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REVIEW ARTICLE

Access, excess, and ethics—towards a sustainable distribution model for antibiotics

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Abstract

The increasing antibiotic resistance is a global threat to health care as we know it. Yet there is no model of distribution ready for a new antibiotic that balances access against excessive or inappropriate use in rural settings in low- and middle-income countries (LMICs) where the burden of communicable diseases is high and access to quality health care is low. Departing from a hypothetical scenario of rising antibiotic resistance among pneumococci, 11 stakeholders in the health systems of various LMICs were interviewed one-on-one to give their view on how a new effective antibiotic should be distributed to balance access against the risk of inappropriate use. Transcripts were subjected to qualitative 'framework' analysis. The analysis resulted in four main themes: Barriers to rational access to antibiotics; balancing access and excess; learning from other communicable diseases; and a system-wide intervention. The tension between access to antibiotics and rational use stems from shortcomings found in the health systems of LMICs. Constructing a sustainable yet accessible model of antibiotic distribution for LMICs is a task of health system-wide proportions, which is why we strongly suggest using systems thinking in future research on this issue.

Key words: *Antibiotic distribution, antibiotic resistance, ethics, rational use, systems thinking*

Introduction

It is a well-known fact that antibiotic resistance arises and is enriched under antibiotic pressure and that levels of resistance are linked to amounts used in both the hospital setting and the community (1,2). Because of this, our shortcomings in limiting antibiotic use are often compared with *the tragedy of the commons*, an economics concept that describes the gradual depletion of a common resource where, when exploited, the loss of utility is distributed equally onto an entire population but the gain is concentrated to the person doing the exploiting (3–5).

Leibovici et al. and Millar have explored how present patients' use of antibiotics might decrease the availability of effective antibiotics for future patients. Both conclude that the interests of future patients must be acknowledged when deciding how antibiotics should be used today (6,7). This is referred to as *intergenerational justice* by Millar. Equal access to antibiotics within this generation, *intragenerational justice*, is presented as desirable by Millar, but in conflict with intergenerational justice, as expanding access to antibiotics in low- and middle-income countries (LMICs) to the level of a high-income country (HIC) would cause a higher global drug pressure. This drug pressure would then lead to new resistance emerging, which in turn could threaten future patients' access to antibiotics (8).

Many LMICs still struggle with a high burden of communicable diseases in general and pneumonia in particular (9,10). Pneumonia is one of the leading causes of under-five mortality in LMICs, with an urban–rural and rich–poor gap in both mortality and access to antibiotics within each country (11). However, over the counter (OTC) sales of antibiotics to patients lacking valid prescriptions occur frequently at pharmacies and other drug sellers, which are the first points of care for many patients in LMICs (10,12–16). Thus, insufficient access to antibiotics and excessive consumption can exist within one LMIC. This makes antibiotic distribution and regulation in LMICs a difficult challenge. It is, however, a crucial one to overcome considering the great effort that is currently made to mobilize resources and create new partnerships to strengthen antibiotic development (17,18). In order to maximize the therapeutic life-span of any new antibiotic, irrational and excessive use must be kept to a minimum. To our knowledge, there is no distribution model that presently achieves a high level of access without excessive use of antibiotics in the LMIC setting.

By *distribution model* we mean the type of providers or health care professionals that will be allowed to stock and dispense a new antibiotic and the circumstances and conditions under which it is to be dispensed. This of course has implications for national governments, ministries of health (MOHs) and drug regulatory authorities (DRAs), which will be touched upon as well.

The purpose of this interview study was to explore how a new antibiotic could be distributed in LMICs to balance access to patients in poor and rural settings against the risk of excessive and inappropriate use.

Materials and methods

Study setting and design

This qualitative interview study addresses antibiotic distribution in LMICs generally. Interviewees were recruited from African, Asian, and European countries. The qualitative analysis was not aimed at finding differences between countries but common challenges and their potential solutions.

Sampling and participants

Sampling was purposive to ensure knowledge on the health systems of several LMICs. Twenty stakeholders were identified, representing the following groups: clinicians, government, HIC donor agencies, non-governmental organizations (NGOs), the World Health Organization (WHO), and the pharmaceutical industry. Fourteen of the contacted stakeholders agreed to participate in the survey. Three were indisposed on the date of the interview. Regrettably the WHO was not represented. Characteristics of the interviewees are shown in Table I.

Data collection and instruments

A scenario of rising airway pathogen resistance to existing antibiotics in a generic LMIC was created as a basis for discussion. In this scenario, a new antibiotic was just about to be introduced into clinical practice. Two different distribution models for the new drug were presented (Text box 1). One was inspired by the distribution of artemisinin combination therapies (ACTs) and emphasized access for all (10,19). The other was focused on restriction to minimize excessive or irrational use.

Table I. Sample description.

Profession	Operational setting	Stakeholder category
Official, malaria NGO	International	NGO
Official, malaria NGO	International	NGO
Co-ordinator, health care NGO	Tanzania	NGO
Health advisor on development research	International	HIC donor agency
MD	Uganda	Clinician
MOH official	Ghana	Government
Project co-ordinator	Pakistan	NGO
Pediatrician	Uganda	Clinician
CEO, pharmaceutical company	Uganda	Industry
AMR task force member, MOH	India	Government
Head of research, pharmaceutical company	India	Industry

Text box 1.   Distribution models for hypothetical scenario.

Model 1: The new antibiotic will be broadly available without prescription. The MOH also explores the possibilities of community case management and point-of-care diagnostics to minimize excessive and unnecessary use

Model 2: The MOH decides to put a tight restraint on the new antibiotic. A physician's prescription will be required to obtain it, and the drug will only be available within the public sector and at certain authorized private pharmacies

A semi-structured interview guide was used during the interviews to cover key issues of sustainability, equity, and feasibility of different models of antibiotic distribution and regulation (Text box 2). Interviews were conducted one-on-one over voice calls ($n = 8$) and in person ($n = 1$). Interviewees 1 and 2 were interviewed together in one group voice call.

Data analysis

Interviews were transcribed verbatim. The qualitative method of analysis used was 'framework' as described

Text box 2.   Interview guide.

How do you perceive the problem of antibiotic resistance?

  Main causes

  Potential solutions

What are your reflections on the first plan of action, and what consequences do you expect?

  Health outcomes—system outcomes

  Access/excess/resistance/sustainability

  Point-of-care diagnostics and community case management

  Public sector versus private sector

  Equity issues

  Possible improvements to prevent further resistance

What are your reflections on the second plan of action, and what consequences do you expect?

  Health outcomes—system outcomes

  Access/resistance/sustainability/black market access/leakage

  Level of restraint—public versus private, hospitals versus pharmacies

  Equity issues

  Trust in health system

  Possible improvements to ensure access

How would you organize the regulation and distribution of a new antibiotic given the current state of the antibiotic pipeline?

  Sustainability

  Equity

  Feasibility

Conclusion—is there anything you would like to add to the discussion?

by Ritchie and Spencer (20). All the transcripts were read through and annotated, similar to the open coding of meaning units found in other forms of thematic analysis. Annotations were then organized into seven themes covering different aspects of the problem at hand. Starting from the annotations and themes, the interviewees' attitudes towards key issues were summarized and entered into a chart for overview. Upon review of the chart and the initial thematic framework, a final thematic framework consisting of four main themes was established (Table II).

This process was both deductive and inductive. We already viewed the access–excess tension as crucial to understanding antibiotic distribution and use in LMICs. Thus, one part of the analysis investigates how the interviewees relate to these concepts. A broad theme of health system improvements became evident when the annotations were added together to form themes. Eventually, codes covering this were successfully sorted under subthemes inspired by the WHO health system framework (21).

Ethical considerations

With the verbal consent of each interviewee, the interviews were recorded. No sensitive personal information was disclosed during the interviews, and confidentiality was promised in that no names were to be published within any presentation of the study.

Table II. Final thematic framework.

Theme	Sub-theme
Barriers to rational access to antibiotics	Drivers of resistance
	Patients
	Public sector
	Private drug sellers
	Governance
Balancing access and excess	Access versus rational use
	Restricting availability
Learning from other communicable diseases	H1N1
	Malaria
A system-wide intervention	Governance
	Information
	Service delivery
	Human resources
	Medicines and technologies
	Finance
	People

Results

The final thematic framework is represented below by the four main themes as headings. The order of the themes in this article does not reflect the order in which different subjects were discussed in the interviews.

Barriers to rational access to antibiotics

Not being driven by profit, the public sector was viewed as potentially rational in its dispensing of antibiotics. However, due to insufficient resources and knowledge, public sector health workers were not seen as able to handle antibiotics in accordance with clinical guidelines.

> *[at public sector providers] there is not enough clinically trained people but even where there are, the system for quality control to ensure adherence to standards are inexistent so many people don't follow guidelines. There is almost no proper supervision system [...] no diagnostic facilities, or they are not adequate. So we end up giving antibiotics.* (MD, Uganda)

Small private sector drug dispensers, while playing an important role in providing affordable access in remote locations, were seen as dubious channels of distribution because of poor staff knowledge and financial interests in selling more drugs. Continuous violations of existing drug regulations and guidelines were seen as a failure of the national governments' regulatory authorities. Poor and remote patient populations were believed to have financial incentives for irrational drug use such as bypassing a proper prescriber and buying incomplete courses of antibiotics.

> *[help-seeking] very often is directly to the pharmacy or to the drug shop because people cannot afford to pay the prescriber. So a lot of this is being driven by pharmacies who are not necessarily staffed by people with the right skills, who are handing out any medication including antibiotics.* (Official at malaria NGO, International)

Balancing access and excess

Introducing a new antibiotic with few or no restrictions was expected to increase access, but also irrational use along with it. Conversely, denying small pharmacies and other private drug sellers the right to stock and dispense the new antibiotic was believed to further hamper the already lacking access to antibiotics for poor and remote patient populations who use these providers as their primary point of care.

> *… it's so much easier to say these things from a city or a developed country perspective. From a perspective of an undeveloped. or developing country. any restriction affects access.* (Head of research at pharmaceutical company, India)

All interviewees were in favor of some form of controlled distribution to protect antibiotics from irrational use and preserve them for future patients for as long as possible. However, if it would save the life of a present patient, most interviewees suggested that the new antibiotic be made available, even in a low-resource setting where the available providers might dispense it irrationally. One suggestion on how to do this with minimized irrational use was to apply different distribution models within one country. The idea was to use always the most advanced health care facilities available in each setting, with village health workers distributing the new antibiotic in remote locations, while accredited pharmacies and hospitals would stock and dispense it in urban areas.

> *Like in India, we have a national rural health mission [with trained community health workers]. This antibiotic can be distributed through that channel in the rural areas, but in urban areas it should be in restricted or at designated retail pharmacies, and for tertiary care public or private sector facilities.* (member of the government's AMR task force, India)

Learning from other communicable diseases

Drawing on the similarities between challenges posed by antibiotic resistance and other communicable diseases, the interviewees brought up potential lessons to be learned. Whereas some of these other diseases received the attention of the highest level of government, antibiotic resistance and distribution were regarded as neglected areas, with poor results to be expected until the gravity of the issue was comprehended by those in power.

> *Unfortunately all diseases except HIV/AIDS and malaria suffer here because the government focuses almost totally on those [...] most of the funds go towards you know … three diseases: malaria, HIV/AIDS … and TB of course.* (CEO at pharmaceutical company, Uganda)

Two specific distribution models for antimicrobials were brought up by interviewees to serve as examples. The distribution of ACTs was held in high regard because of the rapid diagnostic tests (RDTs) being distributed alongside the drugs, allowing for a high diagnostic accuracy even among unskilled health workers in the field.

> *[ACTs] came with a package, a package of distribution, [...] diagnostic tools and [...] laboratory work, and so I think that package or that system is a best practice we can look at and review it and adapt it to suit antibacterial resistance challenges.* (MOH official, Ghana)

Both Indian interviewees mentioned oseltamivir and its distribution in India during the 2009 outbreak of H1N1 as an example of successful restriction of an antimicrobial in high demand, even though they did not know precisely under what conditions it was dispensed nor how access or H1N1 mortality were affected.

> *There were lots of cases of H1N1. But there was no panic. [Oseltamivir] was restrained and the system handled it. Of course we did not have millions of people but we. system handled it. So what did we do right?* (Head of research at pharmaceutical company, India)

A system-wide intervention

Many interviewees spoke about adopting a bigger health system perspective on the issue by investing in health system strengthening to deliver the health care infrastructure necessary for an accessible but controlled distribution of a new antibiotic.

> *… with these drugs we must not only invest in the commodity. We must also invest in the system.* (MD, Uganda)

A wide array of interventions was suggested, covering all the WHO health system building blocks (21). A strong emphasis was put on surveillance and the gathering of data on antibiotic use as well as resistance and empowering DRAs because of their pivotal role in enforcing old and new regulations onto both public and private providers.

> *If you could strengthen [the DRA], then even the private sector knowing that there is a monitoring system, that's going to kind of ensure, in a way that the antibiotics I [as a pharmacist] am entrusted with are [. . .] dispensed to and prescribed in a proper manner.* (Co-ordinator at health care NGO, Tanzania)

But there was also a great hope put on all actors being active parts of the solution. Many interviewees spoke about increasing awareness of antibiotic use and resistance at all levels of the health system, especially in the community as that would address the demand side of antibiotic use. If present and future patients would be made aware of the downside of antibiotic use when it is not medically motivated, the distribution system would not be as vulnerable to unskilled or irresponsible prescribers and drug sellers.

> *…if people know common cold you don't treat with antibiotic and you go and somebody gives you an antibiotic you say 'Okay, why? Why are you giving me an antibiotic? I've got a cold. I've got a running nose. What is it that has made you decide I need an antibiotic and not just vitamins and good rest and so on?* (Co-ordinator at health care NGO, Tanzania)

Discussion

We have found that interviewees from all represented stakeholder categories view controlled distribution as a long-term goal for future antibiotics. However, the task of distributing antibiotics in LMICs in an accessible yet sustainable manner is challenged by numerous barriers found throughout the health system. We are faced with a trade-off between wide access to antibiotics and restricted but rational use. In pursuit of a distribution model for a new antibiotic some lessons might be learnt from studying other communicable diseases, but the extent of the barriers indicate that health system strengthening interventions will be needed.

The ethical considerations on the distribution of a new antibiotic in LMICs among the interviewees can be best summed up as a strong consensus that a new antibiotic must be protected from excessive and irrational use, but also that it should be made available where it could save lives even if that is through a provider that might dispense it in violation of rules and guidelines. Both standpoints can be found in earlier articles discussing the ethical aspects of antibiotic distribution, the latter being referred to as a 'rescue rule' by Leibovici et al. (6,7,22). Even if they are commonly shared, these ethical standpoints provide little guidance on how to practically address the problem and can only serve as conditions that a distribution model must meet.

Our interviewees suggested that lessons could be learned from other communicable diseases such as H1N1 influenza and malaria. There are concerns among microbiological researchers and the WHO that reckless use of oseltamivir or ACTs may accelerate the development of resistance (19,23,24). Despite having this in common, they have been distributed quite differently.

ACTs have been distributed using unskilled providers such as village health workers and small drug stores, with wide access as a major aim (10). The later addition of intuitive and affordable rapid diagnostic tests (RDTs) for malaria into this package and heavy subsidizing of diagnostics and treatment at private and public providers were supposed to increase access and diagnostic accuracy in the field as well as the rationality of ACT dispensing (10,25). One of our interviewees suggested that finding a similar diagnostic test for bacterial infections should be a research priority. Okeke et al. have produced a list of properties that a field diagnostic should possess in order to decrease unnecessary dispensing of antibiotics. Besides showing etiology and antibiotic susceptibility, such a field diagnostic should be affordable, intuitive, and deliverable to remote locations. While optimistic,

they conclude that several technological and financial barriers will prolong the time until such a test is ready for clinical practice (26). Looking at malaria, presumptive treatment is still high in most countries, and testing remains low, especially in the informal private sector and at the community care level (10). Interview studies with health workers in Cameroon and Kenya have indicated that RDT use and adherence depend on a variety of social and practical factors (27,28). An affordable and powerful diagnostic tool, it seems, is not enough to achieve test effectiveness in the field. We must look beyond medical technology alone to achieve rational use with a level of access as high as that achieved with ACTs.

Meanwhile, oseltamivir in India during the 2009 H1N1 is an example of restricted use. For fear of development of resistance, oseltamivir was initially only to be used within Indian hospitals. As 2009 progressed, 480 accredited pharmacies were allowed to stock and sell it, but only when presented with a valid prescription issued by a physician (29,30). Regrettably, there is no data on access at the community level. In two studies performed at hospitals, the mean time between developing symptoms of influenza at home and receiving oseltamivir as an in-patient was five days as opposed to the ideal two, indicating that the drug was too restricted to be accessible in time for a majority of the patients (31,32). While insufficiently studied, oseltamivir distribution in India is an example of an effort to limit irrational use of an antimicrobial in high demand, this coming from a health system where OTC sales of antibiotics seem to be a common occurrence (12,13). As such, it should make for an interesting case study on how restriction of antimicrobials could be implemented in a LMIC and how it would affect access.

Some interviewees suggested using different distribution models in rural and urban settings. By mapping locally available health care infrastructure, both private and public, solutions could be tailored to fit different local conditions within one country. This could offer an affordable third path between access and restriction where, if there were the political will, the distribution of a new antibiotic would be as rational and accessible as locally possible. Actual enforced drug restrictions that are different between urban and rural areas are unknown to us, but using health workers with brief education and training to increase access to drugs and health care in rural areas is common practice in many LMICs (11,33).

Many interviewees viewed private drug sellers as important in providing access, but also prone to dispense antibiotics in an irrational manner. A recent mixed methods study on antibiotic dispensing practices of private pharmacies in Vietnam by Nga et al. highlights the strong financial incentives involved (16). Nearly 20% of the revenue of both rural and urban private pharmacies came from illegal OTC sales of antibiotics. The most common reason for selling antibiotics to a patient without a proper prescription was fear of losing customers. Regrettably the Vietnamese DRA is not enforcing existing drug laws, and this practice continues unpunished (16). No positive incentives for private drug sellers to improve their dispensing of antibiotics were discussed in our interviews. However, there are existing interventions in LMICs where positive incentives have been used. The aim of the Accredited Drug Dispensing Outlet (ADDO) project in Tanzania was to raise the quality of drugs and advice given at rural drug shops. After pledging to adhere to certain standards, drug shops received business training, access to micro-finance, and permission to sell some prescription-only drugs, including antibiotics (34). Hundreds of drug shops have joined the initiative and been accredited over the years, but the quality of advice and care given has been disappointing in audits. Despite this, none of the drug shops has lost accredited status (15). It seems even with positive incentives, negative incentives such as the possibility of DRAs revoking the licenses of misbehaving pharmacies are important and must not be overlooked.

Several interviewees stressed the importance of community knowledge on antibiotic resistance. Raising community awareness could lead to fewer patients requesting antibiotics as customer requests have proven to be an important current driver for irrational dispensing (16). While traditionally regarded as an altruistic choice, Battin et al. have pointed out that one might abstain from using antibiotics for egoistic reasons as well. The motivation would be to avoid exposing one's microbiome to unnecessary selection pressure (35). This of course assumes a fair amount of microbiological knowledge. Interventions aimed at raising antibiotic awareness done in HICs show promise, as decreased prescription and consumption of antibiotics have been seen following media campaigns targeting the general population (36,37).

The use of systems thinking in health systems strengthening and policy research has gained ground in recent years because of its ability to handle sub-system intersecting issues and to bridge the gap between policy-makers and researchers (21,38). Bigdeli et al. have already suggested using systems thinking to increase access to all medicines in LMICs (39). We argue that antibiotic distribution in particular would benefit from systems thinking because of the system-wide implications of this study. Our interviewees suggested interventions targeting all

six WHO health system building blocks and identified various barriers to a sustainable yet accessible distribution of antibiotics (21). Many of these interventions would be big and expensive projects, but, using systems thinking, interventions can be conceptualized and their consequences mapped, thus helping MOHs to prioritize.

Conclusions

While access to effective antibiotics has traditionally been looked upon as an issue of pharmaceutical development, the emerging resistance and the loss of effective antibiotics depend on how they are used. Our findings suggest that constructing a sustainable yet accessible model of antibiotic distribution for LMICs is a task of health system-wide proportions.

The tension between access and rational use, as described by many of the interviewees, stems from shortcomings found in the health systems of LMICs. In order to safeguard new antibiotics for present and future patients, national governments and MOHs, regardless of economic status, must strengthen their health systems in ways that facilitate an improved antibiotic distribution. In this venture we strongly suggest using systems thinking.

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