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Policies to Address Antibiotic Resistance in Low- and Middle-Income Countries

National and International Action on Antimicrobial Resistance

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INTRODUCTION

Just a few years ago, antibiotic resistance had a low global profile. Newspaper articles were few and focused most often on individual, heart-rending cases of methicillin-resistant *Staphylococcus aureus*—MRSA, the superbug. The stories today are broader in scope and more frequent. In the United States, the Centers for Disease Control and Prevention (CDC) released a report in 2013 estimating that 2 million Americans become ill every year from resistant infections and 23,000 die from them (CDC 2013). Over the past decade, the World Health Organization (WHO) has issued several reports that have drawn some attention, but the global discussion still lacks a strong voice from low- and middle-income countries (LMICs), where the problems and solutions differ in some important ways from those in high-income countries.

Despite heightened awareness in high-income countries and recognition that antibiotic resistance is a global problem, the issue is still not on the agenda for most low-income countries and some middle-income countries. For example, in a report of the U.S. Agency for International Development (USAID 2014) of its major health accomplishments in recent years, "resistance" figures prominently in discussions of malaria and tuberculosis but is not mentioned at all in relation to common bacterial infections. The priorities of bilateral aid agencies, such as USAID and the British Department for International Development (DfID), influence the priorities recognized by recipient country governments, whose own resources are most often directed at the same problems. AIDS, malaria, and tuberculosis have taken the lion's share of health funding in the past decade. Although pneumonia and other causes of deaths among infants and children have been prioritized for decades, the role played by antibiotic resistance in those deaths has been largely ignored.

This report provides a snapshot of activities related to antibiotic resistance *policy* in LMICs around the world as of early 2014. We do not attempt to catalogue every study of antibiotic resistance in a hospital (such studies can be found almost everywhere) or identify individuals interested in and conducting research on the subject (who also exist the world over). The intention is to report on the capacity (inside or outside government) to analyze the situation, formulate policy, and/or influence the government or professionals to change antibiotic policy toward improving the use of antibiotics.

Capacity to understand and act on evidence and directives related to antibiotic resistance is needed in LMICs. Unlike adding a new childhood vaccine to the suite already delivered (which requires assessment and deliberate steps), action against antibiotic resistance is even more complex, requiring increased awareness by health professionals and, ideally, the public, as well as behavior change for all, which is often the most difficult end to achieve. Because of lack of priority and stretched resources, antibiotic resistance may not find "receptors" unless these have been cultivated. The report discusses projects that have been successful at doing just this.

For information on the level of commitment, activity, and interest in the issue, we also surveyed the WHO regional offices about the status of antibiotic resistance policy in LMICs in their respective regions.

The reasons why antibiotic resistance is a concern in LMICs may be obvious, but we start with some information to ground this belief and to point out the special problems that must be considered when recommending policy in LMICs.

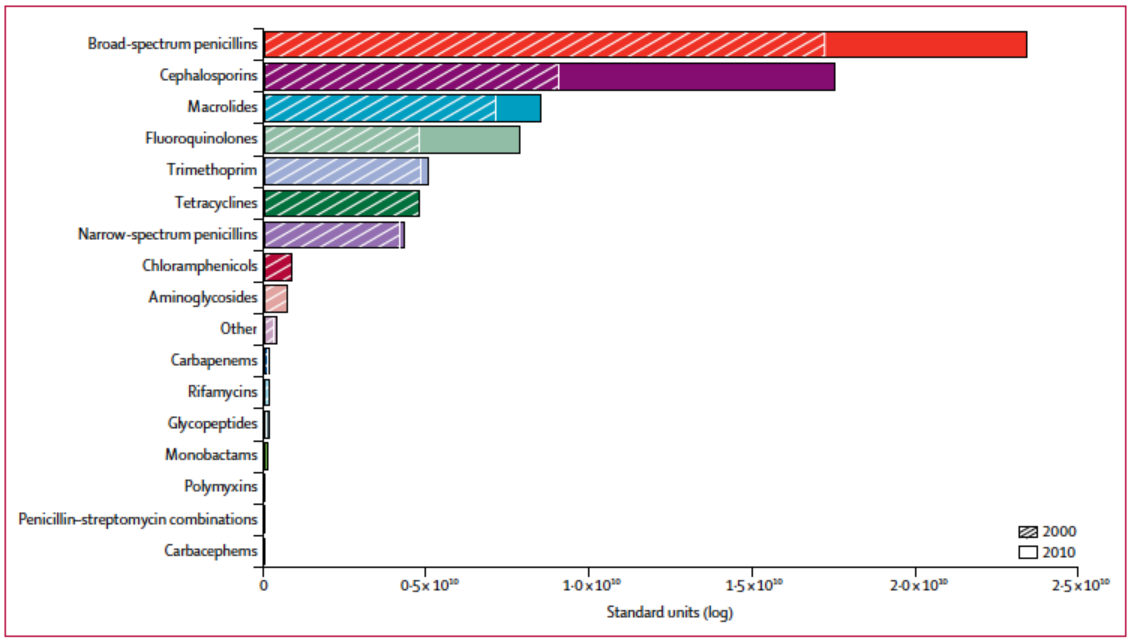
Increasing Antibiotic Use with Rising Incomes

The world is consuming more antibiotics, with most of the increase occurring in LMICs. The most comprehensive analysis to date (and the first on a global scale since 1987) of global antibiotic use is based on the IMS Health MIDAS database of retail and hospital pharmacy sales estimates in 71 countries (Van Boeckel et al. 2014). Between 2000 and 2010, the consumption of antibiotics in these 71 countries increased 36 percent, from 54 billion (10^9) standard units to 74 billion standard units. Three-quarters of the increase is accounted for by the five "BRICS" countries—Brazil, Russia, India, China, and South Africa—which accounted for only one-third of the global population increase over the same period. The biggest data gaps are in sub-Saharan Africa and Asia, but the largest countries (including Nigeria) are included.

India consumes the largest volume of antibiotics in the world, but at 10.7 units per person, Indians consumed about half of the amount per person as in the United States, at 22.0 units per person. China, the second-largest consumer by volume, used 7.5 units per person. Overall consumption (though not true for every antibiotic class) in high-income countries was stable or declining, with a few exceptions, notably Australia and New Zealand, where consumption tripled (to 87 and 70 units per person in 2010, respectively).

By antibiotic class, more than half (55 percent) of the worldwide consumption in 2010 consisted of cephalosporins and broad-spectrum penicillins, and the greatest absolute increases were in those classes (Figure 1). Cephalosporins were also near the top of the list in relative terms, nearly doubling in use. The class with the greatest increase, the monobactams, increased more than 20-fold during the 11-year period analyzed. Increases were also noted in two last-resort classes, carbapenems (45 percent) and polymixins (13 percent).

Figure 1



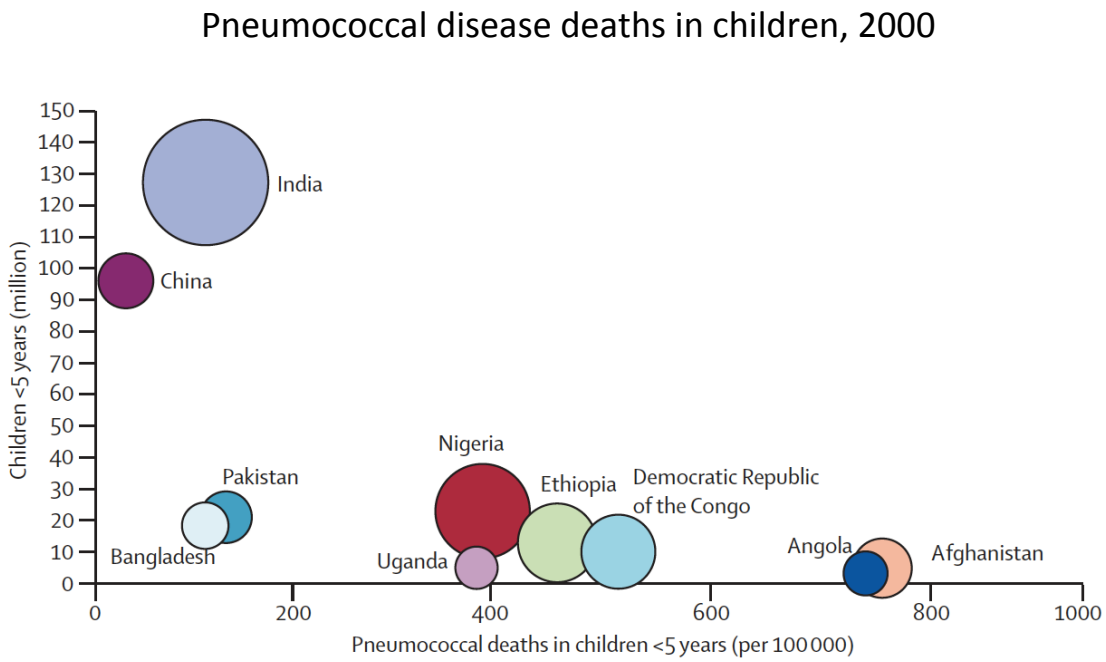
Global antibiotic consumption, by class, in 2000 and 2010
Standard units are defined as a single dose unit (i.e., pill, capsule, or ampoule).
SOURCE: (Van Boeckel et al. 2014)

The Dual Problem of Overuse and Lack of Access

In the world's rich countries, underuse of antibiotics is relatively rare. Some people lack consistent access to health care, but even in the United States, where many lack insurance, in emergencies (such as severe infection), most people do make their way to a hospital for treatment. As a result, preventable deaths from infection are relatively few, among both children and adults. Not so in low-income countries and for the poor in middle-income countries.

More children in LMICs die from lack of access to antibiotics than, in all probability, die from resistant infections. We base this on an estimated 800,000 deaths from pneumococcal disease in children under 5, nearly all of them in LMICs (Figure 2) (O'Brien et al. 2009). Counting adults and children who die from other highly treatable infections would increase this number. Since the pneumococcal estimate was made, a growing number of countries have added pneumococcal vaccination for newborns, which should dramatically reduce this toll. The basic observation still holds, however.

Figure 2

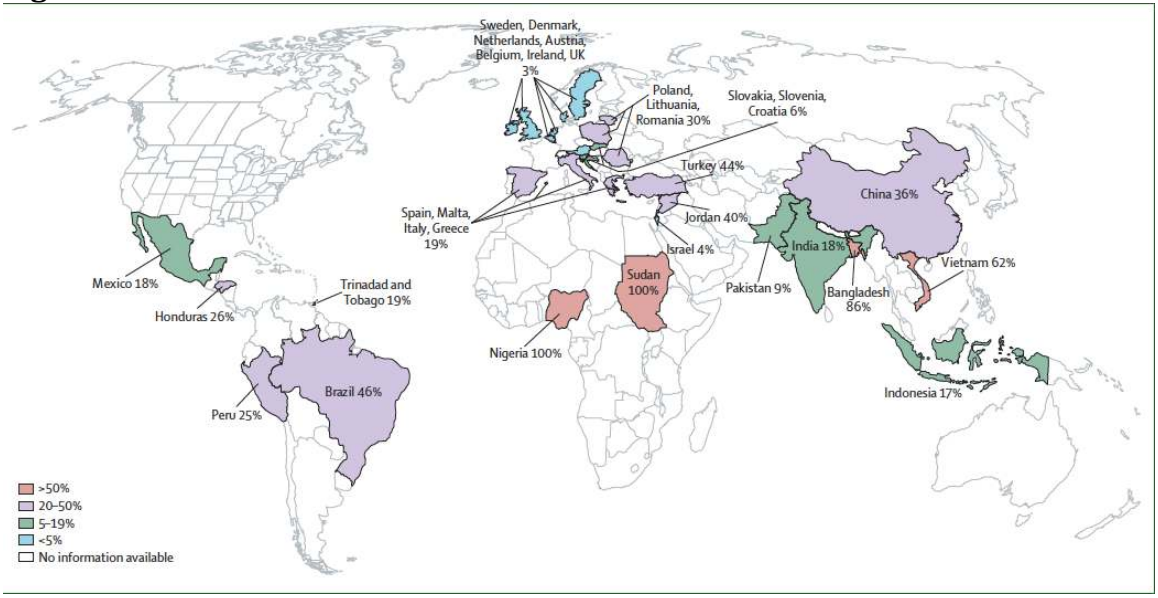


Ten countries with the most pneumococcal deaths in children <5 years. Bubble size indicates the number of pneumococcal deaths.

SOURCE: O'Brien et al. 2009

It is difficult to quantify the extent of antibiotic overuse in LMICs. In high-income countries, overuse has been documented time and again in hospitals and in outpatient prescribing. A recent study by CDC demonstrates a wide range of antibiotic prescribing levels in intensive-care units in U.S. hospitals, implying overuse at least in hospitals at the high end (Fridkin et al. 2014). The same phenomena occur in LMICs, with the added dimension of often-rampant over-the-counter antibiotic sales without prescriptions. A systematic review of studies that quantified nonprescription sales found a highly variable proportion of antibiotic sales without prescriptions, ranging up to 100 percent in the few studies found in Africa (Morgan, Okeke, Laxminarayan, Perencevich, and Weisenberg 2011) (Figure 3).

Figure 3



Frequency of nonprescription use of antimicrobials in the general population, based on published works

In small areas, countries with similar frequency of nonprescription antimicrobial use have been grouped.

SOURCE: Morgan et al. 2011

ANTIMICROBIAL USE AND RESISTANCE POLICIES IN LMICs

No international database tracks information on policy responses to antibiotic practices related to resistance. To begin such a compendium, we contacted all WHO regional offices and, through them, a number of WHO country offices, focusing on the LMICs (as defined by World Bank income categories). During the same period that CDDEP was preparing this report, WHO was collecting information through a survey sent to all WHO regional offices, asking for country-level responses in two main areas: antimicrobial resistance surveillance and resistance levels (from surveillance or from ad hoc studies) to specific antibiotics in common bacterial pathogens. The results were published this year in *Antimicrobial Resistance: Global Report on Surveillance* (WHO 2014). Information on surveillance, which is similar to information gathered in our own survey, is included here.

The CDDEP survey about existing policies addressed antibiotic use and resistance, the existence of an antibiotic resistance surveillance system, and capacity to address antibiotic resistance through formally constituted bodies. We sought to answer the following questions through emails and phone calls, as well as from available written reports:

> Are there national policies restricting the availability of antibiotics without a prescription, and are these policies enforced?

Is there a national-level body constituted to deal with antibiotic issues, including resistance, or a ministry of health office with an explicit mission that includes antimicrobial resistance?

Are there any national or regional laboratories with the ability to identify resistant bacteria?

Is there a national monitoring or reporting system for antibiotic resistance?

Does the country participate in any regional infection control networks?

Are there national antibiotic policies that specifically address antibiotic resistance?

Are there any regulations or policies regarding the use of antibiotics in livestock or aquaculture?

Has there been a major report on use of antibiotics in animals or humans in the country emphasizing antibiotic resistance?

Have there been any public education campaigns on the use of antibiotics?

From some regional offices, information was available only at an aggregate level for the region. For other regions, country-specific information was available.

Table 1 summarizes the information obtained.

Regional Office for Africa

The Regional Office for Africa (AFRO) includes 26 of the 36 low-income countries in the world and 20 middle-income countries in Africa. Four of the low-income countries (Kenya, Tanzania, Mozambique, and Uganda) have Global Antibiotic Resistance Partnership (GARP) working groups, as does one of the middle-income countries, South Africa (see below, under Country-Level Programs). These countries and Ghana (with the help of ReAct, also discussed under Country-Level Programs) appear to have the only national-level groups constituted specifically to understand and formulate policy around antibiotic resistance.

About three-quarters of AFRO member countries have a medicine policy emphasizing rational use of antibiotics, but in every case, enforcement is poor (J.-B. Ndihokubwayo, personal communication, March 7, 2014). Likewise, although many countries in Africa have placed restrictions on the use of antibiotics without a prescription, these regulations also go unenforced (J.-B. Ndihokubwayo, personal communication, March 7, 2014). Compounding the problem, essential medicines (including antibiotics) are often not in stock in health facilities, and counterfeit antibiotics are reported to be common in the

region (Ndihokubwayo, Yahaya, Desta, and Ki-zerbo 2013) (J.-B. Ndihokubwayo, personal communication, March 7, 2014).

There is limited laboratory capacity for monitoring antibiotic resistance in LMICs in Africa, although studies have been performed on certain isolates to first-line drugs, including a study of *Shigella* isolates and another of *Neisseria meningitides* isolates in 18 countries (Ndihokubwayo, Yahaya, Desta, and Ki-zerbo 2013).

According to WHO (WHO 2014), surveillance occurs only in a few countries, resulting in a scarcity of accurate and reliable antimicrobial resistance (AMR) data, and there is no formal collaboration among regional surveillance programs.

Regional Office for the Eastern Mediterranean

The Regional Office for the Eastern Mediterranean (EMRO) is responsible for mostly middle- and high-income countries. LMICs represented by EMRO include two low-income countries, Afghanistan and Somalia, as well as 13 middle-income countries.

Respondents from the WHO country offices in Egypt, Lebanon, Pakistan, and Syria provided information for this report. Of these four countries, Syria was the only country that did not have a national policy restricting the availability of antibiotics without a prescription. The other three countries had such a policy; however, respondents from all three countries reported that the policies were not enforced or were minimally enforced (K. Agha, H. El Bushra, M. Elmahdawy, A. Rashid, personal communications, February 22–March 2, 2014).

Neither Egypt nor Lebanon reported having a national-level body to address antibiotic issues, including resistance. Pakistan and Syria both reported having such a national body, but without adequate funding, resources, or leadership. Pakistan established its body, the Division of Pharmacy Services of the Drug Authority of Pakistan (DRAP), in November 2012. This group is currently drafting rules and regulations but has yet to have a formal meeting. In Syria, three national bodies deal with antibiotic resistance: the Central Infection Prevention and Control Committee, the Directorate of Drug Affairs, and the Department of Infection Control in Hospitals Directorates. Despite the presence of these national bodies, the WHO officer in Syria reported that the priority given to antimicrobial resistance had been declining, due in no small part to the current civil war (K. Agha, H. El Bushra, M. Elmahdawy, A. Rashid, personal communications, February 22–March 2, 2014).

Lebanon and Syria have national laboratories with the ability to identify resistant bacteria; however, neither country has such a laboratory that produces reports or has a monitoring or reporting system for antibiotic resistance. Neither country participates in a regional infection control network (K. Agha, H. El Bushra, M. Elmahdawy, A. Rashid, personal communications, February 22–March 2, 2014).

The only country reporting the existence of a national antibiotic policy specifically addressing antibiotic resistance was Lebanon. Only Pakistan reported having a policy

regarding the use of antibiotics in animal husbandry; however, the policy was not enforced. None of the respondents from the four EMRO countries were aware of a major report on the use of antibiotics in animals or humans in their country. Lebanon was the only country reporting that there had been a public education campaign on the use of antibiotics; further information on the education campaign was not provided (K. Agha, H. El Bushra, M. Elmahdawy, A. Rashid, personal communications, February 22–March 2, 2014).

According to WHO (WHO 2014), national efforts for AMR surveillance are "relatively advanced" for tuberculosis, HIV and malaria, but weak for the broader AMR spectrum. In 2002 and 2013, EMRO adopted resolutions to address AMR; however, action is still fragmented.

Regional Office for Europe

All non-European Union (EU) countries in Europe are LMICs, and the middle-income countries of Bulgaria, Hungary, and Romania are EU members. All of the non-EU countries have expressed interest in working with the WHO Europe Regional Office on antibiotic resistance, and most have assigned AMR focal points and are seeking to create intersectoral committees to work on issues related to AMR (D. Lo Fo Wong and S. Nahrgang, personal communications, March 5–7, 2014).

Most high-income EU countries have policies related to antibiotic resistance and participate in the European Surveillance on Antimicrobial Resistance Network (EARS-Net), a surveillance system run by the European Centre for Disease Prevention and Control. Additionally, WHO-Europe, the European Society of Clinical Microbiology and Infectious Diseases, and the Dutch Public Health Institute are collaborating on a surveillance network called the Central Asian and European Surveillance of Antimicrobial Resistance network (CAESAR), which is beginning to conduct AMR surveillance in non-EU European countries. CAESAR uses the same methodology as EARS-Net, and data from the two systems will be comparable. As of March 2014, four countries are submitting surveillance data to CAESAR (D. Lo Fo Wong and S. Nahrgang, personal communications, March 5–7, 2014).

Most LMICs in Europe do not have policies prohibiting the sale of antibiotics without a prescription, and those that do are not able to enforce them. Approximately two-thirds of European LMICs report that over-the-counter sales of antibiotics do occur. Likewise, most LMICs in Europe have policies specifically addressing antibiotic resistance, but enforcement is problematic. Approximately one-third of European LMICs have policies regarding the use of antibiotics for animal husbandry (D. Lo Fo Wong and S. Nahrgang, personal communications, March 5–7, 2014).

Although most European LMICs have laboratories capable of identifying resistant bacteria, there is little collaboration between laboratories, and laboratory capacity varies across the continent. There are no strong regional infection control networks.

Fifteen non-EU countries participated in the European Antibiotic Awareness Day in 2013, and a few LMICs in Europe reported having carried out a public education campaign on antibiotic use in the past five years (D. Lo Fo Wong and S. Nahrgang, personal communications, March 5–7, 2014).

Regional Office for the Americas

The Pan American Health Organization (PAHO) is the WHO regional office for the Americas, including LMICs in Latin America and the Caribbean. All the LMICs in the region except for Haiti (the only low-income PAHO country) are middle-income countries. Many countries in the region are active in the Latin American Antimicrobial Resistance Surveillance Network (ReLAVRA) a surveillance network coordinated by PAHO, which collects data from national reference laboratories (NRLs). ReLAVRA was created in 1996 and now has 21 participating countries, including 17 MICs, that contribute to ReLAVRA. Data from these networks have been compiled and published regularly by PAHO, in Spanish (WHO 2014).

Regional Office for South-East Asia

The Regional Office for South-East Asia (SEARO) met in 2013 to discuss surveillance for antimicrobial resistance and gauge progress on the Jaipur Declaration of 2011 (discussed below), a commitment to tackling antibiotic resistance in Southeast Asia. The meeting also involved trainings for antibiotic susceptibility testing and the use of the WHONET software (WHO 2013).

At the time of the meeting, most SEARO countries were in the process of forming committees to deal with issues related to antimicrobial resistance, and some countries already had such committees. Almost all countries had policies on antibiotics and national plans for containing the spread of antibiotic resistance. With the exception of Sri Lanka, however, most countries had not passed any regulations on antibiotic use in humans or animals, and only about half of SEARO countries had rational prescription plans for antimicrobials (WHO 2013).

Laboratory capacity in LMICs in SEARO is relatively strong. Most SEARO LMICs carry out lab-based surveillance, and many have implemented prescription auditing and infection control procedures. In response to the 2011 Jaipur Declaration, nearly all SEARO countries have launched public education campaigns on the use of antibiotics (WHO 2013). However, the region does not yet have a coordinated system of AMR surveillance (WHO 2014).

Regional Office for the Western Pacific

The Regional Office for the Western Pacific (WPRO) includes one low-income country (Cambodia) and several middle-income countries. One of these middle-income countries, Vietnam, has a GARP working group, discussed later in this report. In addition to

information from WPRO, we received country-specific information from Cambodia, Fiji, Kiribati, Laos, and Tuvalu. Of these countries, Cambodia was the only one to report no national policy restricting the availability of antibiotics without a prescription. In Laos, such a policy exists, namely the Law on Drugs and Medical Products, which also prohibits the sale of counterfeit medicines. Policies, however, were reported as being minimally or not enforced. In Fiji, Kiribati, and Tuvalu, policies restrict the availability of antibiotics without a prescription and are reportedly enforced (A. Costa, K. Nahapetyan, S. Phongphachanh, personal communications, March 5–6, 2014).

Of the respondents, Cambodia was the only WPRO country that reported having a national-level body constituted to deal with antibiotic issues including resistance; however, funding and resources for this established body were reported as inadequate (A. Costa, K. Nahapetyan, S. Phongphachanh, personal communications, March 5–6, 2014).

With the exception of Tuvalu, all reporting WPRO LMICs had laboratories with the ability to identify resistant bacteria. The laboratories in Cambodia and Laos produce monthly reports. Kiribati has a national reporting system for antibiotic resistance that has produced a report in the past five years and was the only country that reported having an enforced policy specifically addressing antibiotic resistance. No other country reported having any policy addressing resistance. None of the WPRO LMICs reported participation in a regional infection control network (A. Costa, K. Nahapetyan, S. Phongphachanh, personal communications, March 5–6, 2014).

Laos was the only country with a policy regarding the use of antibiotics for animal husbandry, a report on antibiotic use in humans, or a public education campaign on the use of antibiotics. The Law on Livestock Production and Veterinary Matters includes regulations on use of antibiotics in animals; however, monitoring is irregular. The Laos Food and Drug Department carried out a public education campaign on antibiotic use using TV, radio, posters, brochures, and magazines (A. Costa, K. Nahapetyan, S. Phongphachanh, personal communications, March 5–6, 2014).

Cambodia has conducted a study on antibiotic resistance, which will be made public shortly (A. Costa, personal communication, March 5, 2014).

According to WHO (WHO 2014), previous efforts (beginning in the 1980s) to share AMR findings were interrupted by a series of emergencies in the early 2000s. Many member states continue with surveillance on a national level and WPRO has begun to revive regional surveillance.

Table 1. Antimicrobial resistance policies and surveillance in LMICs

WHO regional office	Countries represented	National-level bodies concerned with antibiotic issues, including GARP working groups	Enforcement of policies concerning use of antibiotics without prescription	National policies related to antibiotic resistance and rational use	Policies concerning livestock or aquaculture	Major reports or public education campaigns	Antimicrobial resistance surveillance (WHO 2014)
Africa (AFRO)	26 low-income 20 middle-income	4 low-income countries with GARP working groups (Kenya, Tanzania, Mozambique, Uganda) 1 middle-income county with GARP working group (South Africa) Ghana also has national-level antibiotic resistance group	Poor policy enforcement[1]	Approximately 3/4 of AFRO nations have policies emphasizing rational use[1] Enforcement is poor[1]			Surveillance occurs only in few countries Scarcity of accurate and reliable AMR data WHO member states endorsed Integrated Disease Surveillance and Response in 1998 No formal collaboration among regional surveillance programs Available data show increased drug resistance
Eastern Mediterranean (EMRO)	2 low-income 13 middle-income Responses came only from middle-income countries (Egypt, Lebanon, Pakistan, and Syria)	No national-level body in Egypt or Lebanon[2] Pakistan and Syria have national-level bodies[2] Pakistan and Syria lack funding, resources, and leadership[2]	Syria was only respondent without national policy restricting use of antibiotics without prescription In other three countries, enforcement is minimal at best[2]	Lebanon was only country to report national antibiotic policy regarding resistance[2]	Pakistan was only country with policy on use of antibiotics in animal husbandry; policy is not enforced[2]	No respondents were aware of major report on use of antibiotics in animals or humans in their country[2] Lebanon reported public education campaign on use of antibiotics[2]	Limited availability of reliable data hinders estimates of AMR issues Lack strong national surveillance of ABR Lack collaboration with animal health sectors In 2002 and 2013 EMRO adopted resolutions to address AMR; action is not unified
Europe (EURO)	All non-EU countries in Europe are LMICs Middle-income countries (Bulgaria, Hungary, and Romania) are EU members	All non-EU countries are interested in working with WHO Europe[3] Most are seeking to create committees focused on issues related to AMR[3]	For LMICs with policies, enforcement is difficult[3]	Most LMICs have policies addressing antibiotic resistance; enforcement is problematic[3]	Approximately 1/3 of European LMICs have policy on antibiotic use for animal husbandry[3]	Study of antibiotic resistance patterns in LMICs appeared in *The Lancet* (March 2014)[3] 15 non-EU countries participated in European Antibiotic Awareness Day in 2013[3]	Most EU countries have strong national and international surveillance for AMR; surveillance is less robust in non-EU countries European Antimicrobial Resistance Surveillance Network (EARS-Net) includes all EU countries plus Norway and Iceland EARS-Net includes surveillance of 8 indicator pathogens for bloodstream infections and meningitis plus surveillance of AMR

						Some European LMICs had education campaigns in past five years[3]	Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CESAR) focuses on support of non-EARS-Net countries in developing their own ABR surveillance systems Foodborne and Waterborne Diseases and Zoonoses Network collects AMR data for foodborne bacteria and publishes findings in annual report
The Americas (PAHO)	All LMICs in region (including Latin America and Caribbean) are middle-income except Haiti, which is low-income					Data from PAHO surveillance network are regularly published by PAHO in Spanish	Latin American Antimicrobial Resistance Surveillance Network (ReLAVRA) was created in 1996, led by WHO Americas/PAHO to collect data from national reference laboratories (NRLs) ReLAVRA involves NRLs from 21 different countries, including 17 middle-income countries ReLAVRA allows English-speaking countries in Caribbean to share data but not to directly participate in network
South-East Asia (SEARO)		Most SEARO countries were forming committees to deal with antimicrobial resistance as of SEARO meeting in 2013[4] Some countries already had committees at time of SEARO meeting[4]		Almost all SEARO countries had policies on antibiotics and planned to contain antibiotic resistance as of 2013 SEARO meeting[4]	Countries except Sri Lanka had not passed regulations on antibiotic use in humans or animals as of 2013 SEARO meeting[4]	Nearly all SEARO countries have launched public education campaigns in response to Jaipur Declaration[4]	Region does not yet have systematic data collection efforts for AMR Health ministers of region declared their commitment to combat AMR via Jaipur Declaration All 11 member states agreed to contribute to regional database and become involved in regional consultative process

Western Pacific (WPRO)	1 low-income country (Cambodia) Several middle-income countries (see Tables 1, 2) Information provided by WPRO, Cambodia, Fiji, Kiribati, Laos, and Tuvalu	Vietnam has GARP working group Cambodia was only respondent to report national-level body for antibiotic issues; funding and resources reported as inadequate[5]	Cambodia was only respondent to report no national policy restricting antibiotic availability without prescription[5] Laos has policies, but they are not well enforced[5] Other respondents report restrictive policies that are enforced[5]		Laos was only country to report policy on use of antibiotics for animal husbandry[5]	Laos released report on antibiotic use in humans[5] Laos Food and Drug Department carried out public education campaign on antibiotic use[5] Cambodia's study on antibiotic resistance will be made public shortly[6]	Previous efforts (beginning in 1980s) to share AMR findings were interrupted by series of emergencies in early 2000s Many member states continue with ABR surveillance on national level WPRO has begun to revive regional AMR surveillance Upper-middle-income countries have AMR surveillance programs like those in high-income countries, but with larger gaps Thoroughness of surveillance varies more in lower-middle-income countries

SOURCE: Authors

1 - J.-B. Ndihokubwayo, personal communication, March 7, 2014
2 - K. Agha, H. El Bushra, M. Elmahdawy, A. Rashid, personal communications, February 22–March 2, 2014
3 - D. Lo Fo Wong and S. Nahrgang, personal communications, March 5–7, 2014
4 World Health Organization 2013
5 - A. Costa, K. Nahapetyan, S. Phongphachanh, personal communications, March 5–6, 2014
6 - A. Costa, personal communication, March 5, 2014
7 - (WHO 2014)

COUNTRY-LEVEL PROGRAMS IN LMICs

Antibiotic resistance is a global problem, but the solutions have a strong local component. Behavior change among health professionals and the public, guided often by government guidelines, laws, and regulations, will be required to "bend the curve," as has happened in Europe. The global scan summarized in the previous section of this report suggests that some countries (especially middle-income countries) have begun to put in place measures to address antibiotic resistance, but most low-income countries (particularly in Africa) have not. In this section, we highlight efforts to establish the means to address these issues at the country level. The Global Antibiotic Resistance Partnership, a project of the Center for Disease Dynamics, Economics & Policy (CDDEP), is featured.

Global Antibiotic Resistance Partnership

GARP began in 2008 with funding from the Bill & Melinda Gates Foundation. The aim has been to develop sustained local capacity to formulate and promote locally relevant policy related to antibiotic use and resistance in LMICs.

For several years prior, CDDEP had been examining the policy process and analyzing options for the United States, in a project called Extending the Cure. That effort, which continues, gave CDDEP entrée into the global discussion about antibiotic resistance, mainly among the high-income countries. The low- and middle-income countries were largely silent.

Antibiotic resistance has gained prominence in recent years, but in 2008, it was not something that everyone talked about. Importantly, it was not a high priority among the main bilateral health funders, such as USAID and DfID. AIDS, malaria and tuberculosis were—and remain—the highest priorities.

Yet it was clear that antibiotic use was growing in LMICs, the bacterial disease burden was high, and the loss of effective treatments for common infections could have even more dire consequences in poor countries than in high-income countries. In the United States, some people die from antibiotic-resistant infections, but a major consequence is economic: later-generation antibiotics are significantly more expensive, and extended stays increase can double (or more) hospital bills. In low-income countries, however, those newer antibiotics are simply not available at all, and in middle-income countries, availability may be limited.

An obvious question is whether the policy prescriptions from the United States and Europe could simply be applied in LMICs. Because of overuse, lack of access, and lack of enforcement capability in many countries, it was apparent that policy solutions would have a greater chance of success if local experts customized them to the local context.

The GARP concept was, therefore, to identify local experts in each country, assemble them into a working group, and provide them with the resources to meet, discuss, and analyze the national situation regarding antibiotic use and resistance, identify critical data gaps, and work toward developing locally relevant policy that could be adopted by government and private sector organizations, such as hospitals and professional societies.

GARP was established in 2009–2010 in four countries—Kenya, India, Vietnam and South Africa—chosen because they represented a range of conditions, particularly in type of government, culture, and income level. After promising starts and progress in those countries (phase 1), a second grant was awarded, and programs were established in four additional countries (phase 2): Mozambique, Tanzania, Nepal, and Uganda.

CDDEP has provided support in each country to hold meetings and employ a half- or full-time coordinator for three to five years, after which countries are expected to raise the modest amounts needed to sustain the working group and any activities that it chooses to do.

GARP Working Groups

CDDEP found no models for the proposed approach, which was to create multidisciplinary, multisectoral groups and empower them to participate in a national policy process. The aim was that they would become trusted advisers to government, professional groups, and the public (e.g., through the media). The working group members would be volunteers, but a paid staff person (the coordinator) was essential for the group to be productive.

CDDEP identified potential working group members in each country through literature searches and networking with professional contacts. Chairpersons were selected for their stature in the scientific and/or academic community and for affiliation with a prominent academic or scientific organization. In two cases (Vietnam and Uganda), the secretariat itself is the prominent organization and a principal investigator has assembled the working group, including the chairperson, in consultation with CDDEP.

From the beginning, GARP working groups included experts in both human and veterinary medicine, from the public and private sectors, and representing a range of scientific and health disciplines. Invariably, some group members were acquainted with or knew of other members, but no one knew everyone else; the mix of disciplines (especially animal and human sciences) was unusual—and is one of GARP's hallmarks. Moreover, in no country does the GARP working group duplicate another group, although interests may overlap (e.g., in Kenya, the Infection Prevention Network-Kenya [IPNET-Kenya], started by the GARP-Kenya vice chair, deals with infection and antibiotic use in hospitals). In some countries, the GARP

working group is the only entity inside or outside government with the antibiotic resistance mandate.

GARP-Kenya

GARP-Kenya is a good example of how the project has evolved in specific countries. Kenya was the first GARP project, beginning work in 2009 with a "situation analysis," which has become standard for newly organized GARP projects. The situation analysis was not focused narrowly on studies of antibiotic resistance but looked at a range of factors impinging on antibiotic use and access in both humans and animals: the burden of infectious disease, which vaccines are in use and the coverage rates, the antibiotic supply chain, antibiotic use patterns and variation in these characteristics around the country. The situation analysis was the foundation document for the working group to define an evidence-based policy agenda for the coming years, including a research agenda aimed at filling important information gaps.

The situation analysis had additional value in Kenya, as elsewhere, as a means of building cohesiveness among the working group with a high-quality collaborative product that was recognized externally as authoritative and novel. It was a calling card that could be used to approach government and others and signaled seriousness of purpose.

<u>Gap-Filling Research</u>

CDDEP offered to fund small research projects (on the order of US$10,000) that would produce information to fill important knowledge gaps identified in the situation analysis. In Kenya, two projects were funded.

1. Antibiotic use in food animals
This was a first-of-its-kind study of antibiotic resistance levels in bacteria cultured from carcasses (of cows, pigs, and chickens) in slaughterhouses and in retail meat, coupled with interviews of farmers and herders in the same areas from which the slaughtered animals came. The bacterial sampling, culture, and analysis were carried out by Dr. Samuel Kariuki, chair of the GARP-Kenya working group, and Patrick Irungu, a young academic agricultural economist who has since become a member of the working group, conducted the fieldwork. The farmers and herders were asked about many things, including their practices related to antibiotics use.

This project was small and limited to the area around Nairobi, but it was used as a pilot to approach FAO for a larger project involving a nationwide sample, which has been completed.

Antibiotic use was widespread among all farmers and herders. Tetracyclines, sulfonamides, penicillins, and streptomycins were the most frequently used. Most

antibiotics were purchased directly at agro-vet stores, without the intervention of veterinarians (mainly because they are scarce and inaccessible for most animal husbandry men). Antibiotic resistance was equally prevalent in samples from all three types of animals: most bacteria cultured from beef were resistant to most of the commonly used antibiotics, about half those cultured from chicken were resistant to some antibiotics, and a smaller percentage of those cultured from pigs were resistant.

Other findings suggested effective interventions. One, in particular, was that nongovernmental organizations (NGOs) that provided support to farmers and herders often gave them free antibiotics. Not surprisingly, this increased antibiotic use (though it was not necessarily appropriate use). NGOs also provided other types of support—restocking, water provision, and animal dips for parasites—that had no effect on antibiotic use.

This study (awaiting publication) provided a baseline and some interesting findings but also opened the conversation about antibiotic use in food animals.

2. Knowledge, attitude, perception, and pricing of antibiotics in hospitals in two areas of Kenya

Another small study—in and around Nairobi and in western Kenya in Nyanza province, was conducted by the Ecumenical Pharmaceutical Network, led by Donna Kusemererwa, then vice-chair of the working group and current vice-chair of the new GARP-Uganda working group. The study included public, private, and mission hospitals in both regions. At least four individuals were interviewed at each hospital: a medical professional and one person each from pharmacy, laboratory, and administration.

Not surprisingly, the large majority of professionals interviewed in the study were aware of the seriousness of antimicrobial resistance as a national problem, but many fewer it found a problem at their own hospital. The survey (awaiting publication) points to missing information (e.g., a survey of practices) and indicates what is and is not known by health professionals.

The associated study of antibiotic pricing (Kusemererwa et al. 2013) found that cash-flow problems force hospitals to engage in significant purchasing of small lots, even though large-quantity purchases result in lower costs per dose. It also found a wide range of markups—from 50 percent to 400 percent—for individual antibiotics, depending on where they were sold.

GARP-Kenya 2014

GARP-Kenya has matured into an independent group, incorporating in 2014 as an autonomous arm of IPNET-Kenya. A sampling of its recent activities includes the following:

- November 2013: two-day workshop on antimicrobial stewardship in Mombasa, with participation from around Africa (and Haiti), following an infection prevention and control meeting;
- November 2013: presentation on antimicrobial stewardship to the National Infection Prevention Control Committee at the invitation of the Infection Prevention and Control Unit of the Ministry of Health;
- November 2013: the first "antibiotic awareness week" in Kenya; and
- February–March 2014: presentations on antimicrobial use, with the Ministry of Health, to the health executive members in each county (formerly states) on antimicrobial use in Kenya.

Policy research priorities for the coming year have been set, and GARP-Kenya is seeking funding for specific projects and a small amount of unrestricted funding for administrative costs (meetings and salary for the half-time coordinator, who is vital to continued progress).

After several years of CDDEP nurturing, GARP-Kenya has become a trusted adviser to government and a recognized source of expertise for the country.

The GARP Network
(http://www.cddep.org/projects/global_antibiotic_resistance_partnership)

The first four GARP country projects have evolved in somewhat different directions, but have all succeeded in creating a hub of antibiotic resistance expertise and activity. In Vietnam, for example, the secretariat is the Oxford University Clinical Research Unit (OUCRU) in Hanoi. The working group is chaired by Dr. Nguyen Van Kinh, director of the Infectious Disease Hospital (under the Ministry of Health) in which OUCRU is housed. GARP-Vietnam therefore has close ties to government. The GARP "brand" has been useful in setting policy research apart from purely scientific and clinical work, and gives voice to the policy implications of basic research.

GARP working groups in other countries—for example, Kenya and Nepal (where the secretariat is the Nepal Public Health Foundation)—have found value in being independent of their governments because of turnover and even new constitutions. While it is important for governments to take action for antibiotics, authoritative groups outside government have obvious value.

GARP-Uganda is the last of the eight GARP projects started under the Gates Foundation grants; its inaugural meeting was held in February 2014. The secretariat is lodged in the Uganda National Academy of Sciences, an organization whose main mission is to advise government.

CDDEP's challenge is to move beyond the intensive process needed to fledge the current eight projects and grow the GARP network organically. GARP has now become moderately well known, enough to stimulate demand from non-GARP

countries. Rwanda, for example, has asked GARP-Kenya about starting a project there, and in the course of conducting the survey for this paper, CDDEP was queried about new country projects.

ReAct—Action on Antibiotic Resistance (http://www.reactgroup.org/)

Sweden has been a leader in reducing antibiotic resistance within its borders. Since 2005, it also has led in LMICs, with ReAct operating from Uppsala University. The website describes ReAct this way:

> ReAct is an independent global network for concerted action on antibiotic resistance. ReAct aims for profound change in awareness and action to manage the interacting social, political, ecological and technical forces that drive the rising rate of resistant human and animal infection and the rapid spread of resistance within and between communities and countries. (http://www.reactgroup.org/who-we-are.html)

Like GARP, ReAct is an ongoing project, not an organization. Its funding comes mainly from the Swedish International Development Cooperation Agency (SIDA), the Swedish Ministry of Health and Social Affairs and Uppsala University.

ReAct has supported and conducted many activities in Asia, Latin America, and Africa and has raised the global profile of antibiotic resistance. It has partnered with a large number of civil society organizations (CSOs, e.g., the Ecumenical Pharmaceutical Network and GARP) and has supported WHO on matters of antibiotics and antibiotic resistance.

In 2014, ReAct's major activity is the Civil Society Organization Project, a concerted effort to engage CSOs involved in child and maternal health, women's issues, and education and environment, using its networks of individuals in Southeast Asia, Latin America, and Ghana.

Country Engagement

A centerpiece of ReAct's country engagement has been Ghana. In November 2013, after several years of preparation and activity, an AMR "technical task team" (TTT) was established in the Ministry of Health, with the express purpose of developing comprehensive national policy on antibiotic use and resistance. The TTT looks very much like a GARP working group in its range of expertise and subject areas, including both human and animal use of antibiotics. The main difference is that the TTT has more government representation than do GARP working groups, and the connection with the government is direct.

Because of ReAct's consistent support over a period of years, the Ghana TTT is likely to be a strong internal advocate for maintaining antibiotic effectiveness and can be called on as a representative voice in global debates.

Alliance for the Prudent Use of Antibiotics (http://www.tufts.edu/med/apua/)

Founded in 1981, the Alliance for the Prudent Use of Antibiotics (APUA) is the oldest of the organizations devoted to protecting antibiotics. It began including LMICs in Latin America and then Africa in its formal network around the turn of the 21st century.

Like ReAct, APUA participates in the global debate but also has country involvement in the form of chapters. The APUA website lists 65 country chapters, including 30 in resource-poor countries. Their activity levels vary. Some do not meet even annually, and virtually all suffer from a lack of resources. APUA has provided small grants for specific research projects in the past but does not appear to be doing so now, and it has never provided support for general chapter operations.

All eight GARP countries have APUA chapters, with many overlaps in membership between APUA and GARP working groups. However, the only country of the eight with current APUA activity appears to be Nepal, where the leader of the APUA group has participated in drawing up antibiotic use guidelines in consultation with the Ministry of Health.

WHO EFFORTS IN ANTIMICROBIAL RESISTANCE

WHO Global Strategy for Containment of Antimicrobial Resistance, 2001

WHO made its first major statement on antibiotic resistance in 2001 when it issued the WHO Global Strategy for Containment of Antimicrobial Resistance, which underscored the importance of containing the spread of antibiotic resistance while also combating the challenge of lack of access to appropriate antibiotics. The report recognized the health, societal, and financial costs of the global spread of antimicrobial resistance and put forth a "people-centered" approach to containing resistance, with key messages for prescribers and dispensers, hospitals, governments and health systems, drug and vaccine developers, and the general public (WHO 2001). The report additionally encouraged cooperation between governments, health professionals, and NGOs and warned against promotion of antibiotics by pharmaceutical companies. It recognized the risk of overuse of antimicrobials in food-producing animals. The importance of strengthening and understanding different health systems was emphasized, as was the importance of collecting and interpreting data on antimicrobial use and resistance patterns. The report also highlighted the need to understand which interventions were feasible and cost-effective.

For patients and the general population, recommended interventions were focused on prevention and education. Strategies for infection prevention at the personal and household level included immunizations and personal and food hygiene. The strategies focused on educating communities in proper use of antibiotics, as well as alternatives to antibiotic treatment (WHO 2001).

Education and prevention were also major components of the intervention strategy for prescribers and dispensers. Prescribers and dispensers needed to be educated on infection prevention and control and proper antimicrobial use, while also educating their patients on these topics. Improving appropriate disease diagnostics and treatment was another element of the intervention package for prescribers: the report stressed that these should be incorporated into education programs, including continuing education programs (WHO 2001).

Hospitals were encouraged to create systems to monitor antibiotic use and implement guidelines and oversight for both antibiotic use and infection control. Important elements of the proposed interventions for hospitals were a feedback mechanism for prescribers and diagnostic laboratories capable of collecting data on resistance. Lastly, hospitals were encouraged to limit the influence of pharmaceutical promotion within their hospitals, which was also mentioned as a strategy for prescribers and dispensers (WHO 2001).

The 2001 WHO document called for containment of antimicrobial resistance to be recognized by national governments as a policy priority, with adequate funding and a task force comprising personnel from different sectors. Government officials and health systems were implored to work on policies to limit antimicrobial use, oversee quality of antibiotics, and implement appropriate surveillance for infectious diseases, antibiotic use, and antibiotic resistance. Additionally, policies were recommended for restricting and monitoring antimicrobial use in food animals (WHO 2001).

Governments were also asked to work with drug and vaccine researchers to encourage innovation in developing new drugs, vaccines, and treatment standards. Policymakers were encouraged to ease the process for developing and approving new antimicrobials (WHO 2001).Lastly, the strategic plan called for collaboration at the international level, among governments and among related professions and sectors (WHO 2001).

This report was released on September 11, 2001, and therefore did not receive much publicity, and although the importance of antibiotic resistance continued to grow, it was not yet widely recognized as a global threat.

World Health Day 2011: Antimicrobial Resistance: No Action Today, No Cure Tomorrow

Ten years after releasing the 2001 report, WHO declared antimicrobial resistance the public health priority that would be the theme of its annual World Health Day. WHO put forth a set of recommendations on combating antimicrobial resistance and encouraged national governments to commit to its proposed policy package (Box 1).

Box 1. WHO's Policy Package to Combat Antimicrobial Resistance
World Health Day 2011

(1) commit to a comprehensive, financed national plan with accountability and civil society engagement

(2) strengthen surveillance and laboratory capacity

(3) ensure uninterrupted access to essential medicines of assured quality

(4) regulate and promote rational use of medicines in animal husbandry and to ensure proper patient care

(5) enhance infection prevention and control

(6) foster innovations and research and development of new tools

Source: (World Health Organization 2011b)

WHO urged governments and other stakeholders to commit to the policy package and collaborate to avoid "the next global crisis" (Chan 2011) of "regressing to the pre-antibiotic era" (WHO 2011a) (WHO 2011b).

The Evolving Threat of Antimicrobial Resistance: Options for Action, 2012

The year following the AMR-themed World Health Day, WHO published its second major report on antimicrobial resistance: *The Evolving Threat of Antimicrobial Resistance: Options for Action*. This report focused on five aspects of containment from the 2011 policy package: surveillance, regulations and rational use, antimicrobial use in food-producing animals, health center infection control and prevention, and technology and innovation. The report included an update on progress in each sphere, while giving examples of policies, government action, and international cooperation on these topics, with the message that political action and commitment were critical to combating antimicrobial resistance. Knowledge and action gaps were also listed. Recurring themes in the challenges for different sectors included (1) lack of appropriate technologies, laboratory capacity, and data on antimicrobial use and resistance (both in humans and animals); (2) underrepresentation of certain geographical regions in antimicrobial surveillance,

policies, and research, as well as lack of coordination between countries and surveillance systems; and (3) lack of commitment of resources to tackling AMR (WHO 2012).

Though not a main focus of the report, the environmental aspects of antibiotic use and resistance, including the presence of antimicrobials in soil and water, were noted as a topic for future examination and attention (WHO 2012).

Throughout the 2012 report, WHO emphasized the importance of government and policy initiatives to collaborate on identifying and controlling antimicrobial resistance. WHO also explained its own involvement moving forward on this topic, stating that "the role of WHO is to facilitate action worldwide through stimulating political commitment, advocating for action, shaping collaborations between different stakeholders, facilitating development of evidence-based guidance, norms and standards, and tools for countries to implement specific interventions and evaluations," as well as to "defin[e] an AMR research agenda" (WHO 2012b).

Antimicrobial Resistance: Global Report on Surveillance, 2014

Antimicrobial Resistance (WHO 2014) reports the results of the survey of antibiotic resistance discussed earlier, plus information on antimicrobial resistance related to several disease-specific programs. These include tuberculosis, HIV, malaria, and gonorrhea. The available data (which are sparse) support a finding of high resistance rates of common bacterial pathogens to the antibiotics commonly used to treat them. However, this information comes mainly from ad hoc studies and not ongoing surveillance, which is needed to analyze trends and determine the success or failure of interventions intended to moderate the spread of AMR.

The report concludes with recommendations to (1) develop "harmonized surveillance" for antibiotic resistance which includes humans, food animals and the food chain; (2) develop strategies for population-based AMR surveillance, including health and economic impacts; and (3) strengthen regional and global coordinated surveillance.

WHO Regional Office Efforts

In addition to publishing reports and overseeing projects, WHO conducts antibiotic resistance work and research through its regional and country offices. Focal persons for antimicrobial resistance have been assigned in many of these offices.

The Regional Office for Africa issued a short report in 2013 on the state of antimicrobial resistance in Africa, outlining some of the challenges for documenting and restricting antimicrobial resistance in Africa. The report encouraged a set of actions for combating AMR in Africa, calling for national policies, improved

laboratory capacity and surveillance, and improved medicine regulation (Ndihokubwayo et al. 2013). This was accompanied by a WHO-AFRO manual, *Guide for Establishing Laboratory-Based Surveillance for Antimicrobial Resistance*, which was intended to support countries seeking to establish surveillance for AMR (World Health Organization Regional Office for Africa 2013).

The Pan American Health Organization, the WHO regional office for the Americas, dedicates a section of its website to antimicrobial resistance, with annual technical reports from 2005 to 2010, guidelines for antimicrobial susceptibility testing, and other resources on antimicrobial resistance (Pan American Health Organization 2014).

The WHO Regional Office for South-East Asia has a comprehensive web page on antimicrobial resistance, including technical, educational, and advocacy materials. SEARO holds regional meetings to collaborate on antimicrobial resistance containment and surveillance. The report from its most recent meeting, held in Chennai in June 2013, included a compilation of national indicators of progress on implementing measures set forth in the Jaipur Declaration on Antimicrobial Resistance, a declaration composed by the SEARO member countries in 2011 urging action on antimicrobial resistance (World Health Organization Regional Office for South-East Asia 2014).

The Regional Office for Europe also has a comprehensive web page on antimicrobial resistance that includes a strategic plan on antibiotic resistance, policy documents, and data on resistance. Also available are fact sheets and laboratory guidelines for antimicrobial susceptibility testing (World Health Organization Regional Office for Europe 2014).

The WHO Regional Office for the Eastern Mediterranean (EMRO) has less regionally specific information on antimicrobial resistance readily available; however, contacts for antimicrobial resistance have been established in some EMRO country offices (A. Mafi, personal communication, February 20, 2014). The Regional Office for the Western Pacific also has little information available on its website about antimicrobial resistance.

GLOBAL RESOLVE TO MAINTAIN ANTIBIOTIC EFFECTIVENESS

In the past few years, statements affirming the need to protect antibiotics and the need for action at the country level have been promulgated. The Jaipur Declaration, the CDDEP Call to Action, and the Chennai Declaration, directed specifically at LMICs, are described below. The World Health Assembly in June 2014 is profiled at the end of this section.

Jaipur Declaration

On 6 September 2011, during the 29th Meeting of Ministers of Health of countries of the World Health Organization's South-East Asia Region, health ministers from 11 countries signed the Jaipur Declaration on Antimicrobial Resistance. This declaration goes beyond antibiotics, addressing resistance concerns across pathogens (HIV/AIDS, malaria, tuberculosis, etc.) and flagging the threat that growing resistance, both global and regional, could become a critical impediment to containing these diseases and achieving the Millennium Development Goals (MDGs), in particular MDG 6 (combating HIV/AIDS, malaria, and other diseases).

The Jaipur Declaration makes the case that irrational use of antimicrobials is the single most significant driver of resistance. It urges governments to commit to preserving the efficacy of antimicrobials. It calls on national, regional, and global leaders to develop mechanisms to work with the private health sector, industry, and communities to tackle the multisectoral determinants of resistance. The declaration emphasizes the need to develop national antibiotic policies, implement and enforce regulations on the use of antimicrobial agents, strengthen legislation against manufacture and sale of counterfeit antimicrobials, and ensure rational use.

A Global Call to Action to Preserve the Power of Antibiotics

On 3–5 October 2011, policymakers, researchers, and members of the public health community from around the world came together for the *1st Global Forum on Bacterial Infections: Balancing Treatment Access and Antibiotic Resistance*. The Global Forum was convened by CDDEP as the culmination of the first phase of GARP. Held in New Delhi, the Global Forum was the first event of its kind to be held in a low- or middle-income country. Delegates to the forum shared recent research findings and debated policy solutions to extend antibiotic access to those without it and, at the same time, maintain a focus on antibiotic resistance.

Prior to the forum, a global *New Delhi Call to Action to Preserve the Power of Antibiotics* (available on the Global Forum website, www.globalbacteria.org) was developed and shared with Global Forum partner organizations (ReAct, ISC) and high-level ministerial counterparts in GARP countries. During the forum itself, the document was signed by Hon. Prof. Peter Anyang' Nyong'o, Minister for Medical Services of the Republic of Kenya and Member of Parliament for the Kisumu Rural Constituency; Hon. Robert Joseph Mettle-Nunoo, Deputy Minister for Health, Ghana; and Hung Thai Cao, Vice Director of Medical Services Administration and Senior Official in the Ministry of Health, Vietnam.

The *New Delhi Call to Action* describes antibiotics as a global common resource and recognizes the importance of ensuring their preservation. It represents the first global effort of this nature. Following the forum, CDDEP and GARP continued to pursue government-level signatories, with the overall aim of drawing further

attention to the coexisting issues of antibiotic access and preservation. On 20 March 2012, the Vietnamese minister of health, Prof. PhD. Nguyen Thi Kim Tien, added her signature to the *Call to Action,* and during the summer of 2012, the *Call to Action* was signed by the ministers of health of Mozambique and South Africa.

Given the urgent need to learn more about antibiotic use in agriculture in developing-country settings and its potential effects on the emergence and spread of resistant pathogens, GARP is also exploring the possibility of expanding the signatories of the *Call to Action* to include ministers of agriculture.

The Chennai Declaration

In August 2012, a first-ever meeting bringing together all Indian Medical Societies was held to discuss the importance of antibiotic resistance in India. Held in Chennai, India, the meeting was intended to begin to formulate a roadmap of actions critical to containing resistance domestically and to forge consensus around the necessary steps.

Participants included high-level central and state government policymakers, members of the National Accreditation Board of Hospitals, the Medical Council of India, the Indian Council of Medical Research, the Drug Controller General of India, and the World Health Organization. The primary output of the meeting was the Chennai Declaration—a draft document titled "A Roadmap to Tackle the Challenge of Antimicrobial Resistance" that was published in the *Indian Journal of Cancer* (Ghafur et al. 2012) and shared with all stakeholders.

The declaration highlights steps that must be taken by the various actors involved in containing antibiotic resistance. The overall timeline is five years, with intermediate milestones at one- and two- years. Priority areas were identified:

- Over-the-counter sales of antibiotics
- In-hospital antibiotics monitoring
- Surgical antibiotics prophylaxis monitoring sheets
- Creation of an autonomous antibiotics policy accreditation agency
- Stepping up of infectious control facilities in hospitals
- Regulation of antibiotic usage in veterinary practice
- Restrictions on over-the-counter sales of antibiotics for animal use
- National antibiotics resistance monitoring network
- Monitoring of antibiotic residues in food of animal origin
- National advisory board to prepare guidelines for infection prevention in India
- Clinical research to explore existing options to treat multidrug-resistant Gram-negatives
- Curriculum changes to encourage rational antibiotic use and infection control
- Encouragement of research to develop new molecules
- Active contribution of medical societies

- Publishing of editorials on tackling resistance
- Engagement of media and NGOs
- Measures to improve sanitation
- Hospital accreditation agencies
- Stepping up of microbiology laboratory facilities in the country
- Encouragement of use of similar software to monitor antibiotic use and resistance levels in hospitals throughout the country

March 2014 saw adoption at the federal level of the Schedule H1 to the Drugs and Cosmetics Act, which restricts the sale of 46 over-the-counter drugs, including antibiotics and anti-TB drugs.

World Health Assembly Proposed Resolution

At its meeting in January 2014, the World Health Assembly (WHA) Executive Board recommended a resolution called "Combating antimicrobial resistance, including antibiotic resistance," proposed by Australia, China, Costa Rica, Ghana, Japan, Libya, Mexico, Netherlands, Qatar, Sweden, Thailand, United Kingdom of Great Britain and Northern Ireland, and the United States. The resolution was adopted by the WHA at its annual meeting in May 2014.

A WHA resolution does not have the force of law, but it can be used to drive WHO activities and, importantly, the budget. It is also a call to action for all WHO member countries and WHO country and regional offices. The resolution specifies nine areas for action:

- increasing political awareness, engagement, and leadership;
- national, regional, and local action in infection prevention and control;
- national plans and strategies and international collaboration to contain antimicrobial resistance;
- human and financial resources to implement plans;
- strengthening overall pharmaceutical management systems;
- surveying and monitoring antimicrobial resistance and use in all relevant sectors;
- improving, among care providers, the public and other sectors and stakeholders, awareness of (1) the threat posed by antimicrobial resistance, (2) the need for responsible use of antibiotics, and (3) the importance of infection prevention and control measures;
- encouraging and supporting research and development, including new business models, to develop new drugs and maintain the effectiveness of existing ones; and
- collaborating with WHO in developing and implementing a draft global action plan to combat antimicrobial resistance that is based on all available evidence and best practices.

The resolution calls for a "draft global action plan to combat antimicrobial resistance" to be submitted to the WHA Executive Board in 2015, and a progress report on other aspects of the resolution.

ANALYSIS OF EFFORTS IN LMICs

We have pointed out specific instances of actions being taken in LMICs to address the presumed causes of antibiotic resistance by reducing consumption where antibiotics are overused. In India, sales of carbapenems were banned in retail pharmacies, and in Kenya, antimicrobial stewardship programs are being put in place in hospitals across the country. These actions are, to our knowledge, relatively few. These are necessary steps and very hopeful, but we are aware of no evidence that these beginnings have yet resulted in measurable reductions in antibiotic resistance levels, either at national levels or in individual institutions. Few middle-income countries and fewer (if any) low-income counties have surveillance data adequate to determine current levels or current trends in antibiotic resistance.

Change is occurring, however. Some antibiotic resistance information exists for the middle-income countries that participate in EARS-Net: Bulgaria, Hungary, and Romania. Hungary, for example, has reported some data for 10 years. For the non-EU European countries, CAESAR will soon release data. Individual countries in other regions (e.g., Cambodia) are undertaking county reports, though we are not aware of any yet available.

LIMITING THE SPREAD OF ANTIMICROBIAL RESISTANCE IN LMICs

Many actions can and no doubt will be taken in LMICs to address antibiotic resistance. As in all countries, opportunities exist both to reduce the need for antibiotics and to curb unnecessary use. These can be grouped in five main categories, discussed in more detail below:

- Reduce need for antibiotics by improving public health (immunization, infection control, sanitation).
- Phase out antibiotic use for growth promotion in agriculture.
- Change incentives for prescribing antibiotics and non-prescription sales.
- Invest in antibiotic resistance surveillance for clinical guidance and policy.
- Ensure political commitment to the threat of resistance.

Not included in this list is the development of new antibiotics and diagnostics—two global concerns. LMICs can be encouraged to contribute to the development of these products, but that is less important than steps they can take to preserve the effectiveness of existing products.

Reduce the need for antibiotics by improving public health

Increased use of vaccines and improved sanitation will reduce the infectious disease burden and generally improve the health of populations. A secondary effect that may never be mentioned as a rationale for adopting or expanding vaccination is reduction in demand for antibiotics. The most important "antibiotic-sparing" vaccines are pneumococcal and *Haemophilus influenzae* vaccines, which are the main preventable causes of infant and childhood pneumonia (and infections at some other sites). Rotavirus vaccine is also antibiotic sparing, even though the target organism is a virus, which is unresponsive to antibiotics, because antibiotics are used increasingly for uncomplicated (watery) diarrhea—mostly inappropriately, instead of oral rehydration solution—in many LMICs (Santosham et al. 2010). Reducing the incidence of diarrhea should reduce that inappropriate use. WHO and national governments can also reemphasize the effectiveness of oral rehydration therapy.

Other vaccines could also have an antibiotic-sparing effect, including seasonal influenza (for pregnant women in particular), cholera, and typhoid. These vaccines are not used routinely. The latter two are recommended for outbreaks in endemic countries, but WHO recommends seasonal influenza vaccination for all pregnant women, both to reduce their own chances of contracting influenza and to protect their infants during the first months of life. Influenza vaccine can be delivered during prenatal visits, which most pregnant women have, wherever they live.

Protected water supplies, sewage disposal and uncontaminated food also reduce infectious disease rates, especially enteric diseases, and their reduction leads to fewer antibiotic treatments. These three elements are basic to healthy lives; the antibiotic-sparing effects are secondary but still important and worth recognizing.

Phase out antibiotic use for growth promotion in agriculture

Most high-income countries have taken steps to eliminate the use of ultralow doses of antibiotics to accelerate growth in food animals, but no such prohibitions have been put in place in LMICs. It has been difficult to get reliable information on the use of antibiotics in animals at all, and it is unclear how widespread their use for growth promotion might be. However, we do know that the demand for food, and for animal protein, will continue to increase as population increases and as incomes rise. If the practice of growth promotion is not yet widespread, legal prohibitions can stop it from becoming established.

Change incentives for prescribing antibiotics and nonprescription sales

Changing incentives is about changing behavior. Incentives are often but not always economic, and more than most factors, they are country specific. Where physicians also sell drugs, or where hospital budgets depend heavily on drug sales, it is in the economic (and perhaps survival) interest of the physician or hospital to maintain a

certain level of sales. Pharmacies may also respond to customer demand for antibiotics without prescriptions, especially where prescription-only laws and regulations are poorly enforced. The first step is understanding the existing incentives, which may never have been fully described or studied. In GARP countries, the description of incentives for antibiotic use and sales is part of the initial situation analysis.

Invest in antibiotic resistance surveillance for clinical guidance and policy

The need for antibiotic resistance surveillance has been recognized and recommended repeatedly, but few low-income countries have conducted any surveillance; the record is somewhat better for middle-income nations. Regional networks have improved reporting. Notably, most of the countries in Central and South America have been contributing data to RaLEVRA, a network coordinated by PAHO. In Europe, most of the non-EU countries (mostly middle-income) have begun contributing to the CAESAR network, which was developed in close collaboration with EARS-Net at the European Centre for Disease Prevention and Control. No such network is active in Africa, which has the least developed antibiotic resistance surveillance of any region. WHO provides some guidance for countries to invest in surveillance, including some support of the WHONet software for recording and reporting resistance data.

Ensure political commitment to the threat of resistance

Many factors contribute to political commitment. Although commitment must be at the national level, global prioritization of an issue is important. The global spotlight on antibiotic resistance is very recent and has as yet had little influence on national commitment. This means prioritization by health ministries and, since at least some of the activities will require domestic funding, finance ministries. Because antibiotic resistance has not been addressed in many countries, ready-made tools (such as WHONet) and model policies and priorities (such as the milestones proposed by CDDEP) can also help spur political commitment that translates into action. Joint declarations and calls to action can help to ignite national commitment, which can be followed by adoption of specific goals.

DISCUSSION

Signs are now appearing that global will has gathered behind the need to curb antibiotic resistance. In some high-income countries, will has been matched by action, which requires more political resolve than anything else. The technical elements for surveillance, monitoring, and enforcement of laws and regulations already exist or can be quickly mobilized. The same is not true in most low-income countries and many middle-income countries, however.

This report has highlighted the need for more country-level capacity in LMICs to receive, understand, and act on global directives and guidance and to make combatting antibiotic resistance a priority of bilateral aid agencies and national ministries of health—something that has not yet happened.

The GARP model (with its several variations) and the ReAct-assisted model in Ghana are the most successful examples of developing this capacity *de novo* in LMICs. The GARP model features a working group of largely independent scientists, academicians, and clinicians, with government representation, as well as a paid half- or full-time staff member. Working group members serve as volunteers for set terms, and most meetings are held in low-cost academic or government venues. The modest overall funding is important when groups become independent of outside funding and must raise their own funds.

The country-by-country GARP and ReAct models are not the only ones possible and, indeed, are possibly not appropriate for certain countries. The bilateral aid agencies could catalyze antibiotic policy groups in their beneficiary countries by prioritizing the issue and starting in-country programs.

Since putting antibiotic resistance on the global agenda in 2001, WHO has made only intermittent contributions to solving the problem. Passage of the resolution may be first step in sustaining progress for the next decade.

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