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Tackling antimicrobial resistance at global and local scales

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Antibiotic resistance, similar to climate change, is a shared global problem, but unlike climate change, national and local action produces direct localized benefits in addition to improving the global situation.

Global need for antibiotics, and antibiotic resistance

Along with clean water, sanitation, and vaccines, antibiotics were responsible for the vast improvements in health and longevity in high-income countries over the past century. The critical question is how we can responsibly scale up access to antibiotics in low- and middle-income countries (LMICs) while minimizing the threat of resistance and prolonging their effectiveness.

Antibiotic resistance has often been compared to climate change in its scope and scale [1]. Actions undertaken by any single country have the potential to adversely (or positively) affect other countries. For example, improved water, sanitation, vaccination, and pharmaceutical regulation in India can have global benefits if this results in reducing selection pressure for resistant strains of bacteria to evolve and spread elsewhere, such as with the notorious New Delhi metallo-beta-lactamase (NDM)-1. Unlike the uniform global increase in carbon dioxide levels caused by fossil fuel burning, however, the effects of antibiotic use on resistance levels are as much local as they are global, and effective conservation measures benefit the local population directly as well as contributing to the global good. Use of antibiotics is growing in LMICs, particularly in the BRICS (Brazil, Russia, India, China, and South Africa) countries [2]. LMICs are likely to be the hardest hit by declining effectiveness of antibiotics because of their greater burden of infectious disease in both human and animal populations, the lack of access to affordable second- and third-line antibiotics, and because of suboptimal infection-prevention measures in hospitals and communities.

Similar to climate change, some solutions, particularly those involving innovation, can be developed at a global level, but policy actions have to be undertaken at a national or local level. In 2001, the World Health Organization released an often-neglected report on antibiotic resistance on September 11, 2001, the same day as the terrorist attack on New York and Washington, DC [3]. The report laid out more than 60 actions for countries to take to tackle resistance. The report singled out changes in behavior that would

be most important to make by healthcare workers, patients (and their caregivers), livestock farmers, and those who sell antibiotics. In this article, we outline briefly the global and national actions that will contribute to maintaining effective antibiotic coverage over the long term.

Global responsibilities

New antibiotics are needed, regardless of the success of efforts to reduce antibiotic demand, but much more could be done in terms of product and delivery innovation of diagnostics, vaccines, and infection control programs to reduce the need for antibiotics. Every new vaccine developed and introduced for a bacterial disease, and for some viral diseases, reduces the need – and the demand – for antibiotics. We illustrate this using diagnostics as an example of research and development and a global financing scheme as an example of how access can be improved responsibly.

Research and development: diagnostics

One reason that antibiotics are overused is uncertainty about whether a patient has a bacterial infection, but even when that information is available it is not always acted on appropriately. In a recent Center for Disease Dynamics, Economics & Policy (CDDEP) study in six US hospitals, 60% of inpatients were started on antibiotics on admission, one-third of whom were afebrile and had a normal white blood cell count at the start of therapy [4]. Cultures were ordered before treatment for 60% of these patients, more than half of whom were negative for bacterial infections. In response, antimicrobials were stopped or narrowed in only one-third of patients with negative urine cultures and one-half of those with negative blood cultures.

The problem may be more severe in low-resource settings, where healthcare facilities are few and dispersed, and a healthcare worker may have only one encounter with the patient. The availability of a rapid diagnostic test (RDT) that could be used in low-resource settings, such as rural clinics and pharmacies in subSaharan Africa, could be transformative, as it has been for malaria. Malaria RDTs were introduced in the early 2000s and have dramatically reduced demand for curative malaria treatment because, for the first time, it is quick and relatively inexpensive to distinguish which patients have malaria before initiating treatment (http://siteresources.worldbank.org/INTMALARIA/Resources/AMFmProcessEvaluation.pdf). Similar, affordable, dipstick-based tests have yet to be deployed for bacterial infections.

Financing

The Affordable Medicines Facility for malaria (AMFm) is an example of innovative antimicrobial drug financing,

with the dual aim of expanding access to high-quality antimalarials and reducing the risk of antimalarial resistance [5]. By the early 2000s, inexpensive chloroquine had lost effectiveness against malaria caused by *Plasmodium falciparum* (the most widespread and lethal species) in Asia and large parts of Africa. Relatively expensive artemisinin derivatives were the only equally effective and robust first-line drugs. Preserving their effectiveness and ensuring access to them became a global necessity and a humanitarian goal. The idea behind AMFm was proposed by a US Institute of Medicine committee commissioned to address the challenges of antimalarial treatment at the beginning of the 21st century [6]. AMFm was created in 2008, after several years of study and development, as an arm of the Global Fund to Fight AIDS, Tuberculosis and Malaria. It would subsidize only high-quality artemisinin-combination therapies (ACTs). The subsidy would mean an end-user price lower than that of unsubsidized artemisinin monotherapy, thereby 'crowding out' inappropriate drugs and encouraging appropriate ones, entirely by a market mechanism.

An eight-country pilot study was conducted and a thorough evaluation found that AMFm was working as anticipated: the price of subsidized ACTs was significantly lower than artemisinin monotherapies, and people were using them in preference to other antimalarials [7]. The evaluators called AMFm 'a game changer'. AMFm still exists, but it has never been globalized, largely because of political opposition. Although the specifics of AMFm are not directly applicable to antibiotics, the idea of a financing mechanism tailored to the biologic and human characteristics of disease and treatment may have relevance.

National responsibilities

The solutions to the antibiotic-resistance problem, particularly as they pertain to conservation of effectiveness, are mainly at national and subnational levels. A few organizations are active in raising awareness and building local health policy capacity around antibiotic resistance in LMICs. One of the most effective has been the Global Antibiotic Resistance Partnership (GARP; www.cddep.org/garp), started 6 years ago by CDDEP. GARP has empowered multisectoral, multiexpertise working groups of national experts in eight countries to craft local solutions that governments and private sector actors equally can embrace. Through GARP, national-level policy formation and implementation has been particularly successful in South Africa, Kenya and Vietnam, and work toward national changes can be seen in all GARP countries [8].

From our work in GARP countries, we identify six characteristics necessary for successful engagement at the country level [8].

Creating an antibiotic-resistance policy space

In most countries, some clinicians and experts on the ground are acutely aware of antibiotic resistance; however, governments and policy makers have not yet recognized it as a priority and have not created a mechanism to address it. A mechanism for experts to gather around the issue is needed for antibiotic resistance to reach the national agenda. In South Africa, Kenya, and Vietnam, GARP

recommendations have led directly to action plans developed in collaboration with the government.

A brain trust of national expertise

Scientific experts and stakeholders from all relevant disciplines – agriculture, veterinary, and human health – and sectors – government, nongovernmental organizations (including faith-based), private enterprise, and academia – can act as a clearinghouse for antibiotic intelligence. This 'working group' becomes a trusted, unbiased source of information and advice. Members can serve as volunteers, but a paid coordinator is essential. In India, Kenya, South Africa, Vietnam, and Nepal, blocs of working group members have been co-opted as short- and long-term government advisors; they are regularly contacted by mass media for expert opinion, and they help to inform the public under the GARP banner. For example, the GARP working group chairman has written on antibiotic resistance in Nepal in *The Nepali Times* (http://nepalitimes.com/article/nation/Antibiotic-resistance,1974).

Permanence

Achieving national-level progress on antibiotic resistance takes time. Stakeholders need to become familiar with the issue, buy into the need to address it, and agree on how to do so. Several years are needed to generate evidence, awareness, and trust before national-level action is likely, but it can then become firmly rooted. In South Africa, commitments and support from a large number of organizations and individuals throughout society, led by the government, place antimicrobial resistance firmly on the public health agenda [9].

Authoritative documentation of antibiotic use and the resistance situation

Situation analyses and research build the platform on which future policies are based. Conducting the analyses allows the working group to master the issue and inform and advise with authority. For example, the GARP-South Africa situation analysis, published as a special issue of the *South African Medical Journal* [9], touched off development of a national antimicrobial resistance strategy. In addition, in Vietnam, GARP-funded research [10] contributed to enhanced enforcement of prescription laws, documentation of antibiotic-resistance patterns [11], and contribution to the global conversation on 'forgotten antibiotics' [12].

Engagement with government

Achieving a cooperative, advisory, or internally incorporated relationship with ministries of health and agriculture will help lead to sustainable national impact. In Vietnam, the GARP working group is embedded within a Ministry of Health Hospital and is advising the Ministry on development and implementation of a National Action Plan on Antimicrobial Resistance, based on their situation analysis [13].

Leading with action

Implementing programs, developing tools, and other activities to improve antibiotic use raises the profile of working

group members, while providing direct benefit. In Kenya, successive GARP-led antibiotic-awareness weeks have been covered by national media (https://www.youtube.com/watch?v=Tuw1J2wc4B8); and curriculum development in Kenya and Nepal is contributing to national progress.

Concluding remarks

While a global set of basic principles to address antibiotic resistance can be articulated, national action by national experts is essential for real progress in every country. LMICs may be similar in their income levels, but not necessarily in how antibiotics are provided, paid for, and used. Pragmatic and implementable solutions have to be tailored to the health-system context of each country by knowledgeable local experts. In many LMICs, external support is needed to start this process, which can then become autonomous. GARP has been successful in playing this role in its current eight partner countries.

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