previous 'play', such as antimicrobial resistance prevalence, could help players make rational use of antimicrobials. 'Complete' information, i.e. information that also disclosed 'strategies' of other 'players' would include antimicrobial use data, something that is currently less effectively collected or studied than is resistance data and which would help support sanctioning systems. The capacity and will to collect and disseminate this data is generally below par, varies with location and is least likely to be in place in developing countries. Antimicrobial resistance surveillance is not cheap but must be viewed as an essential 'organization' cost required to monitor a common resource[11,16].

When monitoring and sanctioning systems for common resources function solely in that role, a second-order dilemma or tragedy is created because of the absence of incentives to monitor or punish[63]. It is, however, possible to collect a large proportion of surveillance data in a manner that also assists individual patient care, so that the expense of isolating, culturing and testing organisms will have multiple, synergistic functions. It also presents less of an ethical dilemma if antibacterials were withheld from patients for whom the absence of bacterial infection, or a diagnosis of non-threatening bacterial infection has been unequivocally confirmed.

In addition to supporting rational prescribing of antimicrobials, the collection and dissemination of susceptibility data beyond the clinic, is the first and necessary step for engaging all users of the commons. In a public goods experiment that measured altruistic behaviour of players to prevent climate change, experimenters found that well-informed players made larger and more frequent monetary contributions than less informed players[64]. As with climate change, another global scale common-resource problem, most users of antimicrobials cannot see gross deterioration susceptibility unless they are infected with a resistant organism and are told so by their caregivers, the gatekeepers. This has an important consequence: users to not have the necessary information to voluntarily develop or support 'mutually agreed upon' containment strategies[65]. Engaging the public in the scientific evidence supporting an impending tragedy of the commons is not a novel idea as the scientific community is instrumental in informing the public and policymakers about the threat from climate change, another unobtrusively deteriorating commons.

Resistance containment strategies have predominantly been piloted in countries where antimicrobial use control may be easier to implement; that is, countries like the USA and Denmark where gate-keepers are already in place and the activities of existing diagnostic laboratories are easily adapted to perform a monitoring function[32]. One approach would be to continue to focus containment planning and implementation in those areas, to reduce the need for capital investment. However, because of the heavy infectious disease burden in many less affluent countries, ignoring or under-prioritizing containment in those countries could undermine global containment. Furthermore studies on human altruism suggest that a plan that encourages free-riding is unlikely to be long-lasting. Strong reciprocators, who bear the costs of cooperation and altruistic punishment, enhance cooperation but participants who act 'selfishly' for any reason (including necessity) can break it down[44]. If developing countries are not engaged in the resolution of the resistance crisis, international cooperation will not be sustained. Potential 'free riders' need to be provided with cooperation incentives, which may be more useful than sanctions in promoting cooperation, in those cases where moral legitimacy prevents mutual agreement of sanctions[44,49,66]. Support for diagnostic development and surveillance systems is one incentive that would improve antimicrobial utilization in developing countries, as well as overall management of infectious diseases. It would also be the first step in generating comparative data, which is essential for establishing cooperation-enhancing reputation in the commons[17].

A Branco Weiss Fellow's approach to studying resistance

Drug resistance is an evolutionary phenomenon. Microorganisms become resistant because of mutations in their DNA or by acquiring DNA from another sources. Microbiologists, like myself, study resistance genes and the organisms that harbour them in order to understand what they encode, how they function and how they are acquired. However, resistance genes would be of much less significance if they were not selected by antimicrobials, which are used and misused by humans. As much as a rigorous study of the micro-organism will illuminate our understanding of resistance, containing the problem will require an understanding of, and intervention in the anthropomorphic contributors to selection and spread of resistant organisms. Therefore resistance can only be addressed through an integrative and multidisciplinary approach, for which a Branco Weiss fellowship offers unique support.

The resistance problem is much better studied in industrialized countries than in developing ones. I am interested in the molecular basis for resistance in West Africa and in identifying risk factors for emergence and spread. We use the intestinal commensal *Escherichia coli* as an indicator organism to study mechanisms of resistance and spread. *E. coli* can be collected non-invasively, cultured rapidly on affordable media, easily stored and transported and is amenable to molecular analysis. Using this organism, resistance dynamics can be studied irrespective of host health status and because *E. coli* acquires resistance to some drugs by mutations and others by acquiring extrachromosomal DNA horizontally, we can track and elucidate multiple mechanisms simultaneously.

Because resistance is understudied in West Africa, we are uncovering different genetic mechanisms and are beginning to piece together a basis for the rapid spread of resistance. Spread, it appears, may be more important than emergence in many contexts so that interfering with person-to-person transmission of resistant organisms and genes, which could also impact disease dissemination, should be a priority intervention. With respect to risk factors for resistance, key among my observations is that rational use of antimicrobials is not only impacted by widespread availability of these drugs without prescription, but also the dearth of diagnostic facilities to determine when they are needed.

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ACKNOWLEDGEMENTS. I thank Dominic Johnson and Harini Nagendra, for helpful discussions. Resistance research on resistance in Nigeria and Ghana is greatly facilitated by my collaborators, Oladiipo Aboderin, Adebayo Lamikanra, Mercy Newman and Japheth Opintan and their research teams.